Fluid REStriction in Heart failure versus liberal fluid UPtake: the FRESH-UP study

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Protocol ID	NL75112.091.20 / NCT04551729
Short title	FRESH-UP
Version	2.0
Date	30th November 2020
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PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Chronic heart failure (HF) is an increasing global health concern with over 20 million patients worldwide. Although it is common practice for clinicians to advice fluid restriction to prevent symptoms and hospitalisations due to fluid retention, there is no evidence to support this treatment strategy, as also stated in the most recent HF guidelines. Moreover, fluid restriction is associated with thirst distress and may adversely impact quality of life (QoL).

Objective: To investigate the effect of liberal fluid intake versus fluid restriction on QoL in chronic HF.

Study design: Multi-centre open-label 1:1 randomized clinical trial with 6 months follow-up.

Study population: Adult clinically stable outpatient chronic HF patients (n=498).

Intervention: On a background of standard guideline-directed medical therapy patients will be randomized to an advice by the treating physician and/or HF specialized nurse of either fluid restriction of 1500cc/24hours versus liberal fluid intake for a period of 3 months.

Main study parameters/endpoints: Primary study parameters are QoL at 3 months after randomization, as assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score; and thirst distress using a validated thirst distress scale. Secondary and other study parameters are QoL as assessed with the KCCQ Clinical Summary Score and each of the separate domains, QoL as assessed with a visual analogue scale (EQ-5D-5L), serum biomarkers (NT-proBNP, sodium, osmolality); and the occurrence of adverse events such as death, hospitalisations and need for iv-loop diuretics during the 6-month follow-up.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants will be recruited and followed at the specialized HF outpatient clinic according to standard clinical practice with a 3-month interval including standard laboratory analyses (renal function, electrolytes, NT-proBNP). Subjects will be randomized for 3 months to an advice of either liberal fluid intake or fluid restriction of 1500cc/24hours, of which the latter is current standard clinical practice. At baseline and after 3 months, participants will be asked to fill out a QoL questionnaire. In addition, subjects will be asked to report their daily fluid intake at week 6.

In terms of benefits and risks, fluid restriction in HF leads to an undesirable sensation of thirst. For patients with HF, thirst can be distressing and can decrease quality of life. There is no evidence that fluid restriction reduces symptom burden or adverse events such as HF hospitalizations due to fluid retention, whereas liberal fluid intake may result in increased quality of life due a decrease in thirst. Given the vast target population of chronic HF patients worldwide, and the simplicity of the intervention, potentially millions of HF patients may benefit from the results of this study.

1. INTRODUCTION AND RATIONALE

Chronic heart failure (HF) is a huge global health problem, affecting approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age. HF has a large burden of disease with high morbidity adversely affecting overall quality of life (QoL). The goals of treatment in patients with chronic HF are to improve their clinical status, functional capacity and QoL, prevent hospital admission and reduce mortality (1, 2).

Symptoms and signs of chronic HF, such as orthopnea and peripheral edema, may arise from fluid retention, which could lead to serious adverse events such as hospitalization. In light of this, it has been common clinical practice for many decades to advice chronic HF patients to limit their fluid intake to 1500cc/24 hours. Strikingly, this advice is not based on clinical evidence but mainly on intuition. Moreover, the limited data available demonstrate that fluid restriction in HF is not more beneficial than liberal fluid intake (3-6).

In the absence of supportive evidence, the Northern American Guidelines give fluid restriction a Class IIa/ level of evidence C recommendation, and the European Guidelines provide only a general recommendation supporting fluid restriction for symptomatic HF, without providing a level of evidence (1, 2, 7). Despite the fact that the guidelines state that there is no supportive evidence for fluid restriction, it is in daily practice recommended by many cardiologists, specialized heart failure nurses and dieticians to virtually every chronic HF patient.

While the beneficial effect of fluid restriction in chronic HF is uncertain, it has been suggested that it may even adversely impact these patients (3, 8, 9). Fluid restriction as a daily part of chronic HF care is from a *patients' perspective* considered to be most challenging and cumbersome, because 1) patients have to monitor fluid intake, 2) fluid restriction leads to thirst distress and 3) it constantly confronts patients with their chronic disease. As a consequence, non-adherence is common, which may detrimentally impact doctor-patient relationship and/or patient's self-esteem (8). All of these factors of fluid restriction may contribute to a reduced QoL for HF patients.

In light of the above and the need for more data on the effect of fluid management in chronic HF, we designed a randomized clinical trial on the effect of liberal fluid intake versus standard fluid restriction on QoL of chronic HF patients.

2. OBJECTIVES

This study investigates the hypothesis that liberal fluid intake has significant beneficial effects on QoL as compared to standard fluid restriction on QoL in outpatient chronic HF patients, without signals of potential safety issues. Specifically, we will investigate the following.

