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Short title: Assessor blinded RCT investigating taurolidine-citrate-heparin locks for the prevention of CLABSI.

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Article summary

Abstract

Introduction The efficacy of taurolidine containing lock solutions for the prevention of central line associated bloodstream infections (CLABSI) in paediatric oncology patients is currently still unknown. If the taurolidine-citrate-heparin lock appears to decrease the incidence of CLABSIs, we hope to increase the quality of life for children with cancer by subsequently reducing the central venous access device-removal rate, dispense of antibiotics, days of stay in the hospital and incidence of severe sepsis resulting in intensive care unit admission.

Methods and analysis This assessor blinded randomized controlled trial including 462 patients was designed to compare the taurolidine-citrate-heparin lock to the heparin-only lock for the prevention of CLABSIs in paediatric oncology patients. The primary outcome of this study is the incidence of first CLABSIs from CVAD insertion until the end of the study. An intention-to-treat and per-protocol analysis will be performed. An interim analysis will be performed after the inclusion of 50% of the patients, the results and overall conduct of the trial will be discussed by a data safety monitoring board (DSMB). Inclusion of the study began on the 27th of October 2020. We expect that the planned number of patients can be recruited in 29 months from the defined source population.

Ethics and dissemination The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research registered under number 20/370. The results of this trial will be published in a peer-reviewed journal and subsequently the data will be made available after publication upon reasonable requests.

Registration details: International Clinical Trials Registry Platform of the World Health Organization, NTR6688.

Key words: paediatric oncology, preventive medicine, infection control

Strengths and Limitations

Strengths:

- Designed as an assessor blinded randomized controlled trial
- Stratification for central venous access device type and diagnosis will be performed
- Large paediatric oncology patient cohort (N=462)

Limitations:

- Inclusion and randomization should take place as soon as possible after insertion of the central venous access device, which is not always possible due to clinical and psychological circumstances.
- Locks are instilled once a week during the study since the maximum number of taurolidine-citrate-heparin locks that can be given during a certain time period is currently unknown, more frequent instillations of the lock might result in a higher efficacy.

Introduction

Tunnelled central venous access devices (CVAD) are fundamental in paediatric oncology since they provide long-term venous access. In this patient group, the incidence of central line-associated bloodstream infections (CLABSI) is high. [1] CLABSI incidence rates of 0.1-2.3 per 1,000 CVAD-days have previously been reported, mostly depending on the patient population, CVAD-type and infection definitions used. [2] In our hospital, the Princess Máxima Centre for paediatric oncology, a CLABSI incidence rate of 1.51 per 1,000 CVAD-days has been reported; at least one CLABSI was observed in 30% of the children receiving a CVAD. [3] CLABSI episodes often result in hospital admission, postponement of anticancer treatment, early CVAD removal (15% of all CVADs inserted) and can lead to severe sepsis requiring intensive care unit admission (5% of all patients receiving a CVAD). [3] CLABSIs therefore have a great impact on the quality of life of children diagnosed with cancer and result in high healthcare costs. [1, 4]

Taurolidine-citrate(-heparin) lock solutions (TCHL) are suggested as a promising and safe method for the prevention of CLABSIs. [5, 6] Taurolidine and citrate have anticoagulant, antimicrobial and anti-biofilm properties. No antimicrobial resistance to taurolidine has been reported, which makes taurolidine a more attractable option compared to other antimicrobial lock solutions. [7] Taurolidine causes a chemical reaction with the bacterial cell wall, endotoxins and exotoxins, resulting in irreversible damage to the bacteria, inhibition of bacterial pathogenicity and inhibition of surface adhesion of bacteria. [5, 7-11] The current standard of care in the Netherlands for paediatric oncology patients, is to lock the CVAD with a heparin-only lock (HL) solution for the prevention of malfunctions. The HL however, does not have antimicrobial activity and its use is barely supported by literature. [5] Our meta-analysis including all randomized controlled trials comparing the efficacy of taurolidine containing lock solutions to heparin-, saline- and citrate-only locks in haemodialysis, total parenteral nutrition, and oncology patients showed a pooled incidence rate ratio (IRR) of 0.30 (CI95% 0.19-0.46) in favour of the taurolidine containing lock solutions. Adverse events were all rare and mild. [6] However, these studies were associated with a serious risk of bias and indirectness of evidence. [6] More specifically, in paediatric oncology patients, only two open-labelled randomized controlled trials (N≤112) and four non-randomized controlled trials, have been performed. [12-17] To summarize, these studies did show promising results of the TCHL, but this was not enough evidence to implement the TCHL in paediatric oncology patients. [12-17]

Therefore, this assessor blinded randomized controlled trial including a large patient cohort was designed to compare the TCHL to the HL for the prevention of CLABSIs in paediatric oncology patients. If the TCHL appears to be safe and decreases the incidence of CLABSI, we hope to increase the quality of life for children with cancer by subsequently reducing the CVAD-removal rate, dispense of antibiotics, days of hospital and incidence of severe sepsis resulting in intensive care unit admission.

Methods

Design and setting

The CATERPILLAR-study is an investigator-initiated, assessor blinded, randomized controlled trial comparing the incidence of CLABSI between the TCHL to the HL in paediatric oncology patients. In total 462 patients are expected to be recruited from the Princess Máxima Centre for paediatric oncology, Utrecht, the Netherlands over 29 months. Patients will be randomized (1:1) into the HL or TCHL study arm. Patients will be followed up from CVAD insertion until the first CLABSI episode, CVAD-removal, second CVAD insertion or death with a maximum study period of 90 days, whichever comes first. The maximum study period of 90 days was chosen since a great deal of the CLABSI episodes occurs within the first 90 days after insertion (median of 60 days after insertion). [1-3] The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule for enrolment, interventions and assessments is described in Fig 1, the SPIRIT checklist can be found under S1 File. This trial is registered in the International Clinical Trials Registry Platform of the World Health Organization (https://trialsearch.who.int/, NTR6688). All research staff working on this study is BROK®-certified (https://nfu-ebrok.nl/).

Patient and public involvement

The patient association Vereniging Kinderkanker Nederland (VKN; https://www.kinderkankernederland.nl/) was involved in the design of this study. The VKN reviewed the protocol and patient information forms, and they assessed the burden for patients to participate in the research. Currently yearly meetings are held between the researcher and VKN to discuss the progress of the trial. The advice given by the VKN is strongly taken into account

by the researchers. Furthermore, the VKN will be involved in the plan for the dissemination of the trial results after completion of the trial.

In the first months after diagnosis, patients will receive their oncologic treatment at the Princess Máxima Centre. After one-two months, a minority of the patients will also be treated in the shared care hospitals close to their homes in the first 90 days. These patients will return at least every three weeks to the Princess Máxima Centre and will then receive their randomized lock. In between, all patients will receive a HL. The total number of lock days per patient will be taken into account/corrected for during the analyses as described below. Shared care data of the included patients will be shared with the Princess Máxima Centre.

Participants

All consecutive paediatric oncology patients (hematologic, solid and neurologic malignancies), treated at the Princess Máxima Centre for Pediatric Oncology, ranging from 0-19 years old, receiving a tunnelled CVAD (tunnelled external CVAD or totally implantable venous access port (TIVAP)) for the first time or if their previous CVAD has been removed >12 months ago, will be asked to participate in this study. Further inclusion criteria are: a radiological, cytological or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies), planned need for central vascular access of >90 days, written consent signed according to local law and regulations, parents/guardians or patient are willing and able to comply with the trial procedure. Exclusion criteria are: a previous CVAD removed < 12 months ago, expected treatment for a majority of the follow-up time in a different hospital than the Princess Maxima Centre for paediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Centre at least once every 3 weeks, primary immunological disorder, contra indications such as: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia, documented bacteraemia in the period from 24h before catheter insertion until inclusion, insertion of the CVAD at the same site as a previously confirmed central venous thrombosis (CVT), pregnant, not willing to use adequate contraceptives, or breast-feeding patients.

Informed consent procedure

Informed consent is obtained within one week after CVAD insertion, however, if this is not possible due to clinical circumstances, patients may be included within four weeks after CVAD insertion. Patients, parents and/or legal

guardian are given verbal information and information in writing by the researcher or research nurse. A dated and signed informed consent form will be obtained from each patient, parent and/or legal guardian depending on the age of the patients. The research or research nurse will then also sign the consent form. A copy will be given to the patient and/or parents. The inclusion and exclusion criteria are thereafter checked by the researcher.

Randomization and blinding

Patients will be randomized by the research physician or nurse with a method of minimization into the HL or TCHL study arm (1:1) with the use of an online randomization service by internet called ALEA® (https://www.aleaclinical.eu/). Stratification will be done according to two factors: CVAD type (TIVAP or external tunnelled CVAD) and diagnosis (hematologic or solid, lymphoma, and neurologic malignancies). The expert panel, evaluating all possible CLABSI episodes, will be blinded for the allocated treatment. The allocated treatment will not be revealed to the expert panel or described in the parts of the electronic patient files which the expert panel will use to evaluate the possible CLABSI episodes. The patients, parents and/or legal guardians, and the rest of the research and clinical teams, will not be blinded. Complete blinding was logistically to difficult to execute and much more expensive since the design of the HL and TCHL ampoules is not similar.

Intervention

Patients will receive a lock solution of 0.8-1.5mL, depending on the CVAD-type as described in Table 1, containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/mL (TauroLock-Hep100™, Cablon Medical, Leusden, the Netherlands and TauroPharm GmbH, Waldbüttelbrunn, Germany) or heparin 100 IU/mL only after each treatment in the Princess Máxima Centre with a maximum of once a week. The locks will remain in situ until the CVAD is used again. Before the CVAD is used again, the previously instilled study locks (TCHL and HL) will be removed from all lumina. If a blood culture is obtained while the lock is still in situ, at least 2mL of blood is aspirated and discarded for the prevention of false negative blood culture results. If the CVAD is used more than once a week, in the home care setting or in a shared care hospital, the CVAD will be locked with a non-study related HL following the standard of care protocol in the Netherlands.

Table 1 Lock volumina

CVAD	Type	Diameter (Fr)	Maximal catheter volume (ml)	Lock volume (ml)
TIVAP	Babyport®	4.5	0.80	1.0
	Low-profile®	6.5	1.04	1.5
	Standard®	6.5	1.28	1.5
External tunnelled CVAD	Single lumen	6.6	0.74	1.0
	Double lumen	6.0 or 7.0	0.70/0.70 or 0.90/0.80	1.0/1.0
	Triple lumen	6.0	0.75/0.62/0.62	1.0/0.8/0.8

CVAD; Central Venous Access Device, TIVAP; Totally Implantable Venous Access Port.

Outcomes

The primary outcome of this study is the incidence of first CLABSIs from CVAD insertion until the end of the study. A blinded expert panel of one paediatric infectiologist and two medical microbiologists will judge each positive blood culture episode during the study period as a CLABSI or non-CLABSI bacteraemia following the Centers for Disease Control and Prevention CLABSI criteria. [18] All non-unanimous judgements will be discussed between the experts until they all agree. If the experts still disagree, the final judgement is based on the judgement of the majority. Additionally, all experts will be asked to answer if their result following the CLABSI criteria aligns with their clinical judgement.

The secondary outcomes of this study are: the cumulative incidence of CLABSI from CVAD insertion, the incidence of central venous thromboses (CVT) (i.e. if the patient has (1) peripheral veins that have a non-compressible segment, or (2) there is an echogenic intra-luminal thrombus or an absence of flow in the central venous system (76)), bacteraemia episodes (i.e. every non-CLABSI related positive blood culture), local infections (i.e. positive exit-site culture, erythema, purulent drainage or tenderness within 2 cm of the CVAD track and exit-site), CVAD-removal, cultured micro-organisms causing CLABSI, days of hospital admission due to CLABSIs/CVTs, the dispense of thrombolysis and systemic antibiotic treatment due to CLABSIs/CVTs, and safety of the locks in terms of (serious) adverse events, and intensive care unit admission or death due to CLABSIs/CVTs.

Data collection and management

Data is entered pseudonymized from paper case report forms and electronic patient files in Castor EDC (Castor EDC v2021.1, CATERPILLAR-study v.6.21) by trained local data managers in the Princess Máxima Centre. All data (incl. shared care hospital data) should be entered within 90 days after the end of study date of each patient. Regular

quality checks are performed by a central data manager and independent monitor three times a year. The database will be locked after all data has been cleaned and all necessary changes have been made. The data will be stored for at least 15 years. After the manuscript is published, the data will become available upon reasonable requests.

The following data will be collected: patient characteristics (age, gender, diagnosis, treatment protocol, administration of prophylactic systemic antibiotics (i.e. trimethoprim/sulfamethoxazole, ciprofloxacin, or anti-mycotics)), CVAD characteristics (surgery date, type, introduction method, lumen amount/diameter, access vein and side, complications during procedure, removal date and reason), lock characteristics (date instillation and removal, type, method of removal, (serious) adverse events during lock instillation and removal (following common terminology criteria for adverse events (CTCAE) version 5.0, November 27, 2017)), treatment for possible malfunction (i.e. impossibility to aspirate or flush the CVAD)), suspicion of CLABSI characteristics (start date episode, symptoms, neutropenia (incl. duration and lowest neutrophil count during episode: very severe <100, severe 500-1.000, moderate 500-1.000, mild 1.000-1.500x10^6/L)), blood culture results, treatment method of CLABSI, hospital/intensive care unit admission days, death, judgement of episode by expert panel (i.e. CLABSI, mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI), or bacteraemia due to other reasons), reasons for non-CLABSI related bacteraemia (i.e. not enough blood cultures obtained, contamination/colonization, CVAD in situ for <48 hours, infection at a different site)), suspicion of local infection characteristics (start date episode, symptoms, culture results, treatment, hospital/intensive care unit admission days, death), suspicion of a CVT characteristics (start date episode, symptoms, radiological imaging, location, treatment, hospital/intensive care unit admission days, death) and end of the study reasons.

Safety considerations

(Serious) adverse events with a possible or definite relationship to the locks are registered during the study (CTCAE version 5.0, November 27, 2017). Registration of all (serious) adverse events would lead to the registration of too many adverse events in these oncologic patient groups. Adverse events of special interest, due to their known relationship to the HL or TCHL are: oral dysesthesias, neck/chest wall pain, dysgeusia, nausea, vomiting, allergic reactions, and heparin induced thrombocytopenia. Patients will be followed-up for the occurrence of (serious) adverse events until 30 days after the last study lock was given. The Princess Máxima Centre will report serious

adverse events within the appropriate time-frame (i.e. within 7 days of first knowledge in case of life threatening situations or death, and within 15 days in all other cases) to the accredited ethics committee that approved the protocol.

Data safety monitoring board (DSMB)

A DSMB is established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. Three DSMB meetings will be held: one start of the study session, a second closed session after the inclusion of 50% of the patients where the interim analysis will be presented, and a third session at the end of the study. The DSMB will not be blinded and consists of a paediatric surgeon, infectious disease specialist and medical statistician.

Statistical methods

Sample size calculation

Assuming a CLABSI rate of 12.8%, an estimated total number of 412 patients is needed to detect a difference between group proportion of 7.8%, with a two-sided α of 0.05 and power of 80% (two-sided Z-Test with unpooled variance). [19-24] The CLABSI rate of 12.8% was based on the data from the CVAD complication database of the Princess Máxima Centre, partially published by van den Bosch et al. 2019, using the same inclusion and exclusion criteria and follow-up period as described for this study. [3] The estimated reduction of 12.8% to 5.0% was based on previously performed randomized controlled trials (RCT), of which the vast majority showed a reduction of at least more than 60%; IRR of 0.30 (CI95%0.19-0.46). For paediatric oncology specifically, two RCTs have been performed which showed reductions of 74% and 77%. [6] For each patient that prematurely drops-out of the study an extra patient will be included, we estimated that an extra 50 patients would be needed to account for potential drop-outs. The drop-out inflated total sample size is therefore calculated as 462 patients, 231 per group.

Interim analysis

An interim analysis will be performed after the inclusion of 231 patients. A stopping rule was defined for a one sided test at an α level of 0.025 for the null hypothesis: experimental incidence ≥ control incidence. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the experimental.

The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on α- and β-spending functions. As α-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 2.35$ and as β-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 3.2$.

Statistical analysis

The primary data analyses will be performed with the intention-to-treat (ITT) principle (i.e. inclusion of all patients that were randomized). Additionally, a per-protocol (PP) analysis will be performed excluding patients who were not included within one week after CVAD insertion, patients who never received the intervention and patients who missed three or more of the minimal amount (once every three weeks) of locks during the follow-up period. Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. Differences between treatment groups with respect to baseline characteristics will be analysed by using a Chi-square (or Fisher Exact in the presence of small numbers), and two-tailed t-test for categorical or continuous variables respectively. In case of violation of the normality assumption a non-parametric test such as the Wilcoxon rank test will be applied.

For the primary outcome, the percentages and incidence rates (IR) of first CLABSIs per 1,000 CVAD-days will be reported for both study groups and compared by computing an IRR. The exact confidence limits for the IRRs will be based on the polynomial algorithm for person time data [25, 26]. The nominal alpha level for the primary outcome in the final analysis will be equal to 0.045 due to the interim analysis [19-24].

The cumulative incidence of CLABSI from CVAD insertion will be estimated by using a competing risk model [27] with CVAD removal due to non-CLABSI related reasons or death as competing events. To assess the difference between the cumulative incidence for the intervention (TCHL) and control (HL) group, the Gray's test will be used. [28]

To estimate the effect of risk factors on the occurrence of CLABSI, a Cox specific proportional hazard regression model from CVAD insertion will be estimated. Well known time fixed risk factors for a CLABSI to be incorporated into the model are diagnosis (haematological disease versus other diagnoses), CVAD type (TIVAP versus tunnelled

external CVADs). Furthermore, total parenteral nutrition (TPN) administration will be used in the model as time-dependent covariate). [27]

A landmark analysis at 28 days after CVAD insertion will be performed. The same risk factors as discussed above will be incorporated in the Cox specific hazard regression model with additional covariate number of lock days. The landmark point of 28 days was chosen based on clinical reasons, the first lock should have been given within the first four weeks after CVAD insertion. [29]

For the secondary outcomes, the percentages and IRs per 1,000 CVAD-days will be reported and compared by computing IRRs.

All analyses concerning the competing risk model will be performed in RStudio version 1.3.1093 (United States of America) environment by using the cmprisk library. IBM SPSS Statistics for Windows version 26.0 (United States of America) will be used to perform all other statistical analyses.

Study timeline

Inclusion of the study began on the 27th of October 2020. We expect that the planned number of patients can be recruited in 29 months from the defined source population. The planned study timeline is described in Table 2.

Table 2 Planned study schedule

Months after start inclusion	What?	Description
0	Start inclusion	Planned start of the study
14.5	Interim database lock and interim analysis	After the inclusion of 50% of the patients
29	Stop inclusion	After the inclusion of 462 patients
32	Stop follow-up	After a period of 3 months after the inclusion of the last patient
32 - 36	Database lock, statistical analysis, writing the clinical study reports, and drafting of the manuscript based on the clinical study reports.	From the stop of follow-up until manuscript submission.
36	Manuscript submission	Four months after the study has stopped.

Ethics and dissemination

The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research registered under number 20/370 (https://www.metcutrecht.nl/), a copy of the trial protocol submitted to the ethics committee can be found under S2 File. The results of this trial will be published in a peer-reviewed journal and subsequently the data (stored for at least 15 years) will be made available after publication upon reasonable requests.

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Figure Legends

Fig 1. SPIRIT schedule of enrolment, interventions and assessments. *Number of visits depending on the treatment schedule and unexpected admissions. Aim is to insert the lock after each visit with a maximum of once weekly.

Author Statement

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Data Statement

The data will be stored for at least 15 years. After the manuscript is published, the data will become available upon reasonable requests.

Conflicts of Interests Statement

The authors declare to have no conflicts of interest.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINTS	Day 0-28 after CVAD surgery (preferably within 1 week)	Day 0-28 after CVAD surgery	Day 0-90 after CVAD surgery Visit 1-13*	Day 0-90 after CVAD surgery Daily patient file screening	Day 90 after CVAD insertion, CLABSI, CVAD removal, second CVAD insertion or death of patient, whichever comes first.
ENROLLMENT					
Eligibility screen	X				
Informed consent	X				
Review inclusion/ exclusion criteria	X				
Allocation		X			
INTERVENTIONS					
HL			X		
TCHL			X		
ASSESSMENTS					
Patient/CVAD characteristics	X	X			X
Lock characteristics			X		
Suspicion of CLABSI characteristics				X	X
Suspicion of local infection characteristics				X	X
Suspicion of CVT characteristics				X	X
(Serious) adverse event monitoring			X	X	X

Fig 1. SPIRIT schedule of enrolment, interventions and assessments.
*Number of visits depending on the treatment schedule and unexpected admissions. Aim is to insert the lock after each visit with a maximum of once weekly.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
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
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
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)

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
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)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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
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)
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

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

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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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
	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
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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
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

	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

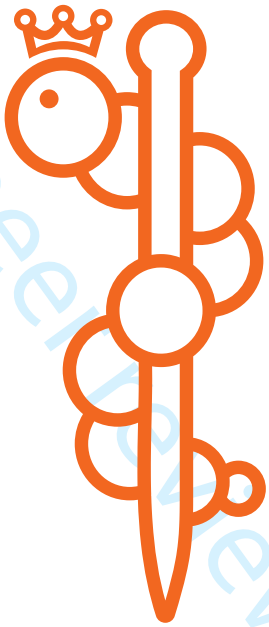
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*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.

RESEARCH PROTOCOL
CATERPILLAR-study
(Version 4.0 19-07-2022)



CATERPILLAR
STUDY

PROTOCOL TITLE 'The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunneled central line-associated bloodstream infections in pediatric oncology patients, a randomized controlled, mono-center trial'

Protocol ID	CATERPILLAR
Short title	Efficacy of TauroLock™-Hep100
EudraCT number	Medical Device study, not applicable.
Version	4.0
Date	19-07-2022
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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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Project leader: Prof. Dr. Wijnen Pediatric Surgeon Princess Máxima Center for Pediatric Oncology	DocuSigned by: Naam ondertekenaar: Prof. dr. M.H.W.A. Wijnen Reden voor ondertekening: Ik keur dit document goed Ondertekentijd: 01-sep-2022 | 8:52 AM CEST 7CB44ED1F7C843CAB8867CDE3D2DE0F2	01-sep-2022 | 8:52 AM CEST

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
ASDIN	American Society of Diagnostic and Interventional Nephrology
BSI	Bloodstream Infection
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CL	Citrate Lock
CLABSI	Central Line Associated Bloodstream Infection
CoNS	Coagulase Negative Staphylococci
CRBSI	Central Line Related Bloodstream Infection
CT	Chemotherapy
CV	Curriculum Vitae
CVAD	Central Venous Access Device
CVT	Central Venous Thrombosis
DSMB	Data Safety Monitoring Board
ERBP	European Renal Best Practice
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
H-CVAD	Hickman®-Central Venous Access Device
HL	Heparin Lock
IB	Investigator's Brochure
IC	Informed Consent
ICU	Intensive Care Unit
IGJ	The Health and Youth Care Inspectorate
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MBI-LCBI	Mucosal Barrier Injury – Laboratory Confirmed Bloodstream Infection
M-EDTA	Minocycline and Edetic Acid
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin-Resistant Staphylococcus Aureus
PL	PowerLine®
RCT	Randomized Controlled Trial
RR	Rate Ratio
(S)AE	(Serious) Adverse Event
SCT	Stem Cell Transplantation
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)

SUSAR	Suspected Unexpected Serious Adverse Reaction
TCHL	Taurolidine Citrate Heparin Lock solution
TCL	Taurolidine Citrate Lock solution
THL	Taurolidine Heparin Lock solution
TIVAP	Totally Implantable Venous Access Port
TPN	Total Parenteral Nutrition
VMO	Voorlopige Medicatie Overdracht
WBP	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Tunneled central venous access devices (CVAD) are fundamental in pediatric oncology for long-term venous access. (3) The incidence of central line-associated bloodstream infections (CLABSI) is high. (4) In the Princess Máxima Center, the incidence rate of CLABSI is 1.51 per 1,000 CVAD-days, CLABSIs are seen in at least 30% of the children with a CVAD, 17% of the inserted CVADs are removed early and 5% of the patients are admitted at an intensive care unit due to CLABSIs. (1) Central venous thrombosis (CVT) is another severe complication of a CVAD, with an incidence rate of 0.02-0.24 per 1,000 CVAD-days. (1, 5-8) After a review of the literature, we concluded that the taurolidine-citrate(-heparin) lock solution (TCHL) is the most promising method for the prevention of CLABSIs and CVTs. (2, 9-50) In the Netherlands, the heparin lock (HL) is the standard of care. The HL however, does not have an antimicrobial activity and its use is barely supported by literature. (9) The TCHL has anticoagulant and antimicrobial activities without reported resistance to taurolidine. (12-50) The TCHL has shown to significantly decrease the CVAD-infection incidence in hemodialysis, total parenteral nutrition, and adult oncology patients compared to citrate, heparin and saline locks (rate ratios ranged from 0.00-0.77). (12-44) In pediatric oncology patients, six studies have been performed. (45-50) Unfortunately, these studies did not deliver enough evidence to implement the TCHL in pediatric oncology patients, mainly due to the small study groups, n-total ≤ 180. (45-50) Therefore, we want to perform an open labelled randomized controlled trial (RCT) in a large patient group (n=462) so that we can finally draw conclusions on the efficacy and safety of the TCHL in pediatric oncology patients. Our goal is to increase the quality of life for children with cancer by reducing the CLABSI-rate, CVAD-removal rate, dispense of antibiotics, days of hospital/intensive care admission, and morbidity/mortality rate due to CLABSI.

Objective: To compare the efficacy of the TCHL to the HL in the prevention of tunneled CLABSIs in pediatric oncology patients.

Study design: Investigator-initiated, mono-center, open-labelled randomized controlled trial (RCT). The patients will be followed-up for 90 days in the Princess Máxima Center for Pediatric Oncology and 21 shared care centers in the Netherlands. All data will be collected in in the Princess Máxima Center for Pediatric Oncology.

Study population: Pediatric oncology patients (n=462), ranging from 0-19 years old, who will receive a tunneled CVAD in the Princess Máxima Center for Pediatric Oncology.

Intervention: Patients in the intervention study arm will receive lock solutions containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. Patients in the control study arm will receive lock solutions containing heparin 100 IU/ml. The lock solutions will be instilled with a maximum of once weekly, and a minimum of once every three weeks. In between, all CVADs will be locked with standard heparin 100 IU/ml.

Main study parameter: Incidence of CLABSI

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The expected side effects are temporarily, caused by a spill-over of citrate, and only described if the TCHL is instilled to fast or if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dysgeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are rare but possible side effects. (34) The locks will be instilled with a maximum of once weekly and a minimum of once every three weeks. For a small number of patients this means that they have to visit the Princess Máxima Center for Pediatric Oncology 1-2 times more during the follow-up period compared to patients that do not participate in the study. After every study-lock instillation, the patients will be asked to answer a questionnaire about the experience of possible side effects. Our hypothesis is that the TCHL will reduce the CLABSI rate compared to the HL. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a reduced mortality rate due to CLABSIs compared to the HL. Additionally, patients will benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development.(12-50)

1. AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	06-08-2020	1.2	Non-substantial	Section 7.3 and appendix 5 and 6: Clarifications of study procedure and patientcard/stickers changed.
2	07-10-2020	1.3	Non-substantial	Section 7.3: Change patientcard/stickers.
3	03-02-2021	2.0	Substantial	Chapter 3.0: Minor formatting/spelling changes and description of expert panel. Section 4.3: Clarification of exclusion criteria. Section 5.1 and 6.6: Clarification of lock aspiration. Section 7.3, 10.2 and 12.2: Change in inclusion period. Section 7.3: Change in study procedure if patients do not visit hospital within 3 weeks. Section 3.0, 7.1.3, 7.4, 13.1, 13.7: Addition of an extra endpoint (second CVAD insertion).

				Section 7.1.3: Clarification of endpoints. Section 10.2: Clarification of informed consent procedure. Section 10.5: Removal of description of compensation fee.
4	24-08-2021	3.0	Substantial	Section 2.0, 7.1.2, 7.1.4, 9.2, appendix 5/6: Local infections added as secondary outcome. Section 2.0, 6.4, 7.1.4, 7.3, 9.2, 12.2, and appendix 5: Liver enzymes will no longer be reported.
5	19-07-2022	4.0	Substantial	Section 4.4: We clarified how to account for drop-outs at the end of the study. Section 9.1 and 9.2: Clarification of statistical analyses for primary and secondary outcomes. Appendix 7: Typo removed.

2. INTRODUCTION AND RATIONALE

Central venous access devices in pediatric oncology patients

Central venous access devices (CVAD) are fundamental in pediatric oncology. CVADs are used for stem cell transplantation (SCT), total parenteral nutrition (TPN), blood sampling, chemotherapy (CT) and other intravenous therapies. Long-term central venous access can be provided by tunneled CVADs. The most commonly inserted CVADs are the Hickman®(H)-CVADs/Powerlines® (PL) and totally implantable central venous access ports (TIVAP), these account for 94.2% of all CVADs inserted in our hospital, the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. Since the official opening of the Princess Máxima Center in June 2018 approximately 35-40 CVADs per month are inserted by surgeons in the operating theatre. (1, 3)

The incidence of central line associated bloodstream infections (CLABSI) ranges between 0.1-2.3 per 1,000 CVAD-days, depending on the patient population and infection definitions used. (4) In our pediatric oncology institution a retrospective study investigating the incidence of CVAD related complications in 201 pediatric oncology patients with 307 CVADs was performed. The incidence rate of CLABSIs was 1.51 per 1,000 CVAD-days, this means that a CLABSI was observed in 29.9% of the patients who received a CVAD. (1) Another severe complication of the CVAD is a central venous thrombosis (CVT), with an incidence rate of 0.02-0.24 per 1,000 CVAD days. (1, 5-8) Both complications frequently result in high morbidity and CVAD-removal rates. Of all CVADs inserted, 17% were removed due to a CLABSI. 41.7% Of the CLABSI episodes were successfully treated with systemic antibiotic treatment (SAT), the other CLABSI episodes eventually resulted in reinfections and/or early removal of the CVAD. Five percent of the patients that received a CVAD were admitted to the intensive care unit (ICU) due to severe sepsis caused by CLABSIs. Additionally, nine cases of CVTs were observed of which four resulted in removal of the CVAD. (1)

CLABSI prevention

There are multiple strategies for the prevention of CLABSIs: e.g. education and training of healthcare providers, carefully weighing the risks and benefits of CVAD insertion, the choice of a CVAD with the minimum number of ports/lumen needed, antimicrobial/antiseptic impregnated CVADs, maximal sterile barrier precautions during insertion, skin preparation with chlorhexidine before CVAD insertion, hand hygiene, catheter site dressing regimens, use of a chlorhexidine wash for skin cleansing, frequent CVAD insertion site checks, antimicrobial CVAD lock prophylaxis, the use of needleless intravascular CVAD systems, removal of the CVAD if the CVAD is no longer required, and limiting the amount of CVAD replacements. (3, 51) In our center, a CLABSI prevention meeting is held frequently to evaluate all of the above stated strategies. Due to the conclusions from these meetings the protocols in our hospital are tightened since January 2020. The following interventions are still under discussion in these CLABSI prevention meetings (e.g. chlorhexidine-impregnated dressings, and CVAD lock prophylaxis). The efficacy and safety of chlorhexidine-impregnated dressings is a strategy that needs to be investigated in the future for patients under 18 years before implementation. However, due to the risk of localized dermatitis associated with chlorhexidine-impregnated dressings in neonate patients, we concluded that the risk would be too high to perform a study in our hospital. (3, 51, 52) Additionally, we agreed that a great deal is to be gained from CVAD lock prophylaxis. More about CVAD lock prophylaxis is described in the next paragraph.

CVAD lock prophylaxis

Lock solutions are used to prevent CVADs from CLABSIs and CVTs [Figure 1]. Different locks are available for pediatric oncology patients, e.g. locks containing vancomycin, minocycline-edetic acid (M-EDTA), ethanol, taurolidine, citrate and heparin. (2, 9)

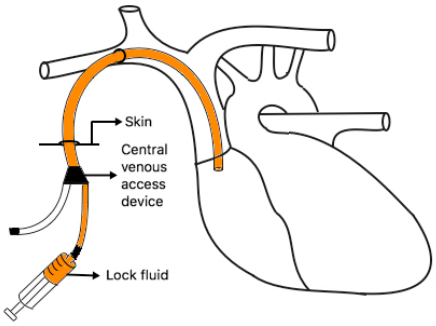


Figure 1: Lock fluid in a central venous access device

In the Netherlands, the heparin lock (HL) is the standard of care to prevent the CVAD from occlusion. (2, 9) The results of a consensus meeting in 2016 on various lock solutions showed that there is barely evidence supporting the HL. They state that the risk of CVAD occlusion is multifactorial and not solely based on blood clotting. Several studies have shown a similar effect of the HL compared to a lock solution containing regular saline. They concluded that a more important factor to prevent CVAD occlusion is an appropriate flushing technique. (9)

Vancomycin containing lock solutions are effective in the prevention of CLABSIs. Abundant antimicrobial use, however, contributes to the development of antibiotic resistance. Therefore, these locks are only recommended in high risk patients. (10, 11, 53)

M-EDTA has antimicrobial and anticoagulant activities. Until so far, one open labelled RCT and one prospective cohort study have been performed to evaluate the efficacy of M-EDTA in pediatric oncology patients. In these studies, the incidence rates of CVAD-related infections were decreased from 6.30 to 1.09, and 2.23 to 0.0 per 1,000 CVAD-days. These studies included 50 and 62 patients and compared the M-EDTA lock with the HL. These studies did not deliver enough evidence to design a study on the efficacy of M-EDTA in children. Additionally, the development of antibiotic resistance is a risk associated with the use of minocycline. (54, 55)

Another antimicrobial lock solution is ethanol. An RCT on the efficacy of the ethanol lock was performed by Wolfs et al., they included 94 pediatric oncology patients. In this study the ethanol lock did not prevent CLABSI treatment failure and it increased CVAD occlusion. (56) A second double-blinded RCT on the efficacy of a lock solution containing ethanol, in 307 pediatric oncology patients, showed a significant decrease of CLABSI from 1.46 to 0.77 per 1,000 CVAD-days without an increase of CVTs. No serious side effects were observed. However, disadvantages of the ethanol lock are the side effects (e.g. nausea, taste alteration, dizziness, blushing, and syncope), and a dwell-in time of two hours after which the lock is removed. The dwell-in time is logistically inconvenient, especially for patients. Additionally, a higher risk of occlusions is suspected with the use of ethanol, and ethanol may interfere with the polymers in some CVADs, degrading the plastic over time. (2, 9, 10)

A lock solution containing taurolidine 1.35% appears to be promising in the prevention of CLABSIs. Different lock combinations containing taurolidine are available, e.g. the

taurolidine-citrate lock (TCL), taurolidine-citrate-heparin lock (TCHL), and taurolidine-heparin lock (THL). (9-11) Taurolidine containing lock solutions offer the many advantages seen with ethanol-based solutions, while avoiding the need for an antibiotic-based solution. (10) Taurolidine containing lock solutions do not require a dwell-in time of two hours after which the lock needs to be removed and can remain in situ for maximum of 30 days (see appendix 2 for the instructions for use). The side-effects associated with taurolidine based locks (e.g. perioral dysesthesia, discomfort of neck and chest, altered taste sensations, nausea and vomiting) are rare and mainly described after the lock is accidentally flushed into the bloodstream. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) The use of the TCL and TCHL resulted in a reduction of the CVAD-infection incidence rate in haemodialysis patients, total parenteral nutrition patients, and oncology patients compared to citrate, saline or heparin locks (rate ratios (RR) ranged from 0.00-0.77). (12-50)

Evaluating the literature published on the different lock solutions our hypothesis is that lock solutions containing taurolidine are the most promising lock solutions for pediatric oncology patients.

Literature on lock solutions containing taurolidine

The majority of the literature published on the efficacy of the lock solutions containing taurolidine were based on haemodialysis patients. Two double-blinded RCTs, four open-labelled RCTs, and eight prospective cohort studies were performed in this patient group. The number of patients included ranged from 13 to 565. The incidence rates per 1,000 CVAD-days were much lower in the THL, TCL, and TCHL groups compared to the HL or CL (RRs ranged from: 0.00-0.58). See table 1 for a summary of the studies performed in haemodialysis patients. Additionally, three systematic reviews were performed concerning haemodialysis patients by Jaffer et al. (2008), Liu et al. (2014), and Kavosi et al. (2016). Jaffer et al. stated that antimicrobial lock solutions decreased CVAD-infection rates without causing significant adverse effects. Liu et al. stated that the TCL significantly reduced the risk of CVAD-related infections and specifically Gram-negative bacterial infections. Kavosi et al. stated that the TCL is superior to heparin, however due to the lack of evidence a confident decision can not yet be made. (12-26)

Table 1: Summary of studies performed in haemodialysis patients (12-26)

Author (year)	Design (adult/pediatric)	Lock type (control – intervention)	Total number of patients or CVADs* (control - intervention	CVAD infections per 1,000 CVAD-days (control – intervention), Rate Ratio (RR), p-value	Number of infections (%/patients or %/cvads*) (control – intervention)	Reduction (control – intervention)	Adverse events
Solomon et al. (2012)	Double-blinded RCT (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4% and taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	174 (34 – 34 and 106)	3.25 - 1.22 and 1.33, RR: 0.38 and 0.41 p<0.01	21 (61.8) – 7 (20.6) and 16 (15.1)	67% and 76%	Addition of heparin reduced the need for thrombolysis
Solomon et al. (2010)	Double-blinded RCT (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4%	107 (54 – 53)	2.38 – 1.34, RR: 0.56 p=0.06 Gram-negative organisms: 1.1 – 0.2, RR: 0.18 p=0.02	23 (42.6) – 11 (20.8)	51%	Greater need for thrombolysis in taurolidine/citrate lock
Betjes et al. (2004)	Open-labelled RCT (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4%	58 (39*-37*)	2.10 – 0.0, RR: 0.00 p=0.05	4 (10.3*) – 0 (0.0*)	100%*	No adverse events observed
Zwiech et al. (2016)	Open-labelled RCT (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	53 (29 – 24)	3.44 – 0.0, RR: 0.00 p<0.05	3 (10.3) – 0 (0.0)	100%	No adverse events observed
Filiopoulos et al. (2011)	Open-labelled RCT (adult)	Heparin 5,000 – taurolidine 1.35% / citrate 4%	119 (58 – 59)	9.92 – 3.67, RR: 0.37 p=0.03	20 (34.5) – 8 (13.5)	61%	More thrombosis in taurolidine/ citrate group, not significant
Winnicki et al. (2017)	Open-labelled RCT (adult)	Citrate 4% lock – taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	106 (54 – 52)	2.7 – 0.67, RR: 0.25 p<0.01	18 (33.3) – 6 (11.5)	66%	Greater need for thrombolysis in citrate lock group
Reidenberg (2018)	Prospective cohort study (adult)	Taurolidine 2.35% / citrate 3.5% / heparin 1000 IU/ml	201	0.28	13 (6.5)	n.a.	Dysgeusia (n=2)
Hulshof et al. (2017)	Prospective cohort study (pediatric)	Heparin 100 IU/ml – taurolidine 2%	23 (7 in cross-over, X-X	12.7 – 4.3, RR: 0.34 p=0.02 (cross over) 14.9 – 3.1, RR: 0.21 p<0.05	X (X) – X (X) (cross-over) 41 (X) - 8 (X)	X	No adverse events observed

			prospective cohort)	(prospective cohort)			
Murray et al. (2014)	Prospective cohort study (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	565 (X tunneled CVAD patients)	Tunneled CVAD patients: 1.59 – 0.69, RR: 0.43 p<0.01	115 (X) – 43 (X)	X	No adverse events observed
Fontsere et al. (2014)	Prospective cohort study (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	31 (single arm)	1.08 – 0.04, RR: 0.04 p=0.02	7 (22.6) – 1 (3.2)	86%	No adverse events observed
Allon et al. (2003)	Prospective cohort study (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4%	50 (30 - 20)	5.6 – 0.8, RR: 0.14 p=0.02	16 (53.3) – 1 (5.0)	91%	Greater need for thrombolysis in the taurolidine/citrate group
Sodeman et al. (2001)	Prospective cohort study (adult)	Taurolidine 1.35% / citrate 4% (all patients received a Dialock access system)	70	0.29	8 (11.4)	n.a.	No adverse events observed
Taylor et al. (2008)	Prospective cohort study (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4% / heparine 5,000 IU/ml	X (X – X)	5.2 - 0.6, RR: 0.12 p<0.01	X (X) – X (X)	89%	No adverse events observed
Geron et al. (2006) Article in Hebrew	Prospective cohort study (adult)	X - Taurolidine 1.35% / citrate 4%	13 (5 with previous infections – 8 new patients)	9.5 - 1.15 (pt with previous infections pre- and post TCL) 0.0 (new pts), RR: 0.12 and 0.00	X (X) – X (X)	X	Patency problems for which addition of heparin to lock solution in 10 patients

In total parenteral nutrition patients, two double-blinded RCTs, three open labelled RCTs, seven prospective cohort studies, and three retrospective study were performed. The number of patients included ranged from six to 270. The incidence rates per 1,000 CVAD-days were much lower in the THL, TCL, and TCHL groups compared to the HL or saline (RRs ranged from: 0.00-0.38). See table 2 for a summary of the studies performed in total parenteral nutrition patients. (27-42, 50)

Table 2: Summary of studies performed in total parenteral nutrition patients (27-42, 50)

Author (year)	Design (adult/pediatric)	Lock type (control – intervention)	Total number of patients or CVADs* (control - intervention	CVAD infections per 1,000 CVAD-days (control – intervention), Rate Ratio (RR), p-value	Number of infections (%/patients or %/cvads*) (control – intervention)	Reduction (control – intervention)	Adverse events
Wouters et al. (2018)	Double-blinded RCT (adult)	Saline 0.9% – taurolidine 2%	105 (52 – 53)	1.49 – 0.29, RR: 0.19 p<0.01	18 (34.6) – 5 (9.4)	73%	No difference in adverse events between saline and taurolidine. Dysgeusia (n=1), dizziness (n=1), erhythema exit-site (n=1) associated with the taurolidine lock.
Tribler et al. (2017)	Double-blinded RCT (adult)	Heparin 100 IU/ml – taurolidine 1.35% / citrate 4% / heparine 100IU/ml	41 (21 – 20)	1.44 – 0.33, RR: 0.23 p<0.01	7 (33.3) – 0 (0.0)	100%	Abnormal taste sensations (n=8), tingling sensation (n=3), nausea and vomiting (n=3) in taurolidine/citrate/heparin-group
Lyszkowska et al. (2019)	Open-labelled RCT (pediatric)	Standard aseptic procedures – taurolidine X / citrate X	86 (49* - 48*)	14.3 – 1.06, RR: 0.07 p=0.01	14 (28.6*) – 1 (2.1*)	93%*	No adverse events.
Klek et al. (2015)	Open-labelled RCT (adult)	Saline 0.9% – taurolidine 1.35% / citrate 4% and taurolidine 2%	30 (10 – 10 and 10)	0.0 – 0.27 and 0.0, p=1.00	0 (0.0) – 1 (10.0) and 0 (0.0)	No reduction	One occlusion in the taurolidine 2% group
Bisseling et al. (2010)	Open-labelled RCT (adult)	Heparin 150 IU/ml – taurolidine 2%	30 (14- 16)	2.02 – 0.19, RR: 0.09 p<0.01	9 (64.3) – 1 (6.3)	90%	No adverse events
Chong et al. (2020)	Prospective cross over study	Heparin X IU/ml - taurolidine 1.35% / citrate 4%	33 (TPN n=13 single arm)	11.1 – 2.9, RR: 0.26 p=0.02	X (X) – X (X)	X	Two patients experienced CVAD occlusion for which one patient switched to a TCHL. One patient experienced nausea and vomiting.
Lambe et al. (2018)	Prospective cohort study (pediatric)	Heparin - taurolidine 1.35% / citrate 4%	126 (86 – 40)	0.89 – 0.25, RR: 0.28 p<0.01	X (X) – 5 (12.5)	X	No adverse events
Jurewitsch et al (2005)	Prospective cohort study (adult)	Heparin – taurolidine 2%	7 (single arm)	10.8 – 0.8, RR: 0.07 p=missing	X (X) – X (X)	X	No adverse events
Chu et al. (2012)	Prospective cohort study (pediatric)	Heparin 10 IU/ml – taurolidine 2%	19 (single arm)	8.6 -1.1, RR: 0.13 p<0.01	47 (247.4) – 10 (52.6)	79%	No adverse events

Al-amin et al. (2013) No full-text available	Prospective cohort study (adult)	X – taurolidine 1.35% / citrate 4%	9 (single arm)	6.39 – 0.0, RR: 0.00 p=X	X (X) – X (X)	X	X
Toure et al. (2012)	Prospective cohort study (adult)	Saline 0.9% – taurolidine 1.35% / citrate 4%	15 (single arm)	6.58 – 1.09, RR: 0.17 p<0.01	36 (240.0) – 6 (40.0)	83%	No adverse events
Taniguchi et al. (2009)	Prospective cohort study (adult)	Heparin – taurolidine 1.35% / citrate 4%	6 (single arm)	0.62 – 0.16, RR: 0.25 p=0.03	21 (350.0) – 4 (66.7)	81%	Dysgeusia (n=1), perioral paraesthesia (n=1), and palpitations (n=1)
Saunders et al (2015)	Prospective cohort study (adult)	Heparin – taurolidine 1.35% / citrate 4%	22 (single arm)	5.71 – 0.99, RR: 0.17 p<0.01	42 (350.0) – 12 (54.5)	85%	No adverse events
Olthof et al. (2014)	Retrospective study (adult)	Heparin 150 IU/ml – taurolidine 2%	212 (545* - 200*)	1.10 – 0.20, RR: 0.18 p=X	464 (85.1*) – 43 (21.5*)	75%	Anaphylactic-like reaction (n=1), burning sensations (n=1), occlusion (n=1), dizziness (n=1), paraesthesia (n=1), nausea or pain (n=1), palpitations or discomfort of the chest (n=2) possibly associated with the taurolidine lock.
Wouters et al. (2018)	Retrospective (adult)	Saline - Taurolidine 2%	280 (10 – 270)	1.58 - 0.60, RR: 0.38, p=0.02	13 (130.0) - 203 (75.2)	42%	9% Of the taurolidine patients experienced mild-moderate pain, nausea, dizziness, dyspnea, palpitations, moderate pain, urticaria, pruritus, nausea and vomiting, flushes, headache, paresthesia, and edema.
Arnoriaga Rodriquez et al. (2018)	Retrospective study (adult)	X – taurolidine 2%	13 (single arm)	3.12 – 0.76, RR: 0.24 p<0.01	38 (292.3) – 4 (30.8)	90%	No adverse events

A randomized phase IV trial performed by Longo et al. in 163 adult oncology patients demonstrated a four-fold relative risk reduction of CVAD-related infections. Four CVAD-related infections were observed in 76 patients receiving a saline lock solution, one CVAD-related infection was observed in 84 patients receiving a TCL. However, this difference was not statistically significant, possibly due to power limitations. The incidence rate of CVAD-related infections in the control group was significantly lower than the one chosen as a reference in the sample size calculation. (57) Another randomized double-blinded study in 150 adult neutropenic hematological patients was performed by Gudiol et al., an incidence rate of 3.75 per 1,000 CVAD days with the TCHL compared to 8.91 per 1,000 CVAD days with the HL was found. This difference was not statistically significant. No adverse events related to the lock solutions were observed. (44)

Six articles were published describing a decrease in the incidence rate of bloodstream infections using a TCL or TCHL in pediatric oncology patients. (45-48, 50) Simon et al. prospectively observed the incidence rate of bloodstream infections (BSI). An overall BSI incidence rate of 3.82 was found in the TCL group (n=94) compared 4.93 in the HL group (n=98), (RR: 0.77, p=0.35). However, the incidence rate of BSI due to coagulase negative staphylococci (CoNs) and methicillin-resistant *Staphylococcus aureus* (MRSA) significantly decreased from 2.30 to 0.45 per 1,000 CVAD-days, (RR: 0.20, p<0.01). Limitations of this study were: the small study group and the not-randomized study design. Additionally, CVAD-infections were defined as every bacteremia instead of CLABSI, including bacteraemia caused by infections located elsewhere in the body. (48) Ince et al. retrospectively observed a decreased incidence rate of CLABSI from 48.5% with the HL (n=33) to 22.8% with the TCL (n=79), p=0.03; CLABSI reduction of 53%. Furthermore, the duration of CVAD use per CVAD increased significantly and the incidence rate of CVAD-removal was lower in the TCL group; 81.2% vs. 33.3%. Limitations were the small study groups and retrospective study design. (47) In an open labelled RCT performed by Dumichen et al. the bacteremia incidence rate per 1,000 CVAD-days decreased from 1.30 with the HL (n=36) to 0.30 with the TCL (n=35), (RR: 0.23, p=0.03). Limitations of this study were the small study groups, that CVAD-infections were defined as every bacteremia instead of CLABSI, and that only a few CVADs were immediately locked with the lock solution after insertion of the CVAD. (45) Handrup et al. performed an open labelled RCT comparing the HL (n=65) with the TCHL (n=64). In this study, the incidence rate of CLABSI decreased significantly from 1.40 to 0.40 per 1,000

CVAD-days, (RR: 0.28, p<0.01). Especially CLABSIs caused by CoNS were reduced by 66% in the TCHL group. Other outcomes were an increased time to first CLABSI since CVAD insertion, a reduction of fungi, Gram-positive and Gram-negative microorganisms in the TCHL group, and similar rates of removal due to CVT. The incidence of overall CVAD survival was similar in both groups. A limitation of this study were the small study groups. (46) Clark et al. performed a prospective cohort study investigating the TCL in pediatric patients (n=19) with oncologic and intestinal diseases. The CLABSI incidence rate decreased from 5.5 to 0.5 per 1,000 CVAD-days (RR: 0.09, p<0.01) with the use of TCL compared to the HL. The mean time to first CLABSI increased from 87 days to 296 days after TCL implementation (p=0.01). There were no episodes of hypocalcaemia observed during TCL implementation. A limitation of this study was the small study group. (49) Chong et al. performed a cross over prospective study investigating the TCL in pediatric oncology patients (n=20). The CLABSI incidence rate decreased from 14.4 to 2.4 per 1,000 CVAD-days (RR: 0.16, p<0.01) with the use of TCL compared to the HL. Two patients experienced central line occlusion for which one switched to the TCHL, one patient experienced nausea and vomiting after lock instillation. (50) All studies performed in pediatric oncology patients are summarized in Table 3. (45-50)

Table 3: Summary of studies performed in pediatric oncology patients (45-50)

Author (year)	Design (adult/pediatric)	Lock type (control – intervention)	Total number of patients or CVADs* (control - intervention	CVAD infections per 1,000 CVAD-days (control – intervention), Rate Ratio (RR), p-value	Number of infections (%/patients or %/cvads*) (control – intervention)	Reduction (control – intervention)	Adverse events
Handrup et al. (2013)	Open-labelled RCT	Heparin 250 IU/ml – taurolidine 1.35% / citrate 4% / heparin 100 IU/ml	112 (64 – 65)	1.4 – 0.4, RR: 0.28, p<0.01	26 (40.6) – 7 (10.8)	74%	Unpleasant taste in the majority of the patients.
Dumichen et al. (2012)	Open-labelled RCT	Heparin 100 IU/ml – taurolidine 1.35% / citrate 4%	71 (36 – 35)	1.3 -0.3, RR: 0.23 p=0.03	9 (25.0) - 2 (5.7)	77%	Taste sensations, nausea and vomiting, discomfort of chest and neck, perioral dysesthesia (n=7, 20%)
Chong et al. (2020)	Prospective cross over study	Heparin X IU/ml - taurolidine 1.35% / citrate 4%	33 (oncologic patients n=20 single arm)	14.4 – 2.4, RR: 0.16 p<0.01	X (X) – X (X)	X	Two patients experienced CVAD occlusion for which one patient switched to a TCHL. One patient experienced nausea and vomiting.
Clark et al. (2018)	Prospective cohort study	Heparin 10-100 IU/ml – taurolidine 1.35% / citrate 4%	19 (oncologic patients n=9 single arm)	5.5 – 0.5, RR: 0.09 p<0.01	39 (205.3) – 5 (26.3)	87%	No adverse events described
Simon et al. (2008)	Prospective cohort study	Heparin 200 IU/ml – taurolidine 1.35% / citrate 4%	179 (90 – 89)	All BSIs: 4.93 – 3.82, RR: 0.77 p=0.35 CoNS/MRSE infections: 2.3 – 0.45, RR: 0.20 p<0.01.	All BSIs: 30 (33.3) – 25 (28.1) CoNS/MRSE infections: 14 (15.5) – 3 (3.4)	All BSIs: 16% CoNS/MRSE infections: 78%	Unpleasant taste after flushing, pain during lock instillation in a peripheral catheter.
Ince et al. (2014)	Retrospective	Heparin 100 IU/ml – taurolidine 1.35% / citrate 4%	108 (33* – 79*)	X	16 (48.5)* – 18 (22.8)*, p=0.03	53%*	X

Evaluating the literature published on the different lock solutions, our hypothesis is that a lock solution containing taurolidine, citrate and heparin (TauroLock-Hep100™) is the most promising, safe and appropriate lock solution for pediatric oncology patients.

