Pilot-scale, single-arm, observational study to assess the utility and acceptability of a wearable hydration monitor in haemodialysis patients

Haemodialysis Outcomes & Patient Empowerment study 02
(HOPE-02)

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PROTOCOL SUMMARY

PRODUCT	Sixty wearable hydration monitor
CLINICALTRIALS.GOV IDENTIFIER	NCT 00000000
PROTOCOL TITLE	Pilot-scale, single-arm, observational study to assess the utility and acceptability of a wearable hydration monitor in haemodialysis patients
COORDINATING INVESTIGATOR	Dr. C. O'Seaghdha, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland
NUMBER OF TRIAL SITES	One: Beaumont Hospital dialysis centre.
STUDY OBJECTIVES	To determine the validity and reproducibility of the fluid status data captured by a wearable hydration monitor (Sixty device) compared with bioimpedance and haemodialysis machine data) in ambulatory haemodialysis patients. To assess the utility and patient acceptability of the Sixty device.
METHODOLOGY	Open, prospective, single-arm observation. Observation period: 3 weeks.
NUMBER OF SUBJECTS	Total randomised: 20
DIAGNOSIS	End Stage Kidney Disease requiring regular ongoing haemodialysis
MAIN CRITERIA FOR INCLUSION	Age ≥18 years, demonstrated understanding of use of the Sixty device and home blood pressure monitor, written informed consent
TEST PRODUCT	Sixty wearable hydration monitor
COMPARATOR PRODUCT	None
END OF STUDY DEFINITION	3 weeks
PRIMARY ENDPOINT	Volume status measured by Sixty device compared to haemodialysis machine and bioimpedance data
SECONDARY ENDPOINTS	Acceptability of Sixty device
INTERIM ANALYSIS	None planned
STATISTICAL METHODS	Descriptive tables or figures will be prepared. Within-patient comparison of fluid status data as determined by different methodologies.

FLOW CHARTS

Flow chart 1 Assessments during observation period

	study observation period (3 weeks)				
	Baseline clinic visit	**At each dialysis session**	**Week 1**	**Week 2**	**Week 3 (end)**
Informed consent	X				
Demographic data (include dialysis & medicines history)	X				
Vital signs, body weight, routine hemodialysis measurements in-clinic[A]	X	X	X	X	X
Assess fluid status with bioimpedance[B]	X		X	X	X
Instruction/patient training on use of Sixty device	X				
Wear Sixty device daily[C]	X	X	X	X	X
Download data and recharge Sixty device[D]		X	X	X	X
Record symptoms related to fluid status[E]	X	X	X	X	X
Record adverse events[F]	X	X	X	X	X
Patient records blood pressure at home once/day[G]	once/day throughout study				
Stop using Sixty device[H]					X
Acceptability of Sixty device questionnaire[I]					X
End of study					X

[A] Routine measurements (at each hemodialysis session) include total fluid removal, interdialytic weight gain (IDWG), proportion of haemodialysis sessions in which IDWG is ≤ 4%, pre-dialysis and post-dialysis weight, pre-dialysis, intradialytic and post dialysis BP and pulse rate.

[B] Fluid status will be assessed by bioimpedance measurements immediately before start and immediately after end of haemodialysis.

[C] Sixty is a wrist-worn hydration monitor. It uses optical spectroscopy and machine learning algorithms to determine hydration level. No data is displayed to the patient. The device should first be worn by the patient for five minutes before the haemodialysis session at the Baseline Visit and throughout that haemodialysis session. It should then be worn throughout the study observation period, including during all haemodialysis sessions.

[D] The data in the Sixty device SD card should be downloaded before the start of each haemodialysis session. The device should then be recharged during the dialysis while the patient is wearing it. The Sixty device will continue to capture data while it is recharging.

[E] Symptoms related to fluid status will be recorded before haemodialysis using the symptom score developed by Kraemer et al[8].

[F] For example, requirement for nursing intervention such as stopping dialysis or administering fluid bolus. Adverse events include, but are not limited to muscle cramps, symptomatic hypotension, access-related complications, hypertension-related symptoms, congestive heart failure, pulmonary edema, requirement for additional unscheduled dialysis, or need for hospitalisation and number and type(s) of BP medications.

