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

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PROTOCOL SUMMARY

PRODUCT	patientMpower app (+ 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
CO-ORDINATING INVESTIGATOR	Dr. C. O'Seaghdha, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland
NUMBER OF TRIAL SITES	Three (dialysis sites under the governance of Beaumont Hospital): ● Beaumont Hospital dialysis center ● Beacon Drogheda Dialysis Unit ● Northern Cross Dialysis Unit
STUDY OBJECTIVES	To assess the effect of self-monitoring using the 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 app (+digital weighing scales & BP monitor) versus sham electronic app (no scales or BP monitor). Usual care for all patients throughout study.
NUMBER OF SUBJECTS	Total randomised: 50 ● patientMpower app followed by sham application: 25 ● sham application followed by patientMpower app: 25
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 app (electronic health journal) + digital weighing scales + BP monitor used daily
COMPARATOR PRODUCT	Sham electronic health journal without linkage to digital weighing scales or BP monitor, and without receiving prompts or alerts.
END OF STUDY DEFINITION	10 weeks
PRIMARY ENDPOINT	Frequency of use of the patientMpower app.
SECONDARY ENDPOINTS	Effect of patientMpower app (+digital weighing scales & BP monitor) 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 (optional measure) Patient-reported symptoms will also be recorded on the app.

INTERIM ANALYSIS	None planned
STATISTICAL METHODS	• Descriptive statistics tables will be prepared • Repeated measures mixed effects models will also be used to compare groups in terms of both categorical and continuous outcomes.

FLOW CHARTS

Flow chart 1: Patient recruitment process

Step	Day	Action
1	- 30 to -7	Study centre publicises the study to potential participants, i.e. the entire cohort of patients on maintenance haemodialysis at Beaumont Hospital. This interaction will be performed by research staff and not by the physicians looking after the medical care of the potential participants. Potential participants will advise research staff of their interest in taking part.
2	0 (Baseline)	At planned usual care haemodialysis visit to study centre, the study will be discussed (face-to-face) with potential participants who have expressed an interest in taking part. Patients will give written informed consent before any study-specific actions[A]. Usual care run-in period starts. Randomisation to either of two possible observation sequences[B] is allocated on or after start of run-in period.
3	0 (Baseline)	Research team advises patientMpower that the patient has started the study and of the allocated group.
4	11 to 14	patientMpower provides information/help (includes instructions on installation of patientMpower app or sham application to patient at the planned date of 2-week usual care haemodialysis visit to study centre[A] . If first period is patientMpower app, digital weighing scales and BP monitor will also be provided to the patient at this time.
5	14 (start of period 1)	Patient starts using patientMpower app or sham application (dependent on randomized allocation)

[A] A paper version of the full-length patient information document will be given to the patient.

[B] The two possible observation sequences are either patientMpower app + digital weighing scales + BP monitor in period 1 followed by sham application in period 2 or sham application in period 1 followed by patientMpower app +

digital weighing scales + BP monitor in period 2. Randomised allocation will be done by contacting an independent randomization service.

[C] patientMpower Ltd will help the patient with installation of patientMpower application and set-up of digital weighing scales and BP monitor (so that patientMpower application and equipment are installed and operating at the start of the patientMpower observation period).

Flow chart 2 Assessments during observation period

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 (+ digital weighing scales & BP monitor)		X				
Patient training on app		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 app					X	
Utility & acceptability of patientMpower app[E]					X	
Start sham application					X	
Measure inferior vena cava diameter[F]		X			X	X
Clinic-reported outcomes (e.g.					X	X

unscheduled additional dialysis)						
End of study						X

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

[B] Fluid intake, weight, BP to be 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 app sought by questionnaire.

[F] Measurement of inferior vena cava (IVC) diameter is optional. A separate informed consent will be sought for permission to measure IVC. Patients can 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 application		X				
[A]Start patientMpower (+ digital weighing scales & BP monitor)				X[A]		
Patient training on app				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 app						X
Utility & acceptability of patientMpower app[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 will be after informed consent and before the start of Period 1. During Period 1, patients will use the sham application (without weighing scales or BP monitor) for approximately four weeks, At the end of period 1, the app will be changed to the active patientMpower app (+digital weighing scales + BP monitor). Patients will use the active patientMpower app (+digital weighing scales + BP monitor) for approximately four weeks. During the sham period, the connection between the BP monitor and weight scales will be disabled and the alerts will not be sent by the application.

[B] Fluid intake, weight, BP to be 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 app sought by questionnaire.

[F] Measurement of inferior vena cava (IVC) diameter is optional. A separate informed consent will be sought for permission to measure IVC. Patients can choose to participate in the study without measurement of IVC.

