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Protocol for Cryoprevention of chemotherapy-induced oral mucositis after autologous stem cell transplantation, a randomized controlled trial

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Keywords:	CHEMOTHERAPY, Myeloma < HAEMATOLOGY, Lymphoma < HAEMATOLOGY, Bone marrow transplantation < HAEMATOLOGY

Administrative information

Title
Protocol for Cryoprevention of chemotherapy-induced oral mucositis after autologous stem cell transplantation, a randomized controlled trial

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ClinicalTrials.gov (NCT03203733)

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Roles and responsibilities
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Contribution: WJ was involved in initial study conception, trial design, intervention development, protocol and manuscript preparation and ethics application. SA was involved in trial design and protocol preparation. GM was involved in statistical advice, input to trial design and protocol preparation.

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The study sponsor will not have ultimate authority over any of the following: study design, collection, management, analysis, interpretation of data, writing or decision to submit the report for publication.

Coordinating centres
Karolinska Trial Alliance (KTA) and Uppsala Clinical Research (UCR)

Steering committee
Java Walladbegi, Anncarin Svanberg, Bengt Furberg

Endpoint adjudication
Karin Garming-Legert, Java Walladbegi, Anncarin Svanberg

Abstract

Introduction: A majority of patients who receive myeloablative therapy prior to stem cell transplantation develop oral mucositis. This adverse cytotoxic effect manifests as oral mucosal erythema and ulcerations and frequently necessitates narcotic analgesia for pain alleviation. Oral mucositis may also interfere with food intake and result in weight loss, a need for parenteral nutrition and impaired quality of life. To date, there have been very few studies of evidence-based interventions for the prevention of oral mucositis. Cooling the oral mucosa using ice chips in conjunction with chemotherapy is known to reduce the severity of oral mucositis although clinical applications are still limited due to several disadvantages. The primary endpoint is therefore to evaluate cooling with an innovative intraoral cooling device (Cooral™) compared with ice cooling in reducing the degree of oral mucositis in patients with myeloma or lymphoma.

Method and analysis: A total of 180 patients from four different university hospitals in Sweden will be randomized to ice or Cooral™ in a proportion of 1:1. The degree of OM will be assessed at eight intraoral locations, in accordance with the Oral Mucositis Assessment Scale (OMAS) and World health organization scale (WHO). Patients will be registered beginning at admission and will continue until discharge or until day +28. The primary variable is studied in a multiple linear regression model. The significance level used is 5%.

Ethics and dissemination: The study protocol, questionnaire, diaries and letter of invitation to participants have been reviewed by the local ethical board in Göteborg. The trial results will be published in a peer-reviewed journal and disseminated to participants.

Strengths and limitations of this study

- Multicenter study evaluating the efficacy and tolerability of Cooral™ and ice cooling in patients with myeloma and lymphoma.
- Prospective randomized controlled trial of 180 patients with blinded evaluation of OM.
- Advancing the understanding of using an alternative cooling method in prevention of OM.
- Unable to evaluate the efficacy and tolerability of Cooral™ in childhood cancer patients.
- Longitudinal study lacking an untreated control group.

Introduction

Background and rationale

Hematopoietic stem cell transplantation (HSCT) is successfully used for a number of malignant blood diseases. In autologous stem cell transplantation (ASCT) the patient's own blood stem cells are used in order to preserve bone marrow function after administration of high doses of cytostatics.

Chemotherapy has many side effects, one of which is oral mucositis (OM). OM is a lesion of the epithelium and the tissue immediately below it in the mouth and throat, affecting up to 80% of patients who receive high doses of cytostatics in preparation for HSCT [1 2]. The lesion of the oral mucosa manifests itself as painful sores in the oral cavity [3] and can require high doses of intravenous morphine for pain relief [4]. Furthermore, OM makes food intake difficult, which can lead to undernourishment, weight loss, and impaired quality of life [5].

Today there are few treatment methods intended to prevent the occurrence of OM. An extensive literature search shows that the best-documented preventive method is cooling of the oral mucous membrane with ice, before, during, and after infusion of cytostatics [6].

Despite well-substantiated documentation, there is limited use of ice cooling as a preventive method in for OM in clinical practice. This may be because ice can give rise to shooting pains in the teeth or other discomfort for the patient, leading to lower adherence. In addition, it is very important that the ice is made from water of good quality so that there is no risk of contamination by microorganisms and consequent risk of infections.

It is of interest to conduct a randomized study comparing Cooral™ and ice cooling as regards prevention of OM and tolerability.

The best documented preventive method for oral mucositis according to Cochrane collaborations.

Specific objectives or hypotheses

The objectives are to compare Cooral™ and ice cooling regards efficacy and tolerability.

Trial design

An open randomized controlled trial with blinded evaluation of OM.

Methods: Participants, interventions, and outcomes

Study setting

Patients with myeloma or lymphoma at Karolinska Hospital (Fig. 1, 2) and Uppsala University Hospital (Fig. 3, 4); and patients with myeloma at the University Hospitals in Linköping and Örebro (Fig. 3) who are to undergo ASCT will be asked to participate in the study.

Eligibility criteria

Inclusion criteria

I. Patients aged 16 or over diagnosed with myeloma or lymphoma

II. Able to communicate in Swedish

III. Treated with melphalan (myeloma), BEAM/ BEAC (lymphoma), before ASCT

Exclusion criteria

I. Patients who do not understand oral and written information in Swedish

II. The patient is taking part in another study which, in the doctor's judgment, can affect the result of this study

III. The patient is receiving post-treatment care at a different hospital than where the stem cell transplant took place and follow-up is not possible

IV. The doctor judges that the patient is for some reason not suitable for the study

Interventions

Ice

Patients will be provided with ice cubes/crushed ice or ice pop 30 minutes before the start of chemotherapy. As the ice melts, the melted liquid is rinsed around in the mouth to cool as large a part as possible of the oral cavity and throat. To achieve cooling of the hindmost part of the throat, the melted liquid is gurgled for a few seconds before it is swallowed or spat out. When the ice or the pop has melted entirely, yet another selected cooling product is taken immediately. The procedure is repeated until 30 minutes after the termination of the cytostatic infusion. Food and drink should be taken either before or after the cytostatic infusion. Cooling continues during conditioning with cytostatics in the treatment schema melphalan (myeloma) and BEAM/BEAC (lymphoma). In lymphoma conditioning cures with a 12-hour infusion time (e.g. Cytarabine) the cooling starts initially 30 minutes before the start of cytostatic treatment and continues 30 minutes after the start of 12-hour cytostatic infusion. Then the patient is provided with ice cubes/crushed ice or ice pop for 30 minutes every 4 hours during the infusion. It is important to end with 30 minutes' cooling of the oral mucous membrane after each completed cytostatics administration.

Cooral™

Before the start of treatment the patient receives clear oral instructions on the use of Cooral™ by the nurse responsible for the patient. The patient him/herself is able to administer the intraoral component until it feels comfortable. Then the responsible staff check to ensure that it has good contact with the oral mucous membrane. Cooling begins 30 minutes before the start of chemotherapy and continues during conditioning with cytostatics in the treatment schema melphalan (myeloma) and BEAM/BEAC (lymphoma). Cooling continues until 30 minutes after the termination of the cytostatic infusion. During treatment the patient may if necessary take out the component and replace it again, for a maximum of 5 minutes. Food and drink should thus be taken before or after chemotherapy. In lymphoma conditioning cures with a 12-hour infusion time (e.g. Cytarabine) the cooling starts initially 30 minutes before the start of cytostatic treatment and continues 30 minutes after the start of 12-hour cytostatic infusion. Then the patient is provided with Cooral™ for 30 minutes every 4 hours during the infusion. It is important to end with 30 minutes' cooling of the oral mucous membrane after each completed cytostatics administration.

Outcomes

The primary objective is to study patients with myeloma or lymphoma undergoing ASCT, to evaluate whether cooling with Cooral™ compared with ice cubes/crushed ice or ice pop succeeds in reducing the degree of OM according to the Oral Mucositis Assessment Scale, OMAS total.

The secondary objectives are to evaluate OMAS total divided according to OMAS ulceration, OMAS erythema, degree of OM according to WHO, tolerability of either cooling method, subjective experience of OM, rating of general quality of life and oral pain, number of days with total parenteral nutrition (TPN), number of hospital days, total dose of opioids, and CRP during time in care.

The tertiary objectives are to evaluate weight loss, LPC (leukocyte plasma concentration), number of days until bone marrow response, S-albumin and body temperature.

Participant timeline

Total cooling time for myeloma (1.5 hrs) and lymphoma (3-6 hrs). All patients are followed beginning at admission and will continue until discharge or until day +28.

Sample size

A sample size of 90 patients per group will give a power of 80% to discover an average difference of at least 0.42 OMAS units [7]. The analysis is based on the standard deviation for OMAS being 1 in both groups, and the use of an independent t-test with a significance level of 5%.

Recruitment

All patients with myeloma or lymphoma at Uppsala University Hospital and Karolinska Hospital; and patients with myeloma at the University Hospitals in Linköping and Örebro who are to undergo ASCT will be asked to participate in the study. Information will be given in connection with stem cell apheresis and in material sent to the patient in connection with the invitation letter with information about admission to the ward for ASCT. Inclusion in the study will take place after written consent on arrival at the ward to be admitted for ASCT. For under-age patients (16–17 years) parents will also be informed and asked if they consent to

their children's participation. Estimated time for inclusion is approximately 1.5 years starting from 12th June 2017.

A total of 180 patients will be recruited and randomized to ice or Cooral™ in a proportion of 1:1. Expected number of patients: from Uppsala University Hospital (80), Karolinska Hospital (70), Linköping University Hospital (15) and Örebro University Hospital (15).

