

# BMJ Open ROBOCOP II (ROBOtic assisted versus conventional open partial nephrectomy) randomised, controlled feasibility trial: clinical trial protocol

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## ABSTRACT

**Introduction** Randomised controlled trials comparing robotic-assisted partial nephrectomy (RAPN) and open PN (OPN) are lacking. Therefore, we aim to report the study protocol and a trial update for a randomised controlled feasibility trial comparing RAPN versus OPN for renal neoplasms.

**Methods and analysis** The ROBOtic assisted versus conventional Open Partial nephrectomy II trial is designed as a single-centre, randomised, open-label, feasibility trial. Participation will be offered to patients with renal neoplasms and deemed feasible for both, OPN and RAPN. We aim to enrol 50 patients within 15 months using a 1:1 allocation ratio. The primary endpoint of the trial is feasibility of recruitment and will be successful if one third of eligible patients agree to participate. Secondary endpoints include perioperative results, health-related quality of life, inflammatory response as well as surgical ergonomics of the operating team. If the primary outcome, feasibility of recruitment, is successful, the secondary results of the trial will be used for planning a confirmative phase III trial.

**Ethics and dissemination** Ethical approval was obtained from the local institutional review board (Ethik-Kommission II at Heidelberg University: 2020-542N). Results will be made publicly available in peer-reviewed scientific journals and presented at appropriate congresses and social media.

**Trial registration number** NCT04534998.

## INTRODUCTION

With approximately 99 200 new diagnoses in Europe in 2018, renal cell carcinoma (RCC) represents a common malignancy in both men and women.<sup>1 2</sup> Surgical resection is the mainstay of curative treatment for RCC. Whenever possible, a nephron sparing approach (partial nephrectomy, PN) should be performed.<sup>3</sup> PN can either be performed by conventional open PN surgery (OPN) or by a minimally invasive approach, incorporating both robotic-assisted PN (RAPN) and laparoscopic

## Strengths and limitations of this study

- There are currently no available data comparing robotic-assisted partial nephrectomy (PN) and open PN from randomised controlled trials (RCTs).
- The ROBOtic assisted versus conventional Open Partial nephrectomy II trial is essential in order to evaluate whether an independent phase III RCT is realistic and to define effect estimates and meaningful endpoints.
- This trial will help overcome well-known challenges of recruitment in surgical trials and to explore facilitators and barriers for participation for both clinicians and patients.
- Analyses are exploratory rather than confirmative.

PN. International guidelines advise towards choosing an approach that best suits the surgeons' expertise.<sup>4</sup> This recommendation is the result of a lack of high-level evidence in support of either approach, be it OPN, RAPN or laparoscopic PN. However, with the recent worldwide surge of adoption of RAPN (eg, a reported increase from 0% in 2006 to 54.4% in 2014 in the USA<sup>5</sup>), randomised evidence supporting this shift from OPN to RAPN is urgently needed in order to adequately justify this change of treatment. Currently, OPN can be seen as the standard of care in Germany and is performed in around 63% of cases, while RAPN is performed in approximately 22% of cases.<sup>6</sup>

Despite being a safe and highly standardised procedure, OPN comes with considerable morbidity such as hernias and flank bulges (in almost 50% of patients), which can be attributed to the open approach and negatively impacts patients' quality of life (QOL).<sup>7 8</sup> Generally, the adoption of minimally invasive surgery to PN has been