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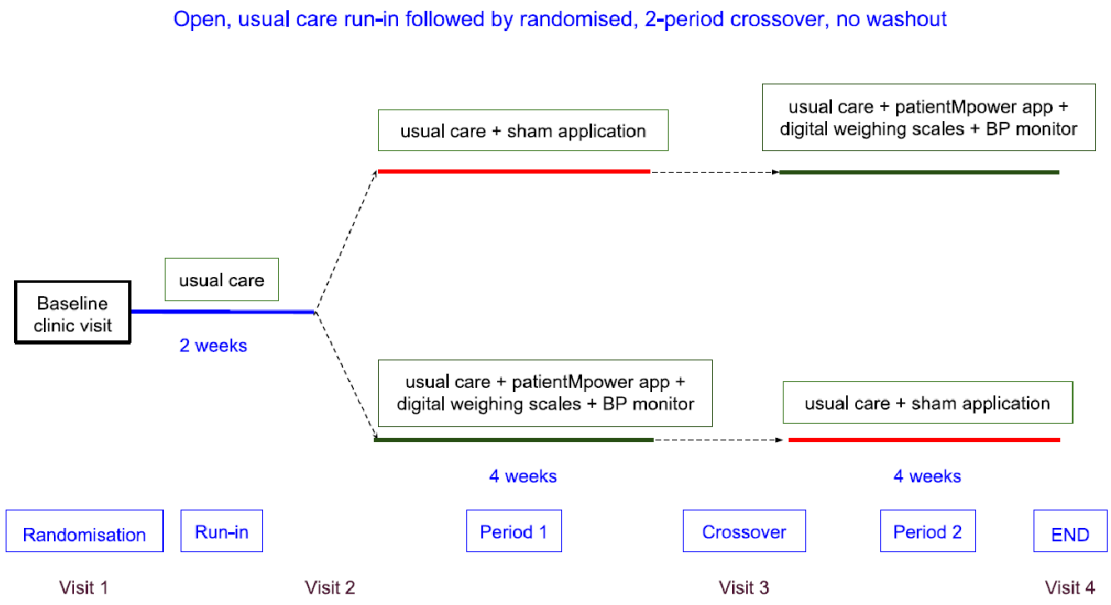
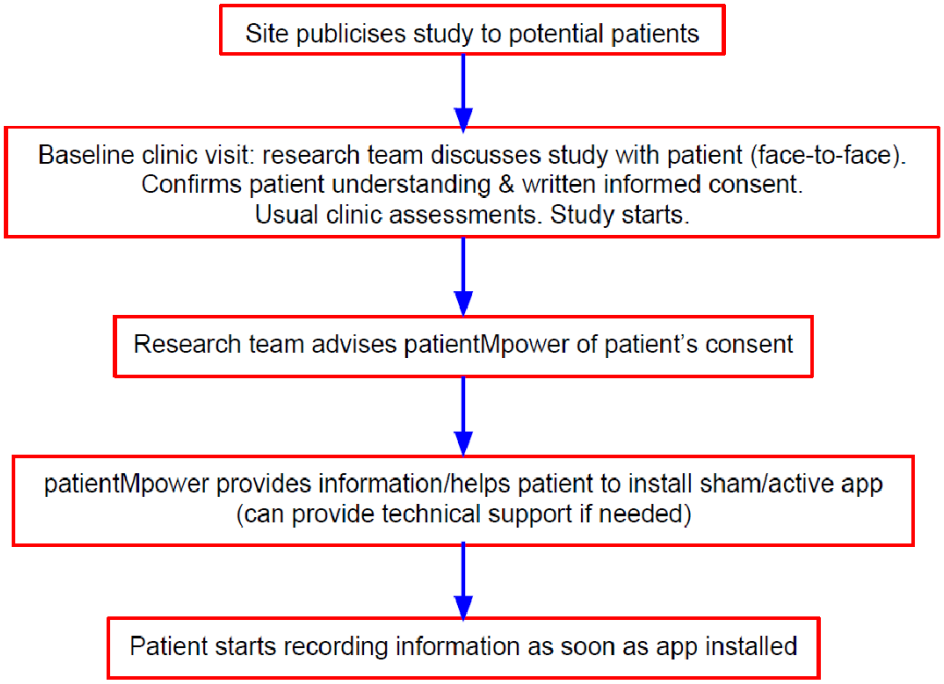


Figure 6.2.1: 1: Patient recruitment process:



List of Abbreviations

BP	blood pressure
CV	cardiovascular
IDWG	interdialytic weight gain (i.e. fluid weight gain between dialysis sessions)
IP	Internet Protocol
IVC	Inferior vena cava
PROM	Patient reported outcome measure
SSH	Secure Shell
SSL	Secure Sockets Layer
TLS	Transport Layer Security

1. Introduction

1.1 Medical background

End stage kidney disease is defined by kidney failure severe enough to require some form of renal replacement therapy. This replacement has three forms, kidney transplant, haemodialysis and peritoneal dialysis. Haemodialysis is the most common form of replacement therapy and usually entails three sessions of dialysis per week on alternate days starting either on Monday or Tuesday. The period between dialysis sessions is known as the inter-dialytic period and as dialysis is delivered on alternate days there is one inter-dialytic period per week that is longer than the other. In order to maintain extracellular fluid balance and to prevent high blood pressure, haemodialysis sessions focus on removing the fluid that was gained between dialysis sessions.

Haemodialysis patients experience high rates of mortality, driven largely by an exceptionally high rate of cardiovascular (CV)-related mortality, which exceeds that of the general population by 10-to 20-fold.[1, 2] High levels of both inter-dialytic weight gain and rate of fluid removal during dialysis have been linked with increased mortality, particularly during the longer interdialytic period[1]. It is postulated that the haemodynamic effects of high fluid removal rates during dialysis may result in cardiovascular morbidity and mortality. An analysis by Flythe et al reported that the risk of all-cause and cardiovascular mortality was increased in patients with dialysis ultrafiltration rates over 10 mL/h/kg.[3] In patients with co-existing congestive heart failure, the risk of all-cause and cardiovascular mortality was increased at ultrafiltration rates between 10 and 13 mL/h/kg.[4]

Dialysis patients need to carefully monitor fluid intake between dialysis sessions to avoid the requirement for unplanned dialysis sessions and/or high rates of ultrafiltration.

Digital medicine platforms which directly record patient experiences (e.g. symptoms, impact on daily life, medication compliance) and measurements (e.g. BP, body weight, temperature, blood sugar levels) have been developed for chronic medical conditions and may be valuable in helping the patients to manage their condition. This approach may be of value in helping haemodialysis patients monitor and manage their fluid intake, medicines compliance and other relevant parameters between haemodialysis sessions. To date this approach has been unexplored in dialysis patients.

1.2 Product profile

The patientMpower application is an electronic health journal, which has been developed for and is used in providing support to patients with breast

cancer, prostate cancer, idiopathic pulmonary fibrosis and post-kidney transplant. The patientMpower application is downloaded as an “app” to a mobile phone or tablet device and patients record various parameters (e.g. BP, weight, temperature, symptoms, medication compliance, impact of their medical condition on daily life) on a daily basis. The patient has a permanent health diary of their self-reported measurements available to them on their mobile device. The app includes a health journal, which allows patients to record symptoms at the time they occur. This is helpful for the patient in monitoring their health and in preparing them for appointments with their healthcare professionals, particularly if there is a long interval between clinic visits. If appropriate, certain clinic-derived measurements (e.g. therapeutic drug levels) can be shared with the patient via the app.

A version of the patientMpower app has been developed for kidney transplant recipients and this is now offered as standard care at the national renal transplantation centre in Ireland. Patients have positively received it and studies of its use are ongoing. However, it is important to recognise that patient demographic factors vary by medical condition and this can have an impact on the utility and acceptability of digital health platforms in the patient user group.