Methods: Assignment of interventions

Sequence generation
Randomization will be done by envelope, managed centrally by the study administration in connection with the stem cell apheresis. Each hospital will be given randomization lists to follow. Randomization will be stratified with regard to department and diagnosis.

Allocation concealment mechanism
The patients will undergo balanced randomization with randomly varying block sizes (two, four or six patients) where one, two, or three experiments are distributed in sequences and one, two, or three controls. A block can be, for example,"ce" if there are two patients, "ceec" and "eeccec" if there are four or six patients respectively. Each hospital is blinded to the size of the blocks.

Implementation
Participants will be assigned by the responsible health care providers.

Blinding (masking)
The dental staff in charge of assessing OM and the statistician will be blinded to the interventions.

Data collection, management, and analysis will be done by Karolinska Trial Alliance (KTA) and Uppsala Clinical Research (UCR), two independent contract research organisations.

Methods: Data collection, management, and analysis

Data collection methods
All measurements, with the exception of the patient's subjective assessment of the cooling method, will be registered beginning at admission and will continue until discharge or until day +28. Cytostatic infusion generally starts on the day after admission. Grading of OM according to OMAS and WHO is done three times a week, for example, Monday, Wednesday, Friday, by a dentist/dental hygienist. For each day the patient is hospitalized, assessment with WHO is also performed by nurses/assistant nurses who are not blinded to the treatment group. Clinical routines differ between study centers and therefore the number of assessments can be lower during the week of admission, depending on when patients are admitted.

Rating of pain is done 1–2 times daily if the patient is kept on the ward. Alternatively, it is done every other day according to the respective department's routine for outpatient care if the patient is at home or in a home-like environment. In the case of outpatients the subjective rating of pain is noted in the patient documentation through daily telephone contact with the responsible nurse.

Assessment of the two cooling methods is performed after completion of ice/Cooral™ cooling in conjunction with cytostatic infusion. Body temperature is registered in the oral cavity or ear in accordance with the department's routines.

Participant retention
Complete follow up of patients who discontinue cooling prematurely or otherwise deviate from the intervention protocol.

Data management
Data will be collected on paper-based checklist created by Sponsor. Each checklist will be identified by a pre-printed trial number and a combination of patient study number (assigned at registration). The Investigator or an authorized staff member will complete the checklist on site. The checklist must be dated and signed by the Investigator upon completion.

The PheedIt-system will be used for data capture of clinical data and this will serve as the clinical database for the study. UCR will be responsible for set-up of the clinical database, support, programming of logical computerized checks, Data Management Plan (DMP) and management of the PheedIt-system. Data from the checklist will be entered, cleaned and validated by Sponsor appointed person. This appointed person should have signed secrecy agreement with each study site and have the task delegated to enter/edit data into the database. The completed patient questionnaires FACT-G version 4, "Cooral cooling", "Cooling with ice/ crushed ice/ ice pop" and "Diary" will also be entered into the clinical database by the Sponsor appointed person. The entered data will be subject to logical computerized checks, the output from these checks will be sent to the Sponsor appointed person for review and action. Actions to be taken by study staff as a result of the review of the check output should be documented e.g. on a Data Clarification Form (DCF). The DCF must be signed and dated by the investigator, thereafter the clinical database can be updated. Any corrections made to entered data will be audited.

The original checklists and questionnaires are source data and will be kept on site. Copies of the checklists and questionnaires will be collected by the Sponsor appointed person.

Statistical methods

All analyses are at population level: Intention-to-treat.

Analysis of the primary variable
The primary endpoint is peak OMAS (total). i.e. the highest measured OMAS total during the time in care. The primary variable is studied in a multiple linear regression model. Fixed explanatory variables are: treatment group, type of cancer, and center. An initial model also includes interaction between treatment and type of cancer and interaction between treatment and center. If the interaction effects are not significant, these are excluded from the final model. The significance level used is 5%.

Analyses of the secondary variables
OMAS ulceration and OMAS erythema indices, analyzed in the same way as peak OMAS (total), i.e., peak value is used as a target variable in a multiple regression model. The same explanatory variables are used as in the final model for peak OMAS (total).

Incidence of OM (grades 1–4 according to WHO) and incidence of severe OM (grades 3–4 according to WHO) are analyzed with the aid of logistic regression with the same explanatory variables as in the final model for peak OMAS (total). Significance level 5%.
Tolerability. Incidence of problems (grades 1–3) and severe problems (grades 4–7) are analyzed in the same way as the incidence of OM and severe OM. Significance level 5%.
Subjective ratings of OM, general quality of life and oral pain are analyzed non-parametrically, above all with the help of Mann-Whitney's U test.

Subjective ratings of OM, general quality of life and oral pain are analyzed non-parametrically, above all with the help of Mann-Whitney's U test.

Quantitative data such as number of days with TPN, number of hospital days, total dose of opioids, and CRP are analyzed with independent t-test, or with Mann-Whitney's U test if the observed data material shows a significant skew. Descriptive statistics and explorative analysis will be used to study any differences between centers.

Analysis of the tertiary variables
Weight loss, LPC, number of days until bone marrow response, S-Albumin and body temperature are analyzed with independent t-test, or with Mann-Whitney U's test if the observed data material shows a significant skew. Descriptive statistics and explorative analysis will be used to study any differences between centers.

Additional analyses
Separate analyses will be conducted with regard to study site and with regard to diagnosis (myeloma/lymphoma).

Missing data
OMAS (total) and WHO performed by dentists/dental hygenist after treatment are replaced with WHO performed by nurses. WHO replacing OMAS (total) will be translated into OMAS (total) [8]. In the final analysis, the dentist assessment is primarily used. For OMAS subindex, the highest value is used as the peak OMAS subindex if at least one OMAS subindex is available after treatment. If there is no OMAS subindex after treatment the patients baseline is used as peak OMAS subindex.

For other secondary/tertiary variables the strategy is to use the mean value of the preceding and following value. If the preceding value is missing, the following value is used. If the following value is missing, the technique used is last value carried forward.

Methods: Monitoring

Data monitoring

To protect the patients' safety during the trial, the results will be monitored by a Data Monitoring Committee (DMC), consisting of an experienced biostatistician and a clinician with long experience of clinical trials. Both are independent of the sponsor and will provide an impartial recommendation for the continuation of the study. Separate working instructions will be provided as a "charter" to the Data Monitoring Committee. A conservative stopping rule according to the O'Brien-Fleming boundary will be applied to minimize the effect of the interim analysis on the statistical strength at the end of the trial.

Interim analysis

The DMC will have two members, an experienced biostatistician and a clinician with considerable experience of clinical trials. The CRO will provide the DMC with a first interim analysis when 100 patients have been treated. Based on the results the DMC will recommend the sponsor to continue or terminate the trial without communicating any results. The DMC will decide about further interim analyses. Before the DMC recommends early termination of the trial it will try to get advice from the FDA.

Harms

Adverse events related to the Cooral/Ice treatment sessions will be assessed by the questions addressed in the patients' questionnaires "Cooral cooling", "Cooling with ice/ crushed ice/ ice pop". The adverse events will be summarized and included in the final rapport of the clinical study. Serious adverse events that are related to the Cooral/Ice treatment sessions will be reported to all sites and principle investigators will be informed/updated. Any errors of the medical device will be documented and taken care of/repaired by the sponsor.

Auditing

The study will be monitored by Karolinska Trial Alliance (KTA) to ensure that it is carried out in accordance with the established study protocol, Helsinki declaration, ISO14155:2011 and other applicable guidelines and regulations. A monitoring plan has been established.

Ethics and dissemination

Research ethics approval
The study was approved by the regional review board in Gothenburg (Dnr: 586-15).

Protocol amendments
Important protocol modifications will be communicated by KTA to investigators, trial participants, trial registries, review board, journals and regulators.

Consent or assent
Written informed consent will be obtained from all patients included in the study.

Confidentiality
Patients will have patient study number, which is linked to their identity for traceability. The study number is used for all documents to ensure that the patient identity is not disclosed. Only the healthcare staff in charge at the clinic have access to journals and "Subject Enrolment and Identification Log" where the patients identity appears. All data will be confidential and password protected throughout the study. Patient identity is protected in the final report and upon publication of the study.

Declaration of interest
Dr. Walladbegi is currently in receipt of a PhD scholarship funded by BrainCool AB. Dr. Svanberg is employed part-time at BrainCool AB. Dr. Gellerstedt reports no conflicts of interest. There were no financial and other competing interests for principal investigators for the overall trial at any of the study sites.

Access to data
Karolinska Trial Alliance (KTA) and Uppsala Clinical Research (UCR), authors and investigators.

Ancilliary and post-trial care
Usual care according to the clinical standard. Participants are insured by QBE and Chubb insurances. Compensation will be given to those who suffer harm from trial participation.

Dissemination policy

a) Publication of full paper.
b) The sponsor has no intention to use professional writers.
c) On request.

Appendices

1. Informed consent materials
2. Quality of life
3. Evaluation of cooling method (tolerability)
4. Diary

Acknowledgement

The authors would like to thank BMSc. Sajjad Saffari for contributing with the design of the flowcharts.

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Figure legends:

Figure 1: Flowchart for patients with myeloma at Karolinska Hospital.
***Day 0*:** Admission, chemotherapy conditioning, oral mucosal cooling along with completion of QoL questionnaire (FACT-G) and evaluation of cooling method. ***Day 1*:** Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.

Figure 2: Flowchart for patients with lymphoma at Karolinska Hospital.
Day -1*:** Admission, along with completion of QoL questionnaire (FACT-G). ***Day*: *-1 to 4
Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. ***Day 5*:** Recovery. ***Day 6*:** Autologous stem cell transplantation (ASCT).
Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.
Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.

