Minor dissertation as Master of Medicine (MMed) in Urology

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Dissertation title:

Is The Learning Curve In Robotic Assisted Laparoscopic Radical Prostatectomies (RALP) in South Africa Comparable to International Standards?

DECLARATION

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Chapter 1: Introduction and Literature review

Is The Learning Curve In Robotic Assisted Laparoscopic Radical Prostatectomies (RALP) in South Africa Comparable to International Standards?

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i) Introduction

Prostate cancer (PCa) is the second most common cancer in men, and the sixth leading cause of cancer death among men worldwide (1). Radical Prostatectomy (RP) is widely considered a gold standard treatment for clinically significant localized PCa in men considered eligible for radical treatment. Radical prostatectomy can be offered as open, laparoscopic, or robot-assisted procedure depending on surgeon experience and institutional availability of equipment.

Modern urological practice has seen the rise of robotic assisted surgeries, robotic assisted laparoscopic radical prostatectomy (RALP) being at the forefront. There has been a rapid increase in the number of American and European centers performing RALP over the last decade. The use of robotics in surgery in South Africa is in its relative infancy, with only six robot systems operating in the entire country at the time of writing this article.

The benefits of having available to the surgeon a comfortable seated position, magnified binocular 3D visualization and number of ergonomic, highly articulated and non-fatigable robotic arms within the tight confines of the boney pelvis seem obvious. Although this new approach appears to offer many benefits to patients, surgeons and institutions alike, some remain hesitant to adopt it for fear of a difficult learning curve that, while undertaken, may compromise functional and oncologic outcomes. As such there has been observed a growing interest over recent years in analyzing and understanding the learning process surrounding RALP.

The general definition of a learning curve is the period during which a surgeon finds the procedure more technically challenging; takes longer to perform; a higher rate of complications is observed; and there is overall lower efficacy because of inexperience. With repetition one typically sees an improvement in these areas with obvious benefit to patients, surgeons, institutions and funders alike.

The aim of the study is to demonstrate a progression in the learning curve of two South Africa based urologists, as each embarks on their first ever series of RALP cases between September 2014 to July 2019. Given there exists no widely accepted definition nor measure of a learning curve, as a surrogate, we seek to assess for improvements in key parameters as each surgeon gains experience with the procedure. An audit of these key parameters for each surgeon's first uninterrupted series of RALP's has been undertaken. We also compare our results to international series with a similar study design, to assess if local South African learning curves are similar to these.

The chosen parameters have been selected to be in line with those already defined in already published international literature, allowing for better comparisons to be made (2–20).

Pre-operative data collected will be required for risk stratification grouping of patients according to the D'Amico Risk group classification. The pre-operative data collected includes:

[A] mean age at time of surgery,
[B] PSA value at diagnosis,
[C] clinical digital rectal findings, and
[D] biopsy Gleason score (ISUP grading)

Post-operative data included the following:

[1] operating/console time, excluding setup/docking time (min),
[2] estimated blood loss (ml),
[3] need for intraoperative blood transfusion (yes/no),
[4] conversion to open surgery (yes/no),
[5] length of post-operative hospital stay (days),
[6] number of patients with positive surgical margins (positive/negative),
[7] percentage of patients in each cohort dry (i.e., not incontinent) at 2/3 and 6 months (%). Incontinence was a subjective questioning of the patient about being dry.
[8] percentage of patients in each cohort potent (i.e., not suffering from erectile dysfunction) at 2/3 and 6 months (%). Potency was assessed using the International Index of Erectile Function (IIEF-5) score.
[9] histological (i.e., Gleason scope or ISUP grading), and
[10] pathological (i.e. TNM staging) data.

Although available literature reports on similar outcomes in international series, to our knowledge there have been no published analysis of South African data. We postulate that in a south African setting we would see similar improvements in key parameters and outcomes when compared to international cohorts.

ii) Literature review

Pubmed and Google searches were done looking for learning curve of robotic assisted laparoscopic radical prostatectomy. In total **seventeen journal articles related to the learning curve of robotic assisted laparoscopic radical prostatectomy (RALP)** 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) Developing a Robotic Prostatectomy Service and a Robotic Fellowship Programme – Defining the Learning Curve

Current Urology 2013; 7: 136–144

Nikhil Vasdeva, Conrad Bishopa, Atoine Kass-Iliyya, Sami Hamid, Thomas A. McNicholas, Venkat Prasad, Gowrie Mohan-S, Timothy Lane, Gregory Boustead, and James M. Adshead.

Department of Urology and Anaesthetics, Hertfordshire and South Bedfordshire Urological Cancer Centre, Lister Hospital, Stevenage, UK

Researchers at a urology oncology centre in the UK retrospectively assessed the learning curve of the 3 surgeons with regard to peri-operative outcomes and oncological results as they underwent their learning curve. This was conducted in an institution recognized by the Royal College of Surgeons of England/British Association of Urological Surgeons as the first robotic fellowship training programme in the UK. All 3 surgeons had extensive previous experience in laparoscopic, open and perineal radical prostatectomies.

300 consecutive patients who underwent robotic radical prostatectomy (RRP) between Nov 2008 – Aug 2012 were analysed. The total number of patients were broken down into three equal groups labelled: Group-1 [1–100]; Group-2 [101–200]; and Group-3 [201–300]. Specific parameters and outcomes were compared across the 3 groups to assess the impact of the learning curve for the procedure.

Assessed parameters and outcomes similar to our study pre-operative data collected included: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay (LOS); pathological data (i.e. histology and TNM stage); positive surgical margin (PSM) status; and continence and potency status post-op

Assessed parameters and outcomes not included in our study were: ASA-score; pre-operative co-morbidities; previous abdominal surgery; duration of catheterization; and complications according to the Clavien-Dindo system.

Age, ASA score, pre-operative co-morbidities and indications for laparoscopic radical prostatectomy were comparable for all three patient groups.

The mean console time for the whole cohort was 224 minutes (range 95–522 min). The mean console time for Groups 1 to 3 was (217 ± 72.6min); (185 ± 51.7min); and (132 ± 38.7min) respectively ($p < 0.001$).

The requirement for intra-operative blood transfusion was 2.3%. There were no conversions to open surgery reported in the cohort.

The mean length of post-op hospital stay (LOS) for the entire cohort was 2.3 days (range 1–12 days). Patients in Group-3 (1.86 ± 1 days) had a significantly shorter stay than in Group-1 (2.58 ± 1.8) ($p = 0.001$). The mean duration of catheterisation improved with each successive Group 1 to 3: (11.2 ± 2.8days); (9.1 ± 3.5days) and (7.9 ± 2.9days) respectively ($p = 0.001$).

In the entire cohort of 300 patients the overall positive surgical margin (PSM) rate was 26.7%. The incidence sub pT2 tumours was 71.6%, for pT3 tumours 26.6% and for pT4 tumours 1.6% (although only 4 were pT4). PSM rates showed improvements among all three surgeons as they progressed through their series. The incidence of PSM in Groups 1 to 3 was: 22%, 32%, and 25% respectively ($p= 0.02$). Of importance is that there were greater numbers of pT3 tumours in Group-3 than in Groups-1 and Group-2. Higher rates of PSM's were

experienced among stage pT3 and pT4 ($p < 0.01$), as well as and serum PSA levels > 10 mg/dl at diagnosis ($p = 0.044$).

The authors concluded that RRP is a safe procedure with low morbidity. As surgeons progress through the learning curve peri-operative parameters and oncological outcomes improve. With appropriate support, training and mentorship RRP can be taught to other surgeons and fellows in a structured mentored modular approach while continuing to improve outcomes for patients. Using a carefully structured mentored approach, RRP can be safely introduced as a new procedure without compromising patient outcomes.

This study is applicable to ours in that it measures similar parameters and outcomes as there is a progression of the three surgeons through their learning curve. Of note is that most of the included outcomes are similar to our own and therefore provide a basis for comparison to our study. The outcomes assessed in this study that would have been beneficial in our own are: previous abdominal surgery; duration of catheterization; and complications according to the Clavien-Dindo system. The fact that the training of the three surgeons was done within a accredited robotic fellowship program would likely suggest that this studies results would provide a good benchmark with which to compare our own.

2) Learning Curve of Robotic Radical Prostatectomy

European Medical Journal Urology, Vol 3, Iss 3, Pp 50-55 (2015)

Muhammed Ersagun Arslan, Abdullah Erdem Canda, Ali Fuat Atmaca, Mevlana Derya Balbay, Ziya Akbulut, Serkan Altinova, and Ahmet Tunc Ozdemir.

Department of Urology, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

Researchers at an academic hospital in Turkey retrospectively assessed a total of 391 patients who underwent a robotic-assisted laparoscopic radical prostatectomy (RARP) in their institution between Feb 2009 - April 2013 among 6 surgeons. The patients were divided into six groups according to the surgeon: group-1 (n=72), Group-2 (n=110), group-3 (n=103), group-4 (n=38), group-5 (n=36), group-6 (n=32). Surgeons 1, 2, and 3 performed the highest volume of procedures and their cases were also examined as three consecutive series in order to evaluate improvement over time

Assessed parameters and outcomes similar to our study pre-operative data collected included: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; biochemical recurrence status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: BMI; ASA score; IPSS score; anastomosis time; and complications.

The three consecutive series of the surgeons with the highest volume of cases (Surgeon-1, -2, and -3) were analysed with regard to operating time (OT), estimated blood loss (EBL), requirement for intra-op blood transfusion, and positive surgical margin (PSM) rate.

In the three series of Surgeon-1, OT was shown to decrease significantly between each consecutive series ($p<0.001$). For Surgeon-2, OT was revealed to decreased significantly between the first and second series, although not between the second and third series ($p<0.001$). For Surgeon-3, OT decreased significantly between the second and third series.

EBL decreased significantly in each consecutive series of Surgeon-3 ($p<0.001$), whereas EBL in the consecutive series of Surgeons-1 and -2 showed a trend towards decreasing in the second and third series when compared with the first series, although this failed to reach statistical significance ($p>0.05$). The blood transfusion rate was significantly higher in Surgeons-1's first series compared with his second and third series ($p=0.015$).

Overall, PSM rates did not change significantly in any of the three surgeons' series, although the rate in Surgeon 2's third series was significantly higher than in the second series with regard to pT3 stage tumours

The median International Index of Erectile Function (IIEF) scores of Surgeon-1's group at 12 months were 13 (range: 6-26) for the first series, 6 (range: 6-24) for the second series, and 21 (range: 6-25) for the third series, which showed a significant improvement in the third series ($p<0.001$). The median IIEF scores of Surgeon-2's group at 12 months were 6 (range: 6-26) for the first series, 18 (range: 6-26) for the second series, and 18 (range: 6-28) for the third series, which showed a significant improvement in both the second and third series ($p=0.01$). The median IIEF scores of Surgeon 3's group at 12 months were 19 (range: 6-26) for the first series, 16 (range: 6-25) for the second series, and 20 (range: 6-28) for the third series, which showed no statistically significant difference between series ($p>0.05$).

The continence rates for Surgeon-1's group at 12 months were 95.8%, 83.3%, and 100% for the first, second, and third series, respectively. The continence rates for Surgeon-2's group at 12 months were 100%, 97.3%, and 100% for the first, second, and third series, respectively. The continence rates of Surgeon-3's group at 12 months were 91.4%, 100%, and 97% for the first, second, and third series, respectively. The 12-month continence rate of Surgeon-1's group was significantly lower in the second series than in the first and third series ($p=0.017$), but there was no significant difference in the series of Surgeon-1 and Surgeon - ($p>0.05$).

The overall complication rate was 11.7% and 34% of these complications were major ones. The overall blood transfusion rate was 2%. The overall PSM rate was 20.4% (9.3% for pT2 tumours and 44% for pT3 tumours). The overall rate of BCR was 9.4%.

In summary, when assessing the 3 consecutive series of the three highest-volume surgeons they found that, over time, for Surgeon-1: operation time (OT) decreased significantly ($p<0.001$), blood transfusion rate decreased significantly ($p=0.015$), estimated blood loss (EBL) decreased ($p>0.05$), and median IIEF score at 12 months improved significantly ($p<0.001$). For Surgeon-2; OT decreased significantly ($p<0.001$), EBL decreased ($p>0.05$), and median IIEF score at 12 months improved significantly ($p=0.01$). For Surgeon-3: OT decreased significantly ($p<0.001$), EBL decreased significantly ($p<0.001$), and PSM rate decreased and median IIEF scores at 12 months improved ($p>0.05$ for both).

The authors concluded that there were significant improvements in OT, EBL, and blood transfusion rates with increasing surgeon experience. There was not a significant change in PSM rates. The OT, EBL, blood transfusion rates, overall complication rates, PSM rates, BCR rates, continence, and potency rates were all similar to previously published studies of RARP. Therefore, RARP can be performed relatively safely even in the learning curve period and the outcomes improve with experience

This study is applicable to ours in that it measures similar outcomes as there is a progression of the three surgeons through their learning curve. Of note is that most of the included outcomes are similar to our own and therefore provide a basis for comparison to our study. Outcomes assessed in this study that would have benefitted our own include BMI and Anastomosis time, as these may provide some insight into how challenging the surgery may be and increasing competence of the surgeon respectively. Complications seem a common theme among these studies that was not fully assessed in our patient cohorts and would likely have been very useful and an outcome to assess progression during the learning curve.

3) Robotic Radical Prostatectomy in the Community Setting - The Learning Curve and Beyond: Initial 200 Cases.

Journal of Urology, Vol. 174, 269–272, July 2005

Patel VR, Tully AS, Holmes R, and Lindsay J.

From the Urology Centres of Alabama, Birmingham, Alabama

Researchers in the USA looked at 200 patients who underwent RALP during a 18month period. This article refers to Dr VR. Patel's first ever analysis of single surgeon and singe centre experience. The 200 patients in the cohort were conveniently divided and then analysed in consecutive groups of 50 cases. Patients were followed up for a mean of 9.7 months.

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative

hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: drop in patient haematocrit; catheter time; and complications.

The operative time (OT) was defined as the time taken from skin incision to fascial closure (the time that the surgeon was present). The mean overall OT was reported in this study to be 141min, while the mean operative time for the consecutive four groups of 50 cases was reported as: 202min, 153.1min, 112.9min; and 106.4min respectively. The mean overall EBL was reported as 75.1ml, while the mean EBL for the consecutive four groups of 50 cases was reported as: 151.2ml, 64.4ml, 34.1ml; and 48.3ml respectively. The mean difference in pre-operative vs post-operative hematocrit was reported as 3 points (range -2 to 15)There were no transfusions during this series of RALP's

The mean duration of post-operative catheterization was 7.9days (range 5-21days). The discharge rate on day one post-surgery was given as 95%.

The PSM rate (presence of cancer cells at the inked margin) was 10.5% for the whole series while among T2, T3 and T4a tumours the PSM rate was reported as 5.7%, 26.2% and 33% respectively. When pts were looked at as the first 100 cases vs the second 100 cases the PSM rate was 13% vs 8%.

Continence at 1-, 3-, 6-, 9- and 12-months was reported in the study as: 47%, 78%, 89%, 92% and 98%, respectively.

The authors concluded that in their initial experience of 200 RALP's, the learning curve was approximately 20-25 cases and that their feeling was that RALP could be safely and effectively into integrated into the management of localized prostate cancer with minimal patient morbidity, and good oncological and functional outcomes.

This study is applicable to ours in that Dr Patel would later in his career go on to become one of the eminent robotic surgeons in modern times, and he has become known for his good oncological and functional outcomes with regards to RALP. As his cohort was broken down into consecutive groups of 50 for his first ever series of 200 cases, this study can provide a valuable benchmark with which to compare our study. It is also the study where Dr Patel is famously quoted as saying that the initial learning curve is 20-25cases.

4) Robotic radical prostatectomy: outcomes of 500 cases

British Journal of Urology International. 2007 May; 99(5):1109-12.

Vipul R. Patel, Rahul Thaly and Ketul Shah.
Centre for Robotic and Computer Assisted Surgery, Division of Urology, Ohio State University, Columbus, OH, USA

Researchers at a centre of excellence report on the outcomes of 500 who underwent RALP over a 30-month period. This article refers to Dr VR. Patel's single surgeon and singe centre experience.