This version of the patientMpower app has specifically been developed to capture parameters, which are relevant for patients who are undergoing regular haemodialysis. Examples of measures, which can be recorded by the patient, include body weight, BP, temperature, activity (steps/day) and medication compliance. In addition, users can report symptoms resulting from their underlying condition or medical treatments.

This study will capture longitudinal data on home measurement (by the patient) of parameters and symptoms relevant to the management of their underlying condition. The effect of self-monitoring of fluid intake, BP and body weight by the patient (using the patientMpower app and a supplied digital weighing scales and BP monitor) on the extent of fluid removal required per dialysis will be assessed and compared with that of the sham application intervention period (no weight or BP monitoring equipment) and also to usual care during the run-in period of observation.

2. Rationale, objectives and benefit-risk assessment

2.1 Rationale for performing the trial

This trial will evaluate if using an electronic health journal (the patientMpower app) to monitor fluid intake, weight gain, medicines compliance and other relevant parameters (e.g. BP) will help haemodialysis patients in their self-management and avoid the requirement for additional unplanned dialysis sessions, high fluid removal (ultrafiltration) rates or other adverse outcomes.

The patientMpower app provides a tool to collect and share this type of information between patients and their healthcare professionals.

This is a pilot scale study to assess if this approach has merit and could be tested and developed further.

As no specific digital patient support platform for haemodialysis patients is available and validated, there is sufficient justification in testing the effectiveness and acceptability of the patientMpower app in a controlled observational setting.

2.2 Trial objectives

The objective of this pilot-scale study is to assess the effect of self-monitoring using the patientMpower electronic health journal [+digital weighing scales & blood pressure (BP) monitor] on outcomes in ambulatory haemodialysis patients.

The primary objective will be to determine the frequency of use of the patientMpower app (+digital weighing scales & BP monitor) in the patients randomized to that observation method. This will be compared to the period of operation of the sham application period and to the baseline standard care run-in period.

Additional objectives are to determine the effect of patientMpower app (+digital weighing scales & BP monitor) 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 IDWG is ≤ 4%.
- pre-dialysis weight.
- pre-dialysis BP
- medication adherence.
- compliance with daily recording of fluid intake, weight, BP.
- requirement for additional unscheduled dialysis.

Patient-reported symptoms will be recorded.

Patients will be randomized to either of two groups followed by the other observation after the cross-over:

usual care run-in period (2 weeks) followed by patientMpower app (digital weighing scales & BP monitor) (4 weeks) followed by sham application (no monitoring equipment) (4 weeks)

OR

usual care run-in period (2 weeks) followed by sham application (no monitoring equipment) (4 weeks) followed by patientMpower app (digital weighing scales & BP monitor) (4 weeks)

An additional objective of this observational study is to assess the acceptability and utility of the patientMpower app in helping haemodialysis patients and their healthcare professional caregivers manage their condition. These will be assessed from both the patient and healthcare professional perspective.

An additional exploratory objective will be to determine the effect of patientMpower app (+digital weighing scales & BP monitor) on inferior vena cava (IVC) diameter. This will be an optional measurement. Patients can choose to participate in the study without measurement of IVC diameter.

2.3 Benefit-risk assessment

The patientMpower app has been evaluated in other clinical settings (e.g. prostate cancer, post kidney transplant and idiopathic pulmonary fibrosis). The kidney transplant version of the patientMpower app is now offered as standard care at the national renal transplantation centre at Beaumont Hospital in Dublin, Ireland. Patients and healthcare professionals have positively received it and studies of its use are ongoing.

It is not expected that the study or patientMpower app will create any additional risks for haemodialysis patients. In the event of any technical problems with the devices (i.e. app, digital weighing scales or BP monitor), patientMpower Ltd will be available to provide technical support. In addition, the on-call nephrology registrar at Beaumont hospital will be available to handle any medical enquiries with regard to BP recordings out of working hours and at weekends.

It is not expected that measurement of IVC diameter will create any additional risks for haemodialysis patients.

3. Description of design and trial population

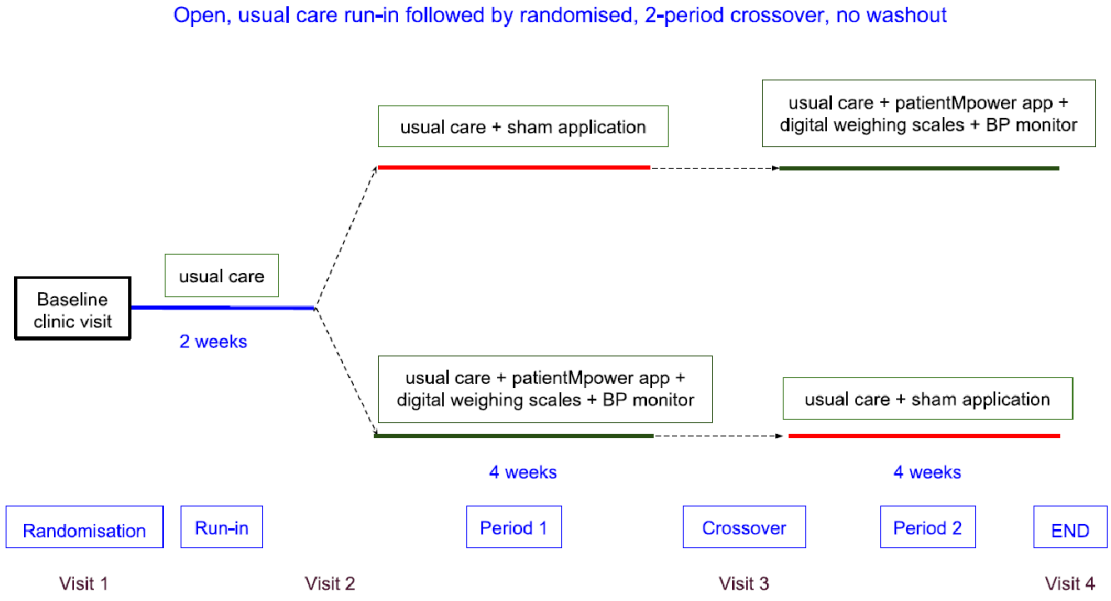
3.1 Overall design and plan

Open-label run-in usual care observation period (run-in period; 2 weeks) followed by randomization to two period crossover observation periods. (2 X 4 weeks).

The study will not make any other changes to the therapeutic interventions offered to the patients.

A diagram of the trial design is shown on Figure 3.1: 1 below.

Figure 3.1: 1 Diagram of trial design



3.1.1 Administrative structure of trial

This is a single centre study at three haemodialysis facilities under the governance of Beaumont Hospital, a tertiary care centre for nephrology in Dublin, Ireland.

The patientMpower app was developed and is owned by patientMpower, Dublin 8, Ireland.

The protocol was designed by Dr. Conall O'Seaghdha (Principal Investigator), Beaumont Hospital, Dublin 9, Ireland, Dr Donal Sexton (co-investigator) and patientMpower Ltd., Dublin 8, Ireland.

The study is sponsored by an unrestricted research grant from the Quality Innovation Corridor Digital Programme of eHealth Ireland.

3.2 Discussion of trial design, including choice of control group

This is a pilot-scale, prospective, open-label, randomized, two-period, cross-over intervention study.

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

Sequence 1: run-in (2 weeks): usual care followed by period 1 (4 weeks): patientMpower app (+digital weighing scales & BP monitor) followed by period 2 (4 weeks): sham application

OR

Sequence 2: run-in (2 weeks): followed by period 1 (4 weeks) sham application followed by period 2 (4 weeks): patientMpower app (+digital weighing scales & BP monitor)

Patients will follow their usual care and haemodialysis programme throughout the study.

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

The crossover design will enable comparison of use of the patientMpower app + usual care with a sham application + usual care alone over a four-week period. Each patient will serve as their own control.

The trial design will also allow assessment of the effect of the patientMpower app on study parameters compared with usual care alone.

Patients enrolled in the study will capture information on relevant parameters on a regular basis (daily for some parameters) using the patientMpower app. Patients will measure body weight at home using the supplied weighing scales and BP using the supplied BP monitor. The patient-measured weight, BP and other patient-reported data will be captured automatically by the patientMpower app.

Clinical assessments (e.g. IDWG, BP, ultrafiltration rate) in the same cohort of patients will be assessed at each dialysis visit including at the beginning, after two weeks (start of Period 1), after six weeks (start of Period 2) and at the end of the study.

This design allows comparison of patient-reported data and their longitudinal trends with clinic-reported data in a cohort of patients undergoing haemodialysis.

This design will also allow evaluation of the utility and acceptability of the patientMpower in a haemodialysis patient population. This will be assessed from both the patient and healthcare professional perspectives.

3.3 Selection of trial population

3.3.1 Main diagnosis for study entry

Require maintenance haemodialysis in an ambulatory care setting.

3.3.2 Inclusion criteria

Aged at least 18 years

Has daily unrestricted access to a suitable smartphone or tablet device at home.

Has an e-mail address.

Has home broadband and/or mobile data as part of their mobile phone service.

Demonstrates understanding of correct use of the patientMpower app, digital weighing scales, BP monitor and other study equipment.
Capable and willing to perform measurements (e.g. weight, BP) at home and record information on the patientMpower app on a daily basis.

Willing to give written informed consent.

3.3.3 Exclusion criteria

Significant confusion or any concomitant medical condition, which would limit the ability of the patient to record symptoms or other parameters on an electronic health journal.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

Patients are free to withdraw from the study at any time without any impact on their ongoing medical care.

The investigator may withdraw a patient from the study at any time if they believe that further participation in the study is not in the best interests of the patients.

3.3.4.2 Discontinuation of the trial

The study may be terminated early if recruitment is significantly behind schedule or if for any other reason, it is unlikely that the study can be completed.

4. Study observational intervention

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

4.1 Observational intervention to be assessed

4.1.1 Identity of observational intervention and comparator(s)

The study observational intervention is an electronic health journal, the patientMpower app (with a supplied digital weighing scales and BP monitor). This has been developed specifically for patients undergoing hemodialysis. The app is an electronic application downloaded to the patient's mobile phone or tablet device. The app is designed to allow the patient to report various parameters relevant to haemodialysis and record these on a regular basis, ideally daily. The information recorded by the patients will be stored in a secure cloud system and will be available to the patient through their phone or mobile device at all times. No personal health data are stored on the phone or mobile device itself.

Patients will be asked to report measurements on the patientMpower app each day. Patient-reported measures (at a minimum) will include body weight (one reading once/day), BP and compliance with relevant medication.

Additional patient-reported measures which can be reported on the patientMpower app include temperature, activity levels and symptoms. These are optional measurements and will only be recorded where practical for the patients.

The control observation will be usual care with a sham electronic application (which will not allow recording of body weight, BP or other measurements.

4.1.2 Method of assigning patients to observational groups

Patients who give informed consent and enter the study will be randomized to either:

- run-in period (usual care; 2 weeks) followed by patientMpower (+ digital weighing scales & BP monitor) + usual care; (4 weeks), followed by sham application + usual care; (4 weeks).

or

- run-in period (usual care; 2 weeks) followed by sham application + usual care; (4 weeks), followed by patientMpower (+ digital weighing scales & BP monitor) + usual care; (4 weeks).

A random sequence, random block number randomization schedule will be used to assign patients to either observation Sequence 1 or observation Sequence 2. (Observation sequences are described above in section 3.2.) The randomization schedule with will be provided by a centralised electronic

randomization service (Sealed Envelope, Clerkenwell Workshops, London EC1R 0AT, UK).

As the study will be conducted in three hemodialysis centers under the governance of Beaumont Hospital a separate randomization schedule will be generated for each centre.

4.1.3 Blinding and procedures for unblinding

4.1.3.1 Blinding

The study is open-label.

4.2 Concomitant therapy, restrictions and rescue treatment

4.2.1 Rescue medication, emergency procedures and additional treatment

If any patient or their healthcare professional has a concern with regard to BP or weight measurements the renal registrar on call at Beaumont Hospital will respond to calls out of hours and at weekends.