Figure 3: Flowchart for patients with myeloma at Uppsala University Hospital and University Hospitals in Linköping and Örebro.
***Day -1*:** Admission. ***Day 0*:** Chemotherapy conditioning, oral mucosal cooling along with completion of QoL questionnaire (FACT-G) and evaluation of cooling method.
***Day 1*:** Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.

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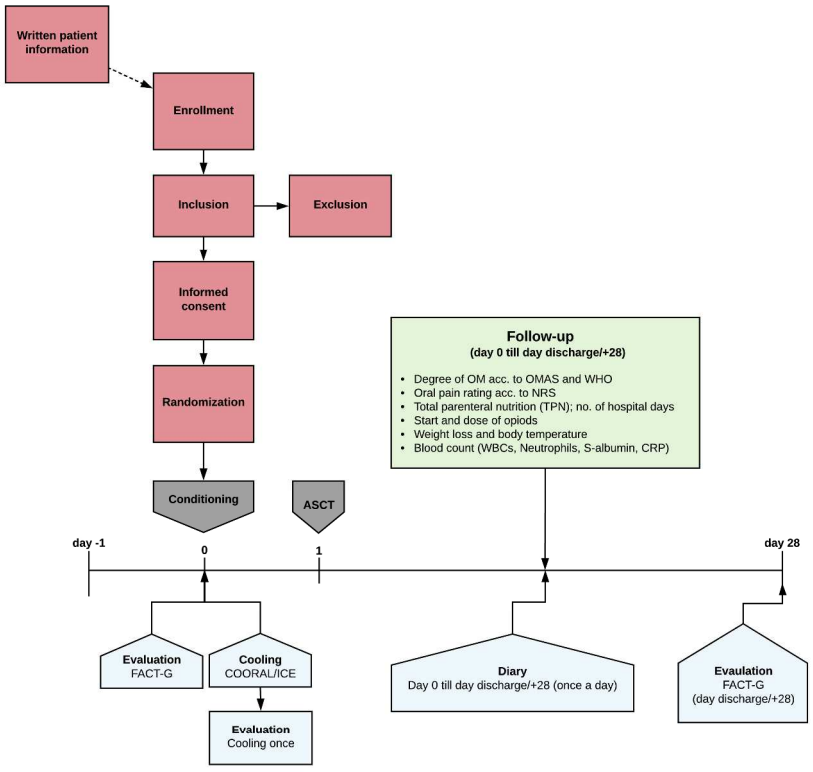
Figure 4: Flowchart for patients with lymphoma at Uppsala University Hospital.
Day -1*:** Admission, along with completion of QoL questionnaire (FACT-G). ***Day*: *0 to 4
Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. ***Day 5*:** Recovery. ***Day 6*:** Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge. Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.



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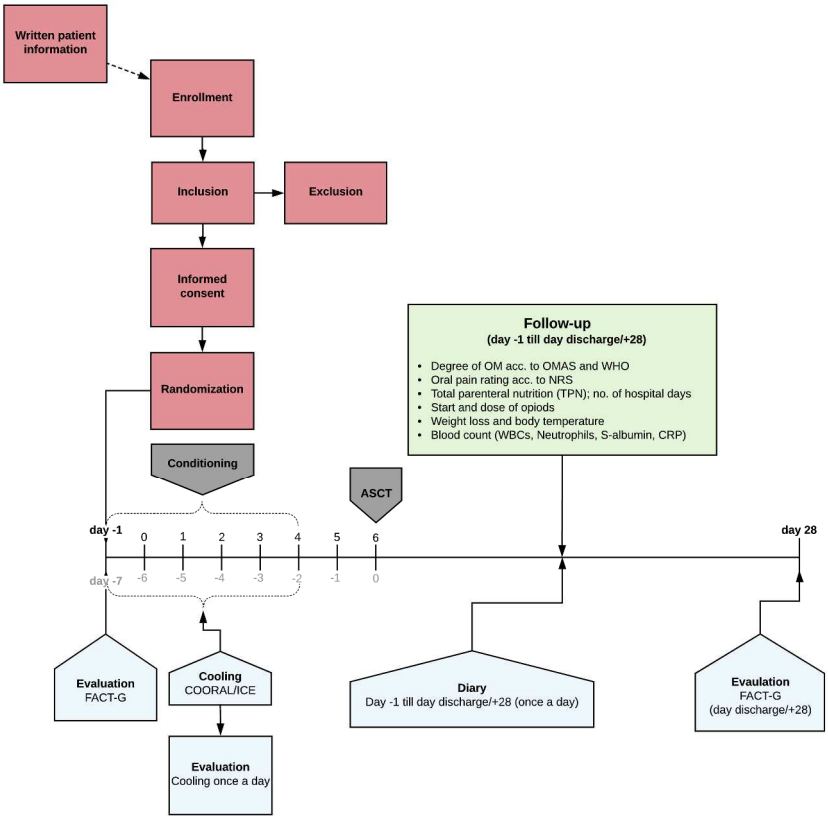

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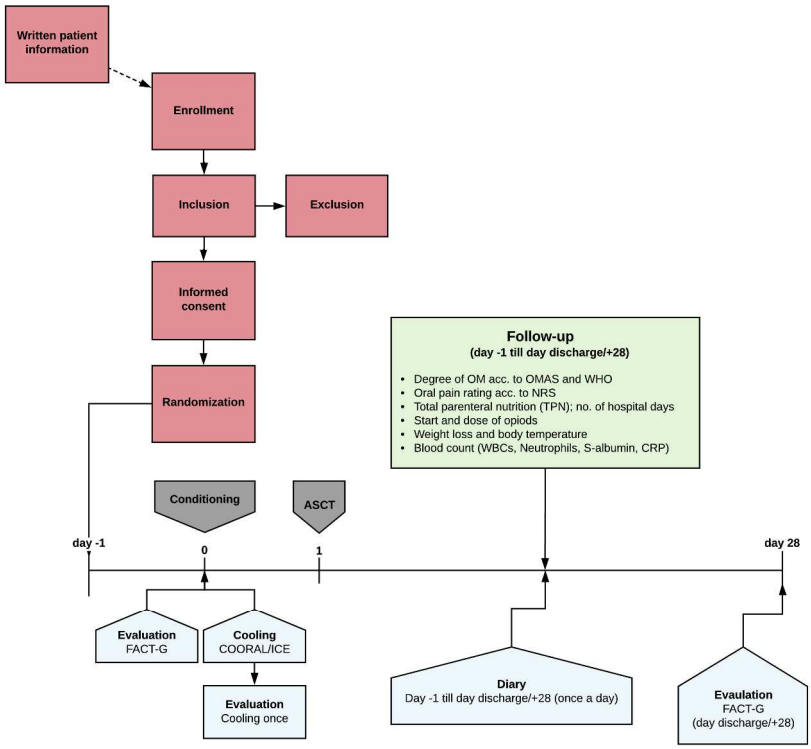

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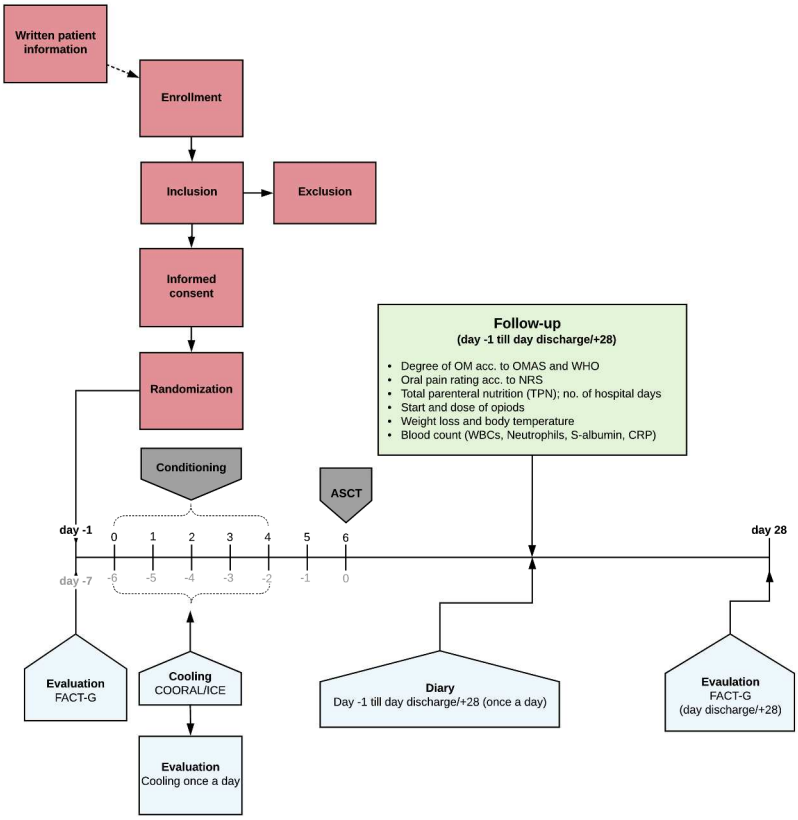

Figure 4: Flowchart for patients with lymphoma at Uppsala University Hospital. Day -1: Admission, along with completion of QoL questionnaire (FACT-G). Day: 0 to 4 Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. Day 5: Recovery. Day 6: Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge. Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.

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Contributorship statement
WJ was involved in initial study conception, trial design, intervention development, protocol and manuscript preparation and ethics application. SA was involved in trial design and protocol preparation. GM was involved in statistical advice, input to trial design and protocol preparation. All authors have fulfilled the ICMJE criteria for authorship.

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The study sponsor will not have ultimate authority over any of the following: study design, collection, management, analysis, interpretation of data, writing or decision to submit the report for publication.

