



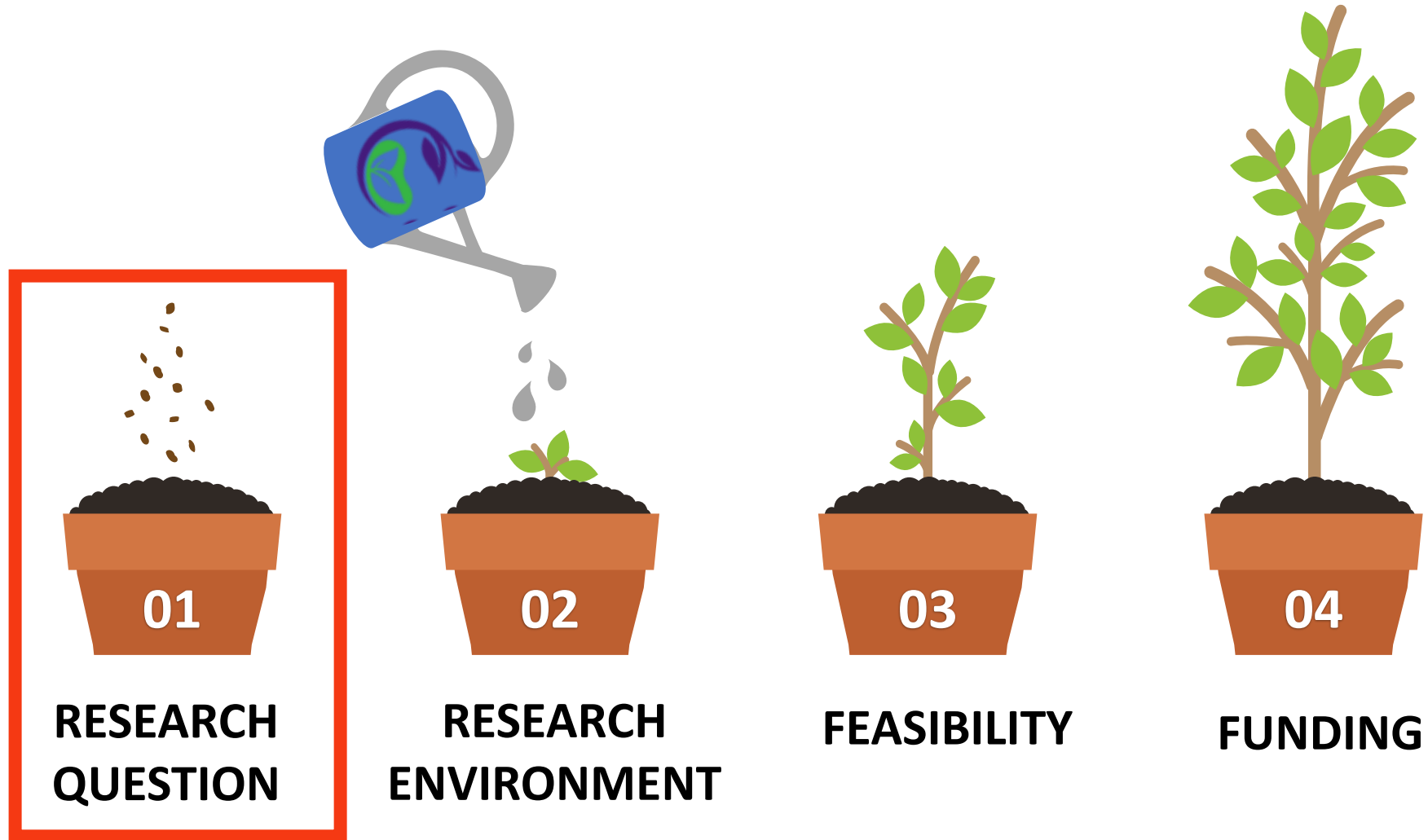
# SOLUTE Trial - Sodium fOr diaLysis oUTcome rEduction

Conor Judge, Xiaolu Deng, Srishi, David Keane, Alberto Alvarez-Iglesias, John Ferguson, Jia Wei Teh, Maria Geraghty, Donal Reddan, Matt Griffin, Mike Walsh, Martin O'Donnell



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GAILLIMHÉ  
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OF GALWAY

# Pragmatic Trials in Haemodialysis



# Adaptive Clinical Trials of Sodium Lowering in Chronic Kidney Disease and Dialysis: Analytic and Methodologic Challenges



RESEARCH  
QUESTION

Dr Conor Judge

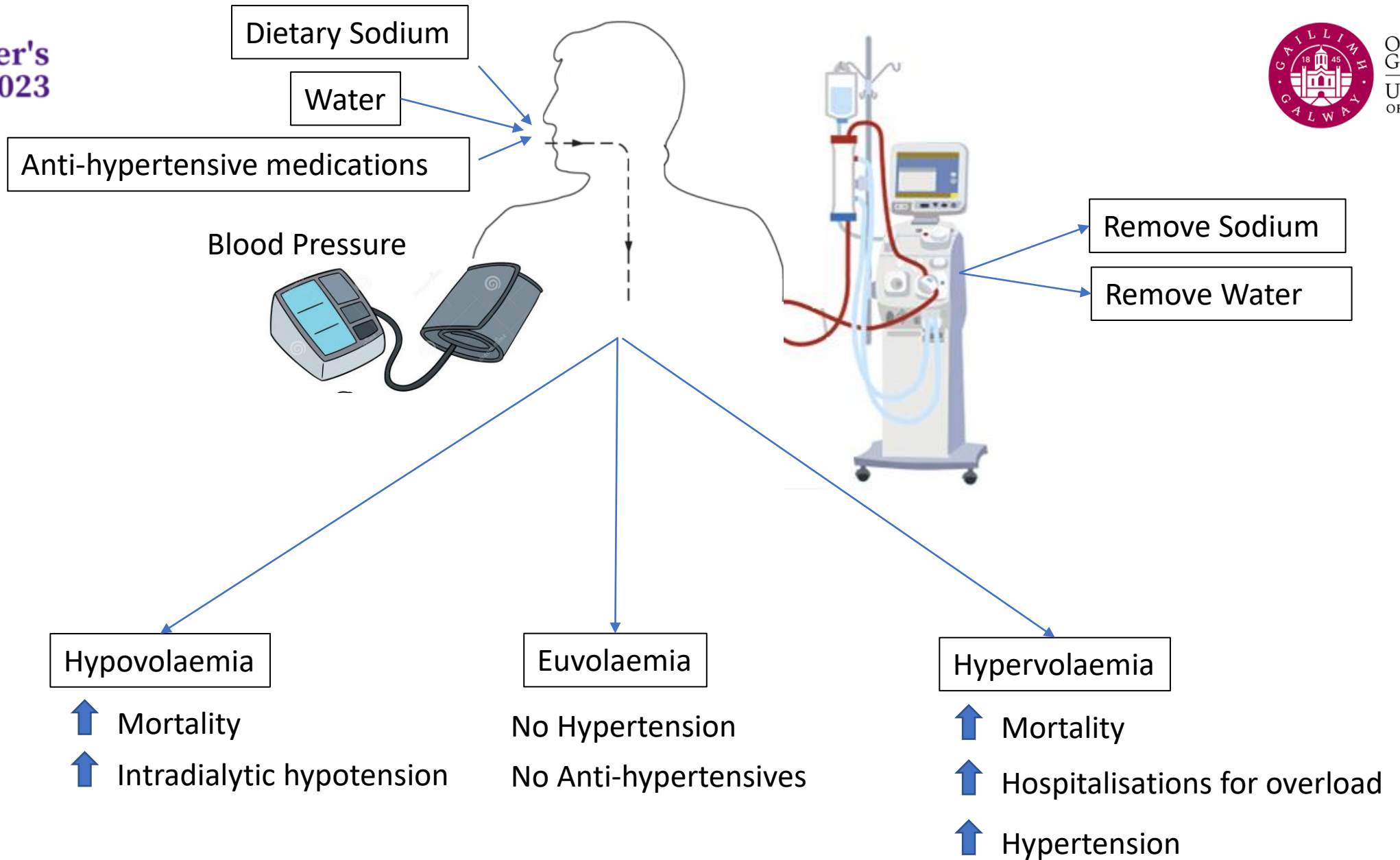
Supervised by:

Martin O'Donnell and Martin O'Halloran

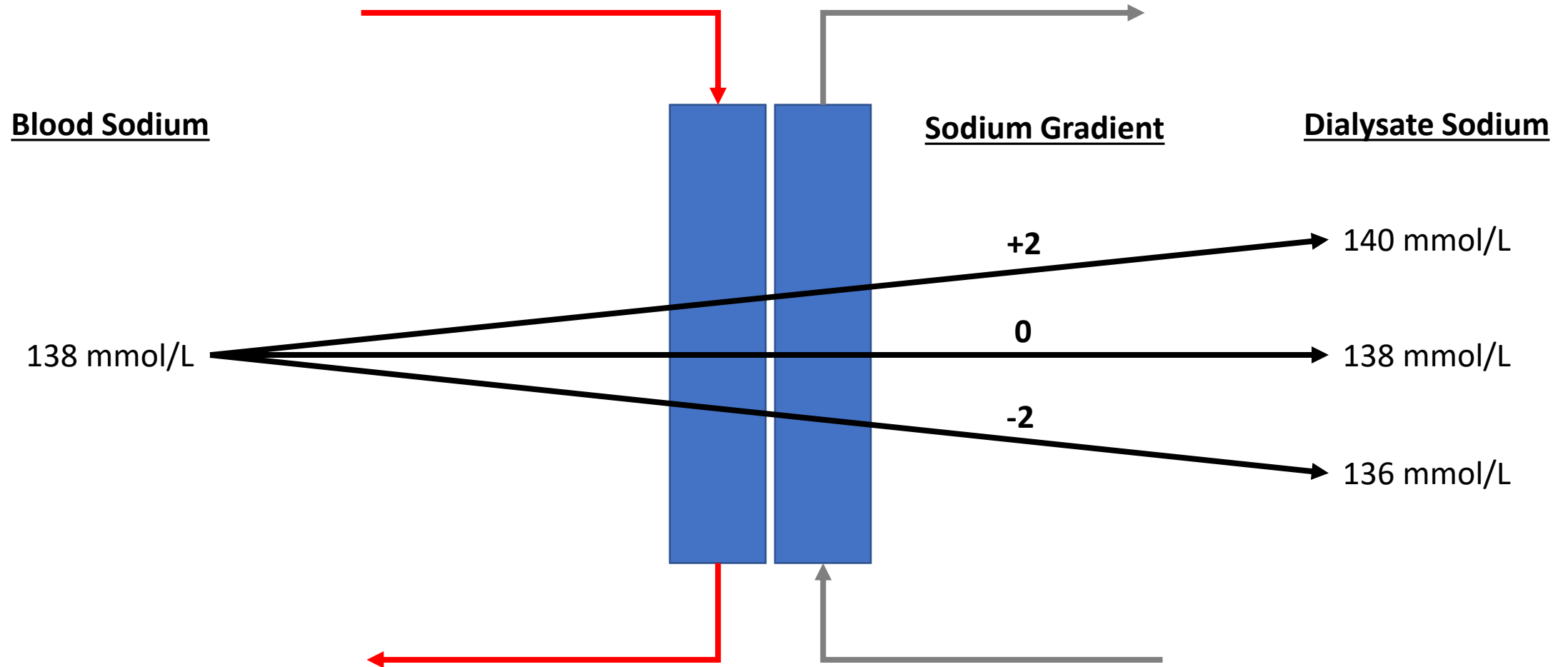




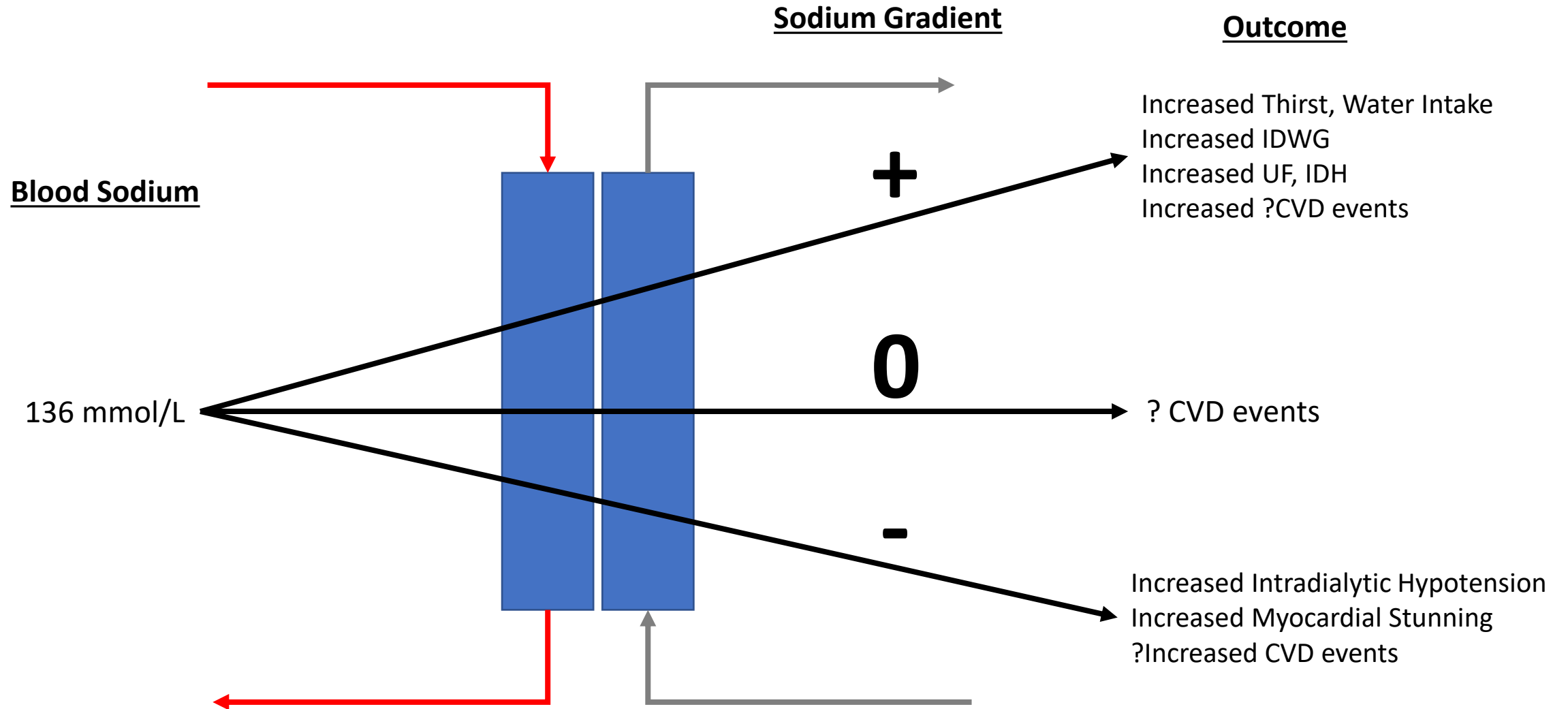
RESEARCH QUESTION

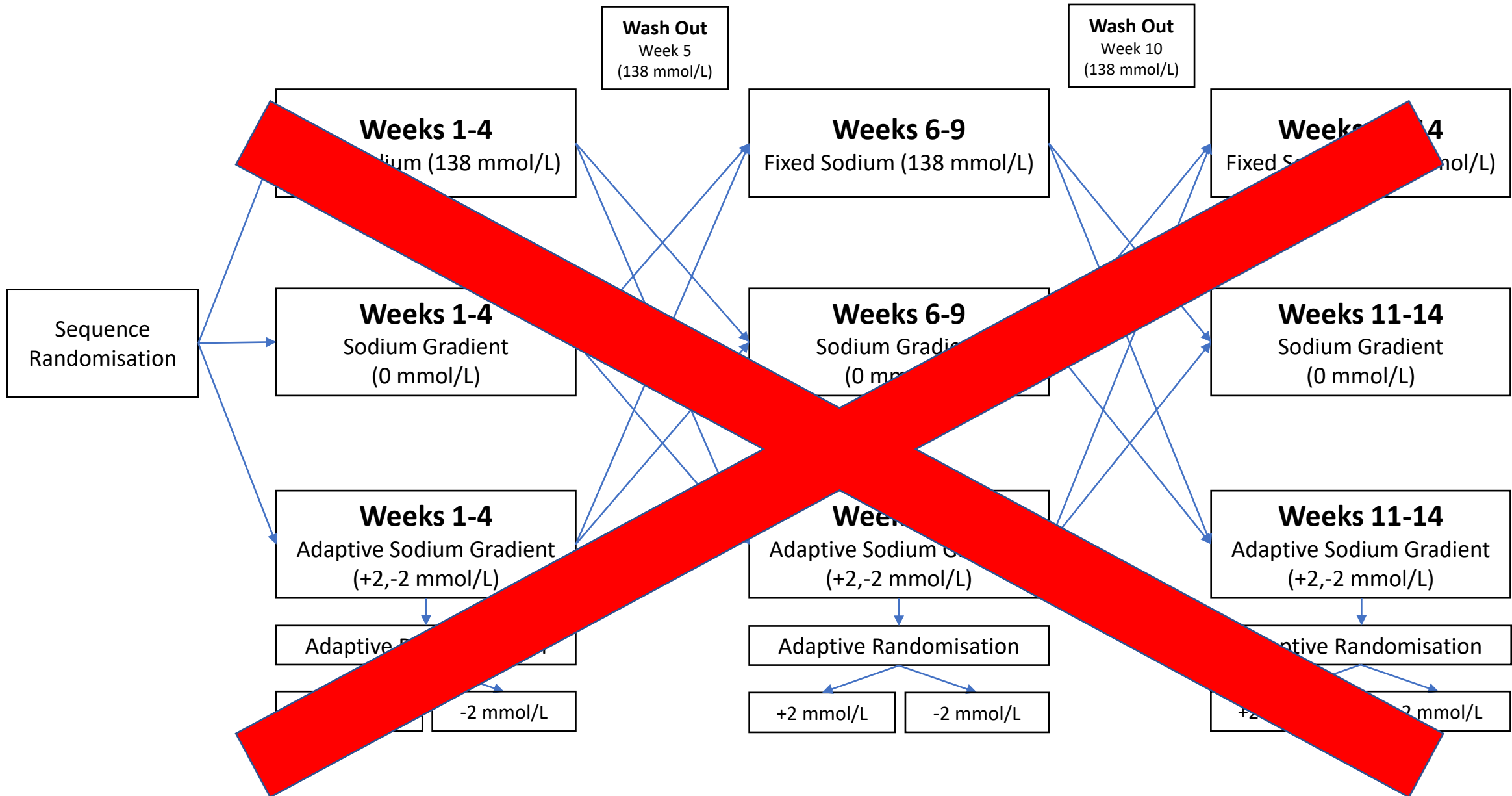


# Sodium Gradient



# Sodium Gradient

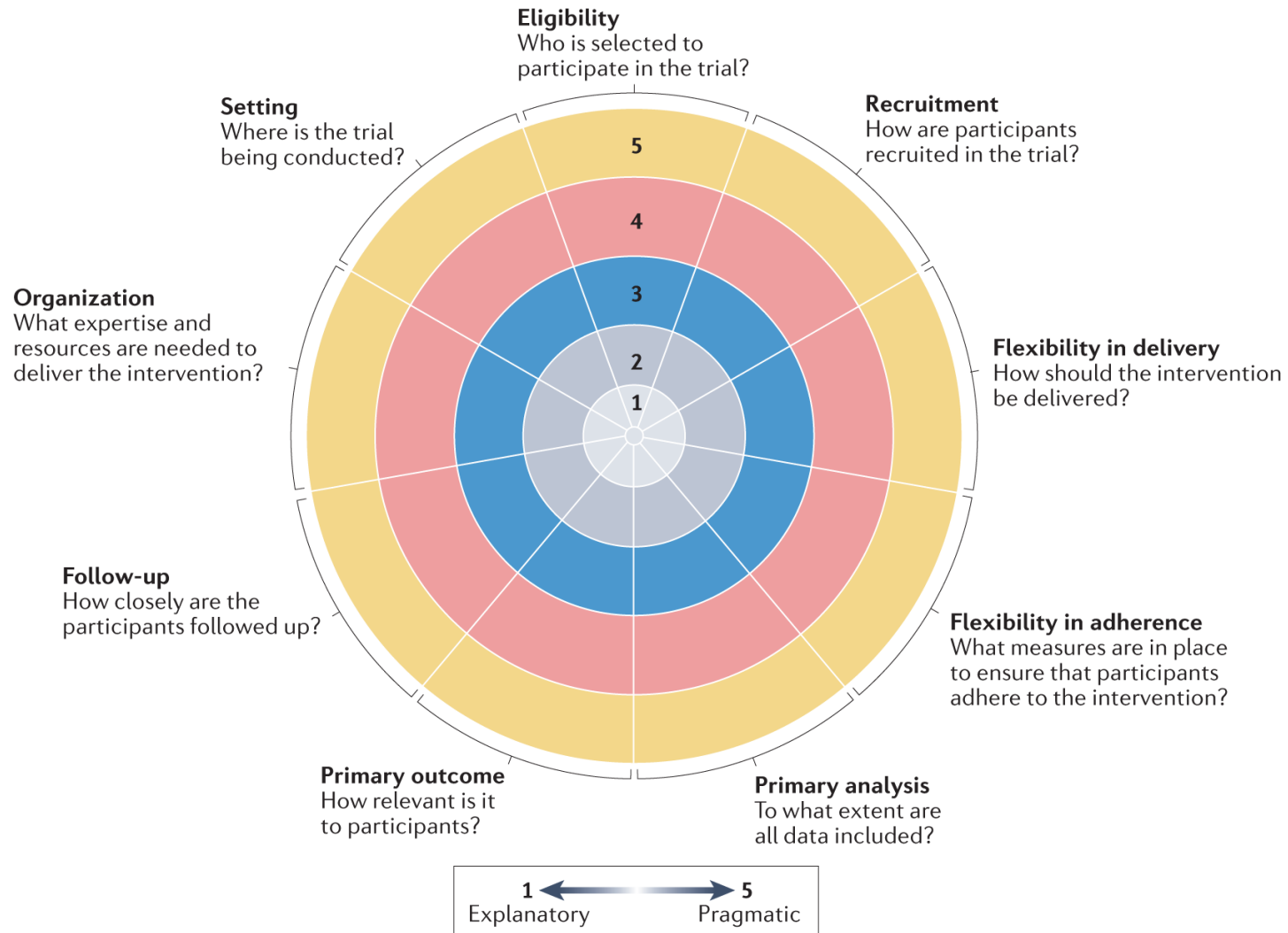


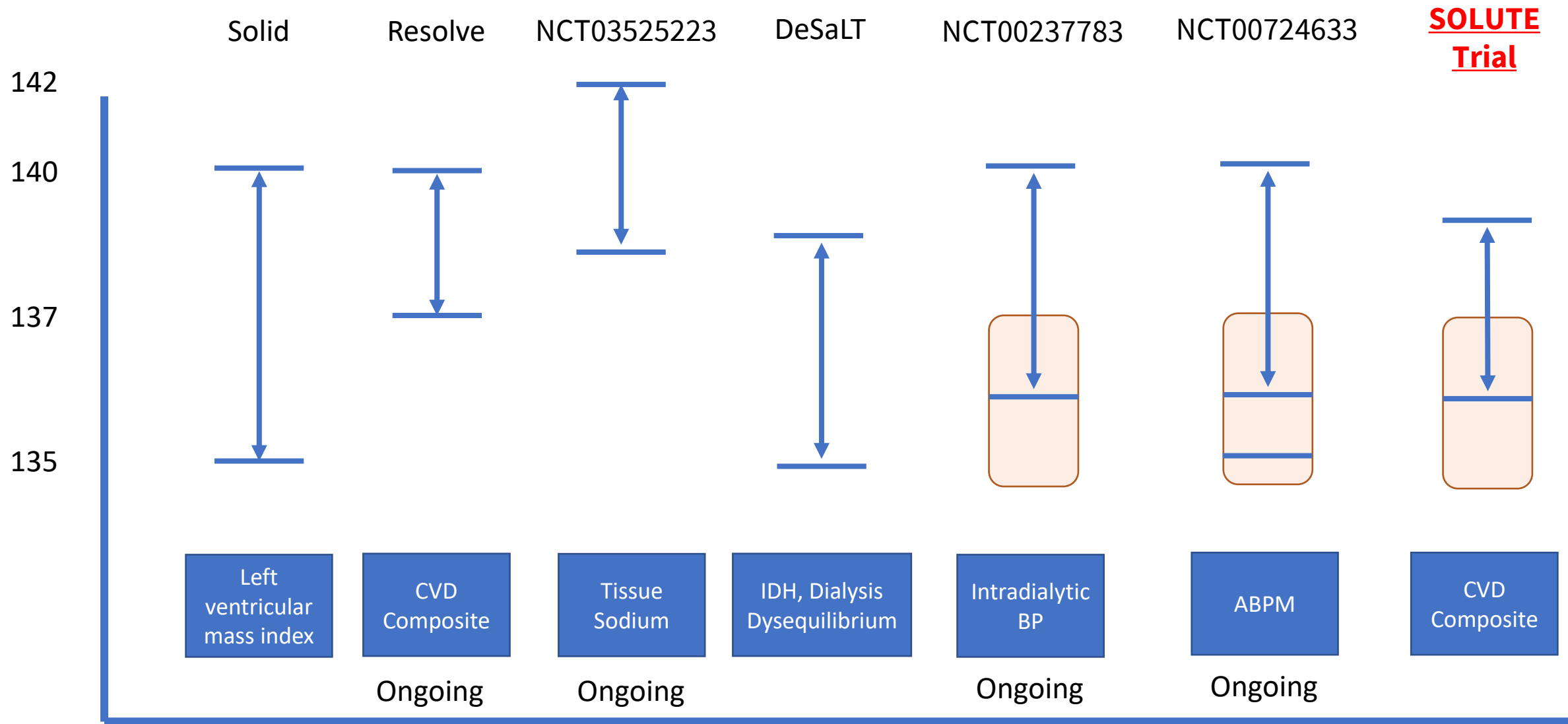


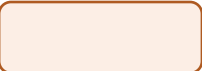
# Gardener's Grove Call



**RESEARCH  
QUESTION**





 = Individualised Dialysate Sodium

 = Dialysate Sodium

# Cochrane Systematic Review



01  
RESEARCH  
QUESTION



Cochrane  
Library

Cochrane Database of Systematic Reviews

## Low dialysate sodium levels for chronic haemodialysis (Review)

Dunlop JL, Vandal AC, Marshall MR

Dunlop JL, Vandal AC, Marshall MR.

Low dialysate sodium levels for chronic haemodialysis.

*Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No.: CD011204.

DOI: [10.1002/14651858.CD011204.pub2](https://doi.org/10.1002/14651858.CD011204.pub2).

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM) for chronic haemodialysis

Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM) for chronic haemodialysis (HD)

**Patient or population:** chronic HD

**Setting:** dialysis units

**Intervention:** Low dialysate [Na+] (< 138 mM)

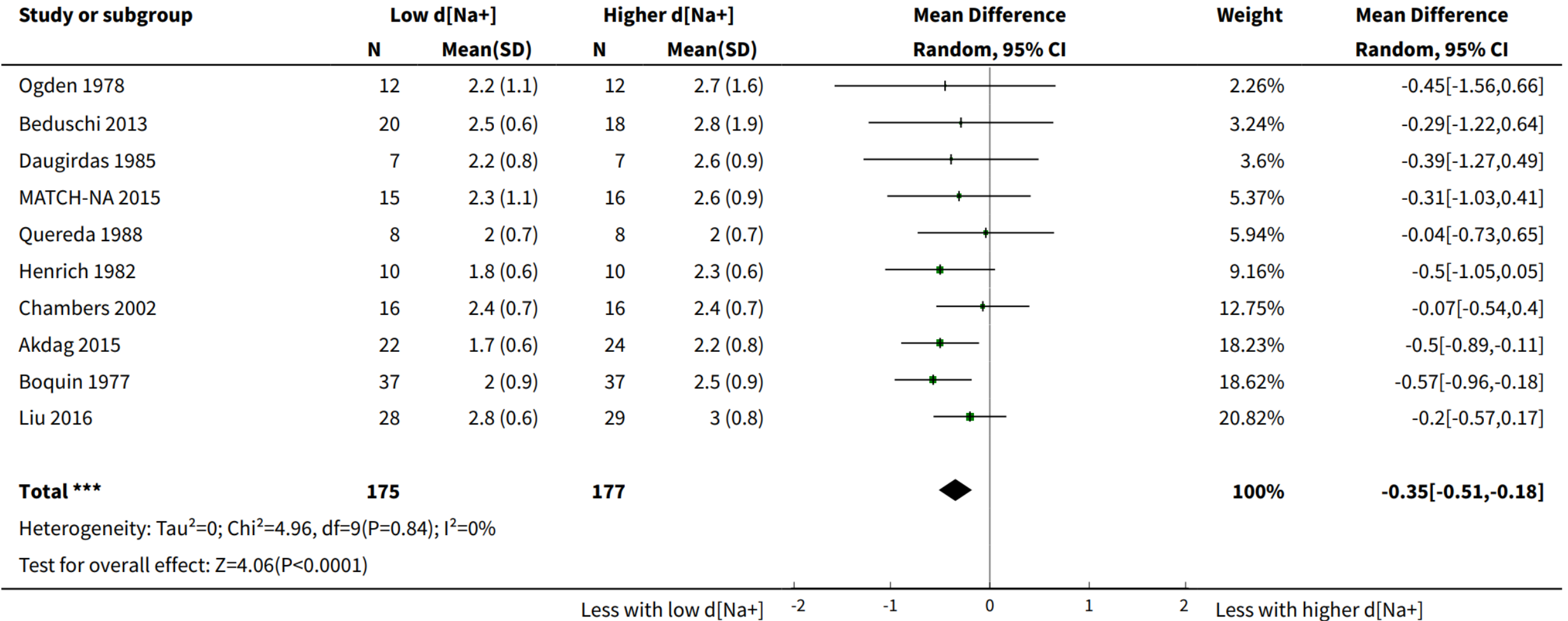
**Comparison:** neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)	Risk with Low dialysate [Na+] (< 138 mM)			
IDWG	The mean IDWG was 2.55 kg	MD 0.35 kg lower (0.51 lower to 0.18 lower)	-	352 (10)	⊕⊕⊕⊕ HIGH
Intradialytic hypotension	110 per 1,000	167 per 1,000 (125 to 222)	RR 1.52 (1.14 to 2.02)	12,570 (7)	⊕⊕⊕⊖ MODERATE 1
Predialysis MAP	The mean predialysis MAP was 104.6 mmHg	MD 3.58 mmHg lower (5.46 lower to 1.69 lower)	-	156 (4)	⊕⊕⊕⊖ MODERATE 2
Postdialysis MAP	The mean postdialysis MAP was 101.0 mmHg	MD 3.26 lower (4.82 lower to 1.7 lower)	-	150 (4)	⊕⊕⊕⊖ MODERATE 2
Antihypertensive medication	The mean number of antihypertensive medications was 3.1	SMD 0.67 SD lower (1.07 lower to 0.28 lower)	-	103 (2)	⊕⊕⊖⊖ LOW 3
Predialysis serum [Na+]	The mean predialysis serum [Na+] was 138.3 mM	MD 1.69 lower (2.36 lower to 1.02 lower)	-	258 (7)	⊕⊕⊕⊖ MODERATE 4
Intradialytic cramps	74 per 1,000	130 per 1,000 (85 to 201)	RR 1.77 (1.15 to 2.73)	12,186 (6)	⊕⊕⊕⊖ MODERATE 5

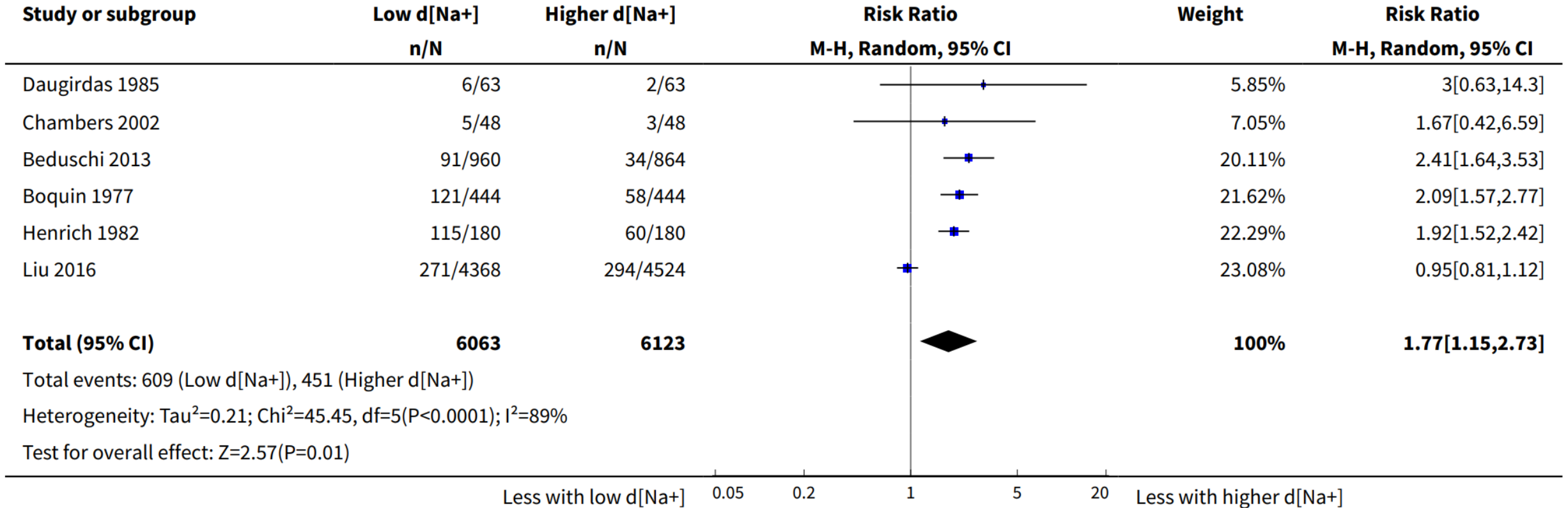
\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** mean difference; **SMD:** standardised mean difference

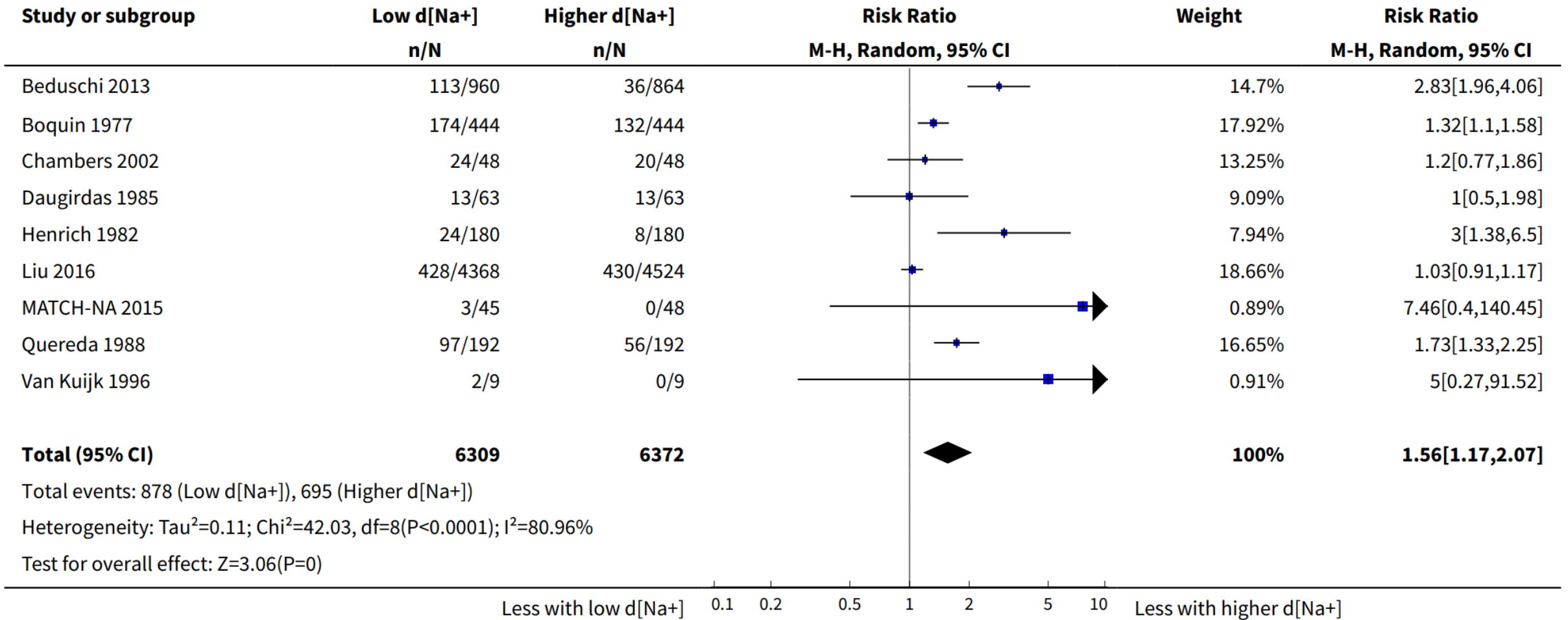
**Analysis 1.1. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 1 Interdialytic weight gain.**



### Analysis 1.7. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 7 HD sessions complicated by intradialytic cramps.



## Analysis 1.8. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 8 HD sessions complicated by intradialytic hypotension.





# Intervention Versus Control



## RESEARCH QUESTION

<u>Intervention sodium</u>	<u>Control sodium</u>
155->140_ramped	140
155->140	140
147->138	139
147->138	139
138->135	138
138->135	138
Zero Gradient	138
Zero Gradient	138
Zero Gradient	138
140->137	140
136	138
150->138	138
138	138
Zero Gradient	138
146->Serum sodium( 135 or 137)	138
135 or 137	138
Zero Gradient	138
Zero Gradient	138
145->138	138
Zero Gradient (136/ 138 / 140)	136 / 138



RESEARCH  
QUESTION

# Background

- The dialysate sodium concentration can easily be adjusted on modern hemodialysis machines, varied across the participating dialysis centers,
  - ranging from 136 to 140 mmol/L, with a median of 138 mmol/L in Ireland and
  - from 136 to 149 mmol/L, with a median of 140 mmol/L in Ontario

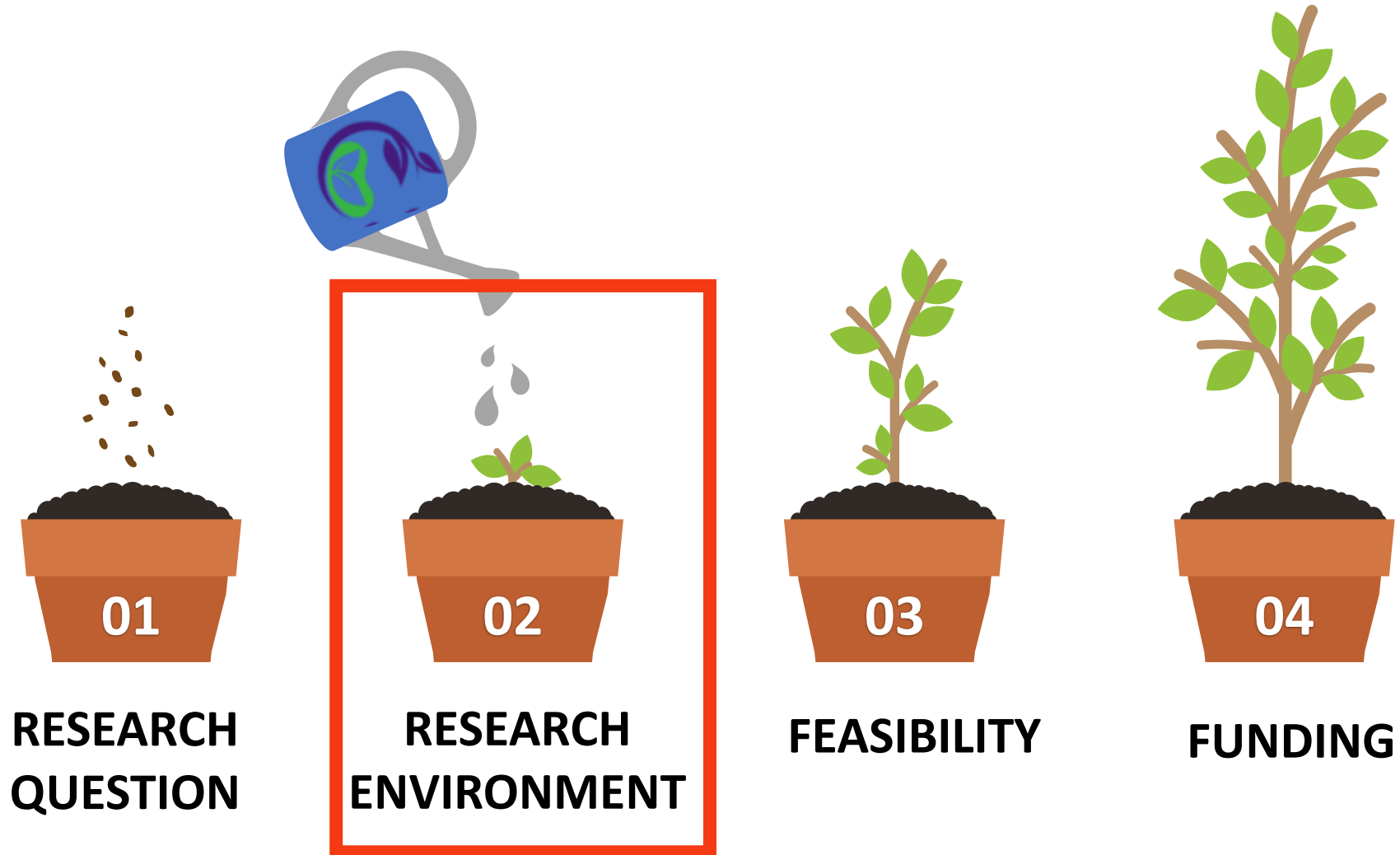


RESEARCH  
QUESTION

# Research Question

- P – Persons with kidney failure requiring dialysis
- I – Zero sodium gradient (Serum  $\text{Na}^+$  minus Dialysate  $\text{Na}^+$ )
- C – Fixed Dialysate Sodium (138 mmol/L)
- O – Composite of major cardiovascular events (hospitalized acute myocardial infarction, hospitalized stroke, and hospitalized heart failure) and cardiovascular-related death
- T – 4 years

# Pragmatic Trials in Haemodialysis



# Pragmatic Registry Based Trial



RESEARCH  
ENVIRONMENT

Fundamental component of a registry based  
trial is a registry!



Feidhmeannacht na Seirbhíse Sláinte  
Health Service Executive



RESEARCH  
INFRASTRUCTURE

# Irish Renal Registry

23/11/2022



Trinity College Dublin  
Coláiste na Tríonóide, Baile Átha Cliath  
The University of Dublin



# Rationale



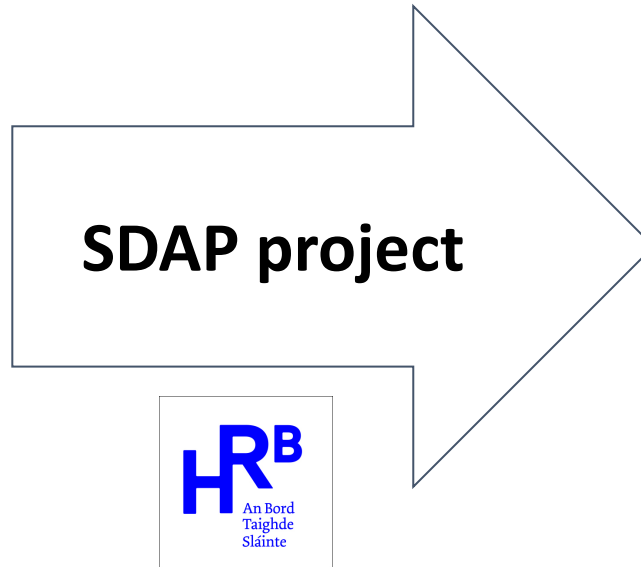
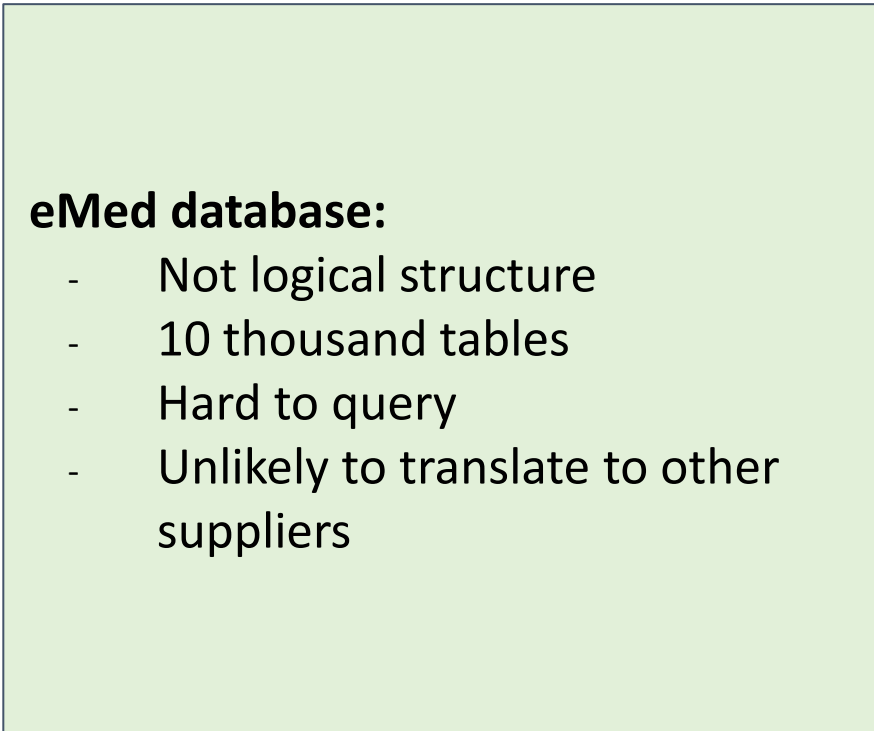
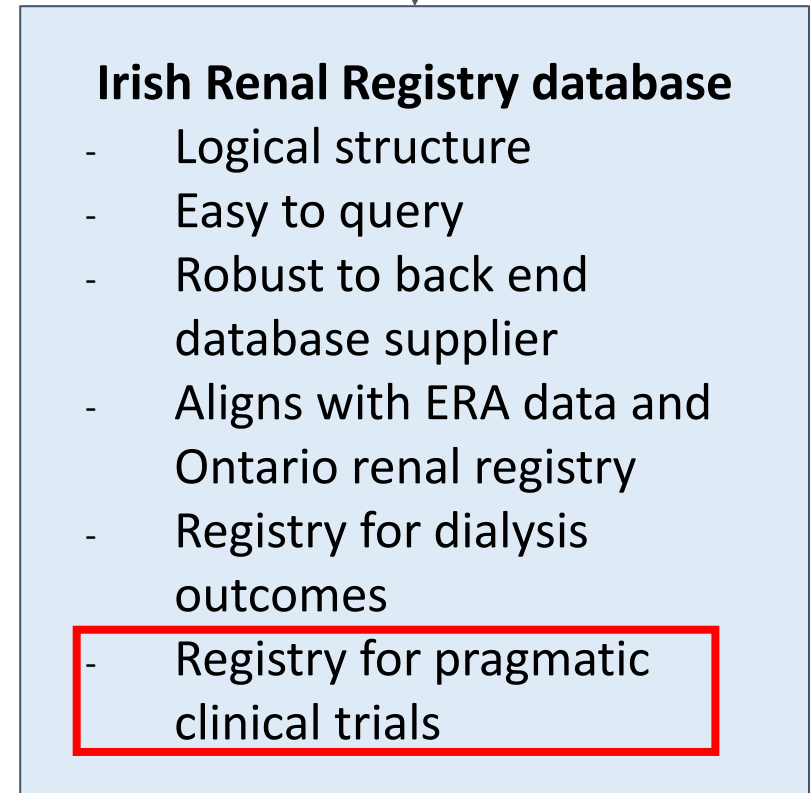
RESEARCH  
INFRASTRUCTURE

- The Kidney Disease Clinical Patient Management System (KDCPMS) is the national renal IT system, collecting clinical data on all dialysis patients in Ireland
- eMed currently not currently set up as a registry with collection of standardised common data elements, validation and regular reporting
- An multi-university, multi-agency Irish Renal Registry would provide the governance, technical, consent and accessibility for use of routinely collected data (research and quality improvement)



Dr David Keane

Dr James Tattersall  
Co-creator of eMed



**eMed database:**

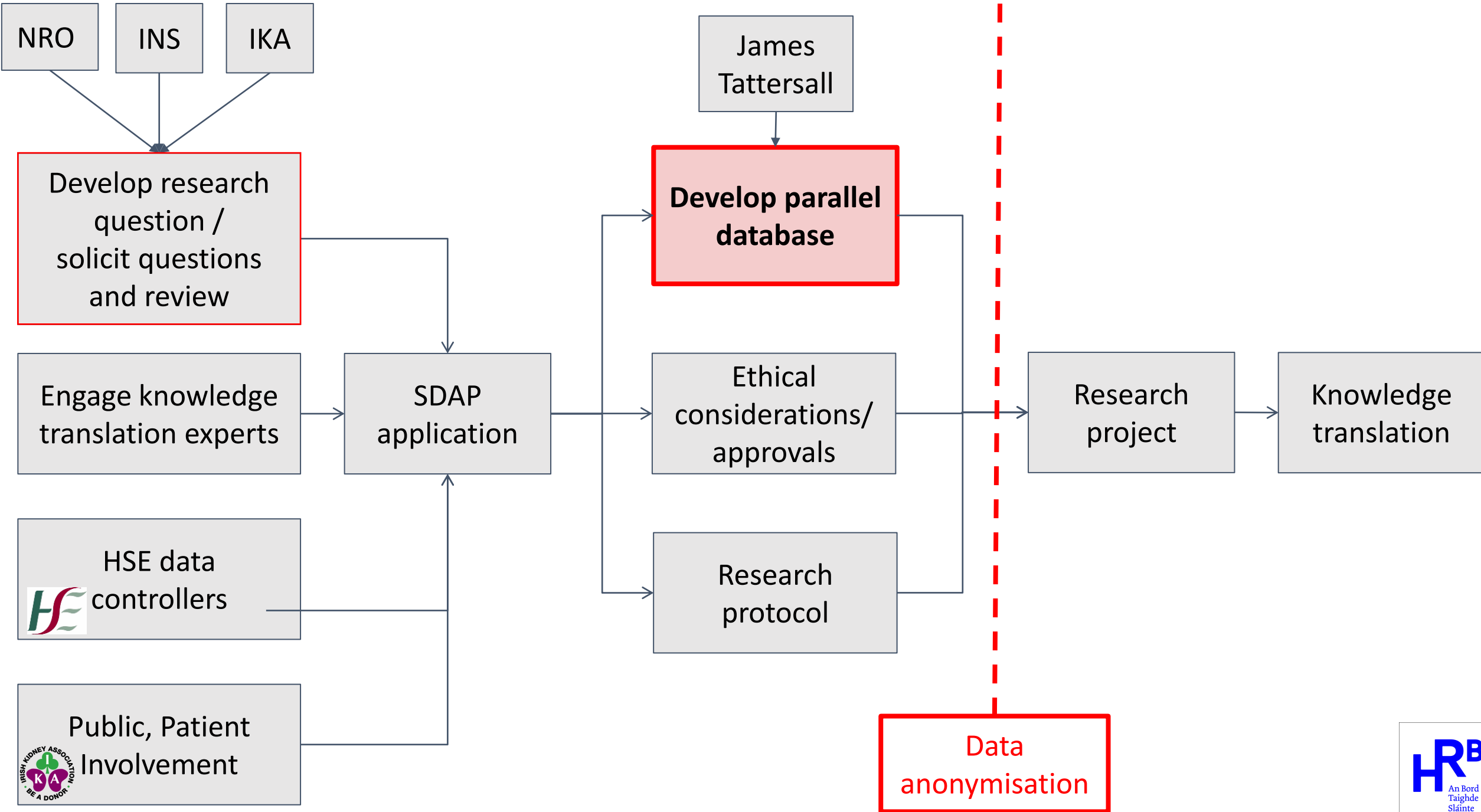
- Not logical structure
- 10 thousand tables
- Hard to query
- Unlikely to translate to other suppliers

**SDAP project**



**Irish Renal Registry database**

- Logical structure
- Easy to query
- Robust to back end database supplier
- Aligns with ERA data and Ontario renal registry
- Registry for dialysis outcomes
- **Registry for pragmatic clinical trials**





02

# RESEARCH INFRASTRUCTURE

NR O    IN S    IK A

Develop research question / solicit questions and review

Engage knowledge translation experts

HSE data controllers

Public, Patient Involvement

SDAP application

Data Linkage to CSO Mortality Data

Registry for Pragmatic Trials

Align variables with ICES Renal Variables

Align variables with ERA-Registry

Develop parallel database

Ethical considerations/approvals

Research protocol

Research project

Knowledge translation

Data anonymisation



# Challenges



## RESEARCH INFRASTRUCTURE

- Needs buy in from key stakeholders
  - National Renal Office (Knowledge User)
  - Office of Clinical Information Officer (Data Controller)
  - Irish Kidney Association (Patient Voice)
  - Irish Nephrology Society (Knowledge Users)
  - Irish Nephrology Society Research Committee (Steering group)
- Research question must be relevant to clinical practice
  - Transparent selection processs for question
  - Important to Irish Nephrology Community
- Planning sustainable management of the registry beyond the HRB award
  - Either HSE or Ongoing Project Grants

# Outcomes



## RESEARCH INFRASTRUCTURE

1. High quality Irish dialysis research
  - Questions of both national and international importance
2. Irish Renal Registry created by and for whole Irish renal community
  - Multi-university, multi-agency, multi-disciplinary, registry
  - Feeds ERA renal registry
3. Focus on training and developing research capacity in Irish Nephrology
  - Irish Renal Registry Fellowship for SpRs or Multi-disciplinary team
4. Enhanced capability of dialysis clinical trials
  - Pragmatic registry trials
  - Data aligned with ERA and Ontario Renal Registry

# Data Linkage



RESEARCH  
INFRASTRUCTURE

- CSO Mortality Data
- National Office of Clinical Audit (Stroke, Myocardial Infarction)
- Primary Care Reimbursement Service (Medications)
- Hospital In-Patient Enquiry (HIPE) Data



An  
Phríomh-Oifig  
Staidrimh

Central  
Statistics  
Office

**NOCA** National Office of  
Clinical Audit

National Renal Office



Prof George Mellotte

European Renal Association



Prof Kitty Jager

Irish Kidney Association



Carol Moore

Royal College of Surgeons



Prof Peter Conlon



Prof Conal O' Seaghda

University of Limerick

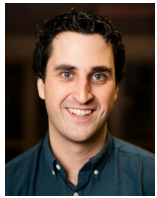


Prof Austin Stack



Dr Leonard Browne

University of Galway



Dr Conor Judge



Dr David Keane



Dr Paul O'Hara



Dr Alberto Alvarez-Iglesias



Dr John Ferguson



Prof Donal Sexton



Prof Mark Little

Trinity



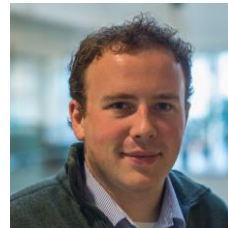
Prof Donal Reddan



Prof Matthew Griffin



Prof Martin O'Donnell



Prof Andrew Smyth

University College Cork



Dr Sarah Moran



Prof Joe Eustace

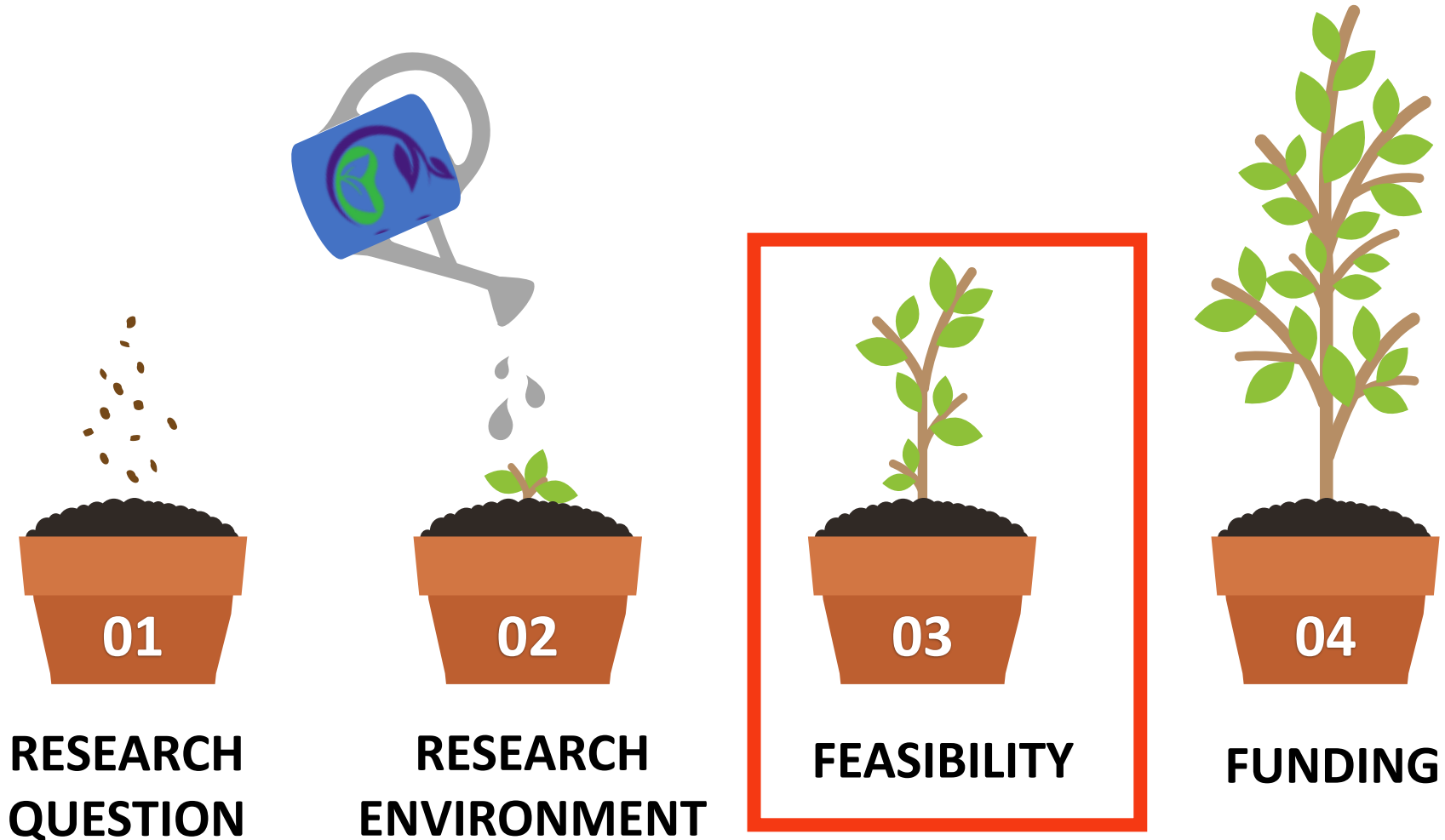


# Public Service Innovation Fund



**RESEARCH  
INFRASTRUCTURE**

# Pragmatic Trials in Haemodialysis





OLLSCOIL NA GAILLIMHE  
UNIVERSITY OF GALWAY

# The Team



Dr Conor Judge



Dr David Keane



Dr Jia Wei Teh



Ms Maria Geraghty



Dr Alberto Alvarez-Iglesias



Dr John Ferguson



Prof Donal Reddan



Prof Matthew Griffin



Prof Michael Walsh



Prof Martin O'Donnell

# Precis-2 wheel for SOLUTE trial



**FEASIBILITY**

# Justification for Cluster Randomisation



FEASIBILITY

- Justification for Cluster Randomisation
  - Hemodialysis patients receive all their treatments at the same centre.
  - HD Nurses follow a standard protocol for all patients under their care
  - For centres randomized to the intervention, nurses will check the result of serum sodium from monthly bloods and set the dialysate sodium to this number.
  - If there was individual prescriptions, this would increase the cross-group contamination.
    - For example, the same nurse cares for different patients in a dialysis centre and if the nurse observed that a patient with zero sodium gradient dialysis had fewer intra-dialytic hypotensive episodes, they may decide to apply this intervention to a patient randomised to the control group, negating the randomisation and contaminating the control group.

Describe how your trial is suitable for implementation as a large multi-centre randomized controlled trial



FEASIBILITY

- Clinical Equipoise
  - Wide variation in dialysate sodium in dialysis centers ranging from 136 to 149 mmol/L, with a median of 140 mmol/L.
- Routine Data Collection
  - Serum sodium (monthly) dialysis bloods so no extra testing resources would be required by local centres or study coordinators.
  - Outcome data (hospitalization, stroke, MI, CVD death), secondary outcome data (BP, IDWG) and adherence data (serum/dialysate sodium) are all routinely collected.
- Intervention
  - Dialysate sodium concentration can be easily modified on modern hemodialysis machines (variation between delivered and prescribed).

# Altered Consent?



FEASIBILITY

- Criteria for altered patient consent (Tri-Council Policy Statement)
  1. The research poses a clear benefit to society and unlikely to adversely affect patient welfare; **Yes, level of evidence?**
  2. The intervention was considered to be of minimal risk to patients (similar to a quality-control measure that could be implemented by a dialysis centre director);  
**Likely, need to confirm with ongoing systematic review**
  3. An informed consent model is impossible and impracticable given our research design and resources; **Yes**
  4. There is a plan to provide a debriefing which also offers patients the possibility of refusing the intervention **Unsure; what was this?**

# Personalised Medication at a policy level



FEASIBILITY

- The zero serum to dialysate sodium gradient approach presented in this trial takes into account individual dietary, residual function and sodium set point.



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Open Access Opinion

## How to Adjust the Sodium Concentration in Dialysate Individually and Practically?

by Jingjing Zhang

Division of Nephrology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA

*Kidney Dial.* 2021, 1(2), 161-163; <https://doi.org/10.3390/kidneydial1020023>

Received: 7 September 2021 / Revised: 16 November 2021 / Accepted: 22 November 2021 /

Published: 14 December 2021

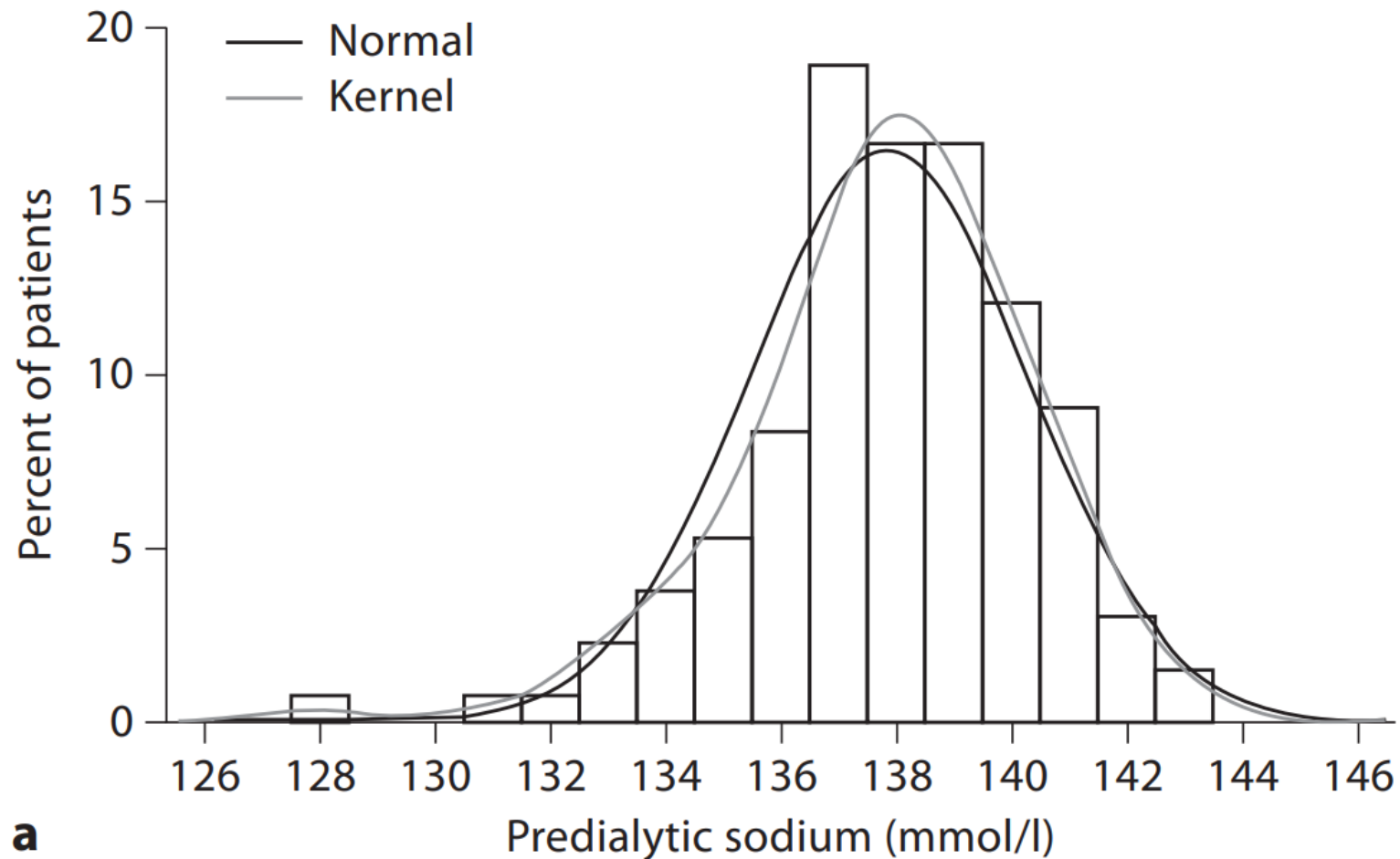
(This article belongs to the Special Issue [Expert Opinions on the \(Hemo\)dialysate Sodium Prescription](#))

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Review Reports

Versions Notes

# Personalised Medication at a policy level



**a**

# Eligibility Criteria



FEASIBILITY

- This trial had 3 inclusion criteria at the level of the hemodialysis center:
  - HD centre >50 outpatients
  - The medical director of the hemodialysis center must be willing to have their center use a randomized policy for dialysate sodium concentration for the duration of the trial.
  - The hemodialysis center must ensure that it can keep primary outcome data (hospitalized acute myocardial infarction, hospitalized stroke, hospitalized heart failure, and cardiovascular related death), secondary outcome data (blood pressure, interdialytic weight gain, and intradialytic hypotension) and adherence data (serum and dialysate sodium concentration).

# Trial Design

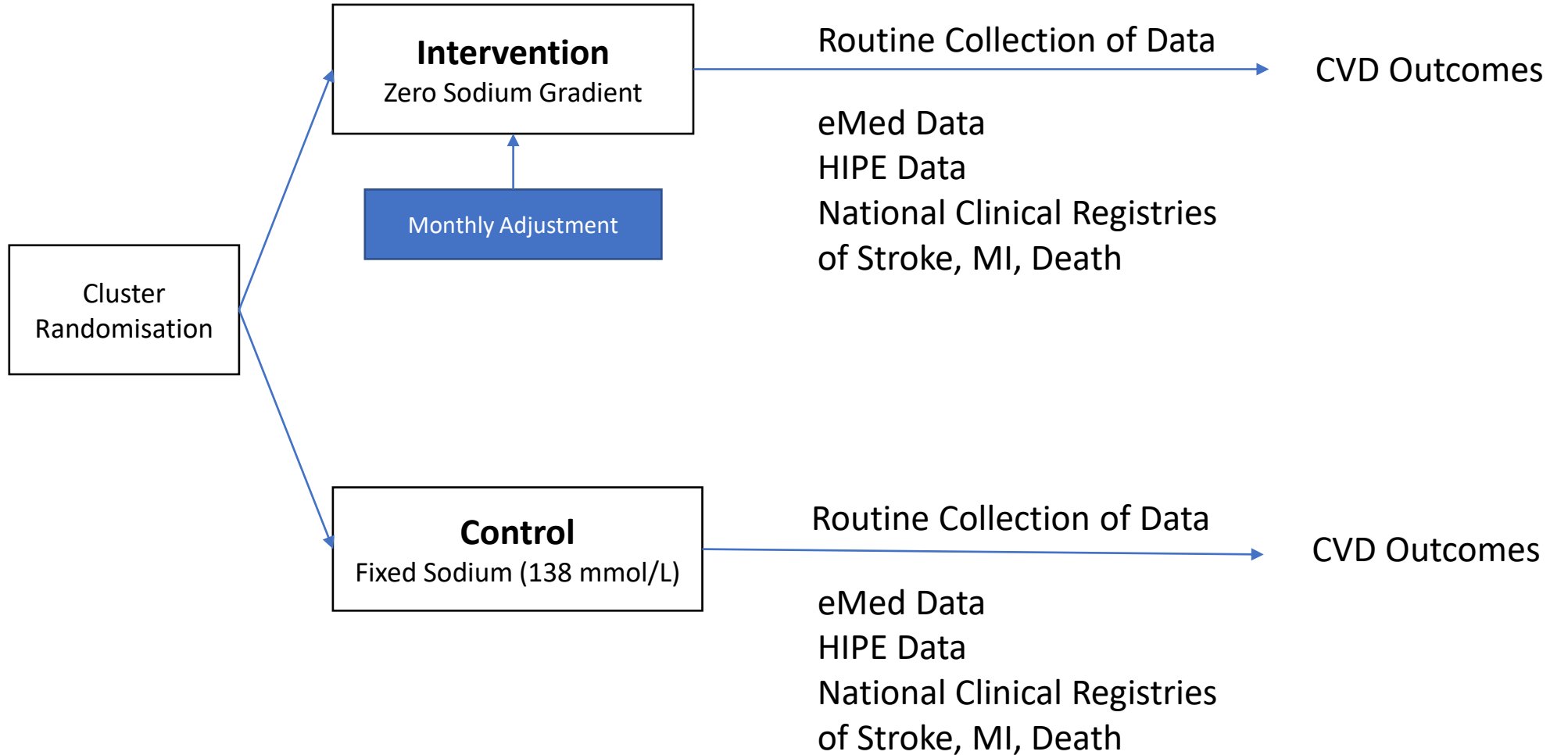


FEASIBILITY

- Cluster Randomized Clinical Trial Versus Individual Level Randomisation
- Phase III
- Outcome-assessment-blinded
- Pragmatic, Registry Data
- Primary outcome:
  - Cardiovascular events (hospitalized acute myocardial infarction, hospitalized stroke and CVD mortality)
- Secondary outcome:
  - Interdialytic Weight Gain (IDWG); Intradialytic Hypotension (IDH)



FEASIBILITY



# Protocol adherence



FEASIBILITY

- Individual patients, in consultation with their nephrologist, may choose to use different dialysate sodium concentrations if necessary.
- In this pragmatic trial, we aim to have at least 90% adherence to the centrally assigned regimen at any given time.

# Implementation Strategy



FEASIBILITY

- Individual patients, in consultation with their nephrologist, may choose to use different dialysate sodium concentrations if necessary.
- In this pragmatic trial, we aim to have at least 90% adherence to the centrally assigned regimen at any given time.

# Ethical Considerations



FEASIBILITY

- Research ethics approval will be obtained for the trial
- Written consent for enrollment, receipt of the assigned sodium regimen, and data collection were waived.
- All patients undergoing hemodialysis at participating centers will be informed about the trial and about their right to opt out of the assigned treatment at their center.
- PPI focus group with the Irish Kidney Association (HRB SDAP)

# Goals, timelines, deliverables, and funding support



## FEASIBILITY

- Goal
  - Develop a grant ready protocol for an international trial (Canada/Ireland) to submit to funding bodies
- Administrative support
  - What would this look like?
- Partnership liaising
  - Public, patient and carer involvement in research
    - PPI Focus Group in Ireland and Canada
  - Active participation of hemodialysis patient on protocol development
    - Both Irish and Canadian
- Ethical analysis
  - Altered consent process
  - How was this done for MyTemp in Canada? Can we emulate this?
  - PPI Focus Group for Irish Altered Consent
- Analysis of existing data sources
  - Ontario Data for sample size calculations
  - Irish Data (eMedRenal) for sample size calculations
  - Development of backend data infrastructure on eMed

# Potential Sample Size



FEASIBILITY

- all haemodialysis patients in Ontario (15,000 patients)
  - 84 haemodialysis centres, fewer clusters
  - Overflow centers combined
- all haemodialysis patients in Ireland (~2,000 patients)
  - 23 haemodialysis centres




## FEASIBILITY

- Reasons for Cluster Level Analysis
  - “individual-level analysis approaches can lead to an inflated type I error rate when the number of clusters is small”
  - “The minimum number of clusters required to maintain the type I error rate at 5% has been suggested to be around 30–40 clusters for mixed models and 40–50 for GEEs”
  - “three reviews of CRTs found median numbers of 21, 25 and 34 of clusters randomized”
- Reasons for Individual Level Analysis
  - Individual with a cluster adjustment (correlation within cluster)
  - “typically lead to higher power and allow adjustment for covariates in a more straightforward way than cluster-level methods”

### JOURNAL ARTICLE

## Cluster randomized trials with a small number of clusters: which analyses should be used?

Clémence Leyrat , Katy E Morgan, Baptiste Leurent, Brennan C Kahan

*International Journal of Epidemiology*, Volume 47, Issue 1, February 2018, Pages 321–331,

<https://doi.org/10.1093/ije/dyx169>

**Published:** 23 August 2017 **Article history** ▼

<b>Outcomes</b>	<b>ICC †</b>	<b>lower 95% CI‡</b>	<b>upper 95% CI‡</b>	<b>CV§</b>
Primary composite cardiovascular outcome	0.008	0.006	0.015	0.2694
Individual components of the primary composite cardiovascular outcome				
Cardiovascular mortality	0.009	0.006	0.016	0.38127
Hospital admission with myocardial infarction	0.002	0.002	0.006	0.31357
Hospital admission with ischaemic stroke <sup>¶</sup>	0.000	0.000	0.004	n/a
Hospital admission with congestive heart failure	0.009	0.007	0.015	0.32671
All-cause mortality or a cardiovascular-related hospital admission	0.018	0.013	0.032	0.29837
All-cause mortality	0.021	0.015	0.032	0.32802
Non-cardiovascular mortality	0.011	0.008	0.019	0.35376

n/a, not applicable

† Kalia et al. (2016) show that there are negative biases when using the binary censoring indicator or the continuous event times to calculate the ICC. However, the recommendation is to use the binary censoring indicator if there is more than minimal censoring (i.e., > 5%) is observed, which we have done here. Calculating the ICC based on the binary censoring indicator is also recommended by Campbell and Walters (2014).

‡ We used 200 bootstrap samples, sampling at the cluster level, to obtain the 2.5 and 97.5 percentiles to obtain the 95% CI.

§ CV calculated based on Hayes and Moulton (2017).

¶ we found a 0 ICC for hospital admission with ischaemic stroke. Because of the within/between variance, the CV could not be calculated. For this outcome, we could assume a very minimal, if any correlation.

# Replicate myTemp Sample Size (Alberto)

For a cluster-randomized trial, suppose now there are  $y$  person-years of follow-up in each cluster. Then  $c$ , the number of clusters required, is given by:

$$c = 1 + (z_{\alpha/2} + z_{\beta})^2 [(\lambda_0 + \lambda_1)/y + k^2(\lambda_0^2 + \lambda_1^2)] / (\lambda_0 - \lambda_1)^2 \quad (2)$$

In this formula,  $k$  is the coefficient of variation (SD/Mean) of the true rates between clusters within each group. Estimation of  $k$  is discussed in a later section.

Review > [Int J Epidemiol. 1999 Apr;28\(2\):319-26. doi: 10.1093/ije/28.2.319.](#)

## Simple sample size calculation for cluster-randomized trials

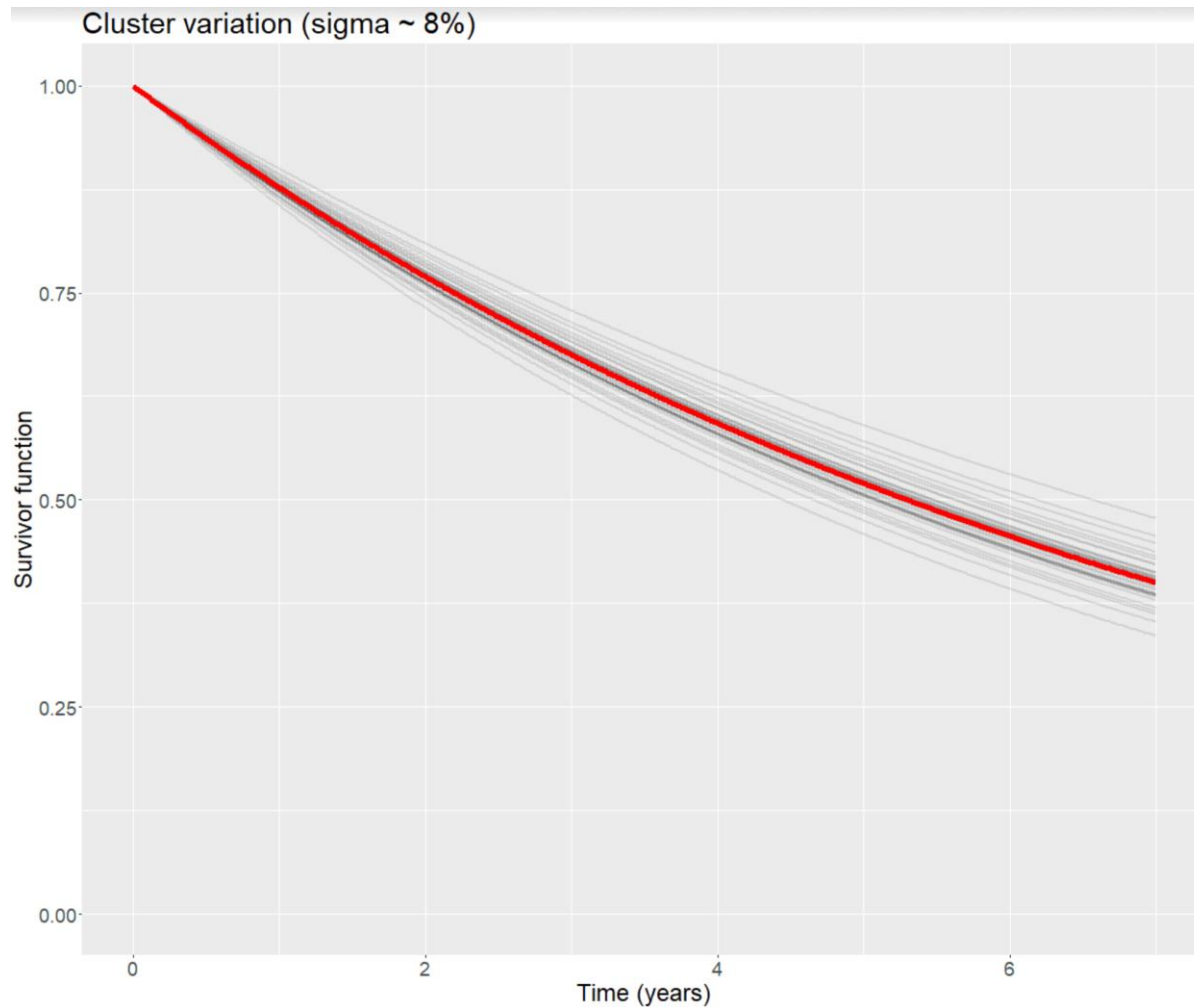
R J Hayes <sup>1</sup>, S Bennett

```
>
> lambda_0 <- 0.095
> lambda_1 <- lambda_0*0.8
> zalphahalf <- abs(qnorm(0.04/2))
> zbeta <- abs(qnorm(0.2))
> k <- 0.216
> y <- 163
>
> cc <- 1+ (zalphahalf + zbeta)^2 * ( (lambda_0 + lambda_1)/y + k^2*(lambda_0^2 + lambda_1^2) ) / (lambda_0 - lambda_1)^2
> cc
[1] 41.39794
```

# Variability in Cluster Size

- Variability in cluster sizes was accounted for by using the harmonic mean of person-time years in the sample size calculation, as suggested by Hayes and Moulton (2017).

# Simulation - Sample Size



This is likely to be bigger

SD assumed here 0.08 (CoV 0.14)

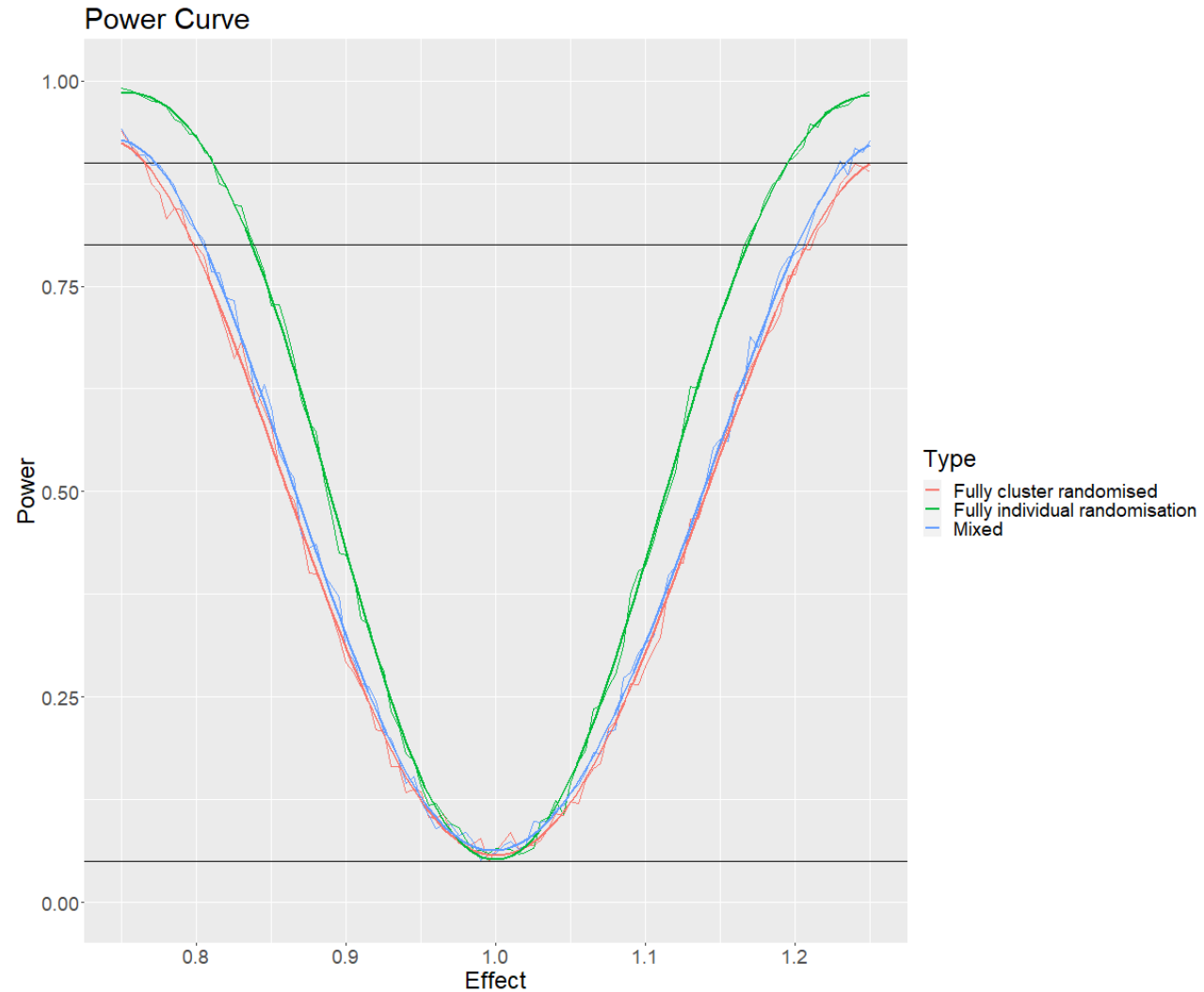
Fixed number of clusters and cluster size

Calculate cluster number based on formula and apply here



FEASIBILITY

# Simulation - Sample Size



# Systematic Review

- Dialysate sodium concentration for patients with maintenance haemodialysis: A systematic review and network meta-analysis.

## Step 2 - PICOT Question

<b>Population</b> Patients with kidney failure requiring haemodialysis
<b>Intervention/Exposure</b> Dialysate Sodium Concentration
<b>Control</b> Different concentration of dialysate sodium
<b>Outcome</b> Patient important (Mortality, MI, Stroke, Heart Failure, CVD Death, All cause mortality) Surrogate outcome (Systolic BP, Diastolic BP, IDWG, IDH)
<b>Time</b> Greater than 3 months

2022-11-04: Diaylsis Blind ON

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2022-01-01	<span>Conor</span>	Use of regional citrate anticoagulation with medium cut-off membrane: pilot report.	Vrecko, Marija Malgaj; Pajek...	
2022-01-01	<span>Conor</span>	A randomized controlled trial of two dialysate sodium concentrations in hospitalized hemodialysis patients.	Causland, Finnian R Mc; Rav...	
2022-01-01	<span>Conor</span>	Effects of Standard and Individualized Dialysate Sodium in Chronic Hemodialysis Patients Upon Echocardiography Parameters.	Eftimovska-Otovikj, Natasha...	
2022-01-01	<span>Conor</span>	Interventions To Attenuate Vascular Calcification Progression in Chronic Kidney Disease: A Systematic Review of Clinical Trials.	Xu, Chelsea; Smith, Edward ...	
2020-01-01	<span>Conor</span>	Effects of Individualized Dialysate Sodium Prescription in Hemodialysis - Results from a Prospective Interventional Trial.	Radhakrishnan, Radhika C; ...	
2021-01-01	<span>Conor</span>	Intraocular Pressure Changes during Hemodiafiltration with Two different Concentrations of Sodium in the Dialysate.	Lerma, Claudia; Saavedra-F...	
2021-01-01		The Predialysis Serum Sodium Level Modifies the Effect of Hemodialysis Frequency on Left-Ventricular Mass: The Frequent Hemodialysi...	Raimann, Jochen G; Chan, C...	

Srishti Dadheech



MSc (Clinical Research)

OLLSCOIL NA GAILLIMHÉ  
UNIVERSITY OF GALWAY

# Public, Patient and Carer Involvement

- Meetings with IKA about Renal Registry
  - Floated the idea of pragmatic trials
- Meeting with expert patient Maciej Doczyk
- Meeting with PPI ignite manager in Galway
  - Advice re funding option for patient co-applicant
  - Advice re funding for Patient Advisory Group

# Pragmatic Trials in Haemodialysis