4.2.1.1 Management of acute exacerbations

Any exacerbations of the patient's underlying medical condition(s) should be treated according to standard procedures.

4.2.1.2 Management of other adverse events

Any other adverse events should be treated according to standard procedures.

4.2.2 Restrictions

4.2.2.1 Restrictions on concomitant treatment

There are no restrictions on concomitant treatment. All concomitant treatments as prescribed by the patients' healthcare professionals are allowed. Patients will continue to take all medicines and other treatments as prescribed by their healthcare professionals. As per the co-interventions protocol (Appendix 10.1), all nephrologists working at Beaumont Hospital will be asked not to alter their usual fluid balance management during the study.

4.2.2.2 Restrictions on diet and life-style

The study does not mandate any additional restrictions on diet or life-style. Patients will continue to follow all instructions on diet, exercise and lifestyle as directed by their healthcare professionals.

4.3 Treatment compliance

Patients will use the patientMpower app to record daily compliance with medications prescribed for management of their haemodialysis and associated medical conditions.

5 Variables and their assessment

5.1 Efficacy

The objective of this pilot-scale cross-over open label randomized study is to assess the effect of self-monitoring using the patientMpower electronic health journal [+digital weighing scales & BP monitor] on outcomes in ambulatory haemodialysis patients (see section 5.1.1.2 below).

The primary objective will be to determine the effect of the patientMpower app (+digital weighing scales & BP monitor) on total fluid removed by dialysis during the patientMpower observation period (compared with the sham period).

The frequency of use of the patientMpower app (+digital weighing scales & BP monitor) and patient-reported symptoms will be recorded.

The acceptability and utility of the patientMpower app in helping haemodialysis patients and their healthcare professional caregivers manage their condition will be assessed (from both the patient and healthcare professional perspective).

5.1.1 Efficacy endpoints

5.1.1.1 Primary endpoint

The primary endpoint will be the level of engagement of patients with the patientMpower app.

The primary endpoint variables are:

- number of patients asked to take part in the study
- number patients who give informed consent to take part in the study

- number consented patients who download the app to their smartphone or tablet device
- number patients who use the app at least once after downloading
- number of patients who use 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
- frequency of recording study parameters (weight, BP) at home

5.1.1.2 Secondary endpoints

The secondary endpoints include determination of the effect of patientMpower app (+digital weighing scales & BP monitor) 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, weight, BP.
- requirement for additional unscheduled dialysis.

The secondary endpoint variables include

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

Symptoms (e.g. dyspnoea, fatigue, oedema, headache, thirst, light-headedness) will be recorded by the patients.

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

- using the patientMpower app helped me to take the correct dose of my medicines every day (strongly agree/agree/disagree/strongly disagree)

- using the patientMpower app 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 app versus not using it (yes, no preference, no)
- my difficulty rating in using the patientMpower app (very easy, easy, difficult, very difficult)
- what was the effect of using the patientMpower app 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 app after the end of the study (yes, no)

This will also be assessed by the healthcare professional's response to the following questions:

- preference for using the patientMpower app versus not using it (yes, no preference, no)
- difficulty rating in using the patientMpower app (very easy, easy, difficult, very difficult)
- did using the patientMpower app help me to help the patient manage their health better? (yes, no)
- did using the patientMpower app help the patient to take their medicines at the correct dose every day (yes, no)
- do I believe the patient should continue using the patientMpower app after the end of the study (yes, no)
- what other measurements, reminders or information would be useful to have on the patientMpower app? (Open text for healthcare professional to give opinion)

An additional exploratory secondary endpoint will be to determine the effect of patientMpower app (+digital weighing scales & BP monitor) on inferior vena cava (IVC) diameter (measured immediately pre-dialysis) . This will be an optional measurement. Patients can choose to participate in the study without measurement of IVC diameter. The variables for this endpoint are longitudinal and transverse IVC diameter.

5.1.2 Assessment of efficacy

The primary efficacy endpoint data will be assessed by (a) comparison of the endpoint variables observed in the patientMpower (+digital weighing scales & BP monitor) + usual care period with the sham application + usual care period and (b) comparison of the endpoint data in both randomized observation periods with the run-in period data.

The secondary efficacy endpoint data will be assessed by (a) comparison of the endpoint variables observed in the patientMpower (+digital weighing

scales & BP monitor) + usual care period with the sham application + usual care period and (b) comparison of the endpoint data in both randomized observation periods with the run-in period data.

The acceptability and utility of the patientMpower app will be assessed by analysis of the responses to the patient and healthcare professional questionnaires (described above in 5.1.1.2).

Data on the level of engagement and the patient and healthcare professional opinions on utility and acceptability will be described and tabulated.

5.2 Safety

It is not anticipated that any safety issues will arise from use of the patientMpower app. Issues regarding abnormal blood pressure readings will be addressed by the nephrology department at Beaumont Hospital.

Any adverse events observed with medical treatments should be reported to the manufacturers or suppliers of those treatments.

5.3. Other variables

Demographic data (date of birth, gender, medication prescribed).

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

5.4 Appropriateness of measurements

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

The questionnaires used to assess usefulness and patient acceptability have been used to assess these parameters for other patient support platforms.

6 Investigational plan

Patients who participate in the study will follow their usual care and haemodialysis programme. They will then be randomized a sequence of either the patientMpower app (+ digital scales & BP monitor) + usual care followed by the sham application or vice versa. They will be encouraged to use the patientMpower app, digital weighing scales and BP monitor every day during that observation period to record parameters relevant to their health status (described in section 5.1.1.2 above).

6.1 Visit schedule

The total observation period will be approximately ten (10) weeks. During this time patients can be expected to attend for a haemodialysis session three times a week on average.

