Peritoneal Ultrafiltration for Heart Failure: Lessons from a Randomised Controlled Trial.

Hari Dukka [1], Philip A. Kalra [2], Martin Wilkie [3], Sunil Bhandari [4], Simon J. Davies [5], Jonathan Barratt [6], Iain Squire [6], Aghogho Odudu[2], Nicholas M Selby [1,7], Christopher McIntyre [8], Fiona Robertson [7],Maarten W. Taal[1,7].

Affiliations:

1) University Hospitals of Derby and Burton, Derby, UK.
2) University of Manchester, Manchester, UK.
3) Sheffield kidney Institute, Sheffield, UK.
4) Hull and East Yorkshire NHS Trust, Hull, UK.
5) Faculty of Medicine and Health Sciences, Keele University, UK.
6) University of Leicester, and NIHR Biomedical Research Centre, Leicester, UK.
7) Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Nottingham,UK.
8) The University of Western Ontario, London, Canada.

Abstract:

Peritoneal ultrafiltration (PuF) has been employed for severe heart failure (HF), but evidence for its benefit is lacking. The Peritoneal Dialysis for Heart Failure (PD-HF) study was a multi-centre prospective randomised controlled trial which aimed to investigate this issue. The trial stopped early due to inadequate recruitment. We describe methods, trial activity and lessons learnt.

The trial aimed to recruit 130 participants with severe diuretic resistant HF (NYHA 3/4) and CKD stage 3/4 on optimal medical treatment for ≥4 weeks from six UK centres. Participants were randomised to either continuation of conventional HF treatment or to additionally receive PuF (one overnight exchange using Icodextrin dialysate). Primary outcome was change in six minute walk test (6MWT) between baseline and 28 weeks (end of trial). Secondary outcomes were changes in patient reported quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire , SF 36 health survey results, hospitalisation and mortality.

Over a two year period, 290 patients were screened from which only 20 met inclusion criteria and 10 were recruited. Reasons for ineligibility were fluctuating eGFR, suboptimal HF treatment, frailty and patients being too unwell for randomisation.

Barriers to recruitment included patient frailty with some participants considered only when they were at end of life, unwillingness to engage in an invasive therapy and suboptimal coordination between cardiology and renal services. This is a challenging patient

group in which to perform research and lessons learnt from the PD-HF trial will be helpful in the planning of future studies in this area.

Trial registration number: ISRCTN 22848383.

Key words: Peritoneal dialysis for heart failure, Recruitment difficulties, Symptom control and Quality of life, Peritoneal ultrafiltration for heart failure.

Acute decompensated heart failure (HF) accounts for nearly 1 million hospitalizations per year and high mortality worldwide [1]. Diuretic treatment for fluid overload is often ineffective resulting in slow fluid removal and prolonged hospital admissions [2]. Moreover, diuretic resistance is common and an important predictor of mortality in HF [3]. In observational studies PuF has shown benefit in improving NYHA classification, ejection fraction and frequency of hospital admissions [4]. Efficient removal of potassium with PuF will potentially also allow optimisation of the renin-angiotensin-aldosterone antagonist drug treatment [5]. Against these potential benefits, PuF is associated with risks such as complications associated with peritoneal catheter placement, risk of infection (peritonitis), loss of residual renal function and catheter dysfunction [4, 6]. As it has not yet been established whether, in diuretic resistant HF patients on optimal medical treatment, the potential benefits of PuF outweigh the risks, the Peritoneal Dialysis in Heart Failure (PDHF) study was conceived and the study was funded by British Heart Foundation (grant number-PG/13/27/29864). Unfortunately, the trial was halted early due to inadequate recruitment. Here we report the study design and delivery, and the problems that were encountered during the recruitment period, with the aim of informing future trial design in this challenging patient group.

The PDHF study was a UK multi-centre prospective randomised controlled trial (RCT) to establish whether PuF in patients with treatment resistant HF improves functional capacity, QoL and reduces hospitalizations. Inclusion and exclusion criteria are summarised in Table 1.

Participants were randomly assigned to ongoing medical management, or to medical management plus the insertion of a catheter for peritoneal dialysis and treatment with one 2L overnight exchange of fluid containing Icodextrin. Participant follow up was 32 weeks. The protocol included 5 study visits in total, at screening, baseline (week 4), week 8, week 28 and a final 32 week assessment. The primary end point was change in the six minute walk test (6MWT) between baseline and week 28. The minimum clinically important improvement was regarded as 25m. Secondary end points were change in Kansas city cardiomyopathy questionnaire (KCCQ) at week 8 and 28, change in SF 36 score at week 8 and 28, change in Derby evaluation of illnesses questionnaire at week 8 and 28, HF-related hospitalisation at week 8 and 28, all cause hospitalisation at week 8 and 28, HF related and all-cause mortality at week 8 and 28. Allowing for study attrition of 15% and mortality of 15%, we aimed to recruit 130 participants to yield a final evaluable sample of 90 participants over a period of 18 months which was subsequently extended by 6 months. The trial was registered with clinicaltrials.gov with the international standard randomised controlled number (ISRCTN) -22848383.

290 patients were screened over a two year period, only 20 were considered eligible for the trial. Of these, 10 participants were randomised, 4 in the intervention group and 6 in the control group. The mean age of the participants was 70.1±8.4 years, median NYHA class 3, mean 6 MWT 181.3±49.6 m (one patient declined 6MWT) and mean eGFR 28.6±5.4 ml/min/1.73m^{2}.$^{\cdot\cdot}$ The recruitment process is summarised in consort diagram(figure1).

The main reasons for the high number of ineligible patients were eGFR out of range (most frequently eGFR had improved to >60 ml/min/1.73 m^2), frailty and not being on optimal HF treatment (usually not yet offered sacubitril/valsartan or CRT). In some patients whose eGFR was in range during screening, the eGFR was out of range at the time of enrolment (mostly improved to > 60 ml/min/1.73 m^2). Despite an extension to the recruitment period, after 2 years the trial was stopped on the advice of the data monitoring committee on the grounds that it was extremely unlikely that adequate recruitment would be achieved to produce a clinically or statistically significant result.

The participants in this trial were elderly and multi-morbid with very poor functional status, as evidenced by the baseline mean 6MWT of 181.3±49.6 m (normal value 571 ± 90 m; range 380-782 m). Other reasons for the failure of recruitment were lack of eligible patients, reluctance of patients to participate, variation in configuration of nephrology and cardiology services, variable local practice patterns in different sites which led to longer local approval process and changes to the definition of optimal HF treatment after study inception.

As the configuration of HF services and experience of PuF in HF was different in different sites there was a variable buy-in from different HF nursing teams. Equipoise was also an issue. In some sites HF nursing teams felt that an invasive procedure in multi-morbid patients could be detrimental to their well-being. On the other hand, at sites with experience of PuF in HF, staff were concerned that diuretic resistant HF patients randomised to medical therapy would miss out on the benefits of PuF.

Publication of new evidence supporting the use of Sacubitril/Valsartan for the treatment of HF required a change in the definition of optimal HF treatment during the trial and proved an extra barrier to recruitment [7]. Additionally, more widespread use of resynchronisation therapy as well as outpatient intravenous diuretic therapy further reduced the number of eligible patients.

The response rate from eligible patients was relatively good at 50% but some were inhibited from participating due to anxiety related to possibly having an invasive procedure or on the other hand, being unwilling to be randomised to not receiving PuF as they were desperate for symptomatic relief. By contrast other patients who were screened and eligible were of the opinion that PuF was a cumbersome process to deal with. Lack of a pilot study meant that the trial design could not be based on previous experience.

