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Integrated strategies to prevent intradialytic hypotension: research protocol of the DialHypot study, a prospective randomised clinical trial in hypotension-prone haemodialysis patients

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ABSTRACT

Introduction In patients on maintenance haemodialysis (HD), intradialytic hypotension (IDH) is a clinical problem that nephrologists and dialysis nurses face daily in their clinical routine. Despite the technological advances in the field of HD, the incidence of hypotensive events occurring during a standard dialytic treatment is still very high. Frequently recurring hypotensive episodes during HD sessions expose patients not only to severe immediate complications but also to a higher mortality risk in the medium term. Various strategies aimed at preventing IDH are currently available, but there is lack of conclusive data on more integrated approaches combining different interventions.

Methods and analysis This is a prospective, randomised, open-label, crossover trial (each subject will be used as his/her own control) that will be performed in two distinct phases, each of which is divided into several subphases. In the first phase, 27 HD sessions for each patient will be used, and will be aimed at the validation of a new ultrafiltration (UF) profile, designed with an ascending/descending shape, and a standard dialysate sodium concentration. In the second phase, 33 HD sessions for each patient will be used and will be aimed at evaluating the combination of different UF and sodium profiling strategies through individualised dialysate sodium concentration.

Ethics and dissemination The trial protocol has been reviewed and approved by the local Institutional Ethics Committee (Comitato Etico AVEN, prot. 43391 22.10.19). The results of the trial will be presented at local and international conferences and submitted for publication to a peer-reviewed journal.

Trial registration number ClinicalTrials.gov Registry (NCT03949088).

Strengths and limitations of this study

- The trial has a prospective, randomised, open-label, crossover design; neither patients nor investigators can be blinded to the treatment assignment.
- Only hypotension-prone patients will be enrolled in the study, thus eliminating possible biases determined by the inclusion of haemodynamically stable patients.
- Several different strategies aimed at preventing intradialytic hypotension such as ultrafiltration profiling, sodium modelling, dialysate sodium individualisation and low dialysate temperature will be combined and tested at the same time.

BACKGROUND

Introduction

Removal of the interdialytic fluid gain by ultrafiltration (UF) is a mainstay of renal replacement therapy in patients with end-stage renal disease. However, the time limitation intrinsic to the duration of a standard haemodialysis (HD) session may set the stage for haemodynamic instability. In fact, the patients with a large interdialytic weight gain (IDWG) and/or older patients with heart failure are especially prone to intradialytic hypotension (IDH). Hypotensive events occurring during a standard HD treatment are still very frequent, with a reported incidence varying between 5% and 30% depending on the definition of IDH.[1 2] In view of the growing number of elderly patients with chronic kidney disease and a high cardiovascular comorbidity burden, who will likely need HD at some point in their clinical course, IDH is likely to remain a relevant clinical issue in the near future despite the technological advances in the field of HD.

IDH not only causes patient discomfort but may also contribute to severe consequences, such as delivery of an inadequate dialysis

dose, vascular access thrombosis, as well as cardiac, cerebral and mesenteric ischaemia.[3–6] Moreover, a strong linear correlation between IDH incidence and mortality has been described.[7 8]

In clinical practice, common interventions carried out in response to IDH include setting the patient in the Trendelenburg position, reducing or stopping the UF process and infusing normal saline to restore intravascular volume. In order to prevent IDH, various approaches have also been suggested based on the modulation of UF ('UF profiling'), qualitative changes in dialysate composition (eg, the use of high sodium concentrations) and lowering of dialysate temperature. Furthermore, in recent years, more sophisticated techniques such as blood volume (BV) monitoring and BV monitoring-based biofeedback systems have been developed aiming at the same goal.[9–11] However, no conclusive data are currently available on more integrated approaches combining different interventions.

UF-induced hypovolaemia: pathogenesis and compensatory mechanisms

During a standard HD session, the aim of the UF process is to shift the patient from a state of hypervolaemia to a condition approaching 'dry weight', with usual relative decrease in total plasma volume by 10%–20%.[12] During plasma water removal with ensuing relative hypovolaemia, haemodynamic stability depends on body compensatory processes, the most important of which is plasma refilling. Compensatory refilling rates are usually lower than typical UF rates applied during HD. As a consequence, BV will gradually drop during treatment.[9–12] In addition to plasma refilling, HD-induced hypovolaemia leads to the activation of cardiac and vascular compensatory mechanisms aimed at maintaining cardiac output and blood pressure (BP) values within the normal range.