TauroLock-Hep100™

TauroLock-Hep100™ is a lock solution containing taurolidine 1.35%, citrate 4% and heparin 100 IU/ml. TauroLock-Hep100™ is produced by TauroPharm GmbH, Waldbuttelbrunn, Germany.

Taurolidine is metabolized into water, carbon dioxide, and the amino sulfonic acid taurine, which has an anti-biofilm activity and broad-spectrum antimicrobial activity against fungi (incl. *Candida albicans*), Gram-negative (incl. *Pseudomonas aeruginosa, Stenotrophomonas maltophilia*) and Gram-positive (incl. *Staphylococcus aureus*, coagulase negative

staphylococci*, and enterococci*) bacteria in vitro. (58-61) Taurolidine reduces adherence of bacteria to human epithelial cells and damages the cell walls of bacteria. In vitro, taurolidine even shows anticoagulant activities. (58-61) The major benefit of taurolidine is that in vitro, no evidence of microbial resistance against taurolidine has been found when tested against a broad spectrum of microorganisms. (59, 62) The most commonly described concentration of taurolidine in literature is 1.35% and does not show clinically relevant differences to taurolidine 2.0%. (9, 48, 58, 61, 62) This concentration is at least 10 times higher than the minimal inhibitory concentration $(MIC)_{50}$ for the majority of Gram-negative and Gram-positive microorganisms. (62) As described above, different lock solutions containing taurolidine are available. Olthof et al. tested the amount of microbial growth inhibition between different lock solutions containing taurolidine in vitro. They found minor differences in microbial growth inhibition and stated that these differences would not be relevant in the clinical setting. Furthermore, they found a decrease in thrombus weight due to taurolidine. This was, however, not as effective as citrate or heparin. Therefore, they advised that patients may benefit from the addition of heparin and/or citrate to taurolidine lock solutions. (61) High-dose concentrations of taurolidine (290 mg/kg, 2% taurolidine) have been associated with liver injury in mouse models. Low-dose concentrations of taurolidine (140 mg/kg, 2% taurolidine) which are similar to the TCHL dose did not show significant differences in liver injury compared to the control group (physiologic saline).(63) Lastly, hypersensitivity reactions to taurolidine are possible. (9, 18, 20, 45-48, 50)

Citrate has calcium-chelating properties, which results in both an anticoagulation and antimicrobial activity. (9, 64) Available solutions of citrate have concentrations ranging from 4 to 46%. Pittiruti et al. describes that higher concentrations of citrate are associated with a higher efficacy of CVAD-occlusion prevention. However, the European Renal Best Practice (ERBP), American Society of Diagnostic and Interventional Nephrology (ASDIN) and the Food and Drug Administration (FDA) advise to use a concentration of no more than 4% citrate in the prevention of central line related bloodstream infections (CRBSI), due to a case report of a patient that suffered cardiac arrest secondary to hypocalcaemia after injection of 46.7% citrate in the CVAD. (9) The described side-effects associated with the TCHL are presumably explained by spill-over/accidental flushes of citrate into the bloodstream. These side-effects include perioral dysesthesia, discomfort of neck and chest, dysgeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) All side effects are temporarily, described if the TCHL is instilled to fast, if the TCHL is accidentally flushed instead of aspirated and were only in rare occasions a reason to withdraw from the studies performed. Additionally, hypersensitivity reactions to citrate are possible. (9, 18, 20, 45-48, 50)

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X. Heparin prevents the progression of an obstruction by inhibiting further clot formation and allowing the activation of natural clot lysis. Heparin has a half-life of 1-2 hours. In haemodialysis patients the more frequent need for thrombolysis in patients receiving the TCL compared to the HL is described. (18, 20-22, 25, 26) This however, did not result in a higher frequency of CVAD removal in these patients. (18, 20) Solomon et al. advised to add 500 IU/ml heparin to the lock solution in haemodialysis patients. (20) In pediatric oncology patients, Handrup et al. used the TCL with the addition of 100 IU/ml heparin to prevent the CVAD from occlusions and CVAD-related CVTs. In this study, no CVADs were removed due to occlusion or thrombosis. (46) Due to the possible higher rate of occlusion due to blood clotting using the TCL, and similar rates of CVT/occlusion associated with the addition of heparin 100 IU/ml, we chose for the addition of heparin 100 IU/ml to the TCL. (18, 20) Side effects related to heparin, which are very rare,

are: hypersensitivity reactions, drug incompatibilities, and heparin-induced thrombocytopenia. In rare occasions, when the wrong dosage is used, iatrogenic hemorrhages can occur. (9, 65)

In this study, to avoid the above mentioned side-effects, the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), heparin is added to the solution for the prevention of the more frequent dispense of thrombolytics, and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed during the study.

Purpose of this study

Hypothetically, the TCHL will reduce the CLABSI rate compared to the HL. Additionally, the use of the TCHL may reduce the frequency of systemic antibiotic treatment, result in lower rates of CVAD-removal, fewer days of hospital/ICU admission, and a reduced mortality rate. Patients will benefit directly from reduced and more appropriate antibiotic use, which will also lead to a reduced risk of developing antibiotic resistance. Previous studies performed on the efficacy of the TCL or TCHL in pediatric oncology patients did not include enough patients to confirm the superior efficacy of the TCHL. Therefore, these studies do not deliver enough evidence to implement the TCHL in the pediatric oncology care in the Netherlands. (45-50) Due to the centralisation of the pediatric oncology care in the Netherlands, we are now able to include enough patients to finally draw a conclusion on the efficacy of the TCHL compared to the HL.

2. OBJECTIVES

Primary Objective:
To determine wheter the use of the taurolidine 1.35%, citrate 4%, and heparin 100 IU/ml lock solution (TauroLock™-Hep100) reduces the incidence of first tunneled central line associated bloodstream infections (CLABSI) compared to the heparin 100 IU/ml lock solution, in pediatric oncology patients, with a maximum follow-up of 90 days.

Secondary Objectives:
To compare the efficacy of the taurolidine 1.35%, citrate 4%, and heparin 100 IU/ml lock solution (TauroLock™-Hep100) to that of the heparine 100 IU/ml lock solution on the:

- Time to first tunneled CLABSI since the insertion of the CVAD
- CLABSI incidence per 1,000 CVAD-days
- Incidence of symptomatic CVTs
- Incidence of bacteremia
- Incidence of local infections
- Dispense of thrombolysis/systemic antibiotic treatment due to CLABSIs/CVTs
- Incidence of and reasons for CVAD-removal
- Cultured microorganisms causing CLABSIs
- Days of hospital admission due to CLABSIs/CVTs
- Safety of the TCHL/HL in terms of known side effects, severe adverse events (SAEs), intensive care unit admission, and mortality rate due to CLABSIs/CVTs

3. STUDY DESIGN

The CATERPILLAR study is designed as a mono-centre, investigator initiated, open labelled randomized controlled trial (RCT). Patients who receive their first CVAD or patients who receive a second, third, fourth etc. CVAD after a CVAD-free interval of more than 12 months, will be asked to participate in this study. These patients will be included in 29 months. Patients will be randomized into the HL study arm (n=231) or TCHL study arm (n=231). The lock will be instilled in the Princess Maxima Center with a maximum of once weekly (if admitted at the hospital or regulary visiting the hospital) and a minimum of once every three weeks (instillation before going home or to a different hospital for >1 week). In between, all patients will receive heparin 100 IU/ml. All patients will be followed up from CVAD insertion until the first CLABSI episode, CVAD-removal, second CVAD insertion (excl. stem cell apheresis CVADs) or death with a maximum study period of 90 days, whichever comes first. The maximum study period of 90 days was chosen since a great deal of the CLABSI episodes occur within the first 90 days after insertion. [Figure 2 and 3] (1, 2) All data (incl. shared care hospital data as this is standard of practice) will be collected in the Princess Máxima Center for Pediatric Oncology.

In the first months after diagnosis and CVAD insertion, patients will receive their oncologic treatment at the Princess Máxima Center for Pediatric Oncology. After one-two months, a minority of the patients will be treated in the shared care hospitals close to their homes and will return at least every three-six weeks to the Princess Máxima Center for Pediatric Oncology. Since the majority of the patients will be treated in the Princess Máxima Center in the first 90 days of their treatment (our follow-up time) we concluded that the benefits would not outweigh the expenses and difficult logistical execution of the instillation of the TCHL in all shared care hospitals in the Netherlands.

In consultation with the Trial Pharmacy of the University Medical Center Utrecht (UMCU) we chose for an open-labelled design since blinding of the lock ampoules would be too difficult and expensive since the design of the lock ampoules are not similar. Blinding with labels would not be sufficient. At first, we tried to find pharmacies that could fabricate similar ampoules with Taurolock-Hep100. The fabrication of TauroLock-Hep100 ampoules would cost >4 million euro or a bulk solution should be sent from TauroPharm to the pharmacy, which is also very pricely, logistically difficult and unusual. Another option discussed was to pre-fill syringes by pharmacies or unblinded nurses. This would need to be done for the heparin and TauroLock-Hep100 solution since neither of them are commercially available in 3mL pre-filled syringes. If performed by unblinded nurses the locks will expire after 24 hours and if performed by pharmacies the locks will expire after 7 days. Therefore, this option would also have resulted in high costs and would logistically be difficult to execute. Therefore, we concluded that the advantages did not outweigh the high costs and logistically difficult execution of a double-blinded RCT. Additionally, we formed an expert panel of three blinded specialists (microbiologists and infectiologists) to evaluate all positive bloodcultures and score them as CVAD associated or not.

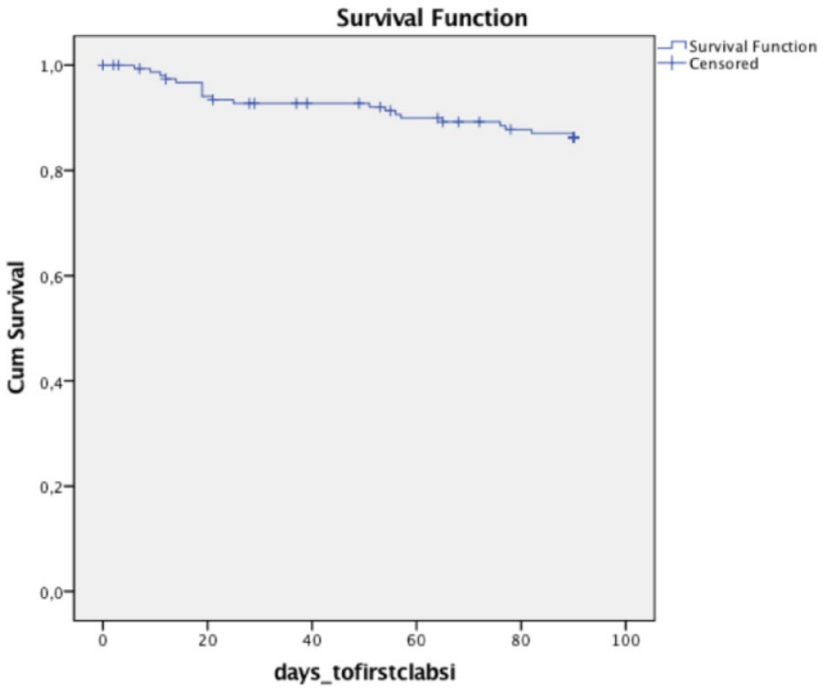


Figure 2: Kaplan-Meier curve of the first 90 days of insertion based on the data from the retrospective study performed by van den Bosch et al. (2019)(1) On the x-axis the days to first observed CLABSI per patient since the insertion of the CVAD. On the y-axis the cumulative CLABSI free survival. A CLABSI in the first 90 days was observed in 12.8% of the patients that received a CVAD.

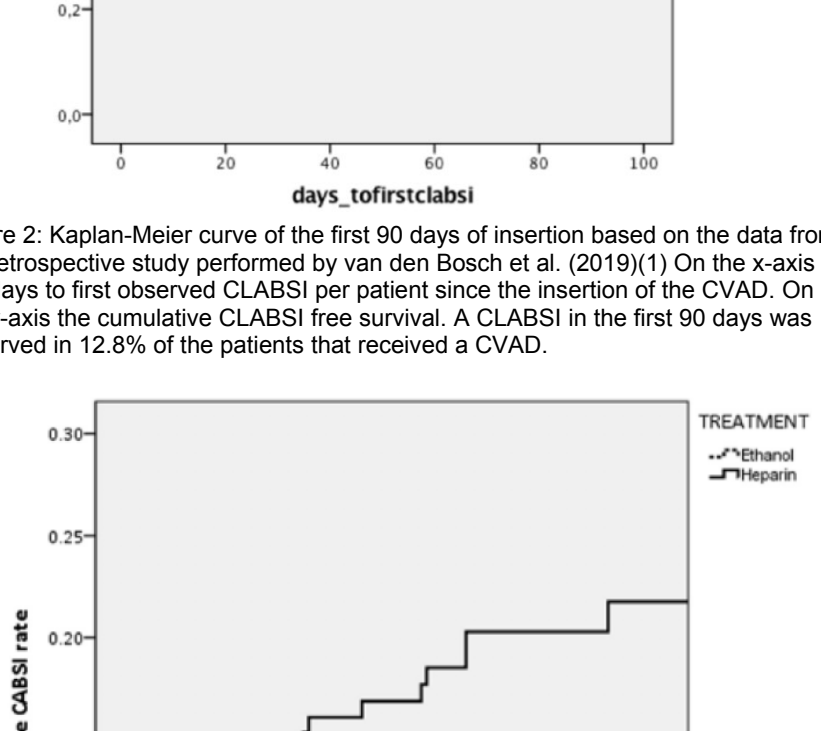


Figure 3: Kaplan-Meier curve of the first 200 days of insertion based on the data from the randomized controlled trial performed by Schoot et al. (2015) (2) On the x-axis the CVAD days to the first observed CLABSI per patient since the insertion of the CVAD. On the y-axis the cumulative CLABSI rate.

4. STUDY POPULATION

4.1 Population

All consecutive pediatric oncology patients (hematologic, solid and neurologic malignancies), treated in the Princess Máxima Center for Pediatric Oncology, ranging from 0-19 years old, receiving a tunnelled CVAD (H-CVAD/PL or TIVAP) for the first time or if their previous CVAD has been removed >12 months ago, will be asked to participate in this study. From May 2018, all pediatric oncology patients in the Netherlands are treated at the Princess Máxima Center for Pediatric Oncology. We expect that the planned number of patients can be recruited in 29 months from the defined source population.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age between 0 - <19 years
- Radiological, cytological or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies)
- H-CVAD/PL or TIVAP to be inserted at the Princess Máxima Center for Pediatric Oncology
- Planned CVAD insertion of >90 days
- Written consent signed according to local law and regulations
- Parents/guardians or patient are willing and able to comply with the trial procedure

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- A previous CVAD removed < 12 months ago.
- Expected treatment for a majority of the follow-up time in a different hospital than the Princess Maxima Center for pediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Center at least once every 3 weeks.
- Primary immunological disorder
- Contra indications: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia.
- Documented bacteremia in the period from 24h before catheter insertion until inclusion
- Insertion of the CVAD at the same site as a previously confirmed CVT
- Pregnant, not willing to use adequate contraceptives, or breast-feeding

4.4 Sample size calculation

Our own database of CVAD associated complications (2015-2017) showed that 12.8% of the patients with an H-CVAD/PL or TIVAP developed at least one CLABSI within 90 days after insertion of their first CVAD (or second/third/etc. CVAD if their previous CVAD was removed >12 months ago). (1)

Group sample sizes of 206 in the TCHL-group and 206 in the HL-group achieve 80% power to detect a difference between the group proportions of 0.0780. The proportion in the TCHL-group (the treatment group) is assumed to be 0.1280 under the null hypothesis and 0.050 under the alternative hypothesis. The proportion in the HL-group (the control group) is 0.1280. The statistic test used is the two-sided Z-Test with unpooled variance.

An interim analysis will be performed after the inclusion of 231 patients. The level of test for the final analysis must be adjusted since part of the alpha will be used in the interim analysis. The level is based on the following computations. The first quantile (for the interim analysis) is set in such a way that the two-sided probability $P(|U1| > q1) = 0.01$ where U1 is the test used at the interim analysis and P means probability. For the law of large numbers U1 has a normal distribution with mean 0 and variance 1. This implies that the first quantile for the interim analysis is equal to 2, 575829. To compute the second quantile the joint distribution (U1, U2), which is bivariate normal with variances 1 and correlation $1/\sqrt{2}$ need to be employed. The second quantile needs to satisfy $P(|U1| > q1$ or $|U2| > q2) = 0,05$, or equivalently, $P(-q1 < U1 < q1, -q2 < U2 < q2) = 0,95$. The second quantile coming from the bivariate joint normal distribution (U1, U2) is equal to 2,002732; the corresponding nominal alpha level for the final analysis is therefore equal to 0.04520606.(66-71)

For each patient that prematurely drops-out of the study an extra patient will be included, we estimated that an extra 50 patients would be needed to account for potential drop-outs. The drop-out inflated sample size was therefore eventually calculated as 462 patients, 231 in each group. Our hypothesis is that the drop-out risk is minimal since all patients are seen regularly in the Prinses Maxima Center for pediatric oncology in the first 90 days of their treatment and the side-effects of the TCHL are minor and rare. The intention to treat principle is used in this study, therefore all patients are included in the final statistical analyses.

Since May 2018 all pediatric oncology patients are diagnosed and treated at the Princess Máxima Center, 550 new patients each year. Approximately 402 (73%) of these patients will receive a CVAD. (4) During the ARISTOCATHS-study, a similar study in the Netherlands investigating the ethanol lock in pediatric oncology children, 728 patients were screened for enrolment in the study, of which 421 (58%) patients were ineligible or declined to participate in the study. (2) In contrast to the ARISTOCATHS-study, during this study, all patients will be included in one center instead of eight and the TCHL is not associated with side effects like the ones associated with the ethanol lcok. Therefore, we hypothesized that 40% of the patients will be excluded or refuse to participate. Therefore, we hypothesized that we are able to include 240 patients each year (20 patients each month). To reach the total number of 462 patients, it will take us approximately 23 months. However, due to the risk of slow accrual, we added six months extra to the inclusion timeframe. Therefore, we estimate that it will take 29 months to include all patients. The last included patient will be followed-up for a maximum of 90 days, therefore the total study duration will be approximately 32 months. [Table 4]

Table 4: Planned study schedule

Months after start inclusion	What?	Description
0	Start inclusion	Planned start of the study
14.5	Interim database lock and interim analysis	After the inclusion of 50% of the patients
29	Stop inclusion	After the inclusion of 462 patients
32	Stop follow-up	After a period of 3 months after the inclusion of the last patient
32 - 36	Database lock, statistical analysis, writing the clinical study reports, and drafting of the manuscript based on the clinical study reports.	From the stop of follow-up until manuscript submission.
36	Manuscript submission	Four months after the study has stopped.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Comparator study arm (HL-study arm): Patients participating in the HL-study arm will receive the current standard of care lock solution containing heparin 100 IU/ml. The HL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. To summarize, the maximum amount of study lock instillations is once every week and the minimum is once every three weeks. The lock volume depends on the CVAD type. [Table 5] The HL will be aspirated from all lumina before instillation of a new lock.

Investigational study arm (TCHL-study arm): Patients participating in the TCHL-study arm will receive the current standard of care lock solution containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. The TCHL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. To summarize, the maximum amount of study lock instillations is once every week and the minimum is once every three weeks. The lock volume depends on the CVAD type. [Table 5] The TCHL will be aspirated from all lumina before instillation of a new lock.

In between the above stated locking moments, the CVADs will be locked with standard heparin 100 IU/ml following the standard protocol of the Princess Máxima Center for Pediatric Oncology, home care institutions and all other shared care centers in the Netherlands.

5.2 Use of co-intervention

All co-interventions can be used as in usual clinical practice.

5.3 Escape medication

All escape medication can be used as in usual clinical practice.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Comparator study arm (HL-study arm)

Patients participating in the HL-study arm will receive the current standard of care lock solution containing heparin 100 IU/ml, 2 ml. The heparin lock will be aspirated before instillation of a new lock solution. The heparin 100 IU/ml lock is the standard of care in the Netherlands for locking CVADs. There is no registered heparin lock product available in the Netherlands. In the Princess Maxima Centre heparin 100 IU/ml, 50 ml is obtained via a so called "collegial delivery of pharmacy compounded medicinal products" (Dutch: "collegiaal doorgeleverde bereiding") This is an exception of The Dutch Medicines Act (www.igj.nl/zorgsectoren/geneesmiddelen-zonder-handelsvergunning/collegiaal-doorleveren). Heparin 100 IU/ml, 50 ml (ZI-number: 16037332) is produced by the Scheldezoom pharmacy (Spoorstraat 16, 4431 NK, 's-Gravenpolder, the Netherlands, https://www.scheldezoom.nl/algemeen). The Scheldezoom pharmacy is a GMP compounding pharmacy for expertise, preservation, and nation-wide delivery of commercially unavailable but rationally necessary medicines (GMP Report submitted in D2. of this METC submission). This product i.e. heparin 100 IU/mL, 50 ml is subsequently used to produce the final product, heparin 100 IE/ml, 2 ml in syringe for patient care. This final product is manufactured by the RIVA™ robot in the Pharmacy of the Prinses Maxima Center for Pediatric Oncology (Productdossier submitted in D2).

An officially registered comparable product is the BD PosiFlush™ Pre-filled Heparin Lock Flush. However, the BD PosiFlush™ Pre-filled Heparin Lock Flush is only registered in the United States of America (USA) and Canada. Therefore this product is not yet available in the Netherlands.(72, 73) The Food and Drug Administration (FDA) transferred the primary responsibility for the regulation of heparin catheter lock-flush solution products from the Center for Drug Evaluation and Research (CDER) to the Center for Devices and Radiological Health (CDRH). Heparin catheter lock-flush solution products are combined drug-device products. The transfer was based on the FDA's determination that the primary mode of action of these heparin catheter lock-flush solution products is that of the device part of the combination. (74) The BD PosiFlush™ Pre-filled Heparin Lock Flush is therefore registered as a medical device in the USA and Canada. (72, 73)

Investigational study arm (TCHL-study arm)

Patients participating in the TCHL-study arm will receive a lock solution containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml (TauroLock™-Hep100). TauroLock™-Hep100 is produced by TauroPharm GmbH, August-Bebel-Straße 51, D-97297, Waldbüttelbrunn (www.taurolock.com). TauroLock™-Hep100 is CE-accredited and registered as a class III medical device. TauroLock™-Hep100 is used in the authorised form for the authorised indication. The certificates, declaration of conformity, and instructions for use can be found in appendix 2. [Appendix 2]

6.2 Summary of findings from non-clinical studies

Comparator study arm (HL-study arm)

There are no non-clinical data of relevance which are additional to the information already included in the other paragraphs.

Investigational study arm (TCHL-study arm)

As described in more detail in the introduction and rationale, in vitro studies show that the TCHL has anti-coagulant, anti-biofilm, and antimicrobial activities, without evidence of

antibiotic resistance to taurolidine. (58-61, 75) Taurolidine has shown a broad-spectrum activity against fungi, Gram-positive and Gram-negative bacteria in vitro. (58-61) High-dose concentrations of taurolidine (290 mg/kg, 2% taurolidine) have been associated with liver injury in mouse models. Low-dose concentrations of taurolidine (140 mg/kg, 2% taurolidine) which are similar to the TCHL dose did not show significant differences compared to the control group (physiologic saline). (63) It was advised by Olthof et al. to add citrate and/or heparin to the lock solution with taurolidine to prevent the CVAD from occlusion. (61)

6.3 Summary of findings from clinical studies

Comparator study arm (HL-study arm)

The HL is the standard of care in the Netherlands to lock CVADs in children and adults. Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in-vivo and in-vitro. (9, 65) Multiple studies have been performed to compare the efficacy of heparin to saline in the prevention of CVAD occlusion. The majority of these reports failed to show a superiority of heparin. (9)

Investigational study arm (TCHL-study arm)

A detailed description of the results and limitations of all clinical studies found in literature on the efficacy of the TCHL is to be found in the introduction section; below you will find a brief summary. The use of the TCL/TCHL showed decreased incidence rates of infections related to the CVAD in haemodialysis patients, total parenteral nutrition patients, and oncology patients compared to lock solutions containing saline or heparin. (12-41, 43, 45-50) Six studies have been performed in pediatric oncology patients. (45-50) Simon et al. performed a prospective cohort study (n = 179) and showed a significant decrease in infections due to CoNS and MRSA in the TCL study arm compared to the HL study arm (0.45 vs. 2.30 per 1,000 CVAD-days, p<0.01), however no difference in the incidence rate of bacteraemia was found between the two study arms. (48) Dumichen et al. performed an open labelled RCT (n = 71) and found a significant decrease in the incidence rate of bacteraemia in the TCL study arm compared to the HL study arm (1.30 vs. 0.30 per CVAD-days, p=0.03). (45) Ince et al. performed a retrospective study (n = 108) and showed a decrease in the CLABSI rate (48.5% vs. 22.8%, p=0.03), an increased duration of CVAD use, and a lower rate of catheter removal in the TCL study arm. (47) Handrup et al. performed the only open labelled RCT (n = 112) to compare the HL with the TCHL in pediatric oncology patients. They found a decrease in the incidence rate of CLABSI (1.40 vs. 0.40 per 1,000 CVAD-days, p<0.01), an increased time to CLABSI, and a reduction of fungi, Gram-positive and Gram-negative microorganisms in the TCHL study arm. Especially, CLABSIs caused by CoNS were reduced by 66% in the TCHL group. The incidence of removal due to occlusion and CVT, and overall CVAD survival were similar in both groups. (46) Recently, Clark et al. performed a prospective cohort study investigating the TCL in pediatric patients (n=19) with oncologic and intestinal diseases. The CLABSI incidence rate decreased from 5.5 to 0.5 per 1,000 CVAD-days (p<0.01) with the use of TCL compared to the HL. The mean time to first CLABSI increased from 87 days to 296 days after TCL implementation (p=0.01). There were no episodes of hypocalcaemia observed during TCL implementation. (49) Chong et al. performed a cross over prospective study investigating the TCL in pediatric oncology patients (n=20). The CLABSI incidence rate decreased from 14.4 to 2.4 per 1,000 CVAD-days (p<0.01) with the use of TCL compared to the HL. Two patients experienced central line occlusion for which one switched to the TCHL, one patient experienced nausea and vomiting. (50) All studies performed in pediatric oncology patients only contained small study groups (n= ≤ 180) and were therefore not considered as enough evidence to implement the TCHL in the pediatric oncology care in the Netherlands. (45-50)

6.4 Summary of known and potential risks and benefits

Comparator study arm (HL-study arm)

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X. Heparin prevents the progression of an obstruction by inhibiting further clot formation and allowing the activation of natural clot lysis. Heparin has a half-life of 1-2 hours when it enters the bloodstream. Used as directed, it is extremely unlikely that the low levels of heparin reaching the blood will have any systemic effect. However, if the heparin does reaches the bloodstream possible side effect can occur: hypersensitivity reactions, heparin-induced thrombocytopenia and drug incompatibilities. In extremely rare occasions, when the wrong dosage is used, iatrogenic hemorrhages can occur. (9, 65)

Investigational study arm (TCHL-study arm)

A detailed description of the risks and benefits of the TCHL is to be found in the introduction section; below you will find a brief summary. Hypothetically, the TCHL will reduce the CLABSI rate. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a lower mortality rate due to CLABSI. Patients will benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development. (12-41, 43-50)

The expected side effects are temporarily, caused by a spill-over of citrate, and only described if the TCHL is instilled to fast or if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dygeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Hypocalcaemia events causing arrhythmias have only been associated with much higher concentrations of citrate, which are not used in this study. Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are possible side effects, but in literature only one patient has been described in whom an anaphylactic-like reaction was observed. (34) Liver-injury is associated with high-concentrations of systemic taurolidine in mouse-models, the TCHL contains low-dose taurolidine, which is not associated with liver-injury. A more frequent dispense of thrombolytics has been associated with lock solutions containing taurolidine and citrate in haemodialysis patients. This was only observed without the addition of heparin. (18, 20-22, 25, 26) In this study, the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), heparin is added to the solution for the prevention of the more frequent dispense of thrombolytics, and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed during the study. If aspiration is not possible, TauroPharm suggests to apply the lock not faster than 1 ml per eight seconds. In this case only a total of ≤2.6ml of the lock solution will reach the bloodstream. (48) The citrate will dilute so fast that no problems concerning the calcium concentration are suspected. (46, 48, 64)

6.5 Description and justification of route of administration and dosage

Comparator study arm (HL-study arm)

Description

Patients participating in the HL-study arm will receive the current standard of care lock solution containing heparin 100 IU/ml. The HL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the

Princess Máxima Center for >1 week the CVAD will be locked and the lock will be be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. The lock volume depends on the CVAD type. [Table 5] The HL will be aspirated before instillation of a new lock. In between, all patients will be locked with heparin 100 IU/ml following the CVAD-manipulation protocol of the Princess Máxima Center for Pediatric Oncology and all shared care hospitals in the Netherlands. (9, 65, 76)

Justification
Guidelines recommend the use of heparin at 10-100 IU/ml for CVAD locking, 10 IU/ml for daily flushing and 100 IU/ml for periodic locking. In the Princess Máxima Center for Pediatric Oncology and all shared care hospitals in the Netherlands we chose for 100 IU/ml since most CVADs are locked periodically. (9, 65, 76, 77) The lock frequency and aspiration of the lock will be performed in this group to make both investigational groups equal.

Investigational study arm (TCHL-study arm)
Description
Patients participating in the TCHL-study arm will receive a lock solution containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. The TCHL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. The lock volume depends on the CVAD type. [Table 5] The TCHL will be aspirated before instillation of a new lock. In between, all patients will be locked with heparin 100 IU/ml following the CVAD-manipulation protocol of the Princess Máxima Center for Pediatric Oncology and all shared care hospitals in the Netherlands. (9, 65, 76)

Justification lock dosage
Available solutions of citrate have concentrations ranging from 4 to 46%. Pittiruti et al. describes that higher concentrations of citrate are associated with a higher efficacy of CVAD-occlusion prevention. However, the European Renal Best Practice (ERBP), American Society of Diagnostic and Interventional Nephrology (ASDIN) and the Food and Drug Administration (FDA) advise to use a concentration of no more than 4% citrate in the prevention of central line related bloodstream infections (CRBSI), due to a case report of a patient that suffered cardiac arrest secondary to hypocalcaemia after injection of 46.7% citrate in the CVAD. (9, 18, 20, 45-48, 50) In order to prevent the above stated side effects we will use citrate 4.0%, we adjusted the lock volumes to the lumen of the CVADs, and we will aspirate the lock before use of the CVAD. If aspiration, on rare occasions, is not possible, TauroPharm suggests applying the lock not faster than 1 ml per eight seconds. If this happens only a maximum total of ≤2.6ml of the lock solution will reach the bloodstream. (48) The citrate will dilute so fast that no problems concerning the calcium concentration are suspected. (64)

Concentrations of 1.35% and 2.0% taurolidine are described in literature, no clinically relevant differences were found between the two concentrations. (9, 48, 58, 61, 62) These concentrations are at least 10 times higher than the MIC_{50} of the majority of Gram-negative and Gram-positive microorganisms. (62) A concentration of 1.35% taurolidine is the most commonly used in pediatric oncology patients. (9, 48) The microbial destruction time of taurolidine in vitro is 30 minutes, therefore the TCHL needs to be in situ for at least >1 hour. (78, 79)

In pediatric oncology patients, heparin 100 IU/ml is added to the TCL, in comparison with the addition of 500 IU/ml heparin, which is used in haemodialysis patients. The TCHL is associated with equal removal rates due to CVT compared to the HL alone in pediatric oncology patients. (46, 64) To further prevent the CVAD from occlusion, proper flushing policies, needle free connectors and no-reflux strategies are used during the administration of the lock solution. (9) Heparin 100 IU/ml is also the preferred dosis for the standard of care heparin lock. (9, 65, 76)

Justification of volume
Literature advices to minimize the lock volume to minimize leakage into the bloodstream. The minimum volume is the volume of the CVAD, since the CVAD lumen has to be filled entirely. During insertion the CVADs will be trimmed to fit the individual child, therefore the volume will be less than the company's stated CVAD priming volume (a difference of 0.02-0.20 ml per 10 cm). The true volumes of the CVAD and the advised lock volumes can be found in table 5. [Table 5] If the positive pressure technique is performed inadequetly, it is possible that a small volume is not injected into the CVAD, therefore all lock volumes are 15-20% higher than the maximal catheter volume (as adviced in literature). (65, 67) The CVAD volume includes the catheter, huber needle with wire (0.3 ml), three-way valve (0.2 ml), and needle-free connector (Clave®) (0.05 ml).

Table 5: Lock Volumina

CVAD	Type	Diameter (Fr)	Maximal catheter volume (ml)	Lock volume (ml)
TIVAP	Babyport®	4.5	0.80	1.0
	Low-profile®	6.5	1.04	1.5
	Standard®	6.5	1.28	1.5
Broviac®	Single lumen	6.6	0.74	1.0
Hickman®	Double lumen	7.0	0.90/0.80	1.0/1.0
Powerline®	Double lumen	6.0	0.70/0.70	1.0/1.0
	Triple lumen	6.0	0.75/0.62/0.62	1.0/0.8/0.8

Justification lock frequency
The instructions for use of TauroLock-Hep100 do not give an advice about the maximum amount of locks that can be instilled in a certain time frame. The instructions only state: "TauroLock-Hep100 will remain inside the access device until the next treatment (for a maximum of 30 days)." The studies performed in pediatric oncology patients Schoot et al., Handrup et al., and Simon et al. all locked the CVAD mostly once and sometimes twice a week. All observed a significant reduction of the amount of CLABSIs. (2, 46, 48) Clark et al. locked the CVAD daily and Ince et al., Chong et al. and Dumichen et al. did not report their lock frequency. (47, 49, 50) Daily locks might be safe, however due to the minimal amount of evidence and the possible side effects associated with high concentrations of citrate, we decided to choose a maximum lock frequency of once a week similar to most performed pediatric oncology studies. (9, 18, 20, 45-48, 50)

We chose for a minimum lock frequency of at least once every three weeks if patients are not seen at the Princess Máxima Center for >1 week so that these patients do not have to travel to the Princess Máxima Center every week only for the study lock. We chose specifically for three weeks since most patients are at least seen once every three weeks at our hospital and the TCHL can remain in situ for a maximum of 30 days. We did not choose for a minimum frequency of >3 weeks since it is possible that in between the lock is removed by

home care or shared care nurses. This way we can ensure that every patient has a lock in situ at least once every three weeks.

6.6 Dosages, dosage modifications and method of administration

Dosages

Lock volume depends on the CVAD type [Table 5]. A minimum of 5 and maximum of 13 locks per patient will be instilled in the follow-up of 90 days.

- TCHL-study arm: taurolidine 1.35%, citrate 4% and heparin 100 IU/ml.
- HL-study arm: 100 IU/ml heparin.

Method of administration

Five steps of administration (48):

1. Flush the device with 10 mL of saline.
2. Withdraw the lock from the vial/ampoule using an appropriate syringe.
3. Instill the lock slowly (not more than 1 mL per second, infants and children less than two years of age not more than 1 mL per 5 seconds) into the access device in a quantity sufficient to fill the lumen completely. [Table 5] The lock will remain inside the access device until the next treatment (for a maximum of three weeks).
4. Prior to the next treatment, the lock must be aspirated from all lumina and discarded. In the advent of inability to aspirate from the device, the lock should be flushed very slowely <1 mL/5 sec.
5. Flush the device with 10 mL of saline.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable, since this study is submitted as a medical device study, see paragraph 6.1.

6.8 Drug accountability

Shipment and receipt

The TCHL will be shipped from the TauroPharm GmbH (Waldbüttelbrunn, Germany) to the clinical trial pharmacy of the Princess Máxima Center for Pediatric Oncology. The HL that will be given as a study lock in the Princess Máxima Center for Pediatric Oncology will be shipped from the Scheldezoom pharmacy (‘s-Gravenpolder, the Netherlands) to the clinical trial pharmacy of the Princess Máxima Center for Pediatric Oncology.

Disposition

After inclusion the physician will register an order (VMO) in the patient file in Chipsoft EZIS/HiX for the randomized lock, either the TCHL or HL. The nurses will recognize in which study arm the patient is randomized by the CATERPILLAR patient-card. Additionally, the nurses can check the order (VMO) for either the TCHL or HL that is registered in the patient file in Chipsoft EZIS/HiX. The research nurses need to double check the lock solution (two signatures need to be written on the “Lock Instillation Form”) and register the batch number or stick the flag label on a paper “Lock Instillation Form” before instillation.

Return

All left over investigational products will return to the Trial Pharmacy of the Princess Máxima Center for Pediatric Oncology and be stored for later use after the study is performed.

Destruction

Expired investigational products will be destructed.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter

Incidence of first tunneled CLABSIs since the insertion of the CVAD. All data-points that are needed for the evaluation of the occurrence of a CLABSI will be collected by the local data-manager. Three experts will blindly and independently judge if a CLABSI or no-CLABSI occurred in all patient based on the collected data and the CLABSI definition described in paragraph 7.1.5. All non unanimous judgements will be discussed between the experts until they all agree. If the experts still disagree, the final judgement will be based on the judgement of the majority.

7.1.2 Secondary study parameters

- Time to first CLABSI since insertion of the CVAD
- CLABSI incidence per 1,000 CVAD-days
- Incidence of symptomatic CVTs
- Incidence of bacteremia
- Incidence of local infections
- Dispense of thrombolysis/systemic antibiotic treatment due to CLABSI or CVT
- Incidence of and reasons for CVAD-removal
- Cultured microorganisms causing CLABSI
- Days of hospital admission due to CLABSI/CVT
- Safety of the TCHL/HL in terms of known side effects, SAEs, intensive care unit admission, and death due to CLABSI/CVT

7.1.3 Endpoints

Endpoints of the study are the first tunneled CLABSI episode (diagnosed by the expert panel), removal of the CVAD, second CVAD insertion (excl. stem cell apheresis CVADs) or death of the patient, whatever endpoint will come first with a maximum study period of 90 days. If an endpoint is reached, no more study locks will be given. The data of the patients will be followed-up until one month after the endpoint was reached.

7.1.4 Other study parameters

Patient characteristics and CVAD insertion:

- Age
- Gender
- Oncologic diagnosis
- Chemotherapy protocol and treatment arm
- Planned administration of prophylactic systemic antibiotics (trimethoprim/sulfamethoxazole = bactrimel®, ciprofloxacin, or anti-mycotics)
- Date of CVAD surgery
- Type of CVAD
- Introduction method (percutaneous/open)
- Lumen amount
- Lumen diameter
- Access vein and side

- Complicated procedure

Lock characteristics:
- During and directly after study lock instillation:
  - Date of lock instillation
  - Type of lock
  - Side effects (Adverse Device Events (ADE) of interest) and grade (CTCAE version 5.0, November 27, 2017)
- Aspiration of the study lock:
  - Date of removal
  - Inadvert lock removal at home
  - Lock aspirated, accidentally flushed, or malfunction
  - In case of malfunction: type of treatment
  - Side effects (Adverse Device Events (ADE) of interest) and grade (CTCAE version 5.0, November 27, 2017)

Suspicion of CLABSI characteristics:
- Start date of episode
- Presence of symptoms
- Is the CVAD inserted for >48 hours
- Allogenic stem cell recipient with diarrhea >1L in 24 hours, or allogenic stem cell recipient with graft versus host disease grade III or IV.
- Neutropenia episode (incl. duration and severity of neutropenia)
- Results of blood cultures (each lumen counts as one separate blood culture): date and microorganisms cultured will be registered.
- Other documented infection at the time of CLABSI with the same pathogen cultured as the blood culture
- CLABSI, MBI-LCBI, BSI, or suspicion CVAD-related infection without a positive bloodculture.
- In case of BSI, the reason why a BSI was scored e.g. not enough blood cultures, no symptoms, contamination, CVAD in situ for <48 hours, infection at a different site with same pathogen.
- Treatment
- Hospital admission and hospital admission days
- Intensive care unit admission and intensive care unit admission days
- Death of the patient

Suspicion of local infection characteristics:
- Start date of episode
- Symptoms
- Results of blood cultures
- Treatment
- Hospital admission and hospital admission days
- Intensive care unit admission and intensive care unit admission days
- Death of the patient

Suspicion of CVT characteristics:
- Date start episode
- Type of symptoms possibly related to a CVT
- Signs of CVT on radiological imaging
- Location thrombus

- Treatment
- Hospital admission days due to CVT
- Intensive care unit admission days due to CVT
- Death of the patient due to CVT

Serious Adverse Device Events (SADEs)

- ADE term (80)
- Start date ADE
- Date ADE turned into SADE
- Category of SADE
- SADE severity (toxicity grade) (80)
- Hospital admission date
- Medical intervention date
- Date SADE was resolved
- Description SADE
- Date of last lock administration and lock dosis
- Relationship of SADE to intervention (possible/definitely)
- Action taken
- Relevant medical history
- Relevant tests performed
- Study intervention discontinued due to the event

End of the study

- Reason end of the protocol
- In case of CVAD removal: reason, date, and catheter tip microorganisms culture
- In case of death of the patient: reason, date

7.1.5 Definitions

Bloodstream infection (BSI)	Every positive blood culture that is impossible to classify as a CLABSI or MBI-LCBI. Reasons why a BSI is scored: only one bloodculture with a common commensal is obtained, two bloodcultures are obtained but ≤2 common commensals or none recognized pathogens are cultured, positive blood cultures without observed symptoms (e.g. fever, chills, or hypotension, for patients <1 year: fever, bradycardia, and apnea), or an infection at another site with the same cultured pathogen is observed.
Chills	Chills described by parents and/or patient or witnessed by a physician.
Central-line associated bloodstream infection (CLABSI)	CLABSI will be scored if the patient meets one of the following criteria: (1) the patient has a recognized pathogen (micro-organisms not registered in the “List of Common Commensales” of the Centers for Disease Control and Prevention) cultured from ≥1 blood cultures, (2) the patient has at least one of the following signs: fever, chills, or hypotension (for patients <1 year: fever, bradycardia, and apnea), AND the same matching potential common 35ommensals (“List of Common Commensales” of the Centers for Disease Control and Prevention) are cultured from ≥2 blood cultures drawn on separate occasions (incl. two blood

	cultures drawn at the same time but from different lumen). Additionally, a CLABSI will only be scored if the CVAD is in situ for >48 hours on the date of the event, if the pathogen cultured is not related to an infection at another site AND if the MBI-LCBI criteria are not met. See appendix 3 for the CLABSI flow-chart. (67, 81)
Local infection (i.e. phlebitis, exit-site or tunnel-infections)	Positive exit-site culture, erythema, purulent drainage or tenderness within 2 cm of the CVAD track and exit-site
Central venous thrombosis (CVT)	If the patient has (1) peripheral veins that have a non-compressible segment, or (2) there is an echogenic intra-luminal thrombus or an absence of flow in the central venous system. (76)
Diarrhea	≥1L Diarrhea in a 24-hour period
Fever	Temperature >38.0°C on two occasions within a 12-hour period, one temperature >38.5°C, or one temperature <35.0°C (for patients of <1 year <36.0°C).
Hypotension	Hypotension criteria per age: ○ 0-3 Months: systolic RR<60 mmHg ○ 3 Months – one years: systolic RR<80 mmHg ○ 1-11 Years: systolic RR <90 mmHg ○ >12 Years: systolic RR<100 mmHg
Malfunction	If it is impossible to aspirate or flush the CVAD.
Mucosal barrier injury laboratory confirmed bloodstream infections (MBI-LCBI)	The mucosal barrier injury laboratory confirmed bloodstream infections (MBI-LCBI) were scored following the criteria of the CDC to exclude BSIs that are possibly the result of the weakened mucosal barrier of the gut in immunocompromised patients, and probably not associated with the CVAD. MBI-LCBI will be scored if: (1) a CLABSI with a recognized pathogen is scored AND the only pathogens cultured are intestinal organisms (micro-organisms registered as MBI Organisms in the "List of Common Commensales", CDC), OR (2) a CLABSI with two or more common commensals is scored AND the commensals cultured are only viridans streptococci. Additionally, the patients must meet one of the following during same hospitalization as the positive blood specimen: (1) the patient is an allogenic stem cell transplant recipient in the past year with grade III or IV gastrointestinal graft versus host disease, or > 1 litre diarrhea in a 24-hour period, OR (2) the patient is neutropenic on two separate days. See appendix 3 for the CLABSI flow-chart. (3, 67, 81-84)
Mild neutropenia	Granulocytes 1000-1500 x 10^6 /L
Moderate neutropenia	Granulocytes 500-1000 x 10^6 /L
Severe neutropenia	Granulocytes < 500 x 10^6 /L

Very severe neutropenia	Granulocytes < 100 x 10^6 /L

7.2 Randomisation, blinding and treatment allocation

Patients will be randomized between two treatment arms: HL- and TCHL-study arm. Randomisation will be done with the method of minimisation. Stratification will be done according to two factors: used type of CVAD (TIVAP or H-CVAD/PL) and diagnosis of cancer (hematologic or solid/neurologic malignancies).

The randomization will be done with the use of an online randomization service by internet (Software as a Service – SaaS) called ALEA®. This web-based randomization program will provide 24 hours 7 days per week service. At the study site, the researcher or research nurse will enter the randomization data in ALEA®. Notification will be sent to the local study team. The local study team will receive a notification with patient identifier, patient study number and the allocated treatment.

7.3 Study procedures

Information to patients

If it is determined that a patient will need a tunneled CVAD, the surgeon/researcher will inform the patient and parents/legal guardian about the CVAD insertion procedure. At the end of this conversation verbal information and information in writing about this study will be given to the patients and parents/legal guardian.

Inclusion

Inclusion (including first lock instillation) should take place within one week after CVAD insertion. However, if this is not possible due to clinical circumstances (i.e. physical and/or psychological) patients may be included (incl. first lock instillation) within four weeks after CVAD insertion. The researcher/research nurse will sign the informed consent papers after the patient and parents/legal guardian. The in- and exclusion criteria will be checked to determine if the patient is eligible for the CATERPILLAR-study. The researcher/research nurse will complete the inclusion details in HiX and will enter the patient information in the randomization programme ALEA®. The local data-manager will complete the “Registration and Baseline Form” in Castor EDC. Patients will be randomized in either the HL- or TCHL-group. The local study team will receive the randomization information. The surgeon/researcher registers an order (VMO) for either the TCHL or HL in the patient file in Chipsoft EZIS/HiX. See appendix 4 for the flow-chart of the study procedure described above. [Appendix 4]

All patients will receive a CATERPILLAR card with “YES and NO stickers” from the research nurse/researcherThis card is used to alert health care providers that the patient is a participant in the CATERPILLAR-study and will show in which group the patient is assigned and what lock volume needs to be instilled. Parents and/or patients will be asked to show the CATERPILLAR-card and stickers each time they visit the hospital.

