Study Protocol

Study Title:	Diuretic Treatment in Acute Heart Failure with Volume Overload Guided by Serial Spot Urine Sodium Assessment
Study Acronym:	DECONGEST
Phase of Development:	IV
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Investigational product:	None
Sponsor:	UZ Brussel
Coordinating/Principal Investigator:	Prof. Dr. Frederik Verbrugge

PROTOCOL SIGNATURE PAGE

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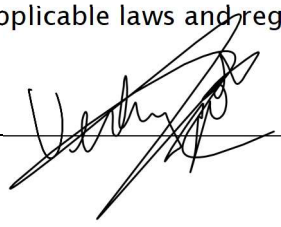
I agree:

- to assume responsibility for the proper conduct of this study
- to conduct the study in compliance with this protocol and any future amendments
- not to implement any deviations from or changes to the protocol without prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
- that I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol
- to ensure that all persons assisting me with the study are adequately informed about the investigational drug and their study-related duties and functions as described in the protocol
- that I am aware of and will comply with the current good clinical practice (GCP) guidelines and ethical principles outlined in the Declaration of Helsinki
- to conduct the study in accordance with all applicable laws and regulations

Printed name: Frederik Verbrugge Signature  Date: 22/04/2024

Universitair Ziekenhuis Brussel

Clinical Trial Center

Universitair Ziekenhuis Brussel

Centrum voor Hart- en Vaatziekten

VUB

Study Protocol

Diuretic Treatment in Acute Heart Failure with Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST) study

1. Primary investigator (PI)

Dr. Frederik Verbrugge (Centrum voor Hart- en Vaatziekten, UZ Brussel)

2. Study design

- Prospective
- Pragmatic
- Interventional
- Randomised
- Open label
- Multicentre (UZ Brussel & Jessa Hospital Hasselt)

3. Purpose & rationale

Signs and symptoms of volume overload are the most frequent reason for hospital admission in patients with heart failure.[1] During such episodes of acute heart failure (AHF), diuretics are the mainstay treatment. Good diuretic efficiency with complete decongestion is associated with better outcomes.[2] However, these targets remain challenging in clinical practice as diuretic resistance occurs frequently and a normal volume status cannot be readily assessed. This at least partly explains why clinical outcomes after an episode of AHF remain dismal, with recent European registry data demonstrating a 1-year rehospitalization rate of 44.4%

(25.9% for heart failure readmissions only) and all-cause mortality of 26.7%.[3] Residual (sub-)clinical congestion is likely an important mediator of this high risk.[4]

Spot urine sodium assessment is a reliable indicator of diuretic response.[5] Its use in AHF has been recommended by the new guidelines on heart failure of the European Society of Cardiology, with the aim of detecting diuretic resistance early to allow appropriate treatment intensification.[6,7] A sodium concentration <50-70 mmol/L on a spot urine sample collected within the time window of diuretic activity (approximately 6 h after administration for intravenous furosemide/bumetanide) indicates poor diuretic response. When confronted with poor diuretic response in the presence of persistent signs of volume overload, more intensive diuretic treatment (i.e., dose increase or combination therapy) and/or ultrafiltration are indicated to ensure proper decongestion.

In addition, observational data suggest that a *high* urine sodium concentration on spot urine sample after diuretic therapy indicates persistent congestion, even when clinical signs of volume overload are not obvious.[5,8,9] Therefore, hypothetically, intensive diuretic therapy in AHF until complete disappearance of clinical signs of volume overload *and* a urine sodium concentration drop <80 mmol/L, with immediate step-up care in case of diuretic resistance (i.e., low urine sodium concentration with *persistent* signs of volume overload), may improve the quality of decongestion and potentially clinical outcomes. This study prospectively examines a systematic approach to diuretic therapy in AHF, based upon serial assessment of sodium concentration on spot urine samples after diuretic administration.

4. Objectives

Primary objective:

To investigate whether a diuretic regimen based on serial assessment of sodium concentration on spot urine samples after diuretic administration improves decongestion versus usual care in AHF, potentially leading to better clinical outcomes.