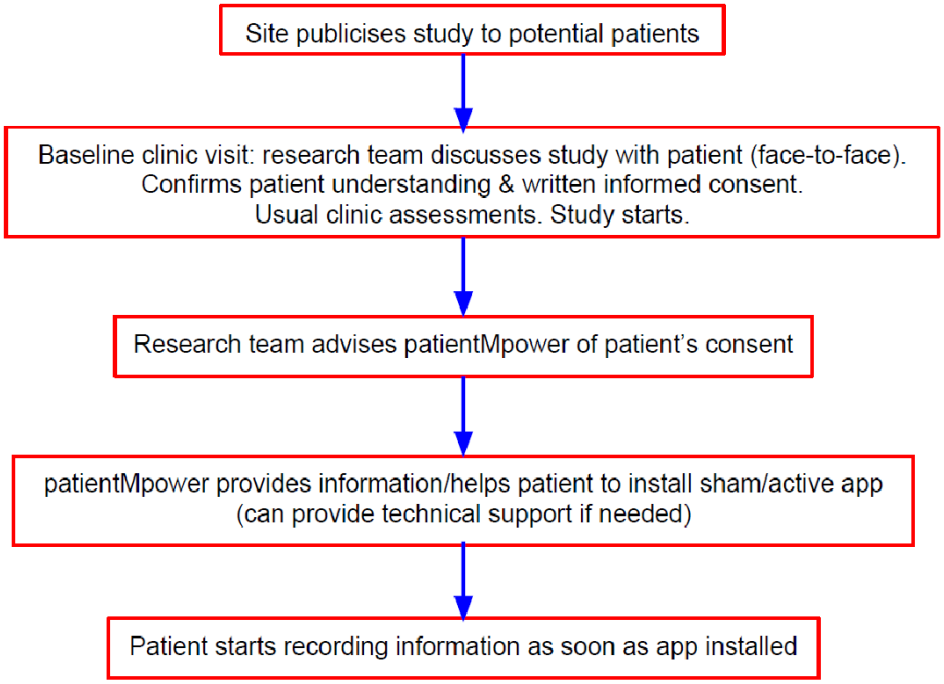
6.2 Details of trial procedures at selected visits

6.2.1 Patient recruitment process

The patient recruitment process is summarized in the flow-chart on page 6 and in Figure 6.2.1: 1 below.

Approximately 300 patients attend for dialysis under the governance of Beaumont Hospital. All eligible individuals will be invited to participate. It is estimated that a total of 50 people will be enrolled in this study.

Figure 6.2.1: 1 Patient recruitment process:



The study centre will publicise the study to their potential patient population.

When potential patients who are interested in the study attend for a usual care haemodialysis visit, the research staff will discuss the study (face-to-face) with the patient. This discussion will include assessing if the patient has a suitable phone/tablet device, internet access and e-mail address.

If the person wishes to participate, they will give informed consent electronically. The patient will receive a paper and electronic copy of the patient information document.

This is the start of the usual care run-in period.

The randomized allocation of the observation group will be done at or after this visit but use of the patientMpower app or sham application will not start until approximately 2 weeks later.

The research team at the study centre will advise patientMpower of email address of people who have given their electronic consent to participate and of the date of the start of run-in.

The independent randomization service will advise patientMpower of the observation sequence allocated by randomization (see Section 3.2 for description).

patientMpower Ltd. will provide information pack (electronic; includes instructions on installation of patientMpower app or sham application, digital weighing scales and BP monitor (if randomized to that sequence) to the patient at the planned date of 2-week usual care haemodialysis visit to study centre.

If required, patientMpower Ltd will contact or meet the patient to offer help with installation of patientMpower app or sham application and pairing of devices (so that all are installed and operating prior at the planned 2-week usual care haemodialysis clinic visit).

6.2.2 Assessments during observation period

The trial procedures at each visit are summarized in the flow chart on page 8.

6.2.2.1 Baseline visit

At a planned usual care haemodialysis visit to study centre, the study centre research team will discuss the study with the patient and confirm their patients understanding of the study processes and their willingness to participate. A paper version of the full-length patient information document will be given to the patient. The patient will have the opportunity to ask questions on the study processes.

Demographic data, vital signs, medical history and concomitant therapy for renal and other relevant conditions will be recorded.

The following parameters will be assessed and recorded in the clinic records:

- actual weight before haemodialysis
- target weight
- actual systolic and diastolic BP before haemodialysis
- ultrafiltration rate at baseline haemodialysis session

The patient will be randomly allocated to one of two possible observation sequences:

EITHER

Sequence 1: run-in (2 weeks): usual care followed by period 1 (4 weeks): patientMpower app (+digital weighing scales & BP monitor) followed by period 2 (4 weeks): sham application

OR

Sequence 2: run-in (2 weeks): followed by period 1 (4 weeks) sham application followed by period 2 (4 weeks): patientMpower app (+digital weighing scales & BP monitor)

Randomisation will be allocated by contacting a centralized randomization service (Sealed Envelope Ltd., London, UK).

The centralised randomization service will automatically advise patientMpower of the observation sequence allocated to the patient.

The patient will attend for haemodialysis as required for a run-in period of approximately 2 weeks. There will be no change to their usual care during this run-in period.

At each haemodialysis visit during run-in the following parameters will be assessed and recorded:

- actual weight before haemodialysis
- target weight
- actual systolic and diastolic BP before haemodialysis
- ultrafiltration rate at baseline haemodialysis session
- any requirement for additional unplanned haemodialysis sessions

6.2.2.2 Week 2 clinic visit (start of randomized observation period 1)

The trial procedures after the Week 2 visit will vary dependent on the observation sequence allocated to the patient.

patientMpower Ltd will contact or meet the patient and help install the patientMpower app or sham application to the patient's mobile phone or tablet prior to this visit.

The patient should bring their mobile phone or tablet device with them to the clinic.

If allocated to observation sequence 1
The patientMpower app will be downloaded to the patient's mobile phone or tablet device prior to or at this visit. (A tablet device will be supplied to the patients if they do not have access to a suitable smart device at home.) The patient will also be supplied with a digital weighing scales and BP monitor.

The patients will be instructed in the correct use of the digital weighing scales and BP monitor and uploading of data to the patientMpower app. The patients' understanding of the patientMpower app, digital weighing scales, BP monitor and the study procedures should be checked before they leave the clinic.

During observation period 1 patients will attend for haemodialysis sessions as usual and will be encouraged to record self-observed parameters on the patientMpower app on a regular basis for about 4 weeks. The following should be recorded by the patient on the patientMpower app each day:

- body weight
- BP
- compliance with medication
- fluid intake
- symptoms

Patients will receive reminders (via the patientMpower app) at appropriate intervals to record study parameters. Other parameters (e.g. steps/day) can be recorded by the patient (if suitable measurement devices are available to the patient.

If allocated to observation sequence 2

The sham platform will be downloaded to the patient's mobile phone or tablet device at or prior to this visit. (A tablet device will be supplied to the patients if they do not have access to a suitable smart device at home.)

During observation period 1, patients allocated to the sham platform, patients will attend for haemodialysis sessions and follow all usual care advice for the next 4 weeks.

At each haemodialyis session the following parameters will be assessed and recorded in the clinic records:

- actual weight before haemodialysis
- target weight
- actual systolic and diastolic BP before haemodialysis
- ultrafiltration rate at each haemodialysis session

If the patient has given consent to measurement of IVC diameter, this will be assessed by ultrasound at this visit. The procedure is described below:

- Lie the patient down at roughly 45 degrees. If images are poor, will attempt other positions such as lying flat and maneuvers to relax abdominal muscles.
- Switch on and prepare the settings for the handheld ultrasound machine or echo machine.
- Use the cardiac preset function.
- Apply ultrasound gel to the ultrasound probe and to the patient's chest.
- Obtain a subcostal view and locate the right atrium.
- Rotate the probe to visualize the IVC.
- Measure both the longitudinal and transverse diameter of the IVC 2 cm below the right atrium and record the anonymised measurements securely on an encrypted drive.

- The diameter lengths are calculated by calibrating against the scale on the right side of the screen.
- Once measurements are taken, let the patient know the procedure is finished and help them to clean the gel.
- Clean the ultrasound probe, apply disinfectant provided and then return the ultrasound machine to its charging bay.

6.2.2.3 Week 6 visit (crossover visit; end period 1; start period 2)

At approximately 4 weeks after starting period 1, patients will return to the clinic for a routine haemodialysis session. At this visit, the following parameters will be assessed and recorded in the clinic records:

- actual weight before haemodialysis
- target weight
- actual systolic and diastolic BP before haemodialysis
- ultrafiltration rate at each haemodialysis session

If allocated to observation sequence 1

The patient will be asked to stop using the patientMpower app for the next four weeks. (The data feed from the digital weighing scales and BP monitor to the patientMpower app will be deactivated by patientMpower Ltd.). The sham application will be activated by patientMpower Ltd.

The patient and healthcare professional opinion on the usefulness and acceptability of the patientMpower app will be assessed and recorded. (The questions are described in section 5.1.1.2 above.)

During observation period 2, patients allocated to the sham platform will attend for haemodialysis sessions and follow all usual care advice for the next 4 weeks.

At each haemodialyis session the following parameters will be assessed and recorded in the clinic records:

- actual weight before haemodialysis
- target weight
- actual systolic and diastolic BP before haemodialysis
- ultrafiltration rate at each haemodialysis session

If allocated to observation sequence 2

The patientMpower app will have been downloaded to the patient's mobile phone or tablet device at or prior to this visit. The patient will also be supplied with a digital weighing scales and BP monitor.

The patient will be instructed in the correct use of the digital weighing scales and BP monitor and uploading of data to the patientMpower app. The patient's understanding of the patientMpower app, digital weighing scales,

BP monitor and the study procedures should be checked before they leave the clinic.

During observation period 2, patients will attend for haemodialysis sessions as usual and will be encouraged to record self-observed parameters on the patientMpower app on a regular basis for about 4 weeks. The following should be recorded by the patient on the patientMpower app each day:

- body weight
- BP
- compliance with medication
- fluid intake
- symptoms

Patients will receive reminders (via the patientMpower app) at appropriate intervals to record study parameters. Other parameters (e.g. steps/day) can be recorded by the patient (if suitable measurement devices are available to the patient.

If the patient has given consent to measurement of IVC diameter, this will be assessed by ultrasound at this visit. The procedure is as described above.

6.2.2.4 Week 10 visit (end period 2; end of study)

At approximately 4 weeks after starting observation period 2, patients will return to the clinic for a routine haemodialysis session.

At this visit, the following parameters will be assessed and recorded in the clinic records:

- actual weight before haemodialysis
- target weight
- actual systolic and diastolic BP before haemodialysis
- ultrafiltration rate at each haemodialysis session

The patient and healthcare professional opinion on the usefulness and acceptability of the patientMpower app will be assessed and recorded. (The questions are described in section 5.1.1.2 above.)

Any relevant clinic outcomes (e.g. additional unscheduled dialysis sessions) will be documented.

If the patient has given consent to measurement of IVC diameter, this will be assessed by ultrasound at this visit. The procedure is as described above.

This visit is the end of the study.

7. Statistical methods and determination of sample size

This a pilot-scale study to assess the feasibility of haemodialysis patients using the patientMpower app to monitor their weight, blood pressure and other relevant parameters to monitor their health.

7.1 Statistical design and model

Prospective, open-label run-in period followed by open randomization to two-period cross over group comparison of patientMpower app (+digital weighing scales & BP monitor) versus sham electronic app (no scales or BP monitor). No washout between observation periods.

Usual care for all patients throughout study.

7.2 Null and alternative hypotheses

Not relevant.

7.3 Planned analyses

Results will be collected and summarized for descriptive statistical display.

The efficacy data of the two observation groups in the randomized observation periods will be compared with each other and separately with the efficacy data of the run-in period using mixed effects models and generalized estimating equations.

7.3.1 Primary analyses

The frequency of use and engagement by patients with the patientMpower app will be tabulated and described.

7.3.2 Secondary analyses

Trends in ultrafiltration rate, pre-dialysis weight and BP at each haemodialysis session will be compared between the two randomized observation periods.

The number of haemodialysis sessions in which the IDWG is ≤4% will be tabulated and compared between the randomized intervention periods and baseline periods.

The total volume of fluid removal in all hemodialysis sessions will be compared between the two randomized observation periods.

Medication adherence will be compared between observation periods.

Data from both randomized observation periods will be compared with the data observed during the run-in period for the same patients.

The observed IVC diameters will be compared between the two randomized observation periods.

Compliance with daily recording of fluid intake, weight, and blood pressure will be tabulated and displayed

Patient-reported symptoms will be tabulated and displayed.