Lock instillation and aspiration

Directly after the insertion of the CVAD, a running intravenous infusion will be connected to the inserted CVAD. The first investigational lock solution will be instilled in the first week after insertion. However, if this is not possible due to clinical circumstances (i.e. physical and/or psychological) patients may receive the first lock within four weeks after CVAD insertion. The other study locks will be instilled in the CVAD lumen once a week if the CVAD is

disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. The lock volume depends on the CVAD type. [Table 5] In between, all patients will be locked with heparin 100 IU/ml following the CVAD-manipulation protocol of the Princess Máxima Center for Pediatric Oncology, home care organizations and all shared care hospitals in the Netherlands.

The research nurse/researcher can use the CATERPILLAR patient-card and VMO in HiX to see in which study group the patient is randomized. The nurses will be asked to double check the ampoule before instillation, two signatures and the batch number need to be written on a paper "Lock Instillation Form". After the instillation of the new study lock solution, the patients will be asked questions concerning the experience of side effects during the lock instillation. The paper "Lock Instillation Form" will be completed by the research nurse. The patients will receive a "Lock in situ YES" sticker with the lock instillation date, that will be attached to the CATERPILLAR-card. Patients and/or parents will be asked to show the card during every visit in a hospital.

If the CVAD is manipulated again, the "Lock in situ YES" sticker on the CATERPILLAR card will alert health care providers that the study lock is in situ and that the lock needs to be aspirated by the research nurse or researcher. If the lock aspiration takes place in the Princess Máxima Center for Pediatric Oncology, again questions concerning the experience of side effects during lock removal will be asked and the "Lock Instillation Form" will be completed. Then the "Lock in situ NO" sticker with the aspiration date and method of removal will be attached to the CATERPILLAR-card.

If the study lock is aspirated in a shared care center or home care setting the nurse will be asked to follow the guidelines on the CATERPILLAR card and stick the "Lock in situ NO" sticker on the CATERPILLAR card with the date and method of removal. The research nurses in the Princess Maxima Center will be asked to register the lock removal date on the "Lock Instillation Form" the next time the patient visits the Princess Maxima Center. If the lock removal date is missing the shared care center will be contacted. If in the shared care centers or at home a regular heparin lock is instilled after the CVAD is used, patients will not be excluded from the study.

The data-manager will enter the information of the "Lock Instillation Form" in the online database "Lock Instillation Form" in Castor EDC.

<u>Suspicion of an (local) infection or CVT in the Princess Máxima Center for Pediatric Oncology</u>

In case of symptoms possibly associated with an (local) infection or CVT (e.g. swelling/pain at the catheter site, face, neck, arm, or shoulder) parents will be asked to contact a nurse or physician from the beginning of the signs of infections. If the patient is seen in the Princess Máxima Center for Pediatric Oncology, the surgeons/pediatric oncologists will inform the research nurse/researcher. Standard of care diagnostic work-up and treatment will be performed. The research nurse/researcher will register all relevant details in Chipsoft EZIS/HiX. The research nurse/researcher will alert the local data-manager and he/she will complete the "Suspicion of a CLABSI", "Suspicion of a local infection" or "Suspicion of a CVT" form in Castor EDC. Episodes of CLABSIs, local infection or CVTs will be monitored until the symptoms have resolved and the patient has recovered. See appendix 5 for the

flow-chart of the study procedures described above. [Appendix 5] If a blood culture is drawn from the CVAD and the TCHL or HL is still in situ, the first 2.0 mL has to be discarded.

Suspicion of an infection or CVT in the shared care hospitals

In case of any symptoms possibly associated with an (local) infection or CVT (e.g. swelling/pain at the catheter site, face, neck, arm, or shoulder) parents will be asked to contact a nurse or physician from the beginning of the signs of infections. It is the standard of care in the Netherlands to inform the Princess Máxima Center for Pediatric Oncology if a patient is seen in a shared care hospital due to treatment complications (e.g. CLABSI, local infection or CVT). The physicians in the shared care hospitals enter the complication data in Chipsoft EZIS/HiX of the Princess Máxima Center for Pediatric Oncology and/or will call the patients' physician in the Princess Máxima Center for Pediatric Oncology. The physician/nurse of the Princess Máxima Center will contact the research nurse/researcher who will register all details in Chipsoft EZIS/HiX. The research nurse/researcher will alert the local data-manager to complete the "Suspicion of a CLABSI", "Suspicion of a local infection" or "Suspicion of a CVT" form in Castor EDC. If information is missing, the shared care centers will be contacted. See appendix 6 for the flow-chart of the study procedures described above. [Appendix 6] If a blood culture is drawn from the CVAD and the HL or TCHL is still in situ, the first 2.0 mL has to be discarded.

End of the study

The patient will reach the end of the study in case of a CLABSI episode, CVAD-removal, second CVAD insertion (excl. stem cell apheresis CVADs) or death of the patient, with a maximum of 90 days. After one of the endpoints of the study has been reached, the research nurse/researcher will enter the end of the protocol details in HiX. The data-manager will complete the "End of the Protocol Form" in Castor EDC. See appendix 7 for the flow-chart of this procedure. [Appendix 7]

Division of tasks

The research nurse and researcher will perform the informed consent procedure, keep track of all patients, make appointments and collect data in HiX. The local data-manager will collect data from HiX and enter this data into Castor. Central data management will check data completeness. The statistical analysis (interim analysis and final analysis) will be performed by a statistician. The DSMB charter submission will be done by the local study team. The manuscript will be written by the researcher and the PI.

"Extra"-procedures

All procedures that subjects undergo are part of the standard medical treatment of the Princess Máxima Center for Pediatric Oncology, except for the following:

- Parents need to show the CATERPILLAR-card to the nurse/physician during every hospital visit.
- In the Princess Máxima Center for Pediatric Oncology every patient participating in the HL- or TCHL-study arm will be asked to answer questions concerning the side effects after each lock instillation and after study lock removal.
- If a blood culture is obtained from a patient and the HL or TCHL is in situ, the first 2.0 mL has to be discarded and the lock is aspirated instead of flushed before instillation of a new lock.
- If the study lock is removed in a shared care hospital or home care setting the nurse will be asked to follow the guidelines on the CATERPILLAR card and stick the "Lock in situ NO" sticker to the card with the aspiration date and reason for removal.

Diagnostic procedures or treatment of these patients will not be postponed due to participation in this study.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time, for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1. Specific criteria for withdrawal

1. Admission of >3 weeks in a hospital outside the Netherlands or a non-participating shared care centre.
2. Hypersensitivity reaction after instillation of the TCHL solution.

7.5 Replacement of individual subjects after withdrawal

The intention to treat principle will be used. Therefore, patients will not be replaced after withdrawal.

7.6 Follow-up of subjects withdrawn from treatment

Subjects that object to further participate in the study will receive the standard of care locks containing heparin 100 IU/ml. Their electronic patient files will be reviewed until 30 days after the last lock instillation.

7.7 Premature termination of the study

The DSMB can advise the sponsor to terminate the study prematurely. The sponsor or METC can decide to terminate a study.

Premature termination criteria:

- If the interim analysis shows an earlier disturbance of equipoise, e.g. major superiority or inferiority of the TCHL. See interim analysis, chapter 10.3, for more details.
- If significantly more or less SAEs/SUSARs are reported in the TCHL-group. See interim analysis description for more details.
- Methodological inaccuracies
- If the conduct is not feasible because of logistics or subject recruitment

If it is decided to terminate the study earlier than indicated in the protocol, all patients and involved hospitals will be informed by the researcher. The study must be stopped immediately. The sponsor is required to report premature termination to the reviewing committee (METC) within 15 days after termination stating the reason for early termination.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 ADEs and SADEs

8.2.1 Adverse device effects (ADEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational products. Only AEs of special interest with a possible or definite relationship (serious adverse device effects ADEs) with the investigational products will be registered. Registration of all AEs would lead to the registration of too many AEs in this patient group.
Registration will be performed according to the definitions of the Common Terminology Criteria for Adverse Events (CTCAE version 5.0, November 27, 2017), incl. severity grade.

ADEs of special interest that are registered:

- Oral dysesthesia: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.
- Neck pain: A disorder characterized by a sensation of marked discomfort in the neck area.
- Chest wall pain: a disorder characterized by a sensation of marked discomfort in the chest wall
- Dysgeusia: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
- Nausea: A disorder characterized by a queasy sensation and/or the urge to vomit.
- Vomiting: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
- Allergic reaction: A disorder characterized by an adverse local or general response from exposure to an allergen.
- Blood and lymphatic system disorders - Heparin induced thrombocytopenia: thrombocytopenia due to the administration of heparin.
- Other ADEs that have not been anticipated before.

The research nurse/researcher will ask the patients and/or parents if any of the above described ADEs occur and register them on the “Lock Registration Form”. All ADE’s will be registered in the Castor EDC database by the local data-manager.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or affect that

- Results in death
- Is life-threatening for the subject, life threatening events are defined as:
  - Circulatory/cardiac insufficiency requiring catecholamines/positive inotropes
  - Respiratory failure requiring intubation/ventilation

- Other clinical situation requiring immediate intervention, e.g. gastro-intestinal bleeding or perforation requiring surgery, cerebral abcessbleeding requiring immediate neurosurgical intervention.
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator

We will only register SAE's that have a possible or definite relationship with the investigational medical devices from informed consent up till 30 days after the last study lock was given to the patient (Serious Adverse Device Events = SADEs). Registration of all SAE's will lead to too many registrations in this patient group. These SADE's must be registered in HiX by the research nurse/researcher and on SADE report forms in Castor EDC by local data-management. Within 24 hours these SADE forms must be sent to the safety desk of the sponsor.

The causality assessment is made using the following:

- Not related: There is no evidence to suggest a causal relationship.
- Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time frame after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The sponsor will report the SADEs to the accredited METC that approved the protocol through the web portal ToetsingOnline (TOL). During this study we are not obliged to report SADEs to the Inspectie Gezondheidszorg en Jeugd (IGZ).

- SADEs that result in death or are life threatening and where a possible/definite causal relationship with the investigational product is suspected, need to be reported through ToetsingOnline within 7 days of first knowledge, followed by a maximum period of 8 days to complete the initial preliminary report.
- All other SADEs, where a possible/definite causal relationship with the investigational product is suspected, will be reported within a maximum period of 15 days after the sponsor has first knowledge of the serious adverse events.

SADEs will be evaluated with the SADE evaluation form. It will be determined if the SADE was anticipated (ASADE) or unanticipated (USADE).

8.3 Follow-up of Serious Adverse Device Events

SADEs need to be reported till 30 days after the last lock was given to the patient, as defined in the protocol. All SADEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

A DSMB will be established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. Details can be found in the "*DSMB Charter of the CATERPILLAR-study*". The interim-analysis is described in chapter 9.3.

The DSMB should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC). The DSMB should inform the Chair of the steering committee if, in their view: The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management; or It becomes evident that no clear outcome would be obtained.

DSMB meetings:

1. Prior to the study start a meeting will be scheduled, to discuss the protocol, trial, analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators.
2. A closed meeting will be scheduled after the inclusion of 231 patients, approximately 14.5 months after the study start. The efficacy and safety data (interim analysis) will be presented. Accumulating information relating to the recruitment and data quality, toxicity details based on pooled data, and total numbers for the primary outcome measure and other outcome measures may be presented, at the discretion of the DSMB.
3. At the end of the study a meeting will be scheduled to allow the DSMB to discuss the final data with the principal investigator.

The members of the DMC for this trial will be:

1. Dr. Marieke Witvliet, Pediatric Surgeon, Wilhelmina Children's Hospital, Utrecht, the Netherlands.
2. Dr. Bart Rijnders, Infectious Diseases, Erasmus Medical Center, Rotterdam, the Netherlands.
3. Prof. Dr. Hein Putter, Medical Statistician, Leids University Medical Center, Leiden, the Nethterlands.

The chair will be: Dr. Marieke Witvliet

The advice(s) of the DSMB will be sent to the principal investigator (Prof. Dr. M.H.W.A. Wijnen) of the study. Should the principal investigator decide not to fully implement the advice of the DSMB, the principal investigator will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

9. STATISTICAL ANALYSIS

The primary data analyses will be performed with the intention to treat principle (i.e. inclusion of all patients that were randomized). Additionally, a per-protocol analysis will be performed excluding patients who were not included within one week after CVC insertion, patients who never received the intervention and patients who missed three or more of the minimal amount (once every three weeks) of locks during the follow-up period. Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. Differences between treatment groups with respect to baseline characteristics will be analyzed by using a Chi-square (or Fisher Exact in the presence of small numbers), and t-test for categorical or continuous variables respectively. In case of violation of the normality assumption a non-parametric test such as the Wilcoxon rank test will be applied.

9.1 Primary study parameter

For the primary outcome, the percentages and incidence rates (IR) of first CLABSIs per 1,000 CVAD-days will be reported for both study groups and compared by computing an IRR. The exact confidence limits for the IRRs will be based on the polynomial algorithm for person time data (85, 86). The nominal alpha level for the primary outcome in the final analysis will be equal to 0.045 due to the interim analysis (66-71).

9.2 Secondary study parameters

The cumulative incidence of CLABSI from CVAD insertion will be estimated by using a competing risk model (87) with CVAD removal due to non-CLABSI related reasons or death as competing events. To assess the difference between the cumulative incidence for the intervention (TCHL) and control (HL) group, the Gray's test will be used. (88)

To estimate the effect of risk factors on the occurrence of CLABSI, a Cox specific proportional hazard regression model from CVAD insertion will be estimated. Well known time fixed risk factors for a CLABSI to be incorporated into the model are diagnosis (hematological disease versus other diagnoses), CVAD type (TIVAP versus tunneled external CVADs) . Furthermore, TPN administration will be used in the model as time-dependent covariate). (87)

A landmark analysis at 28 days after CVAD insertion will be performed. The same risk factors as discussed above will be incorporated in the Cox specific hazard regression model with additional covariate number of lock days. The landmark point of 28 days was chosen based on clinical reasons, the first lock should have been given within the first four weeks after CVAD insertion.(89)

For the secondary outcomes, the percentages and IRs per 1,000 CVAD-days will be reported and compared by computing IRRs.

9.3 Interim analysis

After complete follow-up of the first 231 patients an interim analysis will be performed by the trial statistician. After the interim analysis is performed, the results will be presented at the second DSMB meeting, see chapter 8.4. The stopping rule is based on testing the one-sided test at $\alpha = 0.025$ for H_0: 'experimental incidence ≥ control incidence' against H_1: 'experimental incidence < control incidence'. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the experimental. The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on choices of the α- and β-spending functions. The α-spending function determines how eager or reluctant one is to stop the trial for superiority. The β-spending function determines how eager or reluctant one is to stop the trial because the chance has become small that superiority can be concluded if the trial is continued. As α-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 2.35$. This choice implies that the trial is stopped after 231 patients if the one-sided P-value is smaller than 0.005 (or 0.01 two-sided) in favor of the experimental treatment. As β-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 3.2$. This choice implies stopping the trial after 231 patients if the one-sided P-value is ≥ 0.5, i.e. if the estimated treatment effect at that time is in favor of the control treatment.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, and October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), General Data Protection Regulation (GDPR), Medical Treatment Contracts Act (WGBO), Medical Devices Act (Wmh), and Medical Devices Decree.

10.2 Recruitment and consent

If a patient will receive a tunneled CVAD, the surgeon/researcher will inform the patient and parents/legal guardian about the CVAD insertion procedure and the CATERPILLAR-study. After the verbal information has been given, the information will also be given to the patient and parents/legal guardian in writing. The patient and parents/legal guardian can determine if they want to participate in the study until the CVAD is inserted for <1 week. However, if this is not possible due to clinical circumstances, informed consent can be given within 4 weeks after CVAD insertion. The time to consideration depends on the date of insertion and the hospital admission duration after the CVAD insertion. The time to consideration is at least one day. If the patient and parents/legal guardian agree to participate in the study, the informed consent form will be signed. Additionally, the patient and parents/legal guardian will be asked if they want the researcher to inform all treating physicians/pharmacist about the trial participation, and if, after the completion of the trial, the researcher can ask the patient and parents/legal guardian if they are interested in participating in follow-up studies.

10.3 Benefits and risks assessment, group relatedness

As already described in the introduction, hypothetically, the TCHL will reduce the CLABSI rate. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a reduced mortality rate due to CLABSI. Additionally, patients can benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development. (12-41, 43-50)

The expected side effects are temporarily, caused by a spill-over of citrate, described if the TCHL is instilled too fast, and if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dygeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are possible side effects, but were not observed in the studies evaluated. A more frequent dispense of thrombolytics has been associated with lock solutions containing taurolidine and citrate in haemodialysis patients. (18, 20-22, 25, 26) However, this was only observed without the addition of heparin. (45-50) In this study, for the prevention of the above stated possible side-effects, the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed.

In conclusion, we think the possible positive effects of the TCHL outweigh the remaining minimal and rare side effects of the TCHL.

10.4 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7 of the WMO. Insurance information:

- Insurance company: Aon Risk Solutions
- Type of Insurance: Liability Insurance (including medical malpractice liability).
- Policy no: V0100112728
- Insured: Prinses Maxima Centrum voor Kinderoncologie
- Sum insured: EUR 5,000,000 each and every claim and EUR 15,000,000 in the aggregate.
- Deductible: EUR 25,000 each and every claim
- Insurance period: May 18, 2019 till May 18, 2020
- Conditions: In conformity with the AW Healthcare package wording, including general liability, pollution (sudden & accident) and employer's liability (Dutch law). Further to be agreed and amended to Dutch law.
- Territorial limits: Worldwide, excluding USA/Canada
- Leading insurer: 100% Allied World Assurance Company (Europe) Ltd.

The sponsor also has an insurance for the study subjects which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Insurance information:

- Insurance company: CNA Insurance Company, Ltd
- Type of Insurance: Subject insurance
- Policy no: 10211864
- Insured: Prinses Maxima Centrum voor Kinderoncologie
- Sum insured: EUR 650,000 per subject, EUR 5,000,000 per research project, EUR 7,500,000 each year for all research projects together.
- Insurance period: October 1, 2019 till October 1, 2020, with silent prolongation.
- Territorial limits: The Netherlands

10.5 Incentives

No incentives/compensations are applicable.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The handling of the personal data will comply with the General Data Protection Regulation (GDPR). All data will be handled confidentially and pseudonymised. The database system that we will use is Castor EDC (www.castoredc.com), a user friendly, fully featured, affordable and secure system. Castor has been audited on Good Clinical Practice compliance by Profess Medical Consultancy and has obtained a Good Clinical Practice compliance certificate. The database will have limited excess; an account will be given to the members of the local study team and to a designated monitor. A central subject identification code list in the Princess Máxima Center for Pediatric Oncology will be used to link the data to the subject. The subject identification list will only be available for the local study team. The database and the subject identification list will be kept separately. Data will be stored in the Princess Máxima Center for Pediatric Oncology for a minimum of 15 years.

11.2 Monitoring and Quality Assurance

The monitor organisation: Julius Center (http://portal.juliuscentrum.nl/nl-nl/home.aspx)
Independence of the organisation: The Julius Center is an organisation of the University Medical Center Utrecht which supports research. The Julius Center is not depended on the outcomes of this trial.

Risk classification
Negligible risk

Monitoring frequention
An independent monitor will make one prior to start visit, one site visit in the Princess Máxima Center each four months, and one close-out visit.

Monitoring plan
Study documents and agreements:

- Confirming that the research file is present and complete: Trial Master File and Investigator File.
- Confirming that the study staff is completely instructed on the study procedures, and that back-up agreements are made with other colleagues.

Patient inclusion rate, consent, compliance and Source Document Verification (SDV):

- Checking the inclusion rate and drop-out percentage.
- Checking the informed consent papers: sample of 10%
- Checking the in- and exclusion criteria: sample of first three subjects, afterwards 1-10%
- Checking the protocol compliance: sample of the first three subjects, afterwards 1-10%
- Source Document Verification (SDV): sample of 1-10%; will be performed for a predefined list list of variables which have a clear relationship to the safety and validity of the research (including the primary end-point).

Patient safety

- Verification of Serious Adverse Event (SAE) reporting: sample of 1-10% of the subjects.

Investigational product
- Verification of the patient instructions that are given.

Study procedures
- Verification if the study procedure instructions are accessible.

Laboratory and pharmacy
- Verification if the laboratory is GLP certified
- Verification if the pharmacy is GMP certified

Attention points
- Qualifications of the monitor
- Feedback and follow-up of the observations of the monitor
  - Term of monitor report availability
  - Actions regarding the points of improvement in the monitoring report within the Princes Máxima Center.
- Storage of study files
  - Use of an adequate Clinical Data Management System (CDMS).
  - Correct storage of raw data, corrected data, and back-ups.
  - Presence of an audit trail.

Monitoring reports and storage period
A monitoring report will be written of every monitoring visit. The head of the department of the researcher is responsible for archiving the reports for a minimum of 15 years after the end of the study. The monitoring report and other study documents are available for the Board of Directors of the Princess Máxima Center for pediatric oncology and for the employees assigned by the Board of Directors.

11.3 Amendments
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.4 Annual progress report
The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report
The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The results of this research will be disclosed unreservedly. All parties concerned must justify their actions in this regard. Patients and human subjects are entitled to public disclosure of the results of the trial on the basis of their participation in it (and the arguments that play a role therein).

Both positive and negative trial results will be disclosed. The results of research will be submitted for publication to open access peer-reviewed scientific journals. If the journals do not consider negative results for publication, the research will be disclosed through trial registers, websites or databases.

The basic principles of the Vancouver convention (Uniform requirements for manuscripts submitted to biomedical journals. JAMA 277:927-934,1997) and the editors' statements of a number of authoritative biomedical scientific journals (Davidoff F et al., Sponsorship, authorship and accountability, NEJM 345:825-826, 2001) will be followed.

The sponsor is entitled to examine the manuscript prior to publication and to make comments on it. The sponsor may delay publication for up to three months after analysing the research results.

Disputes will be dealt with by continuing the debate in the form of letters sent to the scientific journal.

None of the parties concerned has a right of veto. The parties concerned must attempt to resolve disputes by negotiation. Should one of the parties feel that it has been disadvantaged, or should any other problem relating to publication arise, the parties can contact the METC for mediation.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Chapter 12.1 is not applicable as the investigational medical device is registered and used within the registered indication.

12.2 Synthesis

Hypothetically, the TCHL will reduce the CLABSI rate compared to the HL. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a reduced mortality rate due to CLABSI compared to the HL. Additionally, patients will benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development. (12-20, 45-48, 50, 59, 62)

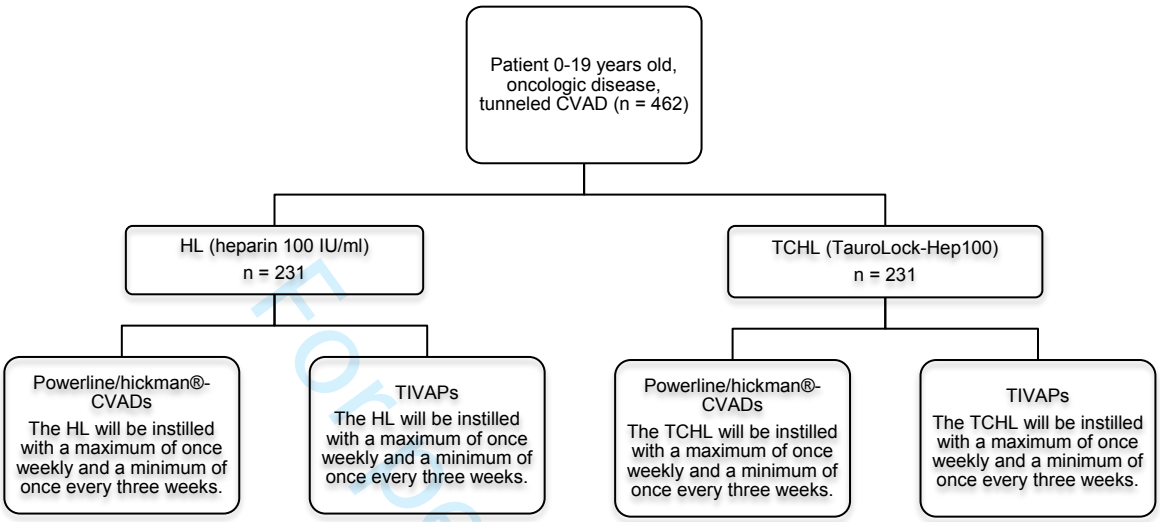
The expected side effects are temporarily, caused by a spill-over of citrate, described if the TCHL is instilled to fast, and if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dygeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are possible side-effects, but only in one patient an anaphylactic-like reaction was observed. (34) Liver-injury is associated with high-concentrations of systemic taurolidine in mouse-models. The TCHL contains low-dose taurolidine, which is not associated with liver-injury. (63) A more frequent dispense of thrombolytics has been associated with lock solutions containing taurolidine and citrate in haemodialysis patients. (18, 20-22, 25, 26) However, this was only observed without the addition of heparin. (45-50) For the prevention of the above stated possible side-effects the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), heparin is added to the solution for the prevention of the more frequent dispense of thrombolytics, and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed during the study. The locks will be instilled with a maximum of once weekly and a minimum of once every three weeks. After every study-lock instillation, the patients will be asked to answer a questionnaire about the experience of possible side effects.

In conclusion, we think the possible positive effects of the TCHL outweigh the remaining minimal and rare side effects of the TCHL. We hope to prove that the TCHL will reduce the CLABSI rate, CVAD-removal rate, dispense of antibiotics, days of hospital/intensive care unit admission, and mortality rate due to CLABSI.

13. APPENDICES

13.1 Appendix 1: Flow-chart lock solutions

In between the study locks, the patients will receive heparin 100 IU/ml locks.



Endpoints of the study, whatever endpoint will come first:

- First tunneled CLABSI
- Removal of the CVAD
- Second CVAD insertion (excl. stem cell apheresis CVADs)
- Death of the patient
- Study period of 90 days

13.2 Appendix 2: TauroLock-Hep100 Documents

ENGLISH **Instructions For Use** 43703GB/14/17

TauroLock™ HEP 100

Catalogue # TP-03

A. Description and Specifications

TauroLock™-HEP100 contains anticoagulants and antimicrobial substances. It is to be used with a port or a catheter-based vascular access device. It is to be instilled in the device lumens between treatments in order to make the internal flow passages resistant to clot formation and hostile to bacterial and fungal growth. The solution must be withdrawn prior to initiating the next treatment. Active ingredients in TauroLock™-HEP100 are (cyclo)-taurolidine, citrate (4%) and heparin (mucosa, 100 IU/mL). Other components include water for injection. The pH is adjusted with citrate and/or sodium hydroxide. The product is sterile filter processed and supplied as a clear, sterile, non-pyrogenic solution.

Note:

For complete details of catheter-based vascular access products, consult the manufacturer's instructions or clinician's manual.

B. Indications

TauroLock™-HEP100 is indicated for those patients who use a port or a silicone or polyurethane catheter-based device as vascular access. TauroLock™-HEP100 is intended to be used as a catheter lock solution. It is to be instilled into the device at the termination of a treatment and withdrawn prior to initiating subsequent treatments (see F4).

C. Contraindications

TauroLock™-HEP100 is contraindicated for patients with a known allergy to (cyclo)-taurolidine, citrate or heparin (mucosa) or when a patient is currently taking medication with known adverse interaction to citrate, heparin or (cyclo)-taurolidine. TauroLock™-HEP100 is also contraindicated for patients with heparin-induced thrombocytopenia or increased bleeding risk.

D. Cautions

1. As a consumable TauroLock™-HEP100 is for single use only. Reuse creates a potential contamination risk for the patient.
2. TauroLock™-HEP100 is not for systemic injection. TauroLock™-HEP100 must be used as a catheter lock solution as described in the access device's instruction for use. Failure to adhere to these instructions may result in inadvertent systemic injection of the solution. Once instilled into the catheter the solution must not be used again after aspiration.
3. The ampoule is for single dose only due to potential risk of contamination.
4. Some patient populations using TauroLock™-HEP100 antimicrobial lock solution may experience a higher frequency of blood clots in the catheter lumen. In the event that access device patency is compromised, follow institutional protocol for restoring flow.
5. The specific fill volume of the access device has to be strictly respected with infants and children less than two years of age due to citrate as an active ingredient.
6. In access devices which were blocked regularly with non-antimicrobial lock solutions (e.g. with heparin, low concentrated citrate or saline) prior to application of TauroLock™-HEP100, viable organisms and endotoxins may be released from the biofilm. The lock solution must be aspirated before the next treatment to prevent very rare anaphylactic reactions which are not attributable to the active ingredients.
7. The concentration of the antimicrobial compound is near to saturation. If not stored or transported according to the instructions under section H, precipitation can occur in the product. Do not use such a precipitated product.

E. Adverse Effects

To date, there are no known adverse effects in humans due to the active ingredient concentrations in TauroLock™-HEP100 when used as directed. There are no known risks associated with concomitant systemic antibiotic therapy or exposure to magnetic fields. TauroLock™-HEP100 may cause mild hypocalcaemic symptoms if instillation is not done slowly as directed.

F. Instillation of TauroLock™-HEP100

Follow the manufacturer's instructions that accompany the particular vascular access product utilized. Specific catheter lock volumes are associated with each device.

1. Flush the device with 10 mL of saline.
2. Withdraw TauroLock™-HEP100 from the container using an appropriate syringe.
3. Instill TauroLock™-HEP100 slowly (not more than 1 mL per second, infants and children less than two years of age not more than 1 mL per 5 seconds) into the access device in a quantity sufficient to fill the lumen completely. **Consult the manufacturer's instructions for the specific fill volume or specify fill volume during implantation. The volume has to be strictly respected.** TauroLock™-HEP100 will remain inside the access device until the next treatment (for a maximum of 30 days).
4. Prior to the next treatment, TauroLock™-HEP100 must be aspirated and discarded according to the institution's waste policy. Prior to initiation of the next treatment, TauroLock™-HEP100 must be withdrawn from the access device and discarded according to the institution's waste policy.
5. Flush the device with 10 mL of saline.

G. Pregnancy and Breastfeeding

No data are available for pregnant and breastfeeding women. For safety reasons TauroLock™-HEP100 should not be used during pregnancy and breastfeeding.

H. Storage and shipment

TauroLock™-HEP100 must be stored at a temperature of 15 to 30°C and must not be shipped at freezing temperature. Do not freeze.

I. Packaging configuration

The following packaging configurations are available for TauroLock™-HEP100: 10 x 3 mL TauroLock™-HEP100 ampoules.

State: 07. December 2015

TauroPharm GmbH · August-Bebel-Straße 51 · D-97297 Waldbüttelbrunn · Germany

Tel: +49 931 304 299 0 · Fax: +49 931 304 299 29

STERILE A Sterile, aseptic fill.

Read instruction for use.

Single use. The ampoule is a single dose.

Do not use when package is damaged.

CE 0123 CE acc. MDD 93/42/EEC, notified body: TÜV SÜD PRODUCT SERVICE GmbH.

kinderoncologie

TauroPharm GmbH
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D-97297 Waldbüttelbrunn
Germany

Tel + 49 (931) 304 299 0
Fax + 49 (931) 304 299 29

DECLARATION OF CONFORMITY

MANUFACTURER:	TauroPharm GmbH August-Bebel-Str. 51 D-97297 Waldbüttelbrunn, Germany
PRODUCT:	TauroLock™-HEP100 (3 ml ampoule)
CLASSIFICATION:	III
CONFORMITY ASSESSMENT ROUTE:	Annex II

We herewith declare that the above mentioned products meet the provisions of the Council Directive 93/42/EEC for medical devices. All supporting documentation is retained under the premise of the manufacturer.

STANDARDS APPLIED:	MDD 93/42 EEC
NOTIFIED BODY:	TÜV SÜD Product Service GmbH Ridlerstrasse 65 D-80339 Munich, Germany Reg. No. 0123
EC CERTIFICATE:	G1 17 05 51963 014 G7 17 06 51963 020
START OF CE-MARKING:	This declaration applies to all CE-marked devices manufactured from the date of issuance until it is either superseded by another declaration or withdrawn.
ISSUED BY:	This Declaration of Conformity is issued by TauroPharm GmbH, which is exclusively responsible for the declared compliance.
PLACE OF ISSUE:	TauroPharm GmbH, D-97297 Waldbüttelbrunn, Germany
SIGNATURE:	..... (Dr. Christian Weis, Managing Director)
DATE:	31. July 2017

TauroPharm GmbH
August-Bebel-Straße 51
97297 Waldbüttelbrunn
Tel. 0049 931 / 304299-0
GERMANY

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate

EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)

No. G7 17 06 51963 020

Manufacturer:

TauroPharm GmbH
August-Bebel-Str. 51
97297 Waldbüttelbrunn
GERMANY

Product:

Irrigation Solutions
Non antibiotic based antimicrobial catheter lock solution

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with MDD Annex II (4). The design of the devices conforms to the requirements of this Directive. For marketing of these devices an additional Annex II certificate is mandatory. See also notes overleaf.

Report no.: 713104720

Valid from: 2017-07-31
Valid until: 2022-07-30

Date, 2017-07-28

Stefan Preiß

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

Page 1 of 2

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate
EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)

No. G7 17 06 51963 020

Model(s):

Taurolock Solutions
- Taurolock Hep TP-02
- Taurolock Hep TP-03

Parameters:

Taurolock with Heparin 500:	TP-02 3ml, 5ml Ampoule, 10 ml Vial
Taurolock with Heparin 100:	TP-03 3ml, 5ml Ampoule, 10 ml Vial

Facility(ies):

TauroPharm GmbH
August-Bebel-Str. 51, 97297 Waldbüttelbrunn, GERMANY

Page 2 of 2

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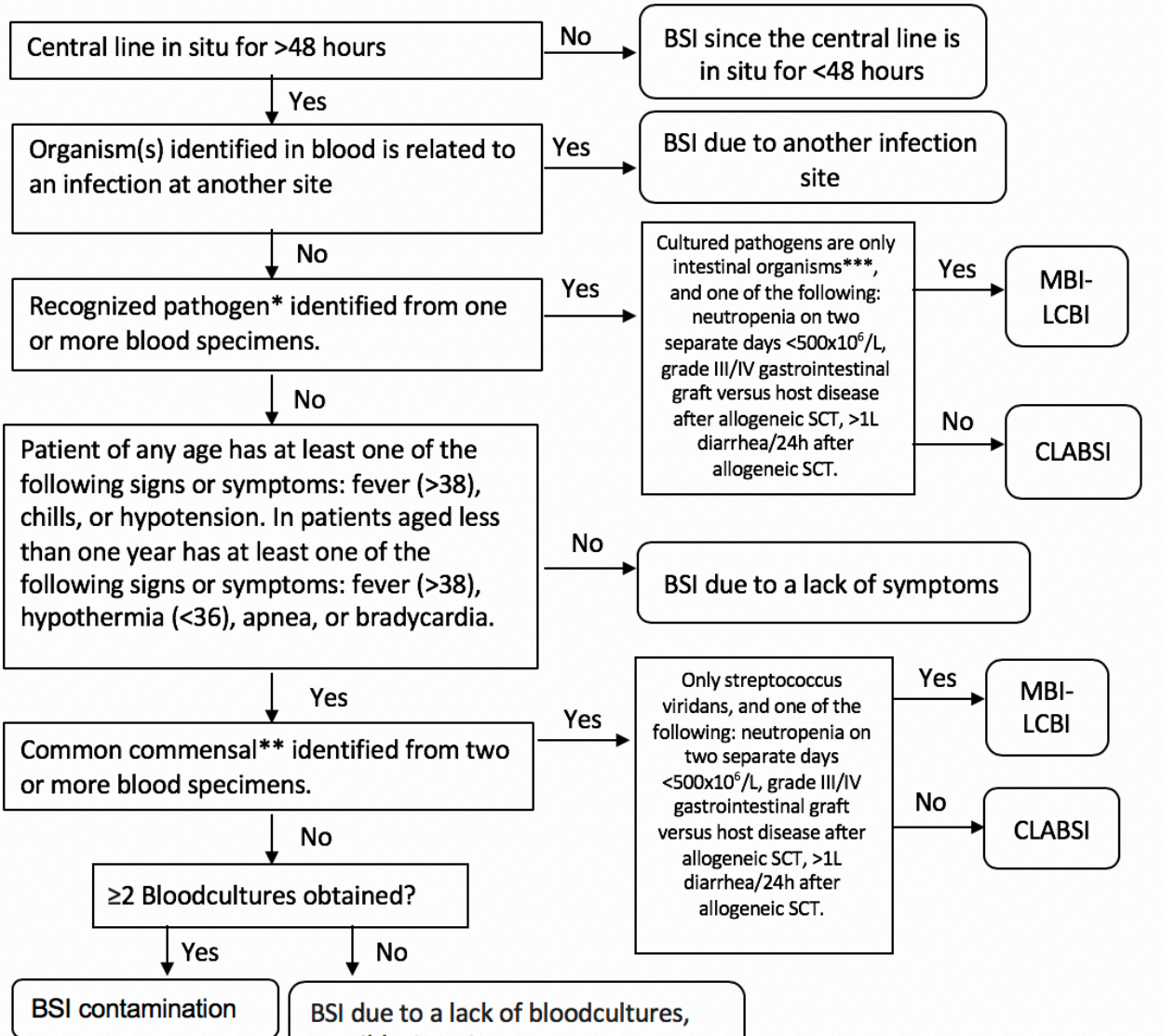
TÜV®

13.3 Appendix 3: Flow-chart suspicion of a CLABSI



CVAD = Central Venous Access Device, BSI = Bloodstream Infection, MBI-LCBI = Mucosal Barrier Injury – Laboratory Confirmed Bloodstream Infection, CLABSI = Central Line Associated Bloodstream Infection, SCT = Stem Cell Transplantation.

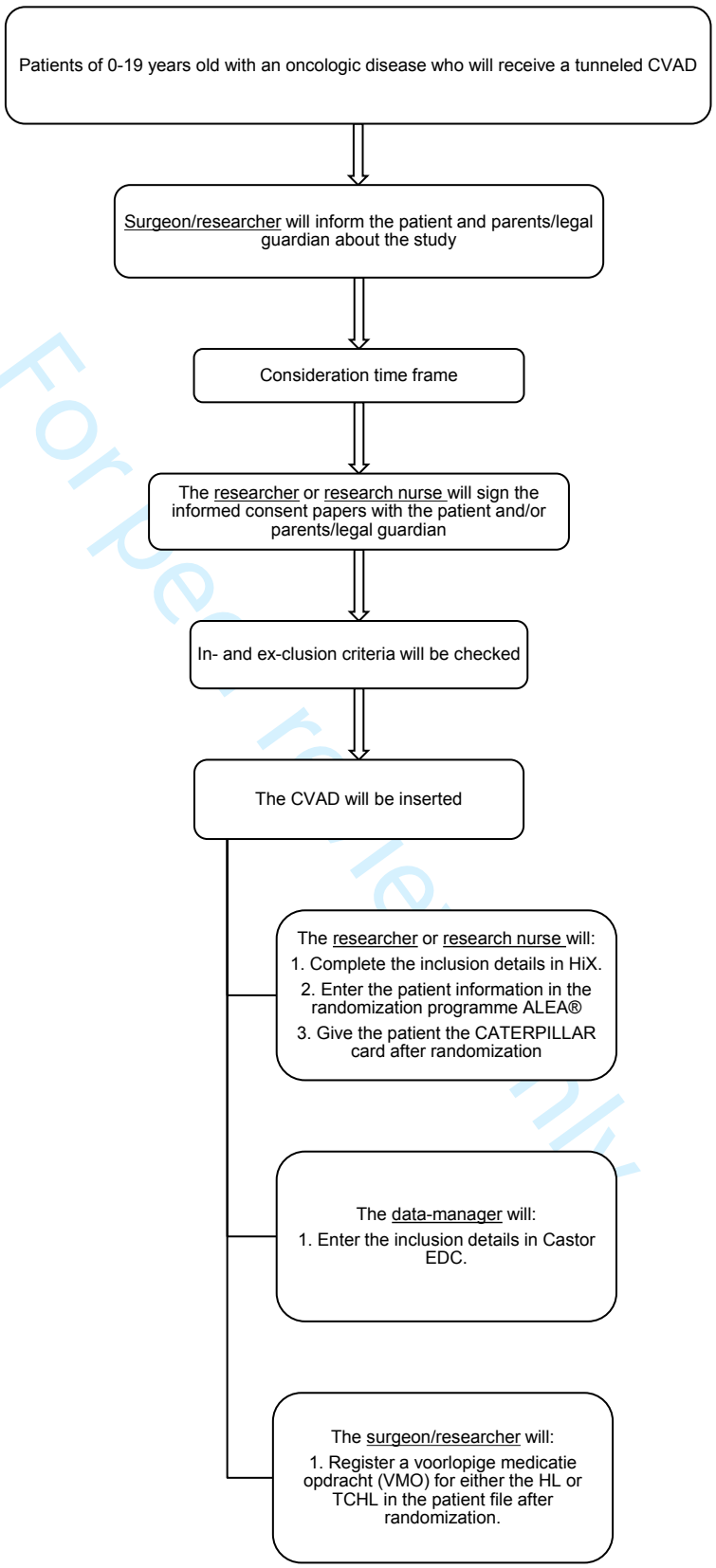
* Recognized pathogens are pathogens that are not included on the NHSN common commensal list (e.g. *S. Aureus*): https://nhsn.cdc.gov/nhsntraining/courses/2016/C18/page3299.html. The following micro-organisms are not included in the common commensal list but are not recognized pathogens: *Campylobacter, C. difficile, Enterpopathogenic E. coli, Listeria spp., Salmonella spp.*, en *Yersinia spp.*

** Common commensals are micro-organisms that are included on the NHSN common commensal list (e.g. *Coagulase-negative staphylococci, Viridians group streptococci, Bacillus spp., Diphtheroids, Aerococcus spp. Micrococcus spp.*): https://nhsn.cdc.gov/nhsntraining/courses/2016/C18/page3299.html.

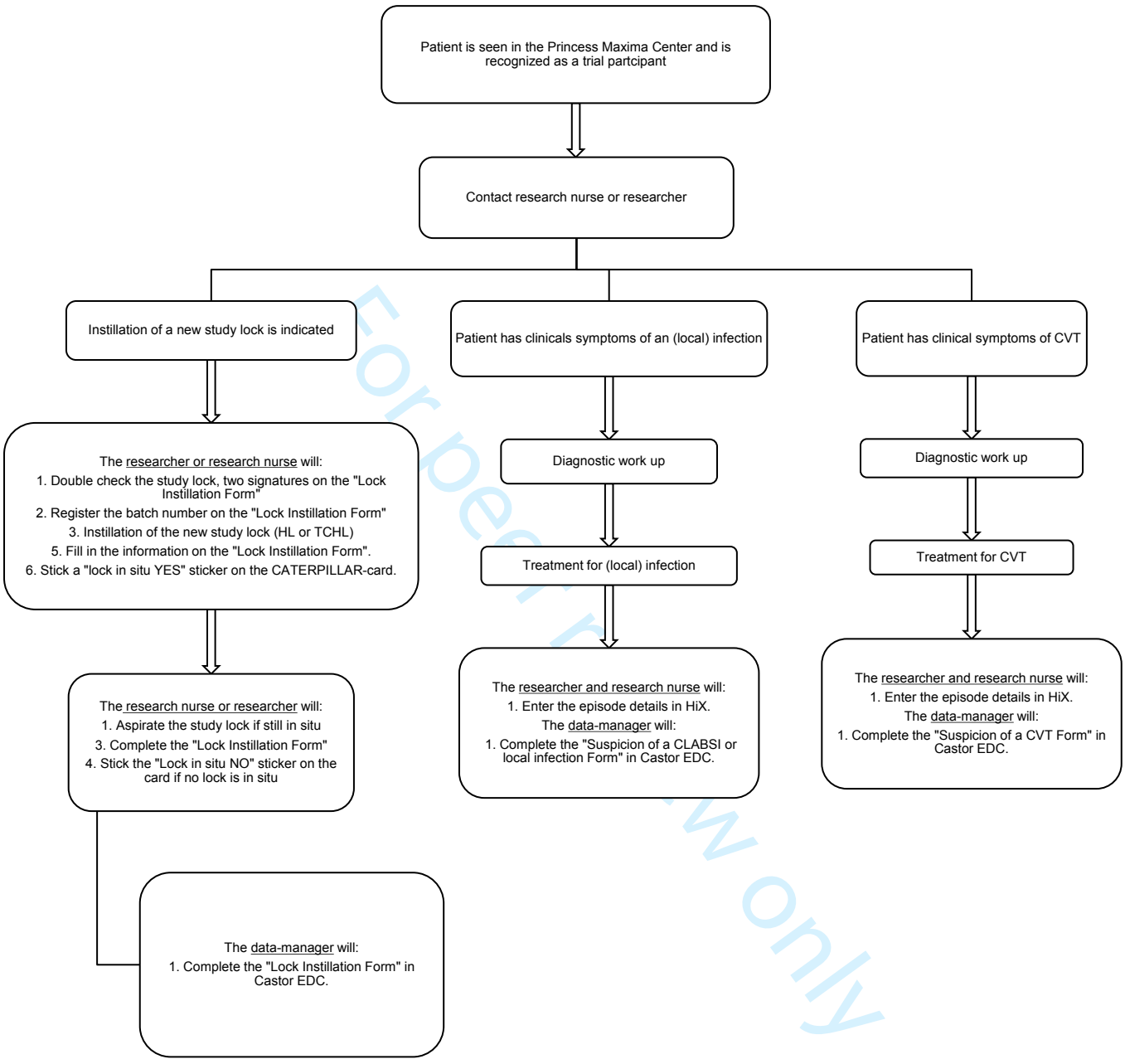
*** Micro-organisms registered as MBI Organisms on the NHSN common commensal list (e.g. *Escherichia coli, Enterobacteriaceae, and Enterococci)*: https://nhsn.cdc.gov/nhsntraining/courses/2016/C18/page3299.html.

**** Viridans streptococci: e.g. *S. mitis, S. oralis, S. salivarius, S. thermophilus, S. vestibularis, S. anginosus, S. sanguinis, S. parasanguinis, S. gordonii, S. mutans, en S. sobrinus.*

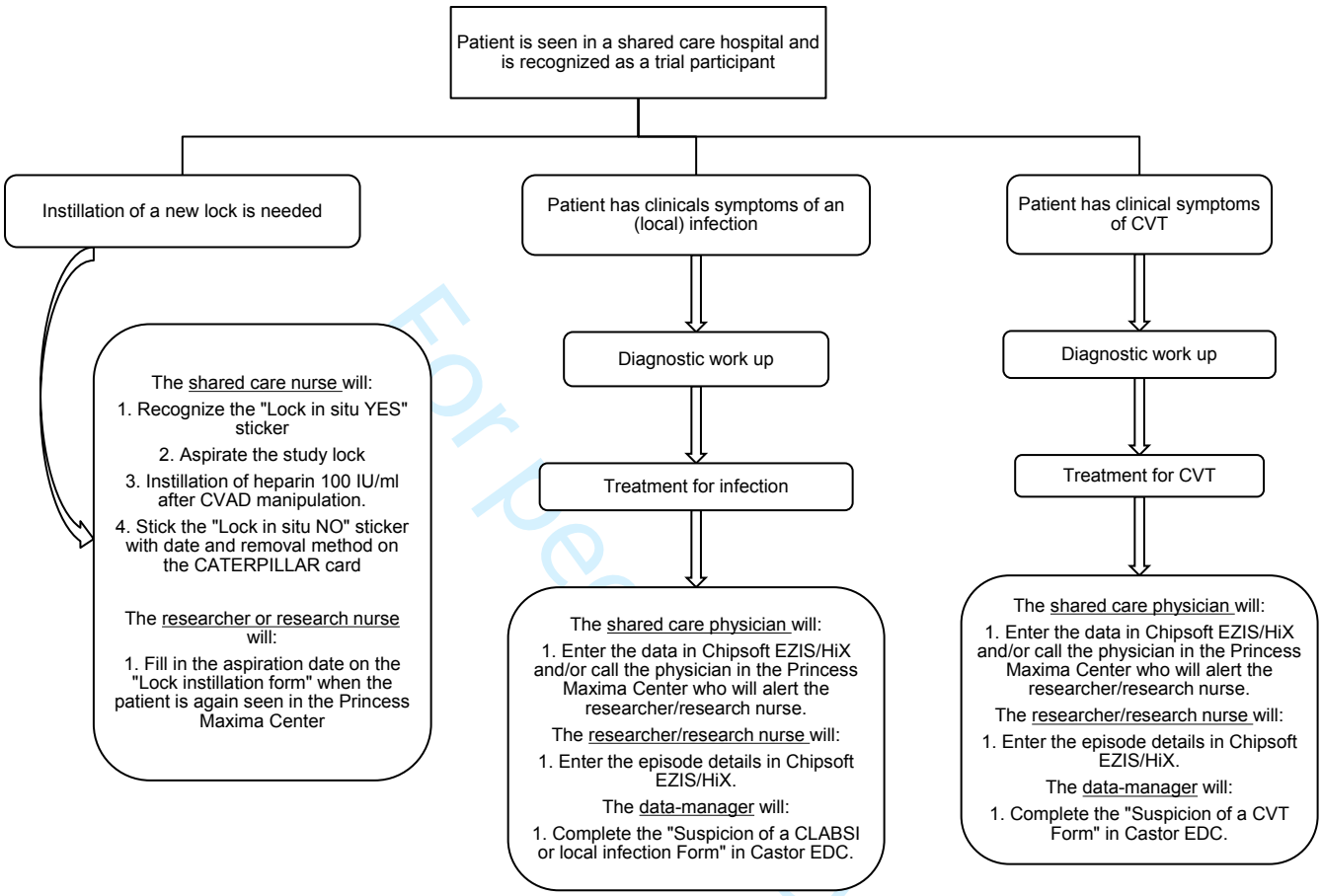
13.4 Appendix 4: Flow-chart study procedure



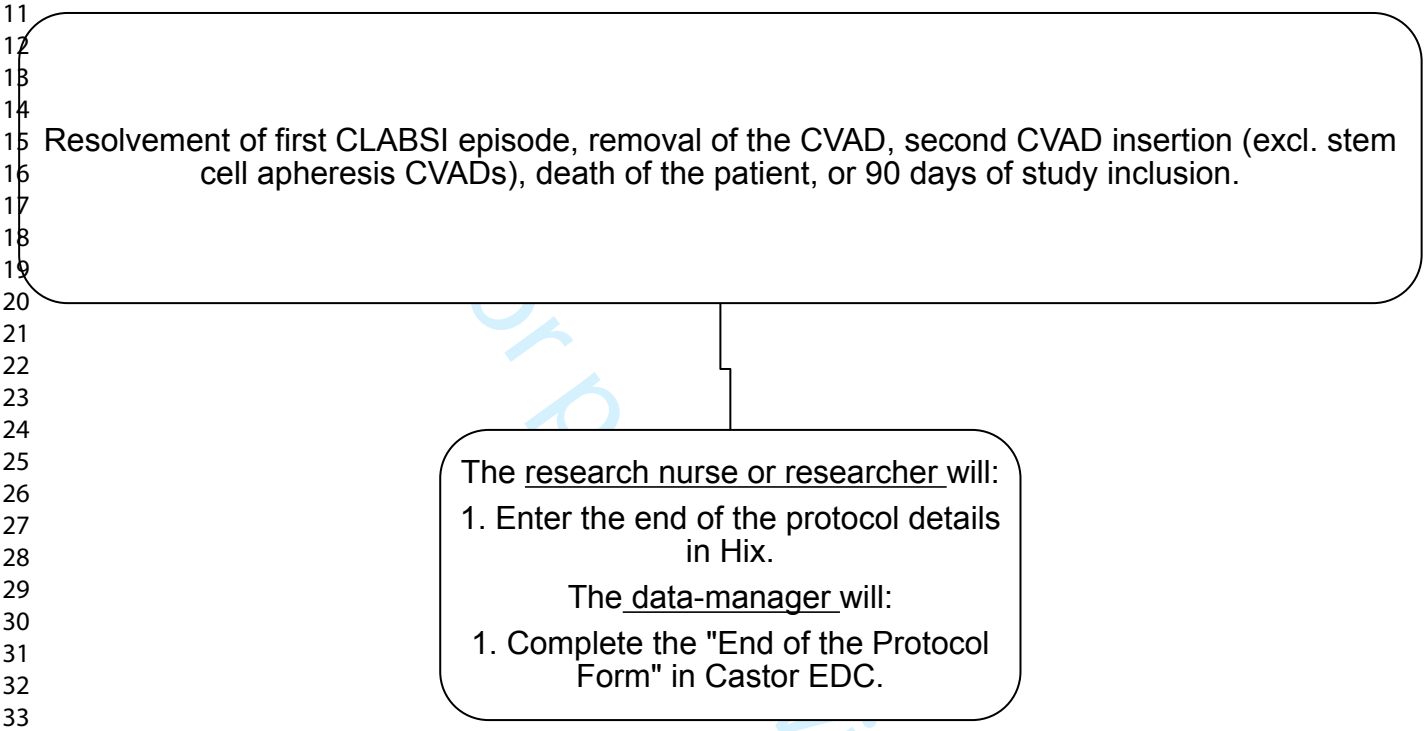
13.5 Appendix 5: Flow-chart study procedure Princess Máxima Center



13.6 Appendix 6: Flow-chart study procedure Shared Care Hospitals



13.7 Appendix 7: End of the Protocol flow-chart



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The CATERPILLAR-study protocol: an assessor-blinded randomized controlled trial comparing taurolidine-citrate-heparin to heparin-only lock solutions for the prevention of central-line associated bloodstream infections in paediatric oncology patients

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The CATERPILLAR-study protocol: an assessor-blinded randomized controlled trial comparing taurolidine-citrate-heparin to heparin-only lock solutions for the prevention of central-line associated bloodstream infections in paediatric oncology patients

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Abstract

Introduction The efficacy of taurolidine containing lock solutions for the prevention of central line associated bloodstream infections (CLABSI) in paediatric oncology patients is still unknown. If the taurolidine-citrate-heparin lock appears to decrease the incidence of CLABSIs, we hope to increase the quality of life of children with cancer by subsequently reducing the central venous access device (CVAD)-removal rates, dispense of antibiotics, hospital admissions and incidence of severe sepsis resulting in intensive care unit admission.