The low recruitment rates imply that a much higher number of recruiting sites (potentially 30-40) would be required. Preparatory research to identify the number of potentially eligible participants would better inform the number of centres needed. Additionally, it is important that all participating sites have similar local policies, arrangements and protocols for service provision of PuF and HF. The cardiology and renal service provision structure were different in different recruiting sites which led to lack of effective collaboration that affected the identification and recruitment of patients. One way of offsetting this problem is development of joint cardio-renal clinics to manage and recruit patients with decompensated HF and CKD. A further important learning point was the impact of differences in staff perception of PuF as a treatment option for HF. Further qualitative research is needed to understand the differences and reasons behind these perceptions before designing a new study [8,9] and the protocol should include robust staff and patient

education about the potential role of PuF as a therapy for HF. Use of approaches such as QuinteT recruitment intervention (QRI) should be considered to improve recruitment into any future trial [9]

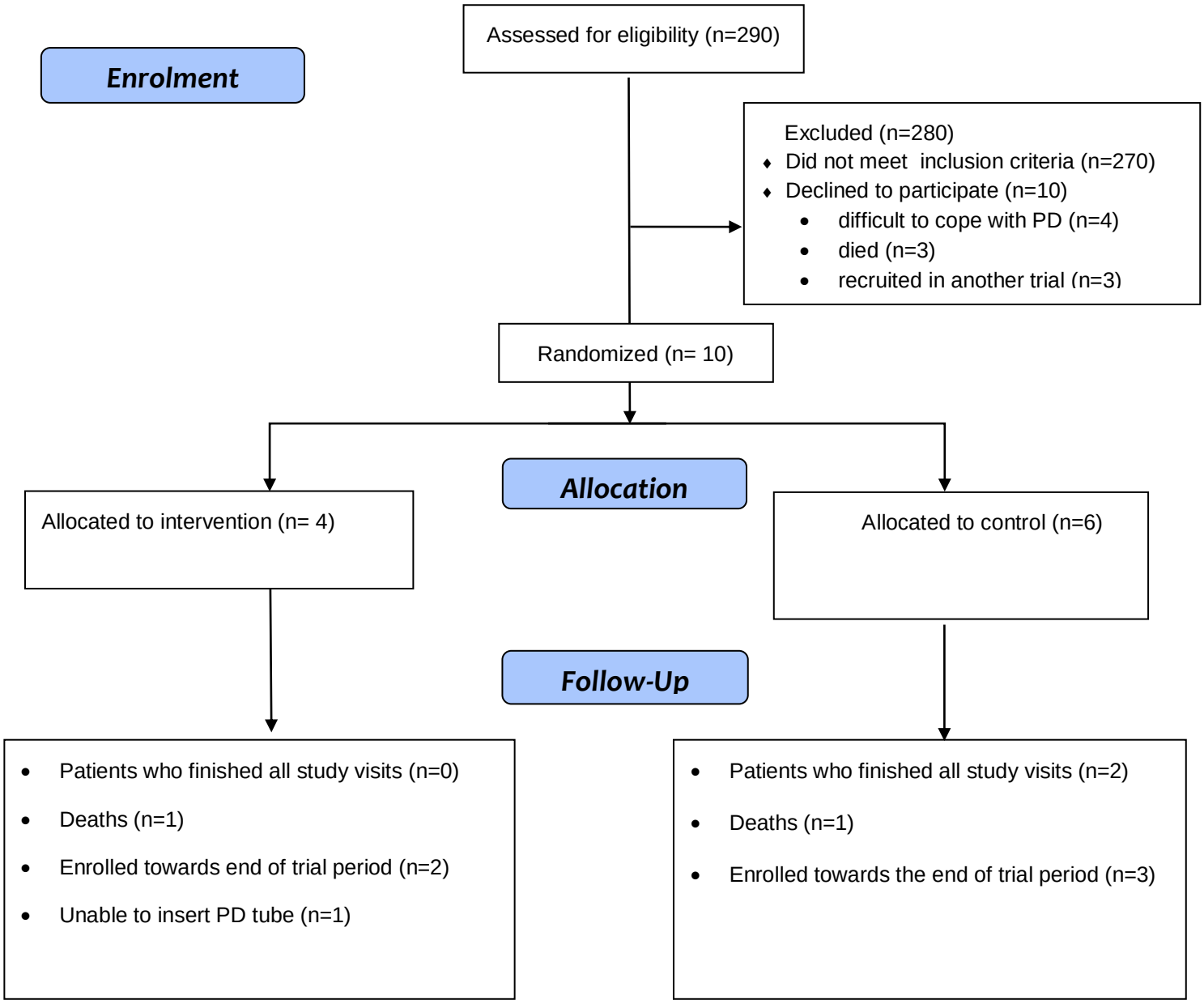
Owing to the challenges associated with the optimal timing of initiation of PuF, our experience suggests that perhaps only a minority of patients with diuretic resistant HF will benefit. Though challenging, further trials are warranted to investigate the risks versus benefits of PuF in this setting and it is hoped that our experience will assist in the design of such trials.