Primary Objective:
To investigate the effect of liberal fluid intake versus standard fluid restriction (1500cc/24hours) on QoL in outpatient chronic HF patients at 3 months after randomization, as assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ) (10) and the validated Thirst Distress Scale (11).
As recently described in a "state-of-the-art-paper" in JACC: Heart Failure, the KCCQ is a well-validated questionnaire specific to HF, is sensitive to change in clinical status, and moreover, a change in KCCQ is predictive of future adverse disease progression (12, 13). For example, whereas an improvement in general well-being in terms mental health is expected to positively affect the score, any deterioration of HF is expected to negatively affect the score. Therefore, the KCCQ is perfectly suited to address both aspects of the hypothesis of this study (i.e. beneficial effects on QoL as well as signals of potential safety issues).
In addition, the Thirst Distress Scale is most likely a sensitive measure to subtle changes in QoL due to differences in lifestyle advice concerning fluid intake.

Secondary Objectives:

- To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on QoL at 3 months after randomization, as assessed with a visual analogue scale (EQ-5D-5L);
- To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on patient reported fluid intake at week 6.
- To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on patient reported thirst intensity (VAS)
- To investigate the effect of liberal fluid intake versus standard fluid restriction (1500cc/24hours) on safety as assessed by the number of occurrence of the composite clinical endpoint death, all-cause hospitalisation and the requirement to apply iv-loop diuretics during the 6-month clinical follow-up duration.

Exploratory objectives:

- To investigate the effect of liberal fluid intake versus standard fluid restriction (1500cc/24hours) on safety as assessed by (time to the first) occurrence of each of the components of the composite clinical endpoint death, all-cause hospitalisation, the requirement of iv-loop diuretics and also unplanned HF hospitalisations during the 6-month clinical follow-up duration;
- To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on the (time to the first) occurrence of acute kidney injury defined as a 50% decline in estimated glomerular filtration rate relative to baseline, or decrease of >30 ml/min/1.73m^2 and to a value below 60 ml/min/1.73m^2 during the 6-month clinical follow-up duration;
- To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on in serum biomarkers (NT-proBNP, sodium, osmolality, haemoglobin, haematocrit) and weight at 3 months after randomization;
- To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on the use of concomitant medication (diuretics in particular)

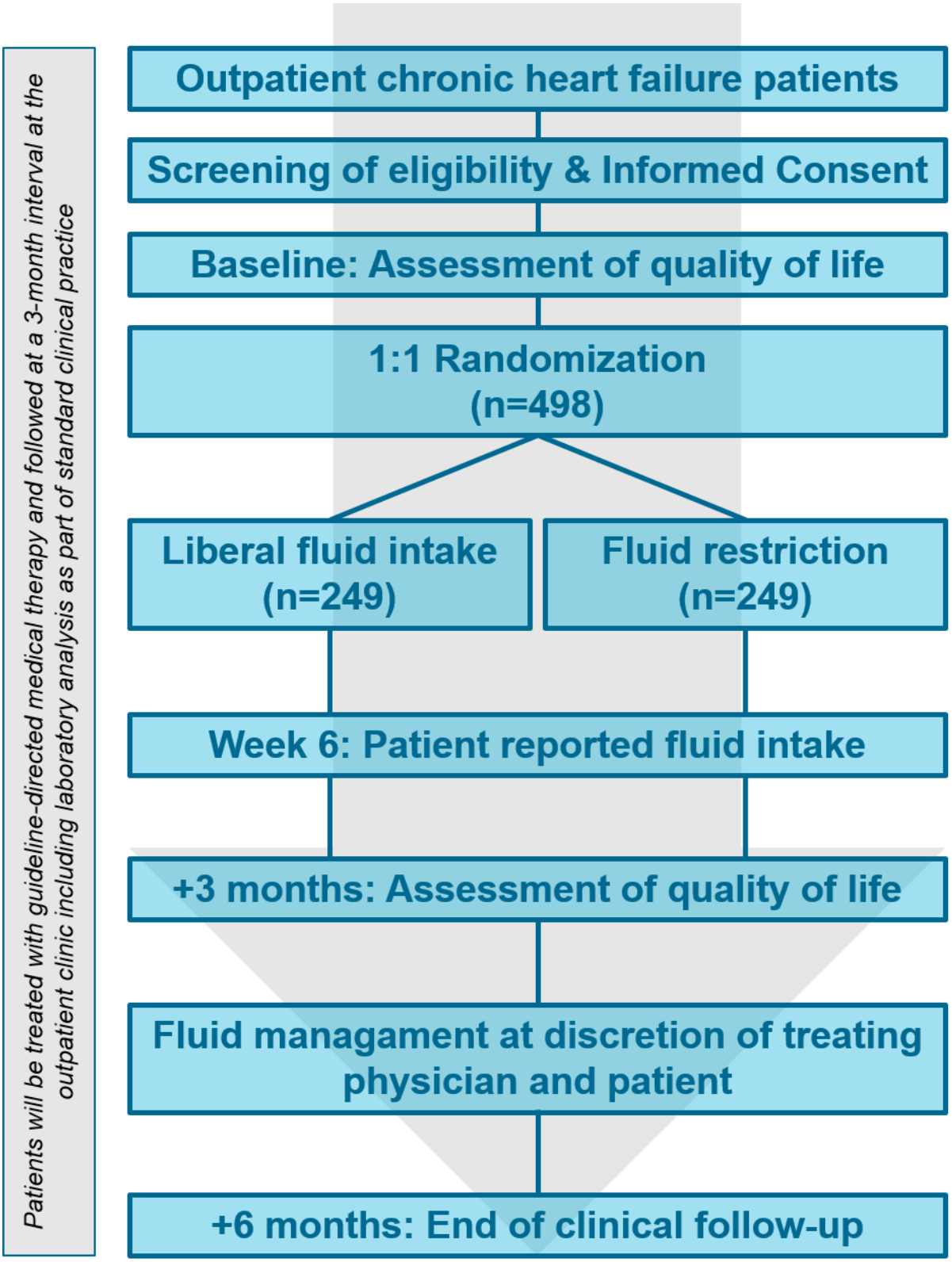
Subgroup analyses:
We aim to perform the following exploratory subgroup-analyses:

