Minor dissertation as Master of Medicine (MMed) in Urology

Candidate: **Christiaan Ernst De Wet**
Supervisor: Lisa Kaestner
University of Cape Town
Student Number: DWTCHR012

Dissertation title:

Do percutaneous nephrostomies for malignant obstructive uropathy improve renal function six months post intervention?

DECLARATION

I, Christiaan Ernst De Wet, 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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Table of contents:

		Page
Chapter 1: Introduction and literature review		**4**
i)	Introduction	**5**
ii)	Literature review	**6**
iii)	In summary	**12**
iv)	References	**13**
Chapter 2: Publication ready manuscript		**14**
a. Title page		**15**
-	Title	
-	Authors	
-	Declaration	
-	Acknowledgements and contributions	
-	Disclaimers	
-	Source(s) of support	
-	Word count	
-	Number of figures and tables	
-	Conflict of interest declaration	
b. Abstract		**16**
c. Introduction		**17**
d. Methods		**18**
i)	Selection and Description of Participants	
ii)	Technical Information	
iii)	Statistics	
e. Results		**19**
f. Discussion		**21**
g. References		**24**
h. Tables		**25**
i. Illustrations (Figures)		**28**
j. Units of Measurements		**31**
k. Abbreviations and Symbols		**31**
l. Appendices		**32**

Chapter 1: Introduction and Literature review

Do percutaneous nephrostomies for malignant obstructive uropathy improve renal function six months post intervention?

Supervisor and Principal investigator: Dr Lisa Kaestner
MBChB (US) FC Urol(SA) MMed (UCT)
Department of Surgery, Division of Urology, E26, Groote Schuur Hospital, University of Cape Town
e-mail: uro.doc@live.com
Contact number: 0844479807

First author: Dr Christiaan Ernst De Wet
MBChB (UFS) FC Urol(SA)
Department of Surgery, Division of Urology, E26, Groote Schuur Hospital, University of Cape Town.
e-mail: ernst_dewet@yahoo.com
Student number: DWTCHR012
Contact number: 0827887873

Co-author: Dr Leon Du Toit
MBChB (US) FCA (SA) MMed (UCT)
Department of Anaesthesia, D23, Groote Schuur Hospital, University of Cape Town
e-mail: leon.alive@gmail.com
Contact number: 0845757330

i) Introduction

Advanced or locally advanced malignant conditions of the pelvis and/or abdomen can cause ureteric obstruction and associated impaired renal function. This obstruction can be managed by performing PCN tube insertion with or without antegrade double J - stent insertion [4].

Having PCN tubes in situ is associated with prolonged hospital stay which affects quality of life [4].The available literature reports clearly on the morbidity associated with PCN, as well as the immediate improvement in renal function post-PCN [1; 2; 3; 4; 6].
Some studies found that patients spend between 23% and 40% of their mean survival time in hospital due to complications associated with nephrostomy tubes [1]. Median survival in a study of 49 patients post percutaneous catheter was 174 days (14–602) [1]. Another study of 211 patients showed a median survival of 5.05 months (95% CI = 3.87-7.11; range 2 - 963 days) [3]. In another big study of 208 patients, the median survival was 144 days (0–1084), with 44 (21.2%) patients dying during hospitalisation [4].In a smaller series of 32 patients, it was reported that each patient spent a mean of 29 days (range, 1–82 days) in hospital from the time of PCN placement until death or the end of the study period. This represented 33.3% of the median survival time (87days) in their study [5]. Most studies report combined major and minor complication rates for PCN placement of 10%, with a mortality rate of between 0.05% and 0.3% [3]. Reported complications related to PCN are pyelonephritis (22.7%), hospital readmission (17.3%), dislodgment of the nephrostomy catheter requiring replacement (9.3%), haematuria (4%), blood transfusion (1.3%), and retroperitoneal haematoma (0.7%) [4].

Mean serum creatinine levels improved from 280umol/L to 150umol/L, post diversion in a large study of 208 patients [4]. In a smaller study of only 22 patients, mean serum creatinine improved from 516 umol/L (range 239–1019) pre-PCN to 168 umol/L (range 85–265) post-PCN [$p<0.0001$]. It took an average of 17 days (range 3–78) to reach the nadir creatinine concentration [6]. There is limited data on the trend in renal function following the expected initial improvement post-PCN. One South African study looked at renal function as measured by serum creatinine pre-PCN, day3 post-PCN, day7 post-PCN and then serum creatinine >7days post-PCN.

It is well known that urinary tract infection (UTI) is a risk factor for developing acute kidney injury. A study by Hsiao et al [7] investigated 790 patients who were admitted for UTI in a tertiary hospital in Taiwan. Of these patients, 12.3% (n=97) developed acute kidney injury, with 0.5% (n=4) of patients necessitating dialysis.

The decision if a patient needs PCN can be difficult. Various prognostication models [1; 3; 4] have been described to assist the clinician and patient with the decision making process. None of these prognostication models has long-term renal function response or UTIs post-PCN as factors affecting survival.

As our primary objective, we described the response in renal function following PCN for obstructive uropathy due to abdominal/pelvic malignant conditions at our institution. We hypothesized that UTI post PCN is associated with poor response in renal function and therefor investigated the role of UTIs in the response in renal function post-PCN. Demographic data were also collected and investigated to determine the association with renal function response post-PCN.

ii) Literature review

Pubmed and Google searches were done looking for renal function and urinary tract infections in patients who had percutaneous nephrostomy for advanced pelvic and/or abdominal malignancy.
9 journal articles and 1 poster presentation were identified to be of help in preparing our research manuscript.
Herewith a summary of the articles used and the impact it had in our study:

1) Prognostic factors in malignant ureteric obstruction

BJUINTERNATIONAL 2009 | 104, 938–941 |
Andrew Lienert, Andrew Ing and Stephen Mark
Urology, Christchurch Hospital, Christchurch, New Zealand

Researchers from Christchurch, New Zealand, had the objective to validate a model to stratify patients with obstructive nephropathy due to malignant ureteric obstruction, associated with a poor prognosis, into different prognostic groups. This was in response to a recent report (Ishioka et al.), identifying low serum albumin, degree of hydronephrosis and number of events related to metastatic disease as prognostic indicators before palliative decompression. They also attempted to identify additional factors that might help to predict a patient's likely prognosis.

A retrospective review of all patients who had a nephrostomy tube inserted for malignant ureteric obstruction was done. 49 Patients fulfilled the inclusion criteria. The median age was 71 years and the median survival was 174 days. The demographic breakdown of their cohort showed 45% being female and 55% being male. The laterality of the PCN showed 22% having bilateral nephrostomies, while 78% only had unilateral PCN. The type of malignancy was recorded as follows: Prostate 15 (30%), Bladder 18 (36%), Colorectal 6 (12%), Cervical 3 (6%), Ovarian 2 (4%), Sarcoma 2 (4%), Pancreatic 2 (4%), and Breast 1 (2%).

On univariate analysis, clinical factors associated with a shorter mean survival were low serum albumin level, low serum sodium and three or more events related to malignant dissemination.

Patient age, gender, serum creatinine, serum potassium, serum calcium, or haemoglobin level were not useful prognostic indicators. Different degrees of hydronephrosis on renal ultrasonography before tube insertion were not associated with a difference in mean survival.

Complications related to the nephrostomy tube were experienced by 39% of patients and 69 separate complications were recorded which required presentation at hospital. Complications included blockage of tube (31 events), displacement of tube (21 events), sepsis (11 events), haemorrhage (one event), and pain requiring inpatient management (five events). No patients died as a direct result of a complication of their tube.

This model stratified patients into three groups with significantly different mean survival times. Patients in the favourable risk group (no risk factors) had a mean survival was 278 days, vs 173 days for the intermediate-risk group (one risk factor) and only 63 days for those in the high-risk group (two or three risk factors).

The researchers were successful in validating the Ishioka et al. model for prognostication post PCN for malignant ureteric obstruction.

The researchers have not looked at renal function response in their series. Comparing bilateral vs unilateral PCN in the univariate analysis could have provided interesting results. We also planned to investigate is the incidence of urinary tract infection, which is lacking from this work.

2) Impact of percutaneous nephrostomy in South African women with advanced cervical cancer and obstructive uropathy

Southern African Journal of Gynaecological Oncology 2017; 9(1):6–10
Matthys Cornelis van Aardt, Judith van Aardt and Arnold Mouton
Obstetrics and Gynaecology, University of Pretoria, Pretoria, South Africa

This South African study did a retrospective audit of all patients with primary untreated cervical cancer with renal impairment secondary to obstructive uropathy. Serum Urea, creatinine and potassium were recorded for patients receiving PCN before insertion and after treatment.

Fifty-four patients fulfilled the inclusion criteria for the study, however only a total of 28 patients received PCN. The mean age of the nephrostomy group was 48.4 years. Seventeen (31.7%) patients were HIV infected and the majority (70.3%) were stage IIIB cervical cancer. Of the patients who received PCN, 11 (39.3%) were classified as severe renal failure and 10 (35.7%) as renal failure.
The serum urea, creatinine and potassium levels were recorded before insertion of the PCN, on days three and day seven after insertion and after treatment or more than one week after nephrostomy insertion. In the PCN group, no mortalities were reported, 11.5% ended with worse renal function, 38.5% had unchanged renal function and 50% had improved renal function post-PCN.

The researchers concluded that in patients with cervical cancer and obstructive uropathy, even if HIV positive, it is safe to offer PCN with minimal complications. An improvement in renal function was shown after PCN. PCN improved the number of patients qualifying for initiation and completion of treatment.

This study is one of a very limited number of studies that looked at renal function at different time periods post-PCN. They looked at specific values on days 3 and 7 post-PCN. They recorded a further value beyond 7days. It is not clear how long after PCN these values were recorded. We aim to be clear on the timing of our best and worst values post-PCN. Using eGFR and CKD-staging might help in categorising our cohort's renal functions more accurate. Although this is a South African study, our cohort will have a completely different demography as we are including all pelvic and abdominal malignant conditions causing ureteric obstruction.

3) Clinical Factors Associated With a Short Survival Time After Percutaneous Nephrostomy for Ureteric Obstruction in Cancer Patients: An Updated Model

Journal of Pain and Symptom Management 255 Vol. 51 No. 2 February2016
Alia Alawneh, MD, Wa'el Tuqan, MD, Ayoub Innabi, MD, Yanal Al-Nimer, MD, Ola Azzouqah, MD, Dalia Rimawi, SP, Ayat Taqash, SP, Maan Elkhatib, MD, and P_al Klepstad, MD, PhD King Hussein Cancer Center (A.A., W.T., A.I., D.R., A.T., M.E.), Amman, Jordan; Hamad Hospital (Y.A.-N.), Doha, Qatar; University of New Mexico (O.A.), Albuquerque, New Mexico, USA; and St. Olavs University Hospital (P.K.), Trondheim, Norway

This paper from Jordan reported on an updated prognostic model to predict overall survival in cancer patients after receiving PCN. The primary objective was to assess survival of patients with malignant urinary obstruction after PCN tube insertion. The secondary objective was to identify factors associated with poor prognosis in this group of patients and externally validate an existing model.
They did a retrospective analysis of 211 patients who had malignant urinary obstruction and received PCN tube insertion. 52.1% received bilateral PCN insertion and 47.9% received unilateral PCN insertion. The most common malignancy in their sample was genitourinary cancer.

The median survival was 5.05 months. On univariate analysis, the factors significantly associated with shorter survival were type of malignancy, bilateral hydronephrosis, serum albumin <3.5 mg/dL, presence of metastasis, ascites, and pleural effusion. They used serum albumin <3.5 mg/dL, pleural effusion, and bilateral hydronephrosis to stratify patients into four prognostic groups: zero risk factors (32 patients), one risk factor (85 patients), two risk factors (78 patients), and three risk factors (16 patients). Median survival for each group was 17.6 months, 7.7 months, 2.2 months, and 1.7 months, respectively.

Serum creatinine prior to PCN was also recorded, with the median overall value of 2mg/dL (177umol/L). The group who had unilateral PCN had median of 1.3mg/dL (115umol/L) and the patients who had bilateral PCN had median serum creatinine of 2.8mg/dL (248umol/L).
They did not investigate renal function response post-PCN. This would have been interesting, as the group who had bilateral PCN had more to gain in terms of renal function recovery. The patients with bilateral nephrostomies did worse in terms of survival time, however.
They concluded that their updated model can be used to identify patients with poor survival after PCN.

4) A prognostic model for survival after palliative urinary diversion for malignant ureteric obstruction: a prospective study of 208 patients

BJU Int 2016; 117: 266–271

Maurício D. Cordeiro, Rafael F. Coelho, Daher C. Chade, Rodrigo R. Pessoa, Mateus S. Chaib, José R. Colombo-Júnior, José Pontes-Júnior, Giuliano B. Guglielmetti and Miguel Srougi
Uro-Oncology Group, Urology Department, University of Sao Paulo Medical School and Institute of Cancer Estate of Sao Paulo, Sao Paulo, Brazil

This is another study reporting on a prognostic model for survival post palliative urinary diversion for malignant ureteric obstruction. This time it was a prospective study of 208 patients that underwent palliative urinary diversion by ureteric stenting 58 patients) or percutaneous nephrostomy (150 patients) in two tertiary care university hospitals. Patients were followed-up for a minimum of 6 months. Factors related to poor prognosis were identified by Cox univariable and multivariable regression analyses, and a risk stratification model was created by Kaplan–Meier survival estimates at 1, 6 and 12 months.

The median (range) survival was 144 days after urinary diversion. Overall survival did not differ by UD type. The number of events related to malignancy (≥4) and Eastern Cooperative Oncology Group (ECOG) index (≥2) were associated with short survival on multivariable analysis. These two risk factors were used to divide patients into three groups by survival type: favourable (no factors), intermediate (one factor) and unfavourable (two factors). The median survival at 1, 6, and 12 months was 94.4%, 57.3% and 44.9% in the favourable group; 78.0%, 36.3%, and 15.5% in the intermediate group; and 46.4%, 14.3%, and 7.1% in the unfavourable group.

The mean serum creatinine level, before and after urinary diversion, was 0.28 and 0.15 mmol/L, (280 and 150 umol/L) respectively. No mention was made of the timing of the serum creatinine post diversion. 71 out of the 150 PCN patients (47%) had bilateral PCN, while 79 had unilateral PCN (53%).

Complications related to PCN were pyelonephritis in 22.7% of patients, hospital readmission in 17.3% of patients, dislodgment of the nephrostomy catheter requiring replacement in 9.3% of patients, haematuria in 4%of patients, blood transfusion in 1.3% of patients, and retroperitoneal haematoma in 0.7% of patients.

The researchers investigated if age is an independent risk factor for survival, but could not be proven in their series.

The investigators concluded that their stratification model may be useful to determine whether urinary diversion is indicated in malignant ureteric obstruction. This study highlights the improvement in renal function post-PCN, as well as the high incidence of UTI in this group of patients.

5) The role of percutaneous nephrostomy in malignant ureteric obstruction

Ann R Coll Surg Engl 2005; 87

JR Wilson, GH Urwin, MJ Stower
Department of Urology, York District Hospital, York, UK

The aims of this UK study were to assess whether PCN placement in malignant ureteric obstruction provided any additional survival benefit or patient morbidity.
They did a retrospective review of 32 patients with a mean age of 68.1 years (16 male, 16 female), who underwent PCN for malignant ureteric obstruction. Data collected for analysis included the site of primary malignancy, mode of presentation, improvement in renal function, median survival, conversion to internal ureteric stents and intervention-related complications.
The median survival following PCN insertion was 87 days and was unrelated to the patient's age and renal function. Those patients with primary underlying gynaecological malignancies appeared to survive almost 4 times as long as those with underlying primary bladder cancer.

