

Diuretic use in patients with residual renal function on hemodialysis (DIURESED)

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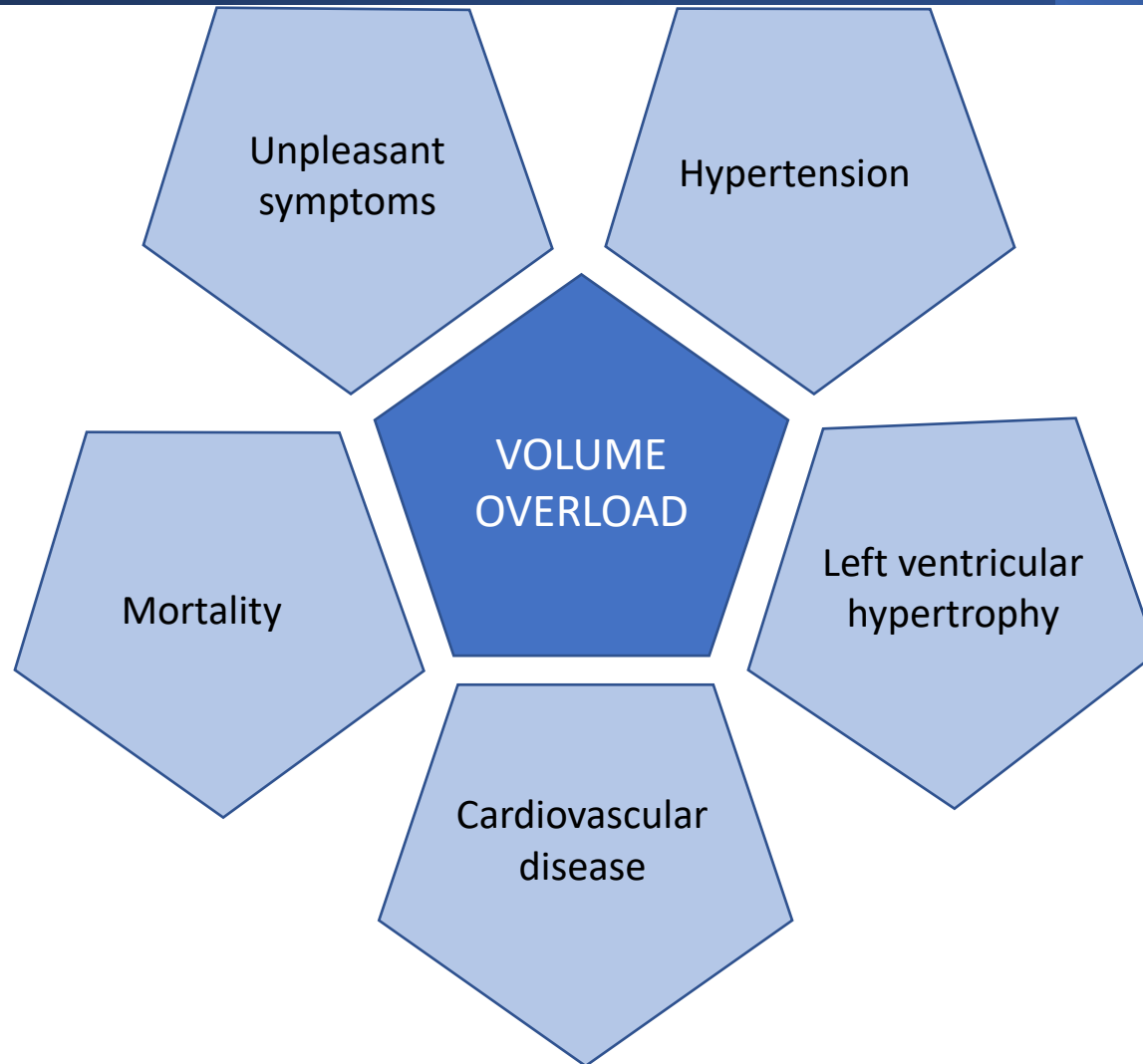


Disclosures

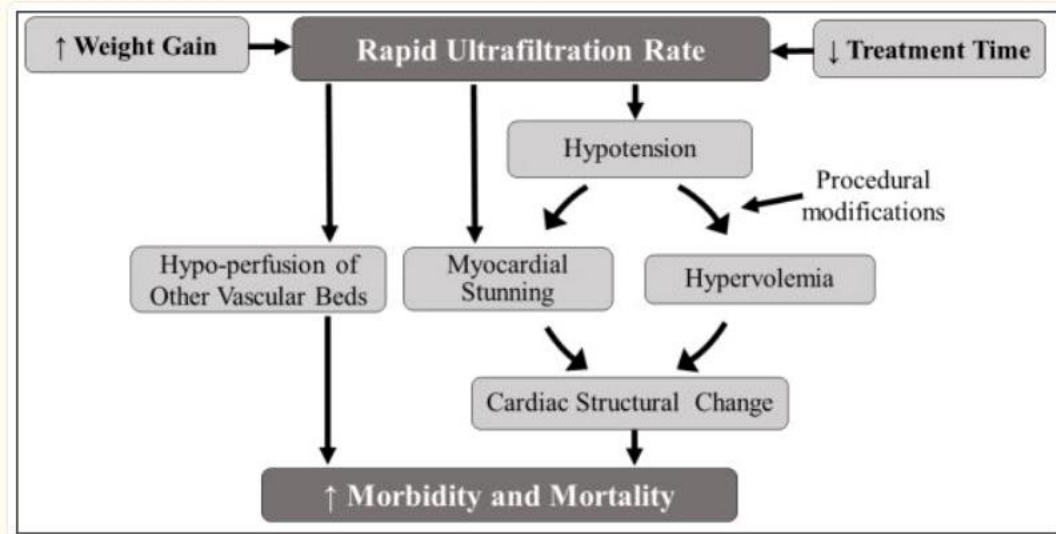
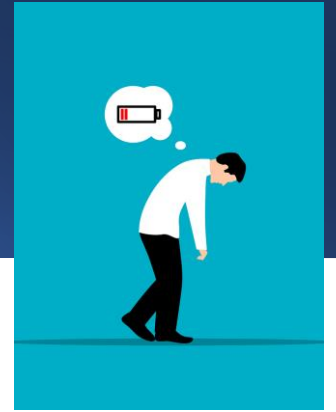
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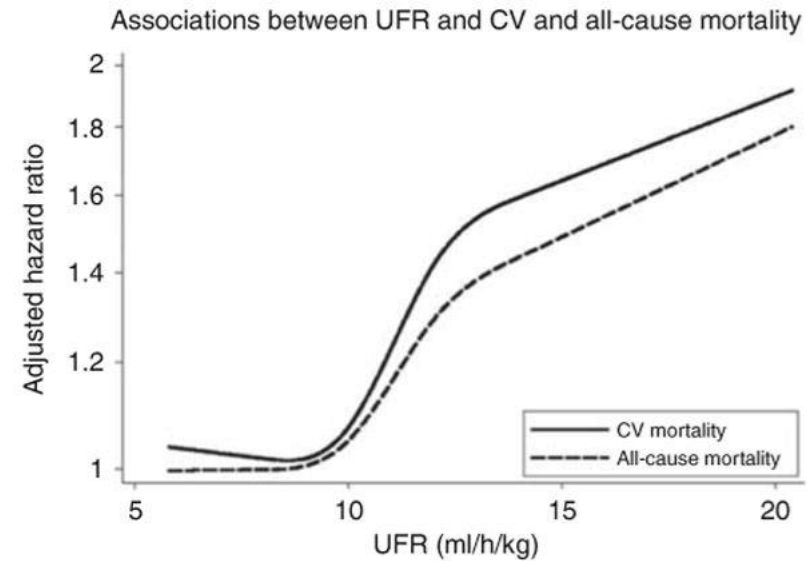
Volume overload in patients on hemodialysis



Ultrafiltration



Assimon et al. Curr Opin Nephrol Hypertens 2016



Flythe et al. Kidney International 2011



Residual renal function and urine output in patient on hemodialysis

- Volume control and clearance of toxins
- Better quality of life
- In observational studies, preserved urine output results in lower interdialytic weight gain and lower intradialytic hypotension
- Improved survival & lower risk of major cardiovascular events and mortality
- LOWER residual renal function associated with uncontrolled hypertension, increased LV mass and increase erythropoietin requirements



Diuretic use in patients on hemodialysis

- Variable use (0-84% in the DOPPS study)

Observational studies suggest a role for diuretic medications

- Bragg-Gresham et al (2007)
 - Lower interdialytic weight gain
 - Lower odds of hyperkalemia
 - 7% lower all-cause mortality risk
 - 14% lower cardiac-specific mortality risk
 - Patients with RRF on diuretic therapy had almost twice the odds of retaining RRF after 1 year compared to those not taking diuretic medications
- Sibbel et al (2019)
 - diuretic use was associated with lower hospitalization, interdialytic weight gain and intradialytic hypotension
- Clinical equipoise regarding impact on residual renal function

Robust, prospective, trial data is lacking

- Van Olden et al. 1992 – Acute and long-term effects of therapy with high dose furosemide in chronic hemodialysis patients
- Chen et al. 2021 – Efficacy and safety of furosemide in the prevention of intradialytic hypotension in hemodialysis patients: protocol for a multicenter RCT
- Flythe et al. 2022 – Efficacy, safety and tolerability of oral furosemide in patients on hemodialysis

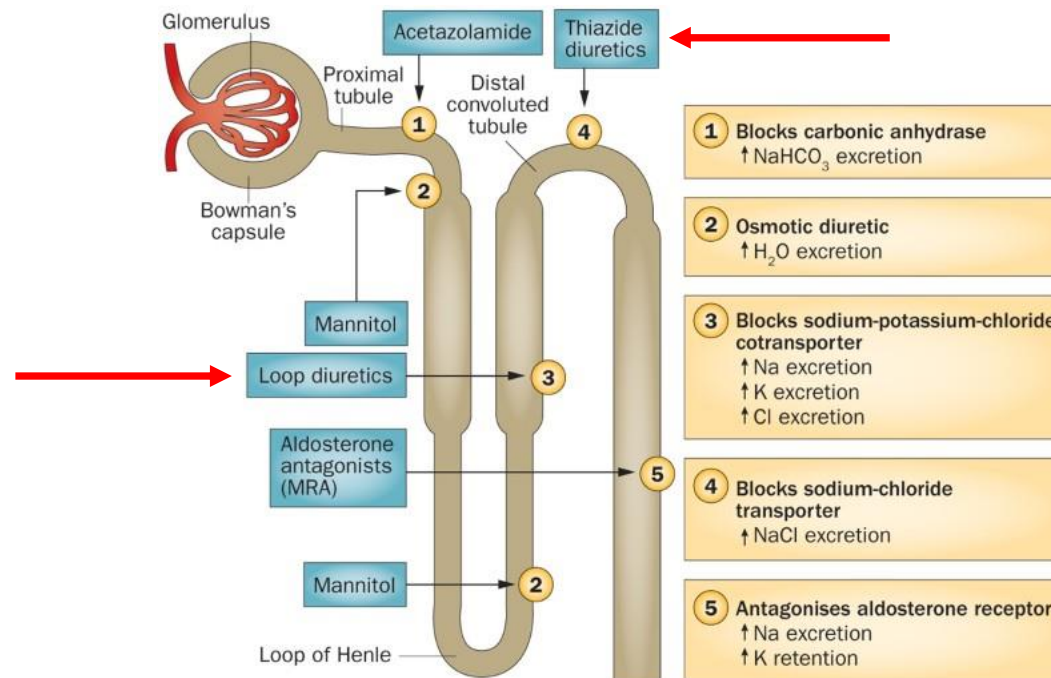
So far...

- Volume overload = bad
- Residual renal function = good
- Diuretics ??

Furosemide & Chlorthalidone



- By combining 2 diuretics that exert their effects in different locations in the nephron, we hope to increase the overall natriuretic and diuretic effect



[Randomized Controlled Trial](#) > *N Engl J Med.* 2021 Dec 30;385(27):2507-2519.
doi: 10.1056/NEJMoa2110730. Epub 2021 Nov 5.

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

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Question

P: In patients who continue to produce urine (≥ 200 cc/24 hours),

I: does the use of diuretic medications

C: compared to no diuretic use

O: reduce the risk of major adverse cardiovascular events or all-cause mortality?

Approach to answering this question

Do diuretic medications work to increase urine output and decrease interdialytic weight gain?

Proof of concept study



Can a pragmatic approach be used?

Feasibility study



Does diuretic use in patients with residual renal function on hemodialysis result in lower MACE and all-cause mortality?

Large, multicenter (pragmatic) RCT

Do diuretic medications work to increase urine output and decrease interdialytic weight gain?

1. Proof of Concept Study

Single center, single arm study of 34 patients at the University of Alberta Hemodialysis center

Our primary objective:

We aim to determine the effects of starting, and escalating doses of diuretic medications (furosemide +/- chlorthalidone) on 24-hour urine output (volume) over a five-week period in patients on hemodialysis who produce >200cc per day of urine.

Secondary objectives are:

- To evaluate the effect of diuretic medications on residual renal function
- To evaluate the effect of different doses of diuretics on interdialytic weight gain, ultrafiltration rates and intradialytic hypotension
- To examine the effect of different doses of diuretics on patient reported outcomes
- To evaluate adverse effects of different doses of diuretics
- To measure urine furosemide levels in this patient population

Eligibility criteria



Inclusion criteria

- Adult patients (age 18 years or older), who are within their first 6 months of chronic (expected to need dialysis for at least 6 months), in-centre, thrice weekly hemodialysis therapy, and
- Residual renal function defined as 24-hour urine volume >200cc, and
- Life expectancy of at least 6 months, and
- Participants must be able to understand the consent process and be able to sign a consent form *or* have a substitute decision maker who is able to understand and sign consent on their behalf. In the case of non-English speaking participants, we will use a translator service to provide study information and obtain consent.

Exclusion criteria

- Unable to complete baseline urine collection
- Documented allergy or adverse reaction to furosemide or chlorthalidone
- Unable to take oral medications
- Patients expecting to change modality (peritoneal dialysis, home dialysis) or to receive a renal transplant in the next 6 weeks
- History of hypokalemia (<3.0 mmol/L), hypomagnesemia (<0.6 mmol/L), or hypocalcemia (<1.9 mmol/L) in preceding 2 weeks
- Already participating in another study and one of the studies could interfere with the other study

Outcomes and data collection

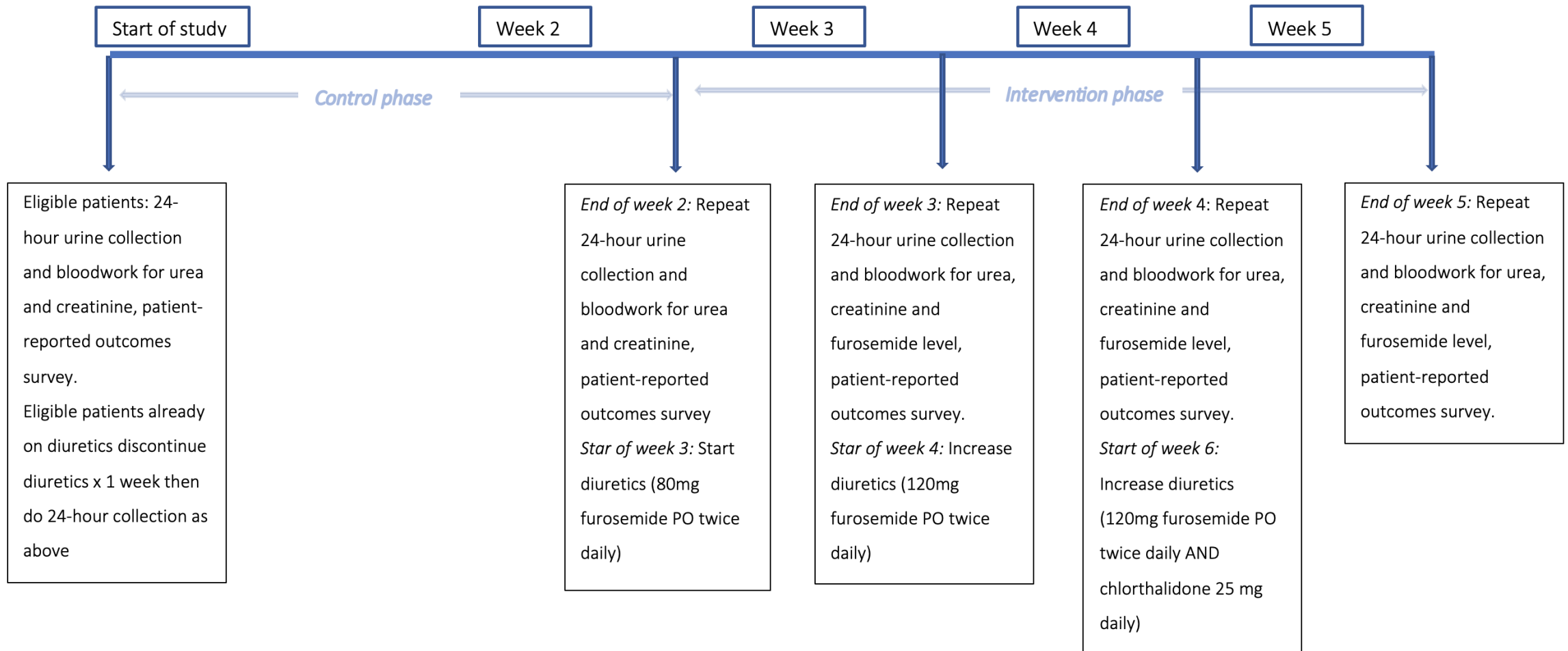
Primary:

- Twenty-four-hour urine collections will be done at screening (this will count as baseline for enrolled patients), at the end of week 2 (to measure change over time with no diuretic use), and during each prescribed diuretic regimen (weeks 3, 4 and 5).

Secondary:

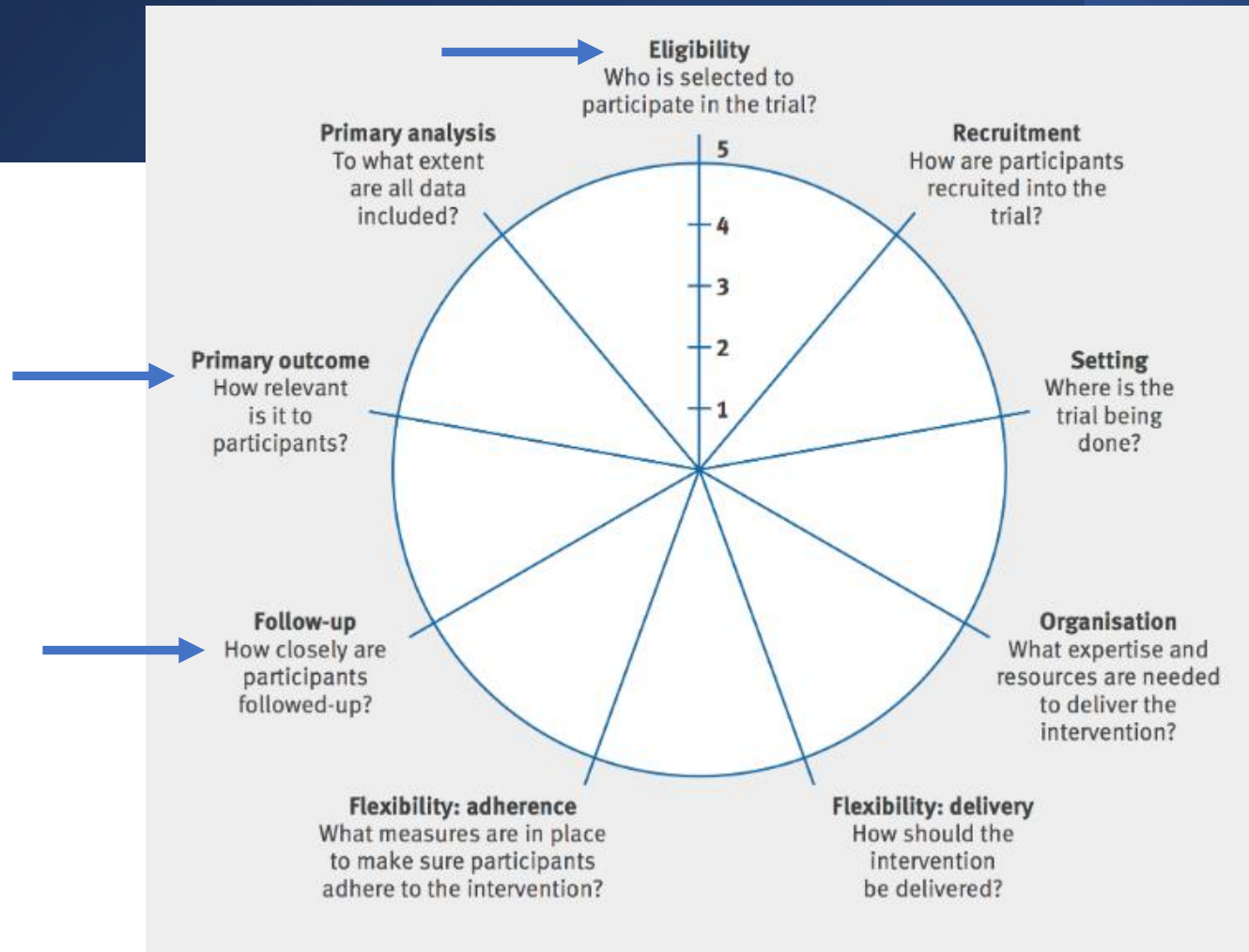
- Residual renal function – calculated based on weekly bloodwork and 24-hour urine collections
- Interdialytic weight gain, ultrafiltration rates and intradialytic hypotension
- Patient reported outcomes – Edmonton Symptom Assessment System-Revised, muscle cramps, frequency, and severity of volume-related symptoms, thirst, and any change in hearing. We will then ask dialysis nurses to provide participants with the same survey at the end of week 2, and on day 7 of each diuretic regimen in weeks 3-5.
- Adverse effects of different doses of diuretics – weekly bloodwork to measure serum sodium, potassium, magnesium, and calcium, as well as creatinine and urea.
- Urine furosemide levels – using the 24-hour urine collections, we will measure the urinary concentration of furosemide during each diuretic regimen.

Figure 1 Study design



Recognized limitations

- Increasing urine output might result in patients feeling thirstier and drinking more water, therefore limiting the benefit of using diuretic medications.
- Short study period so changes in outcomes seen in the short-term may not translate to longer periods of diuretic use
- This study focuses on proof-of-concept and is powered to detect a clinically important change in urine output; while we are measuring other outcomes, including patient reported outcomes, we may lack the power to detect meaningful differences that could be present in a large enough study
- Patients already taking diuretic medications may not tolerate stopping them; if this is the case, we will resume diuretic medications and continue the study protocol starting at the 3-week mark.



Can a pragmatic approach be used?

Why is this question suitable for a pragmatic study design?

Pragmatic

- Broad inclusion criteria; limited exclusion criteria
- Embedded in routine care (no extra follow up appointments)
- Usual hemodialysis bloodwork (nothing additional)
- Leverage the EMR for data collection
- Intervention is already frequently used in this population
- Patient-important outcomes

- Results: can be quickly and broadly implemented

Explanatory

- Individual patient consent
- *Dosing algorithm and medication management*

2. Feasibility Study

Multicenter, open-label, randomized controlled trial



Embedded in routine care, using a pragmatic approach

Recruitment and enrollment done by healthcare personnel who are part of usual care

No local trial coordinators, but site champions

Individual consent – potential role for electronic/video consent

All data obtained from electronic medical records

Broad inclusion criteria; few exclusion criteria

Routine follow up – no additional clinic visits



Randomized 1:1 to diuretic vs. no diuretic

Likely using a dose-titration protocol with goal of maintaining highest tolerated dose

Feasibility outcomes

01

Timely enrollment and follow up: enroll 100 participants and obtain baseline and follow up data within 12 months (hoping for 4 provinces; 2 sites per province)

02

Good adherence to protocol: goal >90% adherence

03

Adherence to allocation: goal >80% adherence

04

Satisfactory enrollment: Enroll at least 10 participants per hemodialysis unit

05

Identify and assess barriers to recruitment and enrollment to address prior to trial proper

06

Assess signals of harm

07

Determine success of pragmatic, embedded approach: able to conduct study with recruitment, consent and enrollment performed by routine staff rather than a research coordinator

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3. Trial Proper

If we are able to demonstrate that a pragmatic approach to this trial is feasible, we are hoping to proceed with a large-scale, multicenter, pragmatic RCT

Thank you



Ph.D. Supervisor

- Dr. Amit Garg

Ph.D. Committee

- Dr. Branko Braam
- Dr. PJ Devereaux
- Dr. Lehana Thebane

Study Team

- Judy Ukrainetz
- Dr. Claire Harris
- Cathy Du Val
- Laura Bennett

CIP Western

- Funding

Gardener's Grove organizers and facilitators



Questions?

Suggestions?

Interested in being involved?

Please feel free to email me with any questions, suggestions or interest in being involved:

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