driven by hopes of tapping into common advantages of minimally invasive surgery. These advantages include but are not limited to less pain, fewer wound infections and a shorter hospital stay thereby resulting in faster recovery.<sup>9</sup> This is in line with results from the previously published ROBOtic assisted versus conventional Open Partial nephrectomy (ROBOCOP) I trial from our group, a propensity score matched analysis comparing OPN and RAPN.<sup>10</sup> This study confirmed advantages of RAPN in terms of reduced complications, length of hospital stay as well as higher postoperative glomerular filtration rate (GFR). Similar findings were reported from randomised controlled trials (RCTs) for bladder and prostate cancer comparing robotic versus open surgery. For instance, the RAZOR trial was able to show non-inferiority of robotic-assisted radical cystectomy compared with open radical cystectomy in terms of progression-free survival but demonstrated advantages for blood loss, perioperative transfusions and length of hospital stay.<sup>11</sup> Similar perioperative findings favouring robotic surgery were reported by Yaxley *et al*<sup>12</sup> comparing robotic-assisted and open radical prostatectomy. Although no clear advantages for either approach were found, robotic-assisted radical prostatectomy is by far the most commonly performed approach for radical prostatectomy.

Looking at kidney cancer, there are currently no published data comparing OPN and RAPN from an RCT. This might be due to the fact that surgical RCTs face unique limitations mainly through the feasibility of randomisation, learning curves, standardisation of procedures as well as patients' and surgeons' equipoise.<sup>13 14</sup> Feasibility trials are helpful as means of specifically addressing these problems as a well-monitored test series with the aim of avoiding pitfalls in later definitive trials.<sup>15</sup> For example, Stensland *et al*<sup>16</sup> found that 25% of genitourinary cancer trials are terminated early with poor recruitment being the number one cause with almost 40%. As a matter of fact, the UK Medical Research Council, Consolidated Standards of Reporting Trials<sup>17</sup> and IDEAL<sup>18</sup> guidelines explicitly recommend conducting feasibility studies to evaluate key uncertainties before definitive evaluation in large scale RCTs.<sup>19</sup> Therefore, a feasibility study comparing RAPN and OPN is urgently needed before larger trials can be conducted to answer this question. If feasibility of such an RCT can be proven, a subsequent larger multicentre confirmatory trial is promising and shall be conducted.

Therefore, the primary aim of the ROBOCOP II RCT is to assess feasibility of recruitment in a clinical setting in preparation of a confirmative multicentre RCT, ROBOCOP III.

## METHODS AND ANALYSIS

### Trial design and setting

The ROBOCOP II trial is designed as a single-centre, randomised, open-label feasibility trial to compare RAPN and OPN, performed at the Department of Urology and

Urological Surgery, University Medical Center Mannheim at Heidelberg University, Germany. The trial started on 16 June 2020. We aim to enrol 50 patients that actually undergo surgery within 15 months using a 1:1 allocation ratio. However, because of the ongoing COVID-19 pandemic, the recruitment might take longer than the previously planned 15 months. The estimated recruitment end date is 15 December 2021. The primary outcome will be feasibility of recruitment.

### Eligibility criteria

Inclusion criteria:

- ▶ Patient must be at least 18 years old and capable of giving consent.
- ▶ Patient must be scheduled for elective PN for localised renal neoplasms.
- ▶ Both a robotic assisted or an open approach for surgery must be possible as determined from preoperative imaging by all operating surgeons.
- ▶ The patient must be able to understand the goal, consequences and alternatives of participation in the trial.
- ▶ Written informed consent.
- ▶ Curative-intent surgery.
- ▶ Abdominal MRI or CT scan.

Exclusion criteria:

- ▶ Patients with a solitary kidney.
- ▶ Patients belonging to a vulnerable patient group.
- ▶ Simultaneous second surgery.
- ▶ Emergency intervention, for example, because of bleeding or perforation.
- ▶ Multiple kidney tumours.
- ▶ Second malignancy that will make PN needless, this does not include secondary malignancies which are under curative treatment or where death from RCC is more likely.

At baseline, patients' biometrical data including age, sex, weight and height will be collected. CT- or MRT scans will be analysed preoperatively in order to record the preoperative aspects and dimensions used for anatomic classification (PADUA),<sup>20</sup> radius exophytic/endophytic nearness anterior/posterior location (RENAL) and Mayo Adhesive Probability (MAP) scores.<sup>21 22</sup>

Healthcare in Germany comprises statutory health insurance, held by about 90% of population and private health insurance, held by about 10% of population.<sup>23</sup> This results in political and social controversies because reimbursement of private health insurance is more lucrative. These two populations might show different health-related behaviours. Therefore, healthcare status will also be recorded in order to analyse differences in the decision-making processes among patients with different backgrounds.