Methods and analysis This assessor-blinded randomized controlled trial including 462 patients was designed to compare the taurolidine-citrate-heparin lock to the heparin-only lock for the prevention of CLABSIs in paediatric oncology patients. Patients receiving their first CVAD at the Princess Máxima Centre for Paediatric Oncology, Utrecht, the Netherlands, are eligible for inclusion. The primary outcome of this study is the incidence of first CLABSIs from CVAD insertion until the end of the study, maximum follow-up of 90 days. An intention-to-treat and a per-protocol analysis will be performed. An interim analysis will be performed after the inclusion of 50% of the patients. The results of the interim analysis and overall conduct of the trial will be discussed by a data safety monitoring board (DSMB).

Ethics and dissemination The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research (number 20/370). Written informed consent for participation in this trial and publication of the trial data is obtained from all patients and/or their parents/guardians. The results of this trial will be published in a peer-reviewed journal and the data will be made available upon reasonable request after publication of the main results manuscript.

Trial registration numbers: Netherlands Trial Register (WHO International Clinical Trials Registry Platform), NTR6688**;** ClinicalTrials.gov, NCT05740150.

Keywords: paediatric oncology, preventive medicine, infection control

Strengths and limitations of this study

- Designed as an assessor-blinded randomized controlled trial.
- Stratification for central venous access device type and diagnosis will be performed.

- Large paediatric oncology patient cohort (N=462).
- Inclusion and randomization should take place as soon as possible after insertion of the central venous access device, which is not always possible due to clinical and psychological circumstances.
- Locks are instilled once a week during the study since the maximum number of taurolidine-citrate-heparin locks that can be given during a certain time period is currently unknown; more frequent instillations of the lock might result in a higher efficacy.

Introduction

Central venous access devices (CVAD) are fundamental in paediatric oncology since they provide long-term venous access. The most commonly used CVADs in paediatric oncology patients are the totally implantable venous access ports (TIVAP) and external tunnelled CVADs. In this patient group, the incidence of central line-associated bloodstream infections (CLABSI) is high. [1] CLABSI incidence rates of 0.1-2.3 per 1,000 CVAD-days have previously been reported, mostly depending on the patient population, CVAD-type and infection definitions used. [2] In our hospital, the Princess Máxima Centre for paediatric oncology, a CLABSI incidence rate of 1.51 per 1,000 CVAD-days has been reported; at least one CLABSI was observed in 30% of the children receiving a CVAD. [3] CLABSI episodes often result in hospital admission, postponement of anticancer treatment, early CVAD removal (15% of all CVADs inserted) and can lead to severe sepsis requiring intensive care unit admission (5% of all patients receiving a CVAD). [3] CLABSIs therefore have a great impact on the quality of life of children diagnosed with cancer and result in high healthcare costs. [1, 4]

Taurolidine-citrate(-heparin) lock solutions (TCHL) are suggested as a promising and safe method for the prevention of CLABSIs. [5, 6] Taurolidine and citrate have anticoagulant, antimicrobial and anti-biofilm properties. No antimicrobial resistance to taurolidine has been reported, which makes taurolidine a more attractable option compared to other antimicrobial lock solutions. [7] Taurolidine causes a chemical reaction with the bacterial cell wall, endotoxins and exotoxins, resulting in irreversible damage to the bacteria, inhibition of bacterial pathogenicity and inhibition of surface adhesion of bacteria. [5, 7-11] The current standard of care in the Netherlands for paediatric oncology patients, is to lock CVADs with a heparin-only lock (HL) solution for the prevention of malfunctions. The HL however, does not have antimicrobial activity and its use is barely supported by literature. [5] Our meta-analysis including all

randomized controlled trials comparing the efficacy of taurolidine containing lock solutions to heparin-, saline- and citrate-only locks in haemodialysis, total parenteral nutrition, and oncology patients showed a pooled incidence rate ratio (IRR) of 0.30 (CI95% 0.19-0.46) in favour of the taurolidine containing lock solutions. Adverse events were all rare and mild. [6] However, these studies were associated with a serious risk of bias and indirectness of evidence. [6] More specifically, in paediatric oncology patients, only two open-labelled randomized controlled trials (N≤112) and four non-randomized controlled trials, have been performed. [12-17] To summarize, these studies did show promising results of the TCHL, but this was not enough evidence to implement the TCHL in paediatric oncology patients. [12-17]

Therefore, this assessor-blinded randomized controlled trial including a large patient cohort was designed to compare the TCHL to the HL for the prevention of CLABSIs in paediatric oncology patients. If the TCHL appears to be safe and decreases the incidence of CLABSI, we hope to increase the quality of life for children with cancer by subsequently reducing the CVAD-removal rate, dispense of antibiotics, days of hospital and incidence of severe sepsis resulting in intensive care unit admission.

Methods and analysis

Design and setting

The CATERPILLAR-study is an investigator-initiated, assessor-blinded, randomized controlled superiority parallel trial comparing the incidence of CLABSI between the TCHL to the HL in paediatric oncology patients with a CVAD (i.e. TIVAP and external tunnelled CVAD). The information in this manuscript aligns with the latest protocol, version number 4.0, 19-07-2022. In total 462 patients with a CVAD are expected to be recruited from the Princess Máxima Centre for paediatric oncology, Utrecht, the Netherlands over 29 months. The Princess Máxima Centre is the centralized hospital for paediatric oncology in the Netherlands (i.e. all patients diagnosed with a paediatric oncologic disease are treated here). Patients will be randomized (1:1) into the HL or TCHL study arm. Patients will be followed up from CVAD insertion until the first CLABSI episode (primary outcome), CVAD-removal, second CVAD insertion or death with a maximum study period of 90 days, whichever comes first. The

maximum study period of 90 days was chosen since a great deal of the CLABSI episodes occurs within the first 90 days after insertion (median of 60 days after insertion). [1-3]

In the first months after diagnosis, patients will receive their oncologic treatment at the Princess Máxima Centre. After one-two months, a minority of the patients will also be treated in one of the 15 shared care hospitals (see supplementary file 1) close to their homes. These patients will return at least every three weeks to the Princess Máxima Centre. The randomized locks (HL or TCHL) will be given when the patient visits the Princess Máxima Centre. The locks are instilled after each treatment cycle, with a maximum of once weekly. When the CVAD is used in between these moments (i.e. more frequent than once a week, in the home care setting, or at one of the shared care hospitals), for both groups, the CVAD will be temporarily locked with a non-study related HL. This was done since the maximum lock frequency for this patient group is unknown and the administration of study locks in all shared care hospitals and the home care setting would logistically be to difficult and the costs would be to high. The effect of this method is deemed minimal since the vast majority of patients visits the Princess Máxima Centre once a week and will then receive their randomized lock as soon as possible. The total number of lock days per patient will be taken into account/corrected for during the analyses as described below. Shared care data of the included patients will be shared with the Princess Máxima Centre.

Subjects can leave the study at any time if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons, if the patient is admitted in a hospital outside the Netherlands or non-participating shared care centre for more than three weeks, or if the patient experienced a hypersensitivity reaction after instillation of the TCHL solution.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule for enrolment, interventions and assessments is described in Fig 1, the SPIRIT checklist was completed (see supplementary file 2). This trial is registered at ClinicalTrials.gov (registration under review). The items from the World Health Organization Trial Registration Data Set can be found in Table 1. All research staff working on this study is BROK®-certified (https://nfu-ebrok.nl/), (see supplementary file 3 for the roles and responsibilities of the study team).

Table 1. Items from the World Health Organization Trial Registration Data Set

Data category	***Information***
Primary registry and trial identifying number	ClinicalTrials.gov, NCT05740150
Date of registration in primary registry	07-09-2017
Secondary identifying numbers	NTR6688 Netherlands Trial Register 12617 Dutch Cancer Society
Source(s) of monetary or material support	Monetary: Dutch Cancer Society (KWF) Material: Cablon Medical and TauroPharm
Primary sponsor	Princess Máxima Centre for Paediatric Oncology
Secondary sponsor(s)	Not applicable
Contact for public queries	Ceder Hildegard van den Bosch C.H.vandenBosch-4@prinsesmaximacentrum.nl +31625395632
Contact for scientific queries	Ceder Hildegard van den Bosch C.H.vandenBosch-4@prinsesmaximacentrum.nl +31625395632
Public title	Central line-associated bloodstream infection prevention using TauroLock-Hep100 in paediatric oncology patients.
Scientific title	The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunnelled central line-associated bloodstream infections in paediatric oncology patients, a randomized controlled, mono-centre trial.
Countries of recruitment	The Netherlands
Health condition(s) or problem(s) studied	Central line associated bloodstream infections
Intervention(s)	Experimental: TauroLock-Hep100 (taurolidine 1.35%, citrate 4%, heparin 100 IU/mL) Active Comparator: Heparin lock (heparin 100 IU/mL)
Key inclusion and exclusion criteria	Inclusion criteria: • Age between 0 - <19 years • Radiological, cytological or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies) • Tunnelled external central venous access device or totally implantable venous access port to be inserted at the Princess Máxima Centre for Paediatric Oncology • Planned central venous access device insertion of >90 days • Written consent signed according to local law and regulations • Parents/guardians or patient are willing and able to comply with the trial procedure Exclusion criteria: • A previous central venous access device removed < 12 months ago. • Expected treatment for a majority of the follow-up time in a different hospital than the

	Princess Maxima Centre for paediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Centre at least once every 3 weeks. • Primary immunological disorder • Contra indications: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia. • Documented bacteraemia in the period from 24h before catheter insertion until inclusion • Insertion of the central venous access device at the same site as a previously confirmed central venous thrombosis • Pregnant, not willing to use adequate contraceptives, or breast-feeding
Study type	Interventional Allocation: Randomized in 2 arms 1:1 Masking: Assessor blinded Primary purpose: Prevention
Date of first enrolment	27-10-2020
Target sample size	462
Recruitment status	Recruiting
Primary outcome(s)	Incidence of central line associated bloodstream infections
Key secondary outcomes	• Time to first central line associated bloodstream infection • Central line associated bloodstream infection incidence per 1,000 central venous access device-days • Incidence of symptomatic central venous thrombosis • Incidence of bacteraemia • Incidence of local infections • Dispense of thrombolysis/systemic antibiotic treatment due to central line associated bloodstream infections/ central venous thrombosis • Incidence of and reasons for central venous access device-removal • Cultured microorganisms causing central line associated bloodstream infections • Days of hospital admission due to central line associated bloodstream infections/ central venous thrombosis • Safety in terms of known side effects, severe adverse events, intensive care unit admission, and mortality rate due to central line associated bloodstream infections/central venous thrombosis

Patient and public involvement

The patient association Vereniging Kinderkanker Nederland (VKN; https://www.kinderkankernederland.nl/) was involved in the design of this study. The VKN reviewed the protocol and patient information forms, and they

assessed the burden for patients to participate in the research. Currently yearly meetings are held between the researcher and VKN to discuss the progress of the trial. The advice given by the VKN is strongly taken into account by the researchers. Furthermore, the VKN will be involved in the plan for the dissemination of the trial results after completion of the trial.

Participants

All consecutive paediatric oncology patients (hematologic, solid and neurologic malignancies), treated at the Princess Máxima Centre for Paediatric Oncology, ranging from 0-19 years old, receiving a CVAD (tunnelled external CVAD or totally implantable venous access port (TIVAP)) for the first time or if their previous CVAD has been removed >12 months ago, will be asked to participate in this study by a research physician or nurse. Further inclusion criteria are: a radiological, cytological or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies), planned need for central vascular access of >90 days, written consent signed according to local law and regulations, parents/guardians or patient are willing and able to comply with the trial procedure. Exclusion criteria are: a previous CVAD removed < 12 months ago, expected treatment for a majority of the follow-up time in a different hospital than the Princess Maxima Centre for paediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Centre at least once every 3 weeks, primary immunological disorder, contra indications such as: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia, documented bacteraemia in the period from 24h before catheter insertion until inclusion, insertion of the CVAD at the same site as a previously confirmed central venous thrombosis (CVT), pregnant, not willing to use adequate contraceptives, or breast-feeding patients.

Informed consent procedure

Informed consent is obtained within one week after CVAD insertion, however, if this is not possible due to clinical circumstances, patients may be included within four weeks after CVAD insertion. Patients, parents and/or legal guardian are given verbal information and information in writing by the research physician or nurse. A dated and signed informed consent form will be obtained from each patient, parent and/or legal guardian depending on the age of the patients (see supplementary file 4). The research physician or nurse will then also sign the consent form. A

copy will be given to the patient and/or parents. The inclusion and exclusion criteria are thereafter checked by the researcher.

Randomization and blinding

Patients will be randomized by the research physician or nurse with a method of minimization into the HL or TCHL study arm (1:1) with the use of an online randomization service by internet called ALEA® (https://www.aleaclinical.eu/). Stratification will be done according to two factors: CVAD type (TIVAP or external tunnelled CVAD) and diagnosis (hematologic or solid, lymphoma, and neurologic malignancies). The expert panel, evaluating all possible CLABSI episodes, will be blinded for the allocated treatment. The allocated treatment will not be revealed to the expert panel or described in the parts of the electronic patient files which the expert panel will use to evaluate the possible CLABSI episodes. The patients, parents and/or legal guardians, and the rest of the research and clinical teams, will not be blinded. Complete blinding was logistically too difficult to execute and much more expensive since the design of the HL and TCHL ampoules is not similar.

Intervention

Patients will receive a lock solution of 0.8-1.5mL, depending on the CVAD-type as described in Table 2, containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/mL (TauroLock-Hep100™, Cablon Medical, Leusden, the Netherlands and TauroPharm GmbH, Waldbüttelbrunn, Germany) or heparin 100 IU/mL at the Princess Máxima Centre after each treatment cycle with a maximum of once a week. The locks will remain in situ until the CVAD is used again. Before the CVAD is used again, the previously instilled study locks (TCHL and HL) will be removed from all lumina. If a blood culture is obtained while the lock is still in situ, at least 2mL of blood is aspirated and discarded for the prevention of false negative blood culture results. A dedicated research nurse will train the hospital staff, patients and parents/guardians and will monitoring adherence to the intervention study protocol as described above. All co interventions that are needed during the trial can be used as in usual clinical practice.

Table 2. Lock volumes

CVAD	Type	Diameter (Fr)	Maximal catheter volume (ml)	Lock volume (ml)
TIVAP	Babyport®	4.5	0.80	1.0

	Low-profile®	6.5	1.04	1.5
	Standard®	6.5	1.28	1.5
External tunnelled CVAD	Single lumen	6.6	0.74	1.0
	Double lumen	6.0 or 7.0	0.70/0.70 or 0.90/0.80	1.0/1.0
	Triple lumen	6.0	0.75/0.62/0.62	1.0/0.8/0.8

CVAD; Central Venous Access Device, TIVAP; Totally Implantable Venous Access Port.

Outcomes

The primary outcome of this study is the incidence of first CLABSIs from CVAD insertion until the end of follow-up. A blinded expert panel of one paediatric infectiologist and two medical microbiologists will judge each positive blood culture episode during the study period as a CLABSI or non-CLABSI bacteraemia following the Centres for Disease Control and Prevention CLABSI criteria. The CLABSI criteria were chosen since they are the most applicable criteria for paediatric oncology patients, since no peripheral blood cultures are obtained in this patient group, which are needed for other existing diagnostic criteria. [18] Judgement of the episodes will be performed based on the patient files and by contacting the treating physician if necessary, the randomization group will not be described in the parts of the patient files that the experts will access for their assessment. All non-unanimous judgements will be discussed between the experts until they all agree. If the experts still disagree, the final judgement is based on the judgement of the majority. Additionally, all experts will be asked to answer if their result following the CLABSI criteria aligns with their clinical judgement.

The secondary outcomes of this study are (measured from CVAD insertion until the end of follow-up): the time to first CLABSI, CLABSI incidence per 1,000 CVAD days, the incidence of symptomatic central venous thromboses (CVT) (i.e. if the patient has (1) peripheral veins that have a non-compressible segment, or (2) there is an echogenic intra-luminal thrombus or an absence of flow in the central venous system (76)), bacteraemia episodes (i.e. every non-CLABSI related positive blood culture), local infections (i.e. positive exit-site culture, erythema, purulent drainage or tenderness within 2 cm of the CVAD track and exit-site), CVAD-removal (incl. reasons why CVAD was removed), cultured micro-organisms causing CLABSI, days of hospital admission due to CLABSIs/CVTs, the dispense of thrombolysis and systemic antibiotic treatment due to CLABSIs/CVTs, and safety of the locks in terms of (serious) adverse events, and intensive care unit admission or mortality due to CLABSIs/CVTs.

Data collection and management

Data is entered pseudonymized from paper case report forms and electronic patient files in Castor EDC (Castor EDC v2021.1, CATERPILLAR-study v.6.21, password-protected access) by trained local data managers in the Princess Máxima Centre. In Castor EDC range checks for data values are incorporated. All study information will be stored in locked cabinets in areas with limited access. Records with personal identifiers, will be stored separately from records identified by a code number. Study information of the patients will not be released outside of the study without written permission of the patients. All data (incl. shared care hospital data) should be entered within 90 days after the end of study date of each patient. Regular quality checks are performed by a central data manager and independent monitor three times a year. The database will be locked after all data has been cleaned and all necessary changes have been made. The principal investigator and research physician will have access to the final trial dataset after completion of the trial. The data will be stored for at least 15 years. After the main results manuscript is published, the data will become available upon reasonable request.

The following data will be collected: patient characteristics (age, gender, diagnosis, treatment protocol, administration of prophylactic systemic antibiotics (i.e. trimethoprim/sulfamethoxazole, ciprofloxacin, or anti-mycotics)), CVAD characteristics (surgery date, type, introduction method, lumen amount/diameter, access vein and side, complications during procedure, removal date and reason), lock characteristics (date instillation and removal, type, method of removal, (serious) adverse events during lock instillation and removal (following common terminology criteria for adverse events (CTCAE) version 5.0, November 27, 2017)), treatment for possible malfunction (i.e. impossibility to aspirate or flush the CVAD)), suspicion of CLABSI characteristics (start date episode, symptoms, neutropenia (incl. duration and lowest neutrophil count during episode: very severe <100, severe 500-1,000, moderate 500-1,000, mild 1,000-1,500x10^6/L)), blood culture results, treatment method of CLABSI, hospital/intensive care unit admission days, death, judgement of episode by expert panel (i.e. CLABSI, mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI), or bacteraemia due to other reasons), reasons for non-CLABSI related bacteraemia (i.e. not enough blood cultures obtained, contamination/colonization, CVAD in situ for <48 hours, infection at a different site)), suspicion of local infection characteristics (start date episode, symptoms, culture results, treatment, hospital/intensive care unit admission days, death), suspicion of a CVT characteristics (start date episode, symptoms, radiological imaging, location, treatment,

hospital/intensive care unit admission days, death) and end of the study reasons. Data of patients that prematurely drop-out of the study, will be collected until the day they dropped out.

Safety considerations

(Serious) adverse events with a possible or definite relationship to the locks are registered during the study (CTCAE version 5.0, November 27, 2017). Registration of all (serious) adverse events would lead to the registration of too many adverse events in these oncologic patient groups. Adverse events of special interest, due to their known relationship to the HL or TCHL are: oral dysesthesias, neck/chest wall pain, dysgeusia, nausea, vomiting, allergic reactions, and heparin induced thrombocytopenia. Patients will be followed-up for the occurrence of (serious) adverse events until 30 days after the last study lock was given. The Princess Máxima Centre will report serious adverse events within the appropriate time-frame (i.e. within 7 days of first knowledge in case of life threatening situations or death, and within 15 days in all other cases) to the accredited ethics committee that approved the protocol. The sponsor has a liability and subject insurance.

Data safety monitoring board (DSMB)

A DSMB is established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. Three DSMB meetings will be held: one start of the study session, a second closed session after the inclusion of 50% of the patients where the interim analysis will be presented, and a third session at the end of the study. The results of the interim analysis will only be presented to the principal and coordinating investigators, trial statistician, and DSMB members. The DSMB will not be blinded and consists of a paediatric surgeon, infectious disease specialist and medical statistician. All three members are independent from the sponsor and have no competing interests. The DSMB will give an advice to the principal investigator, who will make the final decision to terminate or continue the trial (see supplementary file 5 for the DSMB charter).

Statistical methods

Sample size calculation

Assuming a CLABSI rate of 12.8%, an estimated total number of 412 patients is needed to detect a difference between group proportion of 7.8%, with a two-sided α of 0.05 and power of 80% (two-sided Z-Test with unpooled variance). [19-24] The CLABSI rate of 12.8% was based on the data from the CVAD complication database of the Princess Máxima Centre, partially published by van den Bosch et al. 2019, using the same inclusion and exclusion criteria and follow-up period as described for this study. [3] The estimated reduction of 12.8% to 5.0% was based on previously performed randomized controlled trials (RCT), of which the vast majority showed a reduction of at least more than 60%; IRR of 0.30 (CI95%0.19-0.46). For paediatric oncology specifically, two RCTs have been performed which showed reductions of 74% and 77%. [6] For each patient that prematurely drops-out of the study an extra patient will be included, we estimated that an extra 50 patients would be needed to account for potential drop-outs. The drop-out inflated total sample size is therefore calculated as 462 patients, 231 per group.

Interim analysis

An interim analysis will be performed after the inclusion of 231 patients. A stopping rule was defined for a one sided test at an α level of 0.025 for the null hypothesis: experimental incidence ≥ control incidence. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the experimental. The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on α- and β-spending functions. As α-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 2.35$ and as β-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 3.2$.

Statistical analysis

The primary data analyses will be performed with the intention-to-treat (ITT) principle (i.e. inclusion of all patients that were randomized). Additionally, a per-protocol (PP) analysis will be performed excluding patients who were not included within one week after CVAD insertion, patients who never received the intervention and patients who missed three or more of the minimal amount (once every three weeks) of locks during the follow-up period. Categorical data will be presented as contingency tables (frequencies and percentages). All patients will be analysed in the intervention group they were initially randomized in. For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. Differences between treatment groups with

respect to baseline characteristics will be analysed by using a Chi-square (or Fisher Exact in the presence of small numbers), and two-tailed t-test for categorical or continuous variables respectively. In case of violation of the normality assumption a non-parametric test such as the Wilcoxon rank test will be applied.

For the primary outcome, the percentages and incidence rates (IR) of first CLABSIs per 1,000 CVAD-days will be reported for both study groups and compared by computing an IRR. The exact confidence limits for the IRRs will be based on the polynomial algorithm for person time data [25, 26]. The nominal alpha level for the primary outcome in the final analysis will be equal to 0.045 due to the interim analysis [19-24].

The cumulative incidence of CLABSI from CVAD insertion will be estimated by using a competing risk model [27] with CVAD removal due to non-CLABSI related reasons or death as competing events. To assess the difference between the cumulative incidence for the intervention (TCHL) and control (HL) group, the Gray's test will be used. [28]

To estimate the effect of risk factors on the occurrence of CLABSI, a Cox specific proportional hazard regression model from CVAD insertion will be estimated. Well known time fixed risk factors for a CLABSI to be incorporated into the model are diagnosis (haematological disease versus other diagnoses), CVAD type (TIVAP versus tunnelled external CVADs). Furthermore, total parenteral nutrition (TPN) administration will be used in the model as time-dependent covariate). [27]

A landmark analysis at 28 days after CVAD insertion will be performed. The same risk factors as discussed above will be incorporated in the Cox specific hazard regression model with additional covariate number of lock days. The landmark point of 28 days was chosen based on clinical reasons, the first lock should have been given within the first four weeks after CVAD insertion. [29]

For the secondary outcomes, the percentages and IRs per 1,000 CVAD-days will be reported and compared by computing IRRs. Furthermore, the above described analyses will be repeated for subgroups based on diagnosis and CVAD type.

All analyses concerning the competing risk model will be performed in RStudio version 1.3.1093 (United States of America) environment by using the cmprisk library. IBM SPSS Statistics for Windows version 26.0 (United States of America) will be used to perform all other statistical analyses.

Study timeline

Inclusion of the study began on the 27th of October 2020. We expect that the planned number of patients can be recruited in 29 months from the defined source population. The planned study timeline is described in Table 3.

Table 3. Planned study schedule

Months after start inclusion	What?	Description
0	Start inclusion	Planned start of the study
14.5	Interim database lock and interim analysis	After the inclusion of 50% of the patients
29	Stop inclusion	After the inclusion of 462 patients
32	Stop follow-up	After a period of 3 months after the inclusion of the last patient
32 - 36	Database lock, statistical analysis, writing the clinical study reports, and drafting of the manuscript based on the clinical study reports.	From the stop of follow-up until manuscript submission.
36	Manuscript submission	Four months after the study has stopped.

Ethics and dissemination

The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research registered under number 20/370 (https://www.metcutrecht.nl/); a copy of the trial protocol submitted to the ethics committee can be in supplementary file 6. Modifications to the protocol that impact the conduct of the study will require a formal amendment, which will be agreed upon by the medical ethics committee. Written informed consent is obtained from all patients and/or their parents/guardians for participation in the trial and for the publication of their data. The results of this trial will be published in an open access, peer-reviewed journal, presented at international congresses and subsequently the data (stored for at least 15 years) will be made available upon reasonable request after

publication of the main results manuscript. The VKN will be involved in the plan for the dissemination of the trial results to the participants and the public after completion of the trial. All eventually listed authors of the publication of the main results manuscript will have made a substantial, direct, intellectual contribution to the work.

Contributors

C.B., Y.L., A.S., J.B., F.F., M.F., C.V., M.vdW.,and M.W. designed methodology of the study. M.F. and C.B. wrote the statistical plan. C.B. , A.S, M.F, and M.vdW. wrote the original draft of the manuscript. C.B., Y.L., A.S., J.B., F.F., M.F., C.V., M.vdW., and M.W. reviewed and edited the manuscript. A.S., M.F., M.vdW., and M.W. supervised the preparation of this manuscript.

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Data availability statement

The data will be stored for at least 15 years. After the main results manuscript is published, the data will become available upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Figure legend

Figure 1. Schedule of enrolment, interventions and assessments

*Number of visits depending on the treatment schedule and unexpected admissions. Aim is to insert the lock after each visit with a maximum of once weekly.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINTS	Day 0-28 after CVAD surgery (preferably within 1 week)	Day 0-28 after CVAD surgery	Day 0-90 after CVAD surgery Visit 1-13*	Day 0-90 after CVAD surgery Daily patient file screening	Day 90 after CVAD insertion, CLABSI, CVAD removal, second CVAD insertion or death of patient, whichever comes first.
ENROLLMENT					
Eligibility screen	X				
Informed consent	X				
Review inclusion/ exclusion criteria	X				
Allocation		X			
INTERVENTIONS					
HL			X		
TCHL			X		
ASSESSMENTS					
Patient/CVAD characteristics	X	X			X
Lock characteristics			X		
Suspicion of CLABSI characteristics				X	X
Suspicion of local infection characteristics				X	X
Suspicion of CVT characteristics				X	X
(Serious) adverse event monitoring			X	X	X

Fig 1. SPIRIT schedule of enrolment, interventions and assessments / *Number of visits depending on the treatment schedule and unexpected admissions. Aim is to insert the lock after each visit with a maximum of once weekly.

279x215mm (200 x 200 DPI)

Supplementary File 1 List of shared care centers where data will be collected

Medisch Centrum Leeuwarden
Henri Dunantweg 2
8934 AD Leeuwarden
The Netherlands

Universitair Medisch Centrum Groningen
Hanzeplein 1
9713 GZ Groningen
The Netherlands

Isala Zwolle
Dr. Van Heesweg 2
8025 AB Zwolle
The Netherlands

Deventer Ziekenhuis
Nico Bolkesteinlaan 75
7416 SE Deventer
The Netherlands

Medisch Spectrum Twente
Koningplein 1
7512 KZ Enschede
The Netherlands

Ziekenhuis Gelderse Vallei
Willy Brandtlaan 10
6716 RP Ede
The Netherlands

Flevo ziekenhuis
Hospitaalweg 1
1315 RA Almere
The Netherlands

Amsterdam UMC
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands

Dijklander Ziekenhuis
Maelsonstraat 3
1624 NP Hoorn
The Netherlands

Reinier de Graaf Gasthuis
Reinier de Graafweg 5
2625 AD Delft
The Netherlands

Erasmus Medisch Centrum
Dr. Molewaterplein 60
3015 GJ Rotterdam
The Netherlands

Jeroen Bosch Ziekenhuis
Henri Dunantstraat 1
5223 GZ 's-Hertogenbosch
The Netherlands

Admiraal de Ruyter Ziekenhuis
's-Gravenpolderseweg 114
4462 RA Goes
The Netherlands

Catharina Ziekenhuis
Michelangelolaan 2
5623 EJ Eindhoven
The Netherlands

VieCuri
Tegelseweg 210
5912 BL Venlo
The Netherlands

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	
	2b	All items from the World Health Organization Trial Registration Data Set	-	
Protocol version	3	Date and version identifier	-	
Funding	4	Sources and types of financial, material, and other support	-	
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	
	5b	Name and contact information for the trial sponsor	-	
	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	-	
	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)	-	
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	-	
	6b	Explanation for choice of comparators	-	
Objectives	7	Specific objectives or hypotheses	-	

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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)	-	
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	-	
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)	-	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	
	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)	-	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	
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	-	

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	
	12.5		If a composite outcome is used, define all individual components of the composite outcome	
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)	-	
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	-	
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	
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	-	

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	
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	-	
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	
	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	-	

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	
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	-	
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	
	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)	-	
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	-	
	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	-	
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	-	

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	
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)	-	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	
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	-	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	
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	-	
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	-	
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	-	
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	
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	-	

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper 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 and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.

Supplementary File 3 Organisational structure and responsibilities

Principal Investigator and Research Physician
Design and conduct of the CATERPILLAR-study
Preparation of protocol and revisions
Preparation of the case report forms
Organising steering committee meetings
Organising data safety monitoring board meetings
Publication of study reports
Data verification
Screens and recruits study subjects
Obtains Informed Consent
Confirms eligibility
Randomisation
Responsible for trial master file
Makes study related medical decisions
Assesses (serious) adverse device events
Reports (serious) adverse device events

Steering committee (members described on title page of protocol)
Agreement of final protocol
All lead investigators will be steering committee members. Recruitment of patients and liasing with principle investigator
Reviewing progress of study and if necessary agreeing changes to the protocol to facilitate the smooth running of the study.

Trial manager
Study planning
Organisation of steering committee meetings
Provide annual ethics committee report
Advice for lead investigators
Assistance with international review, board/independent ethics committee applications

Data Managers
Entry/correction of data in case report forms in Castor
Resolves data queries
Maintains essential documents
Data verification

Research Nurses
Prepares medical device administrations
Obtains Informed Consent
Stores medical device

Informatiebrief voor deelname aan medisch wetenschappelijk onderzoek met toestemmingsformulier voor ouders/voogd

CATERPILLAR-studie
Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Inleiding

Beste ouders – voogd,

Wij vragen u om uw kind mee te laten doen aan een medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. Om mee te kunnen doen is wel uw schriftelijke toestemming nodig.

Voordat u beslist of u uw kind mee wilt laten doen aan dit onderzoek, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de arts of onderzoeker om uitleg als u vragen heeft. U kunt ook de onafhankelijk arts, die aan het eind van deze brief genoemd wordt, om aanvullende informatie vragen. U kunt er ook over praten met uw partner, vrienden of familie.

Verdere informatie over meedoen aan onderzoek staat op de online pagina ‘Medisch-wetenschappelijk onderzoek’. Deze pagina kunt u vinden via www.rijksoverheid.nl/mensenonderzoek. Er is ook een folder van de VKN (Vereniging Kinderkanker Nederland) over klinisch onderzoek. Deze folder zit in de dagboekagenda die u aan het begin van de behandeling krijgt.

Heeft u of uw kind na het lezen van de informatie nog vragen? Dan kunt u terecht bij de behandelend arts of de researchverpleegkundige, wiens contactgegevens aan het eind van deze informatiebrief genoemd worden. U en uw kind (boven 12 jaar) beslissen samen of uw kind meedoet of niet.

1. Algemene informatie

Dit onderzoek is opgezet door het Prinses Máxima Centrum voor Kinderoncologie en wordt alleen uitgevoerd in Nederland. De KWF Kankerbestrijding vergoedt de kosten van dit onderzoek. Voor dit onderzoek zijn in totaal 462 patiënten nodig. De medisch-ethische toetsingscommissie METC Utrecht heeft dit onderzoek goedgekeurd. Deze commissie heet vanaf 22-1-2022 de medisch-ethische toetsingscommissie NedMec. Algemene informatie over de toetsing van onderzoek vindt u op de online pagina ‘Medisch-wetenschappelijk onderzoek’.

2. Doel van het onderzoek

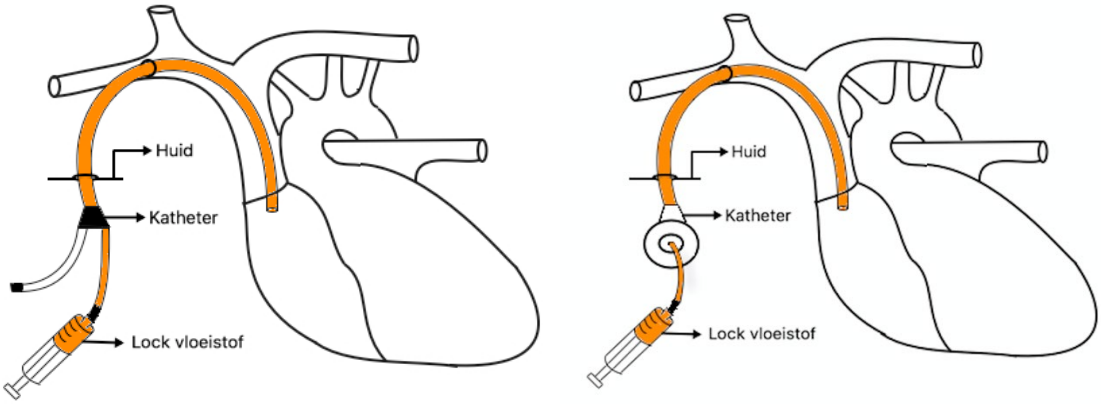
Het doel van dit onderzoek is uitzoeken hoe veilig en effectief het nieuwe medische hulpmiddel TauroLock-Hep100 is in het voorkomen van centrale lijn infecties en de vorming van bloedstolsels in de centrale lijn en port-a-cath (PAC). In dit onderzoek vergelijken we de werking en veiligheid van TauroLock-Hep100 met de werking en veiligheid van de heparine lock. Een lock is een vloeistof waarmee een centrale lijn of PAC gevuld wordt nadat deze gebruikt is. Dit wordt afsluiten van de centrale lijn of PAC genoemd. Heparine wordt op dit moment in Nederland standaard gebruikt voor het afsluiten van de centrale lijn of PAC.

3. Achtergrond van het onderzoek

Voor de behandeling van de ziekte van uw kind moet regelmatig chemotherapie worden toegediend en bloed worden afgenomen. Hiervoor wordt door de chirurg een zogenaamde ‘centrale lijn’ of ‘PAC’ geplaatst. Via deze lijn kan tijdens de behandeling eenvoudig en op een veilige manier chemotherapie worden toegediend en bloed worden afgenomen.

Bij minimaal 1 op de 4 kinderen die een centrale lijn of PAC krijgen, ontstaat tijdens de behandeling een infectie door de centrale lijn of PAC. Gelukkig is zo'n infectie meestal goed te behandelen met het toedienen van antibiotica in het ziekenhuis. Soms moet de centrale lijn of PAC vanwege deze infectie echter vroegtijdig verwijderd worden door middel van een operatie.

Nadat de centrale lijn of PAC gebruikt is voor het toedienen van medicatie of het afnemen van bloed, moet deze worden afgesloten. Dit doen we door de lijn te vullen met een vloeistof. De vloeistof waarmee we de lijn of PAC afsluiten noemen we een 'lock' (zie **afbeelding 1**). Op dit moment wordt de vloeistof 'Heparine' standaard gebruikt als lock. Heparine is een middel dat de vorming van bloedstolsels in de centrale lijn of PAC voorkomt, maar het werkt helaas niet tegen infecties. Daarom zoeken we naar een vloeistof die ook helpt bij het voorkomen van infecties.



Afbeelding 1: Centraal veneuze lijn (links) en PAC (rechts) met lock vloeistof (bijv. Heparine of TauroLock-Hep100)

TauroLock-Hep100 is een andere, nieuwe vloeistof die gebruikt kan worden als lock. TauroLock-Hep 100 voorkomt mogelijk de vorming van bloedstolsels in de centrale lijn of PAC en voorkomt mogelijk ook infecties. Deze vloeistof is al onderzocht bij volwassenen met kanker en bij kinderen met andere aandoeningen én een centrale lijn of PAC. Ook is de TauroLock-Hep100 in kleinere onderzoeken gebruikt bij kinderen met kanker met een centrale lijn of PAC. In deze onderzoeken is TauroLock-Hep100 een veilige en effectieve lock gebleken. In dit onderzoek willen we de TauroLock-Hep100 vergelijken met heparine en aantonen dat deze lock beter is dan de heparine lock. De lock die in dit onderzoek het beste resultaat geeft, kan bij toekomstige patiënten gebruikt worden bij het afsluiten van de centrale lijn of PAC.

4. Wat meedoen inhoudt

Als uw kind meedoet aan het onderzoek, duurt dat in totaal maximaal 90 dagen. Na deze 90 dagen zal de centrale lijn of PAC afgesloten worden met de standaard heparine vloeistof.

Geschiktheidsonderzoek

Eerst bepalen we of uw kind kan meedoen aan het onderzoek. De arts zal hiervoor vragen naar de medische geschiedenis van uw kind.

Onderzoek

De kinderen die meedoen aan dit onderzoek, worden verdeeld in twee gelijke groepen. De helft van de groep krijgt gedurende 90 dagen de standaard heparine lock, de andere groep krijgt de TauroLock-Hep100 lock. Een loting (randomisatie) bepaalt welke lock uw kind krijgt. De behandelend arts en onderzoekers hebben geen invloed op de uitslag van de loting. Algemene informatie over randomisatie vindt u op de online pagina 'Medisch-wetenschappelijk onderzoek'.

Tijdens de onderzoeksperiode wordt de lock maximaal 1x per week en minimaal 1x per 3 weken ingebracht in de centrale lijn of PAC. Dat gebeurt in het Prinses Máxima Centrum. Het inbrengen van de lock wordt zoveel als mogelijk gecombineerd met opnames en afspraken die al gepland worden voor de behandeling van uw kind. De lock blijft in het slangetje van de centrale lijn of PAC aanwezig totdat de centrale lijn of PAC weer gebruikt wordt. Als de centrale lijn of PAC opnieuw gebruikt wordt, zal de vloeistof eerst uit de lijn opgetrokken worden. De vloeistof wordt dus zo min mogelijk het lichaam van uw kind ingespoten.

Als de centrale lijn of PAC tussendoor elders of ongepland wordt gebruikt, bijvoorbeeld tijdens een bezoek aan een ander ziekenhuis in Nederland, zal de lock worden opgetrokken zoals hierboven beschreven en zal de lijn of PAC worden afgesloten met een in Nederland gebruikelijke standaard heparine lock. Als de onderzoeksperiode van 90 dagen is afgelopen zal de centrale lijn of PAC van alle patiënten verzorgd worden met de standaard heparine lock.

Bezoeken en metingen

Er wordt gedurende 90 dagen maximaal 1x per week en minimaal 1x per 3 weken een nieuwe lock ingebracht in het Prinses Máxima Centrum. De lock wordt ingebracht tijdens al geplande afspraken en opnames. Dit zal maximaal 70 minuten in totaal in beslag nemen. Het inbrengen van een TauroLockHep-100 lock verloopt hetzelfde als het inbrengen van een heparine lock. Hoe vaak de lock wordt ingebracht is afhankelijk van hoe vaak de centrale lijn of PAC wordt gebruikt en wanneer u met uw kind in het Prinses Máxima Centrum bent.

Het inbrengen van een lock duurt ongeveer 5 minuten. Na het inbrengen van de lock zullen we uw kind een aantal korte vragen stellen over bijwerkingen. Dit kunnen de bijwerkingen zijn:

- een kortdurende vreemde smaak,
- tintelingen in de mond,
- een drukkend gevoel in nek of borst
- of misselijk gevoel.

We willen graag de bijwerkingen van beide locks goed registreren.

Wat is er meer of anders dan de gebruikelijke zorg?

Als uw kind meedoet aan het onderzoek, dan krijgt uw kind gedurende 90 dagen mogelijk een TauroLockHep-100 lock in plaats van de gebruikelijke heparine lock.

Bij aanvang van de studie ontvangen u en uw kind een CATERPILLAR-deelnemerskaart en Ja/Nee-stickers (zie **afbeelding 2**). We vragen u de deelnemerskaart en stickers van uw kind bij u te houden en te laten zien bij elk ziekenhuisbezoek in het Prinses Máxima Centrum of een ander ziekenhuis. Zo wordt overal herkend dat uw kind deelneemt aan dit onderzoek.

Het inbrengen van de lock zal altijd gecombineerd worden met al geplande afspraken en opnames van uw kind.

Afbeelding 2: CATERPILLAR-deelnemerskaart.

5. Wat wordt er van u en uw kind verwacht

Om het onderzoek goed te laten verlopen, en voor de veiligheid van uw kind, is het belangrijk dat u zich aan de volgende afspraken houdt.

De afspraken dat u en/of uw kind:

- De deelnemerskaart en Ja/Nee-stickers van uw kind bij u draagt en laat zien bij elk ziekenhuisbezoek. Hierop staat dat u meedoet aan dit onderzoek. Er staat ook op wie u in geval van nood moet waarschuwen.
- De afspraken voor het inbrengen van de lock nakomt.
- Vragen beantwoord over het ontstaan van eventuele symptomen na het inbrengen van de lock.

Het is belangrijk dat u contact opneemt met de onderzoeker of research verpleegkundige:

- Als uw kind in een ziekenhuis wordt opgenomen of behandeld.
- Als uw kind plotseling gezondheidsklachten krijgt.
- Als uw kind niet meer wilt meedoen aan het onderzoek.
- Als uw contactgegevens wijzigen.

Anticonceptie en zwangerschap

Is uw dochter in de vruchtbare leeftijd? Dan moet ze voorkomen dat ze tijdens het onderzoek zwanger wordt en mag zij ook niet deelnemen indien zij borstvoeding geeft. De behandelend arts zal met u en uw dochter de meest geschikte voorbehoedmiddelen bespreken. Wordt uw dochter toch zwanger in de onderzoeksperiode? Neem direct contact op met de behandelend arts. Het kan zijn dat dit onderzoek gevolgen heeft voor het ongeboren kind.

Is uw zoon in de leeftijd waarop de mogelijkheid bestaat om een kind te verwekken? Dan dient uw zoon voorbehoedmiddelen te gebruiken om zwangerschap te voorkomen. Men weet namelijk niet zeker of het geneesmiddel nadelige invloed heeft op het sperma. Wordt de partner van uw zoon toch zwanger in de onderzoeksperiode? Neem direct contact op met de behandelend arts. Het kan zijn dat dit onderzoek gevolgen heeft voor het ongeboren kind.

6. Mogelijke bijwerkingen, complicaties en eventuele nadelige effecten

TauroLock-Hep100 kan mogelijk lichte ongemakken geven. Deze ongemakken komen niet vaak voor en zijn niet ernstig gebleken. Uw kind kan de volgende lichte ongemakken ervaren direct na het inbrengen van de TauroLock-Hep100:

- Kortdurende veranderde smaak
- Kortdurende tintelingen in de mond
- Kortdurend drukkend gevoel in de nek of borst
- Kortdurende misselijkheid of overgeven
- Allergische reacties op het middel

TauroLock-Hep100 kan ook nadelige effecten hebben die nog onbekend zijn.

De standaard heparine lock wordt al heel veel gebruikt. Hiervan zijn geen bijwerkingen bekend.

7. Mogelijke voor- en nadelen

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit dat uw kind mee mag doen aan het onderzoek.

Voordelen:

- Als uw kind meedoet aan dit onderzoek en na de loting de TauroLock-Hep 100 lock krijgt, dan kan de TauroLock-Hep100 tijdens de onderzoeksperiode centrale lijn infecties mogelijk voorkomen. Dit is echter nog niet aangetoond en de reden dat we dit onderzoek uitvoeren.

- De deelname van uw kind aan dit onderzoek draagt bij aan meer kennis over het voorkomen van centrale lijn infecties en kan de behandeling van toekomstige patiënten verbeteren.

Nadelen:

- Als uw kind na de loting de TauroLock-Hep100 lock krijgt, dan kan uw kind de al genoemde bijwerkingen ervaren bij het inbrengen van de locks.

8. Verzet van uw kind

Het kan zijn dat uw kind zich tijdens het onderzoek verzet (niet meewerkt). De onderzoeker moet het onderzoek dan direct stoppen. Het is moeilijk om precies te omschrijven wat verzet is. Voor de start van het onderzoek wordt met u overlegd wat als verzet wordt gezien.

Er is in het Prinses Máxima Centrum een team van gespecialiseerde medewerkers (zoals een arts, psycholoog, gespecialiseerde verpleegkundige) beschikbaar om u en uw kind tijdens het onderzoek zo goed mogelijk te begeleiden. Het behandelteam ziet nauwlettend toe op de belasting die deelname aan een onderzoeksprotocol voor uw kind met zich meebrengt. We werken daarom ook zoveel mogelijk volgens landelijke afspraken zoals die door de Nederlandse Vereniging voor Kindergeneeskunde (NVK) zijn vastgelegd ter bescherming van minderjarige onderzoeksdeelnemers. Voor meer informatie hierover verwijzen we u naar de website www.ccmo.nl onder ‘wet en regelgeving’, ‘Gedragscodes’, ‘gedragscodes bij verzet’.

9. Als u niet wilt dat uw kind meedoet of als u wilt dat uw kind stopt met het onderzoek

U beslist zelf of uw kind meedoet aan het onderzoek. Deelname is vrijwillig. Als u niet wilt dat uw kind meedoet, wordt uw kind op de gebruikelijke manier behandeld. De standaard behandeling is de heparine lock.

Als uw kind meedoet, kunt u zich altijd bedenken en uw kind alsnog laten stoppen, ook tijdens het onderzoek. De centrale lijn of PAC zal vanaf dat moment afgesloten worden met de standaard heparine lock. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de behandelend arts. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek.

Als er nieuwe informatie over het onderzoek is die belangrijk voor u en uw kind is, laat de arts dit aan u weten. U wordt dan gevraagd of uw kind mee blijft doen.