[G] The patient will be supplied with an A and D Medical Blood Pressure Monitor (model UA-651BLE) at the baseline visit and will be asked to record their blood pressure at home once/day during the study observation period. The patient will be returned to the investigator at the end of the study.

[H] The Sixty device should be worn until five minutes after the end of the haemodialysis session at the end-of-study visit. The data in the Sixty device SD card should be downloaded after the end of this haemodialysis session. The Sixty device will then be returned to the investigator.

[I] Patient opinions of the Sixty device sought by questionnaire. This is designed to understand the functionality and acceptability requirements. This will explore the experience of the current prototype as well as describe the industrial design, user interface and user experience that is proposed for the commercial product.

List of Figures and Tables

List of Abbreviations and Terms

BP	blood pressure
BVM	blood volume monitoring
CV	cardiovascular
DTIF	Disruptive Technologies Innovation Fund
ECW	extracellular water
HOPE	Haemodialysis Outcomes & Patient Empowerment
IDWG	interdialytic weight gain (i.e. fluid weight gain between dialysis sessions)
L	litre
OH	overhydration
PND	paroxysmal nocturnal dyspnea

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 interdialytic period and as dialysis is delivered on alternate days there is one interdialytic 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 interdialytic 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. Similarly, volume depletion induced by excessive ultrafiltration is associated with myocardial stunning, cerebrovascular events and mortality[3,4].

In one study[5] up to 27% of prevalent dialysis patients were estimated to be volume overloaded. The prevalence increased to 66.2% when patients with mild fluid overload are included. 31.1% of patients met the criteria for normovolaemia and 2.7% were classified as fluid-depleted.

Technology to evaluate the optimal volume status of haemodialysis exists. Use of validated measures of volume such as bioimpedance, however, are limited by time and cost constraints[6]. Volume reduction as guided by alternative interventions, such as blood volume monitoring (BVM) have been associated with increased mortality[7].

Wearable technology which can record patient parameters such as vital signs, electrical rhythms, and serum potassium levels have allowed patients to monitor their conditions in real-time. A similar option for volume monitoring in haemodialysis patients would enable patients and care providers to optimise fluid status and reduce complications associated with under- and overhydration. To date, no specific wearable hydration monitor for haemodialysis patients is available and validated. The purpose of this trial is to compare a wearable hydration monitor against gold standard measurements of volume in haemodialysis patients.

To date, this approach has not been explored in haemodialysis patients.

1.2 Product profile

The Sixty device is a wearable hydration monitor that is currently in development. Photographs of the current prototype and expected final designs are shown in Figure 1.2: 1.

Figure 1.2: 1: Photographs of prototype and expected final design of Sixty device

The prototype device (left-hand image) measures 66mm x 48mm x 10mm. The on/off button and charging port are visible on the top edge. The surface facing the camera will be in contact with the dorsal surface of the user's wrist. The expected final design is shown in the right-hand image. This is expected to be approximately the size of a commercially available smart watch (e.g. Apple watch).

The Sixty device uses diffuse reflectance spectroscopy to measure fluid levels subdermis. Optical sensors shine light of a specific wavelength onto the skin and the amount of light reflected back can be correlated to different body components (e.g. water). The machine learning algorithm is trained using a calibrated data set of known fluid states allowing the device to interpret the data and provide feedback on fluid status.

The prototype device used in this study does not reflect the final aesthetic or "looks like" design, but provides the necessary functionality to establish proof of principle in fluid overloaded patients. It is designed to be very simple to operate, with only one button to turn it on and off. The simple user interface indicates that the device is on/off and is functioning correctly. The prototype device will only collect data and does not provide feedback to the user on their hydration status. Data is collected locally on a memory card (i.e. SD card) which will be removed periodically to recover the data.

The device and battery is designed to run for an extended period and can be charged via a USB cable. Charging the device and collection of data will be coordinated at the haemodialysis study centre to minimise data gaps and to reduce unnecessary complexity for the patient.

Patent acceptability will be assessed.

2. Rationale, objectives and benefit-risk assessment

2.1 Rationale for performing the trial

This trial will evaluate if a wearable hydration monitor (the Sixty device), has validity and reproducibility against gold standard measurements of fluid volume in haemodialysis patients.