### Primary outcome

The primary aim is feasibility of recruitment measured as accrual rate. According to Klabunde *et al*,<sup>24</sup> recruitment attitude seems to vary among different medical specialties:

medical oncologists are for instance more likely to participate in recruitment procedures than surgeons.

Generally, the estimated inclusion rate is derived from other multicentre phase III RCTs. Recently, the LEOPARD-2 trial, which compared open pancreaticoduodenectomy with minimally invasive pancreaticoduodenectomy, reported that 42% of eligible patients eventually participated in the study.<sup>25</sup> Similar data were reported by van der Sluis *et al.*,<sup>26</sup> who were able to include almost 50% of all eligible patients in an RCT comparing open vs minimally invasive esophagectomy. Still, patient accrual represents a barrier in clinical trials. This appears to be the case in urology too, where RCTs with surgical interventions were terminated due to poor patient accrual.<sup>27</sup> Therefore, ROBOCOP II will be deemed successful if one-third of eligible patients agree to participate since this would enable realisation of a phase III trial with approximately 10 high-volume centres within an acceptable period of time.

### Secondary outcomes

A broad range of secondary endpoints will be collected in order to analyse potential endpoints for a future confirmative multicentre RCT.

QOL (baseline, hospital discharge, 30 and 90 days post-operatively): data regarding patients' QoL will be acquired using the following questionnaires: Kidney Disease Quality of Life Short Form,<sup>28</sup> Quality of Life Questionnaire C30 (CAT EORTC (Computerised Adaptive Testing - European organisation for Research and Treatment of Cancer)),<sup>29</sup> 5-level version of EuroQol-5 Dimension.<sup>30</sup> Postoperatively: Convalescence and Recovery Evaluation Score.<sup>31</sup> For patients  $\geq 65$  years old, additional questionnaires validated for elderly patients will be administered: Geriatric Depression Scale,<sup>32</sup> G8 Screening tool,<sup>33</sup> Self-administered Comorbidity Questionnaire.<sup>34</sup>

### Perioperative parameters

- ▶ Operating time.
- ▶ Conversion rate from RAPN to OPN.
- ▶ Conversion to radical nephrectomy.
- ▶ Intraoperative complications.
- ▶ Pleural opening.
- ▶ Damage of renal capsule.
- ▶ Intraoperative blood loss.
- ▶ Blood transfusion.
- ▶ Warm ischaemia time.
- ▶ Trifecta, defined as no major complication, R0-resection status and warm ischaemia time of  $\leq 25$  min.<sup>35</sup>
- ▶ Surgical peculiarities and/or anomalies.

### Surgical ergonomics

To better understand the advantages and disadvantages of each procedure on the surgeons' part, each operating surgeon will fill out two questionnaires in order to assess ergonomics: the Borg Scale and the NASA-TLX questionnaire. The Borg scale focuses on musculoskeletal pain and will be registered preoperatively and postoperatively<sup>36</sup>;

NASA-TLX (Task Load Index) records psychological and physical load, as well as temporal expenditure, frustration, subjective performance and stress, and will only be administered right after the operation.<sup>37</sup>

### Inflammatory markers

We aim to compare leucocytes, C reactive protein, interleukin 6 (IL-6), IL 1 beta (IL-1 $\beta$ ), vascular endothelial growth factor and tumour necrosis factor alpha values in both groups.

### Need for analgesia

These recordings will include need for epidural analgesia, opioids, paracetamol, metamizole and other pain medication.