10. Einde van het onderzoek

Deelname van uw kind aan het onderzoek stopt als:

- De onderzoeksperiode van 90 dagen voorbij is.
- Uw kind een infectie aan de centrale lijn of PAC krijgt.
- De centrale lijn of PAC om een medische reden wordt verwijderd.
- Je een extra centrale lijn krijgt.
- Uw kind een allergische reactie krijgt op het middel.
- Uw kind zelf kiest om te stoppen.
- De onderzoeker het beter voor uw kind vindt om te stoppen.
- Het Prinses Máxima Centrum, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle gegevens kan de onderzoeker u als u dat wilt informeren over de belangrijkste uitkomsten van het onderzoek. Dit gebeurt ongeveer een half jaar na het einde van het gehele onderzoek.

11. Gebruik en bewaren van de gegevens

Voor dit onderzoek worden de persoonsgegevens van uw kind verzameld, gebruikt en bewaard. Het gaat om gegevens zoals naam, adres, geboortedatum en om gegevens over de gezondheid van uw kind. Het verzamelen,

gebruiken en bewaren van de gegevens van uw kind is nodig om de vragen die in dit onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren. Wij vragen voor het gebruik van de gegevens van uw kind uw toestemming. Als u dat niet wilt, kan uw kind niet deelnemen aan dit onderzoek.

Vertrouwelijkheid van de gegevens van uw kind
Om de privacy van uw kind te beschermen, worden de gegevens van uw kind voorzien van een code. De naam en andere gegevens die uw kind direct kunnen identificeren worden apart bewaard. Alleen met de sleutel van de code zijn gegevens tot uw kind te herleiden. De sleutel van de code blijft veilig opgeborgen in de lokale onderzoeksinstelling. Ook in rapporten en publicaties over het onderzoek zijn de gegevens niet tot uw kind te herleiden

Toegang tot de gegevens van uw kind voor controle
Sommige personen en instanties kunnen op de onderzoekslocatie toegang krijgen tot al de gegevens van uw kind. Ook in de gegevens zonder code. Dit is nodig om te kunnen controleren of het onderzoek goed en betrouwbaar is uitgevoerd. Personen en instanties die ter controle toegang krijgen tot de gegevens van uw kind zijn de:

- Veiligheidscommissie die het onderzoek in de gaten houdt.
- Een monitor die door de opdrachtgever is ingehuurd.
- Nationale en internationale toezichthoudende autoriteiten, bijv. de Inspectie Gezondheidszorg en Jeugd.
- De medewerkers van het onderzoeksteam.

Zij zullen de gegevens van uw kind geheim houden. U wordt gevraagd voor deze inzage toestemming te geven.

Bewaartermijn gegevens van uw kind
De gegevens van uw kind moeten 15 jaar worden bewaard op de onderzoekslocatie (het ziekenhuis).

Bewaren en gebruik van gegevens van uw kind voor ander onderzoek
De gegevens van uw kind kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander wetenschappelijk onderzoek op het gebied van de aandoening van uw kind en/of van de verdere ontwikkeling van het product/ de behandelmethode. Daarvoor zullen de gegevens van uw kind minimaal 15 jaar worden bewaard. U kunt op het toestemmingsformulier aangeven of u hier wel of niet mee instemt. Indien u hier niet mee instemt, kan uw kind gewoon deelnemen aan het huidige onderzoek.

Intrekken toestemming
U kunt de toestemming voor gebruik van de persoonsgegevens van uw kind altijd weer intrekken. Dit geldt voor dit onderzoek en ook voor het bewaren en het gebruik van gegevens voor het toekomstig onderzoek. De onderzoeksgegevens over uw kind die zijn verzameld tot het moment dat u de toestemming intrekt worden nog wel gebruikt in het onderzoek.

Meer informatie over de rechten bij verwerking van gegevens van uw kind
Voor algemene informatie over uw rechten bij verwerking van de persoonsgegevens van uw kind kunt u de website van de Autoriteit Persoonsgegevens raadplegen op: https://autoriteitpersoonsgegevens.nl/nl

Bij vragen of klachten over de verwerking van de persoonsgegevens van uw kind kunt u contact opnemen met de Functionaris voor de Gegevensbescherming van het Prinses Máxima Centrum: fg@prinsesmaximacentrum.nl

Registratie van het onderzoek
Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-wetenschappelijke onderzoeken namelijk https://www.trialregister.nl. Daarin zijn geen gegevens opgenomen die naar uw kind herleidbaar zijn. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt dit onderzoek onder 'CATERPILLAR'.

12. Verzekering
Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt schade door het onderzoek. Niet alle schade is gedekt. In **bijlage A** vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

13. Informeren van de huisarts en/of behandelend specialist
Wij informeren de huisarts en andere betrokken medisch specialisten over de deelname van uw kind aan het onderzoek. Dit is voor de veiligheid van uw kind. Als u dit niet goed vindt, kan uw kind niet meedoen aan dit onderzoek.

14. Vergoeding voor meedoen
Deelname van uw kind aan het onderzoek, de locks kosten u niets extra. U krijgt geen vergoeding voor de deelname van uw kind aan het onderzoek.

15. Heeft u vragen?
Als u tijdens het onderzoek of de behandeling vragen of klachten heeft, kunt u altijd terecht bij de behandelend arts van uw kind. Bij vragen of opmerkingen kunt u ook contact opnemen met:

- Drs. Ceder van den Bosch, arts-onderzoeker, bereikbaar via het telefoonnummer: 0650006564
- De researchverpleegkundigen, bereikbaar via het telefoonnummer: 0650173079

Of stuur een e-mail naar: researchnurses@prinsesmaximacentrum.nl

Als u twijfelt over deelname van uw kind aan het onderzoek, dan kunt u een onafhankelijke arts raadplegen die zelf niet bij het onderzoek is betrokken maar wel deskundig is op dit gebied.

- Dr. Bierings is bereikbaar via het telefoonnummer: 088 9725249

Ook als u voor of tijdens het onderzoek vragen heeft die u liever niet aan de onderzoekers stelt dan kunt u contact opnemen met de onafhankelijke arts.

Als u of uw kind een klacht wil indienen, dan kunt u hiervoor contact opnemen met de ombudsvrouw van het Prinses Máxima Centrum. Zij probeert samen met u, uw kind en de betrokkenen tot een oplossing te komen. De ombudsvrouw is dagelijks bereikbaar op het telefoonnummer 0650006416 of via de mail: ombudsvrouw@prinsesmaximacentrum.nl.

16. Ondertekening toestemmingsformulier
Wanneer u voldoende bedenktijd heeft gehad, wordt u gevraagd te beslissen over deelname aan dit onderzoek. Als u toestemming geeft, zullen wij u vragen deze op de bijbehorende toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u aan dat u de informatie heeft begrepen en instemt met deelname van uw kind aan het onderzoek. Het getekende formulier wordt bewaard door de behandelend arts. U ontvangt een kopie van de getekende toestemmingsverklaring.

Met vriendelijke groet,

Prof. Dr. Marc Wijnen, kinderoncologisch chirurg
Drs. Ceder van den Bosch, arts-onderzoeker

Bijlagen:

Bijlage A: Informatie over verzekering

- Online pagina Medisch-wetenschappelijk onderzoek: https://www.rijksoverheid.nl/mensenonderzoek
- Toestemmingsformulier

Bijlage A: Informatie over de verzekering

Voor iedereen die meedoet aan dit onderzoek heeft het Prinses Máxima Centrum voor Kinderoncologie een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde van deelname van uw kind aan het onderzoek. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt. Deze bepalingen staan in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Dit besluit staat op www.ccmo.nl, de website van de Centrale Commissie Mensgebonden Onderzoek (zie 'Bibliotheek' en dan 'Wet- en regelgeving').

Bij schade kunt u direct contact leggen met de verzekeraar of schaderegelaar.

De verzekeraar van het onderzoek is:	
Naam:	CNA Insurance Company Limited.
Adres:	Polarisavenue 140, 2132 JX Hoofddorp
(Polisnummer:	10211864)

De schaderegelaar van het onderzoek is:	
Naam:	Esther van Herk
Adres:	Polarisavenue 140, 2132 JX Hoofddorp
E-mail:	esther.vanherk@cnahardy.com
Telefoonnummer:	+31 (0)23 3036004

De verzekering biedt een maximum dekking van € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.

De verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover u in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
- Schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- Schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen;
- Schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

NL67388.041.20 / CATERPILLAR studie

NL67388.041.20 / CATERPILLAR studie

Toestemmingsformulier voor ouders of voogd

Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Ik ben gevraagd om toestemming te geven, voor deelname van mijn kind aan dit medisch-wetenschappelijke onderzoek:

Naam kind: _____ Geboortedatum __/____/_____

- Ik heb de informatiebrief gelezen. Ik kon aanvullende vragen stellen. Mijn vragen zijn genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik wil dat mijn kind meedoet.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen dat mijn kind toch niet meedoet. Daarvoor hoef ik geen reden te geven.
- Ik geef toestemming voor het informeren van de huisarts en specialist die mijn kind behandelt dat mijn kind meedoet aan dit onderzoek.
- Ik geef toestemming voor het opvragen van informatie bij de huisarts en specialist die mijn kind behandelt over de centrale lijn en eventuele centrale lijn complicaties.
- Ik geef toestemming voor het verzamelen en gebruiken van de gegevens van mijn kind voor de beantwoording van de onderzoeksvraag in dit onderzoek.
- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot alle gegevens van mijn kind kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.
- Ik weet dat mijn kind niet zwanger mag worden/de partner niet zwanger mag maken tijdens het onderzoek. De onderzoeker heeft de meest geschikte anticonceptie voor mijn kind en/of partner met mij besproken.
- Ik geef □ **wel** □ **geen** * toestemming om de persoonsgegevens van mijn kind langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van centrale lijn infecties.
- Ik geef □ **wel** □ **geen** * toestemming om mijn kind na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek.
- Na het ondertekenen van dit toestemmingsformulier zal ik een kopie van de ondertekenpagina ontvangen.
- Ik geef toestemming voor de randomisatie (loting) in dit onderzoek.

Ik ga ermee akkoord dat mijn kind meedoet aan dit onderzoek.

Naam ouder/voogd** : ……..

Handtekening: …… Datum: ____/____/____

Naam ouder/voogd** : ……..

Handtekening: …… Datum: ____/____/____

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* *Doorhalen wat niet van toepassing is.*

** *Wanneer het kind jonger dan 16 jaar is, ondertekenen de ouders die het gezag uitoefenen of de voogd dit formulier. Kinderen van 12 t/m 15 jaar die zelfstandig beslissingen kunnen nemen (wilsbekwaam zijn), moeten ook het Toestemmingsformulier voor kinderen en jongeren ondertekenen.*

De ouder/voogd krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

Toestemmingsformulier voor ouders of voogd

Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Ik verklaar hierbij dat ik bovengenoemde persoon/personen volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de ouder of voogd zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam arts: ……

Handtekening: …… Datum: ____/____/____

Aanvullende informatie is gegeven door (indien van toepassing):

Naam: ……

Functie: ……

Handtekening: …… Datum: ____/____/____

Informatiebrief voor deelname aan medisch wetenschappelijk onderzoek met toestemmingsformulier voor kinderen van 12 tot 16 jaar

CATERPILLAR-studie

Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Beste ……..,
Doe je mee aan een onderzoek? Hier lees je meer over het onderzoek en jouw rechten. Lees dit goed, want dan weet je waarover je kunt beslissen. Je mag rustig nadenken voordat je beslist.
Je ouders krijgen ook informatie over dit onderzoek. Je kunt samen met hen praten over het onderzoek. Zij zullen samen met jou een beslissing nemen.

Meer informatie over meedoen aan een onderzoek kun je online vinden op de pagina 'Medisch-wetenschappelijk onderzoek' via www.rijksoverheid.nl/mensenonderzoek. Er is ook een folder van de VKN (Vereniging Kinderkanker Nederland) over klinisch onderzoek.

Vragen en contact

Heb je vragen? Bespreek ze met je ouders of stel ze aan je dokter, de onderzoeker of de onderzoeksverpleegkundige. Je kunt je vragen hieronder opschrijven.
Je mag de onderzoeker of de onderzoeksverpleegkundige ook altijd bellen of mailen:

- Drs. Ceder van den Bosch bereikbaar via het telefoonnummer 0650006564 of stuur een mail naar C.H.vandenBosch-4@prinsesmaximacentrum.nl
- De onderzoeksverpleegkundige, bereikbaar via het telefoonnummer 0650173079 of stuur een e-mail naar researchnurses@prinsesmaximacentrum.nl.

Wil je praten over het onderzoek met een arts die er niet bij betrokken is? Bel dan met:

- Dr. Bierings, bereikbaar via het telefoonnummer 088 9725249.

Ruimte op jouw vragen op te schrijven:

Tip: neem een foto van je vragen, dan heb je ze bij je als je met de arts/onderzoeker gaat praten.

Over het onderzoek

Dit onderzoek gebeurt in het Prinses Máxima Centrum voor Kinderoncologie. Er doen in totaal 462 kinderen en jongeren mee. Het onderzoek is gecontroleerd en goedgekeurd. De naam van de commissie die de beoordeling heeft gedaan is: METC Utrecht. Nu heet deze commissie METC NedMec.

Waarom dit onderzoek?

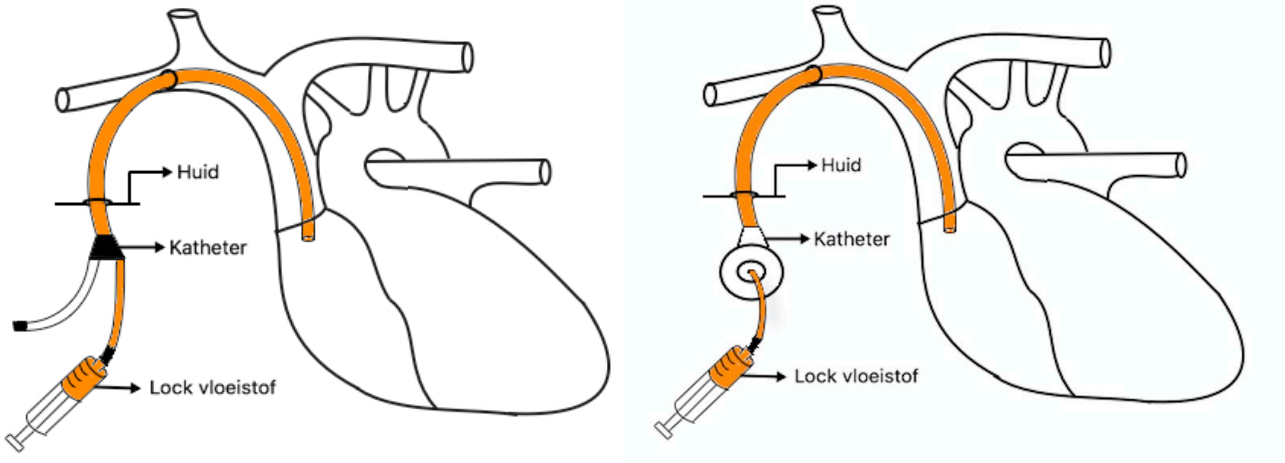
Je ontvangt deze brief omdat bij jou een vorm van kinderkanker is vastgesteld en je voor de behandeling een centrale lijn of port-a-cath (PAC) krijgt (zie **afbeelding 1**).

We willen uitzoeken hoe veilig TauroLock-Hep100 is en hoe goed het werkt tegen het ontstaan van ontstekingen van en samenklontering van bloed in de centrale lijn of PAC. We vergelijken TauroLock met het middel dat we normaal gebruiken om je centrale lijn of PAC mee af te sluiten: Heparine. Zo kunnen we kijken welk middel beter werkt en het meest veilig is. Er zijn twee groepen in het onderzoek, de ene groep krijgt de eerste 90 dagen de standaard heparine lock, de andere groep krijgt de TauroLock.

Achtergrond

Voor de behandeling van je ziekte moeten we regelmatig chemotherapie geven en bloed afnemen. Hiervoor wordt door de chirurg een zogenaamde ‘centrale lijn’ of ‘PAC’ geplaatst (zie **afbeelding 1**). Via deze lijn kan tijdens de behandeling eenvoudig en op een veilige manier chemotherapie worden toegediend of bloed worden afgenomen.

Bij een kwart van de kinderen en jongeren die een centrale lijn of PAC krijgen ontstaat tijdens de behandeling een ontsteking door de centrale lijn of PAC. We noemen dit een infectie. Gelukkig is zo’n infectie meestal goed te behandelen met het toedienen van medicijnen in het ziekenhuis. Soms moet de centrale lijn of PAC vanwege een infectie door de chirurg verwijderd worden met een operatie.



Afbeelding 1: We spuiten een heparine lock of TauorLock (oranje) in je centrale lijn (links) of PAC (rechts).

Nadat de centrale lijn of PAC gebruikt is voor het toedienen van medicijnen of het afnemen van bloed moet deze worden afgesloten door de lijn te vullen met een vloeistof. De vloeistof waarmee we de lijn afsluiten noemen we een ‘lock’ (zie **afbeelding 1**). Op dit moment wordt de vloeistof ‘Heparine’ standaard gebruikt als lock. Heparine is een middel dat de vorming van bloedstolsels (een samenklontering van

bloedrestjes) in de centrale lijn voorkomt. Maar heparine werkt niet goed tegen infecties. Daarom zoeken we naar een vloeistof die ook helpt bij het voorkomen van infecties.

TauroLock is een andere, nieuwe vloeistof die gebruikt kan worden als lock. TauroLock kan mogelijk de vorming van bloedstolsels in de centrale lijn en ook infecties voorkomen. In dit onderzoek willen we de TauroLock vergelijken met heparine en aantonen dat deze lock beter werkt tegen infecties dan heparine. De lock die in dit onderzoek het beste werkt kan bij toekomstige patiënten gebruikt worden voor het afsluiten van de centrale lijn en PAC.

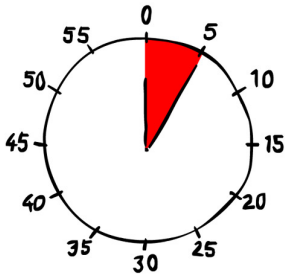
Hoe werkt meedoen?

Het onderzoek duurt in totaal maximaal 90 dagen en zal jou maximaal 70 minuten kosten in totaal. We gaan eerst kijken of je mee kunt doen. Dit duurt ongeveer 5 minuten. We vragen dan naar jouw gezondheid.

Er zijn twee groepen in de studie. De ene groep krijgt de eerste 90 dagen de standaard heparine lock, de andere groep krijgt de TauroLock. We loten van tevoren in welke groep jij zit. Je kunt dit dus niet zelf kiezen. Daarna vertellen we je in welke groep je zit. Wil je meer weten waarom we loten? Dan kun je dit vragen aan de arts of onderzoeksverpleegkundige.

De lock brengen we zo veel mogelijk in tijdens een al geplande afspraak in het Prinses Máxima Centrum. De lock wordt maximaal 1x per week en minimaal 1x per 3 weken ingebracht. Hoe vaak de lock wordt ingebracht is afhankelijk van hoe vaak je centrale lijn of PAC wordt gebruikt en wanneer je in het Prinses Máxima Centrum bent.

- Het inbrengen van de lock duurt ongeveer 5 minuten en doet geen pijn (zie **afbeelding 1 en 2**).
- Daarna vragen we je of je bijwerkingen hebt gevoeld tijdens of vlak na het inbrengen van de lock.
- De lock blijft in het slangetje van je centrale lijn of PAC aanwezig totdat de centrale lijn of PAC weer gebruikt wordt. Als de centrale lijn of PAC opnieuw gebruikt wordt, zal de vloeistof eerst uit de lijn gehaald worden.
- Als je centrale lijn of PAC tussendoor onverwacht of tijdens een bezoek aan een ander ziekenhuis in Nederland wordt gebruikt dan, zal de lijn worden afgesloten met de in Nederland gebruikelijke heparine lock.



Afbeelding 2: Het inbrengen van de lock duurt ongeveer 5 minuten.

Aan het begin van het onderzoek krijg je een CATERPILLAR-deelnemerskaart (zie **afbeelding 4**). We vragen jou en je ouders om de deelnemerskaart bij jullie te houden en te laten zien bij elk ziekenhuisbezoek in het Prinses Máxima Centrum of een ander ziekenhuis. Zo ziet iedereen die je centrale lijn of PAC verzorgd dat je meedoet aan dit onderzoek.

Afbeelding 4: CATERPILLAR- deelnemerskaart.

Na de onderzoeksperiode van 90 dagen is het onderzoek afgelopen. We zullen je centrale lijn of PAC daarna verzorgen met de gebruikelijke heparine.

Over het onderzoeksmiddel

Als je meedoet aan dit onderzoek krijg je de standaard heparine lock of de Taurolock. Heparine werkt tegen de samenklontering van bloed in de centrale lijn of PAC. TauroLock voorkomt de samenklontering van bloed in de centrale lijn of PAC en voorkomt mogelijk ook infecties van de centrale lijn. Taurolock is een al eerder goedgekeurde en geregistreerde vloeistof.

Bijwerkingen

Tijdens het inspuiten van TauroLock kun je misschien last krijgen van een gekke smaak of tintelingen in je mond, misselijkheid of een drukkend gevoel in je nek of borst. Dit komt niet zo vaak voor en gaat binnen enkele minuten weer over. Voel je je vlak na het inbrengen van de lock niet goed? Vertel het meteen aan je ouders zodat zij de dokter of verpleegkundige kunnen bellen.

Risico's

We doen dit onderzoek omdat we nog niet alles weten over TauroLock. De behandeling kan dus ook bijwerkingen hebben die we nu nog niet weten. Daar letten we tijdens het onderzoek goed op.

Ongemakken

Het inbrengen van de lock zal altijd gecombineerd worden met andere afspraken en opnames in het ziekenhuis. Je hoeft dus niet speciaal voor het onderzoek naar het ziekenhuis te komen.

Anders dan normaal

- Als je meedoet aan het onderzoek, dan krijg je na de loting mogelijk een TauroLock in plaats van de gebruikelijke heparine lock.

Belangrijk om te weten:

- Je krijgt een kaartje met telefoonnummers en informatie over het onderzoek. Dit kaartje moet je altijd bij je hebben.
- Ben je zwanger of is je partner zwanger? Vertel het aan de onderzoeker. Die bespreekt dan met jou wat dit betekent voor het meedoen aan het onderzoek.

Voordelen en nadelen:

Het is belangrijk dat je nadenkt over de mogelijke voor- en nadelen voordat je besluit om mee te doen:

- Als je meedoet aan dit onderzoek en na de loting de TauroLock-Hep 100 lock krijgt, dan kan de TauroLock-Hep100 centrale lijn infecties mogelijk voorkomen. Dit is nog niet aangetoond en de reden dat we dit onderzoek uitvoeren.
- Jouw deelname aan dit onderzoek draagt bij aan meer kennis over het voorkomen van centrale lijn infecties en kan de behandeling van toekomstige patiënten verbeteren.
- Als je na de loting de TauroLock-Hep100 lock krijgt, dan kan je de al genoemde bijwerkingen ervaren bij het inbrengen van de locks.
- Het plaatsen van de locks wordt altijd gedaan tijdens de al geplande afspraken en opnames.
- Als je niet meedoet aan het onderzoek heb je geen nadelen. Dan krijg je de behandeling die je normaal ook zou krijgen.

Vergoeding

Er zijn voor jou geen extra kosten verbonden aan deelname aan dit onderzoek.

Jouw rechten

Moet je meedoen?

Nee, je mag **zelf weten** of je meedoet. Als je niet wilt meedoen, dan hoeft dit niet, ook als je ouders dat liever wel willen. Als je wilt meedoen, zet je je handtekening op het formulier. Ook daarna **mag je altijd nog stoppen**, als je liever niet meer wilt. Vertel dat dan wel aan de onderzoeker. Je hoeft niet uit te leggen waarom je stopt.

Als je niet meedoet krijg je de standaardbehandeling. Dit is de behandeling met de heparine lock, die we normaal geven aan kinderen met een centrale lijn.

Toestemming intrekken

Als je wilt stoppen, vertel je dit aan de arts of de onderzoeksverpleegkundige. Dit heet: je toestemming intrekken. De informatie die al is verzameld gebruiken we nog voor het onderzoek.

Jouw gegevens

Voor het onderzoek hebben we twee dingen nodig die van jou zijn:

- ***Persoonsgegevens*** = informatie over wie jij bent, bijvoorbeeld je geboortedatum en waar je woont.

- ***Medische gegevens*** = (ook een soort persoonsgegevens) informatie over je gezondheid, bijvoorbeeld of je ziek bent en of je medicijnen gebruikt.

Deze **twee dingen zijn nodig bij het doen van het onderzoek**. Je ouders geven toestemming zodat wij deze dingen mogen gebruiken. Wil je meer weten over wat we precies doen met jouw gegevens? Vraag het dan aan je ouders, het staat in hun informatiebrief. Je kunt het ook aan de onderzoeker vragen.
De gegevens krijgen **een code,** bijvoorbeeld letters en cijfers. Zo kan een ander niet zien dat de gegevens van jou zijn. Alleen de onderzoeker weet welke code bij wie hoort. Andere mensen zien alleen de code, zij weten dus niet jouw naam.

Verzekering
Er is een verzekering voor dit onderzoek, dat is verplicht. Wil je hier meer over weten? Dan kun je dat aan je ouders vragen. In de informatiebrief voor ouders staat het verder uitgelegd. Je kunt het ook aan de arts of onderzoeksverpleegkundige vragen.

Jouw beslissing

Het formulier
Wil je meedoen? Dan zet je een handtekening op het toestemmingsformulier. We hebben ook een handtekening van jouw ouders/voogd nodig. Wanneer iedereen voor deelname getekend heeft, ontvang je een kopie van dit document.

Ook kun je kiezen of we je later mogen vragen voor een vervolg onderzoek. We geven je dan informatie over het nieuwe onderzoek. Dan kun jij opnieuw beslissen of je wilt meedoen.

Meer weten?

Wil je meer weten over onderzoek of over jouw rechten?
Kijk dan op de website van de VKN (Vereniging Kinderkanker Nederland) www.kinderkankernederland.nl of op www.kindenonderzoek.nl.

Bijlagen:
- Toestemmingsformulier

Toestemmingsformulier voor patiënten, 12-16 jaar

- Ik heb de informatie **begrepen**. Ook kon ik vragen stellen. Mijn **vragen** zijn beantwoord.
- Ik had **genoeg tijd om te beslissen** of ik meedoe.
- Ik weet dat ik **niet verplicht** ben om mee te doen.
- Ik begrijp dat ik **altijd mag stoppen** als ik niet meer mee wil doen.
- Ik geef* □ **wel** □ **geen** toestemming om mij later te vragen voor een vervolgonderzoek.

Ik wil meedoen aan dit onderzoek.

Naam kind: …….

Handtekening: ……. Datum : __ / __ / __

Dit stuk is voor de onderzoeker:

Ik verklaar dat ik het kind volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van het kind zou kunnen beïnvloeden, dan breng ik het kind daarvan tijdig op de hoogte.

Naam arts/onderzoeker (of diens vertegenwoordiger): …….

Handtekening: ……. Datum: __ / __ / __

Aanvullende informatie is gegeven door (indien van toepassing):

Naam: …….

Functie: …….

Handtekening: ……. Datum: ____/____/____

** Doorhalen van niet van toepassing is.*

Het kind krijgt een volledige informatiebrief mee, samen met een (kopie van de) getekende versie van het toestemmingsformulier.

NL67388.041.20 / CATERPILLAR studie

Informatiebrief voor deelname aan medisch wetenschappelijk onderzoek met toestemmingsformulier voor patiënten van 16 jaar en ouder

CATERPILLAR-studie
Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Beste ……..,

Wij vragen je om mee te doen aan een medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. Om mee te doen is wel je schriftelijke toestemming nodig.

Voordat je beslist of je mee wil doen aan dit onderzoek, krijg je uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de arts of onderzoeker om uitleg als je vragen hebt. Je kunt ook de onafhankelijk arts, die aan het eind van deze brief genoemd wordt, om aanvullende informatie vragen. Je kan er ook over praten met je ouders, familie of vrienden.

Verdere informatie over meedoen aan zo'n onderzoek staat op de online pagina 'Medisch-wetenschappelijk onderzoek'. Deze pagina kun je vinden via www.rijksoverheid.nl/mensenonderzoek. Er is ook een folder van de VKN (Vereniging Kinderkanker Nederland) over klinisch onderzoek. Deze folder zit in de dagboekagenda die je aan het begin van de behandeling krijgt.

Heb je na het lezen van de informatie nog vragen? Dan kun je terecht bij de behandelend arts of de researchverpleegkundige, wiens contactgegevens aan het eind van deze informatiebrief genoemd worden. Je beslist zelf of je meedoet of niet.

1. Algemene informatie

Dit onderzoek is opgezet door het Prinses Máxima Centrum voor Kinderoncologie en wordt alleen uitgevoerd in Nederland. De KWF Kankerbestrijding vergoedt de kosten van dit onderzoek. Voor dit onderzoek zijn in totaal 462 patiënten nodig. De medisch-ethische toetsingscommissie METC Utrecht heeft dit onderzoek goedgekeurd. Deze commissie heet vanaf 22-1-2022 de medisch-ethische toetsingscommissie NedMec. Algemene informatie over de toetsing van onderzoek vind je op de online pagina 'Medisch-wetenschappelijk onderzoek'.

2. Doel van het onderzoek

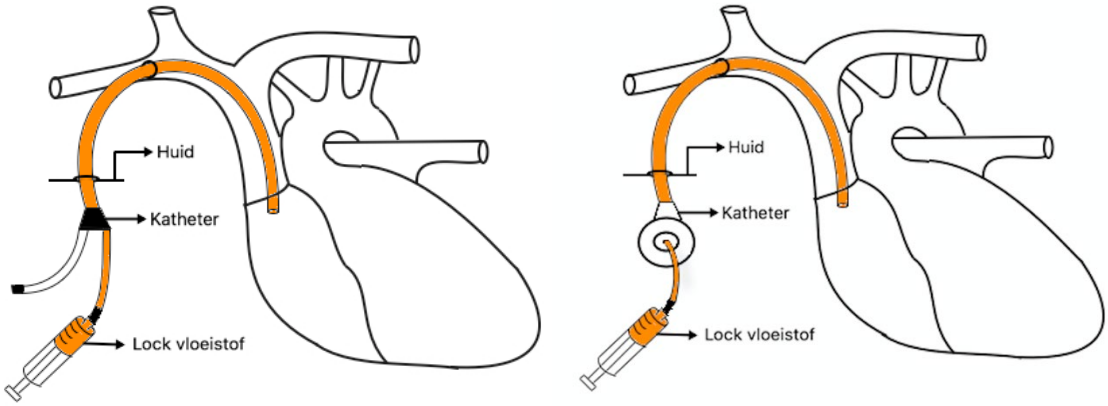
Het doel van dit onderzoek is uitzoeken hoe veilig en effectief het nieuwe medische hulpmiddel TauroLock-Hep100 is in het voorkomen van centrale lijn infecties de vorming van bloedstolsels in de centrale lijn en port-a-cath (PAC). In dit onderzoek vergelijken we de werking en veiligheid van TauroLock-Hep100 met de werking en veiligheid van de heparine lock. Een lock is een vloeistof waarmee een centrale lijn of PAC gevuld wordt nadat deze gebruikt is. Dit wordt afsluiten van de centrale lijn of PAC genoemd. Heparine wordt op dit moment in Nederland standaard gebruikt voor het afsluiten van de centrale lijn of PAC.

3. Achtergrond van het onderzoek

Voor de behandeling van je ziekte moet regelmatig chemotherapie worden toegediend en bloed worden afgenomen. Hiervoor wordt door de chirurg een zogenaamde 'centrale lijn' of 'PAC' geplaatst. Via deze lijn kan tijdens de behandeling eenvoudig en op een veilige manier chemotherapie worden toegediend en bloed worden afgenomen.

Bij minimaal 1 op de 4 patiënten die een centrale lijn of PAC krijgen ontstaat tijdens de behandeling een infectie door de centrale lijn of PAC. Gelukkig is zo'n infectie meestal goed te behandelen met het toedienen van antibiotica in het ziekenhuis. Soms moet de centrale lijn of PAC vanwege deze infectie echter vroegtijdig verwijderd worden door middel van een operatie.

Nadat de centrale lijn of PAC gebruikt is voor het toedienen van medicatie of het afnemen van bloed moet deze worden afgesloten. Dit doen we door de lijn te vullen met een vloeistof. De vloeistof waarmee we de centrale lijn of PAC afsluiten noemen we een 'lock' (zie **afbeelding 1**). Op dit moment wordt de vloeistof 'Heparine' standaard gebruikt als lock. Heparine is een middel dat de vorming van bloedstolsels in de centrale lijn of PAC voorkomt, maar het werkt helaas niet tegen infecties. Daarom zoeken we naar een vloeistof die ook helpt bij het voorkomen van infecties.



Afbeelding 1: Centraal veneuze lijn (links) en PAC (rechts) met lock vloeistof (bijv. Heparine of TauroLock-Hep100)

TauroLock-Hep100 is een andere, nieuwe vloeistof die gebruikt kan worden als lock. TauroLock-Hep 100 voorkomt mogelijk de vorming van bloedstolsels en voorkomt mogelijk ook infecties in de centrale lijn of PAC. Deze vloeistof is al onderzocht bij volwassenen met kanker en bij kinderen met andere aandoeningen én een centrale lijn of PAC. Ook is de TauroLock-Hep100 in kleinere onderzoeken gebruikt bij kinderen met kanker met een centrale lijn of PAC. In deze onderzoeken is TauroLock-Hep100 een veilige en effectieve lock gebleken. In dit onderzoek willen we de TauroLock-Hep100 vergelijken met heparine en aantonen dat deze lock beter is dan de heparine. De lock die in dit onderzoek het beste resultaat geeft, kan bij toekomstige patiënten gebruikt worden bij het afsluiten van de centrale lijn of PAC.

4. Wat meedoen inhoudt

Als je meedoet aan het onderzoek, duurt dat in totaal maximaal 90 dagen. Na deze 90 dagen zal de centrale lijn of PAC afgesloten worden met de standaard heparine vloeistof.

Geschiktheidsonderzoek

Eerst bepalen we of je kunt meedoen aan het onderzoek. De arts zal hiervoor vragen naar je medische geschiedenis.

Onderzoek

De kinderen en jongeren die meedoen aan dit onderzoek, worden verdeeld in twee gelijke groepen. De helft van de groep krijgt gedurende 90 dagen de standaard heparine lock, de andere groep krijgt de TauroLock-Hep100 lock. Een loting (randomisatie) bepaalt welke lock jij krijgt. De behandelend arts en onderzoekers hebben geen invloed op de uitslag van de loting. Algemene informatie over randomisatie vind je op de online pagina 'Medisch-wetenschappelijk onderzoek'.

Tijdens de onderzoeksperiode wordt de studie lock maximaal 1x per week en minimaal 1x per 3 weken ingebracht in je centrale lijn of PAC. Dat gebeurt in het Prinses Máxima Centrum. Het inbrengen van de lock wordt zoveel als mogelijk gecombineerd met opnames en afspraken die al gepland worden voor je behandeling. De lock blijft in het slangetje van je centrale lijn of PAC aanwezig totdat de centrale lijn of PAC weer gebruikt wordt. Als de centrale lijn of PAC opnieuw gebruikt wordt, zal de vloeistof eerst uit de lijn opgetrokken worden. De vloeistof wordt dus zo min mogelijk je lichaam ingespoten. Hoe vaak de lock wordt ingebracht is afhankelijk van hoe vaak je centrale lijn of PAC wordt gebruikt en wanneer je in het Prinses Máxima Centrum bent.

Als de centrale lijn of PAC tussendoor elders of ongepland wordt gebruikt, bijvoorbeeld tijdens een bezoek aan een ander ziekenhuis in Nederland, zal de lock worden opgetrokken zoals hierboven beschreven en zal de lijn of PAC worden afgesloten met een in Nederland gebruikelijke standaard heparine lock. Als de onderzoeksperiode van 90 dagen is afgelopen zal de centrale lijn of PAC van alle patiënten verzorgd worden met de standaard heparine lock.

Bezoeken en metingen

Er wordt gedurende 90 dagen tenminste 1x per 3 weken en maximaal 1x per week een nieuwe lock ingebracht in het Prinses Máxima Centrum. De lock wordt ingebracht tijdens je al geplande afspraken en opnames. Dit zal jou maximaal 70 minuten in totaal kosten. Het inbrengen van een TauroLock-Hep100 lock verloopt hetzelfde als het inbrengen van een heparine lock.

Het inbrengen van een lock duurt ongeveer 5 minuten. Na het inbrengen van de lock zullen we je een aantal korte vragen stellen over het wel of niet ervaren van bijwerkingen. Dit kunnen de bijwerkingen zijn:

- een kortdurende vreemde smaak,
- tintelingen in de mond
- een drukkend gevoel in nek of borst
- of misselijk gevoel.

We willen graag de bijwerkingen van beide locks goed registreren.

Wat is er meer of anders dan de gebruikelijke zorg?

Als je meedoet aan het onderzoek, dan krijg je gedurende 90 dagen mogelijk een TauroLockHep-100 lock in plaats van de gebruikelijke heparine lock.

Bij aanvang van de studie ontvang je een CATERPILLAR-deelnemerskaart en Ja/Nee-stickers (zie **afbeelding 2**). We vragen jou en je ouders om de deelnemerskaart bij jullie te houden en te laten zien bij elk ziekenhuisbezoek in het Prinses Máxima Centrum of een ander ziekenhuis. Zo wordt overal herkend dat je meedoet aan dit onderzoek.

Het inbrengen van de lock zal altijd gecombineerd worden met al geplande afspraken en opnames.

Afbeelding 2: CATERPILLAR Ja/Nee-stickers en deelnemerskaart.

5. Wat wordt er van je verwacht

Om het onderzoek goed te laten verlopen, en voor je eigen veiligheid, is het belangrijk dat je je aan de volgende afspraken houdt.

De afspraken zijn dat jij en/of je ouders:

- De deelnemerskaart en Ja/Nee-stickers bij je draagt en laat zien bij elk ziekenhuisbezoek. Hierop staat dat je meedoet aan dit onderzoek. Er staat ook op wie je in geval van nood moet waarschuwen.
- De afspraken voor het inbrengen van de lock nakomt.
- Vragen beantwoord over het ontstaan van eventuele symptomen na het inbrengen van de lock.

Het is belangrijk dat jij of je ouders contact opneemt met de onderzoeker of research verpleegkundige:

- Als je in een ziekenhuis wordt opgenomen of behandeld.
- Als je plotseling gezondheidsklachten krijgt.
- Als je niet meer wilt meedoen aan het onderzoek.
- Als je contactgegevens wijzigen.

Anticonceptie en zwangerschap

Ben je als vrouw in de vruchtbare leeftijd? Dan moet je voorkomen dat je tijdens het onderzoek zwanger wordt en mag je niet deelnemen indien je borstvoeding geeft. De behandelend arts zal met jou de meest geschikte voorbehoedmiddelen bespreken. Word je toch zwanger in de onderzoeksperiode? Neem direct contact op met je behandelend arts. Het kan zijn dat dit onderzoek gevolgen heeft voor het ongeboren kind.

Ben je als man in de leeftijd waarop de mogelijkheid bestaat om een kind te verwekken? Dan moet je voorbehoedmiddelen gebruiken om een zwangerschap te voorkomen. Men weet namelijk niet zeker of de behandeling nadelige invloed heeft op het sperma. Wordt je partner toch zwanger in de onderzoeksperiode? Neem direct contact op met de behandelend arts. Het kan zijn dat dit onderzoek gevolgen heeft voor het ongeboren kind.

6. Mogelijke bijwerkingen, complicaties en eventuele nadelige effecten

TauroLock-Hep100 kan mogelijk lichte ongemakken geven. Deze ongemakken komen niet vaak voor en zijn niet ernstig gebleken. Je kan de volgende lichte ongemakken ervaren direct na het inbrengen van de TauroLock-Hep100:

- Kortdurende veranderde smaak
- Kortdurende tintelingen in de mond
- Kortdurend drukkend gevoel in de nek of borst
- Kortdurende misselijkheid of overgeven
- Allergische reacties op het middel

TauroLock-Hep100 kan ook nadelige effecten hebben die nog onbekend zijn.

De standaard heparine lock wordt al heel veel gebruikt. Hiervan zijn geen bijwerkingen bekend.

7. Mogelijke voor- en nadelen

Het is belangrijk dat je de mogelijke voor- en nadelen goed afweegt voordat je besluit om mee te doen aan het onderzoek.

Voordelen:

- Als je meedoet aan dit onderzoek en na de loting de TauroLock-Hep 100 lock krijgt, dan kan de TauroLock-Hep100 centrale lijn infecties mogelijk voorkomen. Dit is nog niet aangetoond en de reden dat we dit onderzoek uitvoeren.

- Jouw deelname aan dit onderzoek draagt bij aan meer kennis over het mogelijk voorkomen van centrale lijn infecties en kan de behandeling van toekomstige patiënten verbeteren.

Nadelen:

- Als je na de loting de TauroLock-Hep100 lock krijgt, dan kan je de al genoemde bijwerkingen ervaren bij het inbrengen van de locks.

8. Als je niet wilt meedoen of als je wilt stoppen met het onderzoek

Je beslist zelf of je meedoet aan het onderzoek. Deelname is vrijwillig. Als je niet wilt meedoen, dan word je op de gebruikelijke manier behandeld. De standaard behandeling is de heparine lock.

Als je meedoet, kun je je altijd bedenken en alsnog stoppen, ook tijdens het onderzoek. De centrale lijn of PAC zal vanaf dat moment afgesloten worden met de standaard heparine lock. Je hoeft niet te zeggen waarom je stopt. Wel moet je dit direct melden aan de behandelend arts. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek.

Als er nieuwe informatie over het onderzoek is die belangrijk voor je is, laat de arts dit aan je weten. Je wordt dan gevraagd of je mee blijft doen.

9. Einde van het onderzoek

Je deelname aan het onderzoek stopt als:

- De onderzoeksperiode van 90 dagen voorbij is.
- Je een infectie aan de centrale lijn of PAC krijgt.
- De centrale lijn of PAC om een medische reden wordt verwijderd.
- Je een extra centrale lijn krijgt.
- Je een allergische reactie krijgt op het middel.
- Je zelf kiest om te stoppen.
- De onderzoeker het beter voor je vindt om te stoppen.
- Het Prinses Máxima Centrum, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle gegevens kan de onderzoeker je als je dat wilt informeren over de belangrijkste uitkomsten van het onderzoek. Dit gebeurt ongeveer een half jaar na het einde van het gehele onderzoek.

10. Gebruik en bewaren van de gegevens

Voor dit onderzoek worden je persoonsgegevens verzameld, gebruikt en bewaard. Het gaat om gegevens zoals naam, adres, geboortedatum en om gegevens over je gezondheid. Het verzamelen, gebruiken en bewaren van je gegevens is nodig om de vragen die in dit onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren. Wij vragen voor het gebruik van je gegevens toestemming. Als je dat niet wilt, kun je niet deelnemen aan dit onderzoek.

Vertrouwelijkheid van de gegevens

Om je privacy te beschermen, worden je gegevens voorzien van een code. De naam en andere gegevens die jou direct kunnen identificeren worden apart bewaard. Alleen met de sleutel van de code zijn gegevens tot jou te herleiden. De sleutel van de code blijft veilig opgeborgen in de lokale onderzoeksinstelling. Ook in rapporten en publicaties over het onderzoek zijn de gegevens niet tot jou te herleiden

Toegang tot je gegevens voor controle
Sommige personen en instanties kunnen op de onderzoekslocatie toegang krijgen tot al jouw gegevens. Ook in de gegevens zonder code. Dit is nodig om te kunnen controleren of het onderzoek goed en betrouwbaar is uitgevoerd. Personen en instanties die ter controle toegang krijgen tot je gegevens zijn de:

- Veiligheidscommissie die het onderzoek in de gaten houdt.
- Een monitor die door de opdrachtgever is ingehuurd.
- Nationale en internationale toezichthoudende autoriteiten, bijv. de Inspectie Gezondheidszorg en Jeugd.
- De medewerkers van het onderzoeksteam.

Zij zullen jouw gegevens geheim houden. Je wordt gevraagd voor deze inzage toestemming te geven.

Bewaartermijn gegevens
Je gegevens moeten 15 jaar worden bewaard op de onderzoekslocatie (het ziekenhuis).

Bewaren en gebruik van gegevens voor ander onderzoek
Je gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn voor ander wetenschappelijk onderzoek op het gebied van jou aandoening en/of van de verdere ontwikkeling van het product/ de behandelmethode. Daarvoor zullen je gegevens minimaal 15 jaar worden bewaard. Je kunt op het toestemmingsformulier aangeven of je hier wel of niet mee instemt. Als je hier niet mee instemt, kan je gewoon deelnemen aan het huidige onderzoek.

Intrekken toestemming
Je kunt de toestemming voor gebruik van je persoonsgegevens altijd weer intrekken. Dit geldt voor dit onderzoek en ook voor het bewaren en het gebruik van je gegevens voor toekomstig onderzoek. De onderzoeksgegevens over jou die zijn verzameld tot het moment dat je je toestemming intrekt worden nog wel gebruikt in het onderzoek.

Meer informatie over de rechten bij verwerking van gegevens
Voor algemene informatie over je rechten bij verwerking van je persoonsgegevens kun je de website van de Autoriteit Persoonsgegevens raadplegen op: https://autoriteitpersoonsgegevens.nl/nl

Bij vragen of klachten over de verwerking van je persoonsgegevens kun je contact opnemen met de Functionaris voor de Gegevensbescherming van het Prinses Máxima Centrum: fg@prinsesmaximacentrum.nl

Registratie van het onderzoek
Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-wetenschappelijke onderzoeken namelijk https://www.trialregister.nl. Daarin zijn geen gegevens opgenomen die naar jou herleidbaar zijn. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. Je vindt dit onderzoek onder 'CATERPILLAR'.

11. Verzekering
Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt schade door het onderzoek. Niet alle schade is gedekt. In **bijlage A** vind je meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie je schade kunt melden.

12. Informeren van de huisarts en/of behandelend specialist
Wij informeren je huisarts en andere betrokken medisch specialisten over jouw deelname aan het onderzoek. Dit is voor je eigen veiligheid. Als je dit niet goed vindt, kan je niet meedoen aan dit onderzoek.

13. Vergoeding voor meedoen

Deelname aan het onderzoek en de locks kosten je niets extra. Je krijgt geen vergoeding voor je deelname aan dit onderzoek.

14. Heb je vragen?

Als je tijdens het onderzoek of de behandeling vragen of klachten hebt, kun je altijd terecht bij je behandelend arts. Bij vragen of opmerkingen kun je ook contact opnemen met:

- Drs. Ceder van den Bosch, arts-onderzoeker, bereikbaar via het telefoonnummer: 0650006564. Of stuur een e-mail naar: C.H.vandenBosch-4@prinsesmaximacentrum.nl
- De researchverpleegkundigen, bereikbaar via het telefoonnummer: 0650173079. Of stuur een e-mail naar: researchnurses@prinsesmaximacentrum.nl

Als je twijfelt over deelname aan het onderzoek, dan kun je een onafhankelijke arts raadplegen die zelf niet bij het onderzoek is betrokken maar wel deskundig is op dit gebied.

- Dr. Bierings is bereikbaar via het telefoonnummer: 088 9725249

Ook als je voor of tijdens het onderzoek vragen hebt die je liever niet aan de onderzoekers stelt dan kun je contact opnemen met de onafhankelijke arts.

Als je een klacht wil indienen, dan kun je hiervoor contact opnemen met de ombudsvrouw van het Prinses Máxima Centrum. Zij probeert samen met jou en de betrokkenen tot een oplossing te komen. De ombudsvrouw is dagelijks bereikbaar op het telefoonnummer 0650006416 of via de mail: ombudsvrouw@prinsesmaximacentrum.nl.

15. Ondertekening toestemmingsformulier

Wanneer je voldoende bedenktijd hebt gehad, word je gevraagd te beslissen over deelname aan dit onderzoek. Als je toestemming geeft, zullen wij je vragen deze op de bijbehorende toestemmingsverklaring schriftelijk te bevestigen. Door jou schriftelijke toestemming geef je aan dat je de informatie hebt begrepen en instemt met deelname aan het onderzoek. Het getekende formulier wordt bewaard door de behandelend arts. Je ontvangt een kopie van de getekende toestemmingsverklaring.

Met vriendelijke groet,
Prof. Dr. Marc Wijnen, kinderoncologisch chirurg
Drs. Ceder van den Bosch, arts-onderzoeker

Bijlagen:

Bijlage A: Informatie over verzekering

- Online pagina Medisch-wetenschappelijk onderzoek: https://www.rijksoverheid.nl/mensenonderzoek
- Toestemmingsformulier

NL67388.041.20 / CATERPILLAR studie

Bijlage A: Informatie over de verzekering

Voor iedereen die meedoet aan dit onderzoek heeft het Prinses Máxima Centrum voor Kinderoncologie een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde van jou deelname aan het onderzoek. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt. Deze bepalingen staan in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Dit besluit staat op www.ccmo.nl, de website van de Centrale Commissie Mensgebonden Onderzoek (zie 'Bibliotheek' en dan 'Wet- en regelgeving').

Bij schade kun je direct contact leggen met de verzekeraar of schaderegelaar.

De verzekeraar van het onderzoek is:	
Naam:	CNA Insurance Company Limited.
Adres:	Polarisavenue 140, 2132 JX Hoofddorp
(Polisnummer:	10211864)

De schaderegelaar van het onderzoek is:	
Naam:	Esther van Herk
Adres:	Polarisavenue 140, 2132 JX Hoofddorp
E-mail:	esther.vanherk@cnahardy.com
Telefoonnummer:	+31 (0)23 3036004

De verzekering biedt een maximum dekking van € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.

De verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover je in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- Schade aan jouw gezondheid die ook zou zijn ontstaan als je niet aan het onderzoek had meegedaan;
- Schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- Schade aan je nakomelingen, als gevolg van een negatief effect van het onderzoek op jou of jouw nakomelingen;
- Schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

NL67388.041.20 / CATERPILLAR studie

Toestemmingsformulier voor patiënten, 16 jaar en ouder

Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Ik ben gevraagd om toestemming te geven, voor deelname aan dit medisch-wetenschappelijke onderzoek:

- Ik heb de informatiebrief gelezen. Ik kon aanvullende vragen stellen. Mijn vragen zijn genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik wil meedoen.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen. Daarvoor hoef ik geen reden te geven.
- Ik geef toestemming voor het informeren van mijn huisarts en behandelend specialist dat ik mee doe aan dit onderzoek.
- Ik geef toestemming voor het opvragen van informatie bij mijn huisarts en specialist over de centrale lijn of PAC en eventuele centrale lijn complicaties.
- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.
- Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens voor de beantwoording van de onderzoeksvraag in dit onderzoek.
- Ik weet dat ik niet zwanger mag worden/mijn partner niet zwanger mag maken tijdens het onderzoek. De onderzoeker heeft de meest geschikte anticonceptie voor mij en/of mijn partner met mij besproken.
- Ik geef □ **wel** □ **geen** * toestemming om mijn persoonsgegevens langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van centrale lijn infecties.
- Ik geef □ **wel** □ **geen** * toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek.
- Ik geef toestemming voor de randomisatie (loting) in dit onderzoek.
- Na het ondertekenen van dit toestemmingsformulier zal ik een kopie van de ondertekenpagina ontvangen.

Ik ga ermee akkoord dat ik mee doe aan dit onderzoek.

Naam proefpersoon: ……

Handtekening: …… Datum: ____/____/____

---

* *Doorhalen van niet van toepassing is.*

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

NL67388.041.20 / CATERPILLAR studie

Toestemmingsformulier voor patiënten, 16 jaar en ouder

Officiële titel: De effectiviteit van een lock oplossing met taurolidine, citraat, en heparine voor de preventie van getunnelde centrale lijn-geassocieerde bloedbaan infecties in kinderoncologie patiënten, een gerandomiseerde, mono-center trial.

Ik verklaar hierbij dat ik bovengenoemde persoon volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam arts: ……

Handtekening: …… Datum: ____/____/____

Aanvullende informatie is gegeven door (indien van toepassing):

Naam: ……

Functie: ……

Handtekening: …… Datum: ____/____/____

CATERPILLAR STUDY

DMC CHARTER CATERPILLAR-Study

1. INTRODUCTION	
Name, sponsor's ID and EUDRACT number	The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunneled central line-associated bloodstream infections in pediatric oncology patients, a randomized controlled, mono-centre trial (CATERPILLAR-study) Sponsor's ID: NL67388.041.20
Objectives of trial	Investigator-initiated, mono-center, open-labelled randomized controlled trial to compare the efficacy of the taurolidine-citrate-heparin lock and the heparin lock in the prevention of tunnelled central line associated bloodstream infections in pediatric oncology patients. Patients in the intervention study arm will receive lock solutions containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. Patients in the control study arm will receive lock solutions containing heparin 100 IU/ml. The lock solutions will be instilled with a maximum of once weekly, and a minimum of once every three weeks.
Scope of the charter	The purpose of this document is to describe the roles and responsibilities of the independent DMC for the CATERPILLAR trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical rules and relationships with other committees.
2. ROLES AND RESPONSIBILITIES	
The aims of the committee	To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.
Terms of reference	The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee. The DMC should inform the Chair of the steering committee if, in their view: ○ The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management; **or** ○ It becomes evident that no clear outcome would be obtained.
Specific roles of the DMC	○ Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. ○ Assess data quality, including completeness ○ Monitor recruitment figures and losses to follow-up ○ Monitor compliance with the protocol by participants and investigators ○ Monitor trial conduct – organisation and implementation of trial protocol ○ Monitoring evidence for treatment differences in the main efficacy outcome measures ○ Monitor evidence for treatment harm (eg toxicity data, SAEs, deaths) ○ Decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups ○ Suggest additional data analyses ○ Advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints, or sample size) ○ Monitor planned sample size assumptions ○ Monitor continuing appropriateness of patient information ○ Assess the impact and relevance of external evidence

3. BEFORE OR EARLY IN THE TRIAL	
Input into the protocol by the DMC	All potential DMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the clinical research committee (CRC) of the Princess Maxima Center and the research ethics committee (METC) of the University Medical Center Utrecht. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the trial office and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Start of the trial meeting	A teleconference call will be held with the DMC members before the trial starts or early in the course of the trial, to discuss the protocol, trial, analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. An initial "dummy" report will be given to the DMC to familiarise the DMC members with the format that will be used in the reports.
DMC member registration	DMC members will formally register their assent by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter.
4. Composition	
Membership and size of the DMC	The members of the DMC for this trial are: 1. Dr. Marieke Witvliet, Pediatric Surgeon, Wilhelmina Children's Hospital, Utrecht, the Netherlands. 2. Dr. Bart Rijnders, Infectious Diseases, Erasmus Medical Center, Rotterdam, the Netherlands. 3. Prof Dr. Hein Putter, Medical Statistician, Leids University Medical Center, Leiden, the Nethterlands.
The Chair, how they are chosen and the Chair's role.	The Chair was chosen by the sponsor. The Chair will be: dr. Marieke Witvliet. The Chair is expected to facilitate and summarise discussions.
The responsibilities of the DMC statistician	The DMC membership will include a statistician to provide independent statistical expertise.
The responsibilities of the trial statistician	The trial statistician will produce (or oversee the production of) the report to the DMC, and may participate in the first part of the DMC meetings to explain how the statistical analysis has been performed.
The responsibilities of the trial office team	The trial office team (e.g. trial Manager, data-management etc.) only inputs to the production of the non-confidential sections of the DMC report.
The responsibilities of the PI and other members of the Trial Management Group (TMG)	The PI, may be asked, and should be available, to attend open sessions of the DMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions of the DMC when necessary.
5. Relationships	
Relationships	The sponsor is the Princess Maxima Center. The Principal Investigator (Prof. Dr. M.H.W.A. Wijnen) is the head of the Department of Pediatric Surgery of the Princess Maxima Center for pediatric oncology. The Trial Steering Committee consists of: ○ Prof. Dr. M.H.W.A. Wijnen, Pediatric Surgeon, Princess Maxima Center. ○ Dr. M.D. van de Wetering, Pediatric Oncologist, Princess Maxima Center. ○ Dr. C.P. van de Ven, Pediatric Surgeon, Princess Maxima Center. ○ Prof. Dr. M. Zwaan, Pediatric Oncologist, Head of the Trial Office, Princess Maxima Center. The trial office team consists of: ○ Prof. Dr. M. Zwaan, Pediatric Oncologist, Head of the Trial Office, Princess Maxima Center. ○ MSc Anne Elsinghorst, Trial Manager, Princess Maxima Center. ○ Jan Lieverst, Trial Office, Princess Maxima Center.

	○ Inekee van der Vaart, Trial Office, Princess Maxima Center. ○ Associate Prof. Dr. M. Fiocco, Statistician, Princess Maxima Center. ○ Drs. C.H. van den Bosch, PhD-student, Princess Maxima Center.
Decisions of the DMC	The DMC does not make decisions about the trial but makes recommendations to the Trial Steering Committee and its Chair (Prof. Dr. M.H.W.A. Wijnen).
Payments to DMC members	The meetings will be held by teleconference. If a face-to-face meeting will be held, members will be reimbursed for travel expenses.
The need for DMC members to disclose information about any competing interests	The DMC members will declare any conflicts of interests using the competing interests form (annex 2). These forms will be stored at the Trial Office of the Princess Maxima Center.
6. ORGANISATION OF DMC MEETINGS	
Expected frequency of DMC meetings	The DMC will meet prior to the start of the study and after the inclusion of 231 patients, approximately one year after the start of the study. Before the DMC meeting, the interim analyses should be performed. At the end of the study, another DMC meeting will be organised.
Whether meetings will be face-to-face or by teleconference	The meetings will be held by teleconference.
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Only DMC members and others whom they specifically invite, e.g. the trial statistician, are present in closed sessions. In the session prior to the start of the study and at the end of the study, all those attending the closed session are joined by the PI (Prof. Dr. M.H.W.A. Wijnen), and/or the head of the trial** office (Prof. Dr. Michel Zwaan). 1. Start of the study session. 2. Closed session will be performed after the inclusion of 231patients (50%): DMC discussion of “closed” parts of the report. 3. End of the study session.
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Intended content of material to be available in closed sessions	Accumulating information relating to recruitment and data quality will be presented. The interim analysis will be performed based on the primary outcome measure (central-line associated bloodstream infections) and the stopping rule will be evaluated. The results of the interim analysis will be presented during the meeting. Additionally, safety data will be compared between the two treatment groups and presented (e.g. toxicity details in terms of known of serious adverse events).
Will the DMC be blinded to the treatment allocation	The DMC will not be blinded.
Who will see the accumulating data and interim analysis	The DMC members will see the accumulating data and interim analysis. DMC members do not have the right to share confidential information with anyone outside the DMC, including the PI.
Who will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews)	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the DMC members. The trials office team will collate such information.
To whom the DMC will communicate the decisions/ recommendations that are reached	The DMC usually will report its recommendations writing a document for the Trial Steering Committee. This should be copied to the trial statistician and trial manager and if possible should be sent via the trials office in time for consideration at a TSC meeting.
Whether reports to the DMC be available before the meeting or only at/during the meeting	The DMC will receive the report at least 2 weeks before any meetings.

What will happen to the confidential papers after the meeting	The DMC members should store the papers safely after the meeting. After the trial is reported, the DMC members should destroy all interim reports.
8. DECISION MAKING	
What decisions/recommendations will be open to the DMC	Possible recommendations could include: ○ No action needed, trial continues as planned ○ Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence ○ Stopping recruitment within a subgroup ○ Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up ○ Stopping a single arm of a multi-arm trial ○ Sanctioning and/or proposing protocol changes
Statistical methods	<u>Primary analysis</u> The primary end-point is the incidence of CLABSIs. The percentage of first tunnelled CLABSI in each group will be reported. To test the equality of the two proportions a Binomial test will be used. <u>Stopping rule</u> This method described below will be used as a rule, not as a guideline. After inclusion of the first 231 patients an interim analysis will be performed by the trial statistician. The results will be presented at the second DMC meeting, see chapter 9.4. The stopping rule is based on testing the one-sided test at $\alpha = 0.025$ for H0: 'experimental incidence ≥ control incidence' against H1: 'experimental incidence < control incidence'. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the experimental. The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on choices of the α- and β-spending functions. The α-spending function determines how eager or reluctant one is to stop the trial for superiority. The β-spending function determines how eager or reluctant one is to stop the trial because the chance has become small that superiority can be concluded if the trial is continued. As α-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 2.35$. This choice implies that the trial is stopped after 200 patients if the one-sided P-value is smaller than 0.005 (or 0.01 two-sided) in favor of the experimental treatment. As β-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 3.2$. This choice implies stopping the trial after 231 patients if the one-sided P-value is ≥ 0.5, i.e. if the estimated treatment effect at that time is in favor of the control treatment. <u>Safety analysis</u> Percentages of serious adverse events will be reported for both treatment groups.
How decisions or recommendations will be reached within the DMC	It is recommended that every effort should be made by the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial are considered before any recommendation is made.
When the DMC is quorate for decision-making	Effort should be made for all members to attend. The trial office team will try to ensure that a date is chosen to enable this. Members who cannot attend the meeting should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as

	soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the all DMC members.
Input of DMC members who cannot attend	If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may write comments to the DMC Chair to be used during the discussions.
What happens to members who do not attend meetings	If a member does not attend a meeting, he should attend the next meeting. In case of repeated absence he should be replaced.
Whether different weight will be given to different endpoints (eg safety/efficacy)	A different weight will not be given to the different end-points.
9. REPORTING	
To whom will the DMC report their recommendations/decisions, and in what form	A letter to the head of the Trial Steering Committee (Prof. Dr. M.H.W.A. Wijnen) will be written by the DMC within 3 weeks (format annex 3). A copy of this letter will be lodged with the trial office. This should be copied to the trial statistician and trial manager and if possible should be sent via the trials office in time for consideration at a TSC meeting.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Minutes of the meeting will be made by one of the DMC members, these minutes will be kept at the trial office of the Princess Maxima Center.
What will be done if there is disagreement between the DMC and the body to which it reports	In case of disagreement, a meeting between the groups should be held. It will depend on the reason for the disagreement what information will be presented. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there will be a meeting to allow the DMC to discuss the final data analysis with principal trial investigator. The DMC may wish to see a statement that the trial results will be published in a correct and timely manner.
The information about the DMC that will be included in published trial reports	DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A short summary about DMC meetings should be reported.
Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial	The DMC may wish to be given the opportunity to read and comment on any publications before submission.
Any constraints on DMC members divulging information about their deliberations after the trial has been published	The DMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.

NL67388.041.20 - CATERPILLAR

Annex 1: List of abbreviations

DMC	Data Monitoring Committee
SAE	Serious Adverse Events
PI	Principal Investigator
TMG	Trial Management Group
TSG	Trial Steering Committee

Annex 2: Competing interests form

Potential competing interests of Data Monitoring Committee members for *the CATERPILLAR-study (*NL67388.041.20)

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict eg strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the Trial Office of the Princess Maxima Center.

☐ **No,** I have no competing interests to declare
☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

_____

_____

Name: _____

Signed: _____ Date: _____

Annex 3: Suggested report from DMC to TSC where no recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear Prof. Dr. M.H.W.A. Wijnen

The Data Monitoring Committee (DMC) for the CATERPILLAR trial met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

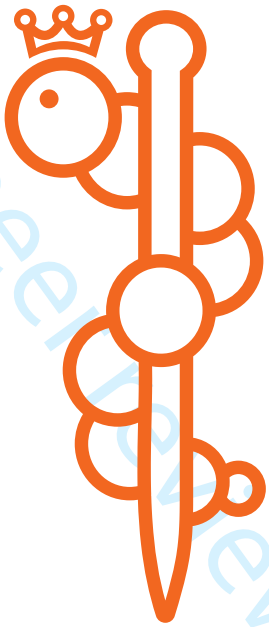
Yours sincerely,

[Name of meeting Chair]
Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:
(1) [*Insert name and role*]
(2) [*Insert name and role*]
(3) [*Insert name and role*]

RESEARCH PROTOCOL
CATERPILLAR-study
(Version 4.0 19-07-2022)



CATERPILLAR
STUDY

PROTOCOL TITLE 'The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunneled central line-associated bloodstream infections in pediatric oncology patients, a randomized controlled, mono-center trial'

Protocol ID	CATERPILLAR
Short title	Efficacy of TauroLock™-Hep100
EudraCT number	Medical Device study, not applicable.
Version	4.0
Date	19-07-2022
Project leader	M.H.W.A. Wijnen, Pediatric Surgeon Princess Máxima Center for Pediatric Oncology Heidelberglaan 25 3584 CS Utrecht the Netherlands M.H.W.A.Wijnen-5@prinsesmaximacentrum.nl
Principal investigator	M.H.W.A. Wijnen, Pediatric Surgeon Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands M.H.W.A.Wijnen-5@prinsesmaximacentrum.nl
Study coordinator	C.H. van den Bosch, PhD-student Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands C.H.vandenbosch-4@prinsesmaximacentrum.nl +31625395632
Clinical researchers	M.D. van de Wetering, Pediatric Oncologist Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands M.D.vandeWetering-4@prinsesmaximacentrum.nl C.P. van de Ven, Pediatric Surgeon Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands C.P.vandeven-4@prinsesmaximacentrum.nl A.F.W. van der Steeg, Pediatric Surgeon Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands A.F.W.vanderSteeg@prinsesmaximacentrum.nl

	Y.G.T. Loeffen, Infectious Diseases Wilhelmina Children's Hospital Heidelberglaan 100, 3584 CX Utrecht Utrecht, the Netherlands Y.G.T.Loeffen-2@umcutrecht.nl Dr. J.T. ter Bruggen and Dr. Frakking Medical Microbiologist Department of Medical Microbiology University Medical Center Utrecht Heidelberglaan 100, 3584 CX Utrecht, the Netherlands
Trial statistician	M.F. Fiocco, Professor of Statistics Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands M.F.Fiocco@prinsesmaximacentrum.nl Leiden University Medical Center (LUMC) Albinusdreef 2, 2333 ZA Leiden, the Netherlands Mathematical Institute – Leiden University Niels Bohrweg 1, 2333 CA Leiden, the Netherlands
Sponsor	Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
Subsidising party	The Dutch Cancer Society (KWF) Delflandlaan 17, 1062 EA Amsterdam, the Netherlands TauroPharm GmbH August-Bebel-Straße 51, D-97297 Waldbüttelbrunn, Germany
Independent expert	Dr. Bierings Pediatric Oncologist Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
Trial and Data Center	Prof. Dr. M. Zwaan Head of Trial and Data Center Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
Pharmacy	Dr. Frederieke Engels, Pharmacist Trial Pharmacy Princess Máxima Center for Pediatric Oncology Heidelberglaan 25, 3584 CS Utrecht, the Netherlands

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor and Head of Trial and Data Center: Prof. Dr. Zwaan Head of Trial and Data Center Princess Máxima Center for Pediatric Oncology	DocuSigned by: Prof. Dr. C.M. Zwaan Naam ondertekenaar: Prof. Dr. C.M. Zwaan Reden voor ondertekening: Ik keur dit document goed Ondertekentijd: 31-aug-2022 | 9:34 PM CEST DD3367F7616B442D81ED81C48F2F2C94	31-aug-2022 | 9:34 PM CEST
Project leader: Prof. Dr. Wijnen Pediatric Surgeon Princess Máxima Center for Pediatric Oncology	DocuSigned by: Naam ondertekenaar: Prof. dr. M.H.W.A. Wijnen Reden voor ondertekening: Ik keur dit document goed Ondertekentijd: 01-sep-2022 | 8:52 AM CEST 7CB44ED1F7C843CAB8867CDE3D2DE0F2	01-sep-2022 | 8:52 AM CEST

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
ASDIN	American Society of Diagnostic and Interventional Nephrology
BSI	Bloodstream Infection
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CL	Citrate Lock
CLABSI	Central Line Associated Bloodstream Infection
CoNS	Coagulase Negative Staphylococci
CRBSI	Central Line Related Bloodstream Infection
CT	Chemotherapy
CV	Curriculum Vitae
CVAD	Central Venous Access Device
CVT	Central Venous Thrombosis
DSMB	Data Safety Monitoring Board
ERBP	European Renal Best Practice
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
H-CVAD	Hickman®-Central Venous Access Device
HL	Heparin Lock
IB	Investigator's Brochure
IC	Informed Consent
ICU	Intensive Care Unit
IGJ	The Health and Youth Care Inspectorate
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MBI-LCBI	Mucosal Barrier Injury – Laboratory Confirmed Bloodstream Infection
M-EDTA	Minocycline and Edetic Acid
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin-Resistant Staphylococcus Aureus
PL	PowerLine®
RCT	Randomized Controlled Trial
RR	Rate Ratio
(S)AE	(Serious) Adverse Event
SCT	Stem Cell Transplantation
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)

SUSAR	Suspected Unexpected Serious Adverse Reaction
TCHL	Taurolidine Citrate Heparin Lock solution
TCL	Taurolidine Citrate Lock solution
THL	Taurolidine Heparin Lock solution
TIVAP	Totally Implantable Venous Access Port
TPN	Total Parenteral Nutrition
VMO	Voorlopige Medicatie Overdracht
WBP	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Tunneled central venous access devices (CVAD) are fundamental in pediatric oncology for long-term venous access. (3) The incidence of central line-associated bloodstream infections (CLABSI) is high. (4) In the Princess Máxima Center, the incidence rate of CLABSI is 1.51 per 1,000 CVAD-days, CLABSIs are seen in at least 30% of the children with a CVAD, 17% of the inserted CVADs are removed early and 5% of the patients are admitted at an intensive care unit due to CLABSIs. (1) Central venous thrombosis (CVT) is another severe complication of a CVAD, with an incidence rate of 0.02-0.24 per 1,000 CVAD-days. (1, 5-8) After a review of the literature, we concluded that the taurolidine-citrate(-heparin) lock solution (TCHL) is the most promising method for the prevention of CLABSIs and CVTs. (2, 9-50) In the Netherlands, the heparin lock (HL) is the standard of care. The HL however, does not have an antimicrobial activity and its use is barely supported by literature. (9) The TCHL has anticoagulant and antimicrobial activities without reported resistance to taurolidine. (12-50) The TCHL has shown to significantly decrease the CVAD-infection incidence in hemodialysis, total parenteral nutrition, and adult oncology patients compared to citrate, heparin and saline locks (rate ratios ranged from 0.00-0.77). (12-44) In pediatric oncology patients, six studies have been performed. (45-50) Unfortunately, these studies did not deliver enough evidence to implement the TCHL in pediatric oncology patients, mainly due to the small study groups, n-total ≤ 180. (45-50) Therefore, we want to perform an open labelled randomized controlled trial (RCT) in a large patient group (n=462) so that we can finally draw conclusions on the efficacy and safety of the TCHL in pediatric oncology patients. Our goal is to increase the quality of life for children with cancer by reducing the CLABSI-rate, CVAD-removal rate, dispense of antibiotics, days of hospital/intensive care admission, and morbidity/mortality rate due to CLABSI.

Objective: To compare the efficacy of the TCHL to the HL in the prevention of tunneled CLABSIs in pediatric oncology patients.

Study design: Investigator-initiated, mono-center, open-labelled randomized controlled trial (RCT). The patients will be followed-up for 90 days in the Princess Máxima Center for Pediatric Oncology and 21 shared care centers in the Netherlands. All data will be collected in in the Princess Máxima Center for Pediatric Oncology.

Study population: Pediatric oncology patients (n=462), ranging from 0-19 years old, who will receive a tunneled CVAD in the Princess Máxima Center for Pediatric Oncology.

Intervention: Patients in the intervention study arm will receive lock solutions containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. Patients in the control study arm will receive lock solutions containing heparin 100 IU/ml. The lock solutions will be instilled with a maximum of once weekly, and a minimum of once every three weeks. In between, all CVADs will be locked with standard heparin 100 IU/ml.

Main study parameter: Incidence of CLABSI

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The expected side effects are temporarily, caused by a spill-over of citrate, and only described if the TCHL is instilled to fast or if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dysgeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are rare but possible side effects. (34) The locks will be instilled with a maximum of once weekly and a minimum of once every three weeks. For a small number of patients this means that they have to visit the Princess Máxima Center for Pediatric Oncology 1-2 times more during the follow-up period compared to patients that do not participate in the study. After every study-lock instillation, the patients will be asked to answer a questionnaire about the experience of possible side effects. Our hypothesis is that the TCHL will reduce the CLABSI rate compared to the HL. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a reduced mortality rate due to CLABSIs compared to the HL. Additionally, patients will benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development.(12-50)

1. AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	06-08-2020	1.2	Non-substantial	Section 7.3 and appendix 5 and 6: Clarifications of study procedure and patientcard/stickers changed.
2	07-10-2020	1.3	Non-substantial	Section 7.3: Change patientcard/stickers.
3	03-02-2021	2.0	Substantial	Chapter 3.0: Minor formatting/spelling changes and description of expert panel. Section 4.3: Clarification of exclusion criteria. Section 5.1 and 6.6: Clarification of lock aspiration. Section 7.3, 10.2 and 12.2: Change in inclusion period. Section 7.3: Change in study procedure if patients do not visit hospital within 3 weeks. Section 3.0, 7.1.3, 7.4, 13.1, 13.7: Addition of an extra endpoint (second CVAD insertion).

				Section 7.1.3: Clarification of endpoints. Section 10.2: Clarification of informed consent procedure. Section 10.5: Removal of description of compensation fee.
4	24-08-2021	3.0	Substantial	Section 2.0, 7.1.2, 7.1.4, 9.2, appendix 5/6: Local infections added as secondary outcome. Section 2.0, 6.4, 7.1.4, 7.3, 9.2, 12.2, and appendix 5: Liver enzymes will no longer be reported.
5	19-07-2022	4.0	Substantial	Section 4.4: We clarified how to account for drop-outs at the end of the study. Section 9.1 and 9.2: Clarification of statistical analyses for primary and secondary outcomes. Appendix 7: Typo removed.

2. INTRODUCTION AND RATIONALE

Central venous access devices in pediatric oncology patients

Central venous access devices (CVAD) are fundamental in pediatric oncology. CVADs are used for stem cell transplantation (SCT), total parenteral nutrition (TPN), blood sampling, chemotherapy (CT) and other intravenous therapies. Long-term central venous access can be provided by tunneled CVADs. The most commonly inserted CVADs are the Hickman®(H)-CVADs/Powerlines® (PL) and totally implantable central venous access ports (TIVAP), these account for 94.2% of all CVADs inserted in our hospital, the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. Since the official opening of the Princess Máxima Center in June 2018 approximately 35-40 CVADs per month are inserted by surgeons in the operating theatre. (1, 3)

The incidence of central line associated bloodstream infections (CLABSI) ranges between 0.1-2.3 per 1,000 CVAD-days, depending on the patient population and infection definitions used. (4) In our pediatric oncology institution a retrospective study investigating the incidence of CVAD related complications in 201 pediatric oncology patients with 307 CVADs was performed. The incidence rate of CLABSIs was 1.51 per 1,000 CVAD-days, this means that a CLABSI was observed in 29.9% of the patients who received a CVAD. (1) Another severe complication of the CVAD is a central venous thrombosis (CVT), with an incidence rate of 0.02-0.24 per 1,000 CVAD days. (1, 5-8) Both complications frequently result in high morbidity and CVAD-removal rates. Of all CVADs inserted, 17% were removed due to a CLABSI. 41.7% Of the CLABSI episodes were successfully treated with systemic antibiotic treatment (SAT), the other CLABSI episodes eventually resulted in reinfections and/or early removal of the CVAD. Five percent of the patients that received a CVAD were admitted to the intensive care unit (ICU) due to severe sepsis caused by CLABSIs. Additionally, nine cases of CVTs were observed of which four resulted in removal of the CVAD. (1)

CLABSI prevention

There are multiple strategies for the prevention of CLABSIs: e.g. education and training of healthcare providers, carefully weighing the risks and benefits of CVAD insertion, the choice of a CVAD with the minimum number of ports/lumen needed, antimicrobial/antiseptic impregnated CVADs, maximal sterile barrier precautions during insertion, skin preparation with chlorhexidine before CVAD insertion, hand hygiene, catheter site dressing regimens, use of a chlorhexidine wash for skin cleansing, frequent CVAD insertion site checks, antimicrobial CVAD lock prophylaxis, the use of needleless intravascular CVAD systems, removal of the CVAD if the CVAD is no longer required, and limiting the amount of CVAD replacements. (3, 51) In our center, a CLABSI prevention meeting is held frequently to evaluate all of the above stated strategies. Due to the conclusions from these meetings the protocols in our hospital are tightened since January 2020. The following interventions are still under discussion in these CLABSI prevention meetings (e.g. chlorhexidine-impregnated dressings, and CVAD lock prophylaxis). The efficacy and safety of chlorhexidine-impregnated dressings is a strategy that needs to be investigated in the future for patients under 18 years before implementation. However, due to the risk of localized dermatitis associated with chlorhexidine-impregnated dressings in neonate patients, we concluded that the risk would be too high to perform a study in our hospital. (3, 51, 52) Additionally, we agreed that a great deal is to be gained from CVAD lock prophylaxis. More about CVAD lock prophylaxis is described in the next paragraph.

CVAD lock prophylaxis

Lock solutions are used to prevent CVADs from CLABSIs and CVTs [Figure 1]. Different locks are available for pediatric oncology patients, e.g. locks containing vancomycin, minocycline-edetic acid (M-EDTA), ethanol, taurolidine, citrate and heparin. (2, 9)

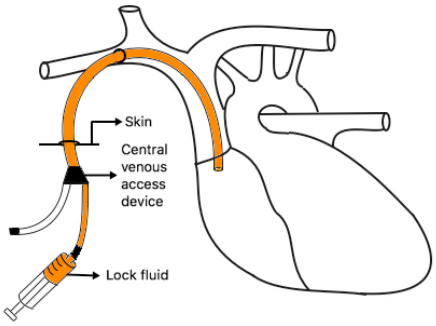


Figure 1: Lock fluid in a central venous access device

In the Netherlands, the heparin lock (HL) is the standard of care to prevent the CVAD from occlusion. (2, 9) The results of a consensus meeting in 2016 on various lock solutions showed that there is barely evidence supporting the HL. They state that the risk of CVAD occlusion is multifactorial and not solely based on blood clotting. Several studies have shown a similar effect of the HL compared to a lock solution containing regular saline. They concluded that a more important factor to prevent CVAD occlusion is an appropriate flushing technique. (9)

Vancomycin containing lock solutions are effective in the prevention of CLABSIs. Abundant antimicrobial use, however, contributes to the development of antibiotic resistance. Therefore, these locks are only recommended in high risk patients. (10, 11, 53)

M-EDTA has antimicrobial and anticoagulant activities. Until so far, one open labelled RCT and one prospective cohort study have been performed to evaluate the efficacy of M-EDTA in pediatric oncology patients. In these studies, the incidence rates of CVAD-related infections were decreased from 6.30 to 1.09, and 2.23 to 0.0 per 1,000 CVAD-days. These studies included 50 and 62 patients and compared the M-EDTA lock with the HL. These studies did not deliver enough evidence to design a study on the efficacy of M-EDTA in children. Additionally, the development of antibiotic resistance is a risk associated with the use of minocycline. (54, 55)

Another antimicrobial lock solution is ethanol. An RCT on the efficacy of the ethanol lock was performed by Wolfs et al., they included 94 pediatric oncology patients. In this study the ethanol lock did not prevent CLABSI treatment failure and it increased CVAD occlusion. (56) A second double-blinded RCT on the efficacy of a lock solution containing ethanol, in 307 pediatric oncology patients, showed a significant decrease of CLABSI from 1.46 to 0.77 per 1,000 CVAD-days without an increase of CVTs. No serious side effects were observed. However, disadvantages of the ethanol lock are the side effects (e.g. nausea, taste alteration, dizziness, blushing, and syncope), and a dwell-in time of two hours after which the lock is removed. The dwell-in time is logistically inconvenient, especially for patients. Additionally, a higher risk of occlusions is suspected with the use of ethanol, and ethanol may interfere with the polymers in some CVADs, degrading the plastic over time. (2, 9, 10)

A lock solution containing taurolidine 1.35% appears to be promising in the prevention of CLABSIs. Different lock combinations containing taurolidine are available, e.g. the

taurolidine-citrate lock (TCL), taurolidine-citrate-heparin lock (TCHL), and taurolidine-heparin lock (THL). (9-11) Taurolidine containing lock solutions offer the many advantages seen with ethanol-based solutions, while avoiding the need for an antibiotic-based solution. (10) Taurolidine containing lock solutions do not require a dwell-in time of two hours after which the lock needs to be removed and can remain in situ for maximum of 30 days (see appendix 2 for the instructions for use). The side-effects associated with taurolidine based locks (e.g. perioral dysesthesia, discomfort of neck and chest, altered taste sensations, nausea and vomiting) are rare and mainly described after the lock is accidentally flushed into the bloodstream. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) The use of the TCL and TCHL resulted in a reduction of the CVAD-infection incidence rate in haemodialysis patients, total parenteral nutrition patients, and oncology patients compared to citrate, saline or heparin locks (rate ratios (RR) ranged from 0.00-0.77). (12-50)

Evaluating the literature published on the different lock solutions our hypothesis is that lock solutions containing taurolidine are the most promising lock solutions for pediatric oncology patients.

Literature on lock solutions containing taurolidine

The majority of the literature published on the efficacy of the lock solutions containing taurolidine were based on haemodialysis patients. Two double-blinded RCTs, four open-labelled RCTs, and eight prospective cohort studies were performed in this patient group. The number of patients included ranged from 13 to 565. The incidence rates per 1,000 CVAD-days were much lower in the THL, TCL, and TCHL groups compared to the HL or CL (RRs ranged from: 0.00-0.58). See table 1 for a summary of the studies performed in haemodialysis patients. Additionally, three systematic reviews were performed concerning haemodialysis patients by Jaffer et al. (2008), Liu et al. (2014), and Kavosi et al. (2016). Jaffer et al. stated that antimicrobial lock solutions decreased CVAD-infection rates without causing significant adverse effects. Liu et al. stated that the TCL significantly reduced the risk of CVAD-related infections and specifically Gram-negative bacterial infections. Kavosi et al. stated that the TCL is superior to heparin, however due to the lack of evidence a confident decision can not yet be made. (12-26)

Table 1: Summary of studies performed in haemodialysis patients (12-26)

Author (year)	Design (adult/pediatric)	Lock type (control – intervention)	Total number of patients or CVADs* (control - intervention	CVAD infections per 1,000 CVAD-days (control – intervention), Rate Ratio (RR), p-value	Number of infections (%/patients or %/cvads*) (control – intervention)	Reduction (control – intervention)	Adverse events
Solomon et al. (2012)	Double-blinded RCT (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4% and taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	174 (34 – 34 and 106)	3.25 - 1.22 and 1.33, RR: 0.38 and 0.41 p<0.01	21 (61.8) – 7 (20.6) and 16 (15.1)	67% and 76%	Addition of heparin reduced the need for thrombolysis
Solomon et al. (2010)	Double-blinded RCT (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4%	107 (54 – 53)	2.38 – 1.34, RR: 0.56 p=0.06 Gram-negative organisms: 1.1 – 0.2, RR: 0.18 p=0.02	23 (42.6) – 11 (20.8)	51%	Greater need for thrombolysis in taurolidine/citrate lock
Betjes et al. (2004)	Open-labelled RCT (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4%	58 (39*-37*)	2.10 – 0.0, RR: 0.00 p=0.05	4 (10.3*) – 0 (0.0*)	100%*	No adverse events observed
Zwiech et al. (2016)	Open-labelled RCT (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	53 (29 – 24)	3.44 – 0.0, RR: 0.00 p<0.05	3 (10.3) – 0 (0.0)	100%	No adverse events observed
Filiopoulos et al. (2011)	Open-labelled RCT (adult)	Heparin 5,000 – taurolidine 1.35% / citrate 4%	119 (58 – 59)	9.92 – 3.67, RR: 0.37 p=0.03	20 (34.5) – 8 (13.5)	61%	More thrombosis in taurolidine/ citrate group, not significant
Winnicki et al. (2017)	Open-labelled RCT (adult)	Citrate 4% lock – taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	106 (54 – 52)	2.7 – 0.67, RR: 0.25 p<0.01	18 (33.3) – 6 (11.5)	66%	Greater need for thrombolysis in citrate lock group
Reidenberg (2018)	Prospective cohort study (adult)	Taurolidine 2.35% / citrate 3.5% / heparin 1000 IU/ml	201	0.28	13 (6.5)	n.a.	Dysgeusia (n=2)
Hulshof et al. (2017)	Prospective cohort study (pediatric)	Heparin 100 IU/ml – taurolidine 2%	23 (7 in cross-over, X-X	12.7 – 4.3, RR: 0.34 p=0.02 (cross over) 14.9 – 3.1, RR: 0.21 p<0.05	X (X) – X (X) (cross-over) 41 (X) - 8 (X)	X	No adverse events observed

			prospective cohort)	(prospective cohort)			
Murray et al. (2014)	Prospective cohort study (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	565 (X tunneled CVAD patients)	Tunneled CVAD patients: 1.59 – 0.69, RR: 0.43 p<0.01	115 (X) – 43 (X)	X	No adverse events observed
Fontsere et al. (2014)	Prospective cohort study (adult)	Heparin 5,000 IU/ml - taurolidine 1.35% / citrate 4% / heparin 500 IU/ml	31 (single arm)	1.08 – 0.04, RR: 0.04 p=0.02	7 (22.6) – 1 (3.2)	86%	No adverse events observed
Allon et al. (2003)	Prospective cohort study (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4%	50 (30 - 20)	5.6 – 0.8, RR: 0.14 p=0.02	16 (53.3) – 1 (5.0)	91%	Greater need for thrombolysis in the taurolidine/citrate group
Sodeman et al. (2001)	Prospective cohort study (adult)	Taurolidine 1.35% / citrate 4% (all patients received a Dialock access system)	70	0.29	8 (11.4)	n.a.	No adverse events observed
Taylor et al. (2008)	Prospective cohort study (adult)	Heparin 5,000 IU/ml – taurolidine 1.35% / citrate 4% / heparine 5,000 IU/ml	X (X – X)	5.2 - 0.6, RR: 0.12 p<0.01	X (X) – X (X)	89%	No adverse events observed
Geron et al. (2006) Article in Hebrew	Prospective cohort study (adult)	X - Taurolidine 1.35% / citrate 4%	13 (5 with previous infections – 8 new patients)	9.5 - 1.15 (pt with previous infections pre- and post TCL) 0.0 (new pts), RR: 0.12 and 0.00	X (X) – X (X)	X	Patency problems for which addition of heparin to lock solution in 10 patients

In total parenteral nutrition patients, two double-blinded RCTs, three open labelled RCTs, seven prospective cohort studies, and three retrospective study were performed. The number of patients included ranged from six to 270. The incidence rates per 1,000 CVAD-days were much lower in the THL, TCL, and TCHL groups compared to the HL or saline (RRs ranged from: 0.00-0.38). See table 2 for a summary of the studies performed in total parenteral nutrition patients. (27-42, 50)

Table 2: Summary of studies performed in total parenteral nutrition patients (27-42, 50)

Author (year)	Design (adult/pediatric)	Lock type (control – intervention)	Total number of patients or CVADs* (control - intervention	CVAD infections per 1,000 CVAD-days (control – intervention), Rate Ratio (RR), p-value	Number of infections (%/patients or %/cvads*) (control – intervention)	Reduction (control – intervention)	Adverse events
Wouters et al. (2018)	Double-blinded RCT (adult)	Saline 0.9% – taurolidine 2%	105 (52 – 53)	1.49 – 0.29, RR: 0.19 p<0.01	18 (34.6) – 5 (9.4)	73%	No difference in adverse events between saline and taurolidine. Dysgeusia (n=1), dizziness (n=1), erhythema exit-site (n=1) associated with the taurolidine lock.
Tribler et al. (2017)	Double-blinded RCT (adult)	Heparin 100 IU/ml – taurolidine 1.35% / citrate 4% / heparine 100IU/ml	41 (21 – 20)	1.44 – 0.33, RR: 0.23 p<0.01	7 (33.3) – 0 (0.0)	100%	Abnormal taste sensations (n=8), tingling sensation (n=3), nausea and vomiting (n=3) in taurolidine/citrate/heparin-group
Lyszkowska et al. (2019)	Open-labelled RCT (pediatric)	Standard aseptic procedures – taurolidine X / citrate X	86 (49* - 48*)	14.3 – 1.06, RR: 0.07 p=0.01	14 (28.6*) – 1 (2.1*)	93%*	No adverse events.
Klek et al. (2015)	Open-labelled RCT (adult)	Saline 0.9% – taurolidine 1.35% / citrate 4% and taurolidine 2%	30 (10 – 10 and 10)	0.0 – 0.27 and 0.0, p=1.00	0 (0.0) – 1 (10.0) and 0 (0.0)	No reduction	One occlusion in the taurolidine 2% group
Bisseling et al. (2010)	Open-labelled RCT (adult)	Heparin 150 IU/ml – taurolidine 2%	30 (14- 16)	2.02 – 0.19, RR: 0.09 p<0.01	9 (64.3) – 1 (6.3)	90%	No adverse events
Chong et al. (2020)	Prospective cross over study	Heparin X IU/ml - taurolidine 1.35% / citrate 4%	33 (TPN n=13 single arm)	11.1 – 2.9, RR: 0.26 p=0.02	X (X) – X (X)	X	Two patients experienced CVAD occlusion for which one patient switched to a TCHL. One patient experienced nausea and vomiting.
Lambe et al. (2018)	Prospective cohort study (pediatric)	Heparin - taurolidine 1.35% / citrate 4%	126 (86 – 40)	0.89 – 0.25, RR: 0.28 p<0.01	X (X) – 5 (12.5)	X	No adverse events
Jurewitsch et al (2005)	Prospective cohort study (adult)	Heparin – taurolidine 2%	7 (single arm)	10.8 – 0.8, RR: 0.07 p=missing	X (X) – X (X)	X	No adverse events
Chu et al. (2012)	Prospective cohort study (pediatric)	Heparin 10 IU/ml – taurolidine 2%	19 (single arm)	8.6 -1.1, RR: 0.13 p<0.01	47 (247.4) – 10 (52.6)	79%	No adverse events

Al-amin et al. (2013) No full-text available	Prospective cohort study (adult)	X – taurolidine 1.35% / citrate 4%	9 (single arm)	6.39 – 0.0, RR: 0.00 p=X	X (X) – X (X)	X	X
Toure et al. (2012)	Prospective cohort study (adult)	Saline 0.9% – taurolidine 1.35% / citrate 4%	15 (single arm)	6.58 – 1.09, RR: 0.17 p<0.01	36 (240.0) – 6 (40.0)	83%	No adverse events
Taniguchi et al. (2009)	Prospective cohort study (adult)	Heparin – taurolidine 1.35% / citrate 4%	6 (single arm)	0.62 – 0.16, RR: 0.25 p=0.03	21 (350.0) – 4 (66.7)	81%	Dysgeusia (n=1), perioral paraesthesia (n=1), and palpitations (n=1)
Saunders et al (2015)	Prospective cohort study (adult)	Heparin – taurolidine 1.35% / citrate 4%	22 (single arm)	5.71 – 0.99, RR: 0.17 p<0.01	42 (350.0) – 12 (54.5)	85%	No adverse events
Olthof et al. (2014)	Retrospective study (adult)	Heparin 150 IU/ml – taurolidine 2%	212 (545* - 200*)	1.10 – 0.20, RR: 0.18 p=X	464 (85.1*) – 43 (21.5*)	75%	Anaphylactic-like reaction (n=1), burning sensations (n=1), occlusion (n=1), dizziness (n=1), paraesthesia (n=1), nausea or pain (n=1), palpitations or discomfort of the chest (n=2) possibly associated with the taurolidine lock.
Wouters et al. (2018)	Retrospective (adult)	Saline - Taurolidine 2%	280 (10 – 270)	1.58 - 0.60, RR: 0.38, p=0.02	13 (130.0) - 203 (75.2)	42%	9% Of the taurolidine patients experienced mild-moderate pain, nausea, dizziness, dyspnea, palpitations, moderate pain, urticaria, pruritus, nausea and vomiting, flushes, headache, paresthesia, and edema.
Arnoriaga Rodriquez et al. (2018)	Retrospective study (adult)	X – taurolidine 2%	13 (single arm)	3.12 – 0.76, RR: 0.24 p<0.01	38 (292.3) – 4 (30.8)	90%	No adverse events

A randomized phase IV trial performed by Longo et al. in 163 adult oncology patients demonstrated a four-fold relative risk reduction of CVAD-related infections. Four CVAD-related infections were observed in 76 patients receiving a saline lock solution, one CVAD-related infection was observed in 84 patients receiving a TCL. However, this difference was not statistically significant, possibly due to power limitations. The incidence rate of CVAD-related infections in the control group was significantly lower than the one chosen as a reference in the sample size calculation. (57) Another randomized double-blinded study in 150 adult neutropenic hematological patients was performed by Gudiol et al., an incidence rate of 3.75 per 1,000 CVAD days with the TCHL compared to 8.91 per 1,000 CVAD days with the HL was found. This difference was not statistically significant. No adverse events related to the lock solutions were observed. (44)

Six articles were published describing a decrease in the incidence rate of bloodstream infections using a TCL or TCHL in pediatric oncology patients. (45-48, 50) Simon et al. prospectively observed the incidence rate of bloodstream infections (BSI). An overall BSI incidence rate of 3.82 was found in the TCL group (n=94) compared 4.93 in the HL group (n=98), (RR: 0.77, p=0.35). However, the incidence rate of BSI due to coagulase negative staphylococci (CoNs) and methicillin-resistant *Staphylococcus aureus* (MRSA) significantly decreased from 2.30 to 0.45 per 1,000 CVAD-days, (RR: 0.20, p<0.01). Limitations of this study were: the small study group and the not-randomized study design. Additionally, CVAD-infections were defined as every bacteremia instead of CLABSI, including bacteraemia caused by infections located elsewhere in the body. (48) Ince et al. retrospectively observed a decreased incidence rate of CLABSI from 48.5% with the HL (n=33) to 22.8% with the TCL (n=79), p=0.03; CLABSI reduction of 53%. Furthermore, the duration of CVAD use per CVAD increased significantly and the incidence rate of CVAD-removal was lower in the TCL group; 81.2% vs. 33.3%. Limitations were the small study groups and retrospective study design. (47) In an open labelled RCT performed by Dumichen et al. the bacteremia incidence rate per 1,000 CVAD-days decreased from 1.30 with the HL (n=36) to 0.30 with the TCL (n=35), (RR: 0.23, p=0.03). Limitations of this study were the small study groups, that CVAD-infections were defined as every bacteremia instead of CLABSI, and that only a few CVADs were immediately locked with the lock solution after insertion of the CVAD. (45) Handrup et al. performed an open labelled RCT comparing the HL (n=65) with the TCHL (n=64). In this study, the incidence rate of CLABSI decreased significantly from 1.40 to 0.40 per 1,000

CVAD-days, (RR: 0.28, p<0.01). Especially CLABSIs caused by CoNS were reduced by 66% in the TCHL group. Other outcomes were an increased time to first CLABSI since CVAD insertion, a reduction of fungi, Gram-positive and Gram-negative microorganisms in the TCHL group, and similar rates of removal due to CVT. The incidence of overall CVAD survival was similar in both groups. A limitation of this study were the small study groups. (46) Clark et al. performed a prospective cohort study investigating the TCL in pediatric patients (n=19) with oncologic and intestinal diseases. The CLABSI incidence rate decreased from 5.5 to 0.5 per 1,000 CVAD-days (RR: 0.09, p<0.01) with the use of TCL compared to the HL. The mean time to first CLABSI increased from 87 days to 296 days after TCL implementation (p=0.01). There were no episodes of hypocalcaemia observed during TCL implementation. A limitation of this study was the small study group. (49) Chong et al. performed a cross over prospective study investigating the TCL in pediatric oncology patients (n=20). The CLABSI incidence rate decreased from 14.4 to 2.4 per 1,000 CVAD-days (RR: 0.16, p<0.01) with the use of TCL compared to the HL. Two patients experienced central line occlusion for which one switched to the TCHL, one patient experienced nausea and vomiting after lock instillation. (50) All studies performed in pediatric oncology patients are summarized in Table 3. (45-50)

Table 3: Summary of studies performed in pediatric oncology patients (45-50)

Author (year)	Design (adult/pediatric)	Lock type (control – intervention)	Total number of patients or CVADs* (control - intervention	CVAD infections per 1,000 CVAD-days (control – intervention), Rate Ratio (RR), p-value	Number of infections (%/patients or %/cvads*) (control – intervention)	Reduction (control – intervention)	Adverse events
Handrup et al. (2013)	Open-labelled RCT	Heparin 250 IU/ml – taurolidine 1.35% / citrate 4% / heparin 100 IU/ml	112 (64 – 65)	1.4 – 0.4, RR: 0.28, p<0.01	26 (40.6) – 7 (10.8)	74%	Unpleasant taste in the majority of the patients.
Dumichen et al. (2012)	Open-labelled RCT	Heparin 100 IU/ml – taurolidine 1.35% / citrate 4%	71 (36 – 35)	1.3 -0.3, RR: 0.23 p=0.03	9 (25.0) - 2 (5.7)	77%	Taste sensations, nausea and vomiting, discomfort of chest and neck, perioral dysesthesia (n=7, 20%)
Chong et al. (2020)	Prospective cross over study	Heparin X IU/ml - taurolidine 1.35% / citrate 4%	33 (oncologic patients n=20 single arm)	14.4 – 2.4, RR: 0.16 p<0.01	X (X) – X (X)	X	Two patients experienced CVAD occlusion for which one patient switched to a TCHL. One patient experienced nausea and vomiting.
Clark et al. (2018)	Prospective cohort study	Heparin 10-100 IU/ml – taurolidine 1.35% / citrate 4%	19 (oncologic patients n=9 single arm)	5.5 – 0.5, RR: 0.09 p<0.01	39 (205.3) – 5 (26.3)	87%	No adverse events described
Simon et al. (2008)	Prospective cohort study	Heparin 200 IU/ml – taurolidine 1.35% / citrate 4%	179 (90 – 89)	All BSIs: 4.93 – 3.82, RR: 0.77 p=0.35 CoNS/MRSE infections: 2.3 – 0.45, RR: 0.20 p<0.01.	All BSIs: 30 (33.3) – 25 (28.1) CoNS/MRSE infections: 14 (15.5) – 3 (3.4)	All BSIs: 16% CoNS/MRSE infections: 78%	Unpleasant taste after flushing, pain during lock instillation in a peripheral catheter.
Ince et al. (2014)	Retrospective	Heparin 100 IU/ml – taurolidine 1.35% / citrate 4%	108 (33* – 79*)	X	16 (48.5)* – 18 (22.8)*, p=0.03	53%*	X

Evaluating the literature published on the different lock solutions, our hypothesis is that a lock solution containing taurolidine, citrate and heparin (TauroLock-Hep100™) is the most promising, safe and appropriate lock solution for pediatric oncology patients.

TauroLock-Hep100™

TauroLock-Hep100™ is a lock solution containing taurolidine 1.35%, citrate 4% and heparin 100 IU/ml. TauroLock-Hep100™ is produced by TauroPharm GmbH, Waldbuttelbrunn, Germany.