Coordinating centres
Karolinska Trial Alliance (KTA) and Uppsala Clinical Research (UCR)

Steering committee
Java Walladbegi, Anncarin Svanberg, Bengt Furberg

Endpoint adjudication
Karin Garming-Legert, Java Walladbegi, Anncarin Svanberg

Abstract

Introduction: A majority of patients who receive myeloablative therapy prior to stem cell transplantation develop oral mucositis. This adverse cytotoxic effect manifests as oral mucosal erythema and ulcerations and frequently necessitates high doses of morphine for pain alleviation. Oral mucositis may also interfere with food intake and result in weight loss, a need for parenteral nutrition and impaired quality of life. To date, there have been very few studies of evidence-based interventions for the prevention of oral mucositis. Cooling the oral mucosa using ice chips in conjunction with chemotherapy is known to reduce the severity of oral mucositis although clinical applications are still limited due to several disadvantages. The primary endpoint is therefore to evaluate cooling with an innovative intraoral cooling device (Cooral™) compared with ice cooling in reducing the degree of oral mucositis in patients with myeloma or lymphoma.
Method and analysis: A total of 180 patients from four different university hospitals in Sweden will be randomized to ice or Cooral™ in a proportion of 1:1. The degree of OM will be assessed at eight intraoral locations, in accordance with the Oral Mucositis Assessment Scale (OMAS) and World health organization scale (WHO). Patients will be registered beginning at admission and will continue until discharge or until day +28. The primary variable is studied in a multiple linear regression model. The significance level used is 5%.
Ethics and dissemination: The study protocol, questionnaire, diaries and letter of invitation to participants have been reviewed by the local ethical board in Göteborg. The trial results will be published in a peer-reviewed journal and disseminated to participants.
Trial registration: ClinicalTrials.gov (NCT03203733)

Strengths and limitations of this study

- Prospective randomized multicenter study with 180 patients evaluating the efficacy and tolerability of two cooling methods.
- Blinded assessment of OM by dentists specialised in Orofacial Medicine & Pathology.
- Longitudinal study lacking an untreated control group.
- Patients younger than 16 years of age are not included in this study.

Introduction

Background and rationale

Hematopoietic stem cell transplantation (HSCT) is successfully used for a number of malignant blood diseases. In autologous stem cell transplantation (ASCT) the patient's own blood stem cells are used in order to preserve bone marrow function after administration of high doses of cytostatics.

Chemotherapy has many side effects, one of which is oral mucositis (OM). OM is a lesion of the epithelium and the tissue immediately below it in the mouth and throat, affecting up to 80% of patients who receive high doses of cytostatics in preparation for HSCT [1 2]. The lesion of the oral mucosa manifests itself as painful sores in the oral cavity [3] and can require high doses of morphine for pain alleviation [4]. Furthermore, OM makes food intake difficult, which can lead to undernourishment, weight loss, and impaired quality of life [5].

Today there are few treatment methods intended to prevent the occurrence of OM. An extensive literature search shows that the best-documented preventive method is cooling of the oral mucous membrane with ice, before, during, and after infusion of cytostatics [6].

Despite well-substantiated documentation, there is limited use of ice cooling as a preventive method in for OM in clinical practice. This may be because ice can give rise to shooting pains in the teeth or other discomfort for the patient, leading to lower adherence. In addition, it is very important that the ice is made from water of good quality so that there is no risk of contamination by microorganisms and consequent risk of infections.

To prevent the occurrence of OM, an intraoral cooling device (Cooral™) has been designed [7]. Cooral™ consists of a closed duct system with continuously circulating water, shaped and dimensioned to cool the cheeks, lips, mouth floor, tongue, and gums. By offering patients Cooral™ we intend to reduce the incidence of OM but also expect to achieve more even cooling distribution in the oral mucous membrane and better tolerability of the cooling temperature compared with ice.

It is of interest to conduct a randomized study comparing Cooral™ and ice cooling as regards prevention of OM and tolerability.

Specific objectives or hypotheses

The objectives are to compare Cooral™ and ice cooling regards efficacy and tolerability.

Trial design

An open randomized controlled trial with blinded evaluation of OM.

Methods: Participants, interventions, and outcomes

Study setting

Patients with myeloma or lymphoma at Karolinska Hospital (Fig. 1, 2) and Uppsala University Hospital (Fig. 3, 4); and patients with myeloma at the University Hospitals in Linköping and Örebro (Fig. 3) who are to undergo ASCT will be asked to participate in the study.

Eligibility criteria

Inclusion criteria

I. Patients aged 16 or over diagnosed with myeloma or lymphoma

II. Able to communicate in Swedish

III. Treated with melphalan (myeloma), BEAM/ BEAC (lymphoma), before ASCT

Exclusion criteria

I. Patients who do not understand oral and written information in Swedish

II. The patient is taking part in another study which, in the doctor's judgment, can affect the result of this study

III. The patient is receiving post-treatment care at a different hospital than where the stem cell transplant took place and follow-up is not possible

IV. The doctor judges that the patient is for some reason not suitable for the study

Interventions

Ice

Patients will be provided with ice cubes/crushed ice or ice pop 30 minutes before the start of chemotherapy. As the ice melts, the melted liquid is rinsed around in the mouth to cool as large a part as possible of the oral cavity and throat. To achieve cooling of the hindmost part of the throat, the melted liquid is gurgled for a few seconds before it is swallowed or spat out. When the ice or the pop has melted entirely, yet another selected cooling product is taken immediately. The procedure is repeated until 30 minutes after the termination of the cytostatic infusion. Food and drink should be taken either before or after the cytostatic infusion. Cooling continues during conditioning with cytostatics in the treatment schema melphalan (myeloma) and BEAM/BEAC (lymphoma). In lymphoma conditioning cures with a 12-hour infusion time (e.g. Cytarabine) the cooling starts initially 30 minutes before the start of cytostatic treatment and continues 30 minutes after the start of 12-hour cytostatic infusion. Then the patient is provided with ice cubes/crushed ice or ice pop for 30 minutes every 4 hours during the infusion. It is important to end with 30 minutes' cooling of the oral mucous membrane after each completed cytostatics administration.

Cooral™

Before the start of treatment the patient receives clear oral instructions on the use of Cooral™ by the nurse responsible for the patient. The patient him/herself is able to administer the intraoral component until it feels comfortable. Then the responsible staff check to ensure that it has good contact with the oral mucous membrane. Cooling begins 30 minutes before the start of chemotherapy and continues during conditioning with cytostatics in the treatment schema melphalan (myeloma) and BEAM/BEAC (lymphoma). Cooling continues until 30 minutes after the termination of the cytostatic infusion. During treatment the patient may if necessary take out the component and replace it again, for a maximum of 5 minutes. Food and drink should thus be taken before or after chemotherapy. In lymphoma conditioning cures with a 12-hour infusion time (e.g. Cytarabine) the cooling starts initially 30 minutes before the start of cytostatic treatment and continues 30 minutes after the start of 12-hour cytostatic infusion. Then the patient is provided with Cooral™ for 30 minutes every 4 hours during the infusion. It is important to end with 30 minutes' cooling of the oral mucous membrane after each completed cytostatics administration.

Outcomes

The primary objective is to study patients with myeloma or lymphoma undergoing ASCT, to evaluate whether cooling with Cooral™ compared with ice cubes/crushed ice or ice pop succeeds in reducing the degree of OM according to the Oral Mucositis Assessment Scale, OMAS total.

The secondary objectives are to evaluate OMAS total divided according to OMAS ulceration, OMAS erythema, degree of OM according to WHO, tolerability of either cooling method, subjective experience of OM, rating of general quality of life and oral pain, number of days with total parenteral nutrition (TPN), number of hospital days, total dose of opioids, and CRP during time in care.

The tertiary objectives are to evaluate weight loss, LPC (leukocyte plasma concentration), number of days until bone marrow response, S-albumin and body temperature.

Participant timeline

Total cooling time for myeloma (1.5 hrs) and lymphoma (3-6 hrs). All patients are followed beginning at admission and will continue until discharge or until day +28.

Sample size

A sample size of 90 patients per group will give a power of 80% to discover an average difference of at least 0.42 OMAS units [8]. The analysis is based on the standard deviation for OMAS being 1 in both groups, and the use of an independent t-test with a significance level of 5%.

Recruitment

All patients with myeloma or lymphoma at Uppsala University Hospital and Karolinska Hospital; and patients with myeloma at the University Hospitals in Linköping and Örebro who are to undergo ASCT will be asked to participate in the study. Information will be given in connection with stem cell apheresis and in material sent to the patient in connection with the invitation letter with information about admission to the ward for ASCT. Inclusion in the study will take place after written consent on arrival at the ward to be admitted for ASCT. For under-age patients (16–17 years) parents will also be informed and asked if they consent to

their children's participation. Estimated time for inclusion is approximately 1.5 years starting from 12th June 2017.

A total of 180 patients will be recruited and randomized to ice or Cooral™ in a proportion of 1:1. Expected number of patients: from Uppsala University Hospital (80), Karolinska Hospital (70), Linköping University Hospital (15) and Örebro University Hospital (15).

Patient and Public Involvement
Comparison of the balance between efficacy and safety for Cooral™ and ice in the prevention of OM is in the best interest of patients. Patients were not involved in the design of this study or in the recruitment or conduct of the study. The study results will be disseminated to study participants orally and in writing. The burden of the interventions will be assessed by the patients themselves. No patient advisers were involved in the design or conduct of the study.

Methods: Assignment of interventions

Sequence generation
Randomization will be done by envelope, managed centrally by the study administration in connection with the stem cell apheresis. Each hospital will be given randomization lists to follow. Randomization will be stratified with regard to department and diagnosis.