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

As no specific wearable hydration monitor for haemodialysis patients is available and validated, there is sufficient justification in testing the effectiveness and acceptability of the Sixty device in a controlled observational setting.

2.2 Trial objectives

The objective of this pilot-scale study is to assess how the Sixty hydration monitoring device functions when used in a range of haemodialysis patients of varying age, gender, body habitus and volume status. Patients with a range of baseline fluid status (ranging from 15% above to 10% below their dry weight as determined by bioimpedance) will be considered for enrollment.

The primary objective is to determine the validity and reproducibility of the data captured by the Sixty device in haemodialysis patients. (The goal is to determine if the data captured by the Sixty device and the additional haemodialysis parameters described can be developed into algorithms that provide actionable insights to better manage fluid overload in the interdialytic period.)

Haemodialysis parameters will be assessed as usual during the study and will include:

- total fluid removal (each haemodialysis session)
- interdialytic weight gain (IDWG)
- proportion of haemodialysis sessions in which IDWG is ≤ 4%.
- pre-dialysis weight
- post-dialysis weight
- pre-dialysis blood pressure (BP)
- intradialytic BP

- post-dialysis BP
- number and type(s) of BP medications
- requirement for nursing interventions (e.g. stopping dialysis or administering fluid bolus)
- adverse events requiring or prolonging hospitalisation
- requirement for additional unscheduled dialysis

Fluid volume data measured by the Sixty device will be compared to recorded extracted fluid and volume status as measured by haemodialysis machine data and bioimpedance findings.

Patient-reported symptoms related to haemodialysis and the underlying medical condition will be recorded before haemodialysis. Symptoms data will be assessed and compared with fluid status data.

Data on BP measured once/day at home during the interdialytic period will also be recorded.

An additional objective of this observational study is to assess the acceptability and utility of the Sixty device (from the patient perspective).

2.3 Benefit-risk assessment

This study is designed to contribute to the development of a multivariate algorithm to help haemodialysis patients monitor and manage their fluid intake. The Sixty device will collect data during multiple haemodialysis sessions allowing the algorithm to be trained to recognise different fluid states, from dry weight to varying degrees of fluid overload. Furthermore, the continuous monitoring in the interdialytic period will capture the “real world” data, and will be used to verify the validity of the algorithm.

The Sixty device prototype will not provide feedback to the patient so it is not expected that the study or the Sixty device will create any additional risks for haemodialysis patients. In the event of any technical problems with the device, the Sixty team will be available to provide technical support.

All patients will receive optimal haemodialysis during the study. In addition, the on-call nephrology registrar at Beaumont hospital will be available to handle any medical enquiries from patients enrolled in the study.

3. Description of design and trial population

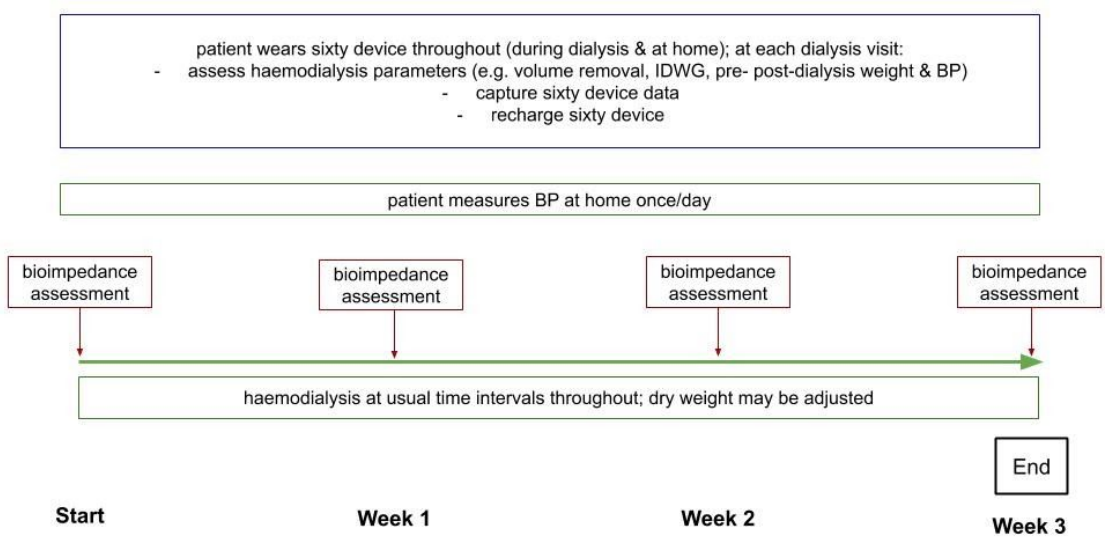
3.1 Overall design and plan

Prospective, open-label run-in observation period with Sixty device (3 weeks).