Twenty patients had bilateral PCN and 12 unilateral PCN placement.

Serum creatinine took a mean of 16.8 days to reach the lowest level post-PCN. Mean serum creatinine pre- and post-PCN were 946.8 umol/L and 235.2umol/L respectively. No mention is made of what happens to renal function once the lowest serum creatinine levels had been reached.

Almost 79% of patients were able to be discharged from hospital – each patient, however, being re-admitted back to hospital on average 1.6 times prior to their death through PCN or internal ureteric stent related events.

Retrospective 'useful quality of life' was seen in less than half of the patient cohort.

The conclusion was that in the presence of malignant ureteric obstruction, palliative PCN may be performed and is effective in improving renal function. Long-term survival is limited and should, therefore, be performed only when the views and wishes of the patient and carers are taken into account and if there is a definitive treatment plan available for the patient as quality of life can be suboptimal.

6) Percutaneous nephrostomy for ureteric obstruction due to advanced pelvic malignancy: have we got the balance right?

Int Urol Nephrol (2013) 45:627–632

Saumya Misra, Charles Coker and Jonathan Richenberg

Department of Urology, Princess Royal Hospital, Brighton and Sussex University Hospitals NHS Trust

This study assessed survival and complication rates post-PCN in patients with ureteric obstruction due to advanced pelvic malignancy. A retrospective case review of all patients who underwent PCN for ureteric obstruction due to pelvic malignancy in one calendar year was conducted to assess indication, survival time, length of stay post-procedure and complications.

They included 22 patients who had 36 nephrostomies performed on them. 50% of patients had bilateral nephrostomies. Prostate cancer was the commonest primary (55 %). Renal failure was the commonest mode of presentation (56 %). Mean serum creatinine for those with renal impairment (n = 16) was 516 umol/L, which improved to 168 umol/L post-PCN, with an average of 17 days to reach the lowest serum creatinine level. Two patients who had unilateral PCN had to be re-admitted due to worsening renal function post-PCN. One patient with bilateral PCN had to be admitted with worsening renal function.

Median survival post-nephrostomy was 78 days, with the subset of bladder cancer patients having the poorest survival. Dislodgement of the nephrostomy tube was the most common complication which led to the greatest morbidity. Patients stayed for a median of 23 days in hospital, which amounted to 29 % of their remaining lifetime spent in hospital.

The investigators concluded that PCN is effective in improving renal function, but it is also a procedure with associated morbidity and does not always prolong survival. The duration of improved renal function remains a void that our study aim to fill.

7) Risk Factors for Development of Acute Kidney Injury in Patients with Urinary Tract Infection

PLOS ONE | DOI:10.1371/journal.pone.0133835 July 27, 2015

Chih-Yen Hsiao, Huang-Yu Yang, Meng-Chang Hsiao, Peir-Haur Hung, Ming- Cheng Wang, Department of Internal Medicine, Ditmanson Medical Foundation Chia-yi Christian Hospital, Chia-yi, Taiwan; Department of Hospital and Health Care administration; Chia-Nan University of Pharmacy and Science, Tainan, Taiwan; Department of Nephrology, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taoyuan, Taiwan; Department of Genetics, University of Alabama at Birmingham, Birmingham, Alabama, United States of America; Department of Applied Life Science and Health, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan; Division of Nephrology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, 21205, United States of America

This was a multinational trial that investigated the clinical characteristics and change of renal function to identify the risk factors for development of AKI in UTI patients.
It was a retrospective study conducted in a tertiary referral centre, where a total of 790 UTI patients necessitating hospital admission were included for final analysis.
Multivariate logistic regression analysis was performed to evaluate the risk factors for AKI in UTI patients. There were 97 (12.3%) patients developing AKI during hospitalization. Multivariate logistic regression analysis showed that patients with older age, diabetes mellitus (DM), upper UTI, afebrile during hospitalization and lower baseline eGFR were associated with increased risk for development of AKI.

Many of the patients requiring PCN for malignant ureteric obstruction have lower baseline eGFR, advanced age, and upper UTI. This will put our study population at a high risk to develop AKI if patient acquires UTI.

8) Percutaneous nephrostomy versus indwelling ureteral stents in the management of extrinsic ureteral obstruction in advanced malignancies: Are there differences?

UROLOGY 64: 895–899, 2004.

JA HYEON KU, SANG WOOK LEE, HWANG GYUN JEON, HYEON HOE KIM, AND SEUNG-JUNE OH
Department of Urology, Seoul National University College of Medicine; and Clinical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea

This group compared the complications and morbidities after placement of a PCN or an internal ureteral stent (IUS) in the management of malignant ureteral obstruction in patients with advanced malignancy.

A retrospective analysis was performed on a total of 148 patients with a mean age of 57.3 years and with malignant ureteral obstruction, who underwent PCN (80 patients) or IUS (68 patients).

The incidence of fever and acute pyelonephritis was expressed as the number of episodes per 100 person-days. They found the accumulated incidence of fever and acute pyelonephritis was not different in the two groups. The accumulated incidence and the incidence of febrile episodes in the IUS group was 10.3% and 0.0004/100 person-days; the corresponding values for the PCN group were 15.0% and 0.2154/100 person-days. The incidence of acute pyelonephritis in the IUS and PCN groups was 0.0002/100 person-days and 0.0005/100 person-days, respectively.

The difference in overall stent-related or catheter-related complications between the IUS and PCN groups was not statistically significant.

They have demonstrated that morbidities after internal or external diversion were minimal in cases of malignant obstruction. However, patients scheduled to receive an IUS should be more carefully monitored for ongoing obstruction than patients scheduled for PCN tube placement.

9) Percutaneous Nephrostomy Tube-related Infections

IDWeek Session: 143. Clinical: UTI, Friday, October 6, 2017

Hanine El Haddad, MD; George Viola, MD MPH; Ying Jiang, MS; Issam Raad, MD; Kenneth V. Rolston, MD and Ariel Szvalb, MD. Section of Infectious Diseases, Baylor College of Medicine, Houston, Texas, Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas

This research was presented as a poster at IDWeek 2017. They wanted to determine whether discordant antimicrobial coverage provided prior to PCN exchange was associated with a higher rate of recurrent infection compared with those who received concordant therapy.

A retrospective review of 780 patients that had undergone initial PCN placement was done. They only included patients that had developed a definite PCN infection, subsequent PCN exchange, with a minimum 30 day post-PCN exchange follow up. PCN infection was defined as the presence of a positive urine culture (≥104 cfu/mL) plus symptoms consistent with a urinary tract infection. Recurrence was defined as a new PCN infection with the isolation of the same organism to the initial episode. Antibiotics were defined as concordant if they had activity against all organisms' isolated based on antimicrobial susceptibilities.

A total of 47 patients met the inclusion criteria. The median age of patients was 59, with 49% being male. The most common underlying tumors were urothelial (45%), cervical (17%) and prostate cancer (15%). The median time to onset of infection was 42 days. Infections were polymicrobial in 50% of the cases. The most common organisms encountered were *Pseudomonas* spp. (36%), *Enterococcus* spp. (23%) and *Escherichia coli* (18%). There were 12 (26%) recurrences occurring at a median time of 27 days. The provision of discordant antibiotics preceding PCN exchange was significantly associated with recurrence of infection (66.7% vs. 12.8%).

Discordant antimicrobial therapy provided during PCN exchange, in the setting of a PCN infection is associated with a higher rate of relapse. Therefore, to decrease the high rate for PCN reinfection, they proposed that prior to PCN exchange secondary to infection, patients should be receiving concordant antimicrobial therapy.

The timing of onset of UTI and the high rate of recurrent infection is of significance in our study.

10) Nephrostomy insertion for patients with bilateral ureteric obstruction caused by prostate cancer

The British Journal of Radiology, 82 (2009), 571–576
J Nariculam, MBBS, MRCS, G Murphy, MBBS, MD, FRCS, C Jenner, RGN, N Sellars, MBBS, MRCP, FRCR, S Gwyther, MBBS, FRCS, FRCR, S G Gordon, FRCS and M J Swinn, BSc, MBBS, FRCS, MSc, MD, FRCS (UROL)
1St Helier Hospital, Carshalton, Surrey, 2Guy's Hospital, London, 3East Surrey Hospital, Redhill and 4Epsom and St Helier NHS Trust, Epsom, Surrey, UK

This study aimed to identify whether bilateral PCN insertion confers any advantage over unilateral PCN insertion for patients with bilateral ureteric obstruction.

In a cohort of 25 patients, 18 underwent bilateral and 7 underwent unilateral PCN insertion. The mean survival time following PCN was 7.5 months for all patients. The data suggest that the nadir serum creatinine after PCN insertion was similar, independent of whether one or two nephrostomies were inserted. The mean baseline creatinine level prior to PCN was 612 umol/L. Following PCN, the mean creatinine level of all patients fell to 187 umol/L, taking an average of 10 days to reach this nadir. Among patients who underwent either unilateral or bilateral PCN, no major differences in post-PCN creatinine levels were seen.
There was also little difference in the serum creatinine levels at the time of death, suggesting that survival after PCN insertion is based on the aggressiveness of the prostate cancer as opposed to the number of nephrostomies inserted.

This is an interesting study that might be of relevance to our study. Perhaps the response in renal function is different between different malignant conditions that have different degrees of aggressiveness.

iii) In Summary:

It is clear from above literature that having PCN is associated with morbidity. This include infection, bleeding, blocked nephrostomy tubes and prolonged hospital stay. This leads to a large proportion of patients spending a significant time of their remaining survival time in hospital.

Literature reports on the improved renal function post-PCN, but with the background of increased morbidity.

Literature is scarce on what happens to renal function after initial improvement post-PCN. Only one study [2] looked at renal function trends in their cohort of cervix carcinoma patients. Renal functions were recorded beyond 7 days post-PCN. 50% of their patients ended up with the same or worse renal function post-PCN. The numbers in this study was small. At least one study [6] reported on three patients of their small cohort of 22 patients, returning with worsening renal failure post-PCN.

Our study determined accurately what the renal function trends are post-PCN within a six-month follow-up.

It is reported in literature that patients with PCN have a high incidence of UTI [8; 4].

It is also known that UTI is a risk factor for developing acute kidney injury, especially in the elderly with comorbidities [7].

To our knowledge, no available research investigated if the development of UTI post-PCN is associated with poor renal function response post-PCN in this specific study population (patients with PCN for malignant ureteric obstruction). We investigated the incidence of UTI in our study population and the association with poor renal function response.

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Chapter 2: Publication-ready manuscript

	Page
a. Title page - Title - Authors - Declaration - Acknowledgements and contributions - Disclaimers - Source(s) of support - Word count - Number of figures and tables - Conflict of interest declaration	**15**
b. Abstract	**16**
c. Introduction	**17**
d. Methods i) Selection and Description of Participants ii) Technical Information iii) Statistics	**18**
e. Results	**19**
f. Discussion	**21**
g. References	**24**
h. Tables	**25**
i. Illustrations (Figures)	**28**
j. Units of Measurements	**31**
k. Abbreviations and Symbols	**31**
l. Appendices	**32**

a. **Title page**

Do percutaneous nephrostomies for malignant obstructive uropathy improve renal function six months post intervention?

Supervisor/Principal Investigator: Dr Lisa Kaestner
MBChB (US) FC Urol(SA) MMed (UCT)
Department of Surgery, Division of Urology, E26, Groote Schuur Hospital, University of Cape Town
e-mail: uro.doc@live.com
Contact number: 0844479807

First author: Dr Christiaan Ernst De Wet
MBChB (UFS) FC Urol(SA)
Department of Surgery, Division of Urology, E26, Groote Schuur Hospital, University of Cape Town.
e-mail: ernst_dewet@yahoo.com
Contact number: 0827887873

Co-author: Dr Leon Du Toit
MBChB (US) FCA (SA) MMed (UCT)
Department of Anaesthesia, D23, Groote Schuur Hospital, University of Cape Town
e-mail: leon.alive@gmail.com
Contact number: 0845757330

Declaration
I hereby declare that this research is done independently and was self-initiated. This research or parts thereof has not been submitted for another degree at any other university. This work has not been published before. The research comply with the principles of the Helsinki Declaration. The research was approved by the UCT Human Ethics Committee (HREC Ref 097/2019) and the Surgery departmental research committee (2018/094).

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All three authors contributed significantly to the design, analysis, and writing of this manuscript. All authors approve the submitted manuscript.

Disclaimers
The views submitted in this research is that of the authors and do not represent that of the institution and/or department which we represent.

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b. Abstract

Background and purpose
Malignant conditions of the pelvis and/or abdomen can cause ureteric obstruction and associated impaired renal function, which can be managed by performing percutaneous nephrostomy (PCN) tube insertion. Nephrostomy tubes are associated with prolonged hospital stay which affects quality of life.

The main objective of this study was to assess the changes in estimated glomerular filtration rate (eGFR) over the first six months following percutaneous nephrostomy for malignant ureteric obstruction. We also explored the role of UTIs in the changes of eGFR following PCN.

Materials and Methods
We performed a retrospective folder review of patients who had PCN procedures at Groote Schuur Hospital for malignant obstructive uropathy from January 2015 to 31 December 2017.
For each included patient, eGFR was recorded at baseline pre-PCN, and at its best and worst value in the first six months after PCN. The timing of baseline, best and worst values were also recorded.
Other data collected included demographic data, type of malignancy, laterality of nephrostomy and presence of confirmed UTI at least one week post PCN.

Results/main findings
A total of 90 patients fulfilled our inclusion criteria. The most common cancers in men were bladder 59% (n=32), prostate 20% (n=11), lymphoma 7% (n=4), and colorectal 4% (n=2). The most common cancers in women were cervix 64% (n=23), bladder 19% (n=7), lymphoma 6% (n=2), colorectal 6% (n=2) and endometrial 6% (n=2). Men were of higher age, median (IQR), 60 (56, 67) years, compared to women, 48 (40, 67). 64% of patients (n=58) had bilateral PCN procedures (as opposed to a unilateral procedure). 52% (n=47) of patients developed at least one episode of UTI post PCN during the six-month observation period.
Median (IQR) timepoint of pre-PCN eGFR measurement was 1.0 (2.0, 0) day pre PCN. The best post-PCN eGFR measurement was 13.0 (6.0, 26.0) days post PCN. The worst post-PCN measurement was 33.5 (14.0, 92.5) days post PCN.
Pre-PCN eGFR, median (IQR), was 9 (5, 26). Post-PCN eGFR improved to 48 (30, 75) before deteriorating to 23 (9, 44) within the six-month follow-up window.
Compared to patients who do not develop UTI post-PCN, those who develop one or more post-PCN UTI(s) have a 6.15 (95% CI: 0.87, 11.43) unit lower eGFR at their worst eGFR measurement.
There are also markedly fewer deteriorations in chronic kidney disease (CKD) stages between best and worst post-PCN interval in those without UTI (42%, 18/43), compared to those with at least one post-PCN UTI (72%, 34/47).

Conclusions
Our study confirmed a similar renal function trend post-PCN for malignant ureteric obstruction across different demographics. It is clear that although most patients' renal function initially improve post-PCN, the general trend for the majority of patients is to deteriorate towards pre-PCN eGFR and CKD stage values.