The acceptability and utility of the patientMpower app will be assessed by analysis of the responses to the patient and healthcare professional questionnaires (described above in 5.1.1.2).

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 (+digital weighing scales & BP monitor) observation period to the sham application period.

7.3.3 Safety analyses

Not relevant

7.3.4 Interim analyses

None planned.

7.3.5 Health economic analyses

The number of additional unscheduled haemodialysis sessions will be recorded and decided upon by the outcome adjudication committee (see Appendix 10.4).

7.4 Handling of missing data

No imputations of missing data will be made.

7.5. Randomisation

At the baseline visit, patients will be randomly allocated to either of two observation periods followed by the other in a cross-over design:
usual care run-in period (2 weeks) followed by patientMpower app (+digital weighing scales & BP monitor) + usual care (4 weeks) followed by sham application + usual care (4 weeks)

or

usual care run-in period (2 weeks) followed by sham application + usual care (4 weeks), followed by patientMpower app (+digital weighing scales & BP monitor) + usual care (4 weeks)

The randomization will be open.

7.6 Determination of sample size

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

8. Informed consent, data protection and trial records

8.1 Study approval, patient information and informed consent

The study will be approved by the relevant ethics committee(s) for the participating centre.

The study will be discussed with each patient and they will be provided with a written document describing the study conditions and procedures.

All patients will give written informed consent before enrollment

8.2 Data quality assurance

All endpoint data will be stored on a central database for analysis. The data as reported by the patients will not be queried before descriptive statistical analysis tables are prepared

8.3 Records

8.3.1 Source documents

The original electronic data will be the source document.

8.3.2 Direct access to source data and documents

Source data verification will not be performed.

8.3.3 Storage of records

Medical data relating to patient care will be stored in the medical records according to the usual procedures of the treatment site(s).

The endpoint data collected by the patients and recorded on the patientMpower app will be stored in a secure cloud database (located in the European Economic Area) managed by patientMpower Ltd. These data will be available to patients indefinitely to aid them in self-management of their medical condition. Patients can request deletion of their data from the patientMpower cloud database at any time.

8.4 Statement of confidentiality

Patients will only be identified by a unique identification number on the trial database and data will be anonymised. All data will be treated as confidential.
Each patient's data is linked to their unique identification number.

The patientMpower application and storage are designed with stringent security protocols. The solution is hosted in Google Compute Engine. The security protocols used include:

- application uses a PostgreSQL database (https://www.postgresql.org/) which is backed up nightly
- application is patched regularly to ensure it is maintained against security vulnerabilities
- only certain Internet Protocol (IP) addresses can login to the cloud infrastructure using Secure Shell (SSH) with IP whitelists and public/private key access only
- built-in firewalls
- encrypted data storage
- patientMpower staff access to the PostgreSQL database, and content system is restricted and monitored
- a unique username and password for each user.
- audit and accounting of all access to the system is recorded. In the event of any staff looking at data without proper authorisation, there is an audit trail of what data was viewed
- data transfer between the patient mobile device and cloud server is sent securely via Transport Layer Security (TLS) and the platform's cloud infrastructure uses an Extended Validation Secure Sockets Layer (SSL) Certificate issued by Digicert (https://www.digicert.com)
- data on the server is encrypted, only authenticated users can access the server

Access to data stored on the patientMpower app will be restricted to named individuals at patientMpower Ltd who will each have a unique userID and password.

8.5 Completion of trial

The trial will be complete when 50 patients have completed the 10-week observation period.

If it appears to be unlikely that the target number of patients can be achieved (e.g. because of slow recruitment) a lower target will be set (after discussion and agreement with investigator sites).

8.6 Protocol violations

All data will be analysed on an intention-to-treat basis without regard to protocol violations.

8.7 Compensation available to the patient in the event of study-related injury

It is not anticipated that any study-related injury will occur

9 References

1. Foley RN, Gilbertson DT, Murray T*, et al.* Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med* 2011; **365:** 1099-1107.

2. Collins AJ, Foley RN, Herzog C*, et al.* Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis* 2010; **55:** S1-420, A426-427.

3. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int* 2011; **79:** 250-257.

4. Assimon MM, Flythe JE. Rapid ultrafiltration rates and outcomes among hemodialysis patients: re-examining the evidence base. *Curr Opin Nephrol Hypertens* 2015; **24:** 525-530.

10. Appendices

Appendix 10.1 Cointerventions protocol

All nephrologists working at Beaumont Hospital will be asked not to alter their usual fluid balance management during the study

Appendix 10.2 Contamination protocol

Patients will be asked not to discuss the details of the study with each other or with the dialysis nurses or any other staff. This is to avoid those in the sham arm from mimicking behaviors in the intervention arm by knowing what it entails.

Appendix 10.3 Steering committee

The steering committee will consist of Dr Conall O'Seaghdha and Dr. Donal Sexton (Beaumont Hospital, Dublin 9, Ireland), Colin Edwards and Eamonn Costello (patientMpower Ltd., The Digital Depot, Thomas Street, Dublin 8, Ireland).

Appendix 10.4 Adjudication committee

The adjudication committee will consist of the Steering Committee and an independent nephrologist physician (not involved in the study). The purpose of the adjudication committee is to review and decide on key clinical outcomes. For example, the adjudication committee will decide whether a dialysis session during the study period was extra and unscheduled or not.

Appendix 10.5 Recruitment of patients

Research assistants will undertake recruitment of participants. These individuals will be independent and will not be physicians or nurses who are responsible for the daily medical care of the potential patients. This is to ensure that dialysis patients do not feel obliged to participate.

Appendix 10.6 Training of personnel

patientMpower Ltd have skilled personnel capable of demonstrating the use of the devices to study patients.

Appendix 10.7 Trial registration on public registry

After research ethics approval, the study will be registered on the international clinical trials registry at www.clinicaltrials.gov.

Appendix 10.8 Funding

This study is funded by the Health Service Executive Quality Innovation Corridor programme.

Appendix 10.9 Incentives for participation:

Patients who take part in the study will be permitted to keep the BP monitor and electronic scales after the study is complete. This equipment will be worth approximately 200 euro. They will be able to continue to use these (with or without use of the patientMpower app) for as long as they wish.