Allocation concealment mechanism
The patients will undergo balanced randomization with randomly varying block sizes (two, four or six patients) where one, two, or three experiments are distributed in sequences and one, two, or three controls. A block can be, for example,"ce" if there are two patients, "ceec" and "eeccec" if there are four or six patients respectively. Each hospital is blinded to the size of the blocks.

Implementation
Participants will be assigned by the responsible health care providers.

Blinding (masking)
The dental staff in charge of assessing OM and the statistician will be blinded to the interventions.

Data collection, management and analysis will be done by Karolinska Trial Alliance (KTA) and Uppsala Clinical Research (UCR), two independent contract research organisations.

Methods: Data collection, management, and analysis

Data collection methods
All measurements, with the exception of the patient's subjective assessment of the cooling method, will be registered beginning at admission and will continue until discharge or until day +28. Cytostatic infusion generally starts on the day after admission. Grading of OM according to OMAS and WHO is done three times a week, for example, Monday, Wednesday, Friday, by a dentist/dental hygienist. For each day the patient is hospitalized, assessment with WHO is also performed by nurses/assistant nurses who are not blinded to the treatment group. Clinical routines differ between study centers and therefore the number of assessments can be lower during the week of admission, depending on when patients are admitted.

The degree of OM is assessed at eight intraoral locations, in accordance with the Oral Mucositis Assessment Scale (OMAS) (graded 0–3 for ulceration and 0–2 for erythema). 0 corresponds to "normal" while 3 and 2 are "sore >3 cm^2" and "severe erythema" respectively. The assessment generates both an average for OMAS ulceration (0–3) and OMAS erythema (0–2) and a total average OMAS (0–5), which is the mean of both ulceration and erythema. Besides OMAS, ulceration and erythema are also assessed with the WHO scale (graded 0–4) where 0 is "no mucositis" and 4 is "ulceration, total parenteral nutrition".

Prior to myeloablative therapy, all patients at each of the four study sites undergo a complete oral/dental examination by a dentist specialised in Orofacial Medicine & Pathology followed by an odontological decontamination. Meticulous information and instructions for oral hygiene maintenance is also received. Patients who develop OM are initially treated with paracetamol or opioids, depending on degree of symptoms, and further assisted by healthcare professionals to maintain a good oral hygiene. In more severe cases, a dentist or a dental hygienist is contacted for assistance and further support with oral care maintenance.

The dental staff responsible for OM assessment were calibrated prior to study start. ICC coefficient: OMAS=0.94 (excellent); WHO=0.67 (good). All other staff involved in the study have undergone a solid education in assessing oral health status according to WHO.

Rating of pain is done with the numeric pain rating scale (NRS)1–2 times daily if the patient is kept on the ward. Alternatively, it is done every other day according to the respective department's routine for outpatient care if the patient is at home or in a home-like environment. In the case of outpatients the subjective rating of pain is noted in the patient documentation through daily telephone contact with the responsible nurse. Body temperature is registered in the oral cavity, ear or axillary region in accordance with the department's routines.

Furthermore, the patients, after cooling ends, assess the tolerability of the respective cooling method with the aid of a questionnaire (*Supplementary file 1*) developed for the study. The questionnaire is intended to give some idea of any discomfort or side effects the patients feel as a result of the cooling method.

The patients assess their perception of oral problems daily with the aid of specific questions in a diary (*Supplementary file 2*) developed for the study. The questions are intended to give a picture of the effect of OM on the patient's general status.

General quality of life is assessed twice during the study period, before the start of treatment and at discharge, with a validated quality of life instrument (*Supplementary file 3*).

Information about total parenteral nutrition (TPN), number of hospital days, total dose of opioids, weight loss, and body temperature will be retrieved from patient records. Laboratory results of blood tests will be retrieved from each department's register of test results.

The result of the assessments is documented on special CRF (case report forms) for the purpose, referred to in the study as "checklists".

Participant retention
Complete follow up of patients who discontinue cooling prematurely or otherwise deviate from the intervention protocol.

Data management
Data will be collected on paper-based checklist created by Sponsor. Each checklist will be identified by a pre-printed trial number and a combination of patient study number (assigned at registration). The Investigator or an authorized staff member will complete the checklist on site. The checklist must be dated and signed by the Investigator upon completion.

The PheedIt-system will be used for data capture of clinical data and this will serve as the clinical database for the study. UCR will be responsible for set-up of the clinical database, support, programming of logical computerized checks, Data Management Plan (DMP) and management of the PheedIt-system. Data from the checklist will be entered, cleaned and validated by Sponsor appointed person. This appointed person should have signed secrecy agreement with each study site and have the task delegated to enter/edit data into the database. The completed patient questionnaires (*Supplementary files 1-3)* will also be entered into the clinical database by the Sponsor appointed person. The entered data will be subject to logical computerized checks, the output from these checks will be sent to the Sponsor appointed person for review and action. Actions to be taken by study staff as a result of the review of the check output should be documented e.g. on a Data Clarification Form (DCF). The DCF must be signed and dated by the investigator, thereafter the clinical database can be updated. Any corrections made to entered data will be audited.

The original checklists and questionnaires are source data and will be kept on site. Copies of the checklists and questionnaires will be collected by the Sponsor appointed person.

Statistical methods

All analyses are at population level: Intention-to-treat.

Analysis of the primary variable
The primary endpoint is peak OMAS (total). i.e. the highest measured OMAS total during the time in care. The primary variable is studied in a multiple linear regression model. Fixed explanatory variables are: treatment group, type of cancer, and center. An initial model also includes interaction between treatment and type of cancer and interaction between treatment and center. If the interaction effects are not significant, these are excluded from the final model. The significance level used is 5%.

Analyses of the secondary variables
OMAS ulceration and OMAS erythema indices, analyzed in the same way as peak OMAS (total), i.e., peak value is used as a target variable in a multiple regression model. The same explanatory variables are used as in the final model for peak OMAS (total).
Incidence of OM (grades 1–4 according to WHO) and incidence of severe OM (grades 3–4 according to WHO) are analyzed with the aid of logistic regression with the same explanatory variables as in the final model for peak OMAS (total). Significance level 5%.
Tolerability. Incidence of problems (grades 1–3) and severe problems (grades 4–7) are analyzed in the same way as the incidence of OM and severe OM. Significance level 5%.
Subjective ratings of OM, general quality of life and oral pain are analyzed non-parametrically, above all with the help of Mann-Whitney's U test.

Subjective ratings of OM, general quality of life and oral pain are analyzed non-parametrically, above all with the help of Mann-Whitney's U test.

Quantitative data such as number of days with TPN, number of hospital days, total dose of opioids, and CRP are analyzed with independent t-test, or with Mann-Whitney's U test if the observed data material shows a significant skew. Descriptive statistics and explorative analysis will be used to study any differences between centers.

Analysis of the tertiary variables
Weight loss, LPC, number of days until bone marrow response, S-Albumin and body temperature are analyzed with independent t-test, or with Mann-Whitney U's test if the observed data material shows a significant skew. Descriptive statistics and explorative analysis will be used to study any differences between centers.

Additional analyses
Separate analyses will be conducted with regard to study site and with regard to diagnosis (myeloma/lymphoma).

Missing data
OMAS (total) and WHO performed by dentists/dental hygenist after treatment are replaced with WHO performed by nurses. WHO replacing OMAS (total) will be translated into OMAS (total) [9]. In the final analysis, the dentist assessment is primarily used. For OMAS subindex, the highest value is used as the peak OMAS subindex if at least one OMAS subindex is available after treatment. If there is no OMAS subindex after treatment the patients baseline is used as peak OMAS subindex.

For other secondary/tertiary variables the strategy is to use the mean value of the preceding and following value. If the preceding value is missing, the following value is used. If the following value is missing, the technique used is last value carried forward.

Methods: Monitoring

Data monitoring

To protect the patients' safety during the trial, the results will be monitored by a Data Monitoring Committee (DMC), consisting of an experienced biostatistician and a clinician with long experience of clinical trials. Both are independent of the sponsor and will provide an impartial recommendation for the continuation of the study. Separate working instructions will be provided as a "charter" to the Data Monitoring Committee. A conservative stopping rule according to the O'Brien-Fleming boundary will be applied to minimize the effect of the interim analysis on the statistical strength at the end of the trial.

Interim analysis

The DMC will have two members, an experienced biostatistician and a clinician with considerable experience of clinical trials. The CRO will provide the DMC with a first interim analysis when 100 patients have been treated. Based on the results the DMC will recommend the sponsor to continue or terminate the trial without communicating any results. The DMC will decide about further interim analyses. Before the DMC recommends early termination of the trial it will try to get advice from the FDA.

Harms

Adverse events related to the Cooral/Ice treatment sessions will be assessed by the questions addressed in the patients' questionnaires "Cooral cooling", "Cooling with ice/ crushed ice/ ice pop". The adverse events will be summarized and included in the final rapport of the clinical study. Serious adverse events that are related to the Cooral/Ice treatment sessions will be reported to all sites and principle investigators will be informed/updated. Any errors of the medical device will be documented and taken care of/repaired by the sponsor.

Auditing

The study will be monitored by Karolinska Trial Alliance (KTA) to ensure that it is carried out in accordance with the established study protocol, Helsinki declaration, ISO14155:2011 and other applicable guidelines and regulations. A monitoring plan has been established.

Ethics and dissemination

Research ethics approval
The study was approved by the regional review board in Gothenburg (Dnr: 586-15).

Protocol amendments
Important protocol modifications will be communicated by KTA to investigators, trial participants, trial registries, review board, journals and regulators.

Consent or assent
Written informed consent (*Supplementary file 4***)** will be obtained from all patients included in the study.