Our data suggest that urinary tract infections play an important role in poor renal function response within six months post-PCN. Future studies should explore whether the development of UTI following PCN is an independent and modifiable risk factor for poor renal outcome.

c. Introduction

Advanced or locally advanced malignant conditions of the pelvis and/or abdomen can cause ureteric obstruction and associated impaired renal function. This obstruction can be managed by performing PCN tube insertion with or without antegrade double J - stent insertion [4].
Having PCN tubes in situ is associated with prolonged hospital stay which affects quality of life [4].

The available literature reports clearly on the morbidity associated with PCN, as well as the immediate improvement in renal function post-PCN [1; 2; 3; 4; 6].

Some studies found that patients spend between 23% and 40% of their mean survival time in hospital due to complications associated with nephrostomy tubes [1]. Median survival in a study of 49 patients post percutaneous catheter was 174 days (14–602) [1]. Another study of 211 patients showed a median survival of 5.05 months (95% CI = 3.87-7.11; range 2 - 963 days) [3]. In another big study of 208 patients, the median survival was 144 days (0–1084), with 44 (21.2%) patients dying during hospitalisation [4].
In a smaller series of 32 patients, it was reported that each patient spent a mean of 29 days (range, 1–82 days) in hospital from the time of PCN placement until death or the end of the study period. This represented 33.3% of the median survival time (87days) in their study [5].
Most studies report combined major and minor complication rates for PCN placement of 10%, with a mortality rate of between 0.05% and 0.3% [3]. Reported complications related to PCN are pyelonephritis (22.7%), hospital readmission (17.3%), dislodgment of the nephrostomy catheter requiring replacement (9.3%), haematuria (4%), blood transfusion (1.3%), and retroperitoneal haematoma (0.7%) [4].

Mean serum creatinine levels improved from 280umol/L to 150umol/L, post diversion in a large study of 208 patients [4]. In a smaller study of only 22 patients, mean serum creatinine improved from 516 umol/L (range 239–1019) pre-PCN to 168 umol/L (range 85–265) post-PCN [p<0.0001]. It took an average of 17 days (range 3–78) to reach the nadir creatinine concentration [6].

There is limited data on the trend in renal function following the expected initial improvement post-PCN. One South African study looked at renal function as measured by serum creatinine pre-PCN, day3 post-PCN, D7 post-PCN and then serum creatinine >7days post-PCN.

It is well known that urinary tract infection (UTI) is a risk factor for developing acute kidney injury. A study by Hsiao et al [7] investigated 790 patients who were admitted for UTI in a tertiary hospital in Taiwan. Of these patients, 12.3% (n=97) developed acute kidney injury, with 0.5% (n=4) of patients necessitating dialysis.

The decision if a patient needs PCN can be difficult. Various prognostication models [1; 3; 4] have been described to assist the clinician and patient with the decision making process. None of these prognostication models has long-term renal function response or UTIs post-PCN as factors affecting survival.

As our primary objective, we described the response in renal function following PCN for obstructive uropathy due to abdominal/pelvic malignant conditions at our institution. We hypothesized that UTI post PCN is associated with poor response in renal function and therefor investigated the role of UTIs in the response in renal function post-PCN.

d. Methods

i) Selection and Description of Participants

All patients who had percutaneous nephrostomy for malignant ureteric obstruction done at Groote Schuur Hospital between 1 January 2015 and 31 December 2017 were included in the study. All malignant conditions were considered for inclusion. Patients had to be followed-up for at least one week post percutaneous nephrostomy. Each patient was followed up for a maximum period of six months post-PCN.

Patients who had failed percutaneous nephrostomy and those who weren't followed up for at least one-week post intervention, were excluded. No children were included in this study.

Approval for this study was obtained from the University of Cape Town, Department of Surgery Departmental Research Committee (Project 2018/094).

Human research ethics committee approval was obtained from the University of Cape Town, Faculty of Health Sciences (HREC REF: 097/2019)

ii) Technical Information

We performed a retrospective folder review of all patients with complete records identified during the specified time period. Data were extracted from the hospital radiology system and the National Health Laboratory Services (NHLS) laboratory system.

Renal function was recorded as per the chronic kidney disease (CKD) staging system, according to estimated Glomerular Filtration Rate (eGFR) values. eGFR was determined using the MDRD equation. The chronic kidney disease (CKD) staging system we used is as follows (according to eGFR values): Stage1 has eGFR ≥90ml/min, Stage2 has eGFR 60-89ml/min, Stage3 has eGFR 30 – 59ml/min, Stage4 has eGFR 15 – 29ml/min and Stage5 has eGFR < 15ml/min [11]. CKD stages and eGFR pre-PCN were compared to the best CKD stage/eGFR post-PCN and worst CKD stage/eGFR within six months post-PCN. A poor response was defined as the worst CKD stage post-PCN the same or worse than the pre-PCN CKD stage. A good response was defined as the worst CKD stage post-PCN better than pre-PCN CKD stage.

Urinary tract infections (UTIs) were diagnosed if a patient had a positive microscopy and culture more than seven days post-PCN. UTI was defined as a single organism cultured in affected urine with a bacteria colony count of >10 000 CFU/ml. UTIs identified within seven days post-PCN were assumed to be related to pre-existing infected urine or colonisation and were not included. UTIs documented more than seven days post-PCN were considered as a new infection.

We collected data for six months post-PCN, as this represents the upper end of the range for median survival for our target population [4].

We collected the following data: 1) demographics, 2) type of malignancy, 3) laterality of the nephrostomy tube, 4) renal function and 5) UTIs.

Demographics collected included the patient's age and sex. We also documented the primary malignant condition that caused the obstructive uropathy and if the PCN tube was inserted unilateral or bilateral.

We grouped CKD Stage1 and 2 together, since the laboratory we used for this trial do not offer specific eGFR values at levels ≥60ml/min. If a patient had an eGFR ≥60ml/min, we classified him/her as *at worst CKD stage 2* and recorded his eGFR to be 75ml/min (midway between CKD stages 1 and 2).

iii) Statistics

Continuous and interval data were described in terms of mean (standard deviation) or median (interquartile range) as appropriate for the data distribution. Categorical data were described as counts and proportions (n/N [%]). The sudent's t-test, Wilcoxon rank sum test and the Wicoxon sign rank test were used to compare continuous and interval groups. Fisher's exact or Chi-squared tests were used to compare categorical groups. Repeated measures ANOVA was planned for testing within and between group differences in eGFR at different time points, grouped by presence or absence of UTI. However, due to differences in timing of measurements, this analysis could not be performed. The differences in eGFR pre- / post- PCN, were stratified according to presence or absence of UTI. Z-test for differences in proportions were used to compare proportions of patients with improved / deteriorated CKD stage following PCN between groups with / without UTI. We performed an exploratory multiple linear regression to evaluate the impact of UTI or worst eGFR outcome. The regression analysis was not planned before the data was analysed. The a priori level of significance was set at 0.05. Statistical analysis was performed using RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.

e. Results

We identified 90 patients that fulfilled our inclusion criteria. The most common cancers in men were bladder 59% (n=32), prostate 20% (n=11), lymphoma 7% (n=4), and colorectal 4% (n=2). The most common cancers in women were cervix 64% (n=23), bladder 19% (n=7), lymphoma 6% (n=2), colorectal 6% (n=2) and endometrial 6% (n=2). Men were of higher median (IQR) age, 60 (56, 67) years, compared to women, 48 (40, 67) years. 64% (58/90) of patients had bilateral PCN procedure (as opposed to a unilateral procedure). 52% (47/90) of patients developed at least one post-PCN UTI during the 6-month observation period. Table 1 reports on the demographic data.

Age is bimodally distributed, largely due to differences in distribution between males and females. (Figure 2). Grouping of age by presence or absence of UTI demonstrates the weight of post-PCN UTIs which occurred in older patients (Figure 3). There is no apparent interaction between sex and UTI status for distribution of age variable (See supplemental Figure 4).

The eGFR variable is skewed at each interval (pre-PCN, best post-PCN and worst post-PCN. The distributions for eGFR are similar between males and females at each interval.

Timing of measurements

Median (IQR) timepoint of pre-PCN eGFR measurement was 1.0 (2.0, 0) day pre-PCN, for best post-PCN eGFR measurement was 13.0 (6.0, 26.0) days post-PCN, and for worst post-PCN measurement it was 33.5 (14.0, 92.5) days post-PCN (Figure 6). The worst eGFR measurement occurred a median 33 (20, 49) days after the best eGFR measurement (p-value < 0.001, pseudomedian difference by Wilcoxon sign rank test). In 69% (62/90, [95% CI: 58%, 78%]) of patients the best eGFR measurement occurred before the worst eGFR measurement. In 8% (7/90, [3%, 16%]) of patients the best eGFR measurement occurred after the worst eGFR measurement. These proportions were significantly different from one another (Chi-squared test for equality of proportions, p-value < 0.001).

eGFR response

Pre-PCN eGFR, median (IQR), was 9 (5, 26). Post-PCN eGFR improved to 48 (30, 75) before deteriorating to 23 (9, 44) within the six-month follow-up window (Figures 7 and Table 3). The (pseudo)median (95% CI) difference between pre-PCN eGFR and best eGFR post-PCN was 30 (25, 26). The (pseudo)median (95% CI) difference between pre-PCN eGFR and worst post-PCN eGFR after was 8.5 (4, 13.5). The (pseudo)median (95% CI) difference between eGFR from best to worst post PCN value was -25 (-20.5, -29.5). See also Table 3 for pairwise comparison and false detection rate adjusted p-values.

CKD stage response

Pearson's Chi-squared test supports independence between CKD stage and interval of measurement; p-value < 0.001. Worst CKD staging post-PCN was consistently better than CKD staging before PCN (p-value 0.0008, simple ordinal regression with cumulative links model). These differences are maximised by the study design that sought to report best and worst values after baseline measurement (Figure 8 and Table 6).

Analysis of interaction between eGFR response and development of post-PCN UTI

Using simple linear regression to estimate the effect of UTI status on worst eGFR after PCN, the crude estimate of effect (95% CI) is -5.10 (-11.54, 1.36) eGFR units, p-value = 0.120, R-squared = 0.03.

Table 5 reports a multiple linear regression for predicting worst eGFR post-PCN. Adding the recorded predictor (eGFR baseline, eGFR improvement post-PCN, Age, Sex, Laterality, and cancer type) into the model improves performance, Adjusted R-squared = 0.37, F-statistic = 6.266 on 10 and 79 degrees of freedom, p-value < 0.0001. In this model the adjusted estimate of UTI effect (95% CI) is -6.15 (-11.43, -0.87). Despite some improvement in performance through log transformation of the baseline eGFR variable, this model demonstrates significant heteroskedasticity in residual diagnostics. The source of non-constant variance is likely due to the non-continuous nature of the eGFR variable above values of 60. (Refer to supplemental Figures 9a-c and 10a-d for regression diagnostics.)

Analysis of interaction between change in CKD stage post-PCN and development of post-PCN UTI

Proportions appear similar when comparing those with and without post-PCN UTIs in the alluvial plots (Figure 11). The proportional breakdown of the worst CKD stage appears slightly better (fewer cases with CKD stage 4 and 5) in those without UTI compared to those who developed at least one UTI post-PCN. There are also markedly fewer deteriorations in CKD stages between best and worst post-PCN interval in those without UTI (42%, 18/43) compared to those with at least one postoperative UTI (72%, 34/47). The difference (95% CI) in proportions is 30% (9%, 52%), p-value = 0.0067 (2-sample test for equality of proportions).

Other demographics

Looking at age distribution and renal function response, the younger age-group (<50years) showed a good response in renal function up to six months post-PCN in 46% (13/28) of patients. In the age-group 50 – 65 years, a good response was found in 41% (14/34) of patients and in the group ≥65 years a good response was found in 32% (9/28) of patients. UTI incidence according to age-groups: The group ≥65 years had incidence of 61% (17/28 patients), the group 50 – 65 years, 59% (20/34 patients) and the group <50 years, 36% (10/28 patients).

In the patients who had bilateral PCN (58 patients), 45% (26/58 patients) had improved CKD-stage up to six months post-PCN, while in the group of patients who had unilateral PCN (32 patients), only 22% (7/32 patients) had improved

CKD stage up to six months post-PCN. The incidence of UTI in the bilateral PCN patients was 55% (32/58 patients), while the unilateral PCN patients had an incidence of 47% (15/32 patients).

Comparing different cancers and percentage of good responders in renal function post-PCN [total]: Bladder Ca 49% [19/39], Cervical Ca 30% [7/23], Haematological malignancies (7 Lymphoma and 1 Multiple myeloma patients) 86% [6/7] and Prostate Ca 18% [2/11].

f. Discussion

Summary of main findings

On average, patients in our study experienced and initial early improvement in renal function (around two weeks post-PCN) followed by a deterioration towards baseline (around one month after PCN). 52% (n=47) of our patients developed at least one UTI following PCN. UTI events were associated with worse eGFR outcome by multiple linear regression, and worse CKD staging by stratified analysis

Limitations of our study

Use of a retrospective design limited our ability to analyse the interaction between UTI and response in renal function. The reason for this is because the outcome of interest was not recorded at standard intervals, and there was large variance in the time at which best and worst renal function values were recorded. Prospective studies can overcome this problem by standardising timepoints for outcome assessment.

We acknowledge that using the CKD staging has not been validates in this specific setting. Our primary research question was adequately answered using the CKD stages.

Another limitation is the fact that the laboratory service we used do not give specific values of eGFR for values >60ml/min. We therefor decided to use CKD stage 2 and eGFR of 75ml/min for all eGFR >60ml/min. The non-continuous nature of eGFR variable introduced difficulty with analysis. This can be overcome by calculating eGFR throughout the range, or using serum creatinine concentration instead of eGFR in regression analysis. We might have obtained more accurate data if we could have distinguish between CKD stages 1 and 2.

Interpretation

eGFR trends post-PCN

To determine eGFR trends from pre-PCN to best and worst eGFR we evaluated the timing when the different values were obtained (Figure 6). The majority of patients (69%) had a best eGFR measurement prior to worst eGFR measurement. Only 8% of patients had their best eGFR measurement after their worst eGFR measurement.

These findings support the hypothesis that patients experience an initial improvement in renal function, followed by a deterioration in function towards pre-PCN values. Available literature is unclear on this topic. This is an important factor to acknowledge when counselling patients for PCN in this setting. Nariculam et al. [10] found that among prostate cancer patients who underwent either unilateral or bilateral PCN, no major differences in post-PCN creatinine levels were seen. They showed little difference in the serum creatinine levels at the time of death, suggesting that survival after PCN insertion is based on the aggressiveness of the prostate cancer as opposed to the number of nephrostomies inserted. This may explain our patients' worsening renal function after initial improvement. Another reason for this deterioration in renal function can be the development of UTI, which had shown to be a risk factor for AKI [7]. Our cohort had a higher incidence of UTI post PCN when compared to available literature, indicating higher risk for developing AKI.

eGFR and CKD stage response post-PCN

We investigated eGFR/CKD stage at three intervals (baseline, best and worst values post-PCN). (Figures 7&8 and Table 3). CKD stage improved significantly following PCN with change from pre-PCN to best post-PCN CKD stage, and deteriorated again from pre-PCN to worst post-PCN CKD stage. Possible causes for this deterioration include progression of primary malignancy, dislodgement/blockage of nephrostomy tubes, pre-renal causes (excluding UTI) and acquiring urinary tract infection secondary to foreign body (nephrostomy tube) in situ.
Unlike similar studies on this topic, this study design sought to report best and worst values after baseline measurement (Figure 8). Our results call in to question the role of PCN in advanced malignancy as we have shown that initial improvements in eGFR and CKD stage are short-lived. There are few other studies which have investigated or shown this conclusively.