Taurolidine is metabolized into water, carbon dioxide, and the amino sulfonic acid taurine, which has an anti-biofilm activity and broad-spectrum antimicrobial activity against fungi (incl. *Candida albicans*), Gram-negative (incl. *Pseudomonas aeruginosa, Stenotrophomonas maltophilia*) and Gram-positive (incl. *Staphylococcus aureus*, coagulase negative

staphylococci*, and enterococci*) bacteria in vitro. (58-61) Taurolidine reduces adherence of bacteria to human epithelial cells and damages the cell walls of bacteria. In vitro, taurolidine even shows anticoagulant activities. (58-61) The major benefit of taurolidine is that in vitro, no evidence of microbial resistance against taurolidine has been found when tested against a broad spectrum of microorganisms. (59, 62) The most commonly described concentration of taurolidine in literature is 1.35% and does not show clinically relevant differences to taurolidine 2.0%. (9, 48, 58, 61, 62) This concentration is at least 10 times higher than the minimal inhibitory concentration $(MIC)_{50}$ for the majority of Gram-negative and Gram-positive microorganisms. (62) As described above, different lock solutions containing taurolidine are available. Olthof et al. tested the amount of microbial growth inhibition between different lock solutions containing taurolidine in vitro. They found minor differences in microbial growth inhibition and stated that these differences would not be relevant in the clinical setting. Furthermore, they found a decrease in thrombus weight due to taurolidine. This was, however, not as effective as citrate or heparin. Therefore, they advised that patients may benefit from the addition of heparin and/or citrate to taurolidine lock solutions. (61) High-dose concentrations of taurolidine (290 mg/kg, 2% taurolidine) have been associated with liver injury in mouse models. Low-dose concentrations of taurolidine (140 mg/kg, 2% taurolidine) which are similar to the TCHL dose did not show significant differences in liver injury compared to the control group (physiologic saline).(63) Lastly, hypersensitivity reactions to taurolidine are possible. (9, 18, 20, 45-48, 50)

Citrate has calcium-chelating properties, which results in both an anticoagulation and antimicrobial activity. (9, 64) Available solutions of citrate have concentrations ranging from 4 to 46%. Pittiruti et al. describes that higher concentrations of citrate are associated with a higher efficacy of CVAD-occlusion prevention. However, the European Renal Best Practice (ERBP), American Society of Diagnostic and Interventional Nephrology (ASDIN) and the Food and Drug Administration (FDA) advise to use a concentration of no more than 4% citrate in the prevention of central line related bloodstream infections (CRBSI), due to a case report of a patient that suffered cardiac arrest secondary to hypocalcaemia after injection of 46.7% citrate in the CVAD. (9) The described side-effects associated with the TCHL are presumably explained by spill-over/accidental flushes of citrate into the bloodstream. These side-effects include perioral dysesthesia, discomfort of neck and chest, dysgeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) All side effects are temporarily, described if the TCHL is instilled to fast, if the TCHL is accidentally flushed instead of aspirated and were only in rare occasions a reason to withdraw from the studies performed. Additionally, hypersensitivity reactions to citrate are possible. (9, 18, 20, 45-48, 50)

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X. Heparin prevents the progression of an obstruction by inhibiting further clot formation and allowing the activation of natural clot lysis. Heparin has a half-life of 1-2 hours. In haemodialysis patients the more frequent need for thrombolysis in patients receiving the TCL compared to the HL is described. (18, 20-22, 25, 26) This however, did not result in a higher frequency of CVAD removal in these patients. (18, 20) Solomon et al. advised to add 500 IU/ml heparin to the lock solution in haemodialysis patients. (20) In pediatric oncology patients, Handrup et al. used the TCL with the addition of 100 IU/ml heparin to prevent the CVAD from occlusions and CVAD-related CVTs. In this study, no CVADs were removed due to occlusion or thrombosis. (46) Due to the possible higher rate of occlusion due to blood clotting using the TCL, and similar rates of CVT/occlusion associated with the addition of heparin 100 IU/ml, we chose for the addition of heparin 100 IU/ml to the TCL. (18, 20) Side effects related to heparin, which are very rare,

are: hypersensitivity reactions, drug incompatibilities, and heparin-induced thrombocytopenia. In rare occasions, when the wrong dosage is used, iatrogenic hemorrhages can occur. (9, 65)

In this study, to avoid the above mentioned side-effects, the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), heparin is added to the solution for the prevention of the more frequent dispense of thrombolytics, and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed during the study.

Purpose of this study

Hypothetically, the TCHL will reduce the CLABSI rate compared to the HL. Additionally, the use of the TCHL may reduce the frequency of systemic antibiotic treatment, result in lower rates of CVAD-removal, fewer days of hospital/ICU admission, and a reduced mortality rate. Patients will benefit directly from reduced and more appropriate antibiotic use, which will also lead to a reduced risk of developing antibiotic resistance. Previous studies performed on the efficacy of the TCL or TCHL in pediatric oncology patients did not include enough patients to confirm the superior efficacy of the TCHL. Therefore, these studies do not deliver enough evidence to implement the TCHL in the pediatric oncology care in the Netherlands. (45-50) Due to the centralisation of the pediatric oncology care in the Netherlands, we are now able to include enough patients to finally draw a conclusion on the efficacy of the TCHL compared to the HL.

2. OBJECTIVES

Primary Objective:
To determine wheter the use of the taurolidine 1.35%, citrate 4%, and heparin 100 IU/ml lock solution (TauroLock™-Hep100) reduces the incidence of first tunneled central line associated bloodstream infections (CLABSI) compared to the heparin 100 IU/ml lock solution, in pediatric oncology patients, with a maximum follow-up of 90 days.

Secondary Objectives:
To compare the efficacy of the taurolidine 1.35%, citrate 4%, and heparin 100 IU/ml lock solution (TauroLock™-Hep100) to that of the heparine 100 IU/ml lock solution on the:

- Time to first tunneled CLABSI since the insertion of the CVAD
- CLABSI incidence per 1,000 CVAD-days
- Incidence of symptomatic CVTs
- Incidence of bacteremia
- Incidence of local infections
- Dispense of thrombolysis/systemic antibiotic treatment due to CLABSIs/CVTs
- Incidence of and reasons for CVAD-removal
- Cultured microorganisms causing CLABSIs
- Days of hospital admission due to CLABSIs/CVTs
- Safety of the TCHL/HL in terms of known side effects, severe adverse events (SAEs), intensive care unit admission, and mortality rate due to CLABSIs/CVTs

3. STUDY DESIGN

The CATERPILLAR study is designed as a mono-centre, investigator initiated, open labelled randomized controlled trial (RCT). Patients who receive their first CVAD or patients who receive a second, third, fourth etc. CVAD after a CVAD-free interval of more than 12 months, will be asked to participate in this study. These patients will be included in 29 months. Patients will be randomized into the HL study arm (n=231) or TCHL study arm (n=231). The lock will be instilled in the Princess Maxima Center with a maximum of once weekly (if admitted at the hospital or regulary visiting the hospital) and a minimum of once every three weeks (instillation before going home or to a different hospital for >1 week). In between, all patients will receive heparin 100 IU/ml. All patients will be followed up from CVAD insertion until the first CLABSI episode, CVAD-removal, second CVAD insertion (excl. stem cell apheresis CVADs) or death with a maximum study period of 90 days, whichever comes first. The maximum study period of 90 days was chosen since a great deal of the CLABSI episodes occur within the first 90 days after insertion. [Figure 2 and 3] (1, 2) All data (incl. shared care hospital data as this is standard of practice) will be collected in the Princess Máxima Center for Pediatric Oncology.

In the first months after diagnosis and CVAD insertion, patients will receive their oncologic treatment at the Princess Máxima Center for Pediatric Oncology. After one-two months, a minority of the patients will be treated in the shared care hospitals close to their homes and will return at least every three-six weeks to the Princess Máxima Center for Pediatric Oncology. Since the majority of the patients will be treated in the Princess Máxima Center in the first 90 days of their treatment (our follow-up time) we concluded that the benefits would not outweigh the expenses and difficult logistical execution of the instillation of the TCHL in all shared care hospitals in the Netherlands.

In consultation with the Trial Pharmacy of the University Medical Center Utrecht (UMCU) we chose for an open-labelled design since blinding of the lock ampoules would be too difficult and expensive since the design of the lock ampoules are not similar. Blinding with labels would not be sufficient. At first, we tried to find pharmacies that could fabricate similar ampoules with Taurolock-Hep100. The fabrication of TauroLock-Hep100 ampoules would cost >4 million euro or a bulk solution should be sent from TauroPharm to the pharmacy, which is also very pricely, logistically difficult and unusual. Another option discussed was to pre-fill syringes by pharmacies or unblinded nurses. This would need to be done for the heparin and TauroLock-Hep100 solution since neither of them are commercially available in 3mL pre-filled syringes. If performed by unblinded nurses the locks will expire after 24 hours and if performed by pharmacies the locks will expire after 7 days. Therefore, this option would also have resulted in high costs and would logistically be difficult to execute. Therefore, we concluded that the advantages did not outweigh the high costs and logistically difficult execution of a double-blinded RCT. Additionally, we formed an expert panel of three blinded specialists (microbiologists and infectiologists) to evaluate all positive bloodcultures and score them as CVAD associated or not.

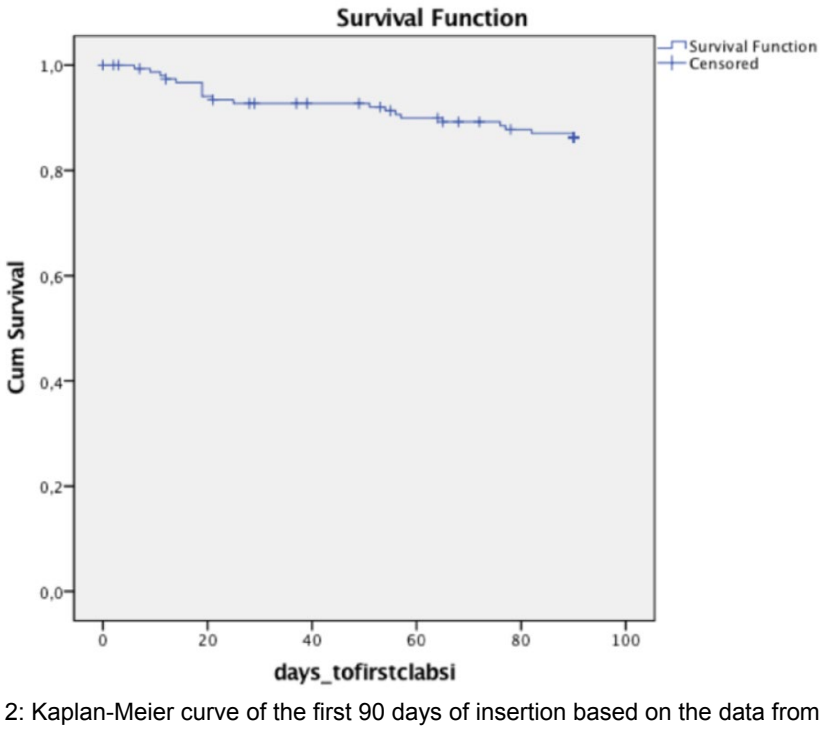


Figure 2: Kaplan-Meier curve of the first 90 days of insertion based on the data from the retrospective study performed by van den Bosch et al. (2019)(1) On the x-axis the days to first observed CLABSI per patient since the insertion of the CVAD. On the y-axis the cumulative CLABSI free survival. A CLABSI in the first 90 days was observed in 12.8% of the patients that received a CVAD.

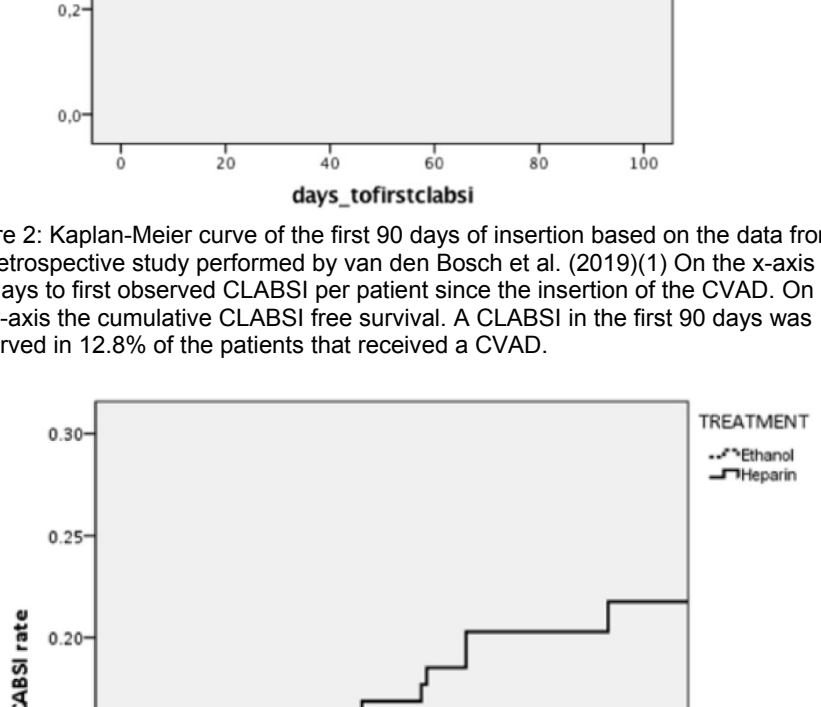


Figure 3: Kaplan-Meier curve of the first 200 days of insertion based on the data from the randomized controlled trial performed by Schoot et al. (2015) (2) On the x-axis the CVAD days to the first observed CLABSI per patient since the insertion of the CVAD. On the y-axis the cumulative CLABSI rate.

4. STUDY POPULATION

4.1 Population

All consecutive pediatric oncology patients (hematologic, solid and neurologic malignancies), treated in the Princess Máxima Center for Pediatric Oncology, ranging from 0-19 years old, receiving a tunnelled CVAD (H-CVAD/PL or TIVAP) for the first time or if their previous CVAD has been removed >12 months ago, will be asked to participate in this study. From May 2018, all pediatric oncology patients in the Netherlands are treated at the Princess Máxima Center for Pediatric Oncology. We expect that the planned number of patients can be recruited in 29 months from the defined source population.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age between 0 - <19 years
- Radiological, cytological or histological proven paediatric malignancy (hematologic, solid, and neurologic malignancies)
- H-CVAD/PL or TIVAP to be inserted at the Princess Máxima Center for Pediatric Oncology
- Planned CVAD insertion of >90 days
- Written consent signed according to local law and regulations
- Parents/guardians or patient are willing and able to comply with the trial procedure

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- A previous CVAD removed < 12 months ago.
- Expected treatment for a majority of the follow-up time in a different hospital than the Princess Maxima Center for pediatric oncology in the first 90 days of inclusion resulting in difficulties/the inability to visit the Princess Maxima Center at least once every 3 weeks.
- Primary immunological disorder
- Contra indications: known hypersensitivity to taurolidine, citrate or heparin, and a history of heparin-induced thrombocytopenia.
- Documented bacteremia in the period from 24h before catheter insertion until inclusion
- Insertion of the CVAD at the same site as a previously confirmed CVT
- Pregnant, not willing to use adequate contraceptives, or breast-feeding

4.4 Sample size calculation

Our own database of CVAD associated complications (2015-2017) showed that 12.8% of the patients with an H-CVAD/PL or TIVAP developed at least one CLABSI within 90 days after insertion of their first CVAD (or second/third/etc. CVAD if their previous CVAD was removed >12 months ago). (1)

Group sample sizes of 206 in the TCHL-group and 206 in the HL-group achieve 80% power to detect a difference between the group proportions of 0.0780. The proportion in the TCHL-group (the treatment group) is assumed to be 0.1280 under the null hypothesis and 0.050 under the alternative hypothesis. The proportion in the HL-group (the control group) is 0.1280. The statistic test used is the two-sided Z-Test with unpooled variance.

An interim analysis will be performed after the inclusion of 231 patients. The level of test for the final analysis must be adjusted since part of the alpha will be used in the interim analysis. The level is based on the following computations. The first quantile (for the interim analysis) is set in such a way that the two-sided probability $P(|U1| > q1) = 0.01$ where U1 is the test used at the interim analysis and P means probability. For the law of large numbers U1 has a normal distribution with mean 0 and variance 1. This implies that the first quantile for the interim analysis is equal to 2, 575829. To compute the second quantile the joint distribution (U1, U2), which is bivariate normal with variances 1 and correlation $1/\sqrt{2}$ need to be employed. The second quantile needs to satisfy $P(|U1| > q1$ or $|U2| > q2) = 0,05$, or equivalently, $P(-q1 < U1 < q1, -q2 < U2 < q2) = 0,95$. The second quantile coming from the bivariate joint normal distribution (U1, U2) is equal to 2,002732; the corresponding nominal alpha level for the final analysis is therefore equal to 0.04520606.(66-71)

For each patient that prematurely drops-out of the study an extra patient will be included, we estimated that an extra 50 patients would be needed to account for potential drop-outs. The drop-out inflated sample size was therefore eventually calculated as 462 patients, 231 in each group. Our hypothesis is that the drop-out risk is minimal since all patients are seen regularly in the Prinses Maxima Center for pediatric oncology in the first 90 days of their treatment and the side-effects of the TCHL are minor and rare. The intention to treat principle is used in this study, therefore all patients are included in the final statistical analyses.

Since May 2018 all pediatric oncology patients are diagnosed and treated at the Princess Máxima Center, 550 new patients each year. Approximately 402 (73%) of these patients will receive a CVAD. (4) During the ARISTOCATHS-study, a similar study in the Netherlands investigating the ethanol lock in pediatric oncology children, 728 patients were screened for enrolment in the study, of which 421 (58%) patients were ineligible or declined to participate in the study. (2) In contrast to the ARISTOCATHS-study, during this study, all patients will be included in one center instead of eight and the TCHL is not associated with side effects like the ones associated with the ethanol lcok. Therefore, we hypothesized that 40% of the patients will be excluded or refuse to participate. Therefore, we hypothesized that we are able to include 240 patients each year (20 patients each month). To reach the total number of 462 patients, it will take us approximately 23 months. However, due to the risk of slow accrual, we added six months extra to the inclusion timeframe. Therefore, we estimate that it will take 29 months to include all patients. The last included patient will be followed-up for a maximum of 90 days, therefore the total study duration will be approximately 32 months. [Table 4]

Table 4: Planned study schedule

Months after start inclusion	What?	Description
0	Start inclusion	Planned start of the study
14.5	Interim database lock and interim analysis	After the inclusion of 50% of the patients
29	Stop inclusion	After the inclusion of 462 patients
32	Stop follow-up	After a period of 3 months after the inclusion of the last patient
32 - 36	Database lock, statistical analysis, writing the clinical study reports, and drafting of the manuscript based on the clinical study reports.	From the stop of follow-up until manuscript submission.
36	Manuscript submission	Four months after the study has stopped.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Comparator study arm (HL-study arm): Patients participating in the HL-study arm will receive the current standard of care lock solution containing heparin 100 IU/ml. The HL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. To summarize, the maximum amount of study lock instillations is once every week and the minimum is once every three weeks. The lock volume depends on the CVAD type. [Table 5] The HL will be aspirated from all lumina before instillation of a new lock.

Investigational study arm (TCHL-study arm): Patients participating in the TCHL-study arm will receive the current standard of care lock solution containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. The TCHL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. To summarize, the maximum amount of study lock instillations is once every week and the minimum is once every three weeks. The lock volume depends on the CVAD type. [Table 5] The TCHL will be aspirated from all lumina before instillation of a new lock.

In between the above stated locking moments, the CVADs will be locked with standard heparin 100 IU/ml following the standard protocol of the Princess Máxima Center for Pediatric Oncology, home care institutions and all other shared care centers in the Netherlands.

5.2 Use of co-intervention

All co-interventions can be used as in usual clinical practice.

5.3 Escape medication

All escape medication can be used as in usual clinical practice.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Comparator study arm (HL-study arm)

Patients participating in the HL-study arm will receive the current standard of care lock solution containing heparin 100 IU/ml, 2 ml. The heparin lock will be aspirated before instillation of a new lock solution. The heparin 100 IU/ml lock is the standard of care in the Netherlands for locking CVADs. There is no registered heparin lock product available in the Netherlands. In the Princess Maxima Centre heparin 100 IU/ml, 50 ml is obtained via a so called "collegial delivery of pharmacy compounded medicinal products" (Dutch: "collegiaal doorgeleverde bereiding") This is an exception of The Dutch Medicines Act (www.igj.nl/zorgsectoren/geneesmiddelen-zonder-handelsvergunning/collegiaal-doorleveren). Heparin 100 IU/ml, 50 ml (ZI-number: 16037332) is produced by the Scheldezoom pharmacy (Spoorstraat 16, 4431 NK, 's-Gravenpolder, the Netherlands, https://www.scheldezoom.nl/algemeen). The Scheldezoom pharmacy is a GMP compounding pharmacy for expertise, preservation, and nation-wide delivery of commercially unavailable but rationally necessary medicines (GMP Report submitted in D2. of this METC submission). This product i.e. heparin 100 IU/mL, 50 ml is subsequently used to produce the final product, heparin 100 IE/ml, 2 ml in syringe for patient care. This final product is manufactured by the RIVA™ robot in the Pharmacy of the Prinses Maxima Center for Pediatric Oncology (Productdossier submitted in D2).

An officially registered comparable product is the BD PosiFlush™ Pre-filled Heparin Lock Flush. However, the BD PosiFlush™ Pre-filled Heparin Lock Flush is only registered in the United States of America (USA) and Canada. Therefore this product is not yet available in the Netherlands.(72, 73) The Food and Drug Administration (FDA) transferred the primary responsibility for the regulation of heparin catheter lock-flush solution products from the Center for Drug Evaluation and Research (CDER) to the Center for Devices and Radiological Health (CDRH). Heparin catheter lock-flush solution products are combined drug-device products. The transfer was based on the FDA's determination that the primary mode of action of these heparin catheter lock-flush solution products is that of the device part of the combination. (74) The BD PosiFlush™ Pre-filled Heparin Lock Flush is therefore registered as a medical device in the USA and Canada. (72, 73)

Investigational study arm (TCHL-study arm)

Patients participating in the TCHL-study arm will receive a lock solution containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml (TauroLock™-Hep100). TauroLock™-Hep100 is produced by TauroPharm GmbH, August-Bebel-Straße 51, D-97297, Waldbüttelbrunn (www.taurolock.com). TauroLock™-Hep100 is CE-accredited and registered as a class III medical device. TauroLock™-Hep100 is used in the authorised form for the authorised indication. The certificates, declaration of conformity, and instructions for use can be found in appendix 2. [Appendix 2]

6.2 Summary of findings from non-clinical studies

Comparator study arm (HL-study arm)

There are no non-clinical data of relevance which are additional to the information already included in the other paragraphs.

Investigational study arm (TCHL-study arm)

As described in more detail in the introduction and rationale, in vitro studies show that the TCHL has anti-coagulant, anti-biofilm, and antimicrobial activities, without evidence of

antibiotic resistance to taurolidine. (58-61, 75) Taurolidine has shown a broad-spectrum activity against fungi, Gram-positive and Gram-negative bacteria in vitro. (58-61) High-dose concentrations of taurolidine (290 mg/kg, 2% taurolidine) have been associated with liver injury in mouse models. Low-dose concentrations of taurolidine (140 mg/kg, 2% taurolidine) which are similar to the TCHL dose did not show significant differences compared to the control group (physiologic saline). (63) It was advised by Olthof et al. to add citrate and/or heparin to the lock solution with taurolidine to prevent the CVAD from occlusion. (61)

6.3 Summary of findings from clinical studies

Comparator study arm (HL-study arm)

The HL is the standard of care in the Netherlands to lock CVADs in children and adults. Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in-vivo and in-vitro. (9, 65) Multiple studies have been performed to compare the efficacy of heparin to saline in the prevention of CVAD occlusion. The majority of these reports failed to show a superiority of heparin. (9)

Investigational study arm (TCHL-study arm)

A detailed description of the results and limitations of all clinical studies found in literature on the efficacy of the TCHL is to be found in the introduction section; below you will find a brief summary. The use of the TCL/TCHL showed decreased incidence rates of infections related to the CVAD in haemodialysis patients, total parenteral nutrition patients, and oncology patients compared to lock solutions containing saline or heparin. (12-41, 43, 45-50) Six studies have been performed in pediatric oncology patients. (45-50) Simon et al. performed a prospective cohort study (n = 179) and showed a significant decrease in infections due to CoNS and MRSA in the TCL study arm compared to the HL study arm (0.45 vs. 2.30 per 1,000 CVAD-days, p<0.01), however no difference in the incidence rate of bacteraemia was found between the two study arms. (48) Dumichen et al. performed an open labelled RCT (n = 71) and found a significant decrease in the incidence rate of bacteraemia in the TCL study arm compared to the HL study arm (1.30 vs. 0.30 per CVAD-days, p=0.03). (45) Ince et al. performed a retrospective study (n = 108) and showed a decrease in the CLABSI rate (48.5% vs. 22.8%, p=0.03), an increased duration of CVAD use, and a lower rate of catheter removal in the TCL study arm. (47) Handrup et al. performed the only open labelled RCT (n = 112) to compare the HL with the TCHL in pediatric oncology patients. They found a decrease in the incidence rate of CLABSI (1.40 vs. 0.40 per 1,000 CVAD-days, p<0.01), an increased time to CLABSI, and a reduction of fungi, Gram-positive and Gram-negative microorganisms in the TCHL study arm. Especially, CLABSIs caused by CoNS were reduced by 66% in the TCHL group. The incidence of removal due to occlusion and CVT, and overall CVAD survival were similar in both groups. (46) Recently, Clark et al. performed a prospective cohort study investigating the TCL in pediatric patients (n=19) with oncologic and intestinal diseases. The CLABSI incidence rate decreased from 5.5 to 0.5 per 1,000 CVAD-days (p<0.01) with the use of TCL compared to the HL. The mean time to first CLABSI increased from 87 days to 296 days after TCL implementation (p=0.01). There were no episodes of hypocalcaemia observed during TCL implementation. (49) Chong et al. performed a cross over prospective study investigating the TCL in pediatric oncology patients (n=20). The CLABSI incidence rate decreased from 14.4 to 2.4 per 1,000 CVAD-days (p<0.01) with the use of TCL compared to the HL. Two patients experienced central line occlusion for which one switched to the TCHL, one patient experienced nausea and vomiting. (50) All studies performed in pediatric oncology patients only contained small study groups (n= ≤ 180) and were therefore not considered as enough evidence to implement the TCHL in the pediatric oncology care in the Netherlands. (45-50)

6.4 Summary of known and potential risks and benefits

Comparator study arm (HL-study arm)

Heparin is a naturally occurring anticoagulant which prevents the coagulation of blood in-vivo and in-vitro. It potentiates the inhibition of several activated coagulation factors, including thrombin and factor X. Heparin prevents the progression of an obstruction by inhibiting further clot formation and allowing the activation of natural clot lysis. Heparin has a half-life of 1-2 hours when it enters the bloodstream. Used as directed, it is extremely unlikely that the low levels of heparin reaching the blood will have any systemic effect. However, if the heparin does reaches the bloodstream possible side effect can occur: hypersensitivity reactions, heparin-induced thrombocytopenia and drug incompatibilities. In extremely rare occasions, when the wrong dosage is used, iatrogenic hemorrhages can occur. (9, 65)

Investigational study arm (TCHL-study arm)

A detailed description of the risks and benefits of the TCHL is to be found in the introduction section; below you will find a brief summary. Hypothetically, the TCHL will reduce the CLABSI rate. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a lower mortality rate due to CLABSI. Patients will benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development. (12-41, 43-50)

The expected side effects are temporarily, caused by a spill-over of citrate, and only described if the TCHL is instilled to fast or if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dygeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Hypocalcaemia events causing arrhythmias have only been associated with much higher concentrations of citrate, which are not used in this study. Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are possible side effects, but in literature only one patient has been described in whom an anaphylactic-like reaction was observed. (34) Liver-injury is associated with high-concentrations of systemic taurolidine in mouse-models, the TCHL contains low-dose taurolidine, which is not associated with liver-injury. A more frequent dispense of thrombolytics has been associated with lock solutions containing taurolidine and citrate in haemodialysis patients. This was only observed without the addition of heparin. (18, 20-22, 25, 26) In this study, the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), heparin is added to the solution for the prevention of the more frequent dispense of thrombolytics, and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed during the study. If aspiration is not possible, TauroPharm suggests to apply the lock not faster than 1 ml per eight seconds. In this case only a total of ≤2.6ml of the lock solution will reach the bloodstream. (48) The citrate will dilute so fast that no problems concerning the calcium concentration are suspected. (46, 48, 64)

6.5 Description and justification of route of administration and dosage

Comparator study arm (HL-study arm)

Description

Patients participating in the HL-study arm will receive the current standard of care lock solution containing heparin 100 IU/ml. The HL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the

Princess Máxima Center for >1 week the CVAD will be locked and the lock will be be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. The lock volume depends on the CVAD type. [Table 5] The HL will be aspirated before instillation of a new lock. In between, all patients will be locked with heparin 100 IU/ml following the CVAD-manipulation protocol of the Princess Máxima Center for Pediatric Oncology and all shared care hospitals in the Netherlands. (9, 65, 76)

Justification
Guidelines recommend the use of heparin at 10-100 IU/ml for CVAD locking, 10 IU/ml for daily flushing and 100 IU/ml for periodic locking. In the Princess Máxima Center for Pediatric Oncology and all shared care hospitals in the Netherlands we chose for 100 IU/ml since most CVADs are locked periodically. (9, 65, 76, 77) The lock frequency and aspiration of the lock will be performed in this group to make both investigational groups equal.

Investigational study arm (TCHL-study arm)
Description
Patients participating in the TCHL-study arm will receive a lock solution containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. The TCHL will be instilled in the CVAD lumen once a week if the CVAD is disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. The lock volume depends on the CVAD type. [Table 5] The TCHL will be aspirated before instillation of a new lock. In between, all patients will be locked with heparin 100 IU/ml following the CVAD-manipulation protocol of the Princess Máxima Center for Pediatric Oncology and all shared care hospitals in the Netherlands. (9, 65, 76)

Justification lock dosage
Available solutions of citrate have concentrations ranging from 4 to 46%. Pittiruti et al. describes that higher concentrations of citrate are associated with a higher efficacy of CVAD-occlusion prevention. However, the European Renal Best Practice (ERBP), American Society of Diagnostic and Interventional Nephrology (ASDIN) and the Food and Drug Administration (FDA) advise to use a concentration of no more than 4% citrate in the prevention of central line related bloodstream infections (CRBSI), due to a case report of a patient that suffered cardiac arrest secondary to hypocalcaemia after injection of 46.7% citrate in the CVAD. (9, 18, 20, 45-48, 50) In order to prevent the above stated side effects we will use citrate 4.0%, we adjusted the lock volumes to the lumen of the CVADs, and we will aspirate the lock before use of the CVAD. If aspiration, on rare occasions, is not possible, TauroPharm suggests applying the lock not faster than 1 ml per eight seconds. If this happens only a maximum total of ≤2.6ml of the lock solution will reach the bloodstream. (48) The citrate will dilute so fast that no problems concerning the calcium concentration are suspected. (64)

Concentrations of 1.35% and 2.0% taurolidine are described in literature, no clinically relevant differences were found between the two concentrations. (9, 48, 58, 61, 62) These concentrations are at least 10 times higher than the MIC_{50} of the majority of Gram-negative and Gram-positive microorganisms. (62) A concentration of 1.35% taurolidine is the most commonly used in pediatric oncology patients. (9, 48) The microbial destruction time of taurolidine in vitro is 30 minutes, therefore the TCHL needs to be in situ for at least >1 hour. (78, 79)

In pediatric oncology patients, heparin 100 IU/ml is added to the TCL, in comparison with the addition of 500 IU/ml heparin, which is used in haemodialysis patients. The TCHL is associated with equal removal rates due to CVT compared to the HL alone in pediatric oncology patients. (46, 64) To further prevent the CVAD from occlusion, proper flushing policies, needle free connectors and no-reflux strategies are used during the administration of the lock solution. (9) Heparin 100 IU/ml is also the preferred dosis for the standard of care heparin lock. (9, 65, 76)

Justification of volume

Literature advices to minimize the lock volume to minimize leakage into the bloodstream. The minimum volume is the volume of the CVAD, since the CVAD lumen has to be filled entirely. During insertion the CVADs will be trimmed to fit the individual child, therefore the volume will be less than the company's stated CVAD priming volume (a difference of 0.02-0.20 ml per 10 cm). The true volumes of the CVAD and the advised lock volumes can be found in table 5. [Table 5] If the positive pressure technique is performed inadequetly, it is possible that a small volume is not injected into the CVAD, therefore all lock volumes are 15-20% higher than the maximal catheter volume (as adviced in literature). (65, 67) The CVAD volume includes the catheter, huber needle with wire (0.3 ml), three-way valve (0.2 ml), and needle-free connector (Clave®) (0.05 ml).

Table 5: Lock Volumina

CVAD	Type	Diameter (Fr)	Maximal catheter volume (ml)	Lock volume (ml)
TIVAP	Babyport®	4.5	0.80	1.0
	Low-profile®	6.5	1.04	1.5
	Standard®	6.5	1.28	1.5
Broviac®	Single lumen	6.6	0.74	1.0
Hickman®	Double lumen	7.0	0.90/0.80	1.0/1.0
Powerline®	Double lumen	6.0	0.70/0.70	1.0/1.0
	Triple lumen	6.0	0.75/0.62/0.62	1.0/0.8/0.8

Justification lock frequency

The instructions for use of TauroLock-Hep100 do not give an advice about the maximum amount of locks that can be instilled in a certain time frame. The instructions only state: "TauroLock-Hep100 will remain inside the access device until the next treatment (for a maximum of 30 days)." The studies performed in pediatric oncology patients Schoot et al., Handrup et al., and Simon et al. all locked the CVAD mostly once and sometimes twice a week. All observed a significant reduction of the amount of CLABSIs. (2, 46, 48) Clark et al. locked the CVAD daily and Ince et al., Chong et al. and Dumichen et al. did not report their lock frequency. (47, 49, 50) Daily locks might be safe, however due to the minimal amount of evidence and the possible side effects associated with high concentrations of citrate, we decided to choose a maximum lock frequency of once a week similar to most performed pediatric oncology studies. (9, 18, 20, 45-48, 50)

We chose for a minimum lock frequency of at least once every three weeks if patients are not seen at the Princess Máxima Center for >1 week so that these patients do not have to travel to the Princess Máxima Center every week only for the study lock. We chose specifically for three weeks since most patients are at least seen once every three weeks at our hospital and the TCHL can remain in situ for a maximum of 30 days. We did not choose for a minimum frequency of >3 weeks since it is possible that in between the lock is removed by

home care or shared care nurses. This way we can ensure that every patient has a lock in situ at least once every three weeks.

6.6 Dosages, dosage modifications and method of administration

Dosages

Lock volume depends on the CVAD type [Table 5]. A minimum of 5 and maximum of 13 locks per patient will be instilled in the follow-up of 90 days.

- TCHL-study arm: taurolidine 1.35%, citrate 4% and heparin 100 IU/ml.
- HL-study arm: 100 IU/ml heparin.

Method of administration

Five steps of administration (48):

1. Flush the device with 10 mL of saline.
2. Withdraw the lock from the vial/ampoule using an appropriate syringe.
3. Instill the lock slowly (not more than 1 mL per second, infants and children less than two years of age not more than 1 mL per 5 seconds) into the access device in a quantity sufficient to fill the lumen completely. [Table 5] The lock will remain inside the access device until the next treatment (for a maximum of three weeks).
4. Prior to the next treatment, the lock must be aspirated from all lumina and discarded. In the advent of inability to aspirate from the device, the lock should be flushed very slowely <1 mL/5 sec.
5. Flush the device with 10 mL of saline.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable, since this study is submitted as a medical device study, see paragraph 6.1.

6.8 Drug accountability

Shipment and receipt

The TCHL will be shipped from the TauroPharm GmbH (Waldbüttelbrunn, Germany) to the clinical trial pharmacy of the Princess Máxima Center for Pediatric Oncology. The HL that will be given as a study lock in the Princess Máxima Center for Pediatric Oncology will be shipped from the Scheldezoom pharmacy (‘s-Gravenpolder, the Netherlands) to the clinical trial pharmacy of the Princess Máxima Center for Pediatric Oncology.

Disposition

After inclusion the physician will register an order (VMO) in the patient file in Chipsoft EZIS/HiX for the randomized lock, either the TCHL or HL. The nurses will recognize in which study arm the patient is randomized by the CATERPILLAR patient-card. Additionally, the nurses can check the order (VMO) for either the TCHL or HL that is registered in the patient file in Chipsoft EZIS/HiX. The research nurses need to double check the lock solution (two signatures need to be written on the “Lock Instillation Form”) and register the batch number or stick the flag label on a paper “Lock Instillation Form” before instillation.

Return

All left over investigational products will return to the Trial Pharmacy of the Princess Máxima Center for Pediatric Oncology and be stored for later use after the study is performed.

Destruction

Expired investigational products will be destructed.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter

Incidence of first tunneled CLABSIs since the insertion of the CVAD. All data-points that are needed for the evaluation of the occurrence of a CLABSI will be collected by the local data-manager. Three experts will blindly and independently judge if a CLABSI or no-CLABSI occurred in all patient based on the collected data and the CLABSI definition described in paragraph 7.1.5. All non unanimous judgements will be discussed between the experts until they all agree. If the experts still disagree, the final judgement will be based on the judgement of the majority.

7.1.2 Secondary study parameters

- Time to first CLABSI since insertion of the CVAD
- CLABSI incidence per 1,000 CVAD-days
- Incidence of symptomatic CVTs
- Incidence of bacteremia
- Incidence of local infections
- Dispense of thrombolysis/systemic antibiotic treatment due to CLABSI or CVT
- Incidence of and reasons for CVAD-removal
- Cultured microorganisms causing CLABSI
- Days of hospital admission due to CLABSI/CVT
- Safety of the TCHL/HL in terms of known side effects, SAEs, intensive care unit admission, and death due to CLABSI/CVT

7.1.3 Endpoints

Endpoints of the study are the first tunneled CLABSI episode (diagnosed by the expert panel), removal of the CVAD, second CVAD insertion (excl. stem cell apheresis CVADs) or death of the patient, whatever endpoint will come first with a maximum study period of 90 days. If an endpoint is reached, no more study locks will be given. The data of the patients will be followed-up until one month after the endpoint was reached.

7.1.4 Other study parameters

Patient characteristics and CVAD insertion:

- Age
- Gender
- Oncologic diagnosis
- Chemotherapy protocol and treatment arm
- Planned administration of prophylactic systemic antibiotics (trimethoprim/sulfamethoxazole = bactrimel®, ciprofloxacin, or anti-mycotics)
- Date of CVAD surgery
- Type of CVAD
- Introduction method (percutaneous/open)
- Lumen amount
- Lumen diameter
- Access vein and side

- Complicated procedure

Lock characteristics:
- During and directly after study lock instillation:
  - Date of lock instillation
  - Type of lock
  - Side effects (Adverse Device Events (ADE) of interest) and grade (CTCAE version 5.0, November 27, 2017)
- Aspiration of the study lock:
  - Date of removal
  - Inadvert lock removal at home
  - Lock aspirated, accidentally flushed, or malfunction
  - In case of malfunction: type of treatment
  - Side effects (Adverse Device Events (ADE) of interest) and grade (CTCAE version 5.0, November 27, 2017)

Suspicion of CLABSI characteristics:
- Start date of episode
- Presence of symptoms
- Is the CVAD inserted for >48 hours
- Allogenic stem cell recipient with diarrhea >1L in 24 hours, or allogenic stem cell recipient with graft versus host disease grade III or IV.
- Neutropenia episode (incl. duration and severity of neutropenia)
- Results of blood cultures (each lumen counts as one separate blood culture): date and microorganisms cultured will be registered.
- Other documented infection at the time of CLABSI with the same pathogen cultured as the blood culture
- CLABSI, MBI-LCBI, BSI, or suspicion CVAD-related infection without a positive bloodculture.
- In case of BSI, the reason why a BSI was scored e.g. not enough blood cultures, no symptoms, contamination, CVAD in situ for <48 hours, infection at a different site with same pathogen.
- Treatment
- Hospital admission and hospital admission days
- Intensive care unit admission and intensive care unit admission days
- Death of the patient

Suspicion of local infection characteristics:
- Start date of episode
- Symptoms
- Results of blood cultures
- Treatment
- Hospital admission and hospital admission days
- Intensive care unit admission and intensive care unit admission days
- Death of the patient

Suspicion of CVT characteristics:
- Date start episode
- Type of symptoms possibly related to a CVT
- Signs of CVT on radiological imaging
- Location thrombus

- Treatment
- Hospital admission days due to CVT
- Intensive care unit admission days due to CVT
- Death of the patient due to CVT

Serious Adverse Device Events (SADEs)

- ADE term (80)
- Start date ADE
- Date ADE turned into SADE
- Category of SADE
- SADE severity (toxicity grade) (80)
- Hospital admission date
- Medical intervention date
- Date SADE was resolved
- Description SADE
- Date of last lock administration and lock dosis
- Relationship of SADE to intervention (possible/definitely)
- Action taken
- Relevant medical history
- Relevant tests performed
- Study intervention discontinued due to the event

End of the study

- Reason end of the protocol
- In case of CVAD removal: reason, date, and catheter tip microorganisms culture
- In case of death of the patient: reason, date

7.1.5 Definitions

Bloodstream infection (BSI)	Every positive blood culture that is impossible to classify as a CLABSI or MBI-LCBI. Reasons why a BSI is scored: only one bloodculture with a common commensal is obtained, two bloodcultures are obtained but ≤2 common commensals or none recognized pathogens are cultured, positive blood cultures without observed symptoms (e.g. fever, chills, or hypotension, for patients <1 year: fever, bradycardia, and apnea), or an infection at another site with the same cultured pathogen is observed.
Chills	Chills described by parents and/or patient or witnessed by a physician.
Central-line associated bloodstream infection (CLABSI)	CLABSI will be scored if the patient meets one of the following criteria: (1) the patient has a recognized pathogen (micro-organisms not registered in the “List of Common Commensales” of the Centers for Disease Control and Prevention) cultured from ≥1 blood cultures, (2) the patient has at least one of the following signs: fever, chills, or hypotension (for patients <1 year: fever, bradycardia, and apnea), AND the same matching potential common 35ommensals (“List of Common Commensales” of the Centers for Disease Control and Prevention) are cultured from ≥2 blood cultures drawn on separate occasions (incl. two blood

	cultures drawn at the same time but from different lumen). Additionally, a CLABSI will only be scored if the CVAD is in situ for >48 hours on the date of the event, if the pathogen cultured is not related to an infection at another site AND if the MBI-LCBI criteria are not met. See appendix 3 for the CLABSI flow-chart. (67, 81)
Local infection (i.e. phlebitis, exit-site or tunnel-infections)	Positive exit-site culture, erythema, purulent drainage or tenderness within 2 cm of the CVAD track and exit-site
Central venous thrombosis (CVT)	If the patient has (1) peripheral veins that have a non-compressible segment, or (2) there is an echogenic intra-luminal thrombus or an absence of flow in the central venous system. (76)
Diarrhea	≥1L Diarrhea in a 24-hour period
Fever	Temperature >38.0°C on two occasions within a 12-hour period, one temperature >38.5°C, or one temperature <35.0°C (for patients of <1 year <36.0°C).
Hypotension	Hypotension criteria per age: ○ 0-3 Months: systolic RR<60 mmHg ○ 3 Months – one years: systolic RR<80 mmHg ○ 1-11 Years: systolic RR <90 mmHg ○ >12 Years: systolic RR<100 mmHg
Malfunction	If it is impossible to aspirate or flush the CVAD.
Mucosal barrier injury laboratory confirmed bloodstream infections (MBI-LCBI)	The mucosal barrier injury laboratory confirmed bloodstream infections (MBI-LCBI) were scored following the criteria of the CDC to exclude BSIs that are possibly the result of the weakened mucosal barrier of the gut in immunocompromised patients, and probably not associated with the CVAD. MBI-LCBI will be scored if: (1) a CLABSI with a recognized pathogen is scored AND the only pathogens cultured are intestinal organisms (micro-organisms registered as MBI Organisms in the "List of Common Commensales", CDC), OR (2) a CLABSI with two or more common commensals is scored AND the commensals cultured are only viridans streptococci. Additionally, the patients must meet one of the following during same hospitalization as the positive blood specimen: (1) the patient is an allogenic stem cell transplant recipient in the past year with grade III or IV gastrointestinal graft versus host disease, or > 1 litre diarrhea in a 24-hour period, OR (2) the patient is neutropenic on two separate days. See appendix 3 for the CLABSI flow-chart. (3, 67, 81-84)
Mild neutropenia	Granulocytes 1000-1500 x 10^6 /L
Moderate neutropenia	Granulocytes 500-1000 x 10^6 /L
Severe neutropenia	Granulocytes < 500 x 10^6 /L

Very severe neutropenia	Granulocytes < 100 x 10^6 /L

7.2 Randomisation, blinding and treatment allocation

Patients will be randomized between two treatment arms: HL- and TCHL-study arm. Randomisation will be done with the method of minimisation. Stratification will be done according to two factors: used type of CVAD (TIVAP or H-CVAD/PL) and diagnosis of cancer (hematologic or solid/neurologic malignancies).

The randomization will be done with the use of an online randomization service by internet (Software as a Service – SaaS) called ALEA®. This web-based randomization program will provide 24 hours 7 days per week service. At the study site, the researcher or research nurse will enter the randomization data in ALEA®. Notification will be sent to the local study team. The local study team will receive a notification with patient identifier, patient study number and the allocated treatment.

7.3 Study procedures

Information to patients

If it is determined that a patient will need a tunneled CVAD, the surgeon/researcher will inform the patient and parents/legal guardian about the CVAD insertion procedure. At the end of this conversation verbal information and information in writing about this study will be given to the patients and parents/legal guardian.

Inclusion

Inclusion (including first lock instillation) should take place within one week after CVAD insertion. However, if this is not possible due to clinical circumstances (i.e. physical and/or psychological) patients may be included (incl. first lock instillation) within four weeks after CVAD insertion. The researcher/research nurse will sign the informed consent papers after the patient and parents/legal guardian. The in- and exclusion criteria will be checked to determine if the patient is eligible for the CATERPILLAR-study. The researcher/research nurse will complete the inclusion details in HiX and will enter the patient information in the randomization programme ALEA®. The local data-manager will complete the “Registration and Baseline Form” in Castor EDC. Patients will be randomized in either the HL- or TCHL-group. The local study team will receive the randomization information. The surgeon/researcher registers an order (VMO) for either the TCHL or HL in the patient file in Chipsoft EZIS/HiX. See appendix 4 for the flow-chart of the study procedure described above. [Appendix 4]

All patients will receive a CATERPILLAR card with “YES and NO stickers” from the research nurse/researcherThis card is used to alert health care providers that the patient is a participant in the CATERPILLAR-study and will show in which group the patient is assigned and what lock volume needs to be instilled. Parents and/or patients will be asked to show the CATERPILLAR-card and stickers each time they visit the hospital.

Lock instillation and aspiration

Directly after the insertion of the CVAD, a running intravenous infusion will be connected to the inserted CVAD. The first investigational lock solution will be instilled in the first week after insertion. However, if this is not possible due to clinical circumstances (i.e. physical and/or psychological) patients may receive the first lock within four weeks after CVAD insertion. The other study locks will be instilled in the CVAD lumen once a week if the CVAD is

disconnected for preferably multiple days (at least >1 hour) until the next treatment. If patients are going home, to a different hospital, or do not have to visit the Princess Máxima Center for >1 week the CVAD will be locked and the lock will be replaced within 3 weeks if they visit the Princess Máxima Center for Pediatric Oncology. The lock volume depends on the CVAD type. [Table 5] In between, all patients will be locked with heparin 100 IU/ml following the CVAD-manipulation protocol of the Princess Máxima Center for Pediatric Oncology, home care organizations and all shared care hospitals in the Netherlands.

The research nurse/researcher can use the CATERPILLAR patient-card and VMO in HiX to see in which study group the patient is randomized. The nurses will be asked to double check the ampoule before instillation, two signatures and the batch number need to be written on a paper “Lock Instillation Form”. After the instillation of the new study lock solution, the patients will be asked questions concerning the experience of side effects during the lock instillation. The paper “Lock Instillation Form” will be completed by the research nurse. The patients will receive a “Lock in situ YES” sticker with the lock instillation date, that will be attached to the CATERPILLAR-card. Patients and/or parents will be asked to show the card during every visit in a hospital.

If the CVAD is manipulated again, the “Lock in situ YES” sticker on the CATERPILLAR card will alert health care providers that the study lock is in situ and that the lock needs to be aspirated by the research nurse or researcher. If the lock aspiration takes place in the Princess Máxima Center for Pediatric Oncology, again questions concerning the experience of side effects during lock removal will be asked and the “Lock Instillation Form” will be completed. Then the “Lock in situ NO” sticker with the aspiration date and method of removal will be attached to the CATERPILLAR-card.

If the study lock is aspirated in a shared care center or home care setting the nurse will be asked to follow the guidelines on the CATERPILLAR card and stick the “Lock in situ NO” sticker on the CATERPILLAR card with the date and method of removal. The research nurses in the Princess Maxima Center will be asked to register the lock removal date on the “Lock Instillation Form” the next time the patient visits the Princess Maxima Center. If the lock removal date is missing the shared care center will be contacted. If in the shared care centers or at home a regular heparin lock is instilled after the CVAD is used, patients will not be excluded from the study.

The data-manager will enter the information of the “Lock Instillation Form” in the online database “Lock Instillation Form” in Castor EDC.

<u>Suspicion of an (local) infection or CVT in the Princess Máxima Center for Pediatric Oncology</u>

In case of symptoms possibly associated with an (local) infection or CVT (e.g. swelling/pain at the catheter site, face, neck, arm, or shoulder) parents will be asked to contact a nurse or physician from the beginning of the signs of infections. If the patient is seen in the Princess Máxima Center for Pediatric Oncology, the surgeons/pediatric oncologists will inform the research nurse/researcher. Standard of care diagnostic work-up and treatment will be performed. The research nurse/researcher will register all relevant details in Chipsoft EZIS/HiX. The research nurse/researcher will alert the local data-manager and he/she will complete the “Suspicion of a CLABSI”, “Suspicion of a local infection” or “Suspicion of a CVT” form in Castor EDC. Episodes of CLABSIs, local infection or CVTs will be monitored until the symptoms have resolved and the patient has recovered. See appendix 5 for the

flow-chart of the study procedures described above. [Appendix 5] If a blood culture is drawn from the CVAD and the TCHL or HL is still in situ, the first 2.0 mL has to be discarded.

Suspicion of an infection or CVT in the shared care hospitals

In case of any symptoms possibly associated with an (local) infection or CVT (e.g. swelling/pain at the catheter site, face, neck, arm, or shoulder) parents will be asked to contact a nurse or physician from the beginning of the signs of infections. It is the standard of care in the Netherlands to inform the Princess Máxima Center for Pediatric Oncology if a patient is seen in a shared care hospital due to treatment complications (e.g. CLABSI, local infection or CVT). The physicians in the shared care hospitals enter the complication data in Chipsoft EZIS/HiX of the Princess Máxima Center for Pediatric Oncology and/or will call the patients' physician in the Princess Máxima Center for Pediatric Oncology. The physician/nurse of the Princess Máxima Center will contact the research nurse/researcher who will register all details in Chipsoft EZIS/HiX. The research nurse/researcher will alert the local data-manager to complete the "Suspicion of a CLABSI", "Suspicion of a local infection" or "Suspicion of a CVT" form in Castor EDC. If information is missing, the shared care centers will be contacted. See appendix 6 for the flow-chart of the study procedures described above. [Appendix 6] If a blood culture is drawn from the CVAD and the HL or TCHL is still in situ, the first 2.0 mL has to be discarded.

End of the study

The patient will reach the end of the study in case of a CLABSI episode, CVAD-removal, second CVAD insertion (excl. stem cell apheresis CVADs) or death of the patient, with a maximum of 90 days. After one of the endpoints of the study has been reached, the research nurse/researcher will enter the end of the protocol details in HiX. The data-manager will complete the "End of the Protocol Form" in Castor EDC. See appendix 7 for the flow-chart of this procedure. [Appendix 7]

Division of tasks

The research nurse and researcher will perform the informed consent procedure, keep track of all patients, make appointments and collect data in HiX. The local data-manager will collect data from HiX and enter this data into Castor. Central data management will check data completeness. The statistical analysis (interim analysis and final analysis) will be performed by a statistician. The DSMB charter submission will be done by the local study team. The manuscript will be written by the researcher and the PI.

"Extra"-procedures

All procedures that subjects undergo are part of the standard medical treatment of the Princess Máxima Center for Pediatric Oncology, except for the following:

- Parents need to show the CATERPILLAR-card to the nurse/physician during every hospital visit.
- In the Princess Máxima Center for Pediatric Oncology every patient participating in the HL- or TCHL-study arm will be asked to answer questions concerning the side effects after each lock instillation and after study lock removal.
- If a blood culture is obtained from a patient and the HL or TCHL is in situ, the first 2.0 mL has to be discarded and the lock is aspirated instead of flushed before instillation of a new lock.
- If the study lock is removed in a shared care hospital or home care setting the nurse will be asked to follow the guidelines on the CATERPILLAR card and stick the "Lock in situ NO" sticker to the card with the aspiration date and reason for removal.

Diagnostic procedures or treatment of these patients will not be postponed due to participation in this study.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time, for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1. Specific criteria for withdrawal

1. Admission of >3 weeks in a hospital outside the Netherlands or a non-participating shared care centre.
2. Hypersensitivity reaction after instillation of the TCHL solution.

7.5 Replacement of individual subjects after withdrawal

The intention to treat principle will be used. Therefore, patients will not be replaced after withdrawal.

7.6 Follow-up of subjects withdrawn from treatment

Subjects that object to further participate in the study will receive the standard of care locks containing heparin 100 IU/ml. Their electronic patient files will be reviewed until 30 days after the last lock instillation.

7.7 Premature termination of the study

The DSMB can advise the sponsor to terminate the study prematurely. The sponsor or METC can decide to terminate a study.

Premature termination criteria:

- If the interim analysis shows an earlier disturbance of equipoise, e.g. major superiority or inferiority of the TCHL. See interim analysis, chapter 10.3, for more details.
- If significantly more or less SAEs/SUSARs are reported in the TCHL-group. See interim analysis description for more details.
- Methodological inaccuracies
- If the conduct is not feasible because of logistics or subject recruitment

If it is decided to terminate the study earlier than indicated in the protocol, all patients and involved hospitals will be informed by the researcher. The study must be stopped immediately. The sponsor is required to report premature termination to the reviewing committee (METC) within 15 days after termination stating the reason for early termination.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 ADEs and SADEs

8.2.1 Adverse device effects (ADEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational products. Only AEs of special interest with a possible or definite relationship (serious adverse device effects ADEs) with the investigational products will be registered. Registration of all AEs would lead to the registration of too many AEs in this patient group.
Registration will be performed according to the definitions of the Common Terminology Criteria for Adverse Events (CTCAE version 5.0, November 27, 2017), incl. severity grade.

ADEs of special interest that are registered:

- Oral dysesthesia: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.
- Neck pain: A disorder characterized by a sensation of marked discomfort in the neck area.
- Chest wall pain: a disorder characterized by a sensation of marked discomfort in the chest wall
- Dysgeusia: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
- Nausea: A disorder characterized by a queasy sensation and/or the urge to vomit.
- Vomiting: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
- Allergic reaction: A disorder characterized by an adverse local or general response from exposure to an allergen.
- Blood and lymphatic system disorders - Heparin induced thrombocytopenia: thrombocytopenia due to the administration of heparin.
- Other ADEs that have not been anticipated before.

The research nurse/researcher will ask the patients and/or parents if any of the above described ADEs occur and register them on the “Lock Registration Form”. All ADE’s will be registered in the Castor EDC database by the local data-manager.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or affect that

- Results in death
- Is life-threatening for the subject, life threatening events are defined as:
  - Circulatory/cardiac insufficiency requiring catecholamines/positive inotropes
  - Respiratory failure requiring intubation/ventilation

- Other clinical situation requiring immediate intervention, e.g. gastro-intestinal bleeding or perforation requiring surgery, cerebral abcessbleeding requiring immediate neurosurgical intervention.
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator

We will only register SAE's that have a possible or definite relationship with the investigational medical devices from informed consent up till 30 days after the last study lock was given to the patient (Serious Adverse Device Events = SADEs). Registration of all SAE's will lead to too many registrations in this patient group. These SADE's must be registered in HiX by the research nurse/researcher and on SADE report forms in Castor EDC by local data-management. Within 24 hours these SADE forms must be sent to the safety desk of the sponsor.

The causality assessment is made using the following:

- Not related: There is no evidence to suggest a causal relationship.
- Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time frame after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The sponsor will report the SADEs to the accredited METC that approved the protocol through the web portal ToetsingOnline (TOL). During this study we are not obliged to report SADEs to the Inspectie Gezondheidszorg en Jeugd (IGZ).

- SADEs that result in death or are life threatening and where a possible/definite causal relationship with the investigational product is suspected, need to be reported through ToetsingOnline within 7 days of first knowledge, followed by a maximum period of 8 days to complete the initial preliminary report.
- All other SADEs, where a possible/definite causal relationship with the investigational product is suspected, will be reported within a maximum period of 15 days after the sponsor has first knowledge of the serious adverse events.

SADEs will be evaluated with the SADE evaluation form. It will be determined if the SADE was anticipated (ASADE) or unanticipated (USADE).

8.3 Follow-up of Serious Adverse Device Events

SADEs need to be reported till 30 days after the last lock was given to the patient, as defined in the protocol. All SADEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

A DSMB will be established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial. Details can be found in the "*DSMB Charter of the CATERPILLAR-study*". The interim-analysis is described in chapter 9.3.

The DSMB should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC). The DSMB should inform the Chair of the steering committee if, in their view: The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management; or It becomes evident that no clear outcome would be obtained.

DSMB meetings:

1. Prior to the study start a meeting will be scheduled, to discuss the protocol, trial, analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators.
2. A closed meeting will be scheduled after the inclusion of 231 patients, approximately 14.5 months after the study start. The efficacy and safety data (interim analysis) will be presented. Accumulating information relating to the recruitment and data quality, toxicity details based on pooled data, and total numbers for the primary outcome measure and other outcome measures may be presented, at the discretion of the DSMB.
3. At the end of the study a meeting will be scheduled to allow the DSMB to discuss the final data with the principal investigator.

The members of the DMC for this trial will be:

1. Dr. Marieke Witvliet, Pediatric Surgeon, Wilhelmina Children's Hospital, Utrecht, the Netherlands.
2. Dr. Bart Rijnders, Infectious Diseases, Erasmus Medical Center, Rotterdam, the Netherlands.
3. Prof. Dr. Hein Putter, Medical Statistician, Leids University Medical Center, Leiden, the Nethterlands.

The chair will be: Dr. Marieke Witvliet

The advice(s) of the DSMB will be sent to the principal investigator (Prof. Dr. M.H.W.A. Wijnen) of the study. Should the principal investigator decide not to fully implement the advice of the DSMB, the principal investigator will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

9. STATISTICAL ANALYSIS

The primary data analyses will be performed with the intention to treat principle (i.e. inclusion of all patients that were randomized). Additionally, a per-protocol analysis will be performed excluding patients who were not included within one week after CVC insertion, patients who never received the intervention and patients who missed three or more of the minimal amount (once every three weeks) of locks during the follow-up period. Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented. Differences between treatment groups with respect to baseline characteristics will be analyzed by using a Chi-square (or Fisher Exact in the presence of small numbers), and t-test for categorical or continuous variables respectively. In case of violation of the normality assumption a non-parametric test such as the Wilcoxon rank test will be applied.

9.1 Primary study parameter

For the primary outcome, the percentages and incidence rates (IR) of first CLABSIs per 1,000 CVAD-days will be reported for both study groups and compared by computing an IRR. The exact confidence limits for the IRRs will be based on the polynomial algorithm for person time data (85, 86). The nominal alpha level for the primary outcome in the final analysis will be equal to 0.045 due to the interim analysis (66-71).

9.2 Secondary study parameters

The cumulative incidence of CLABSI from CVAD insertion will be estimated by using a competing risk model (87) with CVAD removal due to non-CLABSI related reasons or death as competing events. To assess the difference between the cumulative incidence for the intervention (TCHL) and control (HL) group, the Gray's test will be used. (88)

To estimate the effect of risk factors on the occurrence of CLABSI, a Cox specific proportional hazard regression model from CVAD insertion will be estimated. Well known time fixed risk factors for a CLABSI to be incorporated into the model are diagnosis (hematological disease versus other diagnoses), CVAD type (TIVAP versus tunneled external CVADs) . Furthermore, TPN administration will be used in the model as time-dependent covariate). (87)

A landmark analysis at 28 days after CVAD insertion will be performed. The same risk factors as discussed above will be incorporated in the Cox specific hazard regression model with additional covariate number of lock days. The landmark point of 28 days was chosen based on clinical reasons, the first lock should have been given within the first four weeks after CVAD insertion.(89)

For the secondary outcomes, the percentages and IRs per 1,000 CVAD-days will be reported and compared by computing IRRs.

9.3 Interim analysis

After complete follow-up of the first 231 patients an interim analysis will be performed by the trial statistician. After the interim analysis is performed, the results will be presented at the second DSMB meeting, see chapter 8.4. The stopping rule is based on testing the one-sided test at $\alpha = 0.025$ for H_0: 'experimental incidence ≥ control incidence' against H_1: 'experimental incidence < control incidence'. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the experimental. The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on choices of the α- and β-spending functions. The α-spending function determines how eager or reluctant one is to stop the trial for superiority. The β-spending function determines how eager or reluctant one is to stop the trial because the chance has become small that superiority can be concluded if the trial is continued. As α-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 2.35$. This choice implies that the trial is stopped after 231 patients if the one-sided P-value is smaller than 0.005 (or 0.01 two-sided) in favor of the experimental treatment. As β-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 3.2$. This choice implies stopping the trial after 231 patients if the one-sided P-value is ≥ 0.5, i.e. if the estimated treatment effect at that time is in favor of the control treatment.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, and October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), General Data Protection Regulation (GDPR), Medical Treatment Contracts Act (WGBO), Medical Devices Act (Wmh), and Medical Devices Decree.

10.2 Recruitment and consent

If a patient will receive a tunneled CVAD, the surgeon/researcher will inform the patient and parents/legal guardian about the CVAD insertion procedure and the CATERPILLAR-study. After the verbal information has been given, the information will also be given to the patient and parents/legal guardian in writing. The patient and parents/legal guardian can determine if they want to participate in the study until the CVAD is inserted for <1 week. However, if this is not possible due to clinical circumstances, informed consent can be given within 4 weeks after CVAD insertion. The time to consideration depends on the date of insertion and the hospital admission duration after the CVAD insertion. The time to consideration is at least one day. If the patient and parents/legal guardian agree to participate in the study, the informed consent form will be signed. Additionally, the patient and parents/legal guardian will be asked if they want the researcher to inform all treating physicians/pharmacist about the trial participation, and if, after the completion of the trial, the researcher can ask the patient and parents/legal guardian if they are interested in participating in follow-up studies.

10.3 Benefits and risks assessment, group relatedness

As already described in the introduction, hypothetically, the TCHL will reduce the CLABSI rate. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a reduced mortality rate due to CLABSI. Additionally, patients can benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development. (12-41, 43-50)

The expected side effects are temporarily, caused by a spill-over of citrate, described if the TCHL is instilled too fast, and if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dygeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are possible side effects, but were not observed in the studies evaluated. A more frequent dispense of thrombolytics has been associated with lock solutions containing taurolidine and citrate in haemodialysis patients. (18, 20-22, 25, 26) However, this was only observed without the addition of heparin. (45-50) In this study, for the prevention of the above stated possible side-effects, the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed.

In conclusion, we think the possible positive effects of the TCHL outweigh the remaining minimal and rare side effects of the TCHL.

10.4 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7 of the WMO. Insurance information:

- Insurance company: Aon Risk Solutions
- Type of Insurance: Liability Insurance (including medical malpractice liability).
- Policy no: V0100112728
- Insured: Prinses Maxima Centrum voor Kinderoncologie
- Sum insured: EUR 5,000,000 each and every claim and EUR 15,000,000 in the aggregate.
- Deductible: EUR 25,000 each and every claim
- Insurance period: May 18, 2019 till May 18, 2020
- Conditions: In conformity with the AW Healthcare package wording, including general liability, pollution (sudden & accident) and employer's liability (Dutch law). Further to be agreed and amended to Dutch law.
- Territorial limits: Worldwide, excluding USA/Canada
- Leading insurer: 100% Allied World Assurance Company (Europe) Ltd.

The sponsor also has an insurance for the study subjects which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Insurance information:

- Insurance company: CNA Insurance Company, Ltd
- Type of Insurance: Subject insurance
- Policy no: 10211864
- Insured: Prinses Maxima Centrum voor Kinderoncologie
- Sum insured: EUR 650,000 per subject, EUR 5,000,000 per research project, EUR 7,500,000 each year for all research projects together.
- Insurance period: October 1, 2019 till October 1, 2020, with silent prolongation.
- Territorial limits: The Netherlands

10.5 Incentives

No incentives/compensations are applicable.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The handling of the personal data will comply with the General Data Protection Regulation (GDPR). All data will be handled confidentially and pseudonymised. The database system that we will use is Castor EDC (www.castoredc.com), a user friendly, fully featured, affordable and secure system. Castor has been audited on Good Clinical Practice compliance by Profess Medical Consultancy and has obtained a Good Clinical Practice compliance certificate. The database will have limited excess; an account will be given to the members of the local study team and to a designated monitor. A central subject identification code list in the Princess Máxima Center for Pediatric Oncology will be used to link the data to the subject. The subject identification list will only be available for the local study team. The database and the subject identification list will be kept separately. Data will be stored in the Princess Máxima Center for Pediatric Oncology for a minimum of 15 years.

11.2 Monitoring and Quality Assurance

The monitor organisation: Julius Center (http://portal.juliuscentrum.nl/nl-nl/home.aspx)
Independence of the organisation: The Julius Center is an organisation of the University Medical Center Utrecht which supports research. The Julius Center is not depended on the outcomes of this trial.

Risk classification
Negligible risk

Monitoring frequention
An independent monitor will make one prior to start visit, one site visit in the Princess Máxima Center each four months, and one close-out visit.

Monitoring plan
Study documents and agreements:

- Confirming that the research file is present and complete: Trial Master File and Investigator File.
- Confirming that the study staff is completely instructed on the study procedures, and that back-up agreements are made with other colleagues.

Patient inclusion rate, consent, compliance and Source Document Verification (SDV):

- Checking the inclusion rate and drop-out percentage.
- Checking the informed consent papers: sample of 10%
- Checking the in- and exclusion criteria: sample of first three subjects, afterwards 1-10%
- Checking the protocol compliance: sample of the first three subjects, afterwards 1-10%
- Source Document Verification (SDV): sample of 1-10%; will be performed for a predefined list list of variables which have a clear relationship to the safety and validity of the research (including the primary end-point).

Patient safety

- Verification of Serious Adverse Event (SAE) reporting: sample of 1-10% of the subjects.

Investigational product
- Verification of the patient instructions that are given.

Study procedures
- Verification if the study procedure instructions are accessible.

Laboratory and pharmacy
- Verification if the laboratory is GLP certified
- Verification if the pharmacy is GMP certified

Attention points
- Qualifications of the monitor
- Feedback and follow-up of the observations of the monitor
  - Term of monitor report availability
  - Actions regarding the points of improvement in the monitoring report within the Princes Máxima Center.
- Storage of study files
  - Use of an adequate Clinical Data Management System (CDMS).
  - Correct storage of raw data, corrected data, and back-ups.
  - Presence of an audit trail.

Monitoring reports and storage period
A monitoring report will be written of every monitoring visit. The head of the department of the researcher is responsible for archiving the reports for a minimum of 15 years after the end of the study. The monitoring report and other study documents are available for the Board of Directors of the Princess Máxima Center for pediatric oncology and for the employees assigned by the Board of Directors.

11.3 Amendments
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.4 Annual progress report
The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report
The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The results of this research will be disclosed unreservedly. All parties concerned must justify their actions in this regard. Patients and human subjects are entitled to public disclosure of the results of the trial on the basis of their participation in it (and the arguments that play a role therein).

Both positive and negative trial results will be disclosed. The results of research will be submitted for publication to open access peer-reviewed scientific journals. If the journals do not consider negative results for publication, the research will be disclosed through trial registers, websites or databases.

The basic principles of the Vancouver convention (Uniform requirements for manuscripts submitted to biomedical journals. JAMA 277:927-934,1997) and the editors' statements of a number of authoritative biomedical scientific journals (Davidoff F et al., Sponsorship, authorship and accountability, NEJM 345:825-826, 2001) will be followed.

The sponsor is entitled to examine the manuscript prior to publication and to make comments on it. The sponsor may delay publication for up to three months after analysing the research results.

Disputes will be dealt with by continuing the debate in the form of letters sent to the scientific journal.

None of the parties concerned has a right of veto. The parties concerned must attempt to resolve disputes by negotiation. Should one of the parties feel that it has been disadvantaged, or should any other problem relating to publication arise, the parties can contact the METC for mediation.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Chapter 12.1 is not applicable as the investigational medical device is registered and used within the registered indication.

12.2 Synthesis

Hypothetically, the TCHL will reduce the CLABSI rate compared to the HL. Therefore, the TCHL may reduce the administration of antibiotics, result in lower rates of CVAD removal, fewer days of hospital/ICU admission, and a reduced mortality rate due to CLABSI compared to the HL. Additionally, patients will benefit directly from reduced and more appropriate antibiotic use, without the risk of antibiotic resistance development. (12-20, 45-48, 50, 59, 62)

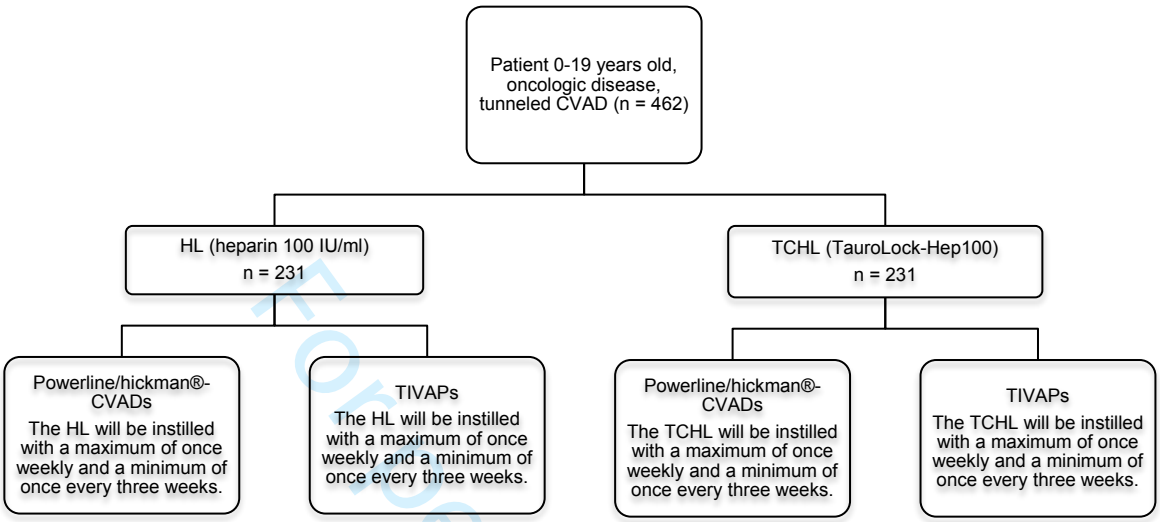
The expected side effects are temporarily, caused by a spill-over of citrate, described if the TCHL is instilled to fast, and if the TCHL is accidentally flushed instead of aspirated: perioral dysesthesia, discomfort of neck and chest, dygeusia, nausea and vomiting. (23, 34, 35, 37, 39, 40, 45, 46, 48, 50) Additionally, hypersensitivity reactions, and heparin induced thrombocytopenia are possible side-effects, but only in one patient an anaphylactic-like reaction was observed. (34) Liver-injury is associated with high-concentrations of systemic taurolidine in mouse-models. The TCHL contains low-dose taurolidine, which is not associated with liver-injury. (63) A more frequent dispense of thrombolytics has been associated with lock solutions containing taurolidine and citrate in haemodialysis patients. (18, 20-22, 25, 26) However, this was only observed without the addition of heparin. (45-50) For the prevention of the above stated possible side-effects the lock volumina are adjusted to the lumen of the CVAD that is inserted, the locks will be aspirated before instillation of a new lock, the locks will be instilled slowly (<1 ml per second), heparin is added to the solution for the prevention of the more frequent dispense of thrombolytics, and an ultrasound of the insertion veins to detect CVTs will be performed if CVT related symptoms are observed during the study. The locks will be instilled with a maximum of once weekly and a minimum of once every three weeks. After every study-lock instillation, the patients will be asked to answer a questionnaire about the experience of possible side effects.

In conclusion, we think the possible positive effects of the TCHL outweigh the remaining minimal and rare side effects of the TCHL. We hope to prove that the TCHL will reduce the CLABSI rate, CVAD-removal rate, dispense of antibiotics, days of hospital/intensive care unit admission, and mortality rate due to CLABSI.

13. APPENDICES

13.1 Appendix 1: Flow-chart lock solutions

In between the study locks, the patients will receive heparin 100 IU/ml locks.



Endpoints of the study, whatever endpoint will come first:

- First tunneled CLABSI
- Removal of the CVAD
- Second CVAD insertion (excl. stem cell apheresis CVADs)
- Death of the patient
- Study period of 90 days

13.2 Appendix 2: TauroLock-Hep100 Documents

ENGLISH **Instructions For Use** 43703GB/14/17

TauroLock™ HEP 100

Catalogue # TP-03

A. Description and Specifications

TauroLock™-HEP100 contains anticoagulants and antimicrobial substances. It is to be used with a port or a catheter-based vascular access device. It is to be instilled in the device lumens between treatments in order to make the internal flow passages resistant to clot formation and hostile to bacterial and fungal growth. The solution must be withdrawn prior to initiating the next treatment. Active ingredients in TauroLock™-HEP100 are (cyclo)-taurolidine, citrate (4%) and heparin (mucosa, 100 IU/mL). Other components include water for injection. The pH is adjusted with citrate and/or sodium hydroxide. The product is sterile filter processed and supplied as a clear, sterile, non-pyrogenic solution.

Note:

For complete details of catheter-based vascular access products, consult the manufacturer's instructions or clinician's manual.

B. Indications

TauroLock™-HEP100 is indicated for those patients who use a port or a silicone or polyurethane catheter-based device as vascular access. TauroLock™-HEP100 is intended to be used as a catheter lock solution. It is to be instilled into the device at the termination of a treatment and withdrawn prior to initiating subsequent treatments (see F4).

C. Contraindications

TauroLock™-HEP100 is contraindicated for patients with a known allergy to (cyclo)-taurolidine, citrate or heparin (mucosa) or when a patient is currently taking medication with known adverse interaction to citrate, heparin or (cyclo)-taurolidine. TauroLock™-HEP100 is also contraindicated for patients with heparin-induced thrombocytopenia or increased bleeding risk.

D. Cautions

1. As a consumable TauroLock™-HEP100 is for single use only. Reuse creates a potential contamination risk for the patient.
2. TauroLock™-HEP100 is not for systemic injection. TauroLock™-HEP100 must be used as a catheter lock solution as described in the access device's instruction for use. Failure to adhere to these instructions may result in inadvertent systemic injection of the solution. Once instilled into the catheter the solution must not be used again after aspiration.
3. The ampoule is for single dose only due to potential risk of contamination.
4. Some patient populations using TauroLock™-HEP100 antimicrobial lock solution may experience a higher frequency of blood clots in the catheter lumen. In the event that access device patency is compromised, follow institutional protocol for restoring flow.
5. The specific fill volume of the access device has to be strictly respected with infants and children less than two years of age due to citrate as an active ingredient.
6. In access devices which were blocked regularly with non-antimicrobial lock solutions (e.g. with heparin, low concentrated citrate or saline) prior to application of TauroLock™-HEP100, viable organisms and endotoxins may be released from the biofilm. The lock solution must be aspirated before the next treatment to prevent very rare anaphylactic reactions which are not attributable to the active ingredients.
7. The concentration of the antimicrobial compound is near to saturation. If not stored or transported according to the instructions under section H, precipitation can occur in the product. Do not use such a precipitated product.

E. Adverse Effects

To date, there are no known adverse effects in humans due to the active ingredient concentrations in TauroLock™-HEP100 when used as directed. There are no known risks associated with concomitant systemic antibiotic therapy or exposure to magnetic fields. TauroLock™-HEP100 may cause mild hypocalcaemic symptoms if instillation is not done slowly as directed.

F. Instillation of TauroLock™-HEP100

Follow the manufacturer's instructions that accompany the particular vascular access product utilized. Specific catheter lock volumes are associated with each device.

1. Flush the device with 10 mL of saline.
2. Withdraw TauroLock™-HEP100 from the container using an appropriate syringe.
3. Instill TauroLock™-HEP100 slowly (not more than 1 mL per second, infants and children less than two years of age not more than 1 mL per 5 seconds) into the access device in a quantity sufficient to fill the lumen completely. **Consult the manufacturer's instructions for the specific fill volume or specify fill volume during implantation. The volume has to be strictly respected.** TauroLock™-HEP100 will remain inside the access device until the next treatment (for a maximum of 30 days).
4. Prior to the next treatment, TauroLock™-HEP100 must be aspirated and discarded according to the institution's waste policy. Prior to initiation of the next treatment, TauroLock™-HEP100 must be withdrawn from the access device and discarded according to the institution's waste policy.
5. Flush the device with 10 mL of saline.

G. Pregnancy and Breastfeeding

No data are available for pregnant and breastfeeding women. For safety reasons TauroLock™-HEP100 should not be used during pregnancy and breastfeeding.

H. Storage and shipment

TauroLock™-HEP100 must be stored at a temperature of 15 to 30°C and must not be shipped at freezing temperature. Do not freeze.

I. Packaging configuration

The following packaging configurations are available for TauroLock™-HEP100: 10 x 3 mL TauroLock™-HEP100 ampoules.

State: 07. December 2015

TauroPharm GmbH · August-Bebel-Straße 51 · D-97297 Waldbüttelbrunn · Germany

Tel: +49 931 304 299 0 · Fax: +49 931 304 299 29

STERILE A Sterile, aseptic fill.

Read instruction for use.

Single use. The ampoule is a single dose.

Do not use when package is damaged.

CE 0123 CE acc. MDD 93/42/EEC, notified body: TÜV SÜD PRODUCT SERVICE GmbH.

kinderoncologie

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Germany

Tel + 49 (931) 304 299 0
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DECLARATION OF CONFORMITY

MANUFACTURER:	TauroPharm GmbH August-Bebel-Str. 51 D-97297 Waldbüttelbrunn, Germany
PRODUCT:	TauroLock™-HEP100 (3 ml ampoule)
CLASSIFICATION:	III
CONFORMITY ASSESSMENT ROUTE:	Annex II

We herewith declare that the above mentioned products meet the provisions of the Council Directive 93/42/EEC for medical devices. All supporting documentation is retained under the premise of the manufacturer.

STANDARDS APPLIED:	MDD 93/42 EEC
NOTIFIED BODY:	TÜV SÜD Product Service GmbH Ridlerstrasse 65 D-80339 Munich, Germany Reg. No. 0123
EC CERTIFICATE:	G1 17 05 51963 014 G7 17 06 51963 020
START OF CE-MARKING:	This declaration applies to all CE-marked devices manufactured from the date of issuance until it is either superseded by another declaration or withdrawn.
ISSUED BY:	This Declaration of Conformity is issued by TauroPharm GmbH, which is exclusively responsible for the declared compliance.
PLACE OF ISSUE:	TauroPharm GmbH, D-97297 Waldbüttelbrunn, Germany
SIGNATURE:	..... (Dr. Christian Weis, Managing Director)
DATE:	31. July 2017

TauroPharm GmbH
August-Bebel-Straße 51
97297 Waldbüttelbrunn
Tel. 0049 931 / 304299-0
GERMANY

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate

EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)

No. G7 17 06 51963 020

Manufacturer:

TauroPharm GmbH
August-Bebel-Str. 51
97297 Waldbüttelbrunn
GERMANY

Product:

Irrigation Solutions
Non antibiotic based antimicrobial catheter lock solution

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with MDD Annex II (4). The design of the devices conforms to the requirements of this Directive. For marketing of these devices an additional Annex II certificate is mandatory. See also notes overleaf.

Report no.: 713104720

Valid from: 2017-07-31
Valid until: 2022-07-30

Date, 2017-07-28

Stefan Preiß

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

Page 1 of 2

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate
EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)

No. G7 17 06 51963 020

Model(s):

Taurolock Solutions
- Taurolock Hep TP-02
- Taurolock Hep TP-03

Parameters:

Taurolock with Heparin 500:	TP-02 3ml, 5ml Ampoule, 10 ml Vial
Taurolock with Heparin 100:	TP-03 3ml, 5ml Ampoule, 10 ml Vial

Facility(ies):

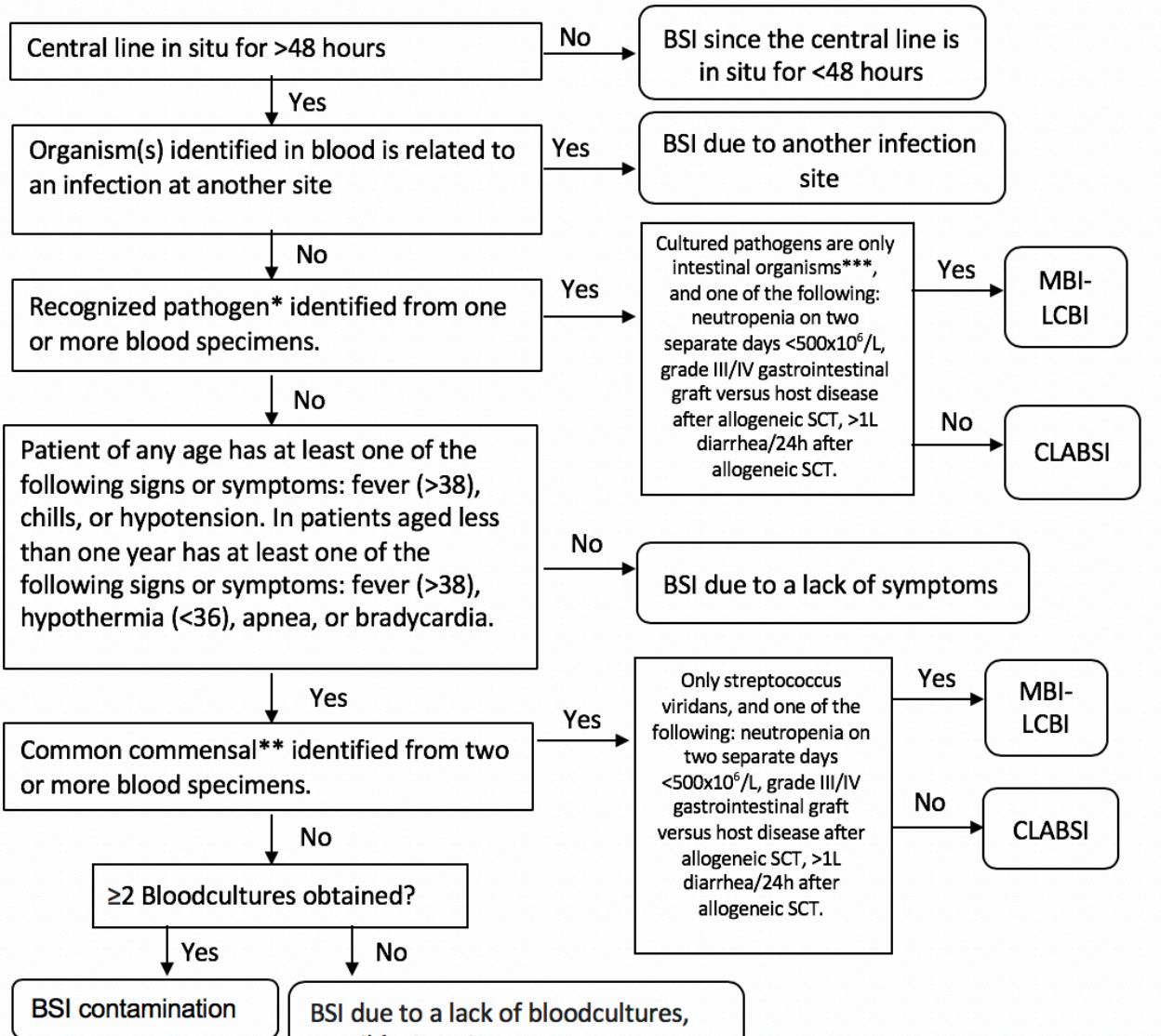
TauroPharm GmbH
August-Bebel-Str. 51, 97297 Waldbüttelbrunn, GERMANY

Page 2 of 2

TÜV SÜD Product Service GmbH · Zertifizierstelle · Ridlerstraße 65 · 80339 München · Germany

TÜV®

13.3 Appendix 3: Flow-chart suspicion of a CLABSI



CVAD = Central Venous Access Device, BSI = Bloodstream Infection, MBI-LCBI = Mucosal Barrier Injury – Laboratory Confirmed Bloodstream Infection, CLABSI = Central Line Associated Bloodstream Infection, SCT = Stem Cell Transplantation.

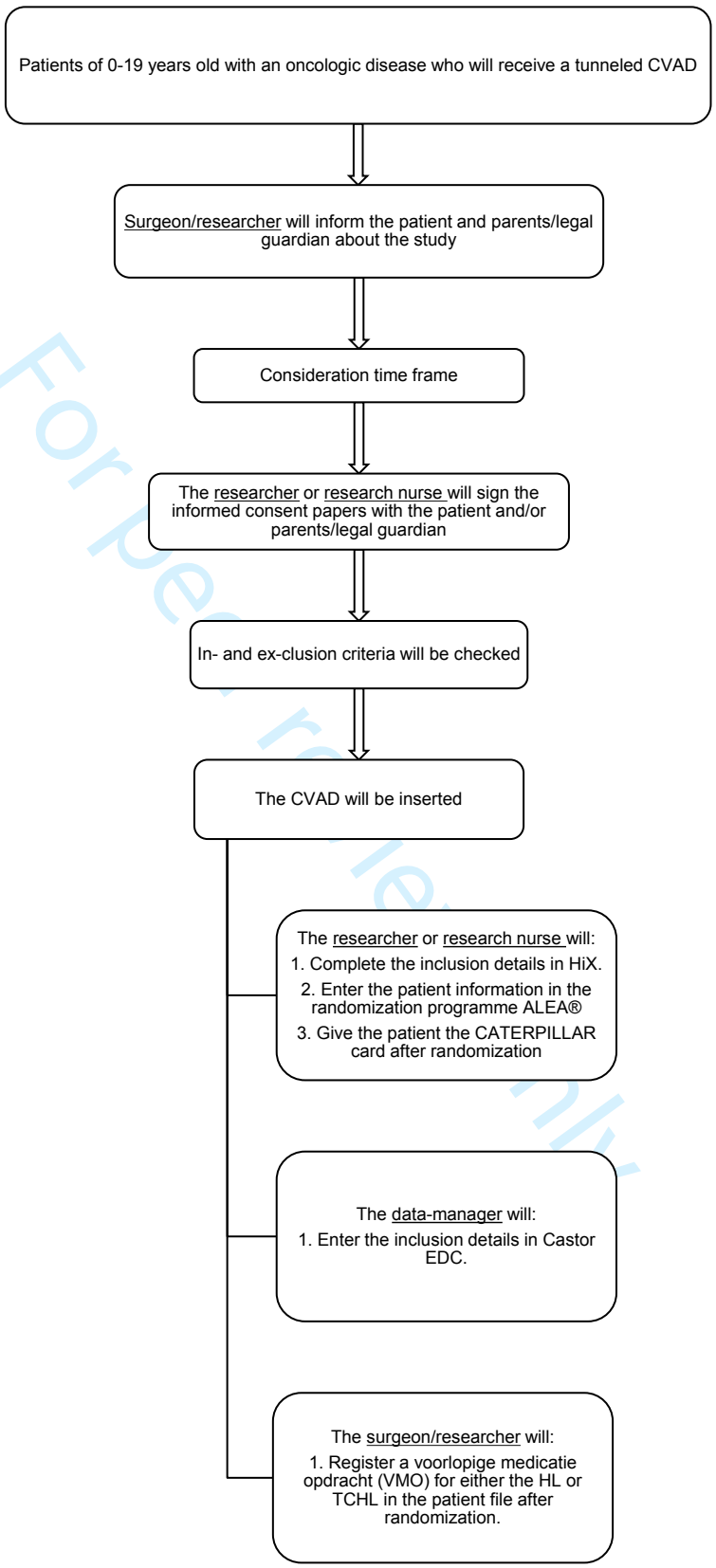
* Recognized pathogens are pathogens that are not included on the NHSN common commensal list (e.g. *S. Aureus*): https://nhsn.cdc.gov/nhsntraining/courses/2016/C18/page3299.html. The following micro-organisms are not included in the common commensal list but are not recognized pathogens: *Campylobacter, C. difficile, Enterpopathogenic E. coli, Listeria spp., Salmonella spp.*, en *Yersinia spp.*

** Common commensals are micro-organisms that are included on the NHSN common commensal list (e.g. *Coagulase-negative staphylococci, Viridians group streptococci, Bacillus spp., Diphtheroids, Aerococcus spp. Micrococcus spp.*): https://nhsn.cdc.gov/nhsntraining/courses/2016/C18/page3299.html.

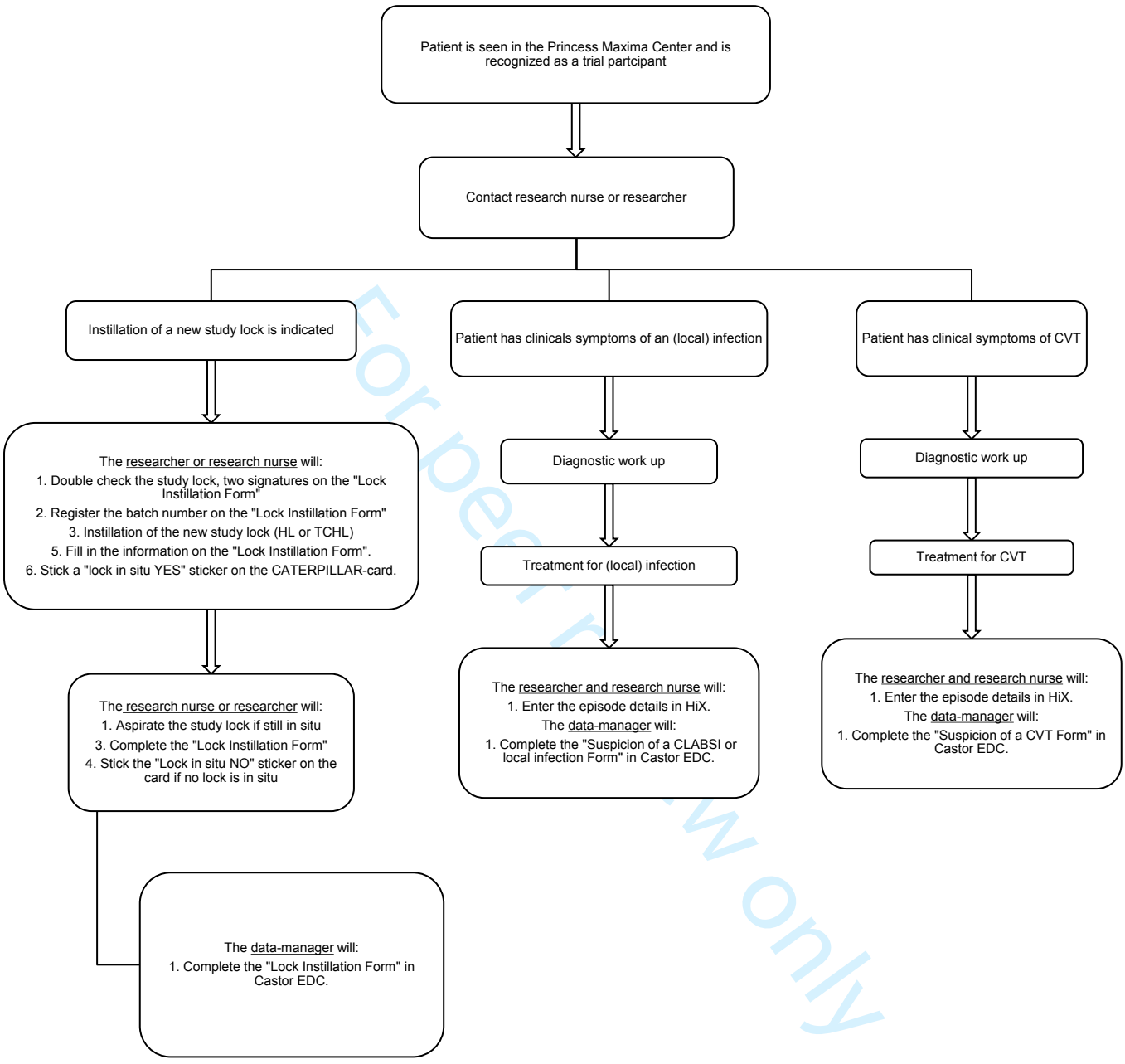
*** Micro-organisms registered as MBI Organisms on the NHSN common commensal list (e.g. *Escherichia coli, Enterobacteriaceae, and Enterococci)*: https://nhsn.cdc.gov/nhsntraining/courses/2016/C18/page3299.html.

**** Viridans streptococci: e.g. *S. mitis, S. oralis, S. salivarius, S. thermophilus, S. vestibularis, S. anginosus, S. sanguinis, S. parasanguinis, S. gordonii, S. mutans, en S. sobrinus.*

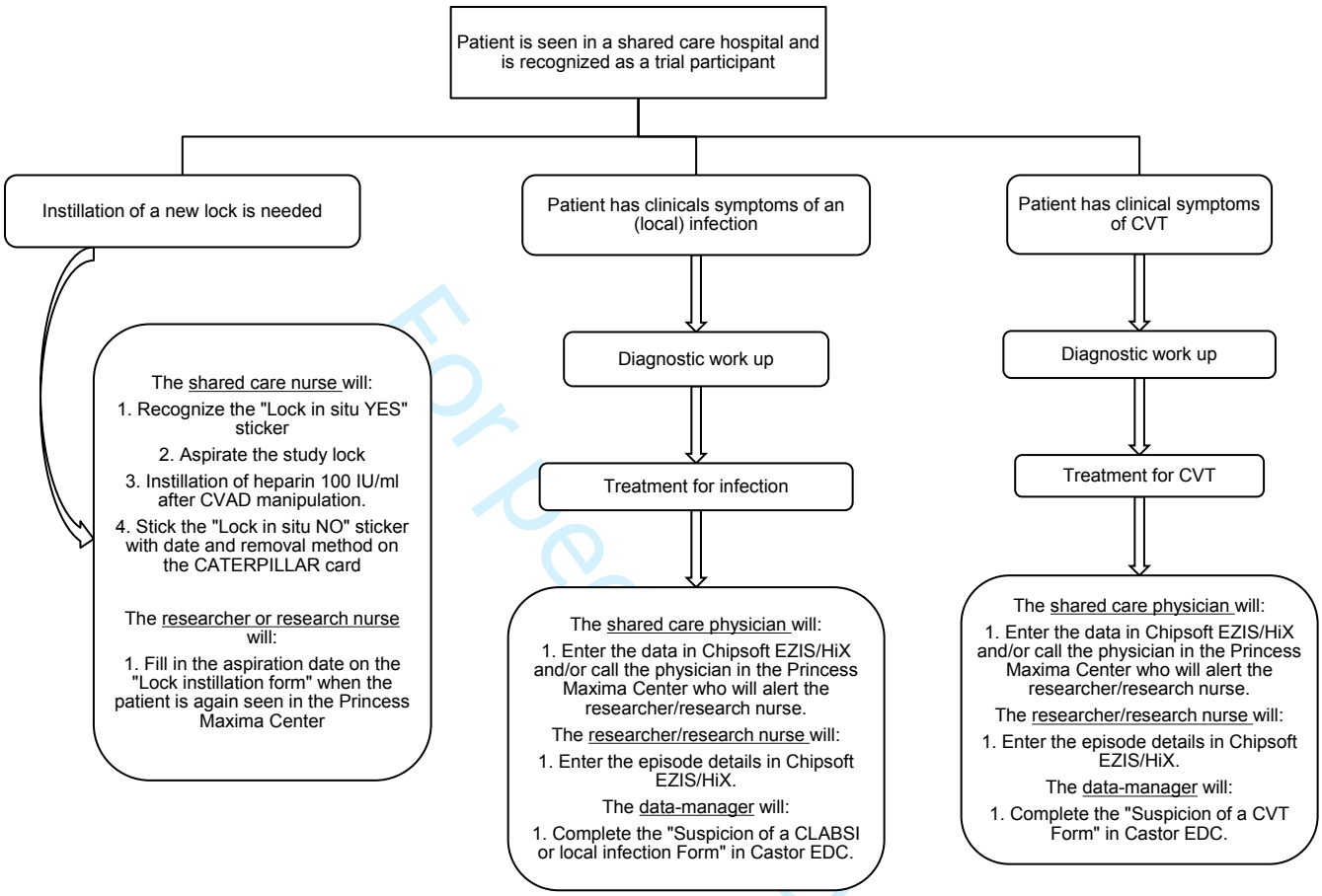
13.4 Appendix 4: Flow-chart study procedure



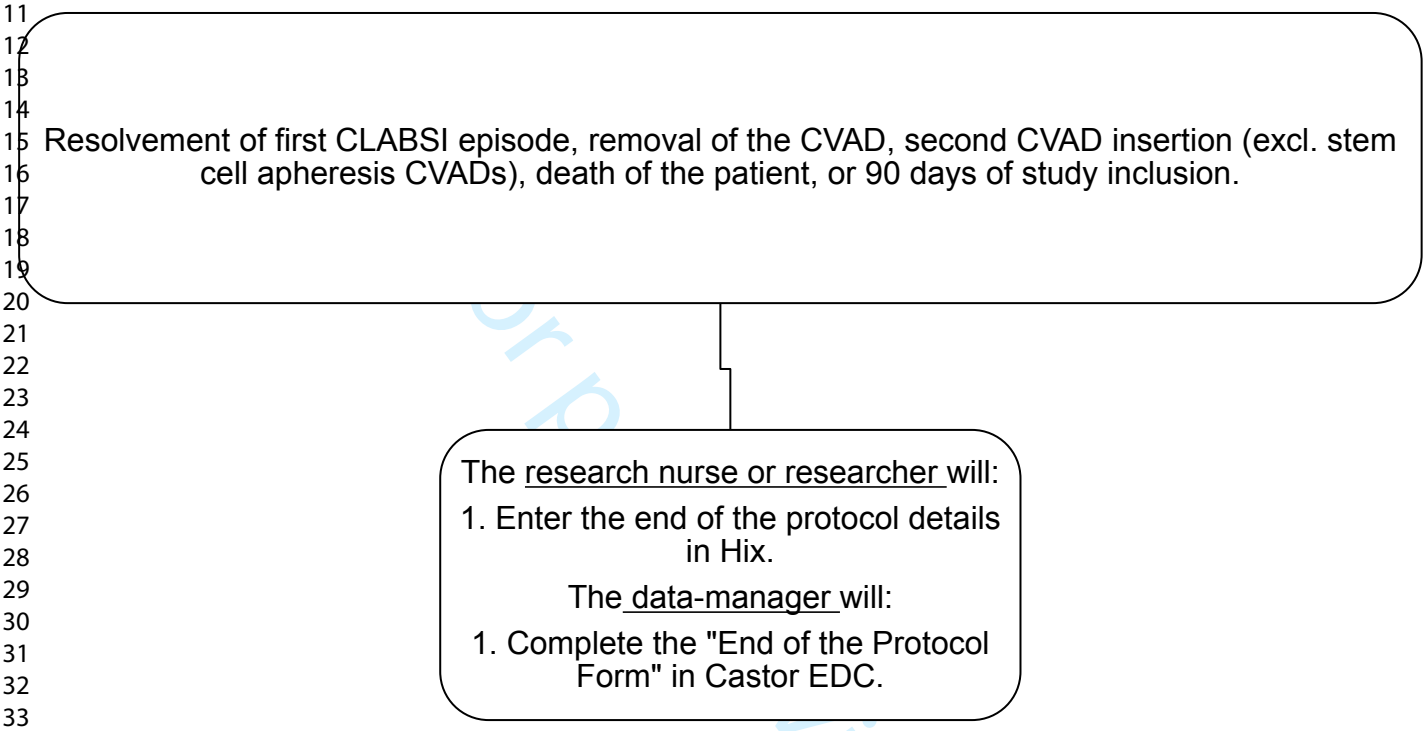
13.5 Appendix 5: Flow-chart study procedure Princess Máxima Center



13.6 Appendix 6: Flow-chart study procedure Shared Care Hospitals



13.7 Appendix 7: End of the Protocol flow-chart



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