Confidentiality
Patients will have patient study number, which is linked to their identity for traceability. The study number is used for all documents to ensure that the patient identity is not disclosed. Only the healthcare staff in charge at the clinic have access to journals and "Subject Enrolment and Identification Log" where the patients identity appears. All data will be confidential and password protected throughout the study. Patient identity is protected in the final report and upon publication of the study.

Declaration of interest
Dr. Walladbegi is currently in receipt of a PhD scholarship funded by BrainCool AB. Dr. Svanberg is employed part-time at BrainCool AB. Dr. Gellerstedt reports no conflicts of interest. There were no financial and other competing interests for principal investigators for the overall trial at any of the study sites.

Access to data
Karolinska Trial Alliance (KTA) and Uppsala Clinical Research (UCR), authors and investigators.

Ancillary and post-trial care
Usual care according to the clinical standard. Participants are insured by QBE and Chubb insurances. Compensation will be given to those who suffer harm from trial participation.

Dissemination policy
The plan for the investigators and sponsors is to publish a full scientific article in a peer reviewed journal. The sponsor has no intention to use professional writers. Public access to the full protocol, participant-level dataset, and statistical code will be provided upon request.

Appendices

1. Evaluation of cooling method (*Supplementary file 1*)
2. Diary (*Supplementary file 2*)
3. Quality of life (*Supplementary file 3*)
4. Informed consent material (*Supplementary file 4*)

Acknowledgement
The authors would like to thank BMSc. Sajjad Saffari for contributing with the design of the flowcharts.

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Figure legends:

Figure 1: Flowchart for patients with myeloma at Karolinska Hospital.
***Day 0*:** Admission, chemotherapy conditioning, oral mucosal cooling along with completion of QoL questionnaire (FACT-G) and evaluation of cooling method. ***Day 1*:** Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.

Figure 2: Flowchart for patients with lymphoma at Karolinska Hospital.
Day -1*:** Admission, along with completion of QoL questionnaire (FACT-G). ***Day*: *-1 to 4
Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. ***Day 5*:** Recovery. ***Day 6*:** Autologous stem cell transplantation (ASCT).
Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.
Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.

Figure 3: Flowchart for patients with myeloma at Uppsala University Hospital and University Hospitals in Linköping and Örebro.
***Day -1*:** Admission. ***Day 0*:** Chemotherapy conditioning, oral mucosal cooling along with completion of QoL questionnaire (FACT-G) and evaluation of cooling method.
***Day 1*:** Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.

Figure 4: Flowchart for patients with lymphoma at Uppsala University Hospital.
Day -1*:** Admission, along with completion of QoL questionnaire (FACT-G). ***Day*: *0 to 4
Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. ***Day 5*:** Recovery. ***Day 6*:** Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge. Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.

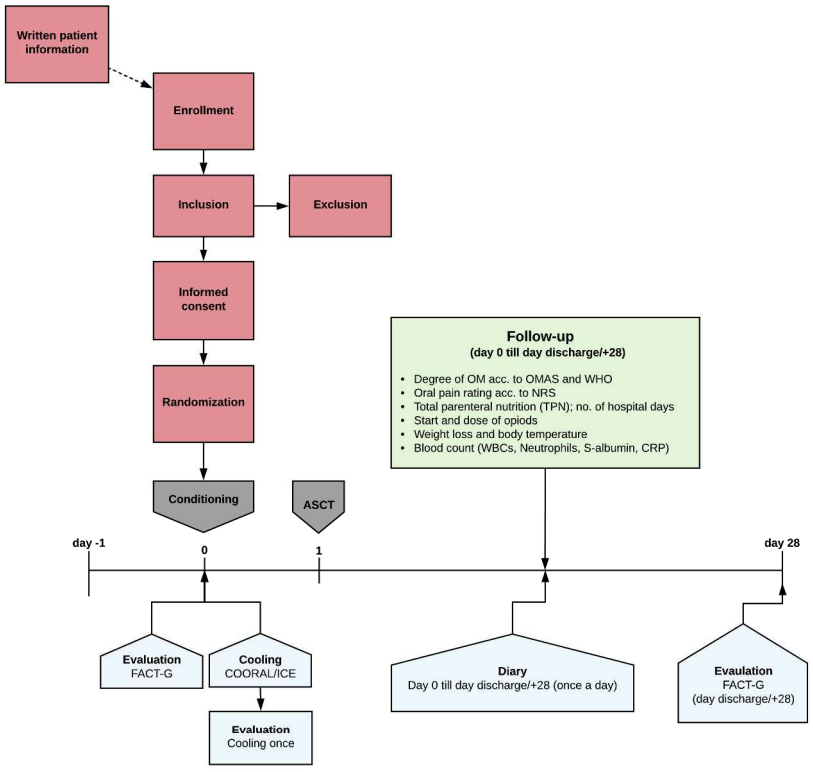

Figure 1: Flowchart for patients with myeloma at Karolinska Hospital. Day 0: Admission, chemotherapy conditioning, oral mucosal cooling along with completion of QoL questionnaire (FACT-G) and evaluation of cooling method. Day 1: Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.

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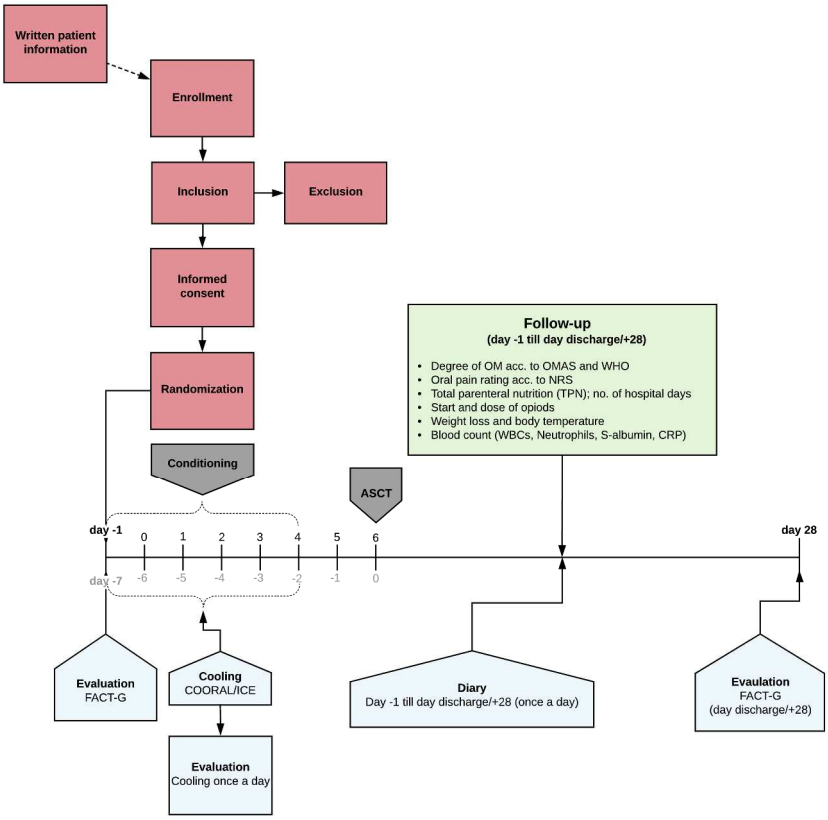

Figure 2: Flowchart for patients with lymphoma at Karolinska Hospital. Day -1: Admission, along with completion of QoL questionnaire (FACT-G). Day: -1 to 4 Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. Day 5: Recovery. Day 6: Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge. Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.

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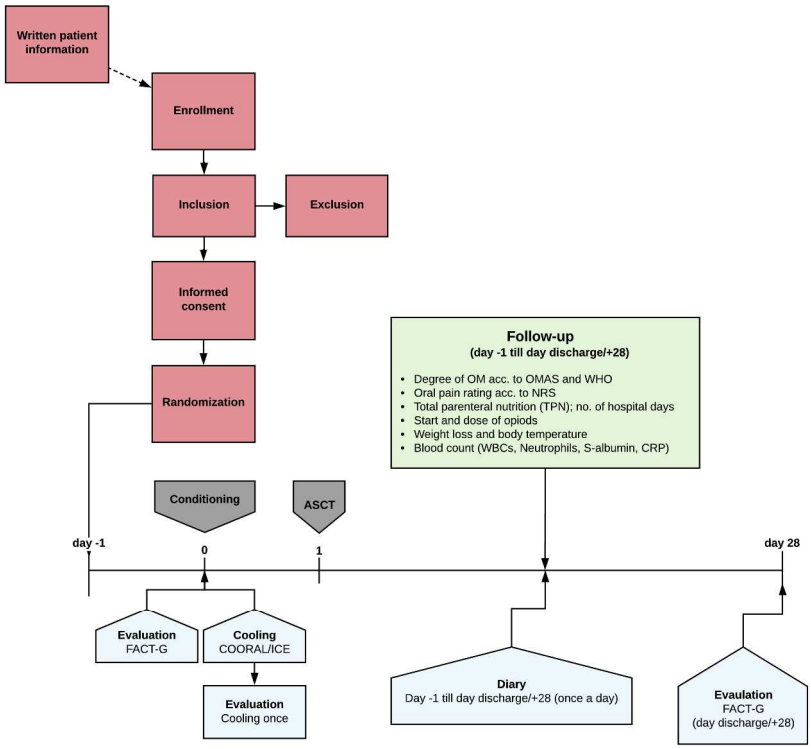

Figure 3: Flowchart for patients with myeloma at Uppsala University Hospital and University Hospitals in Linköping and Örebro. Day -1: Admission. Day 0: Chemotherapy conditioning, oral mucosal cooling along with completion of QoL questionnaire (FACT-G) and evaluation of cooling method. Day 1: Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge.