Interaction between renal function and development of UTI post-PCN

The incidence of UTI in our study (52%) was higher than the reported literature, with reported incidences of UTI/sepsis post-PCN between 15% [8] and 22.7% [4].

Our secondary objective was to analyse the interaction between eGFR response and the development of post-PCN UTI. Multiple linear regression (figure 9) showed that patients who develop one or more post-PCN UTIs have a 6.15 unit lower eGFR at their worst eGFR measurement than those who do not. This could be a useful prognostic indicator in the clinical setting. The prognostication models available do not include this as a factor affecting survival. Prospective research investigating UTIs and its effect on renal function and subsequent survival in the malignant PCN setting might provide better clarity on the subject.

This multiple linear regression is not a perfect model. Non-constant variance remains a problem despite transformation of the pre-PCN eGFR variable. This is most likely due to the mixed nature of the eGFR variables. In this dataset eGFR is recorded as a continuous variable up to 60, but then it becomes categorical, with all values greater than 60 being recorded as 75. Future studies should find a way to calculate absolute eGFR values through the full range of the variable. The model further assumes that all important predictors of worst eGFR outcome were available in this dataset. The model does not consider any temporal information regarding when a given patient experienced the worst post-PCN eGFR.

Proportional breakdown of the worst CKD stage is better in the group without UTI (Figure 11). There were also markedly fewer deteriorations in CKD stages between best and worst post-PCN interval in the patients without UTI. This findings supports our hypothesis that UTI is associated with poor renal function response post-PCN. The poor response in patients who developed UTI post-PCN also applies to patients who initially responded well.

It is described that UTI can cause AKI [7], but in the specific setting of our cohort, evidence is scarce. This finding warrants further investigation in a prospective trial environment. Once the hypothesis is confirmed prospectively, interventions like using prophylactic antibiotics and maybe closed system drainage systems (as opposed to open ended nephrostomies with a drainage bag connected to the skin) should be explored in future research. Regular screening for bacteriuria and treating this can also be explored. It is important to note that most knowledge and management strategies regarding asymptomatic bacteriuria relates to the bladder/ voided samples and not in this specific setting of a possible immunocompromised patient having a PCN tube/s in situ. This might add an additional scenario where asymptomatic bacteriuria should be treated aggressively.

Other considerations

Investigating age distribution, it appears that older patients had worse renal function response and more UTIs. We know that older patients and patients with PCN are more at risk to develop UTI. They usually are more prone to developing AKI post UTI [7]. This will need to be proven with statistical analysis.

A total of 64% of our patients had bilateral PCN. This is in line with the reported literature of incidences ranging from 22% [1] and 72% [10]. The patients who had bilateral PCN showed a higher percentage of improved CKD-stage up to six months post-PCN, when compared to the patients who only had unilateral PCN. Interestingly, the incidence of UTI in the bilateral PCN patients was higher compared to the patients with unilateral PCN 55% vs 47%). This is contrary to our hypothesis that a higher incidence of UTI is associated with poorer renal function response. Nariculam et al. [10]

concluded in their trial of prostate cancer patients that bilateral or unilateral PCN did not influence renal function, measured at the time of death.

When we compare different cancers and the percentage of good responders in renal function post-PCN, it appeared that prostate cancer did the worst in terms of renal function response post-PCN. This is however not statistically significant in our series. One reason for this finding can be due to the older population group that usually gets diagnosed with prostate cancer, who are prone to UTI and AKI. Prostate cancer is often associated with bladder outlet obstruction, sometimes requiring catheterisation and/or surgery, all of which increase the risk for UTI and renal failure. The biological aggressiveness of advanced prostate cancer can also contribute to the poor renal function response. This was demonstrated by Nariculam et al. [10] who reported that renal function is dependent on the aggressiveness of the primary tumour (prostate cancer in their study) and not on the amount of PCN tubes (bilateral or unilateral).

Conclusion

Our study confirmed a similar renal function trend post-PCN for malignant ureteric obstruction across different demographics. Although most patients' renal function initially improves post-PCN, the general trend for the majority of patients is to deteriorate towards pre-PCN eGFR and CKD stage values.

Urinary tract infections appear to play and important role in poor renal function response within six months post-PCN. This however was difficult to prove statistically and should be evaluated prospectively in future studies.

Other demographic factors that appear to have an influence on renal function response post-PCN include type of malignancy, age and laterality of PCN, and theses might require further investigation in future.

In our study, the only modifiable risk factor associated with poor response in renal function post-PCN, seems to be UTIs. This is perhaps an area to explore, to prevent UTIs and in doing so increase the probability of better renal function response post-PCN for malignant ureteric obstruction.

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h. Tables

Table 1: Patient characteristics (N=90), group by presence or absence of one or more post-PCN UTIs.

Variable	No UTI	≥1 UTI	Total
Age			
Mean	55	58	56
Sd	15	12	14
Min	24	31	24
p25	42	56	46
Median	56	60	59
p75	66	67	67
Max	88	78	88
Mode	40	56	56
Sex			
Female	19	17	36
Male	24	30	54
Cancer type			
Bladder	16	23	39
Cervix	14	9	23
Prostate	4	7	11
Colorectal	2	2	4
Lymphoma	3	3	6
Endometrial	1	1	2
Other	3	2	5
Laterality of procedure			
Unilateral	17	15	32
Bilateral	26	32	58

Table 2. Patient outcomes grouped by presence or absence of post-PCN UTI

Variable	No UTI (N=43)	>=1 UTI (N=47)	p-value	Total (N=90)
Timing of measurement				
Preoperative				
mean (sd)	-2.1 (3.1)	-1.2 (1.5)		-1.6 (2.4)
median (p25, p75)	-1. (-2.5, 0.)	-1.0 (-1.5, 0.)	0.414†	-1.0 (-2.0, 0.)
range	-13, 0	-6, 0		-13, 0
Best postoperative				
mean (sd)	17.5 (24.6)	28.9 (33.5)		23.4 (29.9)
median (p25, p75)	11. (4.5, 17.5)	16. (9.5, 31.5)	0.018†	13. (6., 26.)
range	1, 148	1, 154		1, 154
Worst postoperative				
mean (sd)	37.7 (45.4)	68.6 (52.4)		53.8 (51.3)
median (p25, p75)	18. (11., 40.)	45. (24.5, 112.)	0.0004†	33.5 (14., 92.5)
range	2, 174	4, 181		2, 181
GFR				
Preoperative				
mean (sd)	19 (20)	19 (22)		19 (21)
median (p25, p75)	11 (6, 29)	7 (4, 24)	0.342†	9 (5, 26)
range	2, 75	2, 75		2, 75
Best postoperative				
mean (sd)	45 (24)	51 (21)		48 (22)
median (p25, p75)	41 (26, 75)	52 (36, 75)	0.158†	48 (30, 75)
range	7, 75	9, 75		7, 75
Worst postoperative				
mean (sd)	32 (23)	25 (20)		28 (22)
median (p25, p75)	29 (14, 48)	19 (8, 38)	0.128†	23 (9, 44)
range	2, 75	3, 75		2, 75
CKD stage				
Preoperative				
<=2	3 (7%)	4 (9%)		7 (8%)
3	8 (19%)	7 (15%)	0.213‡	15 (17%)
4	5 (12%)	6 (13%)		11 (12%)
5	27 (63%)	30 (64%)		57 (63%)
Best postoperative				
<=2	13 (30%)	15 (32%)		28 (31%)
3	17 (40%)	23 (49%)	0.213‡	40 (44%)
4	8 (19%)	6 (13%)		14 (16%)
5	5 (12%)	3 (6%)		8 (9%)
Worst postoperative				
<=2	12 (28%)	20 (43%)		9 (10%)
3	10 (23%)	12 (26%)	0.238‡	27 (30%)
4	15 (35%)	12 (26%)		22 (24%)
5	6 (14%)	3 (6%)		32 (36%)

†Wilcoxon Rank Sum test, ‡Chi-squared test with continuity correction

Table 3. Pairwise comparison using Wilcoxon sign rank test with p-value adjustment by false detection rate (FDR) method:

	Preoperative eGFR			Best postoperative eGFR		
	Pseudo-median	95% CI	p-value	Pseudo-median	95% CI	p-value
Best postoperative eGFR	30	25, 36	1.0e-14	-		
Worst postoperative eGFR	8.5	4, 13.5	9.4e-05	-25	20.5, 29.5	7.9e-13

Table 4. CKD stage by interval

CKD stage	Pre-PCN	Best Post-PCN	Worst Post-PCN
2+	7	28	9
3	15	40	27
4	11	14	22
5	57	8	32

Table 5. Multiple linear regression for predicting worst eGFR post PCN.

	Estimate	P-value	Lower 95% CI	Upper 95% CI
(Intercept)	-3.66	0.797	-31.38	24.07
>=1 UTI	-6.15	0.025	-11.43	-0.87
Ln(Pre-PCN eGFR)	11.24	2.51e-06	6.90	15.57
eGFR response(Pre~Best)	0.57	7.46e-07	0.36	0.77
Age	-0.16	0.370	-0.51	0.19
Sex (male)	0.15	0.972	-8.07	8.37
Laterality (bilateral)	-1.99	0.540	-8.32	4.35
Reference diagnosis (bladder ca.)				
Diagnosis (cervix ca.)	8.00	0.117	-1.89	17.88
Diagnosis (prostate ca.)	2.71	0.598	-7.31	12.72
Diagnosis (lymphoma)	-5.78	0.381	-18.64	7.08
Diagnosis (other)	-0.06	0.994	-14.43	14.31

Adjusted R-squared = 0.37, F-statistic = 6.266 on 10 and 79 degrees of freedom, p-value = 5.402e-07

Table 6. Cumulative probabilities of CKD categories at three time intervals.

CKD	Baseline		Best		Worst	
	n	proportion	n	proportion	n	proportion
5	57	0.63	8	0.09	32	0.36
4-5	68	0.76	22	0.24	54	0.60
3-5	83	0.92	62	0.69	81	0.90
1-5	90	1.00	90	1.00	90	1.00

i. **Illustrations (Figures)**

Figure 2. Density plot of age variable grouped by sex

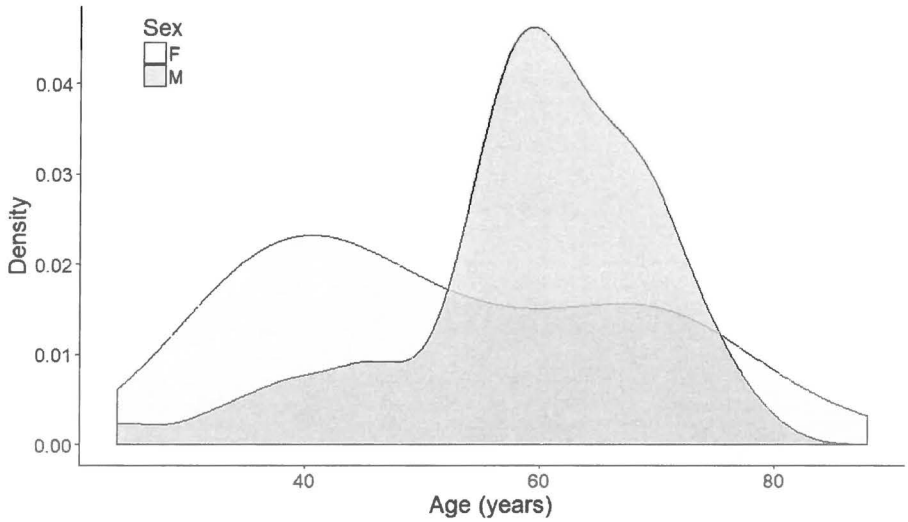


Figure 3. Density plot of age variable grouped by presence or absence of post-PCN UTI

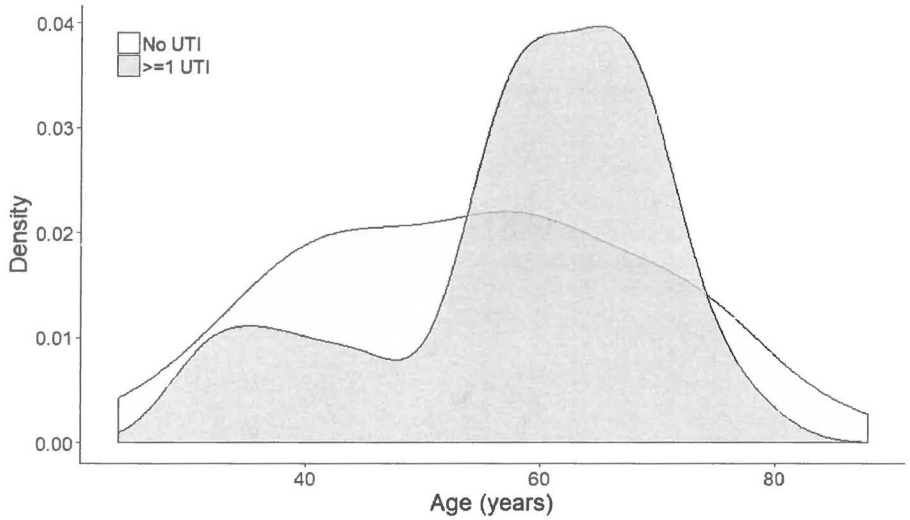


Figure 6. Boxplots of timing of eGFR measurement

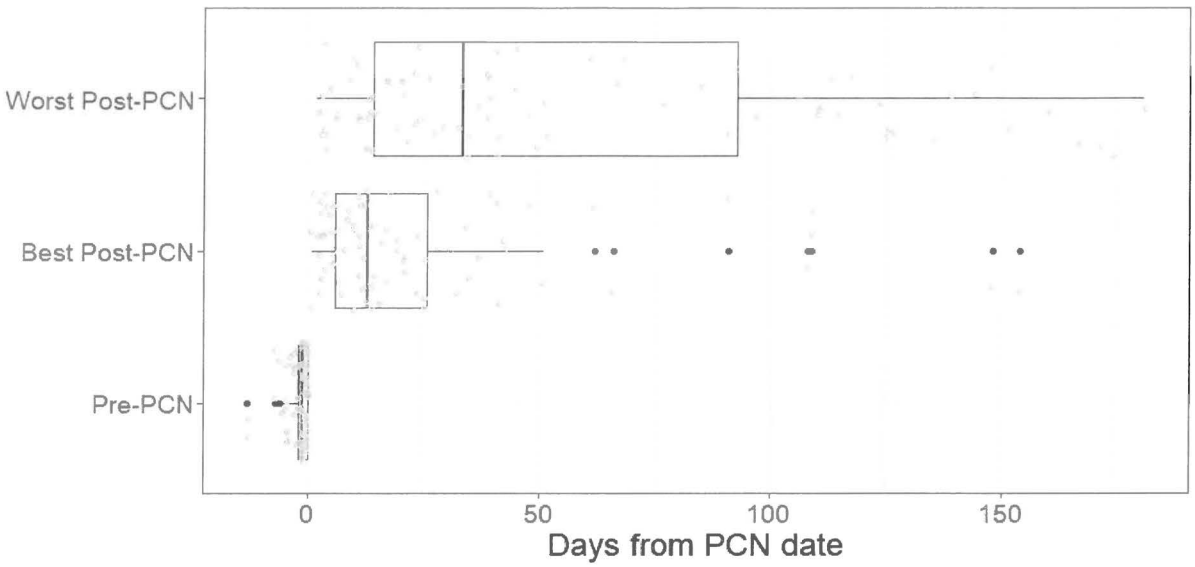


Figure 7. Boxplots of eGFR at three intervals grouped by presence or absence of post-PCN UTI event(s).