BV monitoring

Several non-invasive methods to estimate relative BV (RBV) have been developed. These tools provide real-time and continuous assessment of plasma volume based on the modification of blood constituents (eg, haemoglobin) throughout the entire HD session.[9 13]

Several studies have investigated the relationships between RBV changes during HD, the trend of intradialytic BP values and the occurrence of IDH.[14–19] However, most of these studies failed in demonstrating a link between the magnitude of RBV reduction and the occurrence of hypotensive episodes. RBV generally decreases in two distinct phases: (1) a rapid drop during the first hour of dialysis and (2) a slower decline in the following interval, suggesting an increased refilling of central veins due to BV shifting from the peripheral microcirculation towards the end of the treatment.[20] Interestingly, systolic blood pressure (SBP) seems to follow the same downward trend, showing a rapid decrease in the first 25% of HD, independently of total UF volume or UF rate and a slower decline during the later phases, which is instead correlated to UF parameters.[21]

The drop of RBV below an individual critical threshold is assumed to provoke intradialytic symptoms. However, RBV changes do not directly translate into absolute BV modifications, since these depend on the patient's current volume status. Indeed, the same per cent decrease in RBV may correspond to extremely different absolute volume changes, even in the same patient, and therefore it is impossible to identify a reliable limit for critical RBV, which shows an interindividual variability ranging between 71% and 98% of the initial value.[22]

UF profiling

UF profiling is performed by variably shaping the UF process, instead of setting it at a constant rate, as is usually done in clinical practice (figure 1A). The UF rate shape can be set as a gradual or stepwise decrease (figure 1B,C), with higher rates at the beginning of the session, assuming that at this time point the patient is in a hypervolaemic state and can therefore better tolerate higher amounts of fluid removal during the first phase of treatment. In another possible UF profiling scheme (figure 1D), the UF process is interrupted intermittently, alternating phases in which the UF rate is set approximately to zero and other ones in which it is set to almost two times the value of conventional UF rates.

It has been suggested that stepwise and alternate UF profiling may be responsible for a greater number of symptomatic hypotensive episodes; conversely, the linear descending profile appears to be associated with fewer intradialytic adverse events.[23]

Dialysate sodium

Although sodium is clearly the most represented electrolyte in the dialysate, the optimal dialysate sodium concentration for patients undergoing chronic HD is still an unresolved issue. At present, in most dialysis centres, dialysate sodium is prescribed at a fixed, 'standard' concentration, without accounting for differences in plasma sodium levels among patients. Prescribed sodium concentration in the dialysate is typically higher than that in plasma, thus generating a positive gradient that causes sodium diffusion from dialysate to plasma. This leads to a positive sodium balance with ensuing increased thirst, greater IDWG and eventually volume-dependent hypertension. On the other hand, in the case of a negative concentration gradient, which develops when dialysate sodium concentration is lower than plasma levels, a disproportionate diffusive loss of the electrolyte may occur and may cause hypotensive events or cramps.

While a positive intradialytic sodium balance may be effective both in the prevention and as an acute treatment of intradialytic symptoms, it may also sustain a vicious cycle by hindering the achievement of patient's 'dry' weight and favouring the development of intradialytic complications during the following session.[24 25]