Table 1. Inclusion and exclusion criteria

Inclusion criterion	Exclusion criterion
Age > 18	Does not wish to participate
NYHA grade III or IV	Lacks mental capacity to consent
CKD stage 3-4 (MDRD estimated GFR of 15-59 ml/min/1.73m^2 on 2 occasions > 3 months apart)	CKD stage 5 (estimated GFR <15 ml/min/1.73m^2)
Optimal HF medication* for ≥4 weeks.	Normal renal excretory function (Estimated GFR > 60 mls/min/1.73m^2
Left ventricular ejection fraction ≤ 40% in last 2 years	Haemodynamically significant valvular disease amenable to surgery
Appropriately screened for revascularization and/or cardiac resynchronization therapy	Cardiac or Renal transplantation
Fluid overload and resistant to diuretics	Unsuitable for PD

*Defined as receiving either an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) plus a beta blocker and an aldosterone antagonist. After the recruitment process had started, the definition was altered to include treatment with valsartan/sacubitril if suitable.

Figure 1. Consort Diagram



References

1. Corrao, G., et al., *Burden of new hospitalization for heart failure: a population-based investigation from Italy.* Eur J Heart Fail, 2014. **16**(7): p. 729-36.
2. Lala, A., et al., *Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF).* Circ Heart Fail, 2015. **8**(4): p. 741-8.
3. Verbrugge, F.H., *Editor's Choice-Diuretic resistance in acute heart failure.* Eur Heart J Acute Cardiovasc Care, 2018. **7**(4): p. 379-389.
4. Lu, R., et al., *Peritoneal dialysis in patients with refractory congestive heart failure: a systematic review.* Cardiorenal Med, 2015. **5**(2): p. 145-56.
5. Shah, R., Y. Wang, and J.M. Foody, *Effect of statins, angiotensin-converting enzyme inhibitors, and beta blockers on survival in patients >or=65 years of age with heart failure and preserved left ventricular systolic function.* Am J Cardiol, 2008. **101**(2): p. 217-22.
6. Boudville, N., et al., *Regional variation in the treatment and prevention of peritoneal dialysis-related infections in the Peritoneal Dialysis Outcomes and Practice Patterns Study.* Nephrol Dial Transplant, 2018.
7. McMurray, J.J., et al., *Angiotensin-neprilysin inhibition versus enalapril in heart failure.* N Engl J Med, 2014. **371**(11): p. 993-1004.
8. Elliott, D., et al., *Understanding and Improving Recruitment to Randomised Controlled Trials: Qualitative Research Approaches.* Eur Urol, 2017. **72**(5): p. 789-798.
9. Mills, N., et al., *Training health professionals to recruit into challenging randomized controlled trials improved confidence: the development of the QuinteT randomized controlled trial recruitment training intervention.* J Clin Epidemiol, 2018. **95**: p. 34-44.