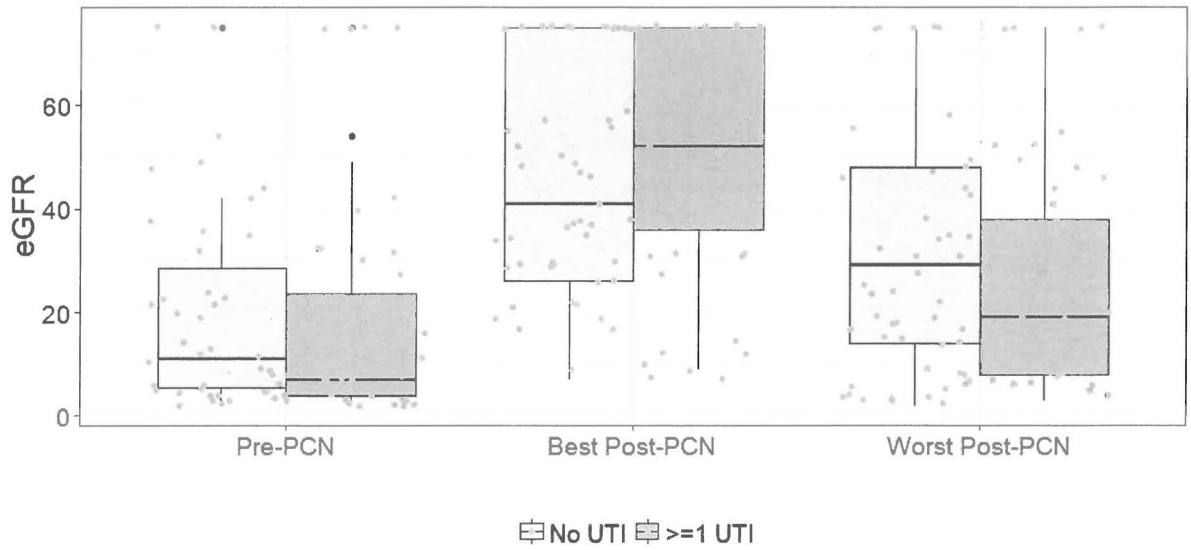


Figure 8. Histograms of CKD stages at three time intervals (pre-PCN, best post-PCN, and worst post-PCN).

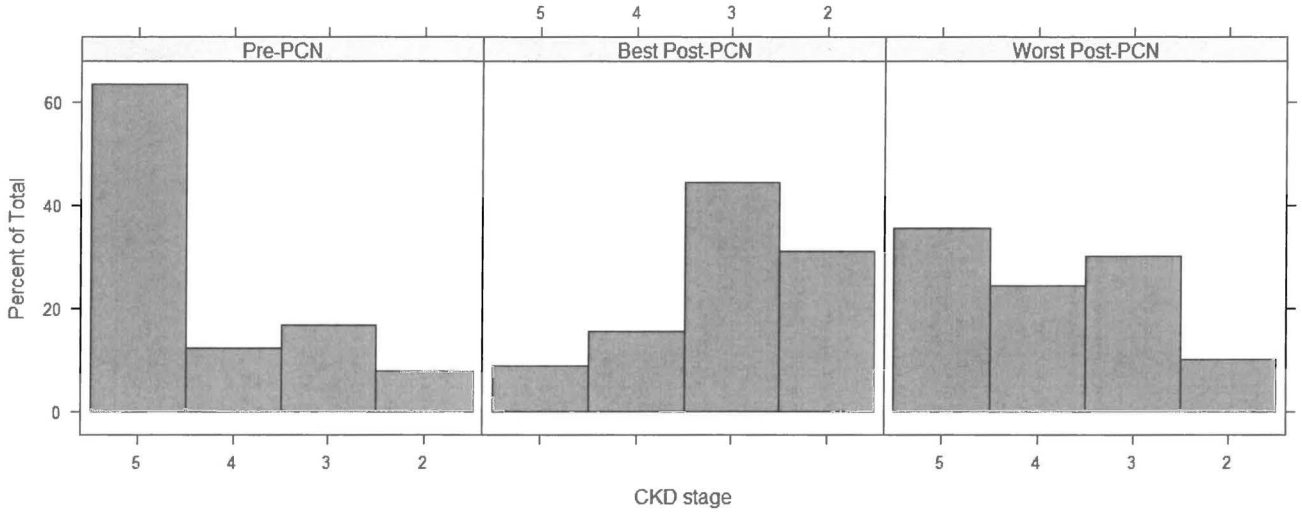
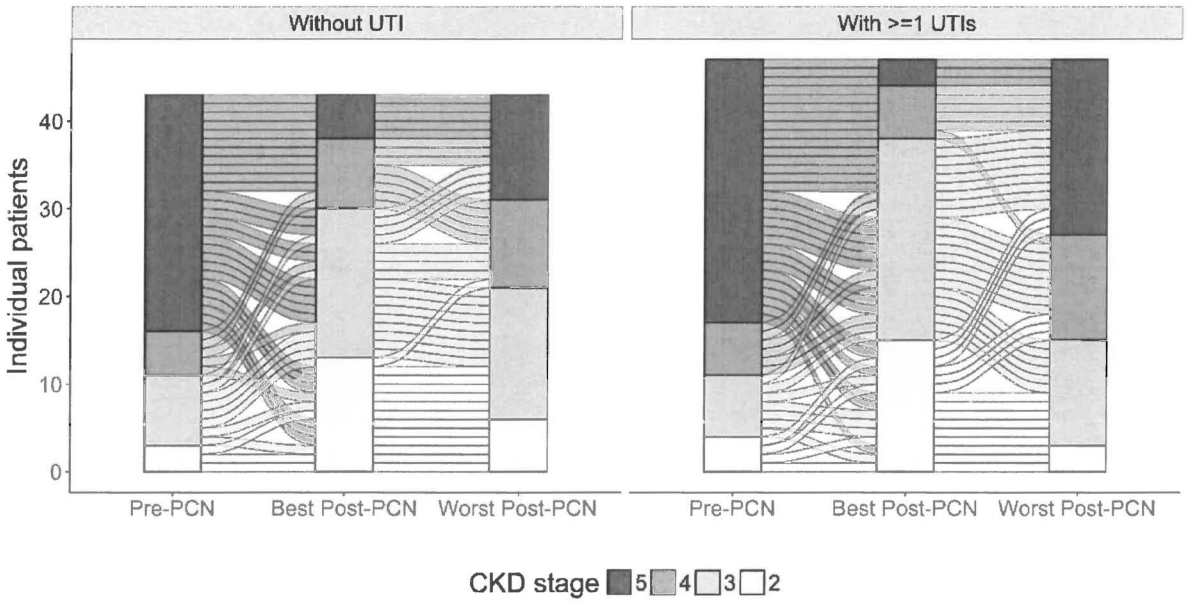


Figure 11. Alluvial plots of patient CKD stage at three intervals. Comparing those at least one postoperative UTI event to those without any postoperative UTI events. Worst stage is dark grey at top of bars, best stage is light grey at bottom of bars.



j. Units of Measurement

Renal function: Measured by estimated Glomerular Filtration Rate (eGFR) in mL/min per 1.73 m^2 according to the MDRD formula.
UTI: Measured in CFU/mL (colony-forming units per millilitre)
Serum creatinine: Measured in umol/L

k. Abbreviations and Symbols

AKI: Acute kidney injury

CFU/mL: colony-forming units per millilitre

CKD: chronic kidney disease

eGFR: estimated Glomerular Filtration Rate

MC&S: Microscopy, Culture & Sensitivity

MDRD: Modification of Diet in Renal Disease (MDRD) equation

PCN: percutaneous nephrostomy

UTI: urinary tract infection
UTIs: urinary tract infections

I. Appendices

i) Supplemental figures
ii) UCT HREC approval letter
iii) Department of Surgery departmental research committee approval letter
iv) ICMJE recommendations for conduct and reporting of research published in medical journal

Appendix i: Supplemental figures

Figure 1. Density plot of age variable

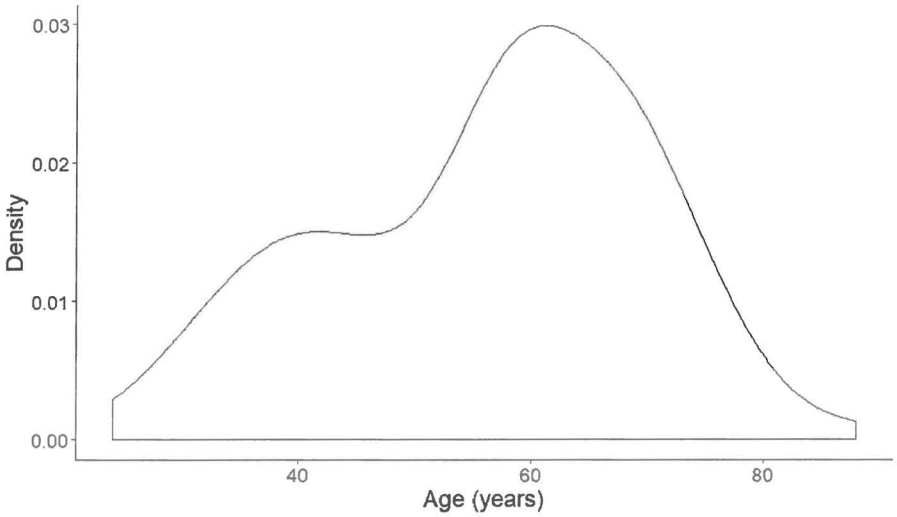
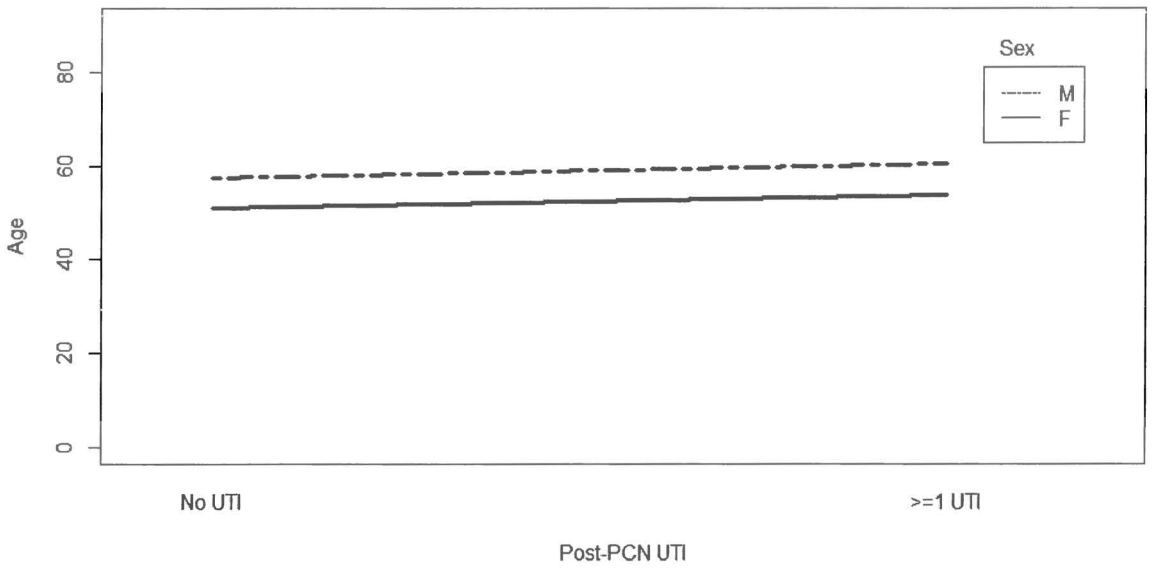
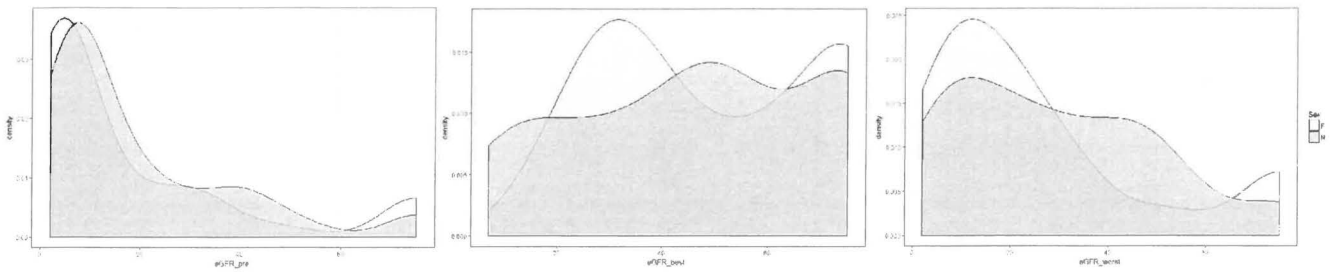


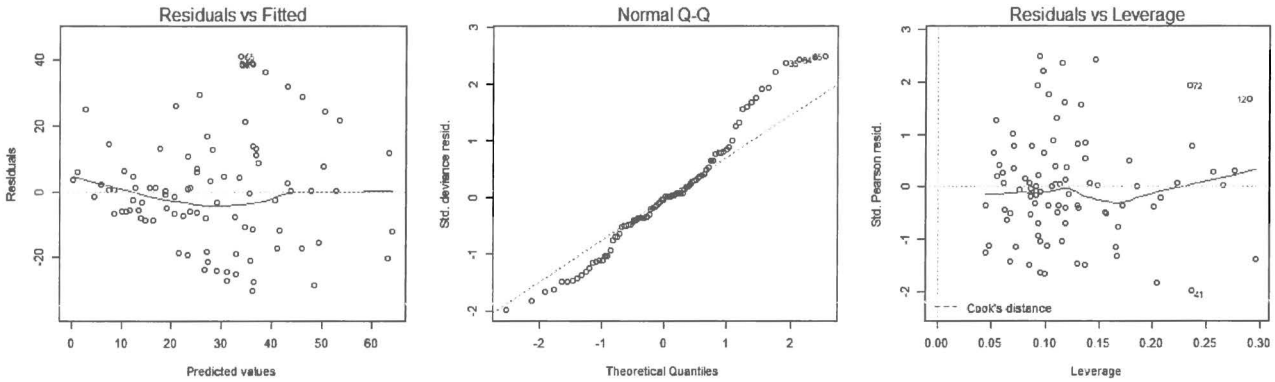
Figure 4. Interaction plot of age variable grouped by sex and presence or absence of post-PCN UTI



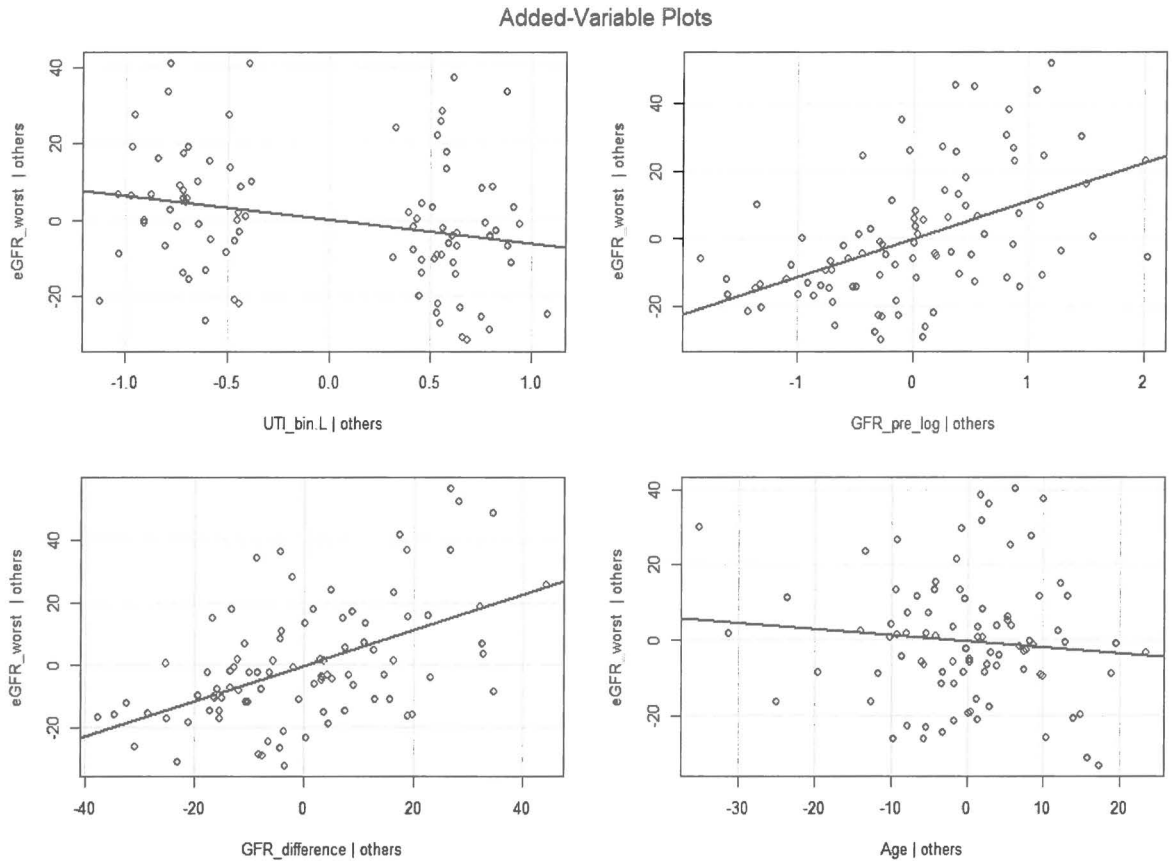
Figures 5a-c. Density distributions of eGFR at three intervals, grouped by sex.