Secondary objectives:

- To provide prospective longitudinal data on the incidence and determinants of diuretic resistance in patients with AHF and low-threshold use of combinational diuretic treatment.
- To investigate the relationship between hemodynamic congestion (i.e., cardiac filling pressures & diastolic function on transthoracic echocardiography) and urine sodium concentration under appropriately dosed diuretics according to a standardised regimen.
- To investigate the relationship between lung congestion (B-lines on lung ultrasound), as well as abdominal organ congestion (venous Doppler echography), and urine sodium concentration under appropriately dosed diuretics according to a standardised regimen.
- To compare diagnostic modalities for decongestion: urine sodium profiling, clinical examination, laboratory biomarkers, transthoracic echocardiography, lung ultrasound, and venous Doppler echocardiography.
- To investigate the relationship between right ventricular function, assessed by transthoracic echocardiography, and abdominal organ congestion, assessed by Doppler echography, as well as its evolution under decongestive treatment.
- To investigate the relationship between left atrial function, assessed by transthoracic echocardiography, and urine sodium balance.

5. Study population

Inclusion criteria:

- At least 18 y/o and able to provide informed consent
- Hospital admission (anticipated stay >24 h after randomisation) with diagnosis of AHF according to the treating physician
- At least one of the following three signs of volume overload:
    - bilateral oedema 2+, indicating clear pitting
    - ascites that is amenable for drainage, confirmed by echography (no obligation to perform abdominal echocardiography, but necessary when presence of ascites is used as an entry criterion for the study)
    - uni- or bilateral pleural effusions that are amenable for drainage, confirmed by chest X-ray or lung ultrasound (no obligation to perform chest X-ray, but necessary when presence of pleural effusions is used as an entry criterion for the study)
- Plasma N-terminal of the pro-hormone of B-type natriuretic peptide (NTproBNP) level >1,000 ng/L

Exclusion criteria:

- No possibility to collect reliable urine spot samples after diuretic administration
- Administration of any diuretic within 6 h before randomisation, except for a mineralo-corticoid receptor antagonist (MRA) or sodium-glucose co-transporter 2 (SGLT2) inhibitor as part of the patient's maintenance treatment for heart failure. Patients can still be included in the DECONGEST study after withholding these diuretics for 6 h, after which randomisation can be performed if they qualify all other criteria.

- Severe kidney dysfunction, defined as an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m² calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[10] at randomisation, and/or previous, current, or planned future renal replacement therapy
- Systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg, or need for inotropes/vasopressor therapy at randomisation
- Any acute coronary syndrome within 30 days prior to enrolment, defined as typical chest pain with a troponin rise above the 99th percentile of normal and/or electrocardiographic changes suggestive of cardiac ischemia
- History of heart or kidney transplantation
- History of mechanical circulatory support
- Known obstructive hypertrophic cardiomyopathy, congenital heart disease, acute mechanical cause of AHF (e.g., papillary muscular rupture), acute myocarditis, or constrictive pericarditis according to the treating physician
- Pregnant or breastfeeding woman
- Concomitant participation in another interventional study

6. Randomisation and allocation concealment

Patients will be randomised through an online website using the Castor Electronic Data Capture system. Block randomisation will be performed, stratified for study centre and left ventricular ejection fraction (<50% versus ≥50%) with variable blocks of 2 or 4 subjects for allocation concealment.

7. Control arm

Usual care according to the treating physician. It is recommended to treating physicians to administer an intravenous loop diuretic dose at least twice a day (or through continuous infusion), with the aim of achieving a urine output 3-5 L per day until the patient is considered

in an optimal volume status as is recommended by current guidelines.[7] It is actively discouraged to switch from intravenous to oral diuretic therapy in the presence of persistent clinical signs of volume overload. Diuretic agents with their dose and administration method (bolus versus continuous infusion) are determined by the treating physician. It is recommended to keep disease-modifying treatments with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin-neprilysin inhibitors, MRAs, and SGLT2 inhibitors unchanged during the period of intravenous diuretic administration, although withdrawal or dose reduction in case of (relative) contraindications is allowed. Urine electrolyte assessment in the control arm is not allowed and qualifies as a major protocol violation as it is a key component of the studied intervention.