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: quality-of-life questionnaires; BMI; catheter time; and complications.

The operative time (OT) was defined as the time taken from skin incision to fascial closure (the time that the surgeon was present). The mean OT was reported in this study to be 130min (range 51–330 min), while the mean operative time for the 50 cases was 202 min, and the mean operative time for patients 400-500 was

<100 min. The mean EBL was reported as 50ml (range 10–300ml) and was noted to decrease as the surgeon gained experience. There were no transfusions during RALP, and the rate post-surgery was 0.4%.

The mean duration of post-operative catheterization was 6.9days (range 5-21days). The discharge rate on day one post-surgery was given as 97%.

The PSM rate was 9.4% for the whole series while among T2, T3a, pT3b and T4 tumours the PSM rate was reported as 2.5%, 23%, 46%, and 53% respectively. The PSM rate for patients 1–100 was 13%; patients 101–200 was 8%; patients 201–300 was 13%; patients 301–400 was 5%; and patients 401–500 was 8%. At a mean follow-up of 9.7 months, the overall biochemical recurrence free survival was 95%, using a cut off PSA level of < 0.1 ng/ml.

27% of patients were reported as immediately continent (no significant leak after catheter removal), and the completely continent rate at 3 and 6 months follow up was reported as 89% and 95% respectively. At 1 year follow up 78% of patients were reported as being potent (+/- requirement of oral medications), while 15% were unable sustain erections capable of penetration, and 7% were using inter-cavernosal injection therapy to achieve a satisfactory erections.

The authors concluded that their initial experience with the procedure showed promising short-term outcomes and that RALP was both safe and feasible to introduce into the management of localized prostate cancer. They also stated that while the initial learning curve was short, additional training was needed when level of complexity of the cases increased. Patients with a greater BMI (>35); a history of previous TURP, and prostates weighing >100 g provided for challenging cases.

This study is applicable to ours in that Dr Patel and his centre of excellence is regarded very highly in terms of functional and oncological outcomes for patients undergoing RALP for adenocarcinoma of the prostate. As his cohort was broken down into consecutive groups of 100 for the PSM rate and to some extent the operating time, the results provides insight into Dr Patel's first ever series of RALP patients and provides a valuable benchmark with which to compare our study.

5) Robot-Assisted Laparoscopic Radical Prostatectomy: Perioperative Outcomes of 1500 Cases

JOURNAL OF ENDOUROLOGY, Volume 22, Number 10, October 2008

Vipul R. Patel, Kenneth J. Palmer, Geoff Coughlin, and Srinivas Samavedi.
Centre for Robotic and Computer Assisted Surgery, Division of Urology, Ohio State University, Columbus, OH, USA

Again, researchers at this centre of excellence report on the outcomes of now 1500 consecutive patients who underwent RALP for adenocarcinoma of the prostate in their institution. Again, this article refers to Dr VR. Patel's single surgeon and singe centre experience.

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: BMI; catheter time; prostate size; and complications.

Mean operative time (OT) was 105min (range 55–300min). Mean estimated blood loss (EBL) was reported as 111ml (range 50–500ml) and there was no requirement for intraoperative transfusion. No patients required conversion to open surgery, although they report one patient requiring conversion to standard laparoscopy after malfunction of the da Vinci system. Two figures (Fig.2 and Fig.3) are included in the article that show a downward trend in both OT's in consecutive groupings of 300 patients. The author notes that OT's and EBL tend to decrease with increasing experience of both the surgeon his team

97% of patients were discharged home on day one post-operation. The mean duration of catheterization was 6.3days (range 4–28days).

The overall PSM rate was reported as 9.3% for the whole series of 1500 patients. The PSM rate for pT2, pT3 and pT4 disease was 4%, 33% and 40% respectively. Of note is that this is that there appears to be some improvement in the PSM rates compared to his first series of 500pts [3] where the rates for pT2, pT3 and pT4 disease was 2.5%, 23%, and 53% respectively. Included in this article were lengthy discussion regarding the decreased complication rates with increased surgical experience, although

The authors stated that the subjective initial learning curve to develop basic competence with the robotic system was 25 cases. Basic competence was defined as the point at which the surgeon felt comfortable with technology, procedure and OT times were <4hrs. There are a number of comparisons made to other contemporary RALP series to which Dr Patel's series is compared. These comparisons were deemed favourable by the author.

This study is applicable to ours in that a comparison can be made to his initial series of 500 patients (mentioned above) to be able to demonstrate that variables such as OT's, EBL and PSM rate all improve further with increasing experience.

6) Early Complication Rates in a Single-Surgeon Series of 2500 Robotic-Assisted Radical Prostatectomies: Report Applying a Standardized Grading System

European Urology. 2010 Jun;57(6):945-52.

Coelho RF, Palmer KJ, Rocco B, Moniz RR, Chauhan S, Orvieto MA, Coughlin G, Patel VR.
Global Robotics Institute, Florida Hospital Celebration Health, Celebration, Florida 34747, USA.

Researchers in the US retrospectively assess the learning curve and peri-operative outcomes of 2500 consecutive robot-assisted laparoscopic radical prostatectomy (RALP) performed by a single surgeon in their centre between August 2003 and February 2009. OF note this single surgeon was once again Dr VP Patel. The cases were divided into groups of 300 to make eight groups in total. The mean values of the parameters/outcomes in each group were then assessed. A median follow-up time of 25 months was reported

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: BMI; ASA-score; catheter time; and complications.

For the entire cohort of 2500 cases, the median operative time (OT) was 90 min (rage: 75–100 min); the median estimated blood loss (EBL) was 100 ml (rage: 100–150 ml); median catheterization time was 5days (range: 4–6 days); conversion to open surgery was reported in 0.08% of cases; median length of hospital stay was 1 day; and 95% of patients were discharged after one day.

The overall positive surgical margin (PSM) rate was reported in this study at 10.6% while for pT2 and pT3 disease it was reported as 5% and 27.5% respectively.

140 complications were observed in 127 patients in the whole series and the trend was reduced complications with increased surgeon experience. The authors also point out a lack of consistency in reporting complications among the published literature of the time. The Clavien-Dindo Classification was used in this study to report the complications.

The authors conclude that complication rates, along with the other parameters reported, were shown to decrease with increase surgeon experience. They recommended that a standardized classification system to analyse surgical complications would be needed in future studies so as to compare complication rates.

This study is applicable to ours in that that it provides an update to Dr Patel's series to now include 2500 cases. The study also reflects on how complications can also decrease substantially with increase operator experience.

7) Critical review of 'pentafecta' outcomes after robot-assisted laparoscopic prostatectomy in high-volume centres

British Journal of Urology International, Volume 108, Issue 6, Sept 2011

Patel VR, Abdul-Muhsin HM, Schatloff O, Coelho RF, Valero R, Ko YH, Sivaraman A, Palmer KJ, Chauhan S.

Global Robotics Institute, Florida Hospital Celebration Health and Department of Urology, University of Central Florida College of Medicine, Celebration, FL, USA,
Albert Einstein Jewish Hospital, Sao Paulo, Brazil,
Department of Urology, University of Caracas, Venezuela , and
Department of Urology, Korea University, South Korea

Researchers in the USA did a review of the literature after performing a Medline search for articles related to the peri-operative outcomes related to robot-assisted laparoscopic prostatectomy (RALP) in high-volume centres. A large number of articles (>20) were individually assessed, and their data reported. Of interest to us is an updated report from Dr VP. Patel's series that now includes 4000 patients performed by a single surgeon and in a centre of excellence. Also of interest is that the weighted means of reported outcomes of 17-19 studies were reported which allows for an overall picture of reported results. Both these have been reported in our study. The pe

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: biochemical recurrence rate and complications.

Although this review looks at multiple studies, we have chosen to focus on Dr Patel's series of 4000 cases as well as the weighted means of the 17-19 studies looked at.

For Dr Patel's series (PS) we see that after 4000 cases the OT we see the following mean values:

Operative time (OT): 75min
Estimated blood loss: 100ml
Length of hospital stay (LOS): 1 day
Overall positive surgical margin (PSM) rate: 10.8%
pT2 and pT3 PSM rates: 5.8% and 26.1%

For weighted means of the 17-19 studies:

Operative time (OT): 174min
Estimated blood loss: 185.8ml
Length of hospital stay (LOS): 1.58 days
Overall positive surgical margin (PSM) rate: 16.2%
pT2 and pT3 PSM rates: 7.7% and 29%

The authors concluded that RALP is a safe and effective procedure for localized prostate cancer.

This study is applicable to ours in that that it provides an update to Dr Patel's series to now include 4000 cases. We see that, besides the operative time decreasing substantially, the other parameters do not show such a dramatic decrease. Additionally, the summary of outcomes, including the weighted means of all the studies evaluated, are a useful comparison to our own outcomes.

8) The first 1000 cases of laparoscopic radical prostatectomy in the UK: evidence of multiple 'learning curves'

British Journal of Urology International, Volume 103, Issue 9, May 2009

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Researchers at in the UK report the initial experience of one surgeon's first ever series of 1000 patients between March 2000 and December 2007. Of note is that the surgeon involved had contemporary experience of >1000 patients in both open radical prostatectomy (ORP) and laparoscopic radical prostatectomy (LRP).

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: use of nerve sparing surgery; operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: BMI; previous abdominal surgery; catheter time; and complications.

The median operative time (OT) was 177min (range 78–600min). There was only one conversion to open surgery in the entire series. The median estimated blood loss (EBL) was 200ml (range 10–1300ml) and 4 (0.4%) patients requires intra-operative blood transfusion. Both of these parameters were assessed in consecutive groups of 50 patients with clear downward sloping of the trendline despite a number of peaks and troughs similar to our cohorts.

The median length of post-operative hospital stay (LOS) was 3 days (range 3–28 days). The median catheterization time was 10 days (range 0.8–120 days). Again, both parameters were assessed in consecutive groups of 50 patients with clear downward sloping of the trendline despite wide variations in the reported medians.

The positive surgical margin (PSM) rate overall was 13.3%, while the PSM rate for pT1, pT2 and pT3 disease was 5.2%, 18.5% and 56.3% respectively. When the PSM rate was assessed according to D'Amico risk groups the study reported rates of 9.1%, 20.3%, and 36.8% for low, intermediate and high risk respectively. At a mean follow-up of 27.7months the biochemical recurrence free survival was reported as 96.1%.

Completely continent (i.e. no pads used) rates increased from 10% immediately after post-op catheter removal to 94.9% at a mean follow-up of 27.7months. A similar trend was seen when potency rate was assessed at 9% immediately post op, to 65.6% at a mean follow up of 27.7 months. Potency was reported being much higher in those patients < 65years of age when compared to older men in the series.

The authors concluded that the learning curve for both OT and EBL plateaued within the first 100-150 cases, while that for both complication and continence rates took longer at 150-200 cases to reach a plateau. The parameter that took the longest to plateau was potency at 700 cases. The authors suggest that structured training programs and a high volume of cases would likely reveal better outcomes. Even then, a large RALP throughput will likely to be required in order to maintain competency so that clinical outcomes remain at the highest level.

This study is applicable to ours in that the single surgeon's whole series is broken into consecutive groups of 50 cases so as to demonstrate the learning curve as it pertains to many of the outcomes we measured in our own study. The author also introduces the concept of an outcome reaching a plateau to suggest that a learning curve has been overcome. It is also the first study we came across that looks at PSM rates as they pertain to

the D'amico risk groups and thus provides a comparison for our own results, albeit with a much higher case volume.

9) First 500 cases of robotic-assisted laparoscopic radical prostatectomy from a single UK centre: learning curves of two surgeons

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Researchers at in the UK report the initial experience of two surgeon's first ever series of 500 patients between 2005 and 2009. The learning curves of the two surgeons were assessed as it pertains to the outcomes listed below. Additionally, the outcomes of the first 100 and last 100 patients were compared to determine the effect of surgeon experience. Of note is that Surgeon-1 had mostly extensive experience in open prostatectomy, while Surgeon-2 had extensive laparoscopic experience; previous cadaveric laparoscopic prostatectomy training; and wet laboratory training with the robot. For both surgeons a structured mentoring programme was used for the implementation of robotic assisted laparoscopic radical prostatectomy (RALP) in their institution.

Assessed parameters and outcomes similar to our study included pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score; and D'amico risk groups. Post-operative data included: use of nerve sparing surgery; operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: prostate volume and weight and complications.

Surgeon-1's series included 330 cases while Surgeon-2's series included 170 cases. Each surgeon had their cohort divided into consecutive groups of 50 patients to be able to assess the impact on the above parameters as each surgeon gained experience in RALP. For Surgeon-1 there were seven consecutive groups labelled: [1-50]; [51-100]; [101-150]; [151-200]; [201-250]; [251-300]; and [301-330]. For Surgeon-2 there were four consecutive groups labelled: [1-50]; [51-100]; [101-150]; and [151-170]. It was noted in a breakdown of case complexity that there was a trend of cases to increase in risk for both surgeons, with more high-risk cases undergoing surgery from approximately case number 75 onward for each surgeon. This trend was also seen in our series.

Median overall operating time (OT), excluding robotic setup time, was 170min (range 63–420min) for both surgeons combined (n = 500). For Surgeon -1's consecutive seven groups the median OT's were reported as: 185min; 180min; 149min; 150min; 163min; 135min; and 131min respectively. For Surgeon-2's consecutive four groups the median OT's were reported as: 237min; 201min; 180min; and 177min respectively. The general trend for both surgeons was towards significantly shorter operating times with increasing experience (P<0.001). See FIG 2. in article for a graphic representation of median OT's.

Median overall estimated blood loss (EBL) was 200ml (range 20-3000ml) for both surgeons combined (n = 500). For Surgeon -1's consecutive seven groups the median OT's were reported as:288ml; 225ml; 150ml; 100ml; 250ml; 150ml; and 100ml respectively. For Surgeon-2's consecutive four groups the median OT's were reported as: 250ml; 250ml; 200ml; and 225ml respectively. Again, the general trend for both surgeons was towards significantly lower EBL with increasing experience (P = 0.029). See FIG 3. in article for a graphic representation of median EBL's.

The overall positive surgical margin (PSM) rate was 24% (for both surgeons combined (n = 500) while the PSM rate was 16.1% for pT2 disease and 85.4% for pT3 disease. For Surgeon-1's consecutive seven groups the SPM rates were reported as:12%; 32%; 26%; 36%; 14%; 20%; and 20% respectively. For Surgeon-2's consecutive four groups the median OT's were reported as: 20%; 36%; 22%; and 25% respectively.

With one-year follow-up completely continent rate (i.e. no pads used), was 91.3% for the entire series. For the last 100 patients in the entire series the complexly continent rate was 83%, which was significantly better than reported 59% for the first 100 patients (*P*=0.007). At 48 months of follow-up, 75% of men who were potent prior to surgery and who underwent bilateral nerve sparing RALP continued to be potent (defined as an IIEF-5 score> 16). In the total series (n=500) 69.2% of men had bilateral nerve-sparing surgery, while 19% and 11.8% had unilateral or no nerve-sparing surgery respectively.

The authors conclude that with regards to the continued improvement in both OT's and EBL by the end of each surgeon's series, it is was possible to define a particular case number at which the learning curve has plateaued. They go on to suggest that with bigger case numbers we would likely see this plateau and thus be able to define a number. They point out that in a large multicentre retrospective study of almost 5000 patients who underwent laparoscopic radical prostatectomy there was a lower risk of recurrence with increasing surgeon experience, and this continued up to 750 cases [1]. This study highlights the importance of interpreting short-term learning curves with caution.

This study is applicable to ours in that is the article that is most similar to our own in terms of two surgeons being analysed for their learning curves, and both their series being broken down into consecutive groups of 50 patients. With a similar study design we can more directly compare out local data to an international series. The trends displayed in the observed outcomes are strikingly similar to our own. Interestingly they also observed that not all outcomes improved with each sequential series as each surgeon gained experience. The increasing complexity of the cases as each surgeon progressed was offered as a potential explanation for this.

10) Learning Curves for Robotic Surgery: a Review of the Recent Literature

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A recent review of relevant literature regarding urological learning curves as it related to robotic assisted surgeries. Learning curves (LC) for four different groups were looked at: Robotic Assisted Laparoscopic Radical Prostatectomies (RALP), virtual reality robotic simulator (VRS), robot-assisted radical cystectomy (RARC), and robot-assisted partial nephrectomy (RAPN). Our attention is focused solely on the section of the article that deals with RALP.

The authors state that the current data available is extremely heterogeneous with little consistency in terms of a definition for learning curve, nor the parameters used as a surrogate to measure. Wheter previous experience in open radical prostatectomy (ORP) has an effect on RALP remains unclear. Herrel and Smith [2] showed that the LC for a surgeon who had performed over 2500 ORP plateaued at 250 procedures. Gumus et al. [3] was able to demonstrate a more rapid plateau in laparoscopically naïve surgeons between 50 and 120 cases.

It would appear that in high-volume centres, surgeons with considerable experience in ORP, who are now learning RALP for the first time, seem to have better oncological and functional outcomes [4, 5]. On the other hand, more recently, the urology trainees are exposed to robotic surgery directly without obtaining any substantial open surgery experience.

Mean OT seems to reach a plateau after 50-200 robotic cases, while positive surgical margin (PSM) rate plateaus somewhere between 50-1600 cases, depending on the author's definition of acceptable PSM rate [6-8]. The plateau for length of stay (mean 1.13 days), pad-free continence, and potency took longer to reach at 200 cases each.

LC for laparoscopic prostatectomy (LRP) is well described by Vickers et al. [1]. The authors retrospectively collected results from 4702 laparoscopic radical prostatectomies (LRP) performed by 29 different surgeons. The 5-year risk of recurrence was 17% (10 cases) to 16% (250 cases) to 9% (750 cases). The risk reduction between 10 and 750 cases was reported as 8.0% (95% CI 4.4–12.0). LRP remains technically demanding and ergonomically more challenging than RALP.

As a consequence, RALP has been reported to have a shorter learning curve [9, 10]; however, these early reports did not have sufficient numbers to identify the plateau of the LC. Good et al. [11], in a study involving 1370 patients, compared results of two different surgeons who were considered to have reached their LC plateau for both LRP and RALP. The surgeon-1 performed 289 LRPs and 531 RALPs, whereas surgeon-2 performed 289 LRPs and 550 RALPs. Both groups had similar proportions of pT2/pT3 cases and similar proportions of nerve-sparing cases. LC duration was found to be essentially the same for operating time (OT), estimated blood loss (EBL), and complication rates (250 cases) whereas the plateau for the PSM rate was reached only later in RALP group (300 vs 250 cases for pT2 disease, p = 0.001 and 250 vs 200 cases for pT3 disease, p=0.003). A sub-group analysis of the LC for apical PSM rate, however, showed a different picture since LC for RALP was 50 cases vs 200 cases for LRP (p<0.001). LC for early continence (EC) was significantly shorter for RALP: 350 cases (LRP group) vs 100 cases (RALP group) (p<0.001). This study demonstrates that RALP has a similar LC to LRP, and it cannot be considered as a procedure who's skill set is easy to acquire.

Furthermore, a recent multicentre study of PSM rates by Sooriakumaran and colleagues [8] demonstrated that a case load of >1000 cases was required before the PSM rate for pT3 disease plateaued. Continued improvement, despite extensive case load in the pT3 PSM, is a very interesting finding since pT3 prostate cancer is known to have a higher risk of biochemical recurrence (BCR) than pT2 disease. The authors note that the resultant superior outcomes in this regard may well translate in a lower rate of BCR in RARP than LRP.

An interesting consideration is whether or not RALP outcomes are adversely when a new surgeon, still early in their LC, is integrated into a high-volume robotic centre. Wang et al. [12] retrospectively analysed the outcomes of 3064 RALP's performed between 2007-2012 in their centre. 2846 RALP's were performed by three experienced robotic surgeons and 218 of these cases by a new surgeon added to the team. The new surgeons, under supervision for 12 months, performed 17-52 cases per year. Outcomes assessed included OT, EBL, PSM rate, biochemical recurrence and complications. Results showed that the only significant predictor of a decrease in probability of major complications was case number (Clavien-Dindo ≥ 3, p=0.025). Case number was a predictor of BCR (p=0.021), with 10.5% risk of BCR at year 1 and 6.6% after 6 years at commencement (p=0.009). Furthermore, case number influenced the OT (p = 0.004) but it did not influence PSM (p =0.816). Overall, the authors conclude that the new surgeon could be integrated into an existing robotic team without compromising the outcomes of the unit.

The LC as it related to an extended pelvic lymphadenectomy (ePLND) at the time of RALP has also been looked at by Di Pierro and colleagues [13]. They prospectively collected data from an experienced single surgeon who performed 233 consecutive RALP plus ePLND cases. The total number of cases was divided chronologically into four quarters labelled groups-1 to -4. Although mean OT did not decrease significantly with experience, there was a significant higher number of resected lymph nodes in the specimens after 60 cases: group-1(13 nodes), group-2(15 nodes), group-3 (17nodes), and group-4 (16 nodes) (p=0.001). After 175 cases the there was a significant decrease in minor (Clavien-Dindo <3) complications observed. Minor complication rates were: group-1(34%), group-2(40%), group-3 (41%), and group-4 (17%) with no change seen in major complications (=0.028).

The authors of this literature review state that their review should inform both trainers and trainees on what outcomes they can expect with increasing experience in RALP. This will facilitate a safer and more efficient training programs for those starting out in RALP.

11) A Critical Analysis of the Learning Curve and Post-learning Curve Outcomes of Two Experience and Volume-Matched Surgeons for Laparoscopic and Robot-Assisted Radical Prostatectomy

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Researchers in the UK and Scotland report on the peri-operative outcomes of two experience- and volume-matched laparoscopic and robotic surgeons who have completed the learning curve with respect to laparoscopic radical prostatectomy (LRP) and robotic sssisted laparoscopic radical prostatectomies (RALP). Given RALP has been reported to have a faster learning curve compared to LRP, the authors of this article have compared the learning curves (LC) of the two approaches. Of interest is that both surgeons had each performed almost identical numbers of each procedure.

Assessed parameters and outcomes similar to our study included pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score; and D'amico risk groups. Post-operative data included: use of nerve sparing surgery; operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence status post-op.

Assessed parameters and outcomes not included in our study were: prostate weight and complications. This study also compared RALP to LRP which was not done in our study.

A total of 1370 patients operated on for their prostate cancer between April 2003-January 2012 at two relatively high-volume United Kingdom urological centres were included in the study. Of these surgeon-1 performed 289 LRPs and 531 RALPs, whereas the surgeon-2 performed 289 LRPs and 550 RALPs.

There were 531 RARP (surgeon-1) patients and 550 LRP (surgeon-2) patients included. Both series were divided into consecutive groups of 50 patients and outcomes were then analysed for each group. The number of cases to reach a plateau was noted for each outcome per surgeon. Scatterplots were used to assess the various outcome measures while locally weighted scatterplot smoothing was used to help determine when 'plateau' of the learning curve was achieved. The authors defined plateau as the point at which increasing experience yielded no further improvement in the outcome measured.

Mean overall operating time (OT), excluding robotic setup time, was 124min (range 108–133min) for surgeon-1's RALP series, with his plateau for OT being reached at 250 cases. For surgeon-2' LRP series the mean overall OT was reported as 131min (range 127-135min) with his plateau also being reached at 250 cases ($p = 0.151$).

Mean overall estimated blood loss (EBL) was 272ml (range 207–290ml) for surgeon-1's RALP series, with his plateau for EBL being reached at 250 cases. For surgeon-2' LRP series the mean overall EBL was reported as 202ml (range 166-250ml) with his plateau also being reached at 250 cases ($p = 0.002$). Operative time and length of stay were reported as lower in the RARP group, while estimated blood loss was greater.

The median length of hospital stay (LOS) was 1day in surgeon-1 (RALP) series, vs 3days in surgeon-2's (LRP) series.

The overall positive surgical margin (PSM) rate was 14% for surgeon-1's RALP series, with his plateau for PSM rate being reached at 300 cases. Surgeon-1's PSM rates for pT2 and pT3 were 6% and 31% respectively and it was noted that the pT3 PSM learning curve for RARP continues to improve even after 500 cases. For surgeon-2' LRP series the mean overall PSM rate was reported as 19% with his plateau also being reached at 200 cases ($p = 0.001$). Surgeon-2's PSM rates for pT2 and pT3 were 12% and 37% respectively. OT and LOS were reported as lower in the RARP group, while EBL was greater. The overall PSM rate and pT2 PSM rate learning curves were reported as being longer for RARP

In this study early continence (EC) was assessed in clinic by asking patients how many pads they were using, with dry being defined as zero pads in a 24-hour period at 3-month follow-up. Overall EC rates for surgeon-1 was 77% (plateau at 100 cases), while for surgeon-2 this was reported as 35% (plateau at 350 cases)

Authors concluded that both RALP and LRP had long LC's. Despite the long LC for RARP, there are benefits to patients with RARP over LRP, especially those linked to RALP offering better apical dissection (apical PSM) and early return to continence (EC).

This study is applicable to ours in that it includes a series of 531 RALP patients that were analysed in consecutive groups of 50 patients, all with similar outcomes to our own study. The use of mean values makes

direct comparison difficult. Mention of the number of patients required to reach a plateau in the LC is interesting and potentially applicable to our study. The study shows superiority of RALP over LRP once LC achieved, which however the LC does not seem to be significantly shorter.

12) Learning Curve Assessment of Robot-Assisted Radical Prostatectomy Compared with Open-Surgery Controls from the Premier Perspective Database

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Researchers in the US retrospectively assess the learning curve of robot-assisted laparoscopic radical prostatectomy (RALP) by making use of a large administrative database consisting of multiple U.S. hospitals and surgeons. The measured outcomes were then used to compare RALP with open radical prostatectomy (ORP) from the same settings.

Assessed parameters and outcomes similar to our study included pre-operative data such as: hospitals were the surgery was performed; age at time of surgery; and morbid obesity. Post-operative data included: operating time; need for intraoperative blood transfusion; need for conversion to open surgery; and length of post-operative hospital stay.

Assessed parameters and outcomes not included in our study was a large focus on complications. This study also compared RALP to ORP which was not done in our study.

The patient cohort was taken from the Premier Perspective Database (Premier, Inc., Charlotte, NC) from 2004 to 2010, and consisted of 71,312 radical prostatectomies (RP) performed at over 300 hospitals in the U.S. by up to 3739 surgeons. Final numbers in the RALP and ORP cohorts were 27,348 and 43,964 respectively. The key endpoints were surgery time, inpatient length of stay, and overall complications. Also looked at were the key endpoints by surgeon case volume.

Within the hospitals with a robot, the mean operating time (OT) for ORP was 204min (standard deviation [SD] = 1.5), while for RALP it was 364min (SD = 1.7; $p < 0.0001$). The mean length of stay (LOS) for ORP was 3.4 days while for RALP is was reported as 2.2 days ($p < 0.0001$).

In terms of looking at the RALP outcomes by case volume, the database for RALP's was divided into six groups of 25 cases, and these were labelled First-25 (n = 5650), Second-25 (n = 4208), Third-25 (n = 2638), Fourth-25 (n = 1914), Fith-25 (n = 1496), and Sixth-25 (n = 1128). In terms of surgery time the mean OT's for the six groups were: 300min, 270min, 258min; 246min, 240min, and 234min respectively.

For length of hospital stay (LOS) the mean number of days for the six groups were: 2.4days, 2.2days, 2.1days, 2.0days, 1.9days, and 2.0days sequentially.

The authors of this study concluded that during the initial 7 years of RALP development in the United States of America, outcomes showed a trend toward decreased operating time, length of hospital stay, transfusion rates, and complications. Learning curve trends for RALP were made evident for these endpoints when grouped by surgeon case load.

This study is applicable to ours in that, although it doesn't look into single surgeon experience and as many outcomes as our own study, it does demonstrate that over a very large patient cohort there are improvements in the outcomes of OT, LOS, transfusion rate and complications as surgeons gain case volume.

13) A comparison of operative and margin outcomes from surgeon learning curves in robot assisted radical prostatectomy in a changing referral practice

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Researchers at in the UK report the initial experience of three surgeon's first ever series of robot-assisted laparoscopic radical prostatectomies (RALP) between 2005 and 2014 at Addenbrooke's Hospital. Comparisons were made between each of the surgeon's first and second group of 50 consecutive cases to assess the learning curve.

Assessed parameters and outcomes similar to our study included pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; and pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; pathological data (i.e. histology and TNM stage); and positive surgical margin status.

Assessed parameters and outcomes not included in our study were: prostate volume and tumour volume

A total of 300 cases, 100 patients for each of the three surgeons, was reviewed. Surgeons were labelled -A, -B and -C. The bassline pre-operative outcomes included, for the 300 patients, a median age of 61.5 years (range 39-74yrs) and a median PSA level of 7.0ng/ml (range 0.5–85ng/ml). For surgeon A to C the median pre-operative Gleason scores were 6, 6 and 7 respectively.

The operative time (OT) across the three surgeons was 215min. The median OT for surgeons-A, -B and C for their first and last 50 patients was: (185 and 180min); (237 and 201min); and (270 and 220min) respectively. When looking at each surgeon's first and last set of 50-patients we can see that surgeon-A's median OT improved by 5min to 180 min, surgeon-B's improved by 27min to 210min, and surgeon-C's improved by 50min to 220min. The mean estimated blood loss (EBL) across the three surgeons was 252ml The median EBL for surgeons-A, -B and C for their first and last set of 50-patients was: (288 and 225ml); (250 and 250ml); and (300 and 200ml) respectively. Both OT and EBL were noted to improve progressively as each of the three surgeons gained experience, regardless of when their training commenced.

The overall to positive surgical margin (PSM) rates for surgeons-A, -B and C were 12%, 20% and 23% for the first 50 cases, and 32%, 36% and 21% for the second 50 cases respectively. With regards to positive surgical margin rates for pT2 disease for surgeons-A, -B and C for their first and last 50 patients was: (10 and 16%); (13 and 12%); and (12 and 8%) respectively. For pT3a disease this was: (9 and 53%); (35 and 57%); and (36 and 30%) respectively, while for pT3b disease this was: (2 and 0%); (4 and 8%); and (6 and 10%) respectively. It was commented on by the authors that there was a progressive increase in the proportion of high risk pT3a cases for each surgeon series as they took on more changing cases.

The authors of this study concluded that despite an upward trend in high risk referrals for RALP over time, there have been no adverse PSM outcomes from surgeons beginning their learning curve at different start times. They go on to give the opinion that their study "provides strong reassurance to centres training robotic surgeons, as well as evidence to allay patient concerns when their operations are being undertaken by a novice robotic surgeon."

This study is applicable to ours in that it includes a series of 300 RALP patients among three surgeons, each with outcomes for their initial 50 cases and then the following 50 cases. The study is also recent (2018) and thus provides contemporary outcomes to which we can compare our cohort of patients.

14) Continued improvement of perioperative, pathological and continence outcomes during 700 robot-assisted radical prostatectomies

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Researchers in the US retrospectively assess the learning curve and peri-operative outcomes of 700 robot-assisted laparoscopic radical prostatectomy (RALP) performed by two surgeons in their centre between 2003-2006. The cases were assessed in groups: Group-1 [cases 1-300], Group-2 [cases 301-500], and Group-3 [cases 501-700].

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: validated quality-of-life questionnaires for continence.

The operating time (OT) was shown to improve with case experience with the mean times for Groups-1, -2, and -3 being reported as 286min, 198min and 190min respectively. Estimated blood loss (EBL) and continence rates at 1, 3, 6 and 12 months follow up was seen to similarly improve but this did not hold true for potency outcomes. pT2 positive surgical margin (PSM) for the consecutive groups were reported as 15%, 10% and 7% respectively.

The authors concluded that long learning curves were observed for the parameters of OT, EBL and pT2 PSM rates in their study.

This study is applicable to ours in that it provides further proof that although peri-operative parameters are shown to improve with surgeon experience, these learning curves are not quick to achieve.

15) Robot-Assisted Laparoscopic Radical Prostatectomy: Technique and Outcomes of 700 Cases

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Researchers in the US retrospectively assessed the peri-operative outcomes of 700 robot-assisted laparoscopic radical prostatectomies (RALP) performed by a single surgeon between May 2007 and October 2008. Unfortunately, the patient cohort was not divided into consecutive groups so as to report on the learning curve.

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; need for intraoperative blood transfusion; need for conversion to open surgery; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: biochemical recurrence rates, quality of life date, and complications.

For the entire 700 patient cohort, the overall mean operative time (OT) was defined and skin incision to closure and was reported as 124 min. Mean robotic time was defined as time spent by the surgeon at the console and was reported as 88min. Mean estimated blood loss (EBL) was 69.3ml and no patients required a blood transfusion.

Positive surgical margin (PSM) rates were reported as 11.9% overall, and 10%, 40% and 57% for pT2, pT3a and pT3b respectively.

The authors conclude that their initial series of 700 cases of RALP show excellent perioperative and postoperative outcomes which are congruent with a high-volume surgeon.

This study is applicable to ours in that it provides further reported outcomes of a 700 patient cohort by which we can compare our own outcomes.

16) Analysis of the Learning Curve of Surgeons without Previous Experience in Laparoscopy to Perform Robot-Assisted Radical Prostatectomy.

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Researchers in Brazil retrospectively assessed the peri-operative outcomes of 119 patients who underwent robot-assisted laparoscopic radical prostatectomies (RALP) by two surgeons without previous experience in laparoscopic prostatectomy between June 2012 to July 2015. The objective of the study was to assess if the learning curve parameters looked at were influenced by the two surgeons lack of previous laparoscopic surgical experience. Both surgeons had extensive previous open radical prostatectomy experience. The total number of cases were divided into 4 groups based on the year of surgery with Group-1 beings cases operated on in 2012, Group-2: 2013, Group-3: 2014, and Group-4: 2015.

Assessed parameters and outcomes similar to our study included retrospectively assessed but prospectively collected data including pre-operative data such as: age at time of surgery; PSA level; clinical digital rectal findings; pre-op biopsy Gleason score. Post-operative data included: operating time; estimated blood loss; length of post-operative hospital stay; pathological data (i.e. histology and TNM stage); positive surgical margin status; and continence and potency status post-op.

Assessed parameters and outcomes not included in our study were: biochemical recurrence rates, prostate weight, PSA density; complications and Partin table calculations.

For the entire 119 patient cohort, the overall median operative time (OT) was reported as 180 min. Mean estimated blood loss (EBL) was 150ml and no patients required a blood transfusion. Median length of hospital stay (LOS) was 2 days. A progressive improvement of continence and sexual potency was reported to be observed in their study sample. All parameters assessed showed a trend towards improved outcomes.

The authors concluded that the results of this study, when compared to other reports in the literature, showed that a lack of previous laparoscopic surgical did not seem to negatively impact the learning curve outcomes they assessed. Although progressive improvements in the outcomes were observed with the passage of time and experience the learning curves were not observed to plateau by 119 cases.

This study is applicable to ours in that it provides evidence that previous training in laparoscopic surgery is not required in order to show progression in a surgeon's learning curve during their initial experience in RALP.

17) The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study

Lancet Oncology 2009; 10: 475–80

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Researchers in the US retrospectively assess the learning curve of a cohort of 4702 patients with prostate cancer (PCa) treated by means if a laparoscopic radical prostatectomy (LRP), by 29 surgeons from seven institutions across Europe and the United States, between January 1998 – June 2007. They used multivariable models to assess if there was an association between surgeon experience and PCa biochemical recurrence, with adjustment for established predictors.

Of note is that this study has very few outcomes and parameters similar to ours and is a large cohort of patients who had their prostate cancer managed laparoscopically, not robotically.

1404 of 4702 (30%) of patients (1404 of 4702) were seen by a surgeon who had done less than 100 previous procedures, while half (50%, 2349) were seen by a surgeon with experience of more than 250 previous procedures.

After adjusting for case mix, greater surgeon experience was associated with a statistically significant lower risk of biochemical recurrence at 5-year follow up(p=0·0053). The 5-year risk of biochemical recurrence decreased with increasing surgeon experience: 17% (10 cases) to 16% (250 cases) to 9% (750 cases). The risk reduction between 10 and 750 cases was reported as 8.0% (95% CI 4.4–12.0). Surgeons with previous experience of open radical prostatectomy (ORP) had significantly poorer results than those whose first operation was laparoscopic (risk difference 12.3%, 95% CI 8·8–15·7). In summary this study found the learning curve to be longer for pure laparoscopic surgery when compared to the open technique, and the results improved up to 750 procedures, when they reached a plateau. When the surgeon already had experience in open surgery, the results were better.

The authors concluded that the learning curve for LRP was slower than the previously reported learning curve for open surgery (p<0·001). Increasing surgical experience is associated with substantial reductions in biochemical recurrence after LRP, but improvements in outcome seem to occur at a slower rate than for open surgery. Laparoscopic radical prostatectomy seems to involve skills that do not translate well from open radical prostatectomy.

This study is applicable to ours in that it demonstrates that different learning curves can be seen within the same surgical procedure depending on what outcome you are analysing. In this study the learning curve for biochemical recurrence does not appear to plateau even up to 750 cases.

iii) <u>In Summary:</u>

Given the lack of a universally agreed upon definition of a LC nor consistency about which outcomes should be measured to track its progress there is a great deal of heterogenicity in the published literature. Saying that, it is clear from above literature that the learning curve (LC) for RALP, indeed any technical procedure, is multi-faceted in that there is no one universal outcome that can be analysed. Instead there are numerous LC outcomes within the overall acquisition of a skill set that ultimately leads to improved functional and oncological outcomes.

These different LC's include ones for operating times (OT), estimated blood loss (EBL), length of hospital stay (LOS), positive surgical margin (PSM) rate, biochemical recurrence (BCR), and complication rate to name a few mentioned in our literature review. Each of these tend to show a trend towards overall improvement albeit at different trajectories. A common theme among all the articles is that case experience improves outcomes, and this can be nurtured within a structured and mentored training program.

It also becomes clear from our review here that, although there are numerous articles looking at predominately American and European LC's in RALP, there is currently no published data on the South African experience. In a country where robotic surgery is in its relative infancy, our study may shed light on what outcomes can be expected locally and perhaps encourage patients, surgeons, institutions and funders alike to strongly consider RALP as a potential gold standard treatment for localized prostate cancer.

iv) References:

1) Vickers AJ, Savage CJ, Hruza M *et al*. **The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study.** *Lancet Oncol* 2009; 10: 475–80
2) Herrel SD, Smith JA. **Robotic –assisted laparoscopic prostatectomy: what is the learning curve?** Urology. 2005;66(5 Suppl):105–7.
3) Gumus E, Boylu U, Turan T, Onol FF. **The learning curve of robot-assisted radical prostatectomy**. J Endourol. 2011;25:1633–7.
4) Ahlering TE. **Robotic versus laparoscopic radical prostatectomy**. Nat Clin Pract Urol. 2004;1:5–9.
5) Guillonneau B, el-Fettouh H, Baumert H, Catheineau X, Doublet, D, Fromont G, et al. **Laparoscopic radical prostatectomy: oncological evaluation after 1000 cases at Montsouris Institute**. J Urol. 2003;169:1261–6.
6) O'Malley PJ, Van Appledorn S, Bouchier-Hayes DM, Crowe H, Costello AJ. **Robotic radical prostatectomy in Australia: initial experience.** World J Urol. 2006;24:165–70.
7) Gyomber D, Bolton D, Webb D, Harewood L, Crosthwaite A. **An analysis of variability of learning curve, margin status and early post operative outcomes in 1200 robot assisted laparoscopic prostatectomies in a multi-user center.** J Urol. 2010;183(4 Suppl. 1): e723.
8) Sooriakumaran P, John M, Leung R, et al. **A multi-institutional study of 3794 patients undergoing robotic-assisted radical prostatectomy shows the learning curve is not as short as previously thought**. Eur Urol Suppl. 2011;10:1569–9056.
9) Menon M, Tewai A, Baize B, et al. **Prospective comparison of radical retropubic prostatectomy and robot-assisted anatomic prostatectomy: the Vattikuti Urology Institute experience**. Urology. 2002;60:864–8.
10) Patel VR, Tully AS, Holmes R, Lindsay J. **Robotic radical prosta- tectomy in the community setting-the learning curve and beyond: initial 200 cases.** J Urol. 2005;174:369–272
11) Good DW, Steward GD, Laird A, Stolzenburg JU, Cahill D, SA MN. **A critical analysis of the learning curve and post-learning curve outcomes of two experience- and volume-matched surgeons for laparoscopic and robot-assisted radical prostatectomy**. J Endourol. 2015;29:1–9.
12) Wang L, Diaz M, Stricker H, Peabody JO, Menon M, Rogers CG. **Adding a newly trained surgeon into a high volume robotic prostatectomy group: are outcomes compromised?** J Robot Surg. 2017;11(1):69–74.
13) Di Pierro GB, Grande P,Wirth JG, Danuser H, Mattei A. **Extended pelvic lymph node dissection at the time of robot-assisted radical prostatectomy: impact of surgical volume on efficacy and complications in a single-surgeon series.** CUAJ. 2015;9(3–4):107–13.

Chapter 2: Publication-ready manuscript

a. Title page

Is the Learning Curve In Robotic Assisted Laparoscopic Radical Prostatectomies (RALP) in South Africa Comparable to International Standards?

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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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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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Nothing to declare. This was unfunded rese.

b. Abstract

Background and purpose
Prostate cancer (PCa) is the second most common cancer in men, and the sixth leading cause of cancer death among men worldwide (1). Radical Prostatectomy (RP) is widely considered a gold standard treatment for clinically significant localized PCa. Robotic assisted laparoscopic radical prostatectomy (RALP) represents a modern minimally invasive technique for performing a RP.

The aim of the study is to demonstrate a progression in the learning curve of two South Africa based urologists, as each embarks on their first series of RALP cases between September 2014 to July 2019. An audit of peri-operative outcomes for each surgeon's first uninterrupted series of RALP's has been undertaken. We also compare our results to international series to assess if local South African outcomes are similar to these.

Materials and Methods
We performed a retrospective audit of all patients who had a RALP with our two urologists between the dates of September 2014 to May 2019. Patients were only excluded if critical data could not be collected. For each included patient we collected peri-operative data.

Pre-operative data collected was required for risk stratification grouping of patients according the D'Amico Risk group classification. Post-operative data included operative details (such as console time and blood loos), functional outcomes (such as potency and continence rates), and pathological outcomes (such a T-staging and positive surgical margin rates).

The total number of patients for each of the two surgeons have been divided into a series of consecutive groups. The first 100 have been divided into groups of 25, and the subsequent patients into groups of 50.

Results/main findings
Our two surgeons have been designated Surgeon-X and Surgeon-Y. A total of 700 patients met our inclusion criteria, 400 and 300 cases for Surgeons-X and -Y respectively. Our study demonstrates that in a South Africa setting, for the parameters of median console time (CT), estimated blood loss (EBL), length of hospital stay (LOS), and positive surgical margins (PSM), there were notable improvements between the first and last groups of each surgeon's series. Although each parameter tends to fluctuate around a median value, there is a general trend towards improved outcomes. For the parameters of post-operative continence and potency our study failed to show a statistically significant improvement in outcomes between the first and last groups in each surgeon's series.

Conclusions

This study demonstrates that, similar to internationally published data, notable improvements in peri-operative outcomes can be observed as each of our two surgeons gain experience in this relatively new operative approach to managing men with localized prostate cancer. The overall picture is one of improved outcomes with each consecutive group analysed and that when individually assessed, these outcomes display differing rates of improvement depending on which is being assessed. When analysing our outcomes of CT, EBL, PSM rate and LOS, we see that our results compare favourably to other internationally published data. For all intents and purposes our learning curve and peri-operative results are on par with our overseas counterparts and in some cases better.

c. Introduction

Prostate cancer (PCa) is the second most common cancer in men, and the sixth leading cause of cancer death among men worldwide (1). Radical Prostatectomy(RP) is widely considered a gold standard treatment for clinically significant localized PCa in men considered eligible for radical treatment. Radical prostatectomy can be offered as open, laparoscopic, or robot-assisted procedure depending on surgeon experience and institutional availability of equipment.

Modern urological practice has seen the rise of robotic assisted surgeries, robotic assisted laparoscopic radical prostatectomy (RALP) being at the forefront. There has been a rapid increase in the number of American and European centers performing RALP over the last decade. The use of robotics in surgery in South Africa is in its relative infancy, with only six robot systems operating in the entire country at the time of writing this article.

The benefits of having available to the surgeon a comfortable seated position, magnified binocular 3D visualization and number of ergonomic, highly articulated and non-fatigable robotic arms within the tight confines of the boney pelvis seem obvious. Although this new approach appears to offer many benefits to patients, surgeons and institutions alike, some remain hesitant to adopt it for fear of a difficult learning curve that, while undertaken, may compromise functional and oncologic outcomes. As such there has been observed a growing interest over recent years in analyzing and understanding the learning process surrounding RALP.

The general definition of a learning curve is the period during which a surgeon finds the procedure more technically challenging; takes longer to perform; a higher rate of complications is observed; and there is overall lower efficacy because of inexperience. With repetition one typically sees an improvement in these areas with obvious benefit to patients, surgeons, institutions and funders alike.

The aim of the study is to demonstrate a progression in the learning curve of two South Africa based urologists, as each embarks on their first ever series of RALP cases between September 2014 to July 2019. Given there exists no widely accepted definition nor measure of a learning curve, as a surrogate, we seek to assess for improvements in key parameters as each surgeon gains experience with the procedure. An audit of these key parameters for each surgeon's first uninterrupted series of RALP's has been undertaken. We also compare our results to international series with a similar study design, to assess if local South African learning curves are similar to these.

The chosen parameters have been selected to be in line with those already defined in already published international literature, allowing for better comparisons to be made (2–20). Pre-operative data collected will be required for risk stratification grouping of patients according the D'Amico Risk group classification. Post-operative data included operative details (such as console time and blood loos), functional outcomes (such as potency and continence rates), and pathological outcomes (such a TNM staging and positive surgical margin rates.

Although available literature reports on similar outcomes in international series, to our knowledge there have been no published analysis of South African data. We postulate that in a South African setting we would see similar improvements in key parameters and outcomes when compared to international cohorts.

d. Methods

i) Selection and Description of Participants

We performed a retrospective folder review and included all patients who had a RALP with our two urologists at private hospitals. For ethical reasons the two urologist, designated Surgeon-X and Surgeon-Y, as well as their identifying patient details have been kept anonymous for the purpose of this study. Surgeon-X recorded his very first patient on 29/9/14, while surgeon-Y recorded his on 06/10/15. Patients were only excluded if critical data regarding perioperative outcomes could not be collected. A total of two patients were excluded from the study for incomplete or missing data. For each included patient we collected peri-operative data.

Approval for this study was obtained from the University of Cape Town, Department of Surgery Departmental Research Committee (Project 2019/023).

Human research ethics committee approval was obtained from the University of Cape Town, Faculty of Health Sciences (HREC REF: 218/2019)

ii) Technical Information

We performed a retrospective folder review of all patients with complete records identified during the specified time period of September 2014 to July 2019. Surgeon Data was extracted from the clinical folders and relevant laboratory records. Pre- and post-operative data was collected.

Pre-operative data collected will be required for risk stratification grouping of patients according to the D'Amico Risk group classification. The pre-operative data collected includes:

[A] mean age at time of surgery,
[B] PSA value at diagnosis,
[C] clinical digital rectal findings (T-Stage), and
[D] biopsy Gleason score (ISUP grading)

Post-operative data included the following:

[1] operating/console time, excluding setup/docking time (min),
[2] estimated blood loss (ml),
[3] need for intraoperative blood transfusion (yes/no),
[4] conversion to open surgery (yes/no),
[5] length of post-operative hospital stay (days),
[6] number of patients with positive surgical margins (positive/negative),
[7] percentage of patients in each cohort dry (i.e., not incontinent) at 2/3 and 6 months (%).
[8] percentage of patients in each cohort potent (i.e., not suffering from erectile dysfunction) at 2/3 and 6 months (%).
[9] histological (i.e., Gleason scope or ISUP grading), and
[10] pathological (i.e. T-staging, not N or M staging) data.

Information regarding post-operative incontinence was assessed by asking the patients if they were wet or dry post op. Although Surgeon-Y made efforts to quantify the number of pads wet for each patient, this was not done by Surgeon-X and was therefore not included for assessment. The completely continent rate was calculated by dividing the number of patients in each group who reported being completely dry (i.e. no leak or pads), by the total number of patients in each group for who such data was recorded. Information regarding potency was more formally assessed by each of the surgeons using the validated International Index of Erectile Function (IIEF-5) score. Both surgeons collected data regarding incontinence and potency, surgeon X at 2- and 6-months post op, while surgeon Y at 3- and 6-months post op.

The total number of patients for each of the two surgeons have been divided into a series of consecutive groups. The first 100 have been divided into groups of 25, and the subsequent patients into groups of 50. These groups for each surgeon have been designated as Group-A [1-25]; Group-B [26-50], Group-C [51-75], Group-D [76-100], Group-E [100-150], Group-F [151-200], Group-G [201-250], Group-H [251-300], Group-I [301-350], and Group-J [351-400].

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. A series of Mann-Whitney *U* tests compared (a) median console time, and (b) IIEF at 6/8 weeks, 6 months and 12 months between surgeons for each of Groups A-H (a series of independent sample *t*-tests did the same analyses for mean length of hospital stay). Kruskal-Wallis tests compared median console time and EBL across groups A-H for each surgeon (a one-way ANOVA did the same analysis for mean length of hospital stay). Chi-square tests were used to determine the association between surgeon and (a) D'amico classification, (b) proportion of patients discharged within one day, (c) PSM rate, and (d) pathological stage for all their patients and then within each group (A-H). Where sample sizes were too small, Fisher's Exact test were performed and described in the results section below. Chi-square tests were also used to determine the association between surgeon and patient incontinence at 6/8 weeks, 6 months and 12 months, for all patients and within each group of patients (A-H).

The a priori level of significance was either set at 0.05, or Bonferroni corrected (noted in the results section when corrections were made). All statistical analyses were performed using Sstatistical Package for Social Sciences (SPSS) Version 25, Armonk, NY: IBM Corp.

e. Results

Our two surgeons have been designated Surgeon-X and Surgeon-Y. A total of 700 patients met our inclusion criteria, 400 patients in Surgeon-X's cohort, and 300 patients in Surgeon-Y's cohort. All patients had biopsy-confirmed adenocarcinoma of the prostate. The pre-operative clinical characteristics of the patients for both surgeons are summarized in table-1. Of importance to note is that although baseline age and pre-operative PSA levels were similar between the cohorts, there were significant differences in the biopsy ISUP grading and D'amico risk groupings (see figure 1).

There was a significant association between pre-operative D'amico classification and Surgeon ($\chi^2 = 52.37$, $p < .001$, $V = 0.27$). A significantly higher proportion on Surgeon-Y's patients were classified as Low Risk, whereas a significantly higher proportion of Surgeon-X's patients were High Risk. When analysing the sub-groups of patients, the association between D'amico classification and Surgeon was only significant in Groups-E ($p = .001$) and -F ($p < .001$).

A breakdown of each surgeon's pathological (pT) staging per group can be found in figure-1

Analysis of Console Times and Conversion to Open Surgery:

Neither of our two surgeons reported any of their patients requiring conversion to open surgery. Median console times (CT) in minutes was calculated for both surgeons (see figure-2). The CT refers to the length of time that the surgeon was operating the robot from the console and did not include anaesthetic nor robot setup/docking times. For Surgeon-X the respective CT's for Groups A to H were: 230min; 177min; 145min; 142min; 130min; 106min; 108min; 115min; 107min, and 113min. For surgeon-Y the respective CT's for Group A to H were: 196min; 150min; 134min; 142min; 133min; 120min; 113min; and 120min.

The overall median CT for Surgeon-X (n=400) was 123min [range 68-296 min]. For Surgeon-X there were 193 patients (48%) that had console times less than or equal to 120min, with only 9 (<5%) of these coming from

groups-C and -D combined, while the remainder came from Group-E onwards (i.e. >100 patients). For Surgeon-X there were 42 patients (10.5%) that had console times of less than or equal to 90min, these occurred exclusively from Group-F onwards (i.e. > 150 patients).

The overall median CT for Surgeon-Y (n=300) was 129min [range 63-263 min]. For Surgeon-Y there were 125 patients (41.6%) that had console times less than or equal to 120min with 6 (<5%) of these coming from groups-C and -D combined, while the remainder came from group-E onwards (i.e. >100 patients). There were 21 patients (7%) that had console times of less than or equal to 90min, these occurred exclusively from Group-E onwards (i.e. >100 patients).

The Kruskal-Wallis test showed that for both Surgeons, median CT differed significantly between sub-groups of patients (Surgeon-X: $H = 141.9$, $p < .001$; Surgeon Y: $H = 100.3$, $p < .001$). For Surgeon-X, median CT was significantly faster in Group-F compared to Groups A-D; Group-G compared to Groups A-D; Group-H compared to Groups -A, -B and -D; Group-J compared to -A, -B and -D; Group-D compared to Groups-A and -B; and Group-C compared to Group-A (see table-3). For Surgeon-Y, median CT was significantly faster in Group-G compared to Groups A-E; Group-F compared to Groups-A and-B; Group-H compared to Groups-A and -B, and Groups -C, -D and -E compared to Group -A (see table-3).

Analysis of Estimated Blood Loss:

Median estimated blood loss (EBL) in ml was calculated for both surgeons (see figure-3). The overall median EBL for Surgeon-X was 75ml [range 0-700 ml], while for Surgeon-Y it was 200ml [range 20-1200ml]. For Surgeon-X the EBL for Groups A to J was: 200ml; 100ml; 100ml; 50ml; 60ml; 50ml; 50ml; 55ml; 78ml; and 50ml respectively. For Surgeon-Y the EBL for Groups A to H was: 200ml; 150ml; 100ml; 200ml; 200ml; 188ml; 178ml; and 200ml respectively. Surgeon-X did not report a requirement for intra-operative blood transfusion, while Surgeon-Y reported only 2 cases in his entire series.

Analysis of Length of Post-Operative Hospital stay:

Mean length of hospital stay (LOS) was for both surgeons was calculated. The overall mean LOS for Surgeon-X was 1.7days [range 1-9 days], while for Surgeon-Y it was 1.5days [range 1-10 days]. For Surgeon-X the mean LOS for groups A to J was: 2.2; 1.7; 1.3; 1.7; 2.0; 1.2; 1.0; 2.0; and 2.0 days respectively. For Surgeon-Y the mean LOS for groups A to H was: 1.7; 1.9; 1.7; 2.0; 1.0; 1.4; 1.0 and 1.0 days respectively.

Significant between-surgeon differences were found in Group-C, with Surgeon-Y's patients having a significantly longer hospital stay (see table-5). A one-way ANOVA showed that there was a statistically significant difference between LOS and Group for Surgeons-X and Surgeon-Y [Surgeon X: $F(9,390) = 3.97$, $p < .001$; Surgeon-Y: $F(7,290) = 2.36$, $p = .023$]. For Surgeon-X, pairwise post-hoc comparisons showed that the differences lay between Group-A and -F ($p = .004$), Group-A and-G ($p = .010$), Group-F and -I ($p = .029$), Group-F and -J ($p = .009$), and Group-G and -J ($p = .029$). For Surgeon-Y, at the Bonferroni corrected p-value, there were no significant between-group differences.

We also calculated the percentage of patients discharged on day one after surgery for both surgeons (see figure-4). For Surgeon-X the percentage of patients discharged on day one for groups A to J was: 20%; 52%; 72%; 52%; 54%; 78%; 74%; 60%; 44%; and 58% respectively. For Surgeon-Y for groups A to H this percentage was: 40%; 24%; 40%; 40%; 66%; 64%; 68%; and 80% respectively.

A significantly higher proportion of patients were discharged after one day for Surgeon-X in Groups-B ($p = .041$) and C ($p = .023$), and a higher proportion were discharged for Surgeon-Y in Group-H ($p = .029$). Irrespective of Group, 58% of patients for both Surgeons were discharged after one day (see table-6)

Analysis of Positive Surgical Margins:

Oncologic outcome is the most significant endpoint for patients with prostate cancer receiving radical prostatectomy. The percentage of patients in each group with pathological positive surgical margins (PSM) was calculated for both surgeons (see figure-5). A PSM was defined as the presence of cancer cells at the inked margin. For Surgeon-X the PSM rate for Groups A to J was: 24%; 32%; 16%; 44%; 18%; 22%; 20%; 22%; 26%; and 22% respectively. For Surgeon-Y the PSM rate for Groups A to H was: 16%; 8%; 8%; 4%; 8%; 8%; 2% and 4% respectively.

Whenever discussing PSM with regard to prostate cancer we already know that there is an association between the pathological stage of the tumour (pT) and the risk of obtaining a PSM. It thus becomes important to assess the pathological staging of each surgeons' sub-groups (see figure-6). Pathological Stage (pT) for Surgeon-X was significantly different compared to Surgeon-Y (p <.001). A significantly higher proportion of patients for Surgeon-X were stage pT2. When comparing sub-groups of patients between surgeons, a significantly higher proportion of patients for Surgeon-X were stage pT2 across all groups, and a significantly higher proportion of patients for Surgeon-Y were stage pT1 for Groups A and B and Stage pT3 for Groups B – E.

The PSM rate for Surgeon-X for his entire series of 400 patients is 23.5%(n=94), with 34% of PSM's (32/94) being pT2 disease while 66% (62/94) were pT3 disease on final histology. For Surgeon-X the PSM rate was 11.7% (32/274) and 50.4% (62/123) for pT2 and pT3 disease respectively. The PSM rate for pT3 disease for Surgeon-X from Groups A to J was: 60%; 100%; 66.7%; 80%; 58.3%; 50%; 44.4%; 36.4%; 58.8%; and 43.5% respectively (see figure-7).

The PSM rate for Surgeon-Y for his entire series of 300 patients is 6.7% (n=20), with none of the PSM's being pT2 disease, while 95% (19/20) were pT3 disease and 5% (1/20) were pT4 disease on final histology. For Surgeon-Y the PSM for pT3 disease was 12.2%(19/156) and for pT4 disease was 10% (1/10). The PSM rate for pT3 disease for Surgeon-Y from Groups A to H was: 80%; 14.3%; 16.7%; 5%; 11.1%; 10%; 6.3%; and 8.7% respectively (see figure-7).

For Surgeon-X (χ^2 = 70.4, p < .001, V = 0.42) and Surgeon-Y (χ^2 = 16.05, p < .001, V = 0.24), the PSM rate was significantly higher among pT3 disease (see table-7). When comparing sub-groups of patients, the PSM rate was significantly higher among pT3 disease in Groups E to J for Surgeon-X, and only in Group-A for Surgeon-Y (see table-8).

Analysis of Post-Operative Continence:

The completely continent rate, defined in methods, was calculated for each surgeon.

For Surgeon-X the completely continent rate at 8 weeks and 6 months post RALP for Groups A to H was: (54.2% and 97%); (41.7% and 94%); (52% and 98%); (44.2% and 98%); (52% and 93%); (63.3% and 96%); (72.7% and 97%); (64.3% and -%) respectively. In Groups-I and -J there was insufficient data at 6 weeks and 6 months follow-up, as well at 6 weeks follow up in group-H, to make any definitive conclusions and so these results have been omitted.

For Surgeon-Y the completely continent rate at 6 weeks and 6 months post RALP for Groups A to G was: (80% and 96%); (68% and 0%); (80% and 0%); (65% and 95.7%); (52% and 98%); (61% and -%); and (39% and -%) respectively. In Groups-G and -H there was insufficient data at 6 months follow-up to make any definitive conclusions and so these results have been omitted.

Analysis of Post-Operative Potency:

Median International Index of Erectile Function (IIEF-5) scores were calculated for both surgeons. Unfortunately, pre-operative potency scores were only assessed in Surgeon-Y's cohort, not Surgeon-X's, with a median score of 20. For both surgeons the majority of patients were performed as either a unilateral or bilateral nerve sparing procedure where it was considered oncologically sound to do so.

For Surgeon-X the percentage of men considered potent, defined as an IIEF-% score ≥16, at 8 weeks and 6 months post RALP for groups A to I was: (15% and 20%); (9.5% and 11%); (8.7% and 13%); (4.3% and 17%); (2.1% and 7%); (6.4% and 7%); (2.1% and 7%); (2.1% and -%); and (9.5% and -%) respectively. In Groups-H and I there was insufficient data at 6 months follow up, as well as Group-J at both 6-week and 6-month follow-up, to make any definitive conclusions and so these results have been omitted.

For Surgeon-Y the percentage of men considered potent, defined as an IIEF-% score ≥16, at 6-weeks and 6-months post RALP for Groups A to H was: (28% and 41.7%); (28% and 37.5%); (30.4% and 39.1%); (35.3% and 47.1%); (32.6% and 42.2%); (24.5% and -%); (38.6% and -%); and (35% and -%) respectively. In Groups-F to -H there was insufficient data at 6-months follow-up to make any definitive conclusions and so these results have been omitted

Analysis of Results in Consecutive Groups of 100 cases:

We then divided each surgeon's series into groups of 100 cases. For Surgeon-X there was significant increase in the mean LOS between both the second (p = 0.001) and third (p = 0.001) 100 patients and the last 100 patients. There was a significant decrease in median CT between the first 100 patients and all subsequent groups. EBL only significantly decreased between the first 100 patients and the second (p = 0.006) and third (p = 0.010) 100 patients.

For Surgeon-Y there was a difference in mean LOS between the groups, the first 100 patients had a median of 2 days, all subsequent groups were 1 day. There was a significant decrease in median console time between the first 100 patients and all subsequent groups (all ps < .007). Estimated blood loss did not differ between groups (p = 0.257).

There was no significant change in PSM rates between the groups for either surgeon 's series (X: p = 0.436; Y: p = 0.190). However, for Surgeon-X, the PSM rate was significantly higher in pT2 disease for the first 100 patients (p = 0.009) compared to subsequent groups of patients. No other significant differences were found.

f. Discussion

Summary of Findings

To our knowledge there are currently no large-scale studies of RALP outcomes that have been reported in South Africa. Our study of 700 patients who underwent RALP demonstrates that in a South Africa setting, for the parameters of median console time (CT), estimated blood loss (EBL), length of hospital stay (LOS), and positive surgical margins (PSM), there were notable improvements between the first and last groups of each surgeon's series. Although each parameter tends to fluctuate around a median value, there is a general trend towards improved outcomes. These can be seen depicted in the slope of each parameters trendline (see figures 2-5 and 7), except for Surgeon-Y's EBL trendline (see figure-3).

There was a significant reduction in the median CT (p < 0.001), EBL (p < 0.001), mean LOS (p = 0.002) between the first and last groups of Surgeon-X's series. Surgeon-X did not have a further statistically significant improvement in any outcome variables in his following two groups (I-J). While there was a significant reduction in the median CT (p < 0.001) between the first and last groups of surgeon-Y's series, there was no significant change in median EBL (p = 0.861) or mean LOS (p = 0.306). There was also no significant change in positive surgical margins between the first and last groups of each surgeon's series (X: p = 0.845; Y: p = 0.091). Furthermore, PSM rate among pT2 (p = 0.492) and pT3 (p = 0.316) disease did not differ between the first and last groups for Surgeon-X's series. For Surgeon-Y, no patients with pT2 disease had a PSM in either the first or last groups. However, a higher proportion of patients with pT3 disease had a PSM in the first compared to the last group (p = 0.013).

Several initial reports on RALP having a favourable learning curve exist (2,5,7), with the eminent robotic surgeon Dr VP. Patel reporting that as little as 20-25 cases are required in order to complete the learning curve of RALP. These reports make the use of RALP rather appealing considering other studies that report a learning curve for laparoscopic radical prostatectomy (LRP) being approximately 250 cases (6,18,21), with some learning curve parameters not reaching a plateau even after 750 cases (22).

These early series however, were unlikely to have sufficient numbers to identify the plateau of the learning curve, that is a number of cases required to no longer demonstrate notable improvements in outcomes. In fact, every procedure and surgeon is likely to have their own distinct learning curve with the number of cases required to become adept varying widely. Add to this that in our study, as in most studies examining a learning curve for a surgical procedure, there are differing numbers of cases required to become proficient depending on which parameter is being assessed. In other words, there are different learning curves within the overall learning curve for RALP.

This can be demonstrated in a study by *Eden et al* (18) reported that the learning curve for both OT and EBL plateaued within the first 100-150 cases, while that for both complication and continence rates took longer at 150-200 cases to reach a plateau. The parameter that took the longest to plateau was potency at 700 cases. *Thompson et al* (4) reported that odds of a pT2 PSM in their series of RALP's only started to become lower after 108 cases and reduced by 55% (OR: 0.45; 95% CI, 0.22–0.92) by the 866th RALP. In the same study the odds of a pT3/4 PSM started to plateau only around 200–300 RARPs with an OR of 1.15 (0.68–1.95) at the 866th RALP. This study also reported potency only reaching a plateau in learning curve around 600-700 cases. A multi-institutional review of 3794 patients showed a learning curve of >1000 cases before the pT3 PSM rate plateaued. The results of a study by *Sooriakumaran et al* (3) involving 3974 patients undergoing RALP suggest that proficiency in RALP involves a much longer learning curve than previously recognized. Mean operating time plateaued only after 750 cases, while 1600 cases would be required to get an overall PSM rate of <10%. All these studies seem to support the notion of RALP being centralized in a small number of high-volume centres where the relevant surgeons may attain the case experience required to offer their patients outcomes of the highest calibre.

In our series we saw that when assessing CT for Surgeon-X, at Group-C it is faster than Groups -A and -B but only seems to plateau by Group-F. For Surgeon-Y, CT at Group-C it is faster than Groups -A and -B and then plateaus. When assessing EBL for Surgeon-X, we saw that at group-F it seems to be lower to other subsequent groups. However, this isn't the plateau because for groups H-J it increases again. Surgeon-Y was not demonstrated to reach a plateau for EBL. No plateaus for the variables of LOS nor PSM could be conclusively demonstrated in either surgeon's series. For the parameters of post-operative continence and potency our study failed to show a statistically significant improvement in outcomes between the first and last groups in each surgeon's series. This is consistent with other internationally published data that reports a high case load (>700) in order to demonstrate a plateau in the learning curve for these parameters.

Although this study was not intended as a comparison between our two surgeons, of interest is the discrepancy in PSM rates between Surgeon-X and -Y (see table-2 and figures 5 and 7). Although Surgeon-Y appears to have a significant lower overall PSM rate (23.5% vs 6.7%) and pT3 PSM rate (50.4% vs 12.2%) it should be noted that significantly higher proportion of Surgeon-X's patients were assessed as D'amico High Risk (see figure-1) and he had higher percentages of pT3 disease in his later series (see figure-6) when compared to Surgeon-Y. Other suggested potential confounder here are the fact that for Surgeon-Y, 273/300 (91%) of the patients in his cohort had a pre-operative multiparametric MRI, while for Surgeon-X this number was substantially lower. This may highlight a potential selection bias for Surgeon-Y's series of cases. Additionally, Surgeon-Y is noted to have been exposed to considerably more laparoscopic surgery prior to the initiation of his RALP series than was Surgeon-X. A study by *Tobias-Machado et al* (13) showed that experienced laparoscopic surgeons were able to attain peri-operative and functional outcomes similar to surgeons who have high levels of experience in RALP, and so this may have an impact in the differences in outcomes.

When comparing our series of 700 patients to that of other contemporary international series (see table-9) we can see that the parameters of operating time (OT), EBL, LOS and PSM rate appear to be as favourable in our setting as in those reported overseas. If we use *Coelho et al's* "critical review of pentafecta outcomes" (26) as a direct comparison, we can see that our CT is better (125min vs 174min); our EBL is better (100ml vs 185.8ml); and our LOS is the same (1.6days vs 1.58days). This comparison is especially true for the important parameters of PSM rates were we see that our overall PSM rate is similar (16.2% vs 14.8%); our pT2 PSM rate is slightly better (7.7% vs 8.92); and our pT3 PSM rate is also slightly better (29% vs 33%). As this study depicts the weighted mean values of 17-19 different international studies, with a total patient cohort of more than 11,500 cases, we feel this is probably the one study that likely represents a fair overall impression of how our results compare to international series.

Of particular interest is the progression in parameters in the four consecutive 200, 500, 1500, 2500 and 4000 patient series of *Patel et al* (2,12,14, 23, 26) that fail to show dramatic improvements in most of the recorded parameters, excepting console time, at even very high single surgeon case experience.

Limitations of our study

We recognise the limitations in our study being of a retrospective nature. We also acknowledge that the number of cases performed by each of our surgeons may be insufficient to adequately demonstrate a plateau in all of the learning curve parameters assessed. If the above-mentioned studies are a true reflection of the numbers needed to demonstrate a plateau, each surgeon would need to perform an excess of 1000-1500 cases for all the learning curves to revel themselves.

Furthermore, there are potential confounders that would very likely affect difficulty of a RALP that were not fully assessed in our study. These include: ASA-score, body mass index (BMI), use of pre-operative multiparametric MRI, previous abdominal surgery, and previous treatments for prostate cancer (i.e. a salvage prostatectomy being performed).

We also recognise that some the parameters assessed, such as CT and LOS, may be a factor of the strengths and weaknesses of factors outside of the surgeon's control. For instance, the number of days a patient remains in hospital post-surgery may be a reflection of inadequate pain control or lack of skilled nursing care.

Additionally, the fact that each surgeon made use of different pathology labs to assess their radical prostatectomy specimens may have an influence on the pathological outcomes reported in this study.

Conclusion

This study demonstrates that, similar to internationally published data, notable improvements in peri-operative outcomes can be observed as each of our two surgeons gain experience in this relatively new operative approach to managing men with localized prostate cancer. The overall picture is one of improved outcomes with each consecutive group analysed and that when individually assessed these outcomes display differing rates of improvement depending on which is being assessed. When analysing our outcomes of CT, EBL, PSM rate and LOS, we see that our results compare favourably to other internationally published data. For all intents and purposes our learning curve and peri-operative results are on par with our overseas counterparts and in some cases better.

Our study also confirms that RALP can feasibly, safely and effectively be introduced in a South Africa setting without functional and oncological outcomes being compromised. Within a structured training and mentorship program it is our feeling that satisfactory outcomes can be achieved along the demonstrated learning curves for those novice surgeons willing to dedicate themselves to this surgical approach. We would agree with the concept of RALP being taught to surgeons and offered to patients in a smaller number of high-volume centres

that will more likely attain the high case experience required to reach their optimal learning curve and thus improve outcomes for their patients.

g. References

1. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. 2018;394–424.
2. Patel VR, Tully AS, Holmes R, Lindsay J. Robotic radical prostatectomy in the community setting - The learning curve and beyond: Initial 200 cases. Journal of Urology. 2005;174(1):269–72.
3. Sooriakumaran P, John M, Leung R, Peters D, Lee D, Wiklund P, et al. 349 a Multi-Institutional Study of 3794 Patients Undergoing Robotic-Assisted Laparoscopic Radical Prostatectomy Shows the Learning Curve Is Not As Short As Previously Thought. European Urology Supplements [Internet]. 2011;10(2):127. Available from: http://dx.doi.org/10.1016/S1569-9056(11)60345-X
4. Thompson JE, Egger S, Böhm M, Haynes AM, Matthews J, Rasiah K, et al. Superior quality of life and improved surgical margins are achievable with robotic radical prostatectomy after a long learning curve: A prospective single-surgeon study of 1552 consecutive cases. European Urology. 2014;65(3):521–31.
5. Menon M, Tewari A, Baize B, Guillonneau B, Vallancien G. Prospective comparison of radical retropubic prostatectomy and robot-assisted anatomic prostatectomy: The Vattikuti Urology Institute experience. Urology. 2002;60(5):864–8.
6. Good DW, Stewart GD, Stolzenburg JU, McNeill SA. Analysis of the pentafecta learning curve for laparoscopic radical prostatectomy. World Journal of Urology. 2014;32(5):1225–33.
7. Tewari A, Srivasatava A, Menon M. A prospective comparison of radical retropubic and robot-assisted prostatectomy: Experience in one institution. BJU International. 2003;92(3):205–10.
8. Good DW, Stewart GD, Laird A, Stolzenburg JU, Cahill D, McNeill SA. A Critical Analysis of the Learning Curve and Postlearning Curve Outcomes of Two Experience- and Volume-Matched Surgeons for Laparoscopic and Robot-Assisted Radical Prostatectomy. Journal of Endourology. 2015;29(8):939–47.
9. Mazzon G, Sridhar A, Busuttil G, Thompson J, Nathan S, Briggs T, et al. Learning Curves for Robotic Surgery: a Review of the Recent Literature. Current Urology Reports. 2017;18(11):1–6.
10. Davis JW, Kreaden US, Gabbert J, Thomas R. Learning Curve Assessment of Robot-Assisted Radical Prostatectomy Compared with Open-Surgery Controls from the Premier Perspective Database. Journal of Endourology. 2013;28(5):560–6.
11. Ou Y-C, Patel V, Yang C-K, Wang J, Tung M-C, Tewari A, et al. The surgical learning curve for robotic-assisted laparoscopic radical prostatectomy: experience of a single surgeon with 500 cases in Taiwan, China. Asian Journal of Andrology. 2014;16(5):728.
12. Patel VR, Thaly R, Shah K. Robotic radical prostatectomy: Outcomes of 500 cases. BJU International. 2007;99(5):1109–12.
13. Tobias-Machado M, Ibrahim Mitre A, Rubinstein M, Fernandes da Costa E, Kyoshi Hidaka A. Robotic-assisted radical prostatectomy learning curve for experienced laparoscopic surgeons: Does it really exist? International Braz J Urol. 2016;42(1):83–9.
14. Patel VR, Palmer KJ, Coughlin G, Samavedi S. Robot-Assisted Laparoscopic Radical Prostatectomy: Perioperative Outcomes of 1500 Cases. Journal of Endourology. 2008;22(10):2299–306.

15. Sharma NL, Papadopoulos A, Lee D, Mcloughlin J, Vowler SL, Baumert H, et al. Learning Curves of Two Surgeons. BJU International. 2010;739–47.

16. Arslan ME. European Medical Journal Urology, Vol 3, Iss 3, Pp 50-55 (2015). Learning Curve of Robotic Radical Prostatectomy [Internet]. 2015;3(3):50–5. Available from: http://mendeley.csuc.cat/fitxers/7c2a23a915757758f609da51eda01397

17. Jaulim A, Srinivasan A, Hori S, Kumar N, Warren AY, Shah NC, et al. A comparison of operative and margin outcomes from surgeon learning curves in robot assisted radical prostatectomy in a changing referral practice. Annals of the Royal College of Surgeons of England. 2018;100(3):226–9.

18. Eden CG, Neill MG, Louie-Johnsun MW. The first 1000 cases of laparoscopic radical prostatectomy in the UK: Evidence of multiple "learning curves." BJU International. 2009;103(9):1224–30.

19. Abboudi H, Khan MS, Guru KA, Froghi S, de Win G, van Poppel H, et al. Learning curves for urological procedures: A systematic review. BJU International. 2014;114(4):617–29.

20. Vasdev N, Bishop C, Kass-Iliyya A, Hamid S, McNicholas TA, Prasad V, et al. Developing a robotic prostatectomy service and a robotic fellowship programme -Defining the learning curve. Current Urology. 2014;7(3):136–44.

21. Secin FP, Savage C, Abbou C, de La Taille A, Salomon L, Rassweiler J, et al. The learning curve for laparoscopic radical prostatectomy: An international multicenter study. International Braz J Urol [Internet]. 2010;36(6):764. Available from: http://dx.doi.org/10.1016/j.juro.2010.08.003

22. Vickers AJ, Savage CJ, Hruza M, Tuerk I, Koenig P, Martínez-Piñeiro L, et al. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. The Lancet Oncology [Internet]. 2009;10(5):475–80. Available from:

23. Coelho RF, Palmer KJ, Rocco B, Moniz RR, Chauhan S, et al. Early complication rates in a single-surgeon series of 2500 robotic-assisted radical prostatectomies: report applying a standardized grading system. Eur Urol 2010; 57: 945–52

24. Carlucci JR, Nabizada-Pace F, Samadi DB. Robot-assisted laparoscopic radical prostatectomy: technique and outcomes of 700 cases. Int J Biomed Sci 2009; 5: 201–8

25. Zorn KC, Wille MA, Thong AE, Katz MH, Shikanov SA, et al. Continued improvement of perioperative, pathological and continence outcomes during 700 robot-assisted radical prostatectomies. Can J Urol 2009; 16: 4742–9.

26. Patel VR, Abdul, Muhsin HM, Schatloff O, Coelho RF, Valero R, et al. Critical review of 'pentafecta' outcomes after robot-assisted laparoscopic prostatectomy in high-volume centres. BJU Int 2011; 108: 1007–17.

g. Tables

Table 1: Patient Pre-Operative Characteristics for Surgeon-X and Surgeon-Y

Surgeon-X	Pre-Op Patinet Charateristics	Surgeon-Y
400	**Number of Patients**	**300**
63 *(41-76)*	**Median Age, years *(range)***	**65** *(41-81)*
5.64 *(0.47-164.0)*	**Median PSA level, ng/mL *(range)***	**6.35** *(0.3-33.0)*
	Pre-Op ISUP Score n / %	
153 / ***38.3%***	*1*	137 / ***45.7%***
140 / ***35%***	*2*	36 / ***12%***
59 / ***14.8%***	*3*	55 / ***18.3%***
29 / ***7.3%***	*4*	31 / ***10.3%***
19 / ***4.8%***	*5*	41 / ***13.7%***
	D'amico Risk Group n / %	
55 / ***13.8%***	*Low*	109 / ***36.3%***
159 / ***39.8%***	*Intermediate*	105 / ***35%***
186 / ***46.5%***	*High*	86 / ***28.7%***

Table 2: Patient Post-Operative Characteristics for Surgeon-X and Surgeon-Y

Surgeon-X	Overall	A [1-25]	B [26-50]	C [51-75]	D [76-100]	E [101-150]	F [151-200]	G [201-250]	H [251-300]	I [301-350]	J [351-400]
Median CT, min *(range)*	**123** *(68-296)*	**230** *(156-296)*	**177** *(121-270)*	**145** *(93-193)*	**142** *(105-230)*	**130** *(91-210)*	**106** *(74-218)*	**108** *(74-258)*	**115** *(70-183)*	**107** *(80-170)*	**113** *(68-199)*
Median EBL, mL *(range)*	**75** *(0-700)*	**200** *(0-700)*	**100** *(50-400)*	**100** *(35-500)*	**50** *(20-500)*	**60** *(20-400)*	**50** *(10-200)*	**50** *(20-400)*	**55** *(20-450)*	**78** *(20-500)*	**50** *(40-400)*
Mean LOS, days *(range)*	**1.7** *(1-9)*	**2.2** *(1-5)*	***1.7*** *(1-4)*	***1.3*** *(1-3)*	***1.7*** *(1-5)*	***1.0*** *(1-3)*	***1.2*** *(1-3)*	***1.0*** *(1-3)*	***2.0*** *(1-5)*	***2.0*** *(1-7)*	***2.0*** *(1-9)*
D/C day 1 (%)	*58.2*	20	52	72	52	54	78	74	60	44	58
PSM Rate Amoung Group, % *(calc)*											
Overall	**23.5** *(94/400)*	**24**	**32**	**16**	**44**	**18**	**22**	**20**	**22**	**26**	**22**
D'amico Low Risk	**10.9** (6/55)	-	8.3	-	-	-	-	10	-	14.3	
D'amico Intermediate Risk	**23.3** (37/159)	4.2	6.3	5.6	14.6	11.9	13.6	7.1	5.9	7.5	15.4
D'amico High Risk	**27.4** *(51/186)*	11.1	12.5	3.8	11.1	11.8	10.4	12.5	16.1	17.4	10
pT2 disease	**11.7** *(32/274)*	15	27.3	9.5	35	5.4	8.8	6.3	10.7	9.1	*3.7*
pT3 disease	**50.4** *(62/123)*	60	100	66.7	80	58.3	50	44.4	36.4	58.8	*43.5*

Surgeon-Y	Overall	A [1-25]	B [26-50]	C [51-75]	D [76-100]	E [101-150]	F [151-200]	G [201-250]	H [251-300]
Median CT, min *(range)*	**129** *(63-263)*	**196** *(136-263)*	**150** *(100-220)*	**134** *(92-239)*	**142** *(105-199)*	**133** *(91-210)*	**120** *(90-200)*	**113** *(63-170)*	**120** *(65-190)*
Median EBL, mL *(range)*	**200** *(20-1200)*	**200** *(75-650)*	**150** *(50-700)*	**100** *(50-500)*	**200** *(30-400)*	**200** *(20-1200)*	**188** *(10-200)*	**178** *(50-1100)*	**200** *(50-900)*
Mean LOS, days *(range)*	**1.5** *(0-10)*	**1.7** *(1-3)*	***1.9*** *(1-3)*	***1.7*** *(1-3)*	***2.0*** *(1-9)*	***1.0*** *(1-3)*	***1.4*** *(0-4)*	***1.0*** *(1-6)*	***1.0*** *(1-10)*
D/C day 1 (%)	*58.7*	40	24	40	40	66	64	68	80
PSM Rate Amoung Group, % *(calc)*									
Overall	**6.7** *(20/300)*	**16**	**8**	**8**	**4**	**8**	**8**	**2**	**4**
D'amico Low Risk	**1.8** *(2/109)*	2.8	-	3.6	-	-	-	-	-
D'amico Intermediate Risk	**5.7** *(6/105)*	2.8	-	-	-	5.9	5	2.8	-
D'amico High Risk	**14** *(12/86)*	7.1	6.3	2.8	2.1	7.7	7.7	-	6.7
pT2 disease	-	-	-	-	-	-	-	-	-
pT3 disease	**12.2** *(19/156)*	80	14.3	16.7	5	11.1	10	6.3	8.7

Table 3. Console time (CT) for both surgeons by sub-groups

		Surgeon-X		Surgeon-Y				
Group	***n***	**Median**	**IQR**	**Median**	**IQR**	***U***	***p***	***r***
A	25	230	186.5 - 254.5	196	178.5 – 230	214.5	.057	0.38
B	25	177	177 – 198.5	150	132.5 - 180	207.5	.042*	0.41
C	25	145	122.5 – 150.5	134	120 – 158	284.5	.587	0.11
D	25	142	125.5 - 175	142	122 – 150	265	.356	0.18
E	50	129.5	110 – 145.5	132.5	119.5 - 160	1099.5	.299	0.15
F	50	106	96.8 – 129	120	103.8 – 140	904	.017*	0.34
G	50	107.5	95.5 - 134	112.5	100 – 125.8	1173.5	.598	0.07
H	50	114.5	93.8 – 136.3	120	105 - 130	1102.5	.309	0.14
I	50	106.5	93 – 131					
J	50	113	95.5 – 129.3					

Note. **p* < .05. ***p* <.006 (at the Bonferroni corrected level).

Table 4. Estimated Blood Loss (EBL) for both surgeons by sub-groups

		Surgeon X		Surgeon Y				
Group	***n***	**Median**	**IQR**	**Median**	**IQR**	***U***	***p***	***r***
A	25	200	150 - 400	200	100 - 350	290.5	.667	0.09
B	25	100	75 - 100	150	100 - 225	193.5	.014*	0.49
C	25	100	50 - 120	100	50 – 300	241.5	.157	0.28
D	25	50	50 - 80	200	150 - 275	76.5	<.001**	0.94
E	50	60	50 - 100	200	100 - 300	504.5	<.001**	0.73
F	50	50	50 - 100	187.5	100 – 357.5	451	<.001**	0.79
G	50	50	50 - 100	177.5	100 – 300	419	<.001**	0.82
H	50	55	50 - 100	200	150 - 350	407	<.001**	0.84
I	50	77.5	50 - 100					
J	50	50	50 - 100					

Note. **p* < .05. ***p* <.006 (at the Bonferroni corrected level).

Table 5. Length of hospital stay (LOS) for both surgeons by sub-groups

		Surgeon-X		Surgeon-Y				
Group	***n***	**Mean**	**SD**	**Mean**	**SD**	***t***	***p***	***d***
A	25	2.2	1.0	1.7	0.7	1.99	.053	0.58
B	25	1.7	0.9	1.9	0.6	-0.72	.475	0.26
C	25	1.3	0.6	1.7	0.6	-2.15	.037*	0.67
D	25	1.7	1.0	2.0	1.7	-0.92	.364	0.22
E	50	1.6	0.7	1.4	0.6	1.34	.183	0.31
F	50	1.2	0.5	1.4[48]	0.7	-1.09	.280	0.33
G	50	1.3	0.5	1.3	0.9	-0.28	.784	>0.01
H	50	1.5	0.8	1.4	1.4	0.45	.656	0.09
I	50	1.9	1.2					
J	50	2.0	1.8					

Note. **p* < .05. ***p* <.006 (at the Bonferroni corrected level).

Table 6. Proportion of patients discharged after one day for both surgeons by sub-groups

Group	*n*	Surgeon-X %	Surgeon-Y %	χ^2	*p*	*V*
A	25	20	40	2.38	.123	0.22
B	25	52	24	4.16	.041*	0.29
C	25	72	40	5.19	.023*	0.32
D	25	52	40	0.73	.395	0.12
E	50	54	65[49]	1.31	.252	0.12
F	50	78	69[48]	1.08	.300	0.11
G	50	74	68	0.44	.509	0.07
H	50	60	80	4.76	.029*	0.22
I	50	44				
J	50	58				

Note. *p < .05. **p <.006 (at the Bonferroni corrected level).

Table 7. Positive Surgical Margin (PSM) rate for both Surgeons by Pathological Staging (pT)

Path Stage	Surgeon-X	Surgeon-Y
PSM pT2	32/274 (11.7%)	0/125 (0%)
PSM pT3	62/123 (50.45%)	19/156 (12.2%)

Table 8. Positive Surgical Margin (PSM) rate for both Surgeons by Pathological Staging (pT)

	Surgeon X				Surgeon Y			
	PSM pT2	PSM pT3	*p*	*V*	PSM pT2	PSM pT3	*p*	*V*
A	3/20	3/5	.070	0.42	0/11	3/4	.009*	0.83
B	6/22	2/2	.101	0.43	0/5	2/11	.458	0.26
C	2/21	2/3	.061	0.51	0/13	2/12	.220	0.31
D	7/20	4/5	.096	0.36	0/5	1/20	.800	0.10
E	2/37	7/12	<.001**	0.59	0/13	4/35	.269	0.18
F	3/34	8/16	.002*	0.46	0/18	3/30	.235	0.20
G	2/34	8/18	.002*	0.46	0/33	1/15	.313	0.22
H	3/28	8/22	.034*	.307	0/27	2/23	.207	0.22
I	3/33	10/17	<.001**	0.54				
J	1/27	10/23	.001**	0.48				

Table 9. Comparison of reported outcomes in published contemporary series

Reference	Year	No. Pts	No Surgeons	OT (min)	EBL (ml)	LOS (days)	D/C day 1 (%)	PSM rate (%) Overall	pT2	pT3	pT4
Patel et al. (2)	2005	200	1	141	75.1	1.1	95	10.5	5.7	26.2	33
Patel et al. (12)	2007	500	1	130	50	-	97	9.4	2.5	(a)23 / (b) 46	53
Patel et al. (14)	2008	1500	1	105	111	-	97	9.3	4	33	40
Coelho et al. (23)	2010	2500	1	90	100	1	95	10.6	5	27.5	-
Patel et al. (26)	2011	4000	1	75	100	1	-	10.8	5.8	26.1	-
Carlucci et al. (24)	2009	700	1	124	69.3	-	-	11.9	10	(a) 40 / (b) 57	-
Zorn et al. (25)	2009	700	2	234	222	1.2	-	18.8	12.9	44.8	-
Sharma et al. (15)	2011	500	2	170	200	-	-	24	16.1	(a)30.4 / (b) 55	100
*Patel et al (26)**	2011	>11,500	multiple	174	185.8	1.58	-	14.8	8.92	33	-
Yen-Chuan Ou et al. (11)	2014	500	1	134	137	-	-	34.2	15.6	41	96
Vasdev et al. (20)	2014	300	3	224	248	2.3	-	26.7	-	-	-
Good et al. (6)	2015	531	2	124	272	1	-	14	6	31	-
Tobias-Machado et al. (13)	2016	60	1	236	245	1.6	-	21.6	12.5	50	-
Our Series	**2019**	**700**	**2**	**125**	**100**	**1.6**	**58.2**	**16.2**	**7.7**	**29**	**25**

Year *= year of publication;* ***OT*** *= Operating Time;* ***EBL*** *= estimated blood loss;* ***LOS*** *= length of hospital stay;* ***D/C day 1*** *= rate of discharge day one after surgery*

The first five studies *(darkened) represent successive publications of a single surgeon's (Dr VP. Patel) experience in RALP*

**This study (highlighted in green) takes the weighted means of 17-19 studies combined and these are the values depicted*

i. Illustrations (Figures)

Figure 1. Surgeon-X and -Y D'amico risk Assessment percentage for both surgeons by sub-groups

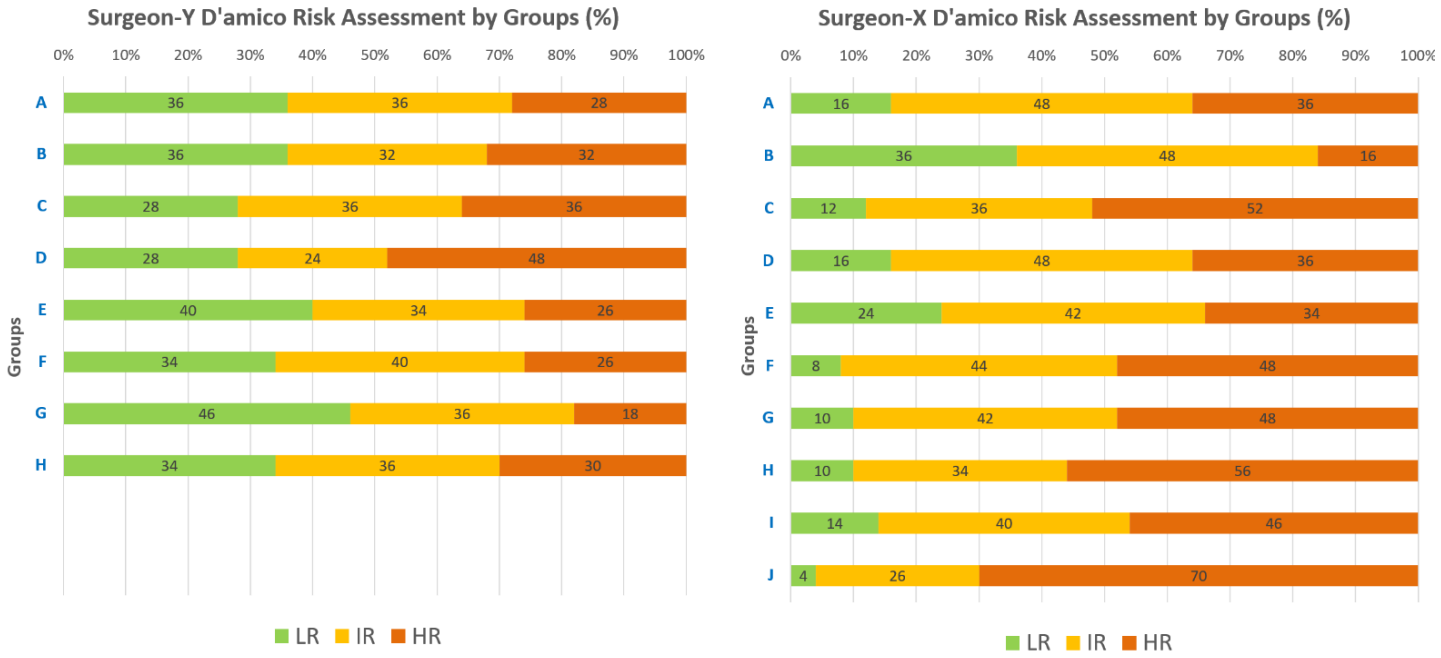


Figure 2. Median Console Times (CT) for both surgeons by sub-groups

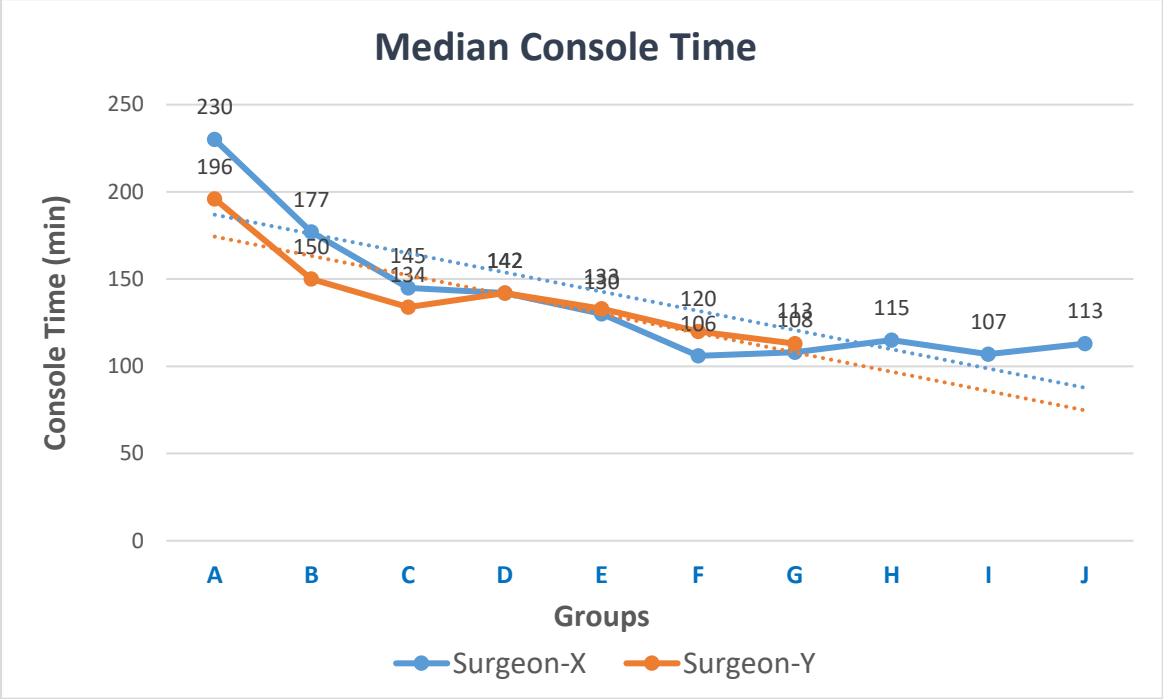


Figure 3. Median Estimated Blood Loss (EBL) for both surgeons by sub-groups

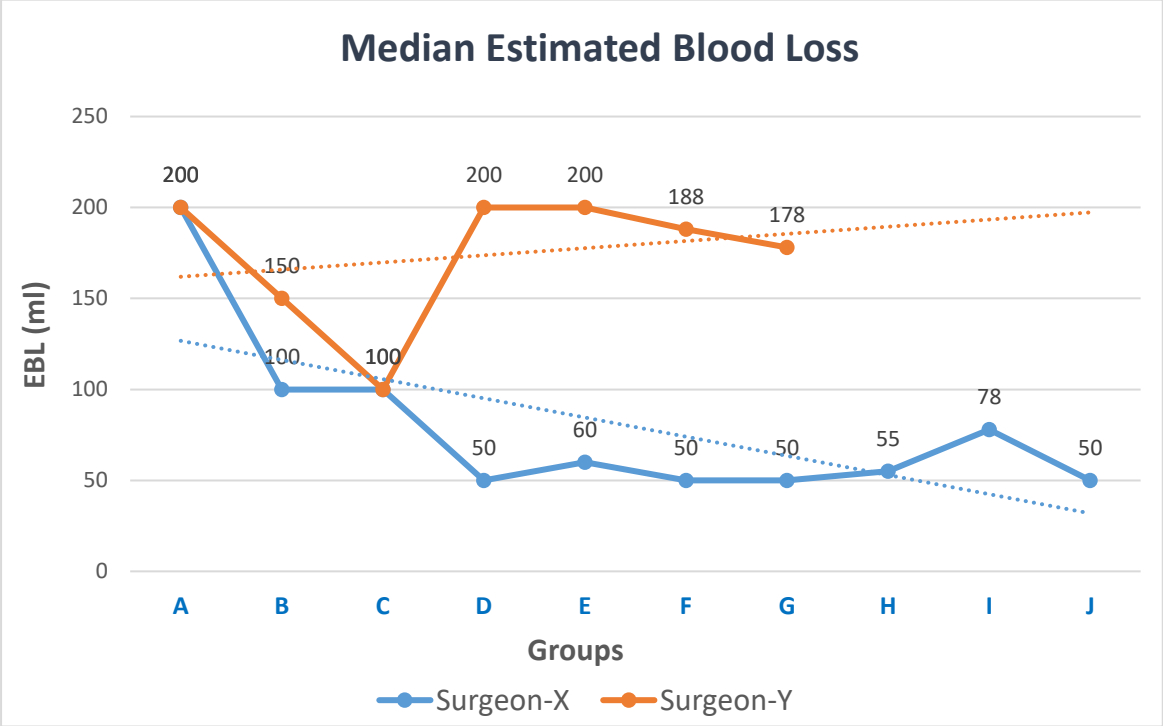


Figure 4. Percentage of Patients Discharged Day One Post Surgery for both surgeons by sub-groups

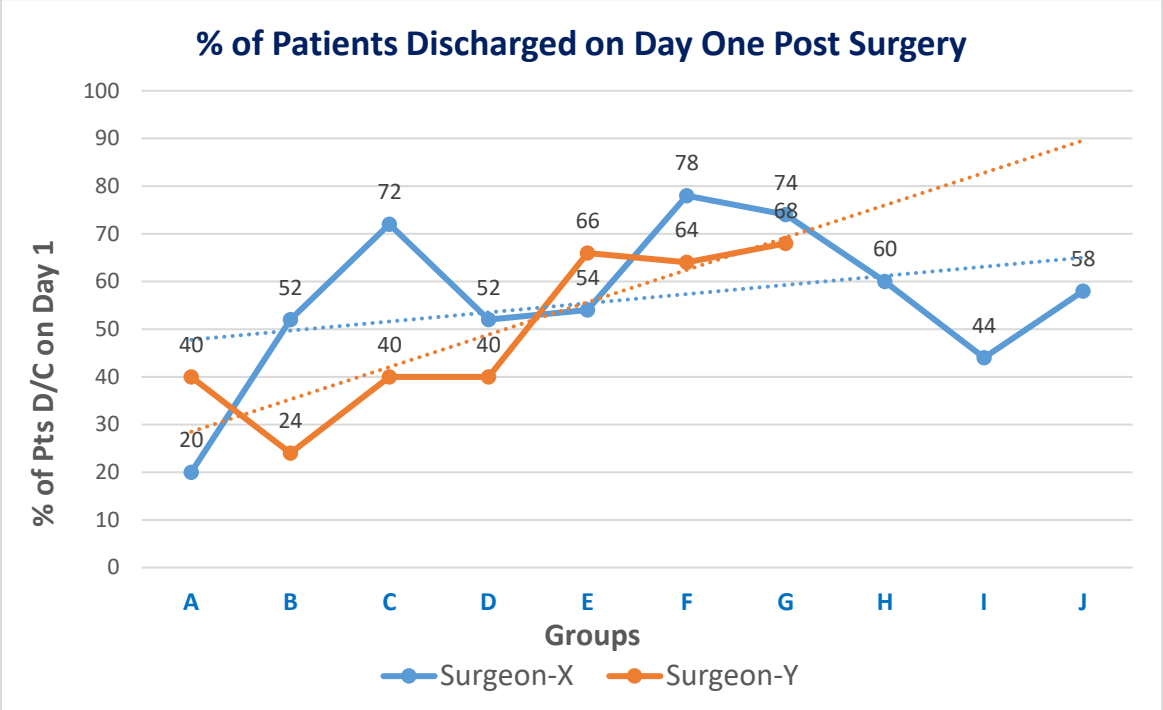


Figure 5. Positive Surgical Margin (PSM) Rate for both surgeons by sub-groups

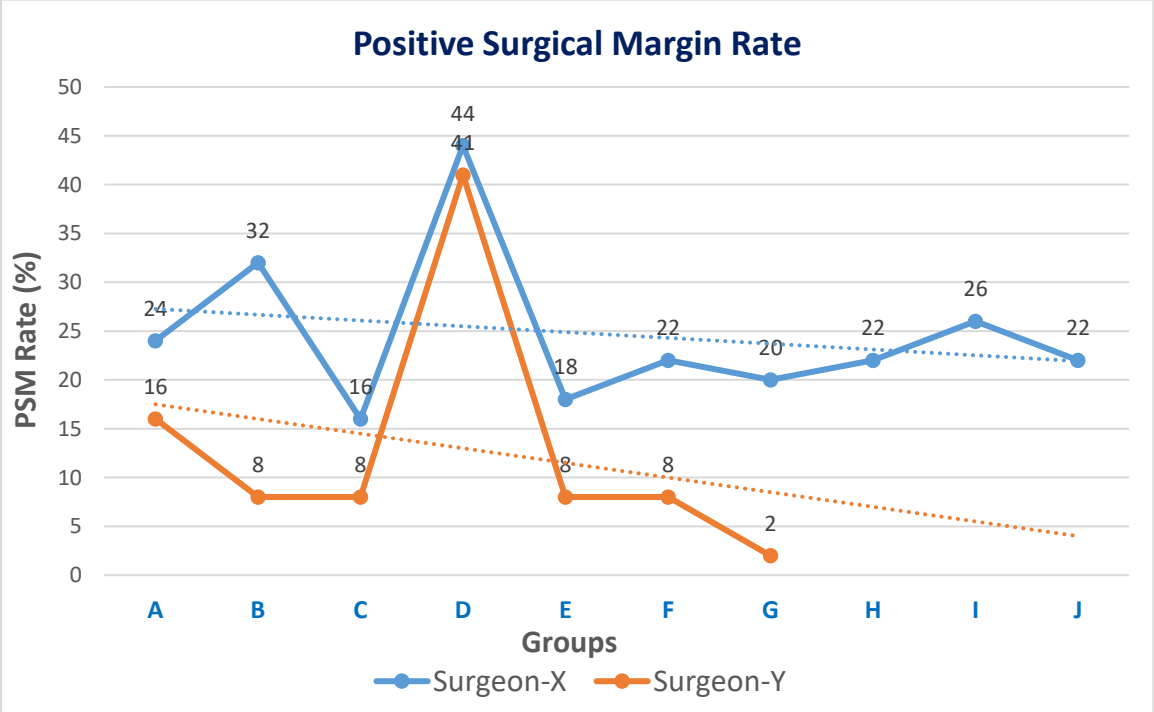


Figure 6. Surgeon-X and -Y Pathological Staging per Group based on Final Histology Report

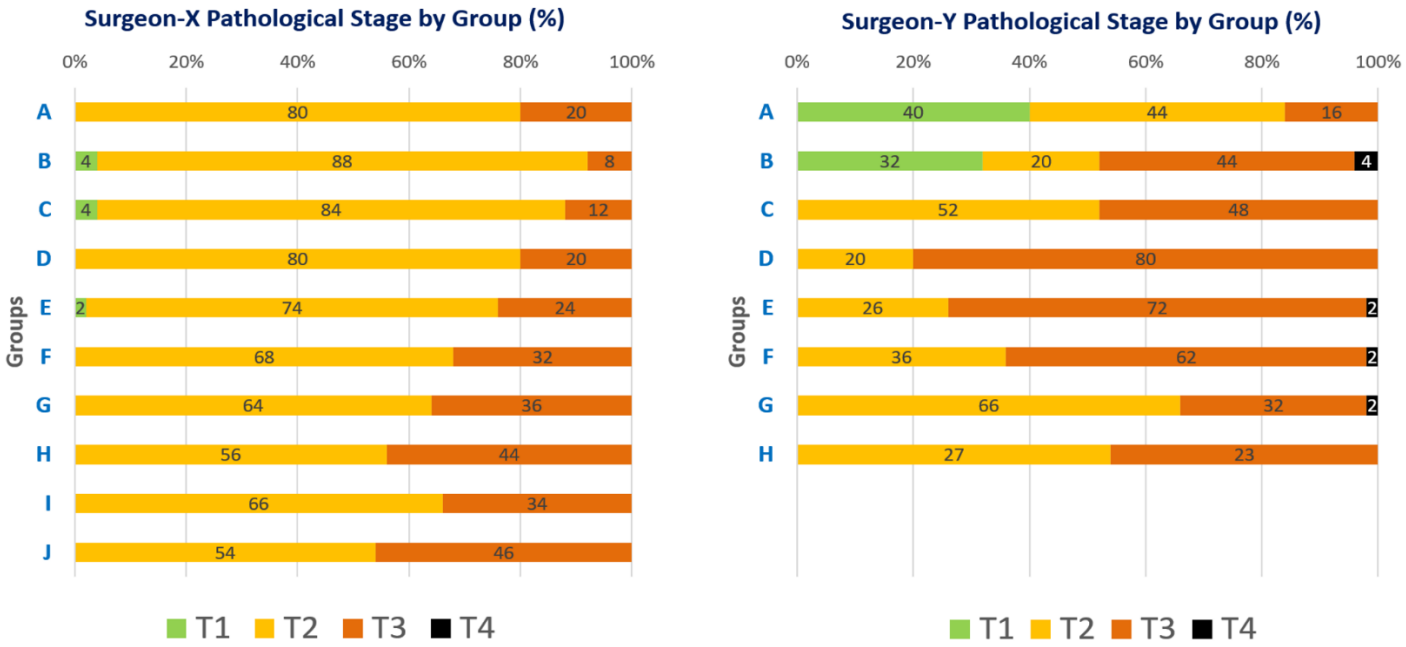
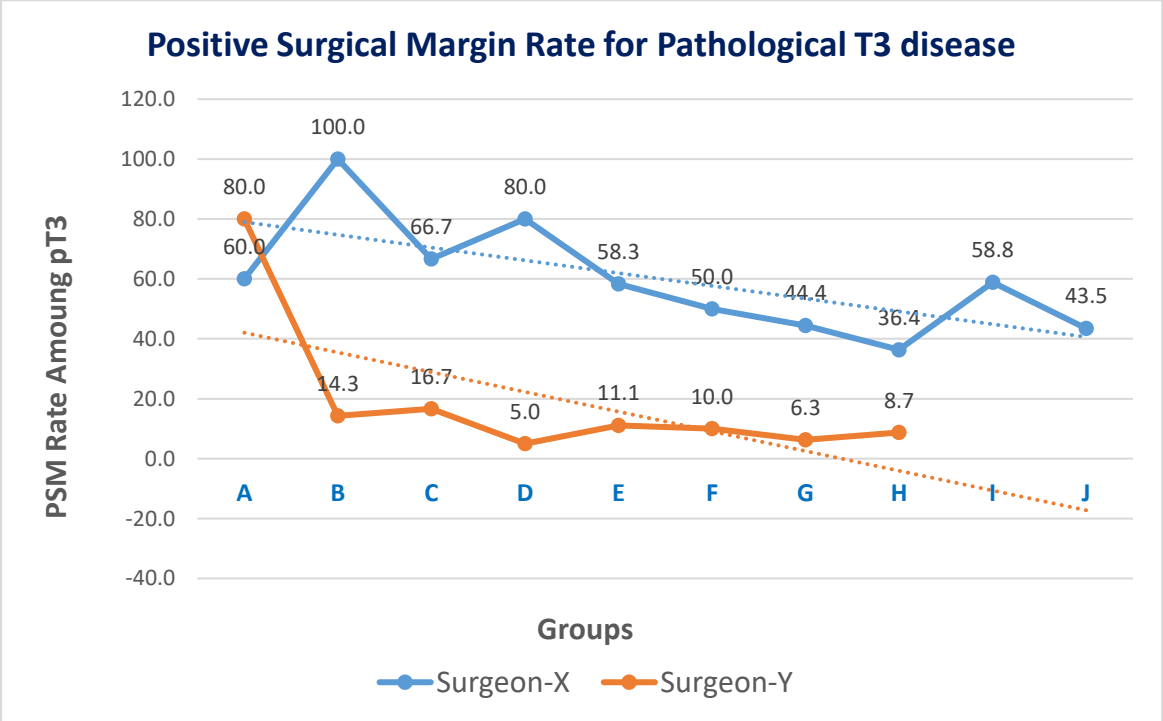


Figure 7. Positive Surgical Margin (PSM) Rate among pathological T3 disease for both surgeons by sub-groups



j. Units of Measurement

operating/console time, excluding setup/docking time (min)

estimated blood loss (ml)

length of post-operative hospital stay (days)

histological outcomes (i.e., Gleason scope or ISUP grading);

pathological data (i.e. TNM staging).

k. Abbreviations and Symbols

PCa: Prostate Cancer

PSA: Prostate-Specific Antigen

LRP: Laparoscopic Radical Prostatectomy

ORP: Open Radical Prostatectomy

RALP: Robotic Assisted Laparoscopic Radical Prostatectomy

CT: Console Time

OT: Operating Time

EBL: Estimated Blood Loss

LOS: Length Of post-operative hospital Stay

PSM: Positive Surgical Margin

ASA: American Society of Anesthesiologists

ISUP: International Society of Urological Pathology

BMI: Body Mass Index

IIEF-5: International Index of Erectile Function score.

l. Appendices

i) Department of Surgery departmental research committee approval letter

ii) UCT HREC approval letter

iii) ICMJE recommendations for conduct and reporting of research published in medical journal

i) **Department of Surgery departmental research committee approval letter**

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

15 Mar 2019

Dr S de Jager

Department of Surgery
University of Cape Town

Dear Dr de Jager

RE: Project 2019/023

PROJECT TITLE: Is The Learning Curve In Radical Robotic Prostatectomies In South Africa Comparable To International Standards?

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,

Yours sincerely

Signature Removed

DR TIMOTHY PENNEL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."

ii) UCT HREC approval letter

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

10 April 2019

HREC REF: 218/2019

Dr Justin Howlett
Urology
E26, NGSH

Dear Dr Howlett

PROJECT TITLE: IS THE LEARNING CURVE IN RADICAL ROBOTIC PROSTATECTOMIES IN SOUTH AFRICA COMPARABLE TO INTERNATIONAL STANDARDS? (MMED CANDIDATE: DR SG DE JAGER)

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 30 April 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.

The HREC acknowledge that the student, Dr Simon Grant de Jager will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

NHREC-registration number: REC-210208-007

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: 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.

HREC 218/2019

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

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

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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.

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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

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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.

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

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-

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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

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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.

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