Figures 9a-c. Diagnostic plots for multiple linear regression



Figures 10a-d. Added variable plots of UTI and continuous predictors in multiple linear regression.



Appendix ii

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

19 February 2019

HREC REF: 097/2019

Dr L Kaestner
Urology
E26, OMB

Dear Dr Kaestner

PROJECT TITLE: DO PERCUTANEOUS NEPHROSTOMIES FOR MALIGNANT OBSTRUCTIVE UROPATHY IMPROVE RENAL FUNCTION SIX MONTHS INTERVENTION? (MMED CANDIDATE: DR C.E DE WET)

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

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix iii

UNIVERSITY OF CAPE TOWN

Department of Surgery
Departmental Research Committee
Dr Timothy Pennel
D24 Office, Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 3430
Email: tim.pennel@uct.ac.za

28 Jan 2019

Dr C De Wet

Department of Surgery
University of Cape Town

Dear Dr De Wet

RE: Project 2018/094

PROJECT TITLE: Do Percutaneous Nephrostomies For Malignant Obstructive Uropathy Improve Renal Function Six Months Post Intervention?

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

signature removed to avoid exposure online

Yours sincerely

DR TIMOTHY PENNEL
CHAIRMAN: RESEARCH COMMITTEE

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals

Updated December 2018

I. About the Recommendations
  A. Purpose of the Recommendations
  B. Who Should Use the Recommendations?
  C. History of the Recommendations
II. Roles and Responsibilities of Authors, Contributors, Reviewers, Editors, Publishers, and Owners
  A. Defining the Role of Authors and Contributors
    1. Why Authorship Matters
    2. Who Is an Author?
    3. Non-Author Contributors
  B. Conflicts of Interest
    1. Participants
      a. Authors
      b. Peer Reviewers
      c. Editors and Journal Staff
    2. Reporting Conflicts of Interest
  C. Responsibilities in the Submission and Peer-Review Process
    1. Authors
      a. Predatory or Pseudo-Journals
    2. Journals
      a. Confidentiality
      b. Timeliness
      c. Peer Review
      d. Integrity
      e. Journal Metrics
    3. Peer Reviewers
  D. Journal Owners and Editorial Freedom
    1. Journal Owners
    2. Editorial Freedom
  E. Protection of Research Participants
III. Publishing and Editorial Issues Related to Publication in Medical Journals
  A. Corrections, Retractions, Republications, and Version Control
  B. Scientific Misconduct, Expressions of Concern, and Retraction
  C. Copyright
  D. Overlapping Publications
    1. Duplicate Submission
    2. Duplicate and Prior Publication
    3. Acceptable Secondary Publication
    4. Manuscripts Based on the Same Database
  E. Correspondence
  F. Fees
  G. Supplements, Theme Issues, and Special Series
  H. Sponsorship of Partnerships
  I. Electronic Publishing
  J. Advertising
  K. Journals and the Media
  L. Clinical Trials
    i. Registration
    ii. Data Sharing
IV. Manuscript Preparation and Submission
  A. Preparing a Manuscript for Submission to a Medical Journal
    1. General Principles
    2. Reporting Guidelines
    3. Manuscript Sections
      a. Title Page
      b. Abstract
      c. Introduction
      d. Methods
        i. Selection and Description of Participants
        ii. Technical Information
        iii. Statistics
      e. Results
      f. Discussion
      g. References
        i. General Considerations
        ii. Style and Format
      h. Tables
      i. Illustrations (Figures)
      j. Units of Measurement
      k. Abbreviations and Symbols
  B. Sending the Manuscript to the Journal

I. About the Recommendations

A. Purpose of the Recommendations

ICMJE developed these recommendations to review best practice and ethical standards in the conduct and reporting of research and other material published in medical journals, and to help authors, editors, and others involved in peer review and biomedical publishing create and distribute accurate, clear, reproducible, unbiased medical journal articles. The recommendations may also provide useful insights into the medical editing and publishing process for the media, patients and their families, and general readers.

B. Who Should Use the Recommendations?

These recommendations are intended primarily for use by authors who might submit their work for publication to ICMJE member journals. Many non-ICMJE journals voluntarily use these recommendations (see www.icmje.org/journals-following-the-icjme-recommendations/). The ICMJE encourages that use but has no authority to monitor or enforce it. In all cases, authors should use these recommendations along with individual journals' instructions to authors. Authors should also consult guidelines for the reporting of specific study types (e.g., the CONSORT

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guidelines for the reporting of randomized trials); see www.equator-network.org.

Journals that follow these recommendations are encouraged to incorporate them into their instructions to authors and to make explicit in those instructions that they follow ICMJE recommendations. Journals that wish to be identified on the ICMJE website as following these recommendations should notify the ICMJE secretariat at www.icmje.org/journals-following-the-icmje-recommendations/journal-listing-request-form/. Journals that in the past have requested such identification but who no longer follow ICMJE recommendations should use the same means to request removal from this list.

The ICMJE encourages wide dissemination of these recommendations and reproduction of this document in its entirety for educational, not-for-profit purposes without regard for copyright, but all uses of the recommendations and document should direct readers to www.icmje.org for the official, most recent version, as the ICMJE updates the recommendations periodically when new issues arise.

C. History of the Recommendations

The ICMJE has produced multiple editions of this document, previously known as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). The URM was first published in 1978 as a way of standardizing manuscript format and preparation across journals. Over the years, issues in publishing that went well beyond manuscript preparation arose, resulting in the development of separate statements, up-dates to the document, and its renaming as "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" to reflect its broader scope. Previous versions of the document may be found in the "Archives" section of www.icmje.org.

II. Roles and Responsibilities of Authors, Contributors, Reviewers, Editors, Publishers, and Owners

A. Defining the Role of Authors and Contributors

1. Why Authorship Matters

Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. The following recommendations are intended to ensure that contributors who have made substantive intellectual contributions to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published.

Because authorship does not communicate what contributions qualified an individual to be an author, some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy. Such policies remove much of the ambiguity surrounding contributions, but leave unresolved the question of the quantity and quality of contribution that qualify an individual for authorship. The ICMJE has thus developed criteria for authorship that can be used by all journals, including those that distinguish authors from other contributors.

2. Who Is an Author?

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged—see Section II.A.3 below. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3. Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript.

The individuals who conduct the work are responsible for identifying who meets these criteria and ideally should do so when planning the work, making modifications as appropriate as the work progresses. We encourage collaboration and co-authorship with colleagues in the locations where the research is conducted. It is the collective responsibility of the authors, not the journal to which the work is submitted, to determine that all people named as authors meet all four criteria; it is not the role of journal editors to determine who qualifies or does not qualify for authorship or to arbitrate authorship conflicts. If agreement cannot be reached about who qualifies for authorship, the institution(s) where the work was performed, not the journal editor, should be asked to investigate. If authors request removal or addition of an author after manuscript submission or publication, journal editors should seek an explanation and signed statement of agreement for the requested

change from all listed authors and from the author to be removed or added.

The corresponding author is the one individual who takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process, and typically ensures that all the journal's administrative requirements, such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and gathering conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer-review process to respond to editorial queries in a timely way, and should be available after publication to respond to critiques of the work and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication. Although the corresponding author has primary responsibility for correspondence with the journal, the ICMJE recommends that editors send copies of all correspondence to all listed authors.

When a large multi-author group has conducted the work, the group ideally should decide who will be an author before the work is started and confirm who is an author before submitting the manuscript for publication. All members of the group named as authors should meet all four criteria for authorship, including approval of the final manuscript, and they should be able to take public responsibility for the work and should have full confidence in the accuracy and integrity of the work of other group authors. They will also be expected as individuals to complete conflict-of-interest disclosure forms.

Some large multi-author groups designate authorship by a group name, with or without the names of individuals. When submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists, and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.

3. Non-Author Contributors

Contributors who meet fewer than all 4 of the above criteria for authorship should not be listed as authors, but they should be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g., "Clinical Investigators" or "Participating Investigators"), and their contributions should be specified (e.g., "served as scientific advisors," "critically reviewed the study proposal," "collected data," "provided and cared for study patients", "participated in writing or technical editing of the manuscript").

Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, editors are advised to require that the corresponding author obtain written permission to be acknowledged from all acknowledged individuals.

B. Conflicts of Interest

Public trust in the scientific process and the credibility of published articles depend in part on how transparently conflicts of interest are handled during the planning, implementation, writing, peer review, editing, and publication of scientific work.

A conflict of interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest.

Financial relationships (such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and science itself. However, conflicts can occur for other reasons, such as personal relationships or rivalries, academic competition, and intellectual beliefs. Authors should avoid entering in to agreements with study sponsors, both for-profit and nonprofit, that interfere with authors' access to all of the study's data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently when and where they choose. Authors may be required to provide the journal with the agreements in confidence.

Purposeful failure to disclose conflicts of interest is a form of misconduct, as is discussed in Section III.B.

1. Participants

All participants in the peer-review and publication process—not only authors but also peer reviewers, editors, and editorial board members of journals—must consider their conflicts of interest when fulfilling their roles in the process of article review and publication and must disclose all relationships that could be viewed as potential conflicts of interest.

a. Authors

When authors submit a manuscript of any type or format they are responsible for disclosing all financial and

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personal relationships that might bias or be seen to bias their work. The ICMJE has developed a Form for Disclosure of Conflicts of Interest to facilitate and standardize authors' disclosures. ICMJE member journals require that authors use this form, and ICMJE encourages other journals to adopt it.

b. Peer Reviewers

Reviewers should be asked at the time they are asked to critique a manuscript if they have conflicts of interest that could complicate their review. Reviewers must disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and should recuse themselves from reviewing specific manuscripts if the potential for bias exists. Reviewers must not use knowledge of the work they're reviewing before its publication to further their own interests.

c. Editors and Journal Staff

Editors who make final decisions about manuscripts should recuse themselves from editorial decisions if they have conflicts of interest or relationships that pose potential conflicts related to articles under consideration. Other editorial staff members who participate in editorial decisions must provide editors with a current description of their financial interests or other conflicts (as they might relate to editorial judgments) and recuse themselves from any decisions in which a conflict of interest exists. Editorial staff must not use information gained through working with manuscripts for private gain. Editors should publish regular disclosure statements about potential conflicts of interests related to their own commitments and those of their journal staff. Guest editors should follow these same procedures.

Journals should take extra precautions and have a stated policy for evaluation of manuscripts submitted by individuals involved in editorial decisions. Further guidance is available from COPE (https://publicationethics.org/files/A_Short_Guide_to_Ethical_Editing.pdf) and WAME (http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals).

2. Reporting Conflicts of Interest

Articles should be published with statements or supporting documents, such as the ICMJE conflict of interest form, declaring:

– Authors' conflicts of interest; and

– Sources of support for the work, including sponsor names along with explanations of the role of those sources if any in study design; collection, analysis, and interpretation of data; writing of the report; the decision to submit the report for publication; or a statement declaring that the supporting source had no such involvement; and

– Whether the authors had access to the study data, with an explanation of the nature and extent of access, including whether access is ongoing.

To support the above statements, editors may request that authors of a study sponsored by a funder with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

C. Responsibilities in the Submission and Peer-Review Process

1. Authors

Authors should abide by all principles of authorship and declaration of conflicts of interest detailed in section IIA and B of this document.

a. Predatory or Pseudo-Journals

A growing number of entities are advertising themselves as "scholarly medical journals" yet do not function as such. These journals ("predatory"or "pseudo-journals") accept and publish almost all submissions and charge article processing (or publication) fees, often informing authors about this after a paper's acceptance for publication. They often claim to perform peer review but do not and may purposefully use names similar to well established journals. They may state that they are members of ICMJE but are not (see www.icmje.org for current members of the ICMJE) and that they follow the recommendations of organizations such as the ICMJE, COPE and WAME. Researchers must be aware of the existence of such entities and avoid submitting research to them for publication. Authors have a responsibility to evaluate the integrity, history, practices and reputation of the journals to which they submit manuscripts. Guidance from various organizations is available to help identify the characteristics of reputable peer-reviewed journals (www.wame.org/identifying-predatory-or-pseudo-journals and www.wame.org/about/principlesof-transparency-and-best-practice). Seeking the assistance of scientific mentors, senior colleagues and others with many years of scholarly publishing experience may also be helpful.

2. Journals

a. Confidentiality

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Editors therefore must not share information about manuscripts, including whether they have been received and are under review, their content and status in the review process, criticism by reviewers, and their ultimate fate, to anyone other than the authors and reviewers. Requests from third parties to use manuscripts and reviews for legal proceedings should be politely refused, and editors should

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do their best not to provide such confidential material should it be subpoenaed.

Editors must also make clear that reviewers should keep manuscripts, associated material, and the information they contain strictly confidential. Reviewers and editorial staff members must not publicly discuss the authors' work, and reviewers must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy paper copies of manuscripts and delete electronic copies after submitting their reviews.

When a manuscript is rejected, it is best practice for journals to delete copies of it from their editorial systems unless retention is required by local regulations. Journals that retain copies of rejected manuscripts should disclose this practice in their Information for Authors.

When a manuscript is published, journals should keep copies of the original submission, reviews, revisions, and correspondence for at least three years and possibly in perpetuity, depending on local regulations, to help answer future questions about the work should they arise.

