PATIENT OUTCOMES IN A PD FIRST PROGRAMME IN CAPE TOWN, SOUTH AFRICA

By

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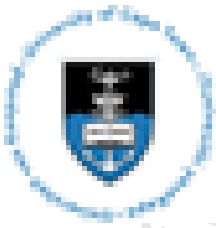

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DECLARATION

I, Bianca Davidson, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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SUPERVISOR

This study was conducted from January 2014 to June in 2015 under the Supervision of Associate Prof. N Wearne. Division of Nephrology, Medicine, University of Cape Town.

As a candidate Supervisor, I have approved this dissertation for submission.

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ABBREVIATIONS

APD	Automated peritoneal dialysis
APOL 1	Apolipoprotein L1 gene
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CAPD	Continuous ambulatory peritoneal dialysis
D/P ratio	Dialysis to peritoneal ratio
ESAs	Erythropoetin stimulating agents
ESRD	End stage renal disease
GDP	Gross domestic product
HR	Hazard ratio
HD	Haemodialysis
ISPD	International Society of Peritoneal Dialysis
KDIGO	Kidney Disease: Improving Global Outcome
LMIC	Low middle-income countries
PD	Peritoneal dialysis
PET	Peritoneal equilibration test
Pmp	Per million population
RRT	Renal replacement therapy
RRP	Renal replacement programme
SA	South Africa
SD	Standard deviation
SES	Socioeconomic circumstances
SSA	Sub Saharan Africa
$	Dollar

GLOSSARY

APD	Form of PD, where fluid is instilled and drained into the abdomen at night via a pre-programmed machine
CAPD	Form of peritoneal dialysis where the patient manually exchanges the peritoneal fluid bags (usually every 4 hours), throughout the day and in the evening.
CKD	Chronic kidney disease [CKD] is a condition characterized by gradual loss of kidney function over time
ESRD	End stage renal disease [ESRD] is a term used to describe chronic irreversible renal failure. At this stage renal replacement is needed in the form of dialysis or transplantation.
D/P ratio	Dialysis to peritoneal ratio – a ratio used to calculate the transport status of the peritoneal membrane. H = high (>0.81) HA =high average (0.65 – 0.8) LA low average (0.5 – 0.64) L = low (<0.5)
Gini Coefficient	The measure of statistical dispersion intended to represent the income distribution of a nation
HD	Is a treatment for patients with end stage renal failure. It is a process of purifying the blood. Removing excess solute, fluid and waste.
Kt/V	Mathematical equation to describe the clearance of small solute urea, as a measure of adequacy.
PD	Is a treatment for patients with end stage renal failure. The treatment uses the patient's peritoneum as a membrane for exchange of fluid and solutes from the blood. Removing waste and excess fluid.

PD-First policy	The policy indicates that PD is initiated wherever possible as the initial mode of dialysis, unless compelling medical, physical or psychosocial factors preclude PD.
Tenckhoff	A soft, flexible indwelling peritoneal catheter, which is inserted into the abdomen. It is inserted between the visceral and parietal peritoneum in the pelvis. It is used in peritoneal dialysis to instill or remove fluid and solute from the abdominal cavity

CHAPTER 1

1.1 Literature Review of Peritoneal dialysis in Africa and PD-First programme in a resource limited setting

1.1.1 Why is CKD a problem?

Chronic kidney disease [CKD] is a rapidly rising health problem. According to the global burden of disease study end stage renal disease [ESRD] as a cause of death, has risen from being ranked 27th in 1999 to 18th in 2010.[1] The risk of developing CKD is described as being "bi-directionally" affected by the level of economic development. In high-income countries the high prevalence of hypertension, diabetes and obesity are linked to the development of CKD. In low-income settings risk factors for developing CKD are multifactorial. Low birth weight, increase in infectious diseases, ethnic or genetic predisposition (APOL1),[2] unregulated food additives, herbal medications and pollutants are all contributing factors[3]. Poverty itself has been assessed as an independent risk factor for microalbuminuria and CKD.[4,5]

In low and middle-income countries [LMICs] with rapid urbanization, or places with high-income inequalities, such as South Africa [SA], there is an overlap in the burden of diseases, with both increased infectious diseases and diseases of lifestyle.

These problems are compounded by the lack of access to health care, medication and a limited numbers of nephrologists. In SA in 2009 there were reportedly 1.8[6] nephrologists per million population [pmp] as compared to 31 pmp in Western Europe. [7]

1.1.2 Dialysis a scarce resource

In systemic review by Liyanage et al, it is estimated that the number of people receiving renal replacement therapy [RRT] will more than double between 2010 and 2030 to a staggering 5.439 million people.[8] To emphasize the extent of the CKD

crisis, it is estimated that less than half of all patients who need dialysis receive it.[8] The accessibility to RRT worsens in LMICs where only 7.2% of the global RRT recipients reside[8]. Africa as a continent has the lowest global access to RRT.

In South Africa we have to ration dialysis, due to limitations of access, particularly to haemodialysis [HD].

1.1.3 Peritoneal Dialysis-First Rationale

Peritoneal dialysis [PD]-First programmes aim to initiate patients wherever possible on PD as their initial mode of dialysis. Mexico was the first country to adopt this policy back in the 1980's, and remains one of the leading utilisers of PD to date.[9,10] Hong Kong and Thailand have adopted a PD-First policy with a PD favoured policy being adopted in Canada, China, India, Spain, Taiwan and the United States.[11,12] This has led to Hong Kong having the highest prevalence of PD in the world at 72.9%[13]. Both Hong Kong and Thailand follow a PD-First policy due to cost-effectiveness.[12,13] The success of established PD First-programmes has been attributed to numerous factors, including the favourable economics in using PD instead of Haemodialysis [HD], reimbursement from medical aids, the education of healthcare providers in improving technique related factors, the careful selection of patients, anti-PD bias being addressed through education and center experience.[11,12]

In developing countries PD fluid is often imported and the financial cost associated with the modality limits its use.[6,14] However in SA, PD fluid is produced locally, which makes PD a markedly more affordable modality, as compared to the rest of Africa. In SA, the cost analysis of PD compared to haemodialysis [HD] is controversial. There are varying reports on the cost discrepancy between the two modalities[6,14]. Okpechi et al states that the annual cost per-patient for PD is about 50% of that for HD if the PD fluid is manufactured and distributed locally[6]. At Groote Schuur Hospital we have adopted a PD-First policy due to financial feasibility and limited accessibility of HD slots.

PD remains an attractive alternative to HD. In our setting it allows for treatment of patients from remote areas, decreases travel time for patients (as they do PD at home) and lessens disruption to employment or education.

1.1.4 PD in Sub-Saharan Africa

The SA Renal Registry data from 2015 report that 36% of the patients in the state service are maintained on PD[15]. This accounts for 85% of PD in Africa.[14] The challenges of practicing PD in SA, include the limited work force, the challenging socioeconomic environment[16], the higher than accepted rate of peritonitis[16] and the rationing of dialysis itself. [6,17] However the day to day practicalities of this modality are far more complex as PD is often used in households without running water or electricity and in informal settlements with communal toilets.

There is a paucity of data on the outcomes of PD programmes in SA and Africa. The only outcome based survival data reported in SA on adults, was from Isla et al from a PD programme in Limpopo. Their 1-year, 2-year and 5-year survival were 86.7%, 78.7% and 65.3% respectively with technique survival of 83.3%, 71.7% and 65.3%[18]. The predictors of poor outcome were low albumin, being underweight, more than one peritonitis event and low haemoglobin.[18] The differences between the cohort in Limpopo and our Institute are (a) we operate a strict PD-First policy, (b) our rationing selection onto renal replacement programme [RRP] is stricter and (c) we are a teaching hospital with a dedicated nephrologist who cares for the PD patients. Considering that at the time of the study in Limpopo they didn't have a certified nephrologist, their results were very encouraging for practicing PD in remote, challenging circumstances.

The role that the socioeconomic status [SES] plays in PD continues to be debated in SA and abroad. In 1994 a study from SA described that peritonitis was associated with age, black race, room – to –occupant ratio, availability of electricity and informal housing, diabetes and several psychological factors.[16] However subsequent to this, in 2001, Katz, I et al reported no link between socioeconomic status and peritonitis.[19] A more recent report from Limpopo also failed to demonstrate that SES was linked to poor survival or technique success. [18] Internationally, BRAZPD, a PD cohort in a country with a similar gross domestic product [GDP] to SA, results

demonstrated that economic status was not independently linked to outcomes [20-23] however in the cohort in Colombia SES was found to influence survival on PD [24] Whether SES is an obstacle or poor predictive factor for outcome requires further investigation.

Data from the rest of Africa is sparse. The only countries to provide low or no cost dialysis are reportedly SA, Mauritius and Sudan.[14] Only SA and Kenya produce their own PD fluid locally.[14] There are isolated reports of centers with successful PD programmes despite the challenges. Senegal and Egypt reported good peritonitis rates for new PD programmes started within in the last 15 years.[25,26] However in Nigeria the prohibitive personal cost of dialysis results in only 6.8% of the population being able to afford treatment for more than 3 months.[27] Sudan reported the successful initiation of a PD programme, and reported a peritonitis rate of 0.87 events per patient year.[28]

1.1.5 The rationale for the Study

The reason for this MPHIL was to review the outcomes of a PD- First programme run in a LMIC with resource constraints. Since PD is a financially viable option in SA and the modality is widely used, it is important to know PD programmes success and limitations. The aim was to audit our programme to help us understand which patients were at greatest risk of adverse events or poor outcomes. Our department will use this information to implement measures to address these issues and hopefully improve our service. As there is such limited literature on PD in LMIC's we hope that this information will be useful to other countries practicing PD in similar settings.

1.1.6 Methodology Aspects

There were two challenging aspects to the analysis of the methodology. The first was describing the adequacy of our dialysis cohort. The conventionally accepted way of presenting the adequacy data is reporting Kt/V, which is a mathematical equation, related to small solute (urea) clearance. Kt/V was not available for all of our patients, as the test was only introduced in our institute in the last 3 years of the

study. The second was the lack of standardized definitions used to describe PD dialysis technique failure.

Adequacy of PD is internationally reported as Kt/V with an accepted goal of a Kt/V of 1.7. However the ISPD guidelines state that: 'adequacy should be interpreted clinically rather than by targeting only solute and fluid removal. Clinical assessment should include clinical and laboratory results, peritoneal and renal clearance, hydration status, appetite and nutritional status, energy level, haemoglobin concentration, responsiveness to erythropoietin therapy, electrolyte status and blood pressure.'[29] Reporting these clinical variables was challenging as they were recorded at multiple visits.