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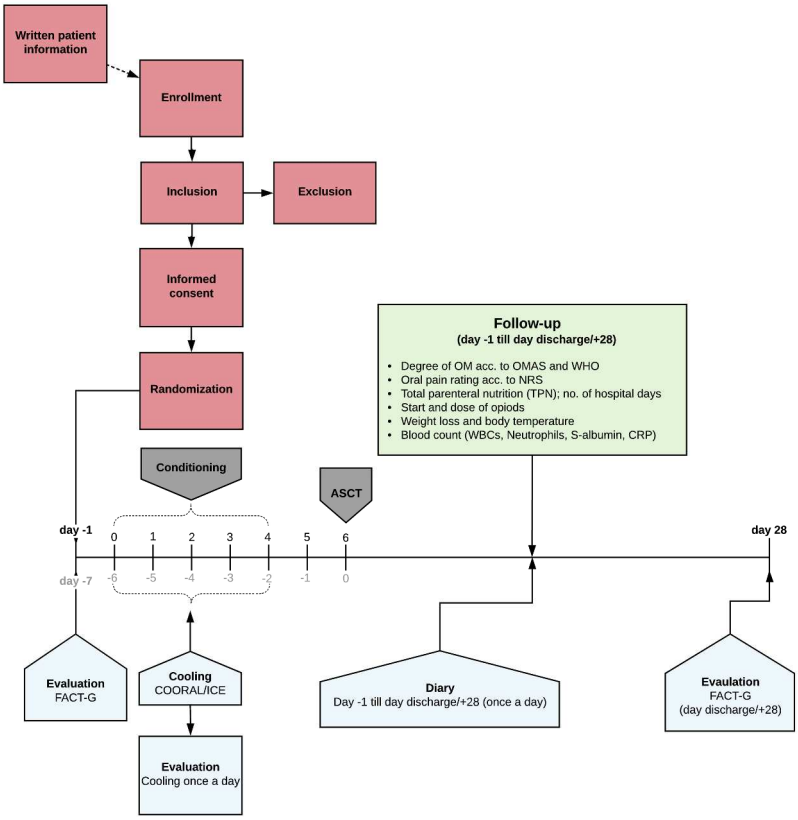

Figure 4: Flowchart for patients with lymphoma at Uppsala University Hospital. Day -1: Admission, along with completion of QoL questionnaire (FACT-G). Day: 0 to 4 Chemotherapy conditioning, oral mucosal cooling along with completion of evaluation of cooling method. Day 5: Recovery. Day 6: Autologous stem cell transplantation (ASCT). Follow up (green box) and perception of oral problems using a diary begins at admission and continues until discharge or day +28. QoL (FACT-G) is evaluated again at discharge. Days highlighted in black indicates the timescale used in this study while grey is routinely used at the hospital.

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Questionnaire about Cooral™ cooling

1. Did you manage to have Cooral™ in your mouth the whole cooling time?

☐ Yes (skip to question 4)

☐ No

2. Roughly how long did you have Cooral™ in your mouth?

☐ 1–20 minutes

☐ 21–40 minutes

☐ 41–60 minutes

☐ 61–80 minutes

☐ 81–100 minutes

☐ >100 minutes but not the full time

3. Which of the following was the reason? Mark the letter or letters.

A ☐ I got cold

B ☐ I became numb

C ☐ It tasted bad

D ☐ I got a headache

E ☐ Shooting pains in my teeth

F ☐ My mouth got sore

G ☐ Poor fit

H ☐ I felt nauseous

I ☐ I felt I needed to vomit

J ☐ It was difficult to swallow

K ☐ It chafed

L ☐ Other.....

4. Was it unpleasant to have Cooral™ in your mouth?

☐ No, not at all (skip to question 6)

☐ No, hardly at all

☐ Yes, a little

☐ Yes, very much so

5. If you experienced some form of discomfort, in what way was it unpleasant? (several alternatives may be chosen)

A ☐ I got cold

B ☐ I became numb

C ☐ It tasted bad

D ☐ I got a headache

E ☐ Shooting pains in my teeth

F ☐ My mouth got sore

G ☐ Poor fit

H ☐ I felt nauseous

I ☐ I felt I needed to vomit

J ☐ It was difficult to swallow

K ☐ It chafed

L ☐ Other.....

6. Did Cooral™ limit your ability to do something else during the time?

☐ No, not at all

☐ No, not very much

☐ Yes, a little

☐ Yes, very much so

7. Other viewpoints.....

8. How painful was the cooling of the oral mucous membrane?

1. ☐ Not at all painful
2. ☐ Slightly painful
3. ☐ Rather painful
4. ☐ Painful
5. ☐ Very painful
6. ☐ Very, very painful
7. ☐ Extremely painful, was forced to break off cooling before the end

Questionnaire about cooling with ice / crushed ice / ice pop

1. Which cooling alternative did you use?

☐ Ice

☐ Crushed ice

☐ Ice pop

2. Did you manage to have the ice in your mouth the whole cooling time?

☐ Yes (skip to question 5)

☐ No

3. Roughly how long did you have ice in your mouth?

☐ 1–20 minutes

☐ 21–40 minutes

☐ 41–60 minutes

☐ 61–80 minutes

☐ 81–100 minutes

☐ >100 minutes but not the full time

4. Which of the following was the reason? Mark the letter or letters.

A ☐ I got cold

B ☐ I became numb

C ☐ It tasted bad

D ☐ I got a headache

E ☐ Shooting pains in my teeth

F ☐ My mouth got sore

G ☐ I felt nauseous

H ☐ I felt I needed to vomit

I ☐ It was difficult to swallow

J ☐ Other.....

5. Was it unpleasant to have the ice in your mouth?

☐ No, not at all (skip to question 7)

☐ No, hardly at all

☐ Yes, a little

☐ Yes, very much so

6. If you experienced some form of discomfort, in what way was it unpleasant? (several alternatives may be chosen)

A ☐ I got cold

B ☐ I became numb

C ☐ It tasted bad

D ☐ I got a headache

E ☐ Shooting pains in my teeth

F ☐ My mouth got sore

G ☐ I felt nauseous

H ☐ I felt I needed to vomit

I ☐ It was difficult to swallow

J ☐ Other.....

7. Did the ice limit your ability to do something else during the time?

☐ No, not at all

☐ No, not very much

☐ Yes, a little

☐ Yes, very much so

8. Other viewpoints.....

9. How painful was the cooling of the oral mucous membrane?

1. ☐ Not at all painful
2. ☐ Slightly painful
3. ☐ Rather painful
4. ☐ Painful
5. ☐ Very painful
6. ☐ Very, very painful
7. ☐ Extremely painful, was forced to break off cooling before the end

Diary

1. Pain in the mouth:

Please circle a figure on the scale below to show how severe the pain in your mouth is NOW

0 1 2 3 4 5 6 7 8 9 10

No pain **Unbearable pain**

2. Impact on taste:

Please circle a figure on the scale below to show the change in your sense of taste NOW

0 1 2 3 4 5 6 7 8 9 10

No change in taste **Very noticeable change in taste**

3. Impact on smell:

Please circle a figure on the scale below to show the change in your sense of smell NOW

0 1 2 3 4 5 6 7 8 9 10

No change in smell **Very noticeable change in smell**

4. Please circle a figure on the scale below to show the effect on the your ability to perform the acts below (**0**=no effect; **10**=maximum effect)

A. Swallow

0 1 2 3 4 5 6 7 8 9 10

B. Drink

0 1 2 3 4 5 6 7 8 9 10

C. Eat

0 1 2 3 4 5 6 7 8 9 10

D. Speak

0 1 2 3 4 5 6 7 8 9 10

E. Sleep

0 1 2 3 4 5 6 7 8 9 10

5. Other viewpoints you would like us to know.

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

2017-10-26
Version 3

dnr: 586-15

Cryoprevention of oral mucositis
Information for patients

Background
You have been diagnosed with lymphoma/multiple myeloma and will undergo an autologous stem cell transplantation. Infusion of stem cells is preceded by conditioning with cytostatics. One side effect which affects a majority of patients receiving this cytostatic infusion is ulceration of the oral cavity, known as mucositis. The sores can make food intake difficult and can also cause pain which may require pain relief. This state, which is believed to be caused by unwanted cytostatic damage to the oral mucous membrane, generally has its onset 3–4 days after completion of cytostatic infusion and can last up to 1 month. Today this can largely be prevented/relieved by continuously chewing ice during the cytostatic infusion.

Cooling results in reduced exposure of the oral mucous membrane to the cytostatics, which in turn can have the result that no sores arise. Certain patients can however find the ice cooling unpleasant. To reduce discomfort we want to investigate whether ice can be replaced with Cooral™ intended to cool the oral mucous membrane.

Aim
The primary aim of the study is to evaluate the ability of Cooral™, compared with ice, to prevent the rise of mucositis in connection with cytostatic infusion. To assess this, two equal-sized groups of patients will be compared. A test group will have cooling with Cooral™ and a control group will have cooling with ice.

Implementation
It will be decided by lot whether you will receive treatment with ice or Cooral™. If you choose not to take part in the study you will receive standard treatment with ice. Cooling with each method is estimated to last a maximum 3–6 hours (lymphoma) or 1.5 hours (myeloma).

During the study period the person responsible for the therapy will repeatedly inspect the oral mucous membrane to assess the degree and extent of mucositis. The oral cavity will be inspected three times a week for four weeks, which means 12 visits to the clinic if you are not an in-patient. Each assessment is estimated to take about five minutes. We also ask you to complete a diary where you answer questions in writing about your oral health and general health, and any difficulties you experience with intake of food and liquids, a quality-of-life questionnaire, and your subjective evaluation of the cooling method. The staff on the ward will help you with instructions on how to fill in the various documents.