8. Intervention

Diuretic administration after randomisation

Immediately after randomisation, patients in the intervention arm receive an intravenous bolus of bumetanide, with the dose depending on the eGFR: 2 mg for >45 mL/min/1.73m²; 3 mg for 45-30 mL/min/1.73m²; or 4 mg for <30 mL/min/1.73m². In addition, an intravenous bolus of 500 mg acetazolamide is administered unless hypernatremia (serum sodium concentration >145 mmol/L) or metabolic acidosis (serum bicarbonate <22 mmol/L) is present. Oral chlorthalidone 50 mg is added in case of hypernatremia (serum sodium concentration >145 mmol/L) or an eGFR <30 mL/min/1.73m². The patient is asked to void empty or, in case of a bladder catheter, any urine present at the time of initial diuretic administration is discarded. A background maintenance infusion with 500 mL dextrose 5% and 3 g $MgSO_4$ is started at an infusion rate of 20 mL/h and continued until switch to oral maintenance treatment (see below). If serum potassium levels are <4 mmol/L at any time during administration of intravenous diuretics, 40 mmol KCl is added to this maintenance infusion. In case of significant hyponatremia <130 mmol/L, the maintenance infusion is replaced by a daily bolus of 3 g $MgSO_4$.

Serial spot urine sodium assessment

After every protocol-specified bolus administration of bumetanide, a spot urine sample is collected for assessment of sodium concentration and a subsequent treatment decision. The first urine within the period of 30 min to 3 h after bumetanide administration is used for analysis.

Subsequent diuretic therapy guided by serial spot urine sodium assessment

After the initial diuretic administration upon randomisation (Day 0), an intravenous bolus of bumetanide is provided twice daily on the next consecutive days. The dose for each bolus is as described above, based on the most recent eGFR value available. A minimal 6 h interval is respected between consecutive bumetanide administrations. Intravenous acetazolamide 500 mg OD is provided together with the first bumetanide dose on any given day unless hypernatremia (serum sodium concentration >145 mmol/L) or metabolic acidosis (serum bicarbonate <22 mmol/L) is present. Oral chlorthalidone is continued at a dose of 50 mg OD in case that it was indicated upon randomisation (see above).

If the spot urine sodium concentration following bumetanide administration is ≥80 mmol/L, the protocol continues with the next bumetanide bolus that is scheduled as described (combined with acetazolamide and/or chlorthalidone as indicated). If the spot urine sodium concentration is <80 mmol/L, there are 2 possibilities: (1) the treating physician finds no clinical arguments for residual volume overload and there is no more than trace oedema, in which case the patient is switched from intravenous diuretics to oral maintenance therapy (see below); or (2) there is residual volume overload and/or more than trace oedema, indicating diuretic resistance. In case of a missing urine sodium concentration because urine spot sampling could not be performed, the previous bumetanide dose that has been administered is repeated.

Approach to diuretic resistance

If the clinical exam and spot urine sodium assessment indicate diuretic resistance (i.e., sodium concentration <80 mmol/L with persistent volume overload), full nephron blockade is applied at the moment of the next scheduled bumetanide dose. The following combination therapy is administered:

- Intravenous acetazolamide 500 mg as bolus, unless hypernatremia (serum sodium concentration >145 mmol/L) or metabolic acidosis (serum bicarbonate <22 mmol/L)
- Intravenous bumetanide 4 mg as bolus
- Oral chlorthalidone 100 mg
- Intravenous potassium canrenoate 200 mg IV as bolus unless hyperkalaemia (serum potassium concentration >5 mmol/L). If the patient is already treated with an oral MRA as part of his/her maintenance therapy, this medication is paused until switch to oral maintenance treatment.

The bumetanide dose is subsequently repeated after 6 h and 12 h (TID) in case of good diuretic response (i.e., spot urine sodium concentration ≥80 mmol/L). The entire combination is repeated after 24 h in case of good diuretic response. This schedule is continued until successful decongestion (spot urine sodium concentration <80 mmol/L and absence of volume overload with no more than trace oedema) or refractory volume overload with spot urine sodium concentration <80 mmol/L despite full nephron blockade. In the latter scenario, all diuretics are withdrawn and ultrafiltration with or without renal replacement therapy is started and continued according to the treating physician.