In the absence of a validated score we opted to use the assessment tool of Fresenius dialysis units worldwide. The tool utilizes clinical variables to assess adequacy. The target ranges for the clinical variables were determined by the KDIGO guidelines. The scoring system describes the amount of time a patient meets the clinical target, and divides them into three groups i.e. never, 0 -<50% of the time, >50% of the time. The KDIGO target ranges for these clinical variables include fluid status of euvolaemia, calcium and phosphate within the physiological ranges (calcium 2.1 – 2.5mmol/L, phosphate <1.5mmol/L), haemoglobin between 9.5 – 11g/dL.[30] Urea (<21mmol/L) represents small solute clearance. Due to the small number of malnourished people in our cohort we set the cut off for acceptable urea at less than 21mmol/L.

The second difficulty was in describing PD technical failure. There is a lack of uniformity in the definitions used to define technique failure in different PD registries.[31] The PDOPPS study that is currently underway, aims to standardize the PD related practice definitions.[31] We have therefore used the definition set out by the PDOPPS to define our cohorts technique failure; "any PD related complication that leads to the permanent cessation of the therapy." [31] For our technique failure we included all patients who underwent modality switch from PD to HD and those that died from a PD related cause.

1.1.7 References

1 Lozano, R. *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2095-2128, doi:10.1016/S0140-6736(12)61728-0 (2012).

2 Kanji, Z. *et al.* Genetic variation in APOL1 associates with younger age at hemodialysis initiation. *J Am Soc Nephrol* **22**, 2091-2097, doi:10.1681/ASN.2010121234 (2011).

3 Stanifer, J. W. *et al.* The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* **2**, e174-181, doi:10.1016/S2214-109X(14)70002-6 (2014).

4 Martins, D. *et al.* The association of poverty with the prevalence of albuminuria: data from the Third National Health and Nutrition Examination Survey (NHANES III). *American journal of kidney diseases : the official journal of the National Kidney Foundation* **47**, 965-971, doi:10.1053/j.ajkd.2006.02.179 (2006).

5 Merkin, S. S. *et al.* Individual and neighborhood socioeconomic status and progressive chronic kidney disease in an elderly population: The Cardiovascular Health Study. *Soc Sci Med* **65**, 809-821, doi:10.1016/j.socscimed.2007.04.011 (2007).

6 Okpechi, I. G., Rayner, B. L. & Swanepoel, C. R. Peritoneal dialysis in Cape Town, South Africa. *Perit Dial Int* **32**, 254-260, doi:10.3747/pdi.2011.00100 (2012).

7 Sharif, M. U., Elsayed, M. E. & Stack, A. G. The global nephrology workforce: emerging threats and potential solutions! *Clin Kidney J* **9**, 11-22, doi:10.1093/ckj/sfv111 (2016).

8 Liyanage, T. *et al.* Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* **385**, 1975-1982, doi:10.1016/S0140-6736(14)61601-9 (2015).

9 Pecoits-Filho, R. *et al.* Overview of peritoneal dialysis in Latin America. *Perit Dial Int* **27**, 316-321 (2007).

10 Cueto-Manzano, A. M. & Rojas-Campos, E. Status of renal replacement therapy and peritoneal dialysis in Mexico. *Perit Dial Int* **27**, 142-148 (2007).

11 Li, P. K. & Chow, K. M. Peritoneal dialysis-first policy made successful: perspectives and actions. *American journal of kidney diseases : the official journal of the National Kidney Foundation* **62**, 993-1005, doi:10.1053/j.ajkd.2013.03.038 (2013).

12 Liu, F. X. *et al.* A Global Overview of the Impact of Peritoneal Dialysis First or Favored Policies: An Opinion. *Perit Dial Int* **35**, 406-420, doi:10.3747/pdi.2013.00204 (2015).

13 Choy, A. S. & Li, P. K. Sustainability of the Peritoneal Dialysis-First Policy in Hong Kong. *Blood Purif* **40**, 320-325, doi:10.1159/000441580 (2015).

14 Abu-Aisha, H. & Elamin, S. Peritoneal dialysis in Africa. *Perit Dial Int* **30**, 23-28, doi:10.3747/pdi.2008.00226 (2010).

15 Davids, M. R., Balbir Singh, G. K., Marais, N. & Jacobs, J. C. South African Renal Registry. *Annual Report 2014*.

16 Lent, R., Myers, J. E., Donald, D. & Rayner, B. L. Continuous ambulatory peritoneal dialysis: an option in the developing world? *Perit Dial Int* **14**, 48-51 (1994).

17 Moosa, M. R. & Kidd, M. The dangers of rationing dialysis treatment: the dilemma facing a developing country. *Kidney Int* **70**, 1107-1114, doi:10.1038/sj.ki.5001750 (2006).

18 Isla, R. A. *et al.* Continuous ambulatory peritoneal dialysis in Limpopo province, South Africa: predictors of patient and technique survival. *Perit Dial Int* **34**, 518-525, doi:10.3747/pdi.2013.00334 (2014).

19 Katz, I. J., Sofianou, L. & Hopley, M. An African community-based chronic ambulatory peritoneal dialysis programme. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* **16**, 2395-2400 (2001).

20 de Andrade Bastos, K. *et al.* Family income and survival in Brazilian Peritoneal Dialysis Multicenter Study Patients (BRAZPD): time to revisit a myth? *Clin J Am Soc Nephrol* **6**, 1676-1683, doi:10.2215/CJN.09041010 (2011).

21 dos Santos Grincenkov, F. R. *et al.* Longitudinal changes in health-related quality of life scores in Brazilian incident peritoneal dialysis patients

(BRAZPD): socio-economic status not a barrier. *Perit Dial Int* **33**, 687-696, doi:10.3747/pdi.2012.00038 (2013).

22 Fernandes, N. M. *et al.* Association of ethnicity and survival in peritoneal dialysis: a cohort study of incident patients in Brazil. *American journal of kidney diseases : the official journal of the National Kidney Foundation* **62**, 89-96, doi:10.1053/j.ajkd.2013.02.364 (2013).

23 Martin, L. C. *et al.* Geographic and educational factors and risk of the first peritonitis episode in Brazilian Peritoneal Dialysis study (BRAZPD) patients. *Clin J Am Soc Nephrol* **6**, 1944-1951, doi:10.2215/CJN.11431210 (2011).

24 Sanabria, M. *et al.* Dialysis outcomes in Colombia (DOC) study: a comparison of patient survival on peritoneal dialysis vs hemodialysis in Colombia. *Kidney Int Suppl*, S165-172, doi:10.1038/sj.ki.5002619 (2008).

25 Mahmoud, K. M. *et al.* Continuous ambulatory peritoneal dialysis in Egypt: progression despite handicaps. *Perit Dial Int* **30**, 269-273, doi:10.3747/pdi.2009.00001 (2010).

26 Niang, A. *et al.* Pilot experience in senegal with peritoneal dialysis for end-stage renal disease. *Perit Dial Int* **34**, 539-543, doi:10.3747/pdi.2011.00327 (2014).

27 Arogundade, F. A., Sanusi, A. A., Hassan, M. O. & Akinsola, A. The pattern, clinical characteristics and outcome of ESRD in Ile-Ife, Nigeria: is there a change in trend? *Afr Health Sci* **11**, 594-601 (2011).

28 Elhassan, E. A. *et al.* Peritoneal dialysis in the Sudan. *Perit Dial Int* **27**, 503-510 (2007).

29 Lo, W. K. *et al.* Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. *Perit Dial Int* **26**, 520-522 (2006).

30 KDIGO. Clinical Practice Guidelines for Evaluation and Management of Chronic Kidney Disease. *Kidney Internaltional Supplements* **3** (2012).

31 Perl, J. *et al.* The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS): Unifying Efforts to Inform Practice and Improve Global Outcomes in Peritoneal Dialysis. *Perit Dial Int* **36**, 297-307, doi:10.3747/pdi.2014.00288 (2016).

1.2 Ethical considerations

Before the study commenced and data was collected, research ethics approval for the project was received from the Faculty of Health Sciences Human Research Committee. Approval number Ref no: R007/2014.

(Ethics approval for the study – see Appendix 2)

The most important ethical consideration in this study was patient confidentiality. The data was collected through a folder review. The retrospective information was confidentially collected by a review of the information already present within the patients' folders. The patients' clinic visits and routine laboratory investigations were not altered and the study followed the best clinical practice guidelines set out by KDIGO. As this was a retrospective folder review, informed consent was waived.

Patient confidentiality was maintained by storing all of the information from the patients' folders, under the unique folder number in the registry. This registry was only accessible via a unique coded password, known only to the investigators. The data was stored on a password locked computer. This was in keeping with the declaration of Helsinki 2013.

The benefit and social value of this study will be in identifying high-risk sub populations within our PD cohort. The information will be used to address sub-optimal therapy/management to improve patient outcomes in a resource-constrained environment.

1.3 Why was PDI chosen – Authors considerations

I have chosen PDI [Peritoneal dialysis International] as my journal of choice for submission for publication. It is a very respected journal in the field of peritoneal dialysis.

PDI has an impact factor of 1.527. It is indexed in major databases used for research (MEDLINE, PUBMED, Science Citation Index). It has a broad reach as it is accessed from over 160 countries, by over 30000 people annually.

The Author has the option for open access and there are no author fees attached. Articles are widely promoted by email, social media and newsletter.

The instructions to the author can be found in appendix 3.

Chapter 2

2.1 Title page

Running Title:

Outcomes of a PD-First Programme in Cape Town, South Africa

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Number of figure and tables

Tables 4 and Figure 1

Supplementary

Supplemental Figure 1

Supplemental Figure 2

Supplemental Figure 3a and 3b

Supplemental Table 1

2.2 Abstract

Background:

South Africa [SA] currently performs the most peritoneal dialysis [PD] in Africa. Yet, outcome data is limited. With the collision of epidemics of communicable and non-communicable diseases in Africa the need for chronic dialysis is escalating. PD remains a life-saving modality especially as haemodialysis is limited in the state sector.

Methods:

We retrospectively analysed all patients undergoing PD at Groote Schuur Hospital from January 2008 until June 2014 and thereafter prospectively until June 2015. Variables included demographics, adequacy, modality, fluid, cardiovascular risk and diabetes. The influences of these variables on peritonitis rate, technique and patient survival were assessed.

Results:

230 patients were initiated on PD, 31 were excluded as they were on PD for < 90 days. The mean age was 39.7 +/- 10.4 years [SD], 49.8% were male and 63.8% were mixed ancestry. 9.8 % were diabetic at dialysis initiation. The average length of time on PD was 17 months (IQR 8 – 32). The peritonitis rate was 0.87 events per patient years. One, 2 and 5 year patient and technique survival was 94.4%, 84.3% and 60.2% and 82.5%, 69.0% and 37.4% respectively. Fluid overload (p=0.019) and low haemoglobin (p=0.001) were independent risk factors for poor survival. African race (HR 1.97, 95% CI (1.16 – 3.37) and fluid overload (p= 0.002) were both predictors of technique failure.

Conclusions:

In our PD-First programme the results are encouraging, despite lack of home visits due to safety, resource limitations and a high disease burden. Technique failure in African race needs further evaluation. Peritoneal dialysis remains a viable, life-saving alternative in an African setting.

Key words:

Peritoneal dialysis, Africa, South Africa, outcomes, PD-First

2.3 Introduction

South Africa [SA] is a country at the southern tip of Sub-Saharan Africa [SSA], with a population of 53 million.[1] It has the highest income inequality in the world with a Gini coefficient of 63.4.[2] In SSA, over half the population lives on less than 1$ per day, and yearly per capita expenditure on health ranges from $9 – $158 compared to over $2000 in Europe.[3]

Chronic Kidney disease [CKD] prevalence is rising worldwide. In SA our high-income inequality is driving a dual epidemic of communicable[4] and non-communicable diseases[5]. This is further illustrated by Jha et al, which reports that people living in the lowest socio-economic quartile are at a 60% greater risk of progressive CKD.[6] Additional contributing factors include low birth weight[7], ethnic or genetic predisposition [8] traditional medications[4] and poverty itself.[6,9] Lack of access to essential medication is also a contributory factor.

Despite the rise in CKD, access to renal replacement therapy [RRT] in low and middle-income countries [LMICs] remains limited.[10] Only 7.2% of the global prevalence of RRT is reported to occur in these regions, and over half of those that need RRT do not have access.[11] In Africa the situation is far worse with only 16% of patients receiving RRT.[11] This situation is exacerbated by a scarcity of specialists. In 2009 there were only 1.8 nephrologists per million population [pmp] in SA,[3] compared to 31 pmp in Western Europe and 22 pmp in Northern America.[12]

SA performs 85% of the peritoneal dialysis [PD] in Africa, [13] of which 36% is performed in state sector hospitals for patients without medical insurance.[14] PD has the advantage of allowing patients from areas remote to a dialysis centre to receive treatment, but with high rates of poverty, unemployment and resource constraints in SA, PD has a unique set of challenges.

The study was performed in a state sector hospital in the Western Cape [WC] Province. The province has an estimated population of 6,362,257 million, with a racial breakdown of 48.8% mixed ancestry; Africans and Caucasians constitute 32.9%% and 15.7% respectively.[15,16] 74.8% of the province's population is

estimated to be uninsured and therefore relies on state medical care.[15] The WC has the highest prevalence of patients accessing RRT in SA [312 pmp], with the state only accounting for 14.7% of these facilities.[14]

Groote Schuur Hospital [GSH] is one of 4 adult state facilities in the province offering dialysis. The hospital provides tertiary medical care to 42% of the WC population i.e. 2.67 million, and transplant and clinical outreach support to a further 10%.[15] State chronic medical care including dialysis is free for those who can't afford it, however due to the expense of RRT, dialysis is rationed. The rationing process is ethically endorsed and strictly adhered to.

The selection criteria for acceptance onto the renal replacement programme [RRP] are based on suitability for transplantation. A committee meeting is held weekly to review patients for suitability for our programme. The committee panel is comprised of nephrologists, physicians, hospital management and social workers. Despite the large drainage population Groote Schuur Renal Unit only accommodates 148 patients for chronic dialysis, 98 for haemodialysis [HD] and 50 for PD. Due to the limitation of access to dialysis and in particular haemodialysis [HD] slots our policy is to promote a PD-First programme. All patients suitable for PD are initiated on PD unless compelling medical, physical or psychosocial factors preclude the use of PD.

The PD-First programme is run by two qualified PD trained sisters. Patient training is undertaken by the PD sisters, in a 2-week intensive, one-to-one basis. Retraining is performed if recurrent peritonitis occurs. All patients have a straight double cuff Tenckhoff catheter inserted by a nephrologist or surgeon. Continuous ambulatory peritoneal dialysis [CAPD] via twin bag, flush-before-fill system is used. A limited number of patients have access to Automated Peritoneal Dialysis [APD] i.e. if working or young adults studying. A nephrologist initially reviews all the patients monthly. Adolescents continue to be seen monthly, while adults are reviewed 3 monthly if clinically stable. This follows the guidelines as set out by the Kidney Disease: Improving Global Outcomes [KDIGO]. [17] Our PD-First programme does not cater for home visits due to staff safety concerns, and is limited by the availability of only glucose-based PD solutions.

To date there is very little information reporting outcomes on PD-First programmes in LMICs.[10] Therefore this study aimed to evaluate the success of our programme in a resource limited setting and identify factors linked to poor outcome.

2.4 Methods

The data was collected at Groote Schuur Hospital retrospectively from 2008 to June 2014, then prospectively until June 2015. All patients starting dialysis in this time period and surviving at least 3 months on the initial dialysis modality were included. The baseline demographics, cause of end stage renal disease [ESRD], biochemistry and cardiovascular risk were documented.

Laboratory investigations and clinical examinations were performed as recommended by the KDIGO guidelines.[17] Peritoneal equilibration test [PET] tests and Kt/V were only routinely available and performed in the last 3 years of the study. The initial PET including Kt/V was performed at six weeks post CAPD initiation. It was only repeated when clinically indicated. Transporter status was defined by the use of a dialysis- to- plasma [D/P] creatinine ratio. High transporter status was (H:>0.81), high average (HA; 0.65-0.8), low average (LA; 0.5 – 0.64) and low transporter (L; <0.5).[18]

In the absence of a validated scoring system of reporting clinical variables as a reflection of adequate dialysis, we based our scoring system on those used by Fresenius dialysis units worldwide. In a resource limited setting with limited access to Kt/v this scoring system is a pragmatic approach to determine how well a patient is being dialysed. This scoring system reflects how often an individual reaches the KDIGO targets. Targets were set for euvolaemia, phosphate (<1.5mmol/L), calcium (2.1 – 2.5mmol/L), haemoglobin [Hb] (9.5 – 11g/dL) and urea (<21 mmol/L). We subdivided these targets into 3 categories: never achieved, achieved >0% but < 50% or ≥ 50% of the time**.** Euvolaemia was determined clinically on routine follow up by nephrologists, where clinical parameters including elevated JVP, pedal oedema and clinical evidence of pulmonary oedema were assessed. Fluid overload was defined as not meeting targeted euvolaemia in > 50% of the patients clinical visits.

Technique failure was defined as “any PD related complication that leads to the permanent cessation of the therapy”.[19] This included peritonitis (refractory), inadequate dialysis, catheter malfunction, leak or patient related reason (not coping), ultrafiltration failure, and death from any PD related cause. Peritonitis and its sub categories of recurrent, relapsing, repeat, refractory and catheter related peritonitis as well as exit site infection were defined using the ISPD guidelines.[20] Mortality data was obtained from patient folders, death certificates, clinic records and patient families. Fluid overload as a cause of death was defined as clinical fluid overload at the time of death with pulmonary oedema.

All statistical analysis was performed using Stata (Version 13.1; Stata Corp, College Station, Texas, USA). Descriptive statistics were used to present the patient’s demographic and clinical characteristics. Continuous variables were presented as means (± standard deviation [SD]) or medians (with interquartile range [IQR]), while categorical variables were presented as frequencies and percentages. For comparison of categorical variables Chi-squared or Fishers exact test were applied, while comparison of continuous variables between groups were compared using Students t-test or Wilcoxon Rank Sum test.

Using death or technique failure as the primary end points, survival probabilities were analyzed using Kaplan-Meier method and hazard ratios were estimated using Cox proportional hazard regression. For analysis examining time to patient death, patients were censored for renal transplantation, patient relocation, transfer off PD programme or remaining on PD at the end of the observation period (30th June 2015). Patients who were no longer transplantable and not offered modality switch from PD to HD, were also censored. For technique survival, patients were censored at their date of renal transplantation or remaining on PD at completion of the study (30th June 2015). Respective risk factors associated with death and technique failure were first assessed using univariate Cox regression for all baseline characteristics including biochemical variables and urine output. Number of peritonitis events, transporter status, and assessment of the percentage of times a patient met adequacy targets (defined above) were included as covariates in the regression. Variables were retained in the multivariable model if they had $p<0.25$ in univariate analysis. Age, race, gender, diabetes and more than 1 peritonitis event were added into the model as they were clinically relevant regardless of statistical contribution.

For effect size measures, both unadjusted and adjusted hazard ratios [HRs] were presented with 95% confidence intervals [CI]. P-values <0.05 were considered statistically significant.

2.5 Results

The study included 199 patients, of whom 99 (49.8%) were male (Table 1). Mixed ancestry was the most common ethnic group, in 63.8% of cases. The median length of time on PD was 17 months. At baseline our patients had a low cardiovascular risk profile with only 19 (9,8%) being diabetic and 34 (17,5%) smoking. Nutritional status at baseline showed a small proportion of patients having a low body mass index [BMI] (<18.5kg/m^2), with 3.6% being underweight and only 6 patients having an albumin less than 30g/L.

The peritonitis rate was 0.87 peritonitis events per patient year. 47.5% of the organisms isolated were gram-positive, 3.96% had pseudomonas and 5.0% fungal peritonitis (Supplemental figure 1). Our culture negative rate (19.5%) met ISPD standards of less than 20%. The percentage of patients that had one event was 22.6%, 2 events 15.1% and 23,3% had 3 or more events.

Figure 1 reflects the adequacy as represented by biochemical and clinical parameters at 6 months, 1 and 2-year time points. Phosphate and urea targets were not achieved more that 50% of the time. Approximately half of patients reached targets for fluid control and haemoglobin.

2.5.1 Patient survival

Our patient survival probability at 1, 2 and 5 years was 94,4%, 84,3% and 60,2% respectively. (Supplemental figure 2) Overall 32 patients died. The most common cause of death was fluid overload (37.5%), followed by infection with no direct relationship to PD (18.8%), infection related to PD (12.5%), malignancy (12.5%), sudden death (9.4%) and miscellaneous (9.4%) (Supplemental table 1). Of those dying from fluid overload, 5 (41.7%) were diabetic and 12 (100%) were HA transporters and only 1 patient had a residual urine output of less than 250ml at

baseline. Of the 32 patients that died 12 were not eligible for modality switch, as they were no longer considered transplant candidates.

Univariate and multivariate analysis of risk factors associated with increased risk of patient death are described in table 2. Independent risk factors for poor survival were 1) not reaching target for haemoglobin [Hb] and 2) fluid overload. Achieving target ranges more than 50% of the time for fluid and haemoglobin reduced the hazard ratio for death by 76% for each variable respectively. Patients with diabetes had nearly 3 times increased risk of death.

2.5.2 Technique survival

Technique survival at 1, 2 and 5 years was 82.5%, 69.0% and 37.4% respectively. (Supplemental figure 2) For those requiring modality switch the commonest cause was peritonitis (50%). Fungal peritonitis accounted for 38.5% of these events. Alternative causes of technique failure were catheter malfunction (24.1%), inadequate or failed PD (14.8%), patient not coping with PD (7.4%) and leak (3.7%). The independent risk factors for poor technique survival were African race (HR 1.97, 95% CI 1.16 – 3.37), and fluid overload (HR 0.30, 95% CI 0.14 – 0.64) (Table 3). Patients reaching euvolaemia less than 50% of the time were 70% less likely to have technique failure compared to those never achieving euvolaemia. Among patients of African ethnicity, 42.2% experienced technique failure, and the reasons were peritonitis in 42% (n=10), catheter malfunction in 29% (n=7), inadequate dialysis in 21% (n=5) and leak in 8% (n=2).

2.6 Discussion

In the state sector in South Africa chronic medical care including dialysis is provided for free for indigent patients, for those receiving a disability grant or state pension. Due to financial constraints dialysis is rationed, via an ethically endorsed selection criteria. This selection process favours younger, fitter, healthier patients as suitability for transplantation is the guiding principle to optimise use of scarce dialysis slots.[21] As a result, our cohort differs from other PD studies. This is evident when comparing our results with countries that don't ration dialysis and have a similar gross domestic

product (GDP), i.e. Mexico, Brazil and Columbia. The average age was 16 – 18 years younger than those in Brazil and Columbia, [22,23] there were strikingly less diabetics (9.8% vs. 20 – 44%) than in the other cohorts,[22-24] and fewer patients had documented cardiovascular disease (Table 4). The differences in our cohort were further evident when reviewing causes of death. Cardiovascular death and infections are the two most common causes of death in PD registry data.[25] However when reviewing our causes of death, fluid overload was the most common cause followed by infection. Only 50% of those dying from infection had an infection related to PD itself.

Patient survival is not inferior to countries with similar GDP, other PD-First programmes or developed countries reporting PD registry data. This can be partially attributed to the selection criteria used, but the results would have been significantly better if transfer to haemodialysis could be guaranteed in all cases. However survival rates were good considering that 12 of the 32 patients that died (37.5%) were no longer transplantable and hence not offered a switch to haemodialysis.

The independent risk factors in our cohort that were linked to poor survival were fluid overload and not meeting target for haemoglobin. The finding that fluid overload accounted for 37.5% of deaths in the absence of cardiovascular disease was one of the major findings in this observational study. This was not related to loss of residual renal function [RRF]. A high transporter status was identified in all of the patients with fluid overload and half were diabetic. It has highlighted the importance of PD fluid and modality choice. Over hydration in PD, has been found to be a predictor of mortality, independent of cardiac failure.[30] Icodextrin is effective at increasing ultrafiltration without impairing residual renal function.[31] APD has also been shown to improve survival in high transporters,[32] and in anuric patients.[33] Unfortunately due to cost constraints our PD programme has limited APD and no access to icodextrin. Motivation to the health authorities for selected availability of icodextrin is a possible option in the setting of ultrafiltration failure.

9.8% of the cohort was diabetic, with relatively little comorbidity. However this group still had a nearly threefold increased risk of death. On multivariate analysis this approached statistical significance with 95% CI of 0.95 – 8.36 and a p value of 0.062. Studies have shown that predictors of long-term survival in diabetic patients

on PD are age, pre-dialysis comorbidity, RRF, adequate nutrition, transporter status and peritonitis.[34-36] Our diabetic cohort was young, well nourished and the majority had good RRF. Despite this they still had a worse survival, likely due poor diabetic control (57% had an HBA1C >8) and HA transport status (100%).

A low haemoglobin in CKD is associated with poor cardiovascular outcomes due to left ventricular hypertrophy and worsening ischaemia.[37] Not reaching KDIGO target for haemoglobin was an independent predictor of poor outcome in our cohort. Anaemia as a poor predictive marker was similarly found in a diabetic cohort in China[38], in BRAZPD[39] and locally in Limpopo.[40] Erythropoetin stimulating agents [ESAs] were previously only available to employed patients. By 2010 all patients had access to Recormon. Recormon was the only available ESA at Groote Schuur during the study period. Currently, due to cost constraints, we are only able to start Recormon when patients commence dialysis. Furthermore, patients often present very late requiring dialysis at presentation. As the majority of our patients were well nourished at baseline we postulate that the likely cause of anaemia in our cohort may be linked to inflammation and inadequate dialysis. Therefore this may be an epiphenomenon.

Being underweight, malnourished and a low albumin have been shown to confer worse survival for patients on PD.[25,41] In SA, Isla et al described that low albumin and low BMI were linked to death or technique failure in their PD cohort in Limpopo.[40] Our cohort had a low prevalence of being underweight (i.e. BMI <18kg/m^2) at baseline (3.6%), and a good mean baseline albumin of 38.7g/dL. Despite very few of our patients being underweight a low BMI did convey a 3.27 times increased risk of death. For every 1g/L increase in albumin, the risk of death decreased by 3%. Our survival data reflects the 'obesity paradox' as being obese conveyed a 17% decreased relative risk of death.

Factors associated with technique failure include age, center experience, distance from center, socioeconomic factors, initial PD modality, diabetes, low albumin and peritonitis.[22-24,42] The two commonest reasons for technique failure in our cohort were peritonitis and catheter malfunction.[42] However on univariate and multivariate analysis only African ethnicity and fluid overload were associated with poor technique survival. African ethnicity in our population is a surrogate marker for

poorer socioeconomic status due to our history of discrimination against Africans resulting in profound income inequalities. The reason for Africans having worse technique survival is however not clear. On subgroup analysis recurrent peritonitis events were not greater in Africans compared with non-Africans, 39% and 37.8% respectively. The impact of socioeconomic status [SES] on technique survival remains debated. In SA**,** Lent et al (1994) showed that poorer SES was associated with peritonitis.[43] However since this study, newer PD techniques (flush-before-fill) have shown decreased peritonitis rates. A local study from Limpopo and the BRAZPD cohort did not demonstrate an association between family income, SES and technique failure.[40,44] Further investigation is required to ascertain why the African subgroup is at an increased risk for technique failure. This is an area in PD that needs clarification in Africa, as room occupancy, running water, electricity and sanitation are still taken into account in our PD-First programme when deciding on modality.

In our PD programme young adults <25 years are offered APD to complete schooling and studies. Young adults have been reported in the literature as a high-risk group for technique failure. However only 15% of our young adults experienced technique failure in the subgroup analysis.

Despite the social challenges the peritonitis rate for our unit was 0.87 episodes per patient year. This is higher than the recommended ISPD standard of 0.67.[20] Our unit has shown a steady decline in our peritonitis rate over the last 15 years. In 1994 the units peritonitis rate was 2.7 [43] and it had declined to 1.7 episodes per patient year in 2002.[3] (Supplemental figure 3b) We attribute this steady decline to newer PD technique, better patient care and education.

Due to the lack of availability of Kt/V, surrogate biochemical and clinical markers for overall small solute clearance, patient wellbeing and dialysis adequacy were obtained. This included bone mineral health, Hb, nutrition, urea and fluid control. Patients who never met the KDIGO targets for these variables had a statistically significant increased chance of death. Phosphate control was particularly poor, but access to phosphate binders is generally limited to calcium carbonate due to resource constraints.

Limitations of this study included firstly, partial retrospective study design and limited Kt/V analysis due to the test only being instituted in the last 3 years of the study. Secondly, no socioeconomic information was collected. This will be important to look at in the future to understand why our African cohort had worse technique survival. Thirdly, there are a limited number of HIV infected patients in our cohort. This is a reflection of the selection criteria for renal replacement endorsed by the Western Cape. Not all provinces select patients in this manner. Therefore it is important to note the lower number of HIV positive patients in our cohort compared to dialysis programs in other parts of SA.[45] Lastly for statistical modeling a mixed-effect modeling technique could also be considered in measuring the effects of repeated laboratory measures on other outcomes. However this analysis would be challenging given the proportion of missing laboratory data from 1 year of follow up. Competing risks analysis in survival modeling for nephrology specific outcomes will be used to produce more reliable adjusted effects for HRs in future analysis.

2.7 Conclusion

This study shows that a PD-First programme can be successfully offered in a resource limited setting. Even without home visits, limited APD and resource constraints limiting icodextrin use. Our results are comparable to larger cohorts, registries in similar GDP brackets and in PD programmes within higher income countries. This is likely to be attributed to the selection criteria that we use in rationing our dialysis, thereby selecting patients who are suitable for transplantation. Being fluid overloaded, diabetic and having low haemoglobin are linked to poor survival. These areas need to be targeted, with possibly selected use of icodextrin and APD. When the success of a programme and access to RRT relies on transplantation and turnover, understanding poor predictive factors and aggressively addressing them is vital for success. Our data supports the use of PD-First programme in South Africa, as it is a life-saving modality in a continent where RRT is scarce.

2.8 References

1 CIA.world.factbook. CIA Factbook. https://www.cia.gov/library/publications/the-world-factbook/geos/sf.html (retrieved December 2016).

2 WorldBank. GINI index (World Bank estimate). http://data.worldbank.org/indicators/SI.POV.GINI/ (Retrieved June, 04: 2016).

3 Okpechi, I. G., Rayner, B. L. & Swanepoel, C. R. Peritoneal dialysis in Cape Town, South Africa. *Perit Dial Int* **32**, 254-260, doi:10.3747/pdi.2011.00100 (2012).

4 Stanifer, J. W. *et al.* The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* **2**, e174-181, doi:10.1016/S2214-109X(14)70002-6 (2014).

5 Mayosi, B. M. *et al.* The burden of non-communicable diseases in South Africa. *Lancet* **374**, 934-947, doi:10.1016/S0140-6736(09)61087-4 (2009).

6 Jha, V. *et al.* Chronic kidney disease: global dimension and perspectives. *Lancet* **382**, 260-272, doi:10.1016/S0140-6736(13)60687-X (2013).

7 Hoy, W. E., Rees, M., Kile, E., Mathews, J. D. & Wang, Z. A new dimension to the Barker hypothesis: low birthweight and susceptibility to renal disease. *Kidney Int* **56**, 1072-1077, doi:10.1046/j.1523-1755.1999.00633.x (1999).

8 Kanji, Z. *et al.* Genetic variation in APOL1 associates with younger age at hemodialysis initiation. *J Am Soc Nephrol* **22**, 2091-2097, doi:10.1681/ASN.2010121234 (2011).

9 Merkin, S. S. *et al.* Individual and neighborhood socioeconomic status and progressive chronic kidney disease in an elderly population: The Cardiovascular Health Study. *Soc Sci Med* **65**, 809-821, doi:10.1016/j.socscimed.2007.04.011 (2007).

10 Wearne, N. *et al.* Continuous ambulatory peritoneal dialysis: perspectives on patient selection in low- to middle-income countries. *Int J Nephrol Renovasc Dis* **10**, 1-9, doi:10.2147/IJNRD.S104208 (2017).

11 Liyanage, T. *et al.* Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* **385**, 1975-1982, doi:10.1016/S0140-6736(14)61601-9 (2015).

12 Sharif, M. U., Elsayed, M. E. & Stack, A. G. The global nephrology workforce: emerging threats and potential solutions! *Clin Kidney J* **9**, 11-22, doi:10.1093/ckj/sfv111 (2016).

13 Abu-Aisha, H. & Elamin, S. Peritoneal dialysis in Africa. *Perit Dial Int* **30**, 23-28, doi:10.3747/pdi.2008.00226 (2010).

14 Davids, M. R., Balbir Singh, G. K., Marais, N. & Jacobs, J. C. South African Renal Registry. *Annual Report 2014*.

15 Western Cape Goverment Health Annual Performance Plan. https://www.westerncape.gov.za/sites/www.westerncape.gov.za/files/department-of-health-annual-performance-plan-2015-2016 (Retrieved June 2016).

16 2011 Census Municipal Report. *Western Cape* **report no.03-01-49** (2011).

17 KDIGO. Clinical Practice Guidelines for Evaluation and Management of Chronic Kidney Disease. *Kidney Internaltional Supplements* **3** (2012).

18 Twardowski ZJ, N. K., Khanna R, Prowant BF, Ryan LP, Moore HL, Nielsen MP. Peritoneal equilibration test. *Perit Dial Bull.* **7**, 138 - 147 (1987).

19 Perl, J. *et al.* The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS): Unifying Efforts to Inform Practice and Improve Global Outcomes in Peritoneal Dialysis. *Perit Dial Int* **36**, 297-307, doi:10.3747/pdi.2014.00288 (2016).

20 Li, P. K. *et al.* Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* **30**, 393-423, doi:10.3747/pdi.2010.00049 (2010).

21 Moosa, M. R. & Kidd, M. The dangers of rationing dialysis treatment: the dilemma facing a developing country. *Kidney Int* **70**, 1107-1114, doi:10.1038/sj.ki.5001750 (2006).

22 de Moraes, T. P. *et al.* Characterization of the BRAZPD II cohort and description of trends in peritoneal dialysis outcome across time periods. *Perit Dial Int* **34**, 714-723, doi:10.3747/pdi.2013.00282 (2014).

23 Sanabria, M. *et al.* Outcomes of a peritoneal dialysis program in remote communities within Colombia. *Perit Dial Int* **35**, 52-61, doi:10.3747/pdi.2012.00301 (2015).

24 Cueto-Manzano, A. M. & Rojas-Campos, E. Status of renal replacement therapy and peritoneal dialysis in Mexico. *Perit Dial Int* **27**, 142-148 (2007).

25 Kwong, V. W. & Li, P. K. Peritoneal Dialysis in Asia. *Kidney Dis (Basel)* **1**, 147-156, doi:10.1159/000439193 (2015).

26 ANZDATA. 38th Report. http://www.anzdata.org.au (accessed 1 November 2016).

27 Ho, Y. W. C., K.F; Choy, B.Y; Fung, K.S; Chen, Y.L; Kwan, T.H; Wong, P.N; Lai, W.M; Yuen, S.K; Lo, S.H.K; Chan, C.K; Leung, C.B. Hong Kong Renal Registry Report 2012. *Hong Kong Journal of Nephrology* **15** (2013).

28 Mircescu, G. *et al.* The success story of peritoneal dialysis in Romania: analysis of differences in mortality by dialysis modality and influence of risk factors in a national cohort. *Perit Dial Int* **26**, 266-275 (2006).

29 Dhanakijcharoen, P., Sirivongs, D., Aruyapitipan, S., Chuengsaman, P. & Lumpaopong, A. The "PD First" policy in Thailand: three-years experiences (2008-2011). *J Med Assoc Thai* **94 Suppl 4**, S153-161 (2011).

30 Jotterand Drepper, V. *et al.* Overhydration Is a Strong Predictor of Mortality in Peritoneal Dialysis Patients - Independently of Cardiac Failure. *PLoS One* **11**, e0158741, doi:10.1371/journal.pone.0158741 (2016).

31 Cho, Y. *et al.* Impact of icodextrin on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* **28**, 1899-1907, doi:10.1093/ndt/gft050 (2013).

32 Johnson, D. W. *et al.* Superior survival of high transporters treated with automated versus continuous ambulatory peritoneal dialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* **25**, 1973-1979, doi:10.1093/ndt/gfp780 (2010).

33 Brown, E. A. *et al.* Survival of functionally anuric patients on automated peritoneal dialysis: the European APD Outcome Study. *J Am Soc Nephrol* **14**, 2948-2957 (2003).

34 Abdel-Rahman, E. M., Wakeen, M. & Zimmerman, S. W. Characteristics of long-term peritoneal dialysis survivors: 18 years experience in one center. *Perit Dial Int* **17**, 151-156 (1997).

35 Maiorca, R. *et al.* Comparison of long-term survival between hemodialysis and peritoneal dialysis. *Adv Perit Dial* **12**, 79-88 (1996).

36 Passadakis, P. S. & Oreopoulos, D. G. Diabetic patients on peritoneal dialysis. *Semin Dial* **23**, 191-197, doi:10.1111/j.1525-139X.2010.00707.x (2010).

37 Wizemann, V., Kaufmann, J. & Kramer, W. Effect of erythropoietin on ischemia tolerance in anemic hemodialysis patients with confirmed coronary artery disease. *Nephron* **62**, 161-165 (1992).

38 Yang, X. *et al.* Clinical outcome and risk factors for mortality in Chinese patients with diabetes on peritoneal dialysis: a 5-year clinical cohort study. *Diabetes Res Clin Pract* **100**, 354-361, doi:10.1016/j.diabres.2013.03.030 (2013).

39 Goncalves, S. M. *et al.* Lack of adequate predialyis care and previous hemodialysis, but not hemoglobin variability, are independent predictors of anemia-associated mortality in incident Brazilian peritoneal dialysis

patients: results from the BRAZPD study. *Blood Purif* **34**, 298-305, doi:10.1159/000342618 (2012).

40 Isla, R. A. *et al.* Continuous ambulatory peritoneal dialysis in Limpopo province, South Africa: predictors of patient and technique survival. *Perit Dial Int* **34**, 518-525, doi:10.3747/pdi.2013.00334 (2014).

41 Kim, Y. K. *et al.* The association between body mass index and mortality on peritoneal dialysis: a prospective cohort study. *Perit Dial Int* **34**, 383-389, doi:10.3747/pdi.2013.00008 (2014).

42 Mehrotra, R. Translating an understanding of the determinants of technique failure to maximize patient time on peritoneal dialysis? *Perit Dial Int* **33**, 112-115, doi:10.3747/pdi.2012.00270 (2013).

43 Lent, R., Myers, J. E., Donald, D. & Rayner, B. L. Continuous ambulatory peritoneal dialysis: an option in the developing world? *Perit Dial Int* **14**, 48-51 (1994).

44 de Andrade Bastos, K. *et al.* Family income and survival in Brazilian Peritoneal Dialysis Multicenter Study Patients (BRAZPD): time to revisit a myth? *Clin J Am Soc Nephrol* **6**, 1676-1683, doi:10.2215/CJN.09041010 (2011).

45 Ndlovu, K. C. Z. & Assounga, A. Continuous Ambulatory Peritoneal Dialysis in Patients with HIV and End-Stage Renal Failure. *Perit Dial Int* **37**, 321-330, doi:10.3747/pdi.2016.00165 (2017).

2.9 Tables:

Table 1: Baseline characteristics of our PD cohort

		All patients (n=199)
Age (years)	Mean +/- SD	39.65 +/- 10.35
Age: 14 – 24yrs	n (%)	19 (9.6)
25 – 44 yrs.	n (%)	110 (55.3)
45 – 60 yrs.	n (%)	70 (35.2)
Males		99 (49.8)
Race: African	n (%)	64 (32.2)
Mixed Ancestry	n (%)	127 (63.8)
White	n (%)	8 (4.0)
Time on PD (months)	Mdn (IQR)	17 (8 – 102)
Mode of dialysis: CAPD	n (%)	181 (92.3)
Primary renal disease		
Hypertension	n (%)	64 (33)
Chronic Glomerulonephritis	n (%)	79 (40.7)
Diabetes	n (%)	14 (7.2)
HIVAN	n (%)	2 (1)
Urological	n (%)	10 (5.2)
Other	n (%)	25(12.9)
Baseline albumin	Mean +/- SD	38.7 (+/- 5.4)
Reason for PD:		
PD-First	n (%)	170 (89.9)
Lack of vascular access*	n (%)	8 (4.0)
Failed Transplant	n (%)	12 (6.0)
Diabetes	n (%)	19 (9.8)
HbA1C >8	n (%)	9 (52.9)
BMI		
Overweight and obese	n (%)	98 (50.5)
Underweight	n (%)	7 (3.6)
Uncontrolled Hypertension	n (%)	141 (73.4)
Smoker	n (%)	34 (17.5)
Smoke > 10 pack yrs.	n (%)	13 (38.2)
HIV	n (%)	6 (3.0)
Chronic Hepatitis B	n (%)	4 (2.0)
Coronary artery disease at baseline**	n (%)	7 (3.6)

*Lack of Vascular Access = patients transferred from HD to PD as they no longer have sufficient vascular access for HD. **(Symptomatic with, or on treatment for ischaemic heart disease. Proven on ECG or angiogram) BMI = body mass index, HIV = human immunodeficiency virus, HIVAN= human immunodeficiency virus associated nephropathy

Table 2: Factors significantly associated with increased risk of patient death.

	Univariate		**Multivariate**	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>40)	0.98 (0.48 – 2.03)	0.961	1.70 (0.69 – 4.15)	0.247
Gender (male)	1.51 (0.74 – 3.09)	0.262	1.65 (0.67 – 4.06)	0.273
Race (African)	1.21 (0.55 – 2.68)	0.638	0.56 (0.20 – 1.59)	0.278
Albumin (per g/L)	0.97 (0.91 – 1.04)	0.410	0.98 (0.91 – 1.07)	0.703
Diabetes	2.93 (1.17 – 7.33)	0.021	2.82 (0.95 – 8.36)	0.062
BMI				
Underweight (<18.5)	4.44 (0.95 – 20.67)	0.057	2.09 (0.35 – 12.32)	0.418
Overweight (30–34.9)	1.54 (0.69 – 3.46)	0.293	1.26 (0.53 – 3.01)	0.597
Obese (>35)	0.63 (0.17 – 2.39)	0.500	0.83 (0.16 – 4.19)	0.819
Urea target (ref: never met target)				
Met target range <50%	0.31 (0.10 – 0.96)	0.042	0.27 (0.07 – 1.02)	0.055
Met target range >50%	0.42 (0.19 - 0.90)	0.026	0.80 (0.26 – 2.47)	0.695
Fluid targets (ref: never met target)				
Met target range <50%	0.19 (0.07 – 0.54)	0.002	0.22 (0.07 - 0.78)	0.019
Met target range >50%	0.20 (0.09 – 0.46)	0.000	0.24 (0.07 – 0.79)	0.019
Haemoglobin (ref: never met target)				
Met target range <50%	0.10 (0.02 – 0.46)	0.003	0.05 (0.01 – 0.31)	0.001
Met target range >50%	0.37 (0.17 – 0.81)	0.012	0.24 (0.09 - 0.69)	0.008

Table 3: Univariate and multivariate factors associated with technique failure

	Univariate		**Multivariate**	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>40)	1.06 (0.65 – 1.72)	0.811	1.39 (0.82– 2.34)	0.220
Gender (male)	1.24 (0.76 – 2.00)	0.392	1.28 (0.76 – 2.16)	0.359
Race (African)	1.78 (1.07 – 2.92)	0.024	1.98 (1.16 – 3.37)	0.013
Albumin (per g/L)	0.98 (0.93 – 1.01)	0.270	0.98 (0.93 – 1.03)	0.387
Peritonitis > 1 event	0.98 (0.60 – 1.58)	0.925	0.99 (0.59 – 1.66)	0.964
Diabetes	1.78 (0.87 – 3.63)	0.110	1.74 (0.82 – 3.70)	0.147
BMI				
Underweight	1.35 (0.32 – 5.72)	0.681	0.74 (0.16 – 3.50)	0.704
Overweight	1.12 (0.66 – 1.92)	0.668	1.03 (0.59 – 1.82)	0.906
Obese	1.01 (0.49 – 2.05)	0.985	1.23 (0.58 – 2.61)	0.581
Fluid targets (ref: never met target)				
Met target range <50%	0.32 (0.16 – 0.65)	0.002	0.30 (0.14 – 0.64)	0.002
Met target range >50%	0.38 (0.22 – 0.67)	0.001	0.39 (0.21 – 0.72)	0.003

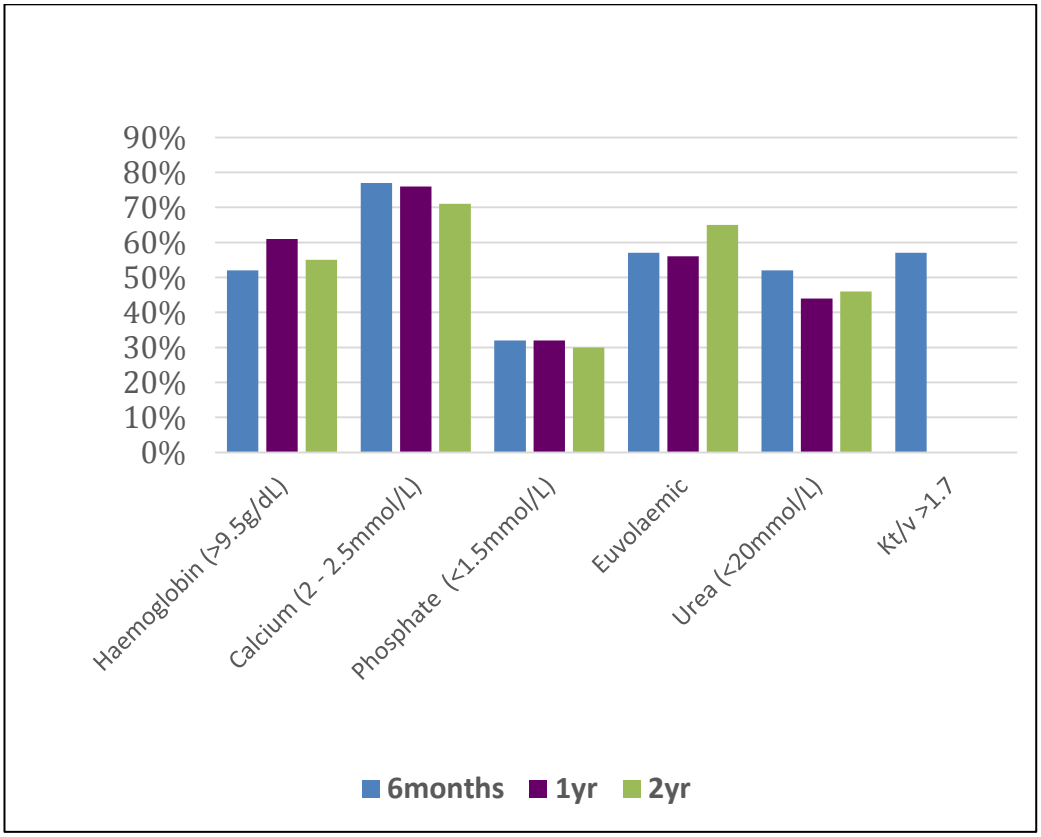
Table 4: Comparing PD cohort's survival from different countries

					Patient Survival			
	Year of Data collection	**GDP per capita $**	**Age years (mean)**	**DM (%)**	**1 year (%)**	**2 year (%)**	**3 year (%)**	**5 year (%)**
Australia[26]	2009 - 2011	56327,72	-	33	94	-	77	61
Hong Kong[27]	1995 - 2009	42422,87	59.2	46	91.1	-	69.6	50.7
New Zealand [26]	2009 – 2011	37807,97	-	43	94	-	71	49
Mexico [24]	2007	9009,26	-	-	90	78	72	-
Romania [28]	1995 - 2001	8972,92	49.5	23	90.6			62.2
Brazil (BRAZPD2) [22]	2004 - 2011	8538,59	59.5	41	85	74	64	48
Columbia [23]	2008 - 2009	6056,15	54	34	92.45	81.5	-	-
Thailand [29]	2008 - 2011	5775.10	-	-.	79	66	-	57
South Africa	2008 - 2015	5691,69	39	9.8	94.4	84.3	-	60.2

2.10 Figures:

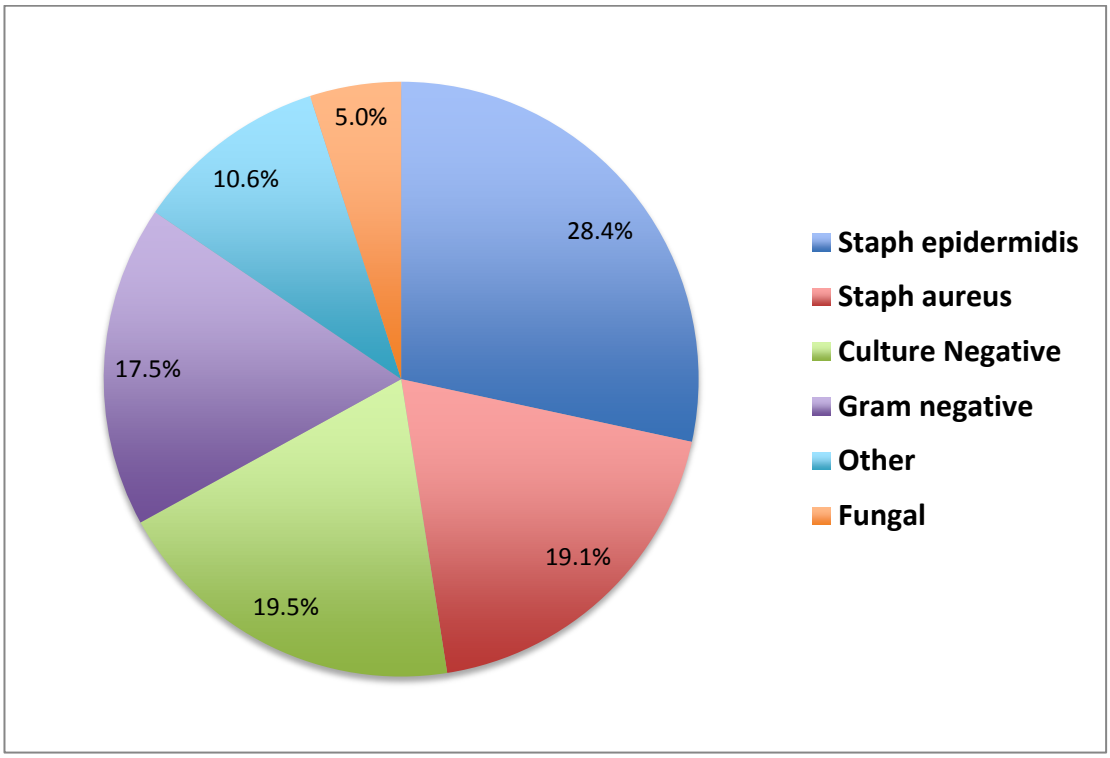
Figure 1: Achieved adequacy targets at 6 months, 1 year and 2 year

Figure one reflects the total percentage of patients achieving KDIGO set targets for biochemical variables at 6 months, 1 year and 2 years.



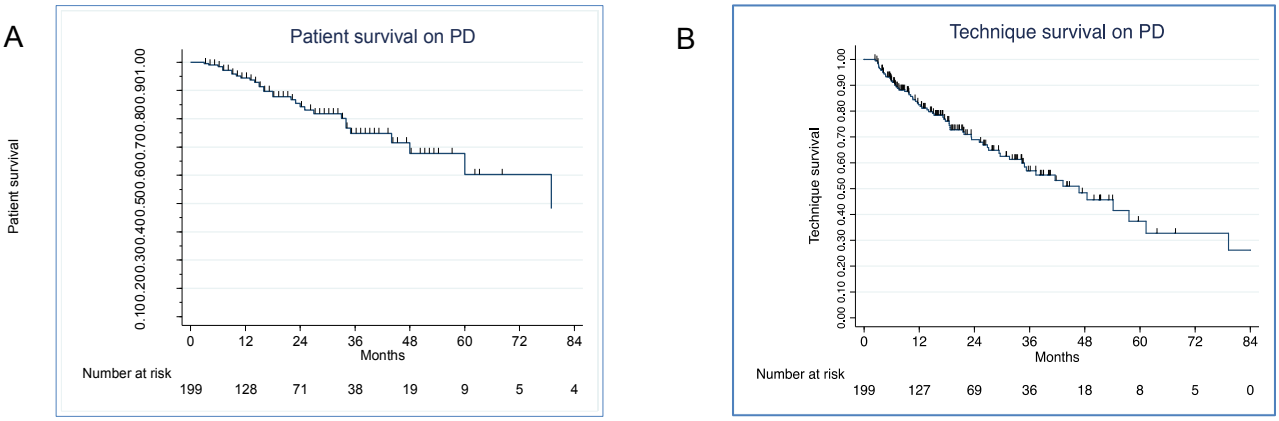
2.11 Supplementary figures and tables

Supplemental Figure 1: Organisms cultured during peritonitis episodes



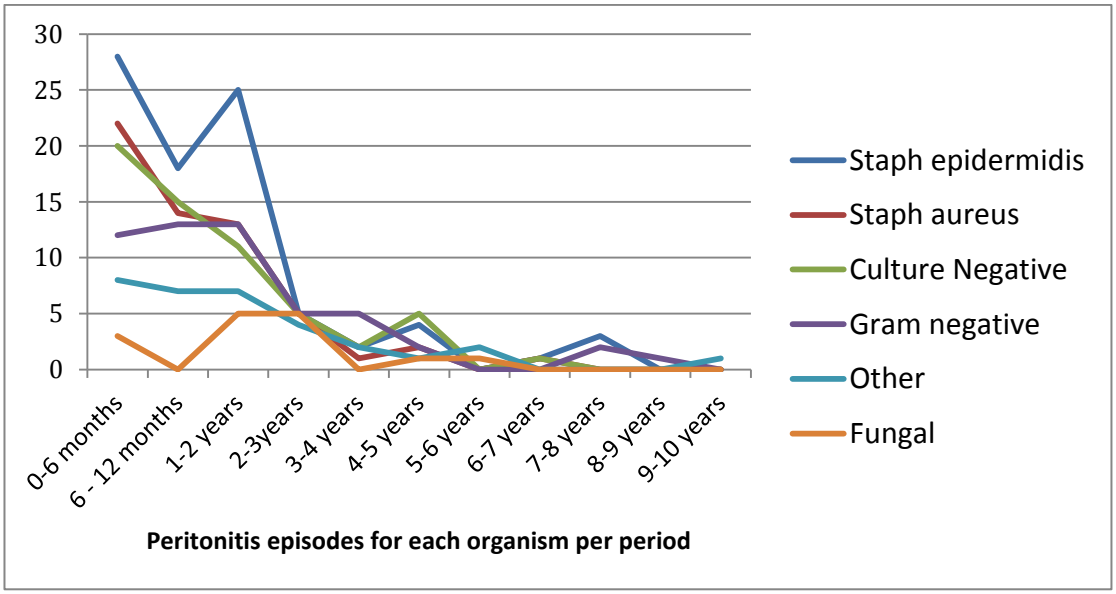
Supplemental Figure 1 reflects the organisms cultured in peritonitis events as reflected as percentage of the total. The group of peritonitis labeled Other comprises: Gram-positive species other (87.5%), TB (6.3%) and multiple organisms (6.3%). The group Gram Negative comprises: Gram Negative other (43.4%), Pseudomonas (22.6%), Klebsiella (20.8%), Acinetobacter (9.4%), E. Coli (3.8%),

Supplemental Figure 2: Kaplan-Meier of patient and technique survival



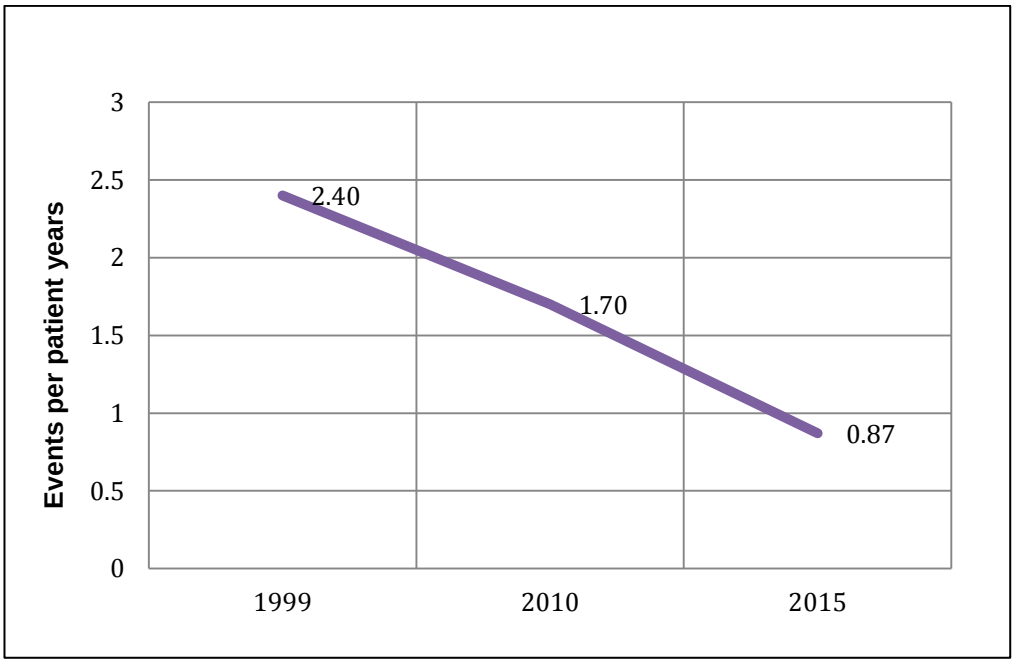
Supplemental figure 2: A) Kaplan-Meier survival curves for patient survival. B) Kaplan-Meier survival curve for Technique survival

Supplemental Figure 3a): Peritonitis episodes per year as reflected by individual organisms



Supplemental Figure 3a) reflects the number of peritonitis episode for each organism per year.

Supplemental Figure 3b): Decreasing Peritonitis Rate at Groote Schuur Hospital over the last 20 years



Supplemental Figure 3b) reflects the decreasing trend of peritonitis episodes per patient years over the last 20 years at Groote Schuur Hospital

Supplemental Table 1: Causes of death in PD cohort

Cause of Death	N = 32	%
Fluid overload	12	37.5
Infection – no relation to PD	6	18.8
Infection – related to PD	4	12.5
Malignancy related	4	12.5
Sudden Death	3	9.4
Trauma	1	3.1
CVA	1	3.1
Unknown	1	3.1

Supplemental Table 1 reflecting causes of death for 32 patients. Reflected as number of deaths and percentage.

Appendix 1: Data capture sheet for Peritoneal Dialysis database

Patient Profile:

Surname: _____ Folder No:_____Sex (M/F)

Initial:_____D. O. B: DD/MM/YY

Start date of PD: DD/MM/YY

Initial / baseline Profile:

Date of baseline: DD/MM/YY

Reason for PD:

- PD First
- Out of vascular access for HD
- Failed transplant
- Patient preference

Cause of ESRF:

- Unknown
- Analgesia
- Chronic GN
- Diabetes
- Familial kidney disease
- HIVAN
- HPT
- Obstructive uropathy
- Urological
- RPGN
- SLE
- Other

Family history of Coronary artery disease (Y/N)

Patient: Weight_____(kg) Height_____ (m) BMI _____(kg/m^2) Waist circumference (cm)

Previous transplant (Y/N) Number of previous transplants.

BP >140/90 (Y/N)

Diabetes (Y/N)

HBA1C:

- Not diabetic
- <7%
- 7-8%
- 8-9%
- 9-10%
- >10%

HIV:

- Positive
- Negative
- Developed HIV on PD

Hepatitis B:

- Negative
- Chronic hepatitis B prior to PD
- Chronic hepatitis B on PD

Smoker:

- Yes – currently
- Yes – prior to PD
- No- never

Pack years:

- N/A
- 1-5 packs/ year
- 5 – 10 packs/ year
- 10 – 15 packs/ year
- >15 packs/ year

Coronary artery disease:

- None
- TIA
- CVA
- UAP
- MI
- PVD

Biochemical profile

Corrected Calcium_____(mmol/L)

Phosphate_____(mmol/L)

Calcium/ Phosphate product_____.

Albumin_____(g/L)

Uric Acid_____(mmol/L)

Creatinine_____(umol/L)

Total cholesterol_____(mmol/L)

LDL cholesterol_____(mmol/L)

Lateral abdominal x-ray score (/24)

Dialysis Adequacy: (documented yearly)

Date of recorded visit: DD/MM/YY

Concern of compliance (Y/N)

Mode of dialysis:

- CAPD
- APD
- Change from CAPD – APD
- Change from APD – CAPD

Dialysis Fluid (number of each glucose containing concentration of bags)

- 1.5% Glucose bags _____(number)
- 2.5% Glucose bags _____(number)
- 4% Glucose bags _____(number)

Biochemical profile:

Hb _____(g/dL)

On recormon

- None
- 2000u
- 4000u
- not available
- not offered

Ferritin:_____(ug/L)

Corrected Calcium:_____(mmol/L)

Phosphate:_____(mmol/L)

Calcium/ Phosphate product_____.

PTH:_____(pmol/L) Parathyroidectomy (Y/N)

Magnesium:_____(mmol/L)

Albumin:_____(g/L)

Urea: _____(mmol/L)

Fluid status:

- Hypovalaemic
- Euvolaemic
- Overloaded

PET/ Kt/V

- Urine volume _____(ml)
- RRF _____(ml/min)
- Cr Clearance Urine _____(ml/min)
- Cr Clearance PD _____(ml/min)
- Total Creatinine Clearance _____(ml/min)
- Kt/V _____(ml/min)
- Ultrafiltration volume _____(ml)
- Transporter status
    - H
    - HA
    - L
    - LA

Peritonitis Event:

Event: DD/MM/YY

Organism:

- Staph Epidermidis
- Staph Aureas
- Pseudomonas
- Fungal
- Culture negative
- Other

Type of Peritonitis:

- Peritonitis event
- Recurrent peritonitis
- Relapsing peritonitis
- Repeat peritonitis
- Refractory peritonitis
- Catheter related infection

Catheter Malfunction:

Date of catheter insertion: DD/MM/ YY

Inserted by:

- Surgeon
- Physician

Event:

- Date: DD/MM/YY
- Type of malfunction:
  - None
  - Infection
  - Internal leak
  - External leak
  - Hydrothorax
  - Inflow problem
  - Outflow problem
  - Migration
  - Hernia
- Associated infection:
  - No antibiotics required
  - Infection requires antibiotics
  - PD antibiotics
  - Systemic antibiotics
  - Requires catheter change
- Requires catheter change: Y/N

Malnutrition and Cardiovascular risk:

- Weight_____(kg)
- Height_____ (m)
- BMI_____ (kg/m^2)
- Waist circumference ___(cm)

- BP greater then 140/90 Y/N
- Diabetes Mellitus
  - (Y/N)
  - HbA1c:
    - <7
    - 7-8%
    - 8-9%
    - 9-10%
    - >10%
- Smoker:
  - Yes – currently
  - Yes – prior to PD
  - No- never

- Pack years:
  - N/A
  - 1-5 packs/ year
  - 5 – 10 packs/ year
  - 10 – 15 packs/ year

    - >15 packs/ year

- Coronary artery disease:
    - None
    - TIA
    - CVA
    - UAP
    - MI
    - PVD
- Uric acid: _____ (mmol/L)
- Cholesterol total: _____ (mmol/L)
- Cholesterol LDL: _____ (mmol/L)
- Creatinine: _____ (umol/L)

Outcome

Adequate dialysis: (Y/N)

Death

Date of death: (DD/MM/YY)

Cause of death:

- CVA
- MI/IHD
- Trauma
- Infection – related to PD
- Infection – no relation to PD
- Fluid overload
- Sudden death
- Malignancy related
- Unknown

Transplant:

- (Y/N)
- Date of transplant: DD/MM/YY

Permanent transfer to HD:

- (Y/N)
- Date of transfer: DD/MM/YY
- Reason for transfer:
    - Inadequate dialysis
    - Peritonitis
    - Catheter malfunction
    - Leak
    - Patient not coping

Patient removed off PD programme:

- Date removed: (DD/MM/YY)
- Reason off removed off PD:
    - Lost to follow up
    - Contract terminated
    - Move to private
    - Relocated
    - Patient not coping
    - Regain renal function

Required rest on HD

- Rest during Tenckhoff insertion
- Peritonitis
- Catheter malfunction
- Failed PD

TB during course of PD

- Treated for TB during course of PD: Y/N
- Date
- TB diagnosis
    - Proven
    - Suspected

Still on PD:

- (Y/N)
- Date of last follow up: DD/MM/YY

Appendix 2: Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • Facsimile [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

07 March 2014

REF NO: R007/2014

Dr B Davidson
Real Unit
Nephrology & Hypertension
E-13 NGSH

Dear Dr Davidson

PROJECT TITLE: A FIFTEEN YEAR REVIEW OF THE OUTCOMES, COMPICATIONS AND ADEQUACY OF PERITONEAL DIALYSIS AT GROOTE SCHUUR HOSPITAL, CAPE TOWN SA

Thank you for submitting your Registry to the Faculty of Health Sciences Human Research Ethics Committee for approval.

The HREC has **approved** the registration of your registry.

The registration of this registry is valid **until 28 February 2017.**

Please provide the HREC with an update if the registry continues beyond this period.
Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

Please provide the HREC with an update if the registry continues beyond this period.

Please quote the HREC REF in all your correspondence.

Yours sincerely

signature removed

pp
PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:R007/2014

Appendix 3: Instructions to the author set out by PDI for original work

Original Article instructions to the Author

- Peer reviewed investigations that represent new and significant contributions to the field.
- Maximum length 3500 words excluding abstract and references;
- 40 references;
- 5 figures and tables;
- Abstract maximum 250 words presented as background, methods, results and conclusion.
- Content can be supplemented with online only material to be formatted by the author and uploaded with the article using the appropriate template. Where methodology is particularly extensive, more detailed information should be provided in the online only supplemental material. The main text of the paper must stand on its own without the supplemental material.

MANUSCRIPT PREPARATION

Peritoneal Dialysis International follows the International Committee of Medical Journal Editors' (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which can be found at http://www.icmje.org/. Authors may refer to ICMJE's "Manuscript Preparation" guidelines in addition to the guide- lines provided below.

GENERAL FORMAT

Write the body of the manuscript as concisely as possible, adhering to the word limits specified for the given manuscript category.

For section and subsection headings, please use the heading styles built into your word processing template.

LEVEL ONE HEADING

LEVEL TWO HEADING

If further divisions of the text are required, use inline headings:

In-line Heading Level One:

In-line Heading Level Two:

Paragraph text .... Paragraph text ....

To facilitate the review process, manuscripts must be in Microsoft Word format. Double space all text, including references and figure legends, and allow adequate margins. Use a common typeface such as Verdana, Arial, Helvetica, or Times in 11 or 12 points. Special or mathematical characters and Greek letters that are not on a standard keyboard must be created by using the Symbol font. Pages should be consecutively numbered, beginning with “1” on the title page.

Focus on the content rather than the look of a submission. Simpler is always better. In running text, formatting other than the usual uses of italic, superscript, and subscript is discouraged. During the copyediting process all extraneous formatting will, in any case, be stripped from the file to ensure smooth intake into the layout programme used by the typesetter.

All papers must contain the following items, when applicable:

- Title Page
- Abstract and Key Words
- Text
- Acknowledgments
- Disclosures
- References
- Figure Legends
- Tables

TITLE PAGE

The first page of the manuscript should include:

1. The Title of the article (80 characters maximum, including spaces);
2. A running title (30 characters maximum, including spaces);
3. The names of the authors (written as first name, initial(s), and surname). Correct: Jane A. Smith, Paul T. Jones, Theresa Ryan. Incorrect: J.A. Smith, P. Jones;
4. The affiliation(s) for each author. For each affiliation, include the name of the department (if any), the institution, the city, the province or state (if applicable), and the country where the work was done. Use superscript Arabic numerals to indicate which authors are associated with which affiliations;
5. Acknowledgements: These include grants, equipment, drugs, and/or

other support that facilitated conduct of the work described in the article or the writing of the article itself;

6. Full details on any possible previous or duplicate publication of any content of the paper (if applicable);
7. The name, postal address, and e-mail address of the corresponding author;
8. The word count for the text only (excluding abstract, acknowledgments, disclosures, tables figure legends, and references);
9. The number of figures and tables; and
10. The details of supplemental online material.

ABSTRACT AND KEY WORDS

For Original Articles, include a structured abstract of no more than 250 words, with the following subheadings:

- Background
- Methods
- Results
- Conclusions (or Summary)

For Review Articles, Consensus Statements, Guidelines, and Short Reports, include an unstructured abstract of no more than 250 words that summarizes the objective, main points, and conclusions of the article. Do not include abstracts for Editorials, Commentaries, and Correspondence.

After the abstract, list up to eight key words or phrases for indexing. The key words should be different from those used in the title. A list of key words is required for all Original Articles, Review Articles, Consensus Statements, Guidelines, and Short Reports. Key words are optional for Correspondence; Commentaries do not have key words. Present the key words in one paragraph, separated by semi-colons, with a period at the end. Only the first key word should be capitalized.

TEXT

Abbreviations and Symbols:

Use abbreviations sparingly and keep to those commonly used in the field. All acronyms and initialisms are to be spelled out on first use in the abstract, the text, and in each table or figure, with the abbreviation following in parentheses. If the term is repeated less than four times in the text, all instances must be spelled out. Abbreviations used in the body of the article should be indicated in the abstract, tables and figures, even if they are used only once or twice in these section, spelling

out the first instance.

Do not begin a sentence with an abbreviation. Spell the phrase out in full or rewrite the sentence. Do not explain abbreviations for units of measurement [3 mL, not 3 milliliters (mL)] or standard scientific symbols [Na, not sodium (Na)]. Do abbreviate long names of chemical substances and terms for therapeutic combinations, such as DNA. Abbreviate names of tests and procedures that are better known by their abbreviations than by the full name (VDRL test, SMA-12). Abbreviate units of measurement when they appear with numerals (measured in milliliters, but 10 mL). Use abbreviations in figures and tables to save space. Explain all abbreviations used in the figure legend or table footnote.

Units of Measurement: Use SI units throughout. When units other than SI units are widely used, they can be indicated in parentheses after the SI unit. The editorial office will provide conversion information with the article when appropriate.

Proprietary and Generic Names: Generic names must be used for all drugs. Include the proprietary name in the following cases: if it is more commonly known than the generic name; to differentiate among drug forms; if a specific trade preparation was used in a study or involved in an adverse effect. If the proprietary name is used, the name and location of the manufacturer must be given in parentheses in the text. Instruments may be referred to by proprietary name; the name and location of the manufacturers must be given in parentheses in the text.

Use of English Language: All papers are published in English, and authors who are not fluent in English are advised to seek editorial help before submitting their papers. This will help to ensure that the academic content of the paper is fully understood by the journal editors and reviewers.

Original Articles: Introduction, Methods, Results, Discussion, Conclusions, Acknowledgments (optional), Disclosures, References, Figure Legends, and Tables. Additional descriptive subheadings may be used if appropriate.

REFERENCES

References in the text are numbered consecutively using Arabic numerals in parentheses. The manuscript's reference list is numbered consecutively, using Arabic numerals, in the order in which the references are first cited in the text. Citations appearing in tables and figures must fit into the numbering sequence from the point at which the table or figure is first mentioned in the text. PDI's citation style follows the Vancouver style, which should be selected if using reference handling software, such as EndNote.

Do:

1. Number references in the order in which they are first cited in the text;
2. Use Arabic numerals in parentheses;
3. Use the reference style of the National Library of Medicine, including the

abbreviations of journal titles, which should be abbreviated according to the style used in the list of Journals Indexed for MEDLINE, posted by the NLM on the Library's Web site (http://www.nlm.nih.gov/tsd/serials/lji.html);

4. Include an "available from" note for documents that may not be readily accessible;
5. Cite symposium papers only from published proceedings;
6. When citing an article or book accepted for publication but not yet published, include the title of the journal (or name of the publisher) and the year of expected publication;
7. When citing an article that has been published online but not yet in print, include the digital object identifier (doi); and
8. Include references to unpublished material in the text, not in the references [for example, papers presented orally at a meeting; unpublished work (personal communications, papers in preparation)] and submit a letter of permission from the cited persons to cite such communications.

Do not use ibid. or op cit.

TABLES

Authors are asked to keep each table to a reasonable size; very large tables packed with data simply confuse the reader and may be included as Supplemental Material (see below). Similarly, try to minimize the use of abbreviations, and if abbreviations must be used, use well-known and accepted forms to minimize the need for the reader to constantly refer to the table legend. The same data should not be presented in both a table and a figure.

Tables are to be numbered using Arabic numerals in the order in which they are cited in the article text. Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Every table column and row should be provided with an explanatory title stub, with units of measure applicable to the row or column clearly indicated.

Tables must be formatted using the table tool in a word processing programme to ensure that columns of data remain aligned when the file is sent electronically for review. The table should be formatted with a horizontal line above the column title stubs, between the column title stubs and the table body, and at the end of the table body. Vertical lines, color, and shading are not to be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in the table legend. Tables must not be embedded as figures or spreadsheet files.

Table legends follow the table body and should be as concise as possible. Footnotes follow the table legend and should be indicated using superscripted lowercase letters (a, b, c, and so on). Tables (together with their footnotes and legends) should be completely intelligible without reference to the text.

All tables (including their associated title, footnotes, and legends) should appear in consecutive numerical order after the references and any figure legends. All tables will be placed close to their text citations during article layout. All tables must be cited in the article text.

FIGURES

Format: Figures for reproduction should approximately fit within the typeset area of the journal. The following resolutions are optimal:

- Black-and-white line drawings, 600–1200 dpi
- Line drawings with some grey or coloured lines, 600 dpi
- Illustrations and photographs, 300 dpi Authors should supply electronic versions of the figure content in EPS, GIF, TIFF, or JPEG format. Other formats, such PDFs, may be used, but are not preferred. Drawings made in Microsoft Word and PowerPoint are discouraged, because the display of such drawings varies with the settings of each computer used to view the file. There is no guarantee that such figures will reproduce exactly as intended by the author. Save each figure in a separate file without its title or legend, and use simple file-naming conventions (for example, Figure 1, Figure 2A).

Figure Legends: Figures are to be numbered using Arabic numerals (1, 2, 3, and so on) in the order in which they are cited in the article text. If a figure has several panels, each panel should be identified using an uppercase alphabetic character (A, B, C, and so on). Each figure should have a title and an explanatory legend that clearly identifies the meaning of any symbols, arrows, numbers, or abbreviations used in the illustration. The legend should permit the figure to be understood without reference to the text.

Title and legend information for each figure should be included with the article text, grouped and placed at the end of the manuscript, after the reference list. All figures will be placed close to their text citations during article layout. Make sure that each figure is cited in the article text.