Editors should not publish or publicize peer reviewers' comments without permission of the reviewer and author. If journal policy is to blind authors to reviewer identity and comments are not signed, that identity must not be revealed to the author or anyone else without the reviewers' expressed written permission.

Confidentiality may have to be breached if dishonesty or fraud is alleged, but editors should notify authors or reviewers if they intend to do so and confidentiality must otherwise be honored.

b. Timeliness

Editors should do all they can to ensure timely processing of manuscripts with the resources available to them. If editors intend to publish a manuscript, they should attempt to do so in a timely manner and any planned delays should be negotiated with the authors. If a journal has no intention of proceeding with a manuscript, editors should endeavor to reject the manuscript as soon as possible to allow authors to submit to a different journal.

c. Peer Review

Peer review is the critical assessment of manuscripts submitted to journals by experts who are usually not part of the editorial staff. Because unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including scientific research, peer review is an important extension of the scientific process.

The actual value of peer review is widely debated, but the process facilitates a fair hearing for a manuscript among members of the scientific community. More practically, it helps editors decide which manuscripts are suitable for their journals. Peer review often helps authors and editors improve the quality of reporting.

It is the responsibility of the journal to ensure that systems are in place for selection of appropriate reviewers. It is the responsibility of the editor to ensure that reviewers have access to all materials that may be relevant to the evaluation of the manuscript, including supplementary material for e-only publication, and to ensure that reviewer comments are properly assessed and interpreted in the context of their declared conflicts of interest.

A peer-reviewed journal is under no obligation to send submitted manuscripts for review, and under no obligation to follow reviewer recommendations, favorable or negative. The editor of a journal is ultimately responsible for the selection of all its content, and editorial decisions may be informed by issues unrelated to the quality of a manuscript, such as suitability for the journal. An editor can reject any article at any time before publication, including after acceptance if concerns arise about the integrity of the work.

Journals may differ in the number and kinds of manuscripts they send for review, the number and types of reviewers they seek for each manuscript, whether the review process is open or blinded, and other aspects of the review process. For this reason and as a service to authors, journals should publish a description of their peer-review process.

Journals should notify reviewers of the ultimate decision to accept or reject a paper, and should acknowledge the contribution of peer reviewers to their journal. Editors are encouraged to share reviewers' comments with co-reviewers of the same paper, so reviewers can learn from each other in the review process.

As part of peer review, editors are encouraged to review research protocols, plans for statistical analysis if separate from the protocol, and/or contracts associated with project-specific studies. Editors should encourage authors to make such documents publicly available at the time of or after publication, before accepting such studies for publication. Some journals may require public posting of these documents as a condition of acceptance for publication.

Journal requirements for independent data analysis and for public data availability are in flux at the time of this revision, reflecting evolving views of the importance of data availability for pre- and post-publication peer review. Some journal editors currently request a statistical analysis of trial data by an independent biostatistician before accepting studies for publication. Others ask authors to say whether the study data are available to third parties to view and/or use/reanalyze, while still others encourage or require authors to share their data with others for review or reanalysis. Each journal should establish and publish their specific requirements for data analysis and post in a place that potential authors can easily access.

Some people believe that true scientific peer review begins only on the date a paper is published. In that spirit, medical journals should have a mechanism for readers to submit comments, questions, or criticisms about published articles, and authors have a responsibility to respond appropriately and cooperate with any requests from the

journal for data or additional information should questions about the paper arise after publication (see Section III).

ICMJE believes investigators have a duty to maintain the primary data and analytic procedures underpinning the published results for at least 10 years. The ICMJE encourages the preservation of these data in a data repository to ensure their longer-term availability.

d. Integrity

Editorial decisions should be based on the relevance of a manuscript to the journal and on the manuscript's originality, quality, and contribution to evidence about important questions. Those decisions should not be influenced by commercial interests, personal relationships or agendas, or findings that are negative or that credibly challenge accepted wisdom. In addition, authors should submit for publication or otherwise make publicly available, and editors should not exclude from consideration for publication, studies with findings that are not statistically significant or that have inconclusive findings. Such studies may provide evidence that, combined with that from other studies through meta-analysis, might still help answer important questions, and a public record of such negative or inconclusive findings may prevent unwarranted replication of effort or otherwise be valuable for other researchers considering similar work.

Journals should clearly state their appeals process and should have a system for responding to appeals and complaints.

e. Journal Metrics

The journal impact factor is widely misused as a proxy for research and journal quality and as a measure of the importance of specific research projects or the merits of individual researchers, including their suitability for hiring, promotion, tenure, prizes, or research funding. ICMJE recommends that journals reduce the emphasis on impact factor as a single measure, but rather provide a range of article and journal metrics relevant to their readers and authors.

3. Peer Reviewers

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Reviewers therefore should keep manuscripts and the information they contain strictly confidential. Reviewers must not publicly discuss authors' work and must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy copies of manuscripts after submitting their reviews.

Reviewers are expected to respond promptly to requests to review and to submit reviews within the time agreed. Reviewers' comments should be constructive, honest, and polite.

Reviewers should declare their conflicts of interest and recuse themselves from the peer-review process if a conflict exists.

D. Journal Owners and Editorial Freedom

1. Journal Owners

Owners and editors of medical journals share a common purpose, but they have different responsibilities, and sometimes those differences lead to conflicts.

It is the responsibility of medical journal owners to appoint and dismiss editors. Owners should provide editors at the time of their appointment with a contract that clearly states their rights and duties, authority, the general terms of their appointment, and mechanisms for resolving conflict. The editor's performance may be assessed using mutually agreed-upon measures, including but not necessarily limited to readership, manuscript submissions and handling times, and various journal metrics.

Owners should only dismiss editors for substantial reasons, such as scientific misconduct, disagreement with the long-term editorial direction of the journal, inadequate performance by agreed-upon performance metrics, or inappropriate behavior that is incompatible with a position of trust.

Appointments and dismissals should be based on evaluations by a panel of independent experts, rather than by a small number of executives of the owning organization. This is especially necessary in the case of dismissals because of the high value society places on freedom of speech within science and because it is often the responsibility of editors to challenge the status quo in ways that may conflict with the interests of the journal's owners.

A medical journal should explicitly state its governance and relationship to a journal owner (e.g., a sponsoring society).

2. Editorial Freedom

The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom, which holds that editors-in-chief have full authority over the entire editorial content of their journal and the timing of publication of that content. Journal owners should not interfere in the evaluation, selection, scheduling, or editing of individual articles either directly or by creating an environment that strongly influences decisions. Editors should base editorial decisions on the validity of the work and its importance to the journal's readers, not on the commercial implications for the journal, and editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views conflict with the commercial goals of the publisher.

Editors-in-chief should also have the final say in decisions about which advertisements or sponsored content, including supplements, the journal will and will not carry, and they should have final say in use of the journal brand and in overall policy regarding commercial use of journal content.

Journals are encouraged to establish an independent editorial advisory board to help the editor establish and maintain editorial policy. Editors should seek to engage a broad and diverse array of authors, reviewers, editorial staff, editorial board members, and readers. To support editorial decisions and potentially controversial expressions of opinion, owners should ensure that appropriate insurance is obtained in the event of legal action against the editors, and should ensure that legal advice is available when necessary. If legal problems arise, the editor should inform their legal adviser and their owner and/or publisher as soon as possible. Editors should defend the confidentiality of authors and peer-reviewers (names and reviewer comments) in accordance with ICMJE policy (see Section II C.2.a). Editors should take all reasonable steps to check the facts in journal commentary, including that in news sections and social media postings, and should ensure that staff working for the journal adhere to best journalistic practices including contemporaneous note-taking and seeking a response from all parties when possible before publication. Such practices in support of truth and public interest may be particularly relevant in defense against legal allegations of libel.

To secure editorial freedom in practice, the editor should have direct access to the highest level of ownership, not to a delegated manager or administrative officer.

Editors and editors' organizations are obliged to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

E. Protection of Research Participants

All investigators should ensure that the planning conduct and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013 (www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). All authors should seek approval to conduct research from an independent local, regional, or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional, or national review body explicitly approved the doubtful aspects of the study. Approval by a responsible review body does not preclude editors from forming their own judgment whether the conduct of the research was appropriate.

Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to locale, and journals should establish their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are de-identified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

When reporting experiments on animals, authors should indicate whether institutional and national standards for the care and use of laboratory animals were followed. Further guidance on animal research ethics is available from the International Association of Veterinary Editors' Consensus Author Guidelines on Animal Ethics and Welfare (http://veteditors.org/ethicsconsensusguidelines.html).

III. Publishing and Editorial Issues Related to Publication in Medical Journals

A. Corrections, Retractions, Republications, and Version Control

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

If a correction is needed, journals should follow these minimum standards:

- The journal should publish a correction notice as soon as possible detailing changes from and citing the original publication; the correction should be on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing.
- The journal should also post a new article version with details of the changes from the original version and the date(s) on which the changes were made.
- The journal should archive all prior versions of the article. This archive can be either directly accessible to readers or can be made available to the reader on request.
- Previous electronic versions should prominently note that there are more recent versions of the article.
- The citation should be to the most recent version.

Pervasive errors can result from a coding problem or a miscalculation and may result in extensive inaccuracies throughout an article. If such errors do not change the direction or significance of the results, interpretations, and conclusions of the article, a correction should be published that follows the minimum standards noted above.

Errors serious enough to invalidate a paper's results and conclusions may require retraction. However, retraction with republication (also referred to as "replacement") can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then retraction with republication of the changed paper, with an explanation, allows full correction of the scientific literature. In such cases, it is helpful to show the extent of the changes in supplementary material or in an appendix, for complete transparency.

B. Scientific Misconduct, Expressions of Concern, and Retraction

Scientific misconduct in research and non-research publications includes but is not necessarily limited to data fabrication; data falsification, including deceptive manipulation of images; purposeful failure to disclose conflicts of interest; and plagiarism. Some people consider failure to publish the results of clinical trials and other human studies a form of scientific misconduct. While each of these practices is problematic, they are not equivalent. Each situation requires individual assessment by relevant stakeholders. When scientific misconduct is alleged, or concerns are otherwise raised about the conduct or integrity of work described in submitted or published papers, the editor should initiate appropriate procedures detailed by such committees as the Committee on Publication Ethics (COPE) (publicationethics.org/resources/flowcharts), consider informing the institutions and funders, and may choose to publish an expression of concern pending the outcomes of those procedures. If the procedures involve an investigation at the authors' institution, the editor should seek to discover the outcome of that investigation; notify readers of the outcome if appropriate; and if the investigation proves scientific misconduct, publish a retraction of the article. There may be circumstances in which no misconduct is proven, but an exchange of letters to the editor could be published to highlight matters of debate to readers.

Expressions of concern and retractions should not simply be a letter to the editor. Rather, they should be prominently labelled, appear on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing, and include in their heading the title of the original article. Online, the retraction and original article should be linked in both directions and the retracted article should be clearly labelled as retracted in all its forms (abstract, full text, PDF). Ideally, the authors of the retraction should be the same as those of the article, but if they are unwilling or unable the editor may under certain circumstances accept retractions by other responsible persons, or the editor may be the sole author of the retraction or expression of concern. The text of the retraction should explain why the article is being retracted and include a complete citation reference to that article. Retracted articles should remain in the public domain and be clearly labelled as retracted.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of other work published in their journals, or they may retract it. If this is not done, editors may choose to publish an announcement expressing concern that the validity of previously published work is uncertain.

The integrity of research may also be compromised by inappropriate methodology that could lead to retraction.

See COPE flowcharts for further guidance on retractions and expressions of concern. See Section IV.g.i. for guidance about avoiding referencing retracted articles.

C. Copyright

Journals should make clear the type of copyright under which work will be published, and if the journal retains copyright, should detail the journal's position on the transfer of copyright for all types of content, including audio, video, protocols, and data sets. Medical journals may ask authors to transfer copyright to the journal. Some journals require transfer of a publication license. Some journals do not require transfer of copyright and rely on such vehicles as Creative Commons licenses. The copyright status of articles in a given journal can vary: Some content cannot be copyrighted (e.g., articles written by employees of some governments in the course of their work). Editors may waive copyright on other content, and some content may be protected under other agreements.

D. Overlapping Publications

1. Duplicate Submission

Authors should not submit the same manuscript, in the same or different languages, simultaneously to more

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than one journal. The rationale for this standard is the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one journal, and the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review, edit the same manuscript, and publish the same article.

2. Duplicate and Prior Publication

Duplicate publication is publication of a paper that overlaps substantially with one already published, without clear, visible reference to the previous publication. Prior publication may include release of information in the public domain.

Readers of medical journals deserve to be able to trust that what they are reading is original unless there is a clear statement that the author and editor are intentionally republishing an article (which might be considered for historic or landmark papers, for example). The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic because it can result in inadvertent double-counting of data or inappropriate weighting of the results of a single study, which distorts the available evidence.

When authors submit a manuscript reporting work that has already been reported in large part in a published article or is contained in or closely related to another paper that has been submitted or accepted for publication elsewhere, the letter of submission should clearly say so and the authors should provide copies of the related material to help the editor decide how to handle the submission. See also Section IV.B.

This recommendation does not prevent a journal from considering a complete report that follows publication of a preliminary report, such as a letter to the editor, a preprint, or an abstract or poster displayed at a scientific meeting. It also does not prevent journals from considering a paper that has been presented at a scientific meeting but was not published in full, or that is being considered for publication in proceedings or similar format. Press reports of scheduled meetings are not usually regarded as breaches of this rule, but they may be if additional data tables or figures enrich such reports. Authors should also consider how dissemination of their findings outside of scientific presentations at meetings may diminish the priority journal editors assign to their work.

Authors who choose to post their work on a preprint server should choose one that clearly identifies preprints as not peer-reviewed work and includes statements of conflicts of interest. It is the author's responsibility to inform a journal if the work has been previously posted on a preprint server. In addition, it is the author's (and not the journal editors') responsibility to ensure that preprints are amended to point readers to subsequent versions, including the final published article.

In the event of a public health emergency (as defined by public health officials), information with immediate implications for public health should be disseminated without concern that this will preclude subsequent consideration for publication in a journal. We encourage editors to give priority to authors who have made crucial data publicly available (e.g., in a gene bank) without delay.

Sharing with public media, government agencies, or manufacturers the scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances; reportable diseases; or public health hazards, such as serious adverse effects of drugs, vaccines, other biological products, medical devices. This reporting, whether in print or online, should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance when possible.

The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the criteria noted in Section III.L. if results are limited to a brief (500 word) structured abstract or tables (to include participants enrolled, key outcomes, and adverse events). The ICMJE encourages authors to include a statement with the registration that indicates that the results have not yet been published in a peer-reviewed journal, and to update the results registry with the full journal citation when the results are published.

Editors of different journals may together decide to simultaneously or jointly publish an article if they believe that doing so would be in the best interest of public health. However, the National Library of Medicine (NLM) indexes all such simultaneously published joint publications separately, so editors should include a statement making the simultaneous publication clear to readers.

Authors who attempt duplicate publication without such notification should expect at least prompt rejection of the submitted manuscript. If the editor was not aware of the violations and the article has already been published, then the article might warrant retraction with or without the author's explanation or approval.

See COPE flowcharts for further guidance on handling duplicate publication.