The study will not make any changes to the usual haemodialysis schedule for 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 the Beaumont Hospital, a tertiary care centre for nephrology in Dublin, Ireland.

The Sixty hydration monitor was developed and is owned by Design to Value Ltd, Innishannon, Cork, Ireland.

The study is being conducted as part of the Haemodialysis Outcomes & Patient Empowerment (HOPE) project supported by the Disruptive Technology Innovation Fund of Ireland (DTIF). The HOPE project is a collaboration between the Royal College of Surgeons in Ireland, Beaumont Hospital, patientMpower Ltd., Digital Depot, Dublin and Sixty (registered as Design to Value Ltd.), Innishannon, Co. Cork. The objective of HOPE is to develop artificial intelligence-enabled software to improve determination and maintenance of fluid balance in haemodialysis patients with a long-term goal of increasing the proportion of patients receiving dialysis at home. This study is a collaboration between all partners in HOPE and the data and outcomes will be shared with all partners. The study is funded by the DTIF.

The protocol was designed by Dr. Conall O'Seaghdha (Principal Investigator), Dr. Vicki Sandys (both of Beaumont Hospital, Dublin 9, Ireland), Design to

Value Ltd, Innishannon, Co. Cork, Ireland and patientMpower Ltd., Digital Depot, Dublin 8, Ireland.

3.2 Discussion of trial design, including choice of control group

This is a pilot-scale, prospective, open-label, single-arm observational study.

All patients will be allocated to the same observation sequence.

Patients will follow their usual haemodialysis regimen throughout the study. Patients' dry weight will be optimised using gold standard care (bioimpedance measurements) during the study.

Clinical assessments (e.g. IDWG, BP, pulse rate, ultrafiltration volume, symptoms) will be assessed at each dialysis visit.

The trial design will allow assessment of the validity and reproducibility of data collected by the Sixty device in haemodialysis patients. Data from the Sixty device will be compared against other validated methods of volume assessment (haemodialysis machine and bioimpedance data) and with observed symptoms in patients across a range of age, genders and volume status.

The study will also allow evaluation of the utility and acceptability of the Sixty device in a haemodialysis patient population. This will be assessed from the patient perspective.

3.3 Selection of trial population

3.3.1 Main diagnosis for study entry

Require maintenance haemodialysis in an ambulatory care setting.

Patients with a range of baseline fluid status (ranging from 15% above to 10% below their dry weight as determined by bioimpedance) will be considered for enrollment.

3.3.2 Inclusion criteria

Aged at least 18 years

Demonstrates understanding of correct use of the Sixty device.

Capable and willing to measure blood pressure at home on a daily basis.

Willing to give written informed consent.

3.3.3 Exclusion criteria

Conditions precluding accurate use of bioimpedance (e.g. limb amputations, severe malnourishment).

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

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 their usual haemodialysis regimen 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 Sixty device is a wearable hydration monitor that is currently in development. It uses diffuse reflectance spectroscopy to measure fluid levels subdermis. Optical sensors shine light of a specific wavelength onto the skin and the amount of light reflected back can be correlated to different body components (e.g. water). The prototype device used in this study provides the necessary functionality to establish proof of principle in fluid overloaded patients. This prototype device will only collect data and will not provide feedback to the user on their hydration status.

There is no comparator intervention.

4.1.2 Method of assigning patients to observational groups

All patients who give informed consent and enter the study will be allocated to the same observation sequence.

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 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 be asked to wear the Sixty device throughout the study observation period (including during haemodialysis sessions).

Patients will be asked to measure blood pressure once/day at home during the study observation period.