### Intraoperative complications

The "intraoperative adverse incident classification" system by the European Association of Urology will be used to monitor intraoperative complications.<sup>38</sup>

### Postoperative complications

The Comprehensive Complication Index (CCI)<sup>39</sup> which was previously validated for major urological surgery and that is based on the Clavien Dindo classification will be used.<sup>40 41</sup> Since several studies showed lack of standardisation when reporting intraoperative and postoperative complications,<sup>42 43</sup> the latter will be assessed according to the EAU guidelines on reporting and grading complications after urologic surgical procedures.<sup>44</sup>

### Kidney function

For measuring kidney function, the GFR and serum creatinine values will be used. GFR will be calculated by means of the Chronic Kidney Disease Epidemiology Collaboration equation.

### Haemoglobin

Together with transfusion rate, change in haemoglobin values and blood loss will be recorded.

### Oncological outcomes

The histological features of the tumour, and the resection status will be recorded.

### Wound healing

The ASEPSIS (Additional treatment, Serous discharge, Erythema, Purulent exudates, Separation of deep tissues, isolation of bacteria, Stay in hospital) Score will help to assess wound healing.<sup>45</sup> Moreover, other optical features and wound pain will be registered, together with potential postoperative development of flank bulges.

### Case costs

Case costs will be recorded by means of diagnosis-related groups. For each participant, the nursing costs will be additionally calculated.

## Interventions

OPN is performed retroperitoneally. A 10–15 cm flank incision above the 11th rib is made in order to access the retroperitoneal space. After the exposure of the kidney and the renal hilum, the tumour is identified and excised by clamping the renal artery with a bulldog clamp. Alternatively, the excision is performed in zero-ischaemia technique, depending on tumour diameter, position and surgeon's preference. Resection margins are adapted by secure two-layered renorrhaphy using monofilament sutures. Gerota's Fascia is closed by a polyfilament running suture and the wounds closed in layers.

RAPN is performed transabdominally in flank position with the robotic system (da Vinci Xi, Intuitive Surgical, Sunnyvale, California, USA). A mini-laparotomy, lateral to the umbilicus, allows the placement of the optical trocar and application of the pneumoperitoneum. Subsequently, three trocars for robotic-assisted surgery, as well as an assistant-trocar are placed. After preparation of the renal hilum, the kidney is exposed, and the tumour excised. Resection of the tumour is either performed by clamping of the kidney vessels or in zero-ischaemia technique. Bleeding vessels and the collecting system will be closed by V-Loc sutures and secured by Hem-o-lok. Renorrhaphy is performed by interrupted single sutures using monofilament and secured by Hem-o-lok as well.

Finally, Gerota's Fascia is closed by V-Loc sutures. Retroperitoneal or abdominal drain placement will be omitted for both procedures, as no advantage was shown in existing literature.<sup>46 47</sup>

## Recruitment and randomisation

Any patient fulfilling the eligibility criteria will be offered to take part in the trial at a screening check-up. In case of uncertainty in terms of malignant potential or feasibility of both approaches, patients will be presented to an interdisciplinary team consisting of experienced radiologists and urologists to ensure need for surgery. Patients who decide to participate will receive an information sheet and will sign informed consent. After that, they will be randomised and informed about the surgical approach. Randomisation will be performed as blocked randomisation on a 1:1 allocation basis using a web-based computer algorithm that was developed for urological trials at the Department of Urology and Urological Surgery, University Medical Center Mannheim by the Heinrich-Lanz-Center for Digital Health, Medical Faculty Mannheim, Heidelberg University. Block size, which was previously set by an associate that was otherwise not involved in the trial, varies randomly and will be kept confidential until trial completion. Concealment will be ensured by using the aforementioned computer algorithm, which will also generate a unique code for each participant.

## Methods against bias

### Selection bias

All eligible patients will be approached consecutively for inclusion into the trial. The choice of the time point of

randomisation is a pragmatic one in order to enable planning of the available operating theatres.

### Performance bias

Only senior attending urologists with a dedicated training in uro-oncological surgery are allowed to participate in the trial. All surgeons are beyond their learning curve as determined from retrospective analysis of perioperative parameters such as trifecta and operating time.<sup>48</sup> This is in line with previous research that estimated the learning curve for RAPN for experienced surgeons between 16 and 25 cases.<sup>49</sup> Additionally, the participating surgeons (PN, PH and MCK) will have to be able to show at least 100 previous PNs and 100 robotic procedures without major adverse events in order to ensure quality of surgical treatment itself. Surgeon will follow standardised techniques as described above.

### Detection bias

All outcomes will be predefined, and most will adhere to strict definitions that do not leave room for interpretation and potential detection bias.

### Statistical analysis

The primary endpoint is the feasibility of recruitment assessed by the accrual rate which is the number of patients fulfilling the eligibility criteria and agreeing to participate in the proposed trial divided by the number of all eligible patients within the recruitment time. Patients that withdraw consent after randomisation and before surgery will be counted as declined participation.

For all secondary outcomes comprehensive data summaries will be given for the whole cohort and stratified by treatment group (if applicable) by means of number of observations and absolute and relative frequencies for categorical and binary variables or mean, SD, median, IQR, Q1, Q3, minimum and maximum. The comparison between the two treatment groups will be based on appropriate statistical tests depending on the distribution of the data; 95% CIs will be reported. For all secondary outcomes, except for safety relevant endpoints (such as complications) and case costs, comparison of groups will be based on three analyses sets to gain more evidence for the planning of a confirmatory trial: (1) The modified intention-to-treat (mITT) set consists of all randomised patients who underwent surgery. Patients will be analysed in the group they were randomised to (converted patients remain in RAPN group); (2) The per-protocol (PP) set consists of all patients treated PP. Patients with major protocol violation, such as change in treatment group or converted patients, will be excluded; (3) The as-treated (AT) set which considers all patients from the mITT set but patients are analysed in the group they were finally treated in (converted patients in OPN group). Safety relevant endpoints will be analysed in the safety set corresponding to the AT set. For secondary outcomes that are candidate outcomes for a subsequent phase III trial (eg, resection status (R0/R1) and change in kidney function),



missing values will be imputed to gain more evidence. In case of longitudinal data, (generalised) linear mixed models for repeated measures will be applied to account for missing values. Otherwise, multiple imputation by fully conditional specification will be applied.<sup>50</sup> Healthcare status will not be analysed by treatment group but for the overall cohort. Descriptive statistics and free text results will be provided. All analyses will be performed using SAS V.9.4 or higher. A statistical analysis plan will be written before data base closure to describe the statistical analysis in more detail. Data analysts will be blinded after assignment to interventions.

### Sample size

Given that this is a feasibility trial, no formal sample size calculation is performed. However, with respect to the primary endpoint, we assume that approximately 35% of eligible patients that fulfil the inclusion criteria will agree to participate in the proposed trial. This leads to a sample size of  $n=25$  patients per group within the planned 15-month recruitment time based on an expected patient number of around 115 patients planned to undergo PN per year. Furthermore, in a subsequent confirmatory trial, candidate outcomes will be evaluated as primary outcome. Considering a 10% drop-out rate, the width of a 95% CI for a standardised effect (normal distribution assumed) with  $n=22$  patients per group is  $2 \cdot z_{0.975} \cdot \frac{1}{\sqrt{22}} = 0.84$ , thus illustrating the precision that can be achieved with this trial.

### Data management/saving

Data will be collected using a personalised case report form (CRF) at predefined time intervals that are summed up in [table 1](#). The data will then be entered in a protected and validated database (<https://climedo.de/>) approved by the German Federal Office for Information Security and by the Federal Ministry of Health. Only authorised members of the ROBOCOP II study group, comprising study nurses and cooperating doctors, will be permitted to enter, store and access patient data. Climedo holds multiple security certificates (eg, Health Information Trust Alliance, Cloud Security Alliance, Health Insurance Portability and Accountability Act—Protected Health Information) and is encrypted with an SSL-based HTTP protocol (HTTPS). The server's physical location is protected by closed-circuit television and multifactor authentication mechanisms for employees. Every participant will receive a unique subject identification code and a unique patient identification number. Analogue data will be stored and secured at the Department of Urology and Urological Surgery, University Medical Center Mannheim. All data management procedures will be conducted according to written standard operating procedures (SOPs) that guarantee efficient conduct in line with Good Clinical Practice (GCP). At the end of the study, data will be stored for long-term preservation to ensure future reuse.

### Study oversight

Quality assurance will be done in cooperation of monitoring, data management and biostatistics following a risk-based strategy. Risks for patient safety, well-being, patient rights and data validity will be identified and preventive or corrective measures will be taken. Monitoring will be done by the Study Center of the German Society of Surgery and includes clinical on-site visits and will follow SOPs to ensure compliance with the trial protocol, the principles of the Declaration of Helsinki and GCP guidelines as well as data protection and other relevant legal aspects.

The monitor as well as third parties such as representatives of the sponsor or regulatory authorities will be granted access to all trial relevant documents (including CRF, source documents, hospital patient charts and other study files by the investigator. Furthermore, the investigator site file including essential trial related documents like log of staff, delegation log or screening and patient identification log will be controlled. The monitor will also perform a close-out visit at the trial centre. Risk-based monitoring strategy will be described in a study specific monitoring manual.

On-site monitoring will focus on patient informed consent, screening and feasibility as well as safety according to CCI including control of correct recording and documentation by data verification. Frequency of monitoring visits will be determined depending on recruitment performance.

### Funding

The study will be sponsored by the Dietmar Hopp Stiftung, a non-profit organisation founded in 1995 to enable the implementation of projects in sports, medicine, social issues and education. The Dietmar Hopp Stiftung will not be involved in designing, conducting, analysing, interpreting or writing of the trial report.

### Patient and public involvement

The trial was initiated since more and more patients actively asked for RAPN, despite the lack of high-level evidence. Therefore, in the end of the study, patients will be asked about their personal treatment goals and what is most important for them (oncological control, kidney function, QoL). Moreover patients, urologists and other medical personnel will be interviewed with semi-structured interviews to analyse their experience with the study and to detect any potential for improvement.

### Limitations

The results of this trial will be exploratory. However, this trial is essential for a better sample size estimation, for the detection of meaningful endpoints and for the acquisition of first randomised data. Moreover, as in the nature of surgical randomised trials, there might be some unforeseen issues coming up. These can be overcome at the current stage and an amendment will be filed and submitted to the ethics committee if needed.

Table 1 SPIRIT flow diagram

	Enrolment	Presurgical screening	Surgery	Postoperative course
<b>Time point</b>	3–5 weeks before surgery	6–10 days preoperatively	Surgery (POD 0)	POD1 POD3 POD5* POD30 POD90
<b>Enrolment:</b>				
Eligibility criteria	x			After wound closure; 6 hours postoperative;
Informed consent	x			12 hours postoperative
Demographics	x	x		
Randomisation (patients blinded until presurgical appointment)	x			
<b>Interventions:</b>				
Open partial nephrectomy (OPN)			x	
Robot-assisted partial nephrectomy (RAPN)			x	
<b>Assessments:</b>				
PADUA, RENAL and MAP Score		x		
Comprehensive Complication Index				x x x
Borg scale, NASA TLX questionnaires (for surgeons)			x	
Patient-reported outcome measures (KDQOL-SF, CAT EORTC QLQ-C30, EQ-5D-5L; for patients over 65: GDS, G8 Screening tool, SCQ; postoperative: CARE-Score)		x		x x x
Intraoperative secondary endpoints (operation time, blood loss, conversion rate, complications, ergonomics, WITT†)			x	
Perioperative secondary endpoints (change in kidney function, analgesia, tissue