A pilot-scale, randomized study comparing self-monitoring of weight and blood pressure via an electronic health journal (patientMpower platform) with usual care in haemodialysis patients

Renal Dialysis patientMpower 02

Statistical Analysis Plan

Version 1.0

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PROTOCOL SUMMARY

PRODUCT	patientMpower intervention (+ digital weighing scales & blood pressure monitor)
CLINICALTRIALS.GOV IDENTIFIER	NCT 03403491
PROTOCOL TITLE	A pilot-scale, crossover randomized study comparing self-monitoring of weight and blood pressure via an electronic health journal (patientMpower platform) with usual care in haemodialysis patients
COORDINATING INVESTIGATOR	Dr. C. O'Seaghdha, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland
NUMBER OF TRIAL SITES	Two (dialysis sites under the governance of Beaumont Hospital): ● Beaumont Hospital dialysis center ● Beacon Drogheda Dialysis Unit
CLINICAL PHASE	Not applicable
STUDY OBJECTIVES	To assess the effect of self-monitoring using the patientMpower intervention [defined as patientMpower app +digital weighing scales & blood pressure (BP) monitor] on outcomes in ambulatory haemodialysis patients.
METHODOLOGY	Prospective, run-in period followed by open-label, randomized, two-period cross-over comparison of patientMpower interevnetion versus sham intervention (defined as sham app with no scales or BP monitor). Usual care for all patients throughout study.
NUMBER OF SUBJECTS	Total randomised: 57 Total in treated dataset: 43 ● patientMpower intervention followed by sham intervention: 20/43 ● sham intervention followed by patientMpower intervention: 23/43
DIAGNOSIS	End Stage Kidney Disease requiring regular ongoing haemodialysis

MAIN CRITERIA FOR INCLUSION	Age ≥18 years, owns a smartphone or tablet device, has an email address, internet access at home, demonstrated understanding of use of patientMpower app, weighing scales and BP monitor, written informed consent
TEST PRODUCT	patientMpower intervention (defined as patientMpower app +digital weighing scales & BP monitor) used daily
COMPARATOR PRODUCT	Sham intervention (defined as sham app with no digital weighing scales or BP monitor, and without receiving prompts or alerts).
DURATION OF OBSERVATION	10 weeks: ~2 weeks usual care run-in followed by two observation periods of 4 weeks each.
END OF STUDY DEFINITION	End of observation period 2 (10 weeks)
PRIMARY ENDPOINTS	Frequency of use of the patientMpower intervention.
SECONDARY ENDPOINTS	Effect of patientMpower intervention on ● total fluid removed by dialysis during the patientMpower observation period ● proportion of haemodialysis sessions in which ultrafiltration rate is ≤ 10 mL/kg/h. ● proportion of haemodialysis sessions in which interdialytic weight gain (IDWG) is ≤ 4%. ● pre-dialysis weight. ● pre-dialysis BP ● medication adherence. ● compliance with daily recording of fluid intake, weight, and BP. ● requirement for additional unscheduled dialysis or isolated ultrafiltration sessions. ● inferior vena cava diameter pre-dialysis (optional measure) Patient-reported symptoms were also recorded on the patientMpower app.
INTERIM ANALYSIS	None

STATISTICAL METHODS	• Descriptive statistics tables prepared • Repeated measures mixed effects models used to compare groups in terms of both categorical and continuous outcomes.

FLOW CHARTS

Flow chart 1: Assessments during observation periods

If allocated to observation sequence 1:

	Run-in (usual care for 2 weeks)	Randomised observation (2 x 4 weeks)
Sequence 1		**Period 1: patientMpower. Period 2: sham**

	Baseline clinic visit	Week 2 clinic visit	Daily (patient reported)	At each dialysis session	Week 6 clinic visit	Week 10
Informed consent	X					
Demographic data (include dialysis & medicines history)	X					
Vital signs, body weight, IDWG at clinic	X	X		X	X	
Ultrafiltration rate	X	X		X	X	
Randomisation	X[A]					
[A]Start patientMpower intervention		X				
Patient training on patientMpower intervention		X				
Patient-reported body weight, BP, fluid intake (daily)[B]			X[B]			
Patient-reported symptoms[C]	X	X	X[C]		X	X
Patient-reported compliance or changes (relevant medicines)[D]			X[D]			
Stop patientMpower intervention					X	
Utility & acceptability of patientMpower intervention[E]					X	
Start sham intervention					X	
Measure inferior vena cava diameter[F]		X			X	X
Clinic-reported outcomes (e.g. unscheduled additional dialysis)					X	X
End of study						X