5 Variables and their assessment

5.1 Efficacy

5.1.1 Efficacy endpoints

5.1.1.1 Primary endpoint

The primary endpoint will be to evaluate the accuracy of the Sixty device data in assessing volume in haemodialysis patients compared to gold standard monitoring techniques. The volume status as measured by the Sixty device will be compared with volume status as measured by bioimpedance, patient symptoms, and traditional haemodialysis parameters.

The primary endpoint variables include:

Comparison of volume status as measured by Sixty device compared to bioimpedance pre- and post-dialysis:

- volume overload as defined by bioimpedance: overhydration (OH)/extracellular water (ECW) > 15% (corresponding to 2.5L)
- normohydration defined as: ECW -6 to + 6% (corresponding to -1.1L to + 1L)

Correlation of volume status with patients' symptoms before haemodialysis based upon the symptom score developed by Kraemer et al[8].

Symptoms of hypovolaemia:

- thirst directly after haemodialysis
- symptomatic hypotension, on change of position
- symptomatic hypotension
- nausea and vomiting
- muscle cramps
- limpness/ tiredness between dialysis sessions
- dizziness between dialysis sessions

Symptoms of hypervolaemia

- chronic coughing (new)
- dyspnea on recumbency
- dyspnea at rest; 1 pillow
- dyspnea at rest: 2 pillow
- dyspnea at rest: 3 pillows
- pretibial oedema
- paroxysmal nocturnal dyspnea (PND)

Correlates of volume status as measured by haemodialysis parameters including:

- total fluid removal (each haemodialysis session)
- IDWG
- proportion of haemodialysis sessions in which IDWG is ≤ 4%.
- pre-dialysis and post-dialysis weight
- pre-dialysis, intradialytic and post dialysis BP
- pulse rate
- requirement for nursing intervention such as stopping dialysis or administering fluid bolus
- adverse events including, but not limited, to muscle cramps, symptomatic hypotension, access-related complications, hypertension-related symptoms, congestive heart failure, pulmonary edema, requirement for additional unscheduled dialysis, or need for hospitalisation
- number and type(s) of BP medications
- home BP measured once/day during the interdialytic period

5.1.1.2 Secondary endpoints

A secondary objective is a descriptive analysis of the data captured by the Sixty device and the additional haemodialysis parameters used to measure volume status in haemodialysis patients. The proportion of haemodialysis sessions in which normohydration was achieved will be recorded.

The patient’s opinion of the acceptability of the Sixty device as assessed by their response to a questionnaire. Examples of questions in the acceptability questionnaire include:

- how do you currently manage your fluid intake in between dialysis sessions?
- on a scale of 1 to 5, how well do you feel in control of fluid status during this interdialytic period? (1 meaning "no control"... with 5 meaning "fully in control with good understanding what triggers fluid overload")
- would you wear a device similar in looks to a FitBit/Apple watch, if it could continuously monitor your fluid status and prompt you when and how much to drink to stay hydrated yet limit fluid overload?
- what are the minimum acceptable functionality that this device would need to have in order for you to wear it (check box list of features such as):

- tells me my hydration level and prompts me on how to manage fluid intake.
- tells the time
- measures heart rate
- measures steps / activity
- measures sleep quality

5.1.2 Assessment of efficacy

The primary and secondary endpoint data will be listed and tabulated or displayed graphically.

The primary endpoint will be assessed by comparison of the fluid status variables observed via the Sixty device with those observed via bioimpedance and haemodialysis machine data and with symptoms.

The acceptability and utility of the Sixty device will be assessed by analysis of the responses to a patient questionnaire.

5.2 Safety

It is not anticipated that any safety issues will arise from use of the Sixty device or bioimpedance assessment. Issues regarding abnormal BP 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 [e.g. date of birth, gender, medical cause of haemodialysis, time since first ever dialysis, vascular access route for haemodialysis, medication(s) prescribed for hypertension].

5.4 Appropriateness of measurements

The primary efficacy endpoint variables are measurements which are important and accepted measures of fluid status and renal function in haemodialysis patients.

6 Investigational plan

Patients who participate in the study will follow their usual haemodialysis regimen and will be asked to wear a wrist-worn hydration monitor (the Sixty device) for approximately three weeks. Patients will also be asked to record BP at home once/day for approximately three weeks. In addition to usual care, participating patients will have fluid status measured by bioimpedance on four occasions.

6.1 Visit schedule

The total observation period will be approximately three weeks. It is anticipated that patients will attend the clinic for haemodialysis three times per week on average. No additional patient visits are required for this study.

6.2. Patient recruitment process

Approximately 300 patients attend for dialysis under the governance of Beaumont Hospital. Eligible individuals will be invited to participate. It is estimated that twenty (20) people will be enrolled in this study.

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

The study observation period can start after written informed consent.

6.3 Details of trial procedures

The trial procedures at each visit are summarized in the flow chart on page 7.

6.3.1 Baseline clinic visit (start of study)

At a planned usual care haemodialysis visit, the study centre research team will discuss the study with the patient and confirm the patient's understanding of the study processes and their willingness to participate. The patient information document will be given to the patient. The patient will have the opportunity to ask questions on the study processes and will be asked to give their written informed consent before any study-specific procedures.

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

At the baseline visit and at each haemodialysis visit during the study the following usual care parameters will be assessed and recorded:

- total fluid removal (each haemodialysis session)
- IDWG
- proportion of haemodialysis sessions in which IDWG is ≤ 4%.
- pre-dialysis and post-dialysis weight
- pre-dialysis, intradialytic and post-dialysis BP
- pulse rate
- requirement for additional nursing intervention (e.g.stopping dialysis, administering fluid bolus)
- adverse events related to the patient's underlying condition (e.g. access-related complications, hypertension-related symptoms, congestive heart failure, pulmonary edema)
- requirement for additional unscheduled dialysis, or need for hospitalisation
- number and type(s) of BP medications

In addition, fluid status will be assessed by bioimpedance immediately before and immediately after the start and end of haemodialysis.

Patient symptoms related to volume status (questions described above in section 5.1.1.1) will be recorded before haemodialysis.

The research team will allocate a Sixty device to the patient and instruct them on correct use of the device. The Sixty device is designed to be simple to operate, with only one button to turn it on and off. The user interface indicates that the device is on/off and is functioning correctly. The device will only collect data and will not provide feedback to the user on their hydration status. Data is collected locally on a memory card (i.e. SD card).

The patient will start to wear the Sixty device and switch it on at least five minutes before the start of haemodialysis at this clinic visit. The patient will wear the Sixty device throughout the haemodialysis session at this and all subsequent haemodialysis sessions during the study observation period. The patient will be asked to wear the Sixty device throughout the study observation period (approximately three weeks), except when bathing, swimming, showering or any other activity which would expose the device to large amounts of water.

The patient will be given a home BP monitor and instructed on its correct use. The patient will be asked to measure BP at home once/day (at any time of day they wish) during the study observation period.

6.3.2 Haemodialysis visits during study observation period

The patient will attend for haemodialysis as required for an observation period of approximately three weeks.

The patient will be asked to wear the Sixty device throughout the study observation period (approximately three weeks), except when bathing, swimming, showering or any other activity which would expose the device to large amounts of water.

At each clinic visit, before the patient starts haemodialysis the research team will remove the SD card from the patient's Sixty device and download the data collected in the previous 2-3 days. The SD card will be re-inserted into the Sixty device and the patient will put on the Sixty device at least five minutes before starting haemodialysis. The patient will wear the Sixty device during the haemodialysis procedure and the Sixty device will be recharged during haemodialysis. (The Sixty device will continue to collect data while recharging.) The patient will continue to wear the Sixty device until the next planned haemodialysis session.

The measurements related to haemodialysis and described in section 6.3.1 (usual care haemodialysis parameters and symptoms) will be recorded at each haemodialysis visit during the study observation period.

The patient will be asked to confirm that they have measured BP at home once/day during the study observation period.

6.3.3 Week 1 and Week 2 clinic visits

The measurements related to haemodialysis and described in section 6.3.1 (usual care haemodialysis parameters and symptoms) will be recorded at this visit.

In addition, fluid status will be assessed by bioimpedance immediately before and immediately after the start and end of haemodialysis.

As described in section 6.3.2 above, the research team will download the data collected by the Sixty device during the previous 2-3 days and recharge the device while the patient is wearing it during haemodialysis.

6.3.4 Week 3 visit (end of study observation period)

Before the patient starts haemodialysis the research team will remove the SD card from the patient's Sixty device and download the data collected in the previous 2-3 days. The Sixty device will be recharged and after recharging,

the patient will wear the Sixty device for at least five minutes before starting haemodialysis and during the haemodialysis procedure.

The measurements related to haemodialysis and described in section 6.3.1 (usual care haemodialysis parameters and symptoms) will be recorded at this visit.

In addition, fluid status will be assessed by bioimpedance immediately before and immediately after the start and end of haemodialysis.

The patient will wear the Sixty device during haemodialysis until at least five minutes after the end of the haemodialysis procedure. At this time, the research team will remove the SD card from the patient's Sixty device and download the data collected during this haemodialysis session.

The patient will return the Sixty device and the home BP monitor to the research team.

The patient will complete a questionnaire to give their opinion on the acceptability of the Sixty device be assessed and recorded.

The study procedures are concluded at this visit.

7. Statistical methods and determination of sample size

This a pilot-scale study to determine the validity and reproducibility of the data captured by the Sixty device in haemodialysis patients.

7.1 Statistical design and model

This is a prospective, open-label, single-arm observational study.

All patients will attend for haemodialysis according to their usual regimen during the study.

7.2 Null and alternative hypotheses

Not relevant.

7.3 Planned analyses

Results will be collected and summarized for descriptive statistical display.

7.3.1 Primary analyses

The objective of this pilot-scale study is to assess how the Sixty hydration monitoring device functions when used in a range of haemodialysis patients of varying age, gender, body habitus and volume status.

The primary endpoint will be assessed by comparison of the endpoint variables observed via the Sixty device with those observed via bioimpedance and haemodialysis machine data and symptoms.

7.3.2 Secondary analyses

The acceptability and utility of the Sixty device will be assessed by analysis of the responses to a patient questionnaire.

7.3.3 Safety analyses

Patient-reported symptoms and adverse events will be tabulated and displayed.

7.3.4 Interim analyses

None planned.

7.3.5 Health economic analyses

Any additional healthcare resource utilisation (e.g. additional unplanned haemodialysis sessions, hospitalisation) will be tabulated and displayed.

7.4 Handling of missing data

No imputations of missing data will be made.

7.5. Randomisation

Not relevant.

7.6 Determination of sample size

This is a pilot-scale study. The sample size (n = 20) was chosen arbitrarily. It is estimated that 10 Sixty devices will be available for testing at the planned date of 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 and any study-specific procedures.

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 and relevant medical records will be the source documents.

8.3.2 Direct access to source data and documents

The research team will ensure that all data entered to the central database is a true record of events. 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 recorded on the Sixty device, haemodialysis parameters (including bioimpedance data) and symptoms data will be stored on a central database managed by patientMpower Ltd. These data will be pseudonymised

and will be shared with Beaumont Hospital research team, Design to Value Ltd. (developer and owner of the Sixty device) and patientMpower Ltd.

8.4 Statement of confidentiality

Patients will only be identified by a unique identification number on the study database (i.e. data will be pseudonymised). All data will be treated as confidential. Each patient's data will be linked to their unique identification number.

8.5 Completion of trial

The trial will be complete when 20 patients have completed the 3-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 the investigator).

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

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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 Recruitment of patients

The study team 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 10.3 Training of personnel

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

Appendix 10.4 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 10.5 Funding

The study is being conducted as part of the Haemodialysis Outcomes & Patient Empowerment (HOPE) project supported by the Disruptive Technology Innovation Fund of Ireland (DTIF). HOPE is a collaboration between the Royal College of Surgeons in Ireland, Beaumont Hospital, patientMpower Ltd., Dublin and Sixty (registered as Design to Value Ltd.), Innishannon, Co. Cork. The study is funded by the DTIF.

Appendix 10.6 Incentives for participation:

There are no incentives for patients to take part in the study.

Signatures

Signed: Date:

Dr Conall O'Seaghdha

On behalf of Beaumont Hospital

Signed: Date:

Mr. Paul McAleese

On behalf of Design to Value Ltd.

Signed: Date:

Dr. Colin Edwards

On behalf of patientMpower Ltd.