What is expected of you?
- Follow the instructions of the care staff for cooling of the mouth before, during and after the cytostatic infusion.
- Complete a diary every day for about a month, complete a general quality-of-life questionnaire twice and make a subjective assessment of the cooling method once (myeloma) or 5–6 times (lymphoma).
- Make 12 visits for inspection of the oral cavity (if **not** hospitalized).

2017-10-26 dnr: 586-15
Version 3

Advantages/risks
A thorough survey of the literature shows that temperature reduction with the aid of ice cooling decreases the occurrence of mucositis. Despite this, the use of cooling with ice has been limited in clinical practice.

There is therefore reason to study whether cooling of the oral mucous membrane with Cooral™ gives better protection against mucositis than ice and/or is tolerated better.

By taking part in the study you can contribute to the development of a new treatment method which can help future patients in a situation similar to the one you are in.

Management of data
The management of your personal data is regulated by the Swedish Personal Data Act (SFS 1998:204). The study will be monitored by KTA-Karolinska Trial Alliance and all data collected during your time in care will be documented and processed in a separate confidential register established for all study participants. Names and personal identification numbers will be replaced by a code list, which will be stored under lock and key, with access authorized only to those in charge of the study. Your responses and your results will be handled in such a way that no unauthorized person can access them. When data from the study are published, it will not be possible to identify any individuals. All data will be kept for 10 years to enable future controls.

Responsibility for personal data
The hospital is responsible for managing your personal data. By participating in the study you give access to your patient records for scrutiny. You can approach the respective personal data representative if you wish an excerpt of the personal data registered about you, and you can obtain help if necessary to make corrections.

Akademiska sjukhuset: tel: 018-611 33 20

Karolinska universitetssjukhuset: tel: 0700 02 84 60

Universitetssjukhuset Linköping: tel: 010-103 74 89

Universitetssjukhuset Örebro: tel: 019-60 272 75

Voluntary participation
Your participation is entirely voluntary and you are fully entitled to cease participation at any time you like during your treatment time. The study has been approved by the Ethical Review Board in Göteborg (dnr: 586-15).

If you have any questions or if you wish to discuss the study, contact your nurse on the ward. Those responsible for the study are (doctor at the respective department) along with Anncarin Svanberg and Java Walladbegi.

2017-10-26
Version 3

dnr: 586-15

Contact details

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751 81 Uppsala

 018-611 42 90/0706-99 75 55

2017-10-26
Version 3

dnr: 586-15

Consent to participate in the study
Cryoprevention of oral mucositis

I have been informed orally and have read the above written information. I have been able to ask questions and have received answers. I consent to participate in the study and am aware that my participation is wholly voluntary, and that I can at any time, without explanation, terminate my participation without that having any effect on my future care.

Signature **Name in block letters**

Date

The above patient has been informed about the design and purpose of the study (completed by the care provider)

Signature **Name in block letters**

(Responsible care provider)

Date

NB. To be signed on the same day by patient and doctor

2017-10-26
Version 3

dnr: 586-15

Cryoprevention of oral mucositis
Information for patients

Background
The child whose guardian you are has been diagnosed with lymphoma/multiple myeloma and will undergo an autologous stem cell transplantation. Infusion of stem cells is preceded by conditioning with cytostatics. One side effect which affects a majority of patients receiving this cytostatic infusion is ulceration of the oral cavity, known as mucositis. The sores can make food intake difficult and can also cause pain which may require pain relief. This state, which is believed to be caused by unwanted cytostatic damage to the oral mucous membrane, generally has its onset 3–4 days after completion of cytostatic infusion and can last up to 1 month. Today this can largely be prevented/relieved by continuously chewing ice during the cytostatic infusion.

Cooling results in reduced exposure of the oral mucous membrane to the cytostatics, which in turn can have the result that no sores arise. Certain patients can however find the ice cooling unpleasant. To reduce discomfort we want to investigate whether ice can be replaced with Cooral™ intended to cool the oral mucous membrane.

Aim
The primary aim of the study is to evaluate the ability of Cooral™, compared with ice, to prevent the rise of mucositis in connection with cytostatic infusion. To assess this, two equal-sized groups of patients will be compared. A test group will have cooling with Cooral™ and a control group will have cooling with ice.

Implementation
It will be decided by lot whether your child will receive treatment with ice or Cooral™. If you choose not to take part in the study the child will receive standard treatment with ice. Cooling with each method is estimated to last a maximum 3–6 hours (lymphoma) or 1.5 hours (myeloma).

During the study period the person responsible for the therapy will repeatedly inspect the oral mucous membrane to assess the degree and extent of mucositis and also to assess the effect of the respective cooling method. The oral cavity will be inspected three times a week for four weeks, which means 12 visits to the clinic if the child is not hospitalized. Each assessment is estimated to take about five minutes. We also ask you to complete a quality-of-life questionnaire on two separate occasions, a diary where you answer questions in writing about your child's oral health and general health, and any difficulties experienced with intake of food and liquids. The staff on the ward will help with instructions on how to fill in the various documents.

What is expected of you?

- Follow the instructions of the care staff for cooling of the mouth before, during and after the cytostatic infusion.
- Complete a diary every day for about a month, complete a general quality-of-life questionnaire twice and make a subjective assessment of the cooling method once (myeloma) or 5–6 times (lymphoma).
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Advantages/risks
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2017-10-26
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Anncarin Svanberg, Reg. Nurse/Doctor
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 018-611 42 90/0706-99 75 55

2017-10-26
Version 3

dnr: 586-15

Consent to participate in the study
Cryoprevention of oral mucositis

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Signature **Name in block letters**

Signature Guardian 1 **Name in block letters**

Signature Guardian 2 **Name in block letters**

Date

The above patient has been informed about the design and purpose of the study (completed by the care provider)

Signature **Name in block letters**

(Responsible care provider)

Date

NB. To be signed on the same day by patient and doctor

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

Section/item	Item No	Description
Administrative information		
Title **Page: 1**	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration **Page: 1**	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 **Page: 1**	3	Date and version identifier
Funding **Page: 1**	4	Sources and types of financial, material, and other support
Roles and responsibilities **Page: 1**	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 **Page: 3**		
Background and rationale **Page: 3**	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 Page: 3	7	Specific objectives or hypotheses
Trial design Page: 3	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 Page: 4	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 Page: 4	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 Page: 4-5	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 Page: 5	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 Page: 5	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 Page: 5	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 Page: 5-6	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation **Page: 6**	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 **Page: 6**	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 **Page: 6**	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) **Page: 6**	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 **Page: 6-7**	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
Page: 8	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 **Page: 8**	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 **Page: 8-9**	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 **Page: 10**	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
Page: 10	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 **Page: 10**	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 **Page: 10**	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 **Page: 11**	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments **Page: 11**	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 **Page: 11**	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 **Page: 11**	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 **Page: 11**	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data **Page: 11**	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 **Page: 11**	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy **Page: 11**	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 **Page: 11**		
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.

Correction: *Protocol for a randomised controlled trial to study cryoprevention of chemotherapy-induced oral mucositis after autologous stem cell transplantation*

Walladbegi J, Svanberg A, Gellerstedt M. Protocol for a randomised controlled trial to study cryoprevention of chemotherapy-induced oral mucositis after autologous stem cell transplantation. *BMJ Open* 2018;**8:**e021993. doi: 10.1136/bmjopen-2018-021993

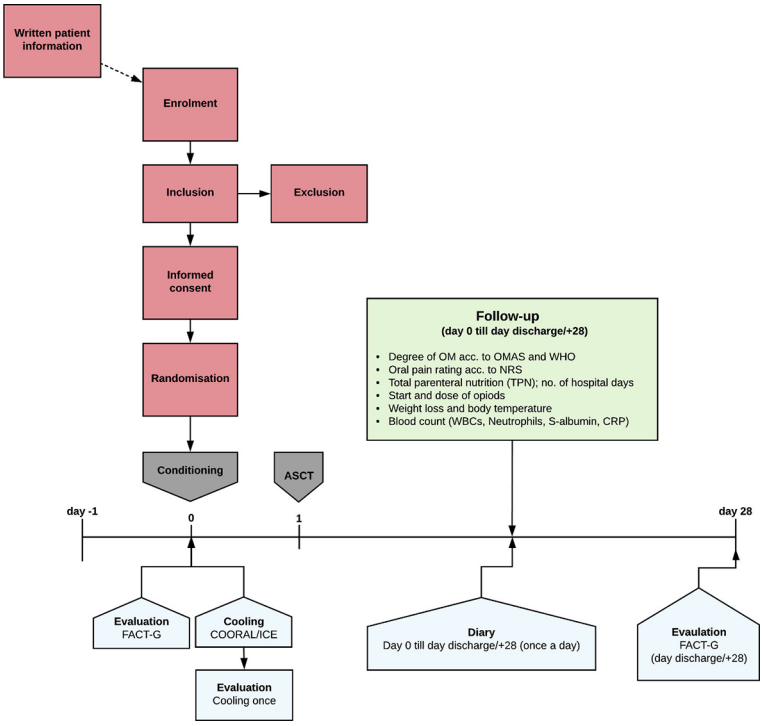
This article was previously published with an error.

In Funding information, the grant number for Vinnova was left out. Therefore, the updated Funding statement is:

This work was supported by BrainCool AB, VINNOVA, grant number 2016-04171 and Gothenburg Dental Society, grant number 2017-12-21.

In Statistical methods under Analyses of the secondary variables section paragraph 4 was appearing twice.

Figure 1 was incorrect. The correct figure is shown below.



BMJ Open 2019;**9**:e021993corr1. doi:10.1136/bmjopen-2018-021993corr1