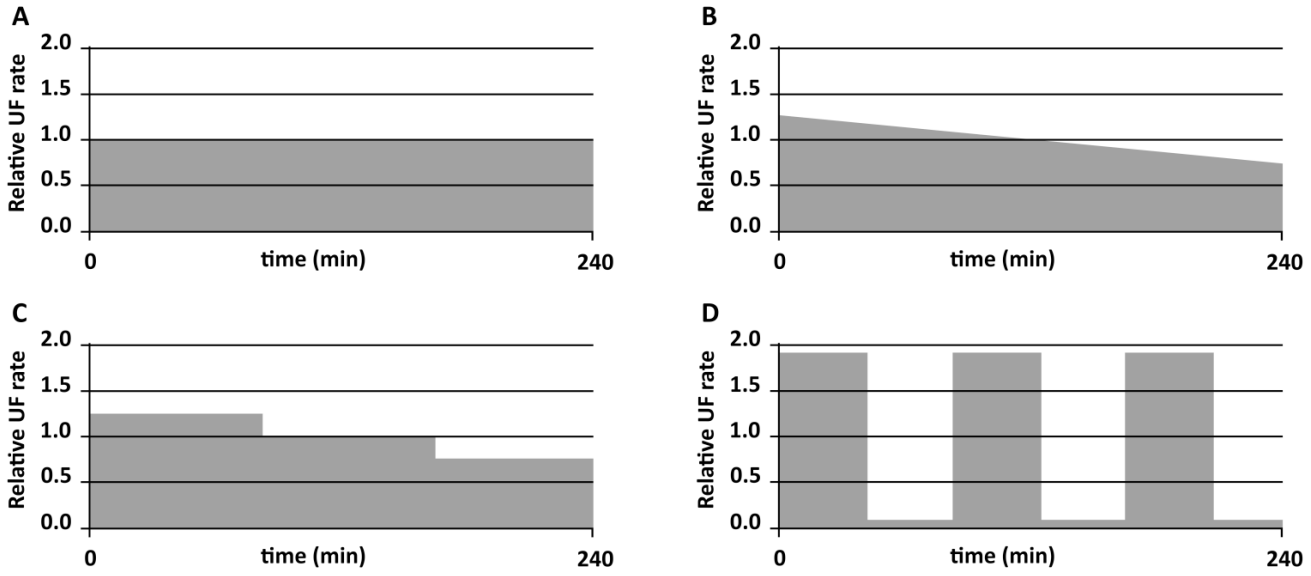

Figure 1 Ultrafiltration (UF) profiling during a 4-hour dialysis session. Constant linear UF rate (A). Linear descending UF profile (B). Stepwise descending UF profile (C). Alternate UF profile (D).

Predialytic serum sodium levels show a wide interindividual distribution, while intraindividual differences are negligible.[25] According to the hypothesis of Keen and Gotch, each subject has an individual 'sodium setpoint',[26] whereby an increase in serum sodium levels, as in the case of a diffusive influx from the dialysate, triggers thirst and increased fluid intake, so that serum sodium concentration can be brought back to the patient-specific setpoint. The increased interdialytic fluid intake leads to a greater IDWG, necessarily requiring higher UF rates and eventually predisposing the patient to a higher risk of IDH and cramps. Indeed, several studies have demonstrated that decreasing sodium balance through dietary restriction or the use of lower dialysate sodium concentrations may result in weaker thirst, reduced IDWG, lower BP values and improved echocardiographic parameters.[27–33]

An ideal treatment should remove the exact amount of sodium accumulated between two consecutive HD sessions, resulting in zero sodium balance. By adjusting net UF volume to match the total interdialytic fluid gain, it should be possible to obtain the removal of a quantity of sodium almost equal to that needed to achieve a neutral sodium balance.[25] Consequently, in order to avoid diffusive sodium overload or depletion, it would be desirable to achieve a diffusive zero sodium gradient, which can be accomplished by aligning the dialysate sodium prescription to the patient's own serum sodium setpoint.

Conventional dialysis applies constant dialysate sodium levels throughout the entire dialysis session, whereas sodium profiling implies a dynamic modification of sodium levels along the treatment. Sodium profiling has been introduced in combination with UF profiling with the aim to obtain greater plasma osmolality, and thus refilling, in those treatment phases characterised by higher UF rates. Dialysate sodium can be lowered gradually or in a stepwise manner, with the latter method showing a stronger effectiveness in reducing intradialytic symptoms when compared with linear profiling.[34 35] However, an inappropriate use of sodium profiling is one of the possible sources of dialysis-related sodium loading, causing increased IDWG and its complications.[15 25 29 36] The putative advantages associated with the use of sodium profiles with a neutral sodium balance need further investigation. However, a reduced number of intradialytic hypotensive events have been observed in some studies investigating the combination of neutral sodium balance profiles and UF profiling.[36 37]

AIM OF THE STUDY

The aim of the present study is twofold: (1) comparing different strategies of UF profiling, dialysate sodium individualisation/sodium profiling and their combination and (2) evaluating the effectiveness of a new UF profile which has been designed with an ascending/descending shape (figure 2).

The goal of the study is to provide better dialysis tolerance and lower rates of intradialytic hypotensive events by

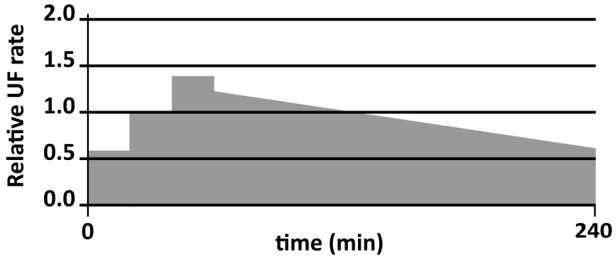

Figure 2 Ascending/descending ultrafiltration (UF) profile.

the application of this UF profile design in combination with a neutral sodium balance.

METHODS

Study design

This is a prospective, randomised, open-label, crossover trial that will be carried out at a single centre. The study will be performed in two phases (see the Study phases section), each of which is divided in several subphases. Each subject will be used as his/her own control.

Participants will be enrolled among patients treated at the Dialysis Center of the Nephrology Unit of Parma University Hospital, Parma (Italy).

Eligibility criteria—inclusion criteria

- Written informed consent (consent form, informative sheet and confidentiality agreement are provided as online supplementary files 1–3).
- Age ≥18 years.
- Three times weekly HD regimen for more than 6 months.
- 'Hypotension-prone patients': ≥2.1 episodes in the nine sessions (ie, ≥3 episodes of IDH in the month) preceding the run-in phase of the study, based on events reported in patients' charts.

Eligibility criteria—exclusion criteria

- IDWG <1.4% of dry weight (corresponding to <1 kg in a 70 kg person).
- Once or two times weekly HD regimen.
- Residual daily urine output >300 mL.
- Active acute disease or hospitalisation in the 8 weeks preceding the run-in phase.

Study phases

First phase: validation of the new UF profile with a standard dialysate sodium concentration. This phase will consist of 9 weeks of treatment (27 HD sessions) for each patient:

1. Run-in: constant Na concentration, constant UF rate—2 weeks (six sessions).
2. Two-step descending Na profile, linear descending UF profile—3 weeks (nine sessions).
3. Washout: constant Na concentration, constant UF rate—1 week (three sessions).
4. Two-step descending Na profile, ascending/descending UF profile—3 weeks (nine sessions).

Patients will be randomly assigned to one of the following sequences:

(1), (2), (3), (4)
(1), (4), (3), (2).

Second phase: combination of UF profiles and testing of the contribution of an individualised dialysate sodium concentration. This phase will consist of 11 weeks of treatment (33 HD sessions) for each patient:

1. Run-in: standard constant Na concentration, constant UF rate—2 weeks (six sessions).
2. Individualised constant Na concentration, constant UF rate—2 weeks (six sessions).
3. Individualised two-step Na profile, linear descending UF profile—3 weeks (nine sessions).
4. Washout: individualised constant Na profile, constant UF rate—1 week (three sessions).
5. Individualised two-step Na profile, ascending/descending UF profile—3 weeks (nine sessions).

Patients will be randomly assigned to one of the following sequences:

(1), (2), (3), (4), (5)
(1), (2), (5), (4), (3).

Dry weight, antihypertensive medications and dialysis parameters will not be modified during the study phases, except for UF rate and dialysate sodium concentration. The patients who will be included in phase 1 will undergo a 2-week or longer washout period before entering phase 2. During these 2 weeks, dry weight and antihypertensive therapy may be re-evaluated and reassessed.

Dialysis prescription

Every patient will undergo a standard HD with the following prescription:

- Blood flow rate: individualised from 250 mL/min to 350 mL/min (this value will be established for each patient at the beginning of the run-in phase on the basis of previous evaluations and will not be changed for the whole duration of the study).
- Dialysate flow rate: 500 mL/min.
- Dialysate composition: $HCO3^-$ 34 mmol/L, K^+ 3 mmol/L, Ca^{2+} 1.25 mmol/L, Mg^{2+} 0.5 mmol/L, Cl^- 111.5 mmol/L, acetate 3.0 mmol/L, glucose 1 g/L.
- Dialysate temperature: 36°C (we will allow the prescription of a dialysate temperature of 35.0°C or 35.5°C, pending a possible patient discomfort as assessed by his/her reports of feeling cold. However, this issue has to be discussed with each patient and resolved before he/she has been enrolled in the trial; each patient will then undergo treatments with the same dialysate temperature for the entire duration of the study. Subsequent changes will not be permitted).
- Session duration: 4 hours.

During each dialysis, session patients will be allowed to drink a maximum amount of 150 mL of water, tea or coffee; eating a snack will also be allowed.

UF profiles

- 'Linear descending' UF profile: this profile provides a constantly decreasing UF rate during dialysis, starting at a UF rate 1.33-fold the average UF rate (33.25% of total UF rate).
- 'Ascending/descending' UF profile: this profile can be divided in two different phases. The first one includes three ascending steps during the first hour of treatment, with each step lasting 20 min (during the first step UF rate is set at 15% of total UF rate, during second step at 25% of total UF rate and during third step at 35% of total UF rate). During the following

3 hours, UF rate is shaped as a linear descending UF profile, with a constantly decreasing UF rate, starting at a UF rate 1.33-fold the average UF rate (33.25% of total UF rate).

Dialysate sodium

First phase

- 'Standard' concentration: the investigators will deem as 'standard' a dialysate sodium concentration of 140 mmol/L, which is the concentration usually prescribed in the local dialysis facility.
- Dialysate sodium profile will be shaped as a descending two-step ramp, with each step consisting of half the total treatment duration (2 hours), and a 6 mmol/L difference between the concentrations set for each of the two steps. Assuming a one-compartment model with variable dialysate sodium, the profile will be set on the basis of an 'equivalent sodium'. This value will correspond to the dialysate sodium concentration expected to produce the same diffusive balance as that provided by a fixed standard concentration (140 mmol/L), that is, 144 mmol/L for the first 2 hours, 138 mmol/L for the last 2 hours.

Second phase

- 'Individualised' concentration: for each patient dialysate sodium concentration will be established on the basis of the average of the sodium plasma values measured by pre-HD sampling during the run-in phase (two repeated measurements before each HD session, for a total of 12 values for each patient). Plasma values will be measured by direct potentiometry.
- Dialysate sodium concentration will be set at the patient's average plasma sodium concentration.
- Dialysate sodium profile will be shaped as a descending two-step ramp, with each step consisting of half the total treatment duration (2 hours), with a 6 mmol/L difference between the concentrations set for each of the two steps. Assuming a one-compartment model with variable dialysate sodium, the profile will be set on the basis of an 'equivalent sodium'. This value will correspond to the dialysate sodium concentration expected to produce the same diffusive balance as that provided by a fixed individualised concentration (equal to the patient's average plasma sodium concentration), that is, 'average +4' mmol/L for the first 2 hours, 'average −2' mmol/L for the last 2 hours.

Definition of 'dry weight', 'UF volume' and 'IDWG'

- Dry weight will be estimated through standard clinical criteria.
- Total UF volume (net fluid to be removed) will be calculated before each session as the difference between patient's weight and his/her dry weight. A limit of 12.5 mL/kg/hour will be considered as maximal total UF volume.
- IDWG will be calculated as the difference between patient's weight at the beginning of the dialysis session and the weight registered at the end of the previous session.

UF and IDWG will be corrected for pre-HD weight (UF%) and dry weight (IDWG%), respectively.

Primary outcome and definition of 'IDH'

The primary outcome will be the incidence of intradialytic hypotensive episodes. Hypotensive events and symptoms (headache, cramps, nausea and vomiting) will be recorded and analysed as both number of episodes and time of occurrence since the beginning of the HD session.

IDH will be defined as follows:

- 'Nadir90 IDH': minimum intradialytic SBP <90 mm Hg.
- 'Symptomatic IDH': decrease in SBP ≥20 mm Hg or in mean arterial pressure (MAP) ≥10 mm Hg associated with symptoms (Kidney Disease Improving Global Outcomes - KDIGO definition).
- 'Asymptomatic IDH': drop in BP (SBP ≥20 mm Hg or MAP ≥10 mm Hg) within a 20 min interval (BP and heart rate will be recorded every 20 min, regardless of symptoms).
- For patients whose SBP is <100 mm Hg at the beginning of treatment, the investigators will consider as IDH any decrease of SBP ≥10%.

Interventions in case of hypotensive events

- Trendelenburg position.
- Temporary stop of UF (10 min), then restart at a UF rate equal to 'total UF—100 mL'.
- Online infusion of 150 mL of saline solution.
- Discontinuation of the session.

BV monitoring

RBV will be evaluated through the BVM system integrated in the dialysis machine. RBV will be recorded every 10 min.

Secondary outcomes

- Incidence of each component of the IDH definition.
- Pre-HD, intra-HD (after every hour of treatment) and post-HD plasma sodium levels as measured by direct potentiometry.
- BP and heart rate values recorded every 20 min, or more frequently if clinically indicated, by machine-integrated Blood Pressure Monitoring (BPM).
- Achievement of UF, defined as:
  - Achievement of dry weight: %target UF_{DW}=UF vol/(pre-HD weight−dry weight)×100.
  - IDWG removal: %target UF_{WG}=UF vol/IDWG×100.
- 'UF failure', defined as %target UF_{DW} <70%.
- 'Session failure', defined as treatment discontinuation before 75% of the prescribed time (before 3 hours of treatment).
- Achieved spKt/V, as assessed by machine-integrated software (total body water calculated using Watson's equation).

Statistical analysis

Sample size and assumptions

Based on our preliminary data, assuming an incidence of hypotensive events of 4/9 of HD sessions with a classic (linear) UF profile, and a reduction in the incidence of IDH by 2/9 sessions with new (ascending/descending) UF profile, we estimated that at least 50 patients in a three-period three-treatment crossover trial would be needed to achieve 85% power to detect such difference between individualised ascending/descending UF profile and linear UF profile, with an alpha level of 0.05, using a two-tailed test if the correlation between paired observations ranges between 0.1 and 0.5. Therefore, we established a target sample of 60 patients, accounting for an approximate dropout rate of 20%.

Statistical methods

We will analyse Bernoulli correlated balanced data employing multilevel mixed-effects logistic regression with unstructured covariance matrix, using the program *melogit* from Stata V.15.1 (2017 StataCorp, College Station, Texas, USA). Patients will be included as a random effect, whereas the indicator variable treatment, period and their interaction will be included as fixed effects. In secondary analyses, we will additionally fit population-average models adopting generalised estimating equations using the program *xtgee* from Stata V.15.1. Finally, we will estimate the difference in the mean systolic and diastolic BP (continuous variables) between UF profile treatment regimens using linear mixed-effects models with the program *mixed* from Stata V.15.1, in which patients will be included as a random effect, whereas treatment, period, dialysis session, hour of dialysis will be included as fixed effects.

Patient and public involvement

For this study protocol, there was no direct patient or public involvement.

Ethics and dissemination

The trial protocol has been reviewed and approved by the local Institutional Ethics Committee (Comitato Etico AVEN, prot. 43391 22.10.19). Participants will be provided with informative sheets describing in full detail trial aims, study phases, eligibility criteria, procedures/interventions, data management, confidentiality and potential benefits/harms. They will be given the chance to discuss at any time any possible doubt with a member of the trial management committee. Prior to enrolment, an informed written consent will be obtained by one of the members of the trial management committee from all participants. Patients will be made aware that participation to this study is strictly voluntary and that consent can be withdrawn at any time. They will also receive a copy of the aforementioned documents.

Researchers will make every effort to preserve patients' confidentiality: alphanumeric codes for participants' identification will be assigned; data managers will store filled Case Report Forms (CRFs) containing patient's data in private locations with limited access; all databases will be password protected. All trial participants will be asked to sign a confidentiality form prior to enrolment.

Any additional healthcare need will be provided by the Italian National Health System; any potential harm derived by the participation to the trial will be covered by the investigating centre, that is, Parma University Hospital, Parma (Italy). Each study participant's follow-up after trial discontinuation will be provided by the Dialysis Center of the Nephrology Unit of Parma University Hospital, Parma (Italy).

The results of the trial will be presented at local and international scientific conferences and will be submitted for publication to a peer-reviewed journal. Data obtained by this study will be shared and available in deidentified form on reasonable request, wherever legally and ethically possible.

Any modification to the protocol impacting on the conduct of the study or the benefit of the participants will have to be communicated to and approved by the local Institutional Ethics Committee prior to the implementation.

Current status of the trial

The enrolment of patients has not begun yet and will commence in a few weeks. Patients' recruitment is expected to continue for at least 2 years.

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