Switch to oral maintenance therapy

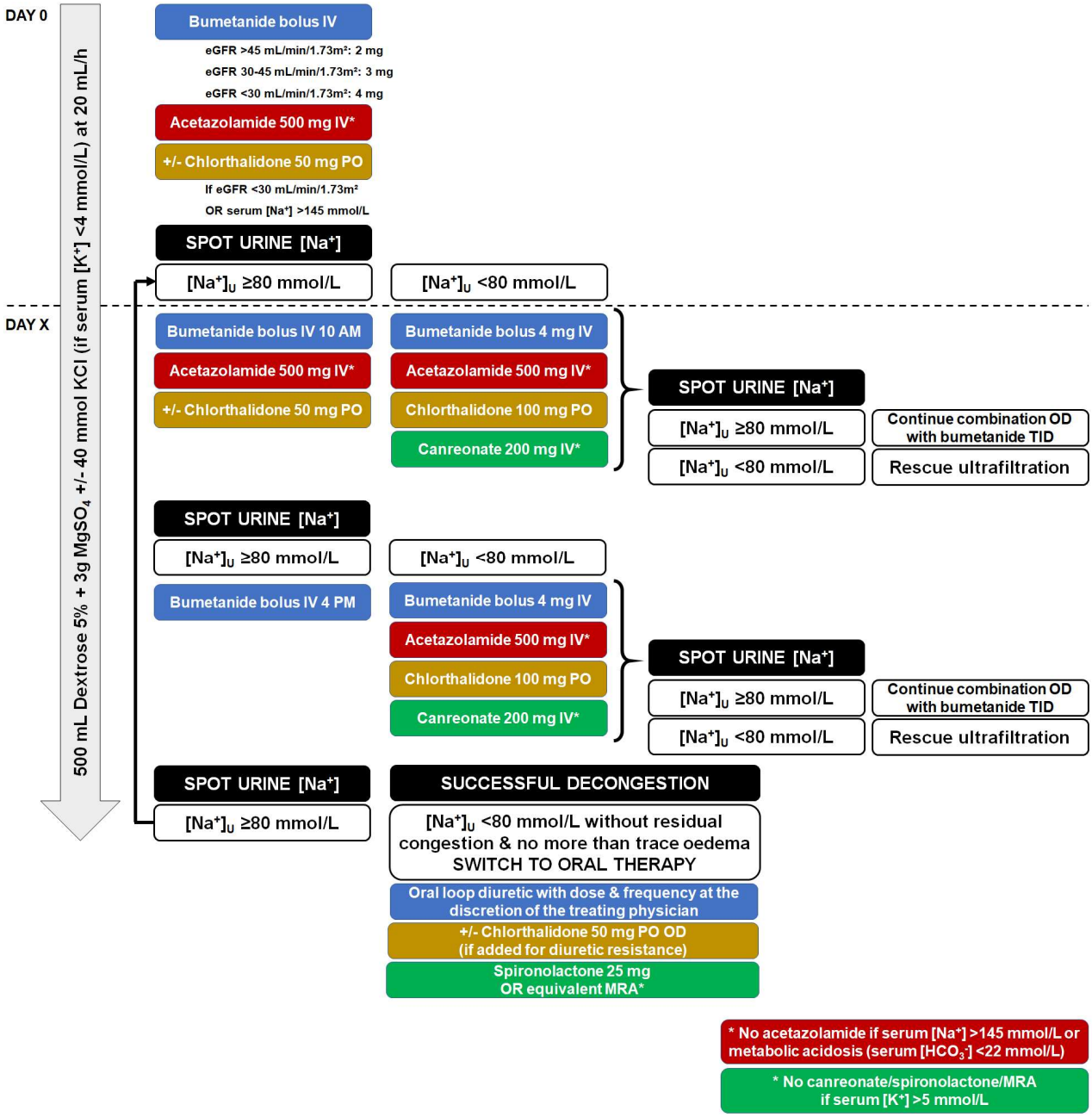
If urine sodium concentration is <80 mmol/L and the treating physician has no clinical arguments for residual volume overload, with no more than trace oedema present, this is considered successful decongestion. Acetazolamide (and potassium canrenoate if it was indicated

according to the study protocol) are stopped. Chlorthalidone is continued at a dose of 50 mg OD only when it was previously added as part of full nephron blockade because of diuretic resistance. If chlorthalidone was started because of hypernatremia and/or low eGFR at randomisation, it is withdrawn. Spironolactone 25 mg OD or an equivalent MRA is started (or continued) unless serum potassium levels are >5 mmol/L and/or eGFR is <20 mL/min/1.71m². Intravenous bumetanide is replaced by an oral loop diuretic with dose and administration frequency at the discretion of the treating physician. The maintenance dextrose 5% infusion is halted.

Neurohumoral blocker treatment

In the intervention group, it is obligatory to keep disease-modifying treatments with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin-neprilysin inhibitors, MRAs, and SGLT2 inhibitors unchanged during the period of intravenous diuretic administration, although withdrawal or dose reduction in case of (relative) contraindications is allowed. Dose up-titration or start of these treatments is allowed *after* transition from intravenous to oral diuretic therapy and recommended in patients with reduced ejection fraction.

Intervention flowchart



9. Safety precautions

Anticipated adverse events, potentially related to the study intervention, include arterial hypotension, acute kidney injury (AKI) and electrolyte disorders. Arterial blood pressure is evaluated throughout the study protocol with continuous invasive measurements or frequent non-invasive assessment by cuff manometry. Serum creatinine, eGFR, and serum electrolyte

levels are followed on a daily base during the administration of intravenous diuretics according to the study protocol and afterwards at the discretion of the treating physician.

Arterial hypotension

In case of significant arterial hypotension, defined as a systolic blood pressure <90 mmHg and/or mean arterial pressure <65 mmHg at any time during the period of intravenous diuretic therapy, all non-diuretic hypotensive medications are withdrawn and the next diuretic administration is postponed until blood pressure recovery. If use of vasopressors or inotropes is clinically indicated according to the treating physician as rescue therapy, the protocolised administration of diuretics is halted and further treatment is at the discretion of the treating physician.

Acute kidney injury

If the serum creatinine doubles (compared to its baseline value at randomisation) at any time during the period of intravenous diuretic therapy and has an absolute value >2 mg/dL, the protocolised administration of diuretics is halted and further treatment is at the discretion of the treating physician.

Electrolyte disorders

- In case of clinically significant hyperkalaemia >5.5 mmol/L, any treatment with renin-angiotensin system blockers and/or MRAs is temporarily interrupted. If serum potassium levels rise further >6.5 mmol/L despite these precautions, the protocolised administration of diuretics is halted and further treatment is at the discretion of the treating physician.
- In case of hypokalaemia <3.5 mmol/L (despite administration of 40 mmol of daily KCl as specified above), oral supplementation is provided as necessary for correction, with target levels of serum potassium >4 mmol/L.

- In case of hypotonic hyponatremia <135 mmol/L, chlorthalidone or potassium canrenoate that is specified according to the study protocol is withheld and treatment with MRA is temporarily interrupted until restauration of a serum sodium level ≥135 mmol/L. In patients with serum sodium levels <130 mmol/L, the hypotonic maintenance infusion will not be administered. In case of severe hyponatremia <125 mmol/L, a bolus of 150 mL hypertonic saline 3% is administered and repeated once daily if necessary, until sodium levels are ≥135 mmol/L.
- In case of hypernatremia >145 mmol/L, additional free water is administered as dextrose 5% to keep serum sodium levels ≤145 mmol/L and the patient will be allowed to have more liberal fluid intake if possible.
- In case of severe metabolic acidosis with serum bicarbonate levels <20 mmol/L, 100 mL of intravenous NaHCO3 8.4% is administered. No further administration of acetazolamide is allowed during the entire study protocol in such cases.

10. Study endpoints

Primary study endpoint:

The primary study endpoint is the win ratio for a hierarchically composed endpoint. The individual components of this endpoint in order of importance are:

1) Death within 30 days after discharge
2) Number of days in hospital from the first 30 days after randomisation
3) Relative NTproBNP decrease from baseline to 30 days after randomisation

Secondary study endpoints:

- Relative NTproBNP decrease from baseline to 30 days after randomisation [%]
- Relative cancer antigen 125 (CA 125) from baseline to 30 days after randomisation [%]
- Length of intravenous diuretic therapy [days]

- Successful decongestion defined as no more than trace oedema, absence of jugular venous distension and no rales upon the moment of transition from intravenous diuretics to oral maintenance therapy
- Five-point Likert scale for overall well-being assessed upon the transition from intravenous diuretics to oral maintenance therapy compared to the moment of randomization (much improved/slightly improved/neutral/slightly worse/much worse)
- Doubling of the serum creatinine or plasma cystatin C compared to baseline with an absolute value >2 mg/dL or >2 mg/L, respectively, or the need for ultrafiltration and/or renal replacement therapy during the index hospital admission (renal safety end-point)
- Systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg or need for vasopressors and/or inotropes during the index hospital admission (hemodynamic safety endpoint)
- Length of the index hospital admission [days]
- Death, non-elective rehospitalization or non-elective medical contact
- Death or non-elective hospital readmission rate

<u>Prespecified exploratory endpoints:</u>

- Five-point Likert scale for overall well-being assessed at discharge and at 30 days after randomisation, compared to the moment of randomization (much improved/slightly improved/neutral/slightly worse/much worse)
- Oedema score (1+: trace to 4+: above the knee) upon transition from intravenous diuretic towards oral maintenance therapy, at discharge, and at 30 days after randomisation
- Weight change from baseline to switch towards oral maintenance therapy [kg]
- Cumulative intravenous loop diuretic dose administered according to the study protocol before transition towards oral maintenance therapy [mg bumetanide equivalents]

- Weight change from baseline to switch towards oral maintenance therapy, adjusted for loop diuretic dose administered [kg per mg bumetanide equivalents]
- Relative NTproBNP change from baseline to switch towards oral maintenance therapy [%]
- Relative CA 125 change from baseline to switch towards oral maintenance therapy [%]
- Change in eGFR (calculated according to the Chronic Kidney Diseases Collaboration formula with creatinine, cystatin C, and both) from baseline to switch towards oral maintenance therapy and to 30 days after randomisation
- Incidence of electrolyte disorders as described in the paragraph “Safety Precautions” (see above) during the phase of intravenous diuretic treatment
- Averaged medial/lateral E/e’ ratio on transthoracic echocardiography upon switch towards oral maintenance therapy, at discharge, and at 30 days after randomisation
- Peak left atrial longitudinal strain on transthoracic echocardiography upon switch towards oral maintenance therapy, at discharge, and at 30 days after randomisation [%]
- Tricuspid annular plane systolic excursion over right ventricular systolic pressure ratio on transthoracic echocardiography upon switch towards oral maintenance therapy, at discharge, and at 30 days after randomisation [mm/mmHg]
- Number of B-lines on lung ultrasound, scanning 8 thoracic sites upon switch towards oral diuretic regimen, at discharge, and at 30 days after randomisation[11]
- VExUS score for venous Doppler measurements as a marker for abdominal venous congestion upon switch towards oral diuretic regimen, at discharge, and at 30 days after randomisation[12]

11. Statistical analysis

Power calculation:

As the primary study end-point is anticipated to be driven mainly by the change in NTproBNP levels, the study is powered for that specific component of the primary end-point, which also constitutes the first secondary end-point. Assuming an average 75% relative decrease in NTproBNP levels at 30 days after discharge compared to baseline in the control group versus an 85% decrease in the intervention group, with a standard deviation of 15%, 94 patients need to be included given a significance level (alpha) of 0.05 to yield a statistical power (1-beta) of 90%. To account for potential drop-out up to 10%, the targeted study sample size is set at 104 subjects.

Main statistical analysis:

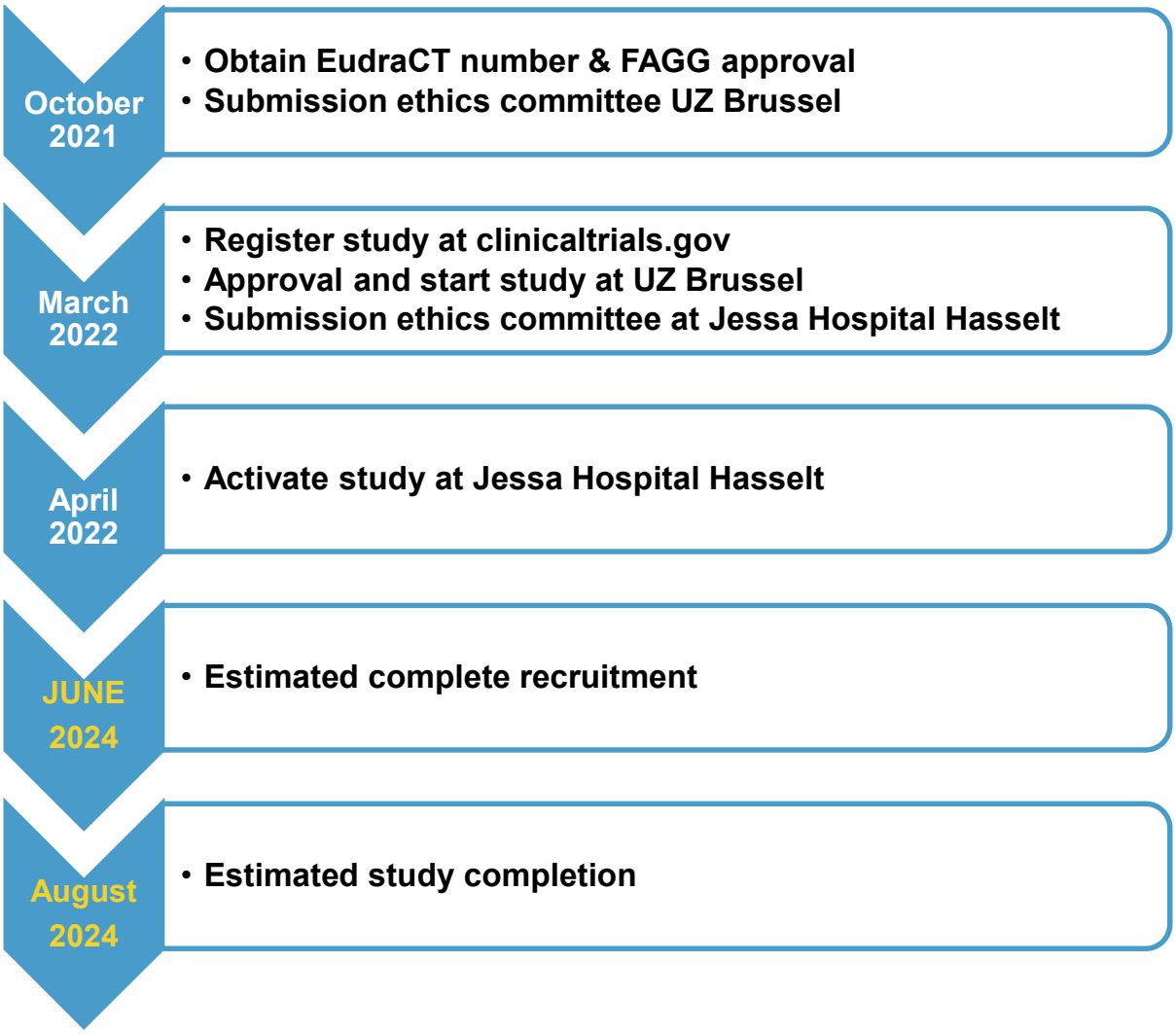
The primary analysis of the study assesses the win-ratio of the hierarchically composed primary end-point using the Finkelstein-Schoenfeld method.[13] This method is based on the principle that each subject in the study is compared to every other subject within each stratum in a pair-wise manner. This method gives the highest importance to all-cause mortality at 30 days after discharge, subsequently to the number of days hospitalised during the 30 days after randomisation and finally to the relative change in NTproBNP levels at 30 days after randomisation compared to baseline.

If the primary study endpoint is positive, secondary endpoints will be assessed in a hierarchical sequence without adjusting for multiple testing. If the primary endpoint or any of the secondary study endpoints is negative, all following endpoints will be considered explorative. Fisher's Exact test, the independent-samples *t*-test and Mann-Whitney *U* test are used as indicated to assess the secondary endpoints. All primary study analyses will be performed according to the intention to treat principle.

12. Data collection

A screening log with the relevant inclusion and exclusion criteria and the randomisation key will be obtained via the Castor Electronic Data Capture system. All other relevant study data will be collected and put in an online accessible Redcap database that is continuously updated by the study researchers. All patients will get an appointment for an in-hospital study visit 30 days after randomisation (or are visited by a study person when they have a prolonged in-hospital stay >30 days during their index hospitalisation) to ensure complete data capturing. Patients who miss their appointment will be contacted by phone and e-mail to identify the reasons of not showing up and minimise loss of data.

13. Timeline



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