[A] Randomisation was after informed consent and before start of Period 1. During Period 1, patients used the patientMpower intervention for approximately four weeks, At the end of period 1, the intervention was changed to the sham intervention (without weighing scales or BP monitor) and the patientMpower intervention was deactivated. Patients used the sham intervention for approximately four weeks. During the sham period, the connection between the BP monitor and weight scales was disabled and the alerts were not sent by the application.

[B] Fluid intake, weight, BP recorded by patient daily.

[C] Patient-reported symptoms include dyspnea, cramps, orthopnea, fatigue, depression, oedema, fatigue, itch. These symptoms are known to be related to fluid overload and to end stage kidney disease.

[D] Medicines compliance reported on patientMpower app daily.

[E] Patient and healthcare professionals' opinions of the patientMpower intervention sought by questionnaire.

[F] Measurement of inferior vena cava (IVC) diameter immediately pre-dialysis was optional. A separate informed consent was sought for permission to measure IVC. Patients could choose to participate in the study without measurement of IVC.

If allocated to observation sequence 2:

	Run-in (usual care for 2 weeks)	Randomised observation (2 x 4 weeks)				
Sequence 2		**Period 1: sham. Period 2: patientMpower**				
	Baseline clinic visit	**Week 2 clinic visit**	**Week 6 clinic visit**	**Daily (patient reported)**	**At each dialysis session**	**Week 10**
Informed consent	X					
Demographic data (include dialysis & medicines history)	X					
Vital signs, body weight, IDWG at clinic	X	X	X	X		X
Ultrafiltration rate	X	X	X	X		X
Randomisation	X[A]					
Start sham intervention		X				
[A]Start patientMpower intervention				X[A]		
Patient training on patientMpower intervention				X		
Patient-reported body weight, BP, fluid intake (daily)[B]				X[B]		
Patient-reported symptoms[C]	X		X	X[C]	X	X
Patient-reported compliance or changes (relevant medicines)[D]				X[D]		
Stop patientMpower intervention						X
Utility & acceptability of patientMpower intervention[E]						X
Measure inferior vena cava diameter[F]		X			X	X
Clinic-reported outcomes (e.g. unscheduled additional dialysis)			X			X
End of study						X

[A] Randomisation was after informed consent and before the start of Period 1. During Period 1, patients used the sham intervention (without weighing scales or BP monitor) for approximately four weeks, At the end of period 1, the intervention was changed to the active patientMpower intervention. Patients used the patientMpower intervention for approximately four weeks. During the sham period, the connection

between the BP monitor and weight scales was disabled and the alerts were not sent by the application.

[B] Fluid intake, weight, BP recorded by patient daily.

[C] Patient-reported symptoms include dyspnea, cramps, orthopnea, fatigue, depression, oedema, fatigue, itch. These symptoms are known to be related to fluid overload and to end stage kidney disease.

[D] Medicines compliance reported on patientMpower app daily.

[E] Patient and healthcare professionals' opinions of the patientMpower intervention sought by questionnaire.

[F] Measurement of inferior vena cava (IVC) diameter immediately pre-dialysis was optional. A separate informed consent was sought for permission to measure IVC. Patients could choose to participate in the study without measurement of IVC.

List of abbreviations

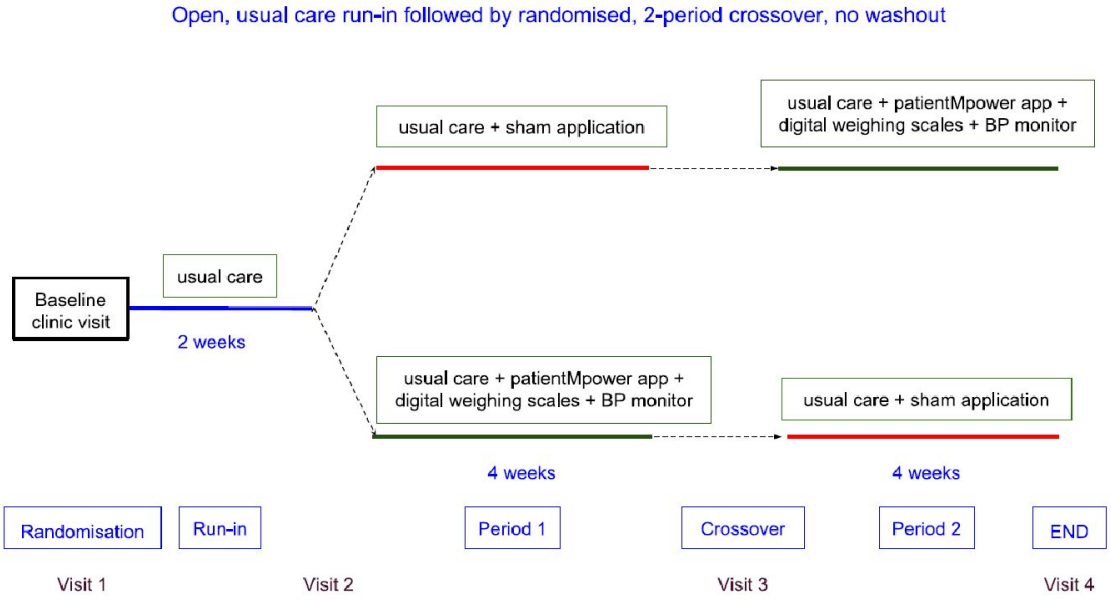
BP	blood pressure
CV	cardiovascular
DBP	diastolic blood pressure
IDWG	interdialytic weight gain (i.e. fluid weight gain between dialysis sessions)
IVC	Inferior vena cava
PROM	Patient reported outcome measure
SD	Standard deviation
SBP	Systolic blood pressure

1. Study protocol and conduct

1.1 Protocol

The first version of the protocol [1] was finalised on 2 August 2017. The design is illustrated in Figure 1.1: 1 below.

Figure 1.1: 1 Study design



1.2 Protocol amendments

The protocol was amended on 20 December 2018.

The following changes (described in protocol amendment 1) were made:

Time interval between informed consent and randomisation

The protocol dated 2 August 2017 stated that randomisation would occur on the same date as informed consent and there would be a run-in period of two weeks between randomisation and the start of Period 1.

Amendment:
Randomisation was done at variable times after the date of informed consent and before the start of observation period 1.

This was necessary to allow flexible scheduling of the start date of observation period 1 (dependent on availability of study equipment and personnel to train patients on study processes).

Data from the five (5) haemodialysis sessions immediately preceding the start of Period 1 was considered as the run-in data.

Definition of reference target weight for each patient

One of the secondary endpoints of the protocol dated 2 August 2017 was the proportion of haemodialysis sessions in which interdialytic weight gain is ≤ 4% (relative to patient's dry weight).

Amendment:
The most recent post-dialysis weight was used as the reference weight target rather than the dry weight.

The "most recent post-dialysis weight" was defined as the mean post-dialysis weight over the previous three (3) haemodialysis sessions before the start of observation period 1.

Reason: for many patients the dry weight on record is historical data and may not be current and appropriate for the patient at time of entry to the study.

Editing of reference target weight by patients

The patientMpower app was modified on 7 December 2018 to enable patients to edit their reference target weight if necessary. Therefore all patients in the group who started the study in mid-November 2018 could edit their reference target weights in the patientMpower intervention period after 7 December 2018 (which was Period 2 for most of those patients). All patients who started the study in January 2019 were able to edit their reference target weights in both Periods 1 and 2.

Primary and secondary endpoints

The protocol dated 2 August 2017 stated that the primary endpoint will be the level of engagement of patients with the patientMpower intervention and that the secondary endpoints will be to determine the effect of the patientMpower intervention on various parameters associated with dialysis, renal health and symptoms.

Amendment (additional secondary endpoint):
The effect of the patientMpower intervention on total fluid removed by dialysis during the patientMpower observation period (compared with the sham period) was an additional secondary endpoint.

Optional additional measurement and secondary endpoint

Some study participants were asked to consent to measurement of the inferior vena cava (IVC) diameter at three time-points during the study. This was an optional assessment and participants could choose to take part in the study without measurement of IVC diameter. There was a separate informed consent form for the measurement of IVC diameter.

The IVC diameter was assessed by ultrasound at the start of observation period 1, start of observation period 2 and end of observation period 2 (end of study). IVC diameter was assessed immediately pre-dialysis at each of these time-points.

1.3 Dates of study conduct

It was intended that the trial would be complete when approximately 50 patients completed the total 10-week observation period.

The first patient was randomised on 7 November 2018 and started observation Period 1 on 08 November 2018. The last patient was randomised on 17 December 2018, started observation Period 1 on 10 January 2019 and completed the study observation period on 07 March 2019.

1.4 Randomisation

The order of observation periods was allocated by using a third-party randomisation service (Sealed Envelope Ltd, 501 Clerkenwell Workshops, 27-31 Clerkenwell Close, London EC1R 0AT, UK).

There were two possible observation sequences post-randomisation:

Sequence 1: period 1 (4 weeks): patientMpower intervention followed by period 2 (4 weeks): sham intervention

OR

Sequence 2: period 1 (4 weeks): sham intervention followed by period 2 (4 weeks): patientMpower intervention

In the initial design, randomisation was to be done on the same date as informed consent. The protocol was amended to allow randomisation to be done at variable times on or after the date of informed consent and before the start of observation period 1. This was necessary to allow flexible scheduling of the start date of observation period 1 (dependent on availability of study equipment and personnel to train patients on study processes).

All patients were randomised from two of the possible treatment centres: Beaumont Hospital Renal Centre and Beacon Renal Dialysis Drogheda.

Observation sequences were generated using random permuted blocks. The block sizes were not disclosed to the trial centre or to patientMpower Ltd. The randomisation is described in references 2 and 3 below.

The randomisation ratio was 1:1 and randomisation was stratified by treatment centre. It was initially planned that patients could be randomised at three possible centres (Beaumont Hospital, Beacon Renal Drogheda and Northern Cross).

1.5 Data management plan

The preparation of listings and tables for analysis is described in the data management plan Version 1.1 dated 11 June 2019.

2. Datasets for analysis

2.1 Dataset definitions

The patient populations to be included in the analyses were defined as follows:

Randomised dataset: all patients who gave informed consent and were randomised.

Treated dataset: all patients in the Randomised dataset who installed the patientMpower application, recorded at least three weight readings with the digital weighing scales (without technical problems) and who started the patientMpower observation period.

≥75% adherence dataset: all patients in the Treated dataset who provided weight data on at least 21 days of the patientMpower observation period.

2.2 Protocol deviations

Data from all patients in the treated dataset were analysed. The primary analysis was of the treated dataset.

Significant protocol deviations included:

- did not start sham application observation period
- did not provide weight data on at least 21 days of the patientMpower observation period
- incorrect order of use of the sham or patientMpower intervention (as determined by the independent randomisation)

Other protocol deviations included:

- did not provide blood pressure data on at least 14 days of the patientMpower observation period
- did not complete a symptoms questionnaire on at least 14 days of the patientMpower observation period

- did not provide information on fluid intake on at least 14 days of the patientMpower observation period

2.3 Duration of follow-up

All data for each patient for the first eight weeks after they started to use the patientMpower or sham intervention were to be included in this analysis.

Where a patient used the patientMpower intervention or sham intervention for less than eight weeks, all of their data were to be included in this analysis.

Where a patient used the patientMpower intervention for more than 4 weeks, the data from day 28 onwards were not to be included in this analysis.

The start of the 28-day observation period is defined as the day after installation of the sham or patientMpower intervention. For example, if the patientMpower app was installed on 28 February 2019, day 1 of the patientMpower intervention observation period is defined as 1 March 2019 and day 28 is defined as 28 March 2019.

3. Summary of design

3.1 Summary of design, including control

This was a pilot-scale, prospective, open-label, randomized, two-period, crossover intervention study.

Each patient was randomized to one of the two possible observation sequences as described above.

Patients followed their usual care and haemodialysis programme throughout the study.

The clinic observations at haemodialysis sessions during the run-in period provided the baseline data for each patient.

3.2 Study population

Adult patients requiring maintenance haemodialysis in an ambulatory care setting.

3.3 Observational intervention

The study observational intervention (the “patientMpower intervention”) was an electronic health journal, the patientMpower app (with a supplied digital weighing scales and BP monitor). The patientMpower app is an electronic application downloaded to the patient’s mobile phone or tablet device. The patientMpower app is designed to allow the patient to report various parameters relevant to haemodialysis and record these on a regular basis, ideally daily.

Patients were asked to report measurements on the patientMpower app each day. Patient-reported measures (at a minimum) included body weight (one reading once/day), BP, fluid intake and symptoms.

Additional patient-reported measures which could be reported on the patientMpower app included temperature, activity levels and compliance with relevant medication.

The control observation was usual care with a sham electronic application (the "sham intervention") which did not allow recording of body weight, BP or other measurements.

3.4 Concomitant therapy, restrictions and rescue treatment

All patients continued to receive all usual care throughout the study as prescribed by their healthcare professionals.

4. Variables for assessment

4.1 Efficacy variables

The objective of this study was to assess the effect of self-monitoring using the patientMpower intervention on outcomes in ambulatory haemodialysis patients.

The acceptability and utility of the patientMpower intervention in helping haemodialysis patients manage their condition was assessed (from the patient perspective).

It had been intended to assess acceptability and utility from the healthcare professional perspective but these data were not collected.

The effect of the patientMpower intervention on total fluid removed by dialysis during the patientMpower observation period was compared with the sham period.

The frequency of use of the patientMpower intervention and patient-reported symptoms was assessed.

The primary endpoint was the level of engagement of patients with the patientMpower intervention.

The primary endpoint variables are:

- number of patients who gave informed consent to take part in the study
- number of consented patients who downloaded the app to their smartphone or tablet device
- number of patients who used the app at least once after downloading
- number of patients who used the app more than once
- frequency of use by each patient
- date intervals between informed consent, download, first use

- date intervals between first and subsequent uses (first use defined as first use of the patientMpower intervention with the digital weighing scales or BP monitor)
- frequency of recording study parameters (weight, BP) at home

The secondary endpoints included determination of the effect of patientMpower intervention on:

- proportion of haemodialysis sessions in which ultrafiltration rate is ≤ 10 mL/kg/h.
- proportion of haemodialysis sessions in which IDWG is ≤ 4%.
- total fluid removed by dialysis during the patientMpower observation period
- pre-dialysis weight
- pre-dialysis BP
- medication adherence
- compliance with daily recording of fluid intake, symptoms, weight, BP
- requirement for additional unscheduled dialysis

The secondary endpoint variables included:

- body weight (measured at home and pre-dialysis at each dialysis session)
- BP (measured at home and pre-dialysis at each dialysis session)
- number of additional unscheduled dialysis sessions
- number and frequency of records of compliance parameters
- compliance with prescribed medicines

The most recent off-dialysis weight was used as the reference weight target rather than the dry weight. The “most recent off-dialysis weight” was defined as the mean post-dialysis weight over the previous three (3) haemodialysis sessions before the start of the patientMpower observation period.

Incidence and severity of named symptoms/day (muscle cramps, feeling “washed out”, light-headedness, dyspnoea, ankle swelling, cough) were recorded by the patients on the patientMpower app. Information on fluid intake/day (categorised as small amount, medium amount, large amount) was also recorded on the patientMpower app.

The patient’s opinion of the utility and acceptability of the patientMpower intervention was assessed by their response to questions (binary and Likert scale):

- using the patientMpower intervention helped me to take the correct dose of my medicines every day (strongly agree/agree/disagree/strongly disagree)
- using the patientMpower intervention gave me more confidence/a greater sense of control in managing my health (strongly agree/agree/disagree/strongly disagree)
- my preference for using the patientMpower intervention versus not using it (yes, no preference, no)
- my difficulty rating in using the patientMpower intervention (very easy, easy, difficult, very difficult)

- what was the effect of using the patientMpower intervention on my well-being and daily life (positive, negative, optional open text field for patient to give opinion)
- do I want to continue using the patientMpower intervention after the end of the study (yes, no)

An additional exploratory secondary endpoint was to determine the effect of patientMpower intervention on inferior vena cava (IVC) diameter (measured immediately pre-dialysis). This was an optional measurement. Patients could choose to participate in the study without measurement of IVC diameter. The variables for this endpoint are longitudinal and transverse IVC diameter and categorisation as 50% collapsible on inspiration (yes/no response).

4.2. Safety variables

All reported adverse events observed were listed.

4.3 Other variables

Demographic data (date of birth, gender, ethnicity, height, weight, concomitant diagnoses, medication prescribed).

Type of smartphone or tablet device (i.e. iPad or Android tablet, iPhone or Android phone).

5. Statistical methods and determination of sample size

5.1 Statistical design and model

This study was a prospective open-label run-in usual care observation (run-in period; 2 weeks) followed by randomization to a two-period crossover observation (two observation periods of 4 weeks with no washout).

Each patient was randomized to one of the two possible observation sequences:

Sequence 1: run-in (2 weeks): usual care followed by period 1 (4 weeks): patientMpower intervention followed by period 2 (4 weeks): sham intervention

OR

Sequence 2: run-in (2 weeks): usual care followed by period 1 (4 weeks): sham intervention followed by period 2 (4 weeks): patientMpower intervention

Patients followed their usual care and haemodialysis programme throughout the study.

The clinic observations at haemodialysis sessions during the run-in period provided the baseline data for each patient.

The crossover design enables comparison of use of the patientMpower intervention + usual care with a sham intervention + usual care over a four-week period. Each patient served as their own control.

The trial design also allowed assessment of the effect of the patientMpower intervention on study parameters compared with usual care alone.

5.2. Null and alternative hypotheses

Not relevant.

5.3 Planned analyses

Results were collected and summarised for statistical display.

Demographic and medical history data were described for the randomised and treated patient populations.

The efficacy endpoints were analysed in the Treated patient population with a confirmatory analysis in the ≥ 75% adherence patient population.

The analyses are described in more detail in the separate document Appendix 1 statistical analysis plan Dialysis B.

Where appropriate, analyses will be tested for treatment order effect. If a treatment order effect is present for an endpoint, the analysis will be changed from within-patient comparison to a between-patient comparison for the first treatment period only (i.e. active or sham).

5.3.1 Primary analysis

The primary efficacy endpoint was assessed by analysis of the responses to the patient questionnaires. This analysis only describes observations during the patientMpower observation period.

Data on the level of engagement with the patientMpower intervention (primary analysis) and the patient and healthcare professional opinions on utility and acceptability were described and tabulated.

5.3.2 Secondary analyses

There were two comparisons of the secondary endpoint data:

(1) data in the patientMpower observation period were compared with the sham application observation period

(2) data in the patientMpower observation period were compared with the usual care run-in period.

The comparisons were done using mixed effects models and generalized estimating equations. The following comparisons were made:

- trends in ultrafiltration rate, pre-dialysis weight and BP at each haemodialysis session
- number of haemodialysis sessions in which the IDWG is ≤4%
- total volume of fluid removal in all hemodialysis sessions within an observation period
- medication adherence
- observed IVC diameter

Compliance with daily recording of fluid intake, weight, and blood pressure were tabulated and displayed.

Patient-reported symptoms were tabulated and displayed.

A possible limitation of the analysis is that there may be a treatment order effect (i.e. carry over effect of behaviours), particularly when moving from the patientMpower observation period to the sham observation period. The data in the patientMpower observation period and the sham intervention observation period were assessed to establish if there was a treatment order effect.

The secondary efficacy endpoint variables are measurements which are important measures of fluid intake and renal function in haemodialysis patients.

5.3.3 Interim analysis

No interim analysis was planned or conducted.

5.4 Handling of missing data

No imputations of missing data were made.

5.5 Determination of sample size.

This was a pilot scale study. The planned sample size (50) was chosen arbitrarily by an estimation of the likely number out of a total of 300 dialysis patients who might enroll in the study.

6. References

1. O'Seaghdha C, Edwards C, Costello E, Sexton D. A pilot-scale, randomized study comparing self-monitoring of weight and blood pressure via an electronic health journal (patientMpower platform) with usual care in haemodialysis patients. Beaumont Hospital and patientMpower Ltd, Dublin, Ireland. Protocol dated 2 August 2017. www.clinicaltrials.gov NCT 03403491.

2. Description of simple randomisation service from Sealed Envelope Ltd. 2017. Simple randomisation service. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/?utf8=%E2%88%9A&name=Dialysispmpstudy&commit=Find+trial (Accessed 25 Sep 2018).
3. Sealed Envelope Ltd. 2017. Create a blocked randomisation list se_list_51115415720010 https://www.sealedenvelope.com/simple-randomiser/v1/lists (Accessed 25 Sep 2018).

Signatures

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