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

Summary of changes

Protocol ID	NL75112.091.20 / NCT04551729
Short title	FRESH-UP
First approved version	2.0
Date of first approved version	30th November 2020
Protocol version	3.0
Date of change	21st July 2021
Section of change	Protocol information page
Description of change	**The following was added:** J.J. Herrmann MD (Radboudumc) R. Pisters MD PhD (Rijnstate)
Rationale for change	New coordinating investigator was added (J.J. Herrmann MD, Radboudumc, Nijmegen, The Netherlands). New including site was added (Rijnstate Hospital, Arnhem, the Netherlands).
Section of change	4.3 Exclusion criteria
Description of change	**The following criterion was added:** • Changes in HF medical therapy in last 14 days prior to randomization.
Rationale for change	To ensure within the protocol that recent pharmacological changes of the study participants could not influence baseline measurements (including Kansas City Cardiomyopathy Questionnaire (KCCQ)).
Section of change	7.4 Data Safety Monitoring Board
Description of change	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. **Was changed to:** The DSMB has two mandates: 1) To perform two interim analyses **when data is available** ~~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 **when data is available** ~~at the enrolment~~ of 33% of the subjects, second **when data is available** ~~at the enrolment~~ of 66% of the subjects.
Rationale for change	To elucidate that the interim analyses will be performed when data from the first 33% and 66% of the study population are available.
Protocol version	3.1
Date of change	21st February 2022
Section of change	Protocol information page
Description of change	**The following was added:** S. van Wijk MD PhD (Zuyderland Medisch Centrum)

Rationale for change	New including site was added (Zuyderland Medisch Centrum, Heerlen, the Netherlands).
Protocol version	4.0
Date of change	1st June 2022
Section of change	Protocol information page
Description of change	To be determined **Was changed to:** **P. Van Der Meer MD PhD (chair; UMCG)** **Remaining members** ~~T~~to be determined
Rationale for change	New chair of the event adjudication committee (EAC) was added (P. Van Der Meer MD PhD (UMC Groningen, Groningen, the Netherlands).
Section of change	2. Objectives
Description of change	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 (11, 12). 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); **Was changed to:** 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) **Overall Summary Score (OSS)** (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 (11, 12). 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 thirst distress at 3 months after randomization, as assessed with TDS-HF (13);** • To investigate the effect of standard fluid restriction (1500cc/24hours) versus liberal fluid intake on QoL at 3 months after randomization, as assessed ~~with~~ **by KCCQ Clinical Summary Score (CSS), each of the KCCQ domains and the proportion of patients with clinically meaningful changes in these scores and** a visual analogue scale (EQ-5D-5L);
Section of change	4.4 Sample size calculation
Description of change	**The following was deleted:** 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.
Section of change	6.1 Study parameters/endpoints
Description of change	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 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);

	Was changed to: 6.1.1 Main study parameters - QoL at 3 months after randomization, as assessed with the KCCQ Overall Summary (OS**S**) Score (10) ~~- QoL at 3 months after randomization, as assessed with the Thirst Distress Scale~~ 6.1.2 Secondary study parameters - **Thirst distress at 3 months after randomization, as assessed with the TDS-HF** (13) - QoL at 3 months after randomization, as assessed with the KCCQ Clinical Summary **Score** (CS**S**) ~~Score~~ and each of the KCCQ domains (10);
Rationale for the three changes above	Based on external peer and editorial review by the Journal of Cardiac Failure of our "rationale-and-design-paper" and second internal statistical review, we improved the quality of our protocol accordingly. The comments and rebuttal letter are included in Appendix A. At the time of submission, and during the review process, only 140 patients were included and therefore no DSMB analysis was performed yet. Because of these changes, the primary research question how quality of life is affected by liberal fluid intake compared to fluid restriction will be answered more unambiguously. The results of the study will be easier to interpret by using one primary endpoint
Section of change	4.4 Sample size calculation
Description of change	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. **Was changed to:** 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~~ **506** patients.

Rationale for change	To correct the inaccurate way of processing the anticipated 10% dropout rate in the sample size calculation using the standard LTF adjustment.
Section of change	8. Statistical analysis
Description of change	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 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. **Was changed to:** 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~~**according to the intention-to-treat principle** ~~(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. **In the unlikely case that any baseline scores on the KCCQ-OSS are missing, these will first be multiply imputed using imputations drawn from the distribution of the full study population. Following this, the imputation model will be specified separately by treatment arm and will include baseline and 3-month KCCQ-OSS as well as any auxiliary variables that are considered to be associated with the outcome or with the probability of missing the 3-month KCCQ scores.** We will also perform a~~n ancillary~~ **sensitivity**~~supportive~~ analysis **to examine the sensitivity of the results to missing data assumptions**~~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~~. **For this sensitivity analysis, a delta-adjustment approach will be applied, with a fixed constant (to be elicited from a panel of experts) added to the values imputed under the standard MAR procedure (22).** 8.4 Secondary study parameters For the secondary parameters **thirst distress, as assessed with the TDS-HF, and** QoL at 3 months after randomization, as assessed with the KCCQ-~~-~~CS-S~~core~~, 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.
Rationale for change	To emphasize that the intention-to-treat method will be used for the primary analysis as described in paragraph 8.2. To increase the generalizability of the possible imputed missing baseline scores, the single imputation method was changed to a multiple imputation method. However, since quality of life measurements are known to be missing not at random, a sensitivity analysis was included.
Section of change	DSMB Charter; Annex 3: interim analysis
Description of change	The following will be the main parameters of interest for the DSMB: • KCCQ scores • The occurrence of HF hospitalizations • The occurrence of death • The occurrence of acute kidney injury These data will be made available to the DSMB before to the interim analyses, should be explicitly discussed and reported by the DSMB in their reports. This trial aims to include 498 patients. The first interim analysis by the DSMB will be performed when data is available on 33% of patients and the second when data is available on 66% of patients. Possible recommendations after the interim analysis could include, but are not exclusive to: • No action needed, trial continues as planned • Early stopping due to harm of a treatment or clear superiority • Sanctioning and/or proposing protocol changes, such as a change in sample size in case of large discrepancies between expected and observed event rates in the control arm. **Was changed to:**

	The following will be the main parameters of interest for the DSMB: • ~~KCCQ scores~~ • The occurrence of HF hospitalizations • The occurrence of death • The occurrence of acute kidney injury These data will be made available to the DSMB before to the interim analyses, should be explicitly discussed and reported by the DSMB in their reports. This trial aims to include ~~498~~**506** patients. The first interim analysis by the DSMB will be performed when data is available on 33% of patients and the second when data is available on 66% of patients. Possible recommendations after the interim analysis could include, but are not exclusive to: • No action needed, trial continues as planned • Early stopping due to harm of a treatment ~~or clear superiority~~ • Sanctioning and/or proposing protocol changes, such as a change in sample size in case of large discrepancies between expected and observed event rates in the control arm.
Rationale for change	To clarify that the DSMB only can make recommendations to the investigators concerning continuation, termination, or other modifications of the study based on safety and not efficacy.
Protocol version	4.1
Date of change	29th September 2022
Section of change	Protocol information page
Description of change	**The following was added:** J.W.M. Van Eck MD PhD MSc (Jeroen Bosch Ziekenhuis)

Rationale for change	New including site was added (Jeroen Bosch Hospital, Den Bosch, the Netherlands).
Section of change	Protocol information page
Description of change	**The following was added:** F.H. Verbrugge MD PhD (UZ Brussel, België) M.L. Handoko MD PhD (Amsterdam UMC)
Rationale for change	New members of the EAC were added (F.H. Verbrugge MD PhD (UZ Brussel, Belgium) and M.L. Handoko MD PhD (Amsterdam UMC, Amsterdam, The Netherlands)).
Protocol version	4.2
Date of change	2nd December 2022
Section of change	Protocol information page
Description of change	**The following was added:** G.C.M. Linssen MD PhD (Ziekenhuisgroep Twente)
Rationale for change	New including site was added (Ziekenhuisgroep Twente, Almelo, the Netherlands).
Protocol version	4.3
Date of change	5th December 2023
Section of change	Protocol information page
Description of change	**The following was added:** S.C.A.M. Bekkers MD PhD (Bernhoven Ziekenhuis)
Rationale for change	New including site was added (Bernhoven Hospital, Uden, the Netherlands).
Protocol version	4.4
Date of change	15th May 2024
Section of change	Protocol information page
Description of change	**The following was added:** E. Wierda MD LLM PhD (Dijklander Ziekenhuis)

Rationale for change	New including site was added (Dijklander Hospital, Hoorn, the Netherlands).