- Gender (male/female)
- Admission hospital (study site)
- HF category (HFrEF/HFmrEF/HFpEF)
- NYHA class (NYHA class II / III)
- Age (above/below median)
- Diuretic dose (above/below median)
- Baseline sodium, urea, creatinine and NT-proBNP concentration (above/below median)

3. STUDY DESIGN

This study is a multi-center open-label 1:1 randomized clinical trial to investigate the effect of liberal fluid intake versus standard fluid restriction on QoL at 3 months after randomization in outpatient chronic HF patients.
In addition to the assessment of QoL by the KCCQ, this study investigates any potential safety issues of liberal fluid intake versus standard fluid restriction during an extended 6-month clinical follow-up duration for HF hospitalizations and mortality.

Duration of the clinical trial
Study flow chart is provided below. Adult chronic HF patients will be asked to participate in the study according to the informed consent procedure as described in detail in paragraph 9.2. Upon providing written informed consent, patients will be asked to fill out questionnaires on QoL. Thereafter, patients will be randomized and receive advice on fluid management accordingly. After 3 months, patients will be invited to the outpatient clinic according to standard clinical practice including laboratory analysis At this outpatient clinic visit, patients will again be asked to complete the same questionnaires. After that, further fluid management can be performed according to the discretion of the treating physician and patient. For clinical follow-up, the patient will again be invited to the outpatient clinical at month 6 according to standard clinical practice for assessment of the safety endpoint regarding death, hospitalization and the need for iv-loop diuretics. This visit will end study participation.


Outpatient chronic heart failure patients
Screening of eligibility & Informed Consent
Baseline: Assessment of quality of life
1:1 Randomization (n=498)
Liberal fluid intake (n=249)
Fluid restriction (n=249)
Week 6: Patient reported fluid intake
+3 months: Assessment of quality of life
Fluid managament at discretion of treating physician and patient
+6 months: End of clinical follow-up
Patients will be treated with guideline-directed medical therapy and followed at a 3-month interval at the outpatient clinic including laboratory analysis as part of standard clinical practice

4. STUDY POPULATION

4.1 Population base

The source population comprises all adult outpatient chronic HF patients at the participating centres (n>1500).

4.2 Inclusion criteria

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

- Diagnosis of chronic HF with NYHA class II/III according to the prevailing guidelines > 6 months prior to randomization (1)
- Adult (age ≥ 18 years)

4.3 Exclusion criteria

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

- Reversible cause of HF (thyroid disorders, severe anemia, vitamin deficiencies)
- Hopital admission for HF within 3 months of randomization
- Chronic HF with NYHA class IV
- Hyponatremia at baseline (sodium <130mmol/l)
- Estimated Glomerular Filtration Rate (eGFR) of < 30ml/min/1.73 m2 at baseline
- Scheduled cardiac surgery within 3 months of randomization
- Recent (within 3 months) coronary intervention (PCI or CABG) or implantation of pacemaker device
- Comorbidity for which fluid restriction is advised by a different treating physician (e.g. nephrologist)
- Life expectancy of less than 6 months
- The treating clinician believes that participation in the study would not be in the best interests of the patient
- Inability to provide informed consent

4.4 Sample size calculation

Sample size calculation was performed with the software package G*Power 3.1.7 and performed as previously described methods for repeated measures ANCOVA analysis, using baseline QoL as a covariate (14).

For our sample size calculation, we assume a correlation of 0.88 between baseline and follow-up KCCQ-OS score (15). Furthermore, we assume a follow-up KCCQ-OS score of 66.25 with a standard deviation of 20 for liberal fluid intake group (16-20). Next, we assume a 2.5-point difference in KCCQ-OS follow-up scores at 3 months between both randomization groups (16-20). To test this difference at a p-value of 0.05 and power of 80%, we need a total of 454 evaluable patients. Anticipating a drop-out rate of 10% we aim to enrol 498 patients. This sample size also allows adequate power to asses a 1.5-point difference in thirst distress at 3 months between both randomization groups (mean score of 16 with a standard deviation of 8 and intraclass correlation of 0.88; p-value: 0.05 and power: 80%).

Both primary hypotheses on QoL by the KCCQ-OS score and thirst distress scale will be tested at a 2-sided 5% significance level. In the case of non-significant findings for the first primary end point (KCCQ), the second primary end point will be tested at the 2-sided 5% significance level but will be regarded as an exploratory end point, and a nominal P value will be produced. No adjustments for multiplicity will be made for secondary or exploratory end points.

Currently, the outpatient HF population of the participating centres comprise >1,500 patients. Based on the excellent logistics of the participating centres and no strict limitations in terms of eligibility of potential subjects, we expect that the required number of inclusions is feasible.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

The investigational treatment concerns an advice by the treating physician and/or specialized HF nurse according to randomization at baseline of either a standard fluid restriction of 1500cc/24 hours or liberal fluid intake for the duration of the study period of 3 months. Currently, fluid restriction of 1500cc per 24 hours is considered standard clinical practice for most HF patients worldwide. Consequently, liberal fluid intake is considered the investigational treatment.

In case of contacts between the participant and the treating physician and/or specialized HF nurse during the study period, the advice according to randomization will be emphasized.

Background medical treatment will be standard guideline-directed medical therapy and lifestyle advice according to standard practice, such as advice on sodium restriction, exercise and how to respond to clinical deterioration.

Specifically, the use of diuretics can be adjusted freely and is not subject to protocol directives. Notably, any change in diuretics will be meticulously registered.

5.2 Discontinuation of study treatment

Participants will be instructed to follow the advice on fluid intake according to randomization. There are no formal stopping rules for discontinuation of study treatment. There are, however, multiple scenarios for which the treating physician at his/her discretion can judge that the advice according to randomization is no longer appropriate and fluid management should be adjusted accordingly. Patients will be instructed to contact their treating physician and/or specialized HF nurse in case of doubt whether to adhere to the randomized treatment regimen.

Scenarios for which discontinuation of fluid restriction may be considered are dehydration, fever or any other scenario that may lead to a decreased circulatory volume with consequent end-organ injury such as prerenal acute kidney injury.

A scenario for which discontinuation of liberal fluid intake may be considered is severe hyponatraemia (<125mmol/L) or progression of HF to NYHA class IV.

Patients for whom study treatment is discontinued will be followed according to study protocol (intention-to-treat principle).

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameters

- QoL at 3 months after randomization, as assessed with the KCCQ Overall Summary (OS) Score (10)
- QoL at 3 months after randomization, as assessed with the Thirst Distress Scale (11)

6.1.2 Secondary study parameters

- QoL at 3 months after randomization, as assessed with the KCCQ Clinical Summary (CS) Score and each of the KCCQ domains (10);
- Proportion of patients with clinically meaningful changes in KCCQ-OS and KCCQ-CS scores (improved: ≥5 points increase; stable: <5 points increase or decrease; declined: ≥5 points decrease);
- QoL at 3 months after randomization, as assessed with a visual analogue scale (EQ-5D-5L);
- Thirst intensity at 3 months after randomization, as assessed with a visual analogue scale;
- Patient reported fluid intake during week 6.
- Events (death, hospitalisations, iv loop diuretic treatment) up to month 6.

6.1.3 Other study parameters

- Serum biomarkers (NT-proBNP, sodium, osmolality, haemoglobin, haematocrit), weight and measures of patient satisfaction on self-care at 3 months after randomization;
- The occurrence of acute kidney injury defined as a 50% decline in estimated glomerular filtration rate relative to baseline, or decrease of >30 ml/min/1.73m^2 and to a value below 60 ml/min/1.73m^2, during the 6-months clinical follow-up duration;
- The occurrence of (temporary) discontinuation of study treatment;
- Baseline variables such as comorbidity, previous fluid restriction, vital parameters and concomitant medication will be acquired.

6.2 Independent event adjudication committee

An independent event adjudication committee will be formed to adjudicate any hospitalizations as either HF-related or not, and to adjudicate the cause of death. The committee comprises three clinical experts with experience in clinical trials and capable of

event adjudication. One of the members is appointed as chair person. The events of interest will be adjudicated as according to a predefined scheme based on consensus by two committee members; in case of non-consensus the third committee member will provide final adjudication. The event adjudication committee members are not involved as investigators and are not part of the DSMB of the current protocol.

6.3 Randomization, blinding and treatment allocation

Randomization will take place after the participant has provided informed consent and is eligible according to the in- and exclusion criteria. The informed consent procedure is described in detail in paragraph 9.2.

At the screening visit, patients will be assigned an incremental subject number according to chronological order after informed consent. The informed consent procedure is described in detail in paragraph 9.2. The subject number remains unchanged during the study and allows the patient to be identified during the whole study.

Patients will be randomized using Castor. Subjects will be 1:1 randomized to either liberal fluid intake or standard fluid restriction. A patient is considered randomized as soon as the randomization is completed in the eCRF (Castor). A patient cannot be randomized more than once in the study.

Inherent to the type of intervention both the investigator/treating physician as well as the subject are not blinded to randomization. However, the members of the event adjudication committee as well as the statistician, who will perform the primary analysis, will be blinded for randomization.

6.4 Study procedures

6.4.1 Baseline visit

For screening of eligibility no additional study procedures are required. In- and exclusion criteria can be derived from the patients' medical record, including results from physical examination and laboratory analysis at baseline, which is performed in the setting of standard clinical practice.

After providing written informed consent, all subjects will be asked to fill out 3 simple and validated questionnaires concerning quality of life: the Kansas City Cardiomyopathy Questionnaire (10), the Thirst Distress Score (11) and the EQ-5D-5L. These procedures will take about 20 minutes in total. Next, all subjects will be randomized by the investigator using the eCRF and will receive lifestyle advice accordingly. All subjects will receive lifestyle advice according to a standardized script.

All subjects will be instructed at baseline on how to report fluid intake in week 6, using a fluid intake diary, which will be provided at baseline.

6.4.2 Week 6: Patient reported fluid intake

All subjects will be notified a few days prior to week 6 by telephone contact by the investigator that they are asked to report fluid intake for 1 week in a fluid intake diary, as provided at baseline, and take the diary with them at the standard 3 months follow-up visit. Importantly, the patients' diary on fluid intake will not be assessed by the treating physician or treating specialized HF nurse, but by an independent study investigator, who is not involved in the treatment of the subject. Patients will be informed about this explicitly at baseline. This is done to promote an honest assessment of daily fluid intake; by removing any pressure on the patient to fill in answers to please the treating professionals.

6.4.3 Follow-up visit at 3 months after randomization

All subjects will undergo laboratory analysis, physical examination and clinical follow-up according to standard clinical practice, at the discretion of the treating physician. At this outpatient clinic visit, all subjects will be asked to again fill out 3 simple and validated questionnaires concerning quality of life: the Kansas City Cardiomyopathy Questionnaire (10). the Thirst Distress Score (11) and the EQ-5D-5L. These procedures will take about 20 minutes in total. Moreover, information will be acquired on the occurrence of clinical events and (temporary) discontinuation of study treatment.
After that, further fluid management will be determined according to the discretion of the treating physician and patient as part of shared-decision making.

6.4.4 Follow-up visit at 6 months after randomization

All subjects will undergo laboratory analysis, physical examination and clinical follow-up according to standard clinical practice, at the discretion of the treating physician. At this outpatient clinic visit specifically, the occurrence of hospitalisations and the need for iv-loop diuretics will be assessed. In case an outpatient clinic visit is not feasible, clinical follow-up will be assessed through telephone contact. Clinical follow-up at 6 months after randomization will end study participation. Hereafter, subjects can participate in a long-term follow-up registry with telephone contact every 6 months on the occurrence of all-cause hospitalization and mortality.

6.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

6.6 Replacement of individual subjects after withdrawal

Subjects will not be replaced. Potential dropout is accounted for in the sample size.

6.7 Premature termination of the study

The study may be terminated if the study procedures are not being performed according to GCP and/or if subjects are placed at undue risk because of clinically relevant findings based on the planned interim-analyses as defined below.

7. SAFETY REPORTING

7.1 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.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. The investigator collects relevant AEs in the eCRF within five working days after obtaining knowledge of the event.

7.2.2 Serious adverse events (SAEs)

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

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- 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.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay within 24 hours after obtaining knowledge of the events via the Castor eCRF. In addition, the investigator will notify the sponsor by e-mail of the occurrence of an SAE. The sponsor will have a central e-mail address for SAE reporting.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.3 Follow-up of adverse events

All AEs 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. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7.4 Data Safety Monitoring Board

Details on the DSMB are described in the attached DSMB Charter.
A DSMB will be established to perform analyses according to the DSMB charter. The composition of the DSMB will comprise a chair clinical expert, a second clinical expert and a statistician with experience in RCTs, independent of the sponsor.

The DSMB has two mandates:
1) To perform two interim analyses at the enrolment of 33% and 66% of the subjects for safety on the occurrence of the composite clinical endpoint death, all-cause hospitalisation and the need for iv-loop diuretics; and for safety on the occurrence of acute kidney injury;
2) To monitor the overall conduct of the trial, i.e. to monitor the enrolment rate.

The above interim stage analyses will be performed for safety on two timepoints based on the number of enrolled subjects. First interim analysis will be performed at enrolment of 33% of the subjects, second at enrolment of 66% of the subjects.
In addition, the overall conduct in terms of enrollment rate will be monitored and in case of non-satisfactory enrollment advice may be given for improvement. Moreover, the DSMB is entitled to stop the study prematurely based on the above mandates.

The advice and reports of the analyses of the DSMB will be sent to the sponsor of the study and to the accredited METC. Should the sponsor decide not to fully implement the

advice of the DSMB, the sponsor 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.

8. STATISTICAL ANALYSIS

SPSS will be used to conduct all statistical analyses.

8.1 Descriptive statistics

Descriptive statistics will be presented by treatment arm. Continuous variables will be summarized using mean ± standard deviation if normally distributed or median (interquartile interval) if not normally distributed. Differences between groups for continuous variables will be tested with Students' t test or Mann-Whitney U test, whichever appropriate. Categorical determinants will be presented with numbers and percentages. Differences between groups for categorical variables will be tested with Chi-square or Fisher exact test, whichever appropriate. A p-value of <0.05 will be considered significant. Measurements that were not performed or not recorded will be treated as missing data. For all analyses, missing data will not be imputed data unless otherwise described.

8.2 Analysis populations

The intention-to-treat principle will be used for the analysis, i.e. in the analysis participants will be included in the randomized assignment study group.

In addition, we will perform an analyses according to the per-protocol principle, i.e. in this analysis participants will be included in case they adhered to the randomized fluid intake regimen. The patient reported fluid intake in week 6 will be used to assess whether the standard fluid restriction arm patients did adhere to the standard fluid restriction of 1500/24 hours.

8.3 Primary study parameters

The difference between the two treatment arms in QoL after 3 months, as assessed with KCCQ OS Score and Thirst Distress Score, will be tested with the use of a repeated measures ANCOVA analysis, using baseline QoL as a covariate. A p-value of <0.05 will be considered significant.

Primarily, we will analyze the data for those patients, of whom both baseline and follow-up are available, similar to previous studies (16, 21). We do not expect a difference in rate of lost-to-follow-up for the primary study parameters, and rates of lost-to-follow-up will be reported for both randomization groups.

We will also perform an ancillary supportive analysis on KCCQ-OS score, in which we will give all "non-responders" at follow-up a score of 10 or 20 points below their baseline score, in case they are respectively alive or deceased.

8.4 Secondary study parameters

For the secondary parameters QoL at 3 months after randomization, as assessed with the KCCQ CS Score, each of the KCCQ domains and the EQ-5D-5L; and thirst intensity at 3 months after randomization, a similar approach as for the primary study parameters will be adopted. The difference between groups in proportion of patients with clinically meaningful changes in KCCQ-OS, KCCQ-CS scores and the percentage of events (death, all-cause hospitalisations, the need for iv-loop diuretics and acute kidney injury) will be tested with Chi-square or Fisher exact test, whichever appropriate. The difference in between groups patient reported fluid intake will be analyzed with a Students' t test or Mann-Whitney U test, whichever appropriate.

8.5 Other study parameters

Time-to-event outcomes will be analyzed using a Cox proportional hazards model, with, if necessary, baseline covariate adjustment in case of unexpected differences in baseline descriptive statistics. The estimated treatment effect will be presented in the form of hazard ratios with 95% confidence intervals. Kaplan-Meier plots will be used to present the pattern of events per treatment group over the follow-up period. The assumption of proportional hazards will be checked using statistical tests and graphical diagnostics based on the Schoenfeld residuals.

ETHICAL CONSIDERATIONS

8.6 Regulation statement

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

8.7 Recruitment and consent

All potential eligible patients will receive a letter (at least one week prior to their upcoming outpatient clinic visit) by their treating physician or heart failure nurse to inform them about the initiation of the study and to ask them to read the study patient information letter carefully prior to their upcoming outpatient clinic visit. The letter by the treating physician / heart failure nurse and the patient information letter specifically states that participation is voluntary and the decision to participate will not affect regular follow-up or the patient-doctor relationship.

During the outpatient clinic visit patients will be informed more into detail by the treating physician and/or specialized HF nurse about the study. In case the patient has no further questions and is willing to participate, written informed consent will be obtained.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

8.8 Benefits and risks assessment, group relatedness

Below a justification of the proposed study is provided. For more detailed information and a structured risk analysis we refer to Chapter 11.

There are only two small comparative, randomized studies performed on the effect of fluid restriction in less <70 patients (3, 4). In these 2 studies, fluid restriction showed no clinical benefit compared to unrestricted fluid intake, while liberal uptake resulted in an improved patient reported outcome, i.e. less thirst. These data underscore the need for more randomized data in larger studies. Subjects will be intensively monitored according to standard clinical practice by their experienced heart failure team. Patients are well instructed, stable at inclusion and familiar with logistics in case of unexpected deterioration. We are therefore convinced that our study is safe. In light of the presumed negative impact of fluid restriction on QoL and potential implications of this trial for millions of HF patients worldwide, we feel that the design of this trial is appropriate.

8.9 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance 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.

8.10 Incentives

Subjects will not receive any special incentives, compensation or treatment through participation in the study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

The data generated will be encoded and a separate patient identification log will be created. The key to the code will only be available to the principal investigator and delegated investigators. The acquired encoded data imputed in the eCRF will be accessible with passwords to the researchers involved; and the monitoring team.

9.2 Monitoring and Quality Assurance

A plan for will monitoring and Quality Assurance will be constructed by the Radboud Technology Centre of Clinical studies. According to the "Richtlijn Kwaliteitsborging Mensgebonden Onderzoek 2019" by the NFU the study is considered moderate risk (22).

9.3 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.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

9.4 Annual progress report

The sponsor 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.

9.5 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.

9.6 Public disclosure and publication policy

It is expected that this study will lead to several abstracts and publications in international peer-reviewed journals. We agree with the CCMO-statement on publication policy and we will therefore act accordingly (23).

10. STRUCTURED RISK ANALYSIS

This chapter focusses into detail on how the study design addresses potential safety concerns. In addition, we underscore the importance of the role of our DSMB, which is described into detail in the DSMB Charter.

10.1 Potential issues of concern

Participants will be advised according to randomization to adhere to either a restricted fluid intake of 1500cc/24hours or a liberal fluid intake regimen.

In general in chronic HF, symptoms and signs, such as orthopnea and peripheral edema, may arise from fluid retention, which could lead to serious adverse events such as hospitalization. In light of this, it has been common clinical practice for many decades to advice chronic HF patients to limit their fluid intake to 1500cc/24 hours. This advice is not based on clinical evidence but mainly on intuition. Moreover, the limited data available demonstrate that fluid restriction in HF may not be more beneficial than liberal fluid intake (3-6).

In the absence of supportive evidence, the Northern American Guidelines give fluid restriction a Class IIa/ level of evidence C recommendation, and the European Guidelines provide only a general recommendation supporting fluid restriction for symptomatic HF, without providing a level of evidence (1, 2, 7). Despite the fact that the guidelines state that there is no supportive evidence for fluid restriction, it is recommended in daily practice by many cardiologists, specialized heart failure nurses and dieticians to virtually every chronic HF patient.

While fluid restriction may not have a beneficial effect in chronic HF, it has been demonstrated that it may even adversely impact these patients in terms of QoL (3, 8). Fluid restriction as a daily part of chronic HF care is from a *patients' perspective* considered to be most challenging and cumbersome, because 1) patients have to monitor intake, 2) fluid restriction leads to thirst distress and 3) it confronts patients with their chronic disease. As a consequence, noncompliance is common, which may detrimentally impact doctor-patient relationship and/or patient's self-esteem (8). All of these factors of fluid restriction may contribute to a reduced QoL for HF patients.

Apart from the potential detrimental effect on QoL, the rationale of fluid restriction in HF management has been questioned by several other investigators previously (3, 5, 6, 24). The limitation of water supply in the diet can aggravate the status of reduced effective circulating volume, which is in itself already present in HF, due to the fall in cardiac output and slowdown in the circulating flow. This reduction in intravascular volume is especially present

in the cases of HF with marked systemic venous hypertension, widespread edema, or ascites (25). In this scenario, the receptors of supraoptic and paraventricular nuclei of the hypothalamus, known to be involved in the secretion of antidiuretic hormone (ADH) in cases of reduced intravascular volume, may be activated as a consequence of the restricted water intake in the diet (26, 27). Thus, due to the non-osmotic stimulation of these receptors, a further release of ADH stimulates reabsorption of water at the level of the renal collecting ducts, and substantial maintenance of the state of widespread edema may occur despite the fluid restriction. Moreover, the limitation of fluid dietary intake may promote reduction in renal blood flow, with worsening of renal filtration (decrease of GFR) and risk of elevation of nitrogenous wastes in the blood (increase of blood urea nitrogen and creatinine). Finally, kidney dysfunction and cardiac ischemia caused by hypoperfusion may concur to provoke rather than prevent a condition of worsening HF.

Although these concerns may seem quite plausible, from the limited data available there is no consistent adverse effect of fluid restriction demonstrated on symptoms of fluid retention, hospital admissions or renal function, as pointed out in systematic reviews and meta-analyses (5, 6).

On the other hand, potential issues of concern may be that in case of randomization to liberal fluid intake an increase of HF signs and symptoms and serious adverse events such as HF hospitalizations and HF-related mortality may occur due to fluid retention more often compared to the fluid restriction arm. However, as previously stated, this is contradicted by the limited available data summarized in systematic reviews and meta-analyses (5, 6). There is, however, one study to suggest that fluid restriction of <1000c/24hours is superior to <2000cc/24hours for the prevention of adverse events such as HF re-admissions (28). It should be acknowledged that this concerns a highly selected population of HF patients. That particular population was recently discharged from the hospital, had a left ventricular ejection fraction <35%, had diuretic resistance with decreased urinary volume (<500 ml/day), and low natriuresis (<60 mEq/day), despite high dose diuretics. This highly vulnerable population with limited diuresis might benefit from strict fluid restriction compared to liberal fluid intake. In that regard, we have decided to exclude patients with poor kidney function and those who have comorbidity for which a different treating physician has prescribed fluid restriction (see exclusion criteria paragraph 4.3). Moreover, to be eligible the HF patients need to be stable for at least 3 months. Lastly, it may be that after the intervention period of 3 months, patients who have been randomized to liberal fluid intake may have an increase of HF signs and symptoms and serious adverse events such as HF hospitalizations and HF-related mortality due to fluid retention more often compared to the fluid restriction arm. Filling pressures may rise during the intervention period. While this may not lead to a change a clinical presentation within the first three months, it may have an effect on the patients' vulnerability for adverse

effects due to fluid retention in the following months. In that regard, we have lengthened clinical follow-up for 3 months after the intervention in order to address this potential safety issue.

Another potential issue of concern may be patients who are hyponatremic. In a small study (n=46), it was suggested that fluid restriction in hyponatremic HF patients might results in higher QoL compared to liberal fluid intake (29). In light of this study, we decided to exclude HF patients with a sodium concentration <130mmol/l (see exclusion criteria paragraph 4.3).

Appreciating the complex nature of chronic HF with potential unexpected deterioration, it is very important that chronic HF patients are well instructed on selfcare management according to professional recommendations (7). Subjects will be enrolled at the excellent specialized multidisciplinary HF outpatient clinics of the participating centers with vast experience in HF patient management. In order to be eligible patients will have to be diagnosed with HF for at least 6 months to ensure that all subjects are adequately instructed on what to do in case of potential deterioration. In case of signs and/or symptoms of either fluid retention or dehydration, the specialized multidisciplinary HF outpatient clinics are well equipped to address these adequately and prevent (further) deterioration. For example, in case of fluid retention, diuretics may be temporarily increased and/or fluid intake may be temporarily restricted. And for example, in case of dehydration, patients may be temporarily instructed to increase their fluid intake or temporarily decrease diuretic use.

Acknowledging the above potential issues of concern and the tailored study design, we consider this study to be safe and appropriate to investigate the effect of fluid restriction versus liberal fluid intake, which may impact the current guidelines for millions of chronic HF patients worldwide.

In addition to the above, a DSMB will be composed to perform 2 safety interim analyses on 1) the occurrence of death, all-cause hospitalisations and the need for iv-loop diuretics; and 2) the occurrence of acute kidney injury at two timepoints to ensure the safe and appropriate continuation of the study.

10.2 Synthesis

There are only two small comparative, randomized studies performed on the effect of fluid restriction in less <70 patients (3, 4). In these 2 studies, fluid restriction showed no clinical benefit compared to unrestricted fluid intake, while liberal uptake resulted in an improved patient reported outcome, i.e. less thirst. These data underscore the need for more randomized data.

From a safety perspective, we will exclude patients with a sodium concentration <130mmol/l and poor kidney function (eGFR < 30ml/min/1.73 m2). Furthermore, patients will be intensively followed up and monitored as usual and in case of decompensation seen by their experienced HF team. Patients are well instructed, stable at inclusion and familiar with logistics in case of unexpected deterioration. Moreover, a DSMB will perform two additional safety analyses. In conclusion, our study design is appropriate in light of the need for randomized data regarding this controversial topic with implications for millions of HF patients worldwide.

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