3. Acceptable Secondary Publication

Secondary publication of material published in other journals or online may be justifiable and beneficial, especially when intended to disseminate important information to the widest possible audience (e.g., guidelines produced by government agencies and professional organizations in the same or a different language). Secondary publication

for various other reasons may also be justifiable provided the following conditions are met:

1. The authors have received approval from the editors of both journals (the editor concerned with secondary publication must have access to the primary version).
2. The priority of the primary publication is respected by a publication interval negotiated by both editors with the authors.
3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
4. The secondary version faithfully reflects the data and interpretations of the primary version.
5. The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the [journal title, with full reference]"—and the secondary version cites the primary reference.
6. The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the NLM does not consider translations to be "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

When the same journal simultaneously publishes an article in multiple languages, the MEDLINE citation will note the multiple languages (e.g., Angelo M. Journal networking in nursing: a challenge to be shared. Rev Esc Enferm USP. 2011 Dec 45[6]:1281-2,1279-80,1283-4. Article in English, Portuguese, and Spanish. No abstract available. PMID 22241182).

4. Manuscripts Based on the Same Database

If editors receive manuscripts from separate research groups or from the same group analyzing the same data set (e.g., from a public database, or systematic reviews or meta-analyses of the same evidence), the manuscripts should be considered independently because they may differ in their analytic methods, conclusions, or both. If the data interpretation and conclusions are similar, it may be reasonable although not mandatory for editors to give preference to the manuscript submitted first. Editors might consider publishing more than one manuscript that overlap in this way because different analytical approaches may be complementary and equally valid, but manuscripts based upon the same dataset should add substantially to each other to warrant consideration for publication as separate papers, with appropriate citation of previous publications from the same dataset to allow for transparency.

Secondary analyses of clinical trial data should cite any primary publication, clearly state that it contains secondary analyses/results, and use the same identifying trial registration number as the primary trial and unique, persistent dataset identifier.

Sometimes for large trials it is planned from the beginning to produce numerous separate publications regarding separate research questions but using the same original participant sample. In this case authors may use the original single trial registration number, if all the outcome parameters were defined in the original registration. If the authors registered several substudies as separate entries in, for example, clinicaltrials.gov, then the unique trial identifier should be given for the study in question, The main issue is transparency, so no matter what model is used it should be obvious for the reader.

E. Correspondence

Medical journals should provide readers with a mechanism for submitting comments, questions, or criticisms about published articles, usually but not necessarily always through a correspondence section or online forum. The authors of articles discussed in correspondence or an online forum have a responsibility to respond to substantial criticisms of their work using those same mechanisms and should be asked by editors to respond. Authors of correspondence should be asked to declare any competing or conflicting interests.

Correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to make available to readers unedited correspondence, for example, via an online commenting system. Such commenting is not indexed in Medline unless it is subsequently published on a numbered electronic or print page. However the journal handles correspondence, it should make known its practice. In all instances, editors must make an effort to screen discourteous, inaccurate, or libellous comments.

Responsible debate, critique, and disagreement are important features of science, and journal editors should encourage such discourse ideally within their own journals about the material they have published. Editors, however, have the prerogative to reject correspondence that is irrelevant, uninteresting, or lacking cogency, but they also have a responsibility to allow a range of opinions to be expressed and to promote debate.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to published material and for debate on a given topic.

F. Fees

Journals should be transparent about their types of revenue streams. Any fees or charges that are required for manuscript processing and/or publishing materials in the journal shall be clearly stated in a place that is easy for potential authors to find prior to submitting their manuscripts for review or explained to authors before they begin preparing their manuscript for submission (http://publica

tionethics.org/files/u7140/Principles_of_Transparency_and_Best_Practice_in_Scholarly_Publishing.pdf).

G. Supplements, Theme Issues, and Special Series

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and may be funded by sources other than the journal's publisher. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should adopt the following principles, which also apply to theme issues or special series that have external funding and/or guest editors:

1. The journal editor must be given and must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to select authors, peer reviewers, and content for the supplement. Editing by the funding organization should not be permitted.
2. The journal editor has the right to appoint one or more external editors of the supplement and must take responsibility for the work of those editors.
3. The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement with or without external review. These conditions should be made known to authors and any external editors of the supplement before beginning editorial work on it.
4. The source of the idea for the supplement, sources of funding for the supplement's research and publication, and products of the funding source related to content considered in the supplement should be clearly stated in the introductory material.
5. Advertising in supplements should follow the same policies as those of the primary journal.
6. Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.
7. Journal and supplement editors must not accept personal favors or direct remuneration from sponsors of supplements.
8. Secondary publication in supplements (republication of papers published elsewhere) should be clearly identified by the citation of the original paper and by the title.
9. The same principles of authorship and disclosure of potential conflicts of interest discussed elsewhere in this document should be applied to supplements.

H. Sponsorship or Partnership

Various entities may seek interactions with journals or editors in the form of sponsorships, partnerships, meetings, or other types of activities. To preserve editorial independence, these interactions should be governed by the same principles outlined above for Supplements, Theme Issues, and Special Series (Section III.G).

I. Electronic Publishing

Most medical journals are now published in electronic as well as print versions, and some are published only in electronic form. Principles of print and electronic publishing are identical, and the recommendations of this document apply equally to both. However, electronic publishing provides opportunities for versioning and raises issues about link stability and content preservation that are addressed here.

Recommendations for corrections and versioning are detailed in Section III.A.

Electronic publishing allows linking to sites and resources beyond journals over which journal editors have no editorial control. For this reason, and because links to external sites could be perceived as implying endorsement of those sites, journals should be cautious about external linking. When a journal does link to an external site, it should state that it does not endorse or take responsibility or liability for any content, advertising, products, or other materials on the linked sites, and does not take responsibility for the sites' availability.

Permanent preservation of journal articles on a journal's website, or in an independent archive or a credible repository, is essential for the historical record. Removing an article from a journal's website in its entirety is almost never justified as copies of the article may have been downloaded even if its online posting was brief. Such archives should be freely accessible or accessible to archive members. Deposition in multiple archives is encouraged. However, if necessary for legal reasons (e.g., libel action), the URL for the removed article must contain a detailed reason for the removal, and the article must be retained in the journal's internal archive.

Permanent preservation of a journal's total content is the responsibility of the journal publisher, who in the event of journal termination should be certain the journal files are transferred to a responsible third party who can make the content available.

Journal websites should post the date that nonarticle web pages, such as those listing journal staff, editorial board members, and instructions for authors, were last updated.

J. Advertising

Most medical journals carry advertising, which generates income for their publishers, but journals should not be dominated by advertisements, and advertising must not be allowed to influence editorial decisions.

Journals should have formal, explicit, written policies for advertising in both print and electronic versions. Best practice prohibits selling advertisements intended to be juxtaposed with editorial content on the same product. Advertisements should be clearly identifiable as advertisements. Editors should have full and final authority for approving print and online advertisements and for enforcing advertising policy.

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Journals should not carry advertisements for products proven to be seriously harmful to health. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other nondisplay advertising, except where required by law. Editors should consider all criticisms of advertisements for publication.

K. Journals and the Media

Journals' interactions with media should balance competing priorities. The general public has a legitimate interest in all journal content and is entitled to important information within a reasonable amount of time, and editors have a responsibility to facilitate that. However media reports of scientific research before it has been peer-reviewed and fully vetted may lead to dissemination of inaccurate or premature conclusions, and doctors in practice need to have research reports available in full detail before they can advise patients about the reports' conclusions.

An embargo system has been established in some countries and by some journals to assist this balance, and to prevent publication of stories in the general media before publication of the original research in the journal. For the media, the embargo creates a "level playing field," which most reporters and writers appreciate since it minimizes the pressure on them to publish stories before competitors when they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has potential to influence financial markets. The ICMJE acknowledges criticisms of embargo systems as being self-serving of journals' interests and an impediment to rapid dissemination of scientific information, but believe the benefits of the systems outweigh their harms.

The following principles apply equally to print and electronic publishing and may be useful to editors as they seek to establish policies on interactions with the media:

- Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication of the original research in the journal, in return for which the journal will cooperate with them in preparing accurate stories by issuing, for example, a press release.
- Editors need to keep in mind that an embargo system works on the honor system—no formal enforcement or policing mechanism exists. The decision of a significant number of media outlets or biomedical journals not to respect the embargo system would lead to its rapid dissolution.
- Notwithstanding authors' belief in their work, very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. When such exceptional circumstances occur, the appropriate authorities responsible for public health should decide whether to disseminate information to physicians and the media in advance and should be responsible for this decision. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors acknowledge the need for immediate release, they should waive their policies limiting prepublication publicity.
- Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters but should be discouraged from offering more detail about their study than was presented in the talk, or should consider how giving such detail might diminish the priority journal editors assign to their work (see Duplicate Publication).
- When an article is close to being published, editors or journal staff should help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the article, or referring reporters to appropriate experts. This assistance should be contingent on the media's cooperation in timing the release of a story to coincide with publication of the article.

L. Clinical Trials

i. Registration

The ICMJE's clinical trial registration policy is detailed in a series of editorials (see Updates and Editorials [www.icmje.org/news-and-editorials/] and FAQs [www.icmje.org/about-icmje/faqs/]).

Briefly, the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance [icmje.org/journals.html] should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

ICMJE uses the date trial registration materials were first submitted to a registry as the date of registration. When there is a substantial delay between the submission of registration materials and their posting at the trial registry, editors may inquire about the circumstances that led to the delay.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-

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related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.

The ICMJE accepts publicly accessible registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html) or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP. The ICMJE endorses these registries because they meet several criteria. They are accessible to the public at no charge, open to all prospective registrants, managed by a not-for-profit organization, have a mechanism to ensure the validity of the registration data, and are electronically searchable. An acceptable registry must include the minimum 21 item trial registration dataset (http://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf or www.who.int/ictrp/network/trds/en/index.html) at the time of registration and before enrollment of the first participant. The ICMJE considers inadequate trial registrations missing any of the 21 data fields, those that have fields that contain uninformative information, or registrations that are not made publicly accessible such as phase I trials submitted to the EU-CTR and trials of devices for which the information is placed in a "lock box." In order to comply with ICMJE policy, investigators registering trials of devices at ClinicalTrials.gov must "opt out" of the lock box by electing public posting prior to device approval. Although not a required item, the ICMJE encourages authors to include a statement that indicates that the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.

The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give ethics review boards considering approval of new studies a view of similar work and data relevant to the research they are considering. Retrospective registration, for example at the time of manuscript submission, meets none of these purposes. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE encourages registration of research with non-trial designs, but because the exposure or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

The ICMJE expects authors to ensure that they have met the requirements of their funding and regulatory agencies regarding aggregate clinical trial results reporting in clinical trial registries. It is the authors', and not the journal editors', responsibility to explain any discrepancies between results reported in registries and journal publications. The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the above criteria if results are limited to a brief (500 word) structured abstract or tables (to include trial participants enrolled, baseline characteristics, primary and secondary outcomes, and adverse events).

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

Editors may consider whether the circumstances involved in a failure to appropriately register a clinical trial were likely to have been intended to or resulted in biased reporting. Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed. The ICMJE emphasizes that such exceptions should be rare, and that authors failing to prospectively register a trial risk its inadmissibililty to our journals.

ii. Data Sharing

The ICMJE's data sharing statement policy is detailed in an editorial (see Updates and Editorials [www.icmje.org/update.html]).

1. As of 1 July 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement as described below.

2. Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

Data sharing statements must indicate the following: whether individual deidentified participant data (including data dictionaries) will be shared ("undecided" is not an

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Table. **Examples of Data Sharing Statements That Fulfill These ICMJE Requirements***

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Not available
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code	Study Protocol, Statistical Analysis Plan, Analytic Code	Study Protocol	Not available
When will data be available (start and end dates)?	Immediately following publication. No end date.	Beginning 3 months and ending 5 years following article publication.	Beginning 9 months and ending 36 months following article publication.	Not applicable
With whom?	Anyone who wishes to access the data.	Researchers who provide a methodologically sound proposal.	Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.	Not applicable
For what types of analyses?	Any purpose.	To achieve aims in the approved proposal.	For individual participant data meta-analysis.	Not applicable
By what mechanism will data be made available?	Data are available indefinitely at (*Link to be included*).	Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (*Link to be included*).	Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (*Link to be provided*).	Not applicable

* These examples are meant to illustrate a range of, but not all, data sharing options.

acceptable answer); what data in particular will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Illustrative examples of data sharing statements that would meet these requirements are provided in the **Table**.

Authors of secondary analyses using shared data must attest that their use was in accordance with the terms (if any) agreed to upon their receipt. They must also reference the source of the data using its unique, persistent identifier to provide appropriate credit to those who generated it and allow searching for the studies it has supported. Authors of secondary analyses must explain completely how theirs differ from previous analyses. In addition, those who generate and then share clinical trial data sets deserve substantial credit for their efforts. Those using data collected by others should seek collaboration with those who collected the data. As collaboration will not always be possible, practical, or desired, the efforts of those who generated the data must be recognized.

IV. Manuscript Preparation and Submission

A. Preparing a Manuscript for Submission to a Medical Journal

1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require

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different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT (www.consort-statement.org) for randomized trials, STROBE for observational studies (http://strobe-statement.org/), PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/), and STARD for studies of diagnostic accuracy (www.stard-statement.org/). Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network (www.equator-network.org/home/) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information. Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. 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.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of figures and tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because tables and figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Conflict of interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals (www.icmje.org/coi_disclosure.pdf), and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and impor-

tant aspects of the study or observations, note important limitations, and not overinterpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential (www.consort-statement.org/resources/downloads/extensions/consort-extension-for-abstracts-2008pdf/). Funding sources should be listed separately after the abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository and/or are being used in a secondary analysis, authors should state at the end of the abstract the unique, persistent data set identifier; repository name; and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved by an independent local, regional or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional or national review body explicitly approved the doubtful aspects of the study. See Section II.E.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance. Authors should use neutral, precise, and respectful language to describe study participants and avoid the use of terminology that might stigmatize participants.

ii. Technical Information

Specify the study's main and secondary objectives—usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid

relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (e.g., percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Published articles should reference the unique, persistent identifiers of the datasets employed.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications (www.ncbi.nlm.nih.gov/pubmed?term=retracted+publication+[pt]).

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify

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references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals: Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's Citing Medicine, 2nd edition (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For radiological and other clinical and diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Before-and-after images should be taken with the same intensity, direction, and color of light. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

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j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

B. Sending the Manuscript to the Journal

Manuscripts should be accompanied by a cover letter or a completed journal submission form, which should include the following information:

A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor address the situation. See also Section III.D.2.

A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form. See also Section II.B.

A statement on authorship. Journals that do not use contribution declarations for all authors may require that the submission letter includes a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work if that information is not provided in another form See also Section II.A.

Contact information for the author responsible for communicating with other authors about revisions and final approval of the proofs, if that information is not included in the manuscript itself.

The letter or form should inform editors if concerns have been raised (e.g., via institutional and/or regulatory bodies) regarding the conduct of the research or if corrective action has been recommended. The letter or form should give any additional information that may be helpful to the editor, such as the type or format of article in the particular journal that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Editors encourage authors to submit these previous communications. Doing so may expedite the review process and encourages transparency and sharing of expertise.

Many journals provide a presubmission checklist to help the author ensure that all the components of the submission have been included. Some journals also require that authors complete checklists for reports of certain study types (e.g., the CONSORT checklist for reports of randomized controlled trials). Authors should look to see if the journal uses such checklists, and send them with the manuscript if they are requested.

The manuscript must be accompanied by permission to reproduce previously published material, use previously published illustrations, report information about identifiable persons, or to acknowledge people for their contributions.

rich4/zai-aim/zai-aim/zai44418/zai0001d18a | murkarv | S=96 | 11/29/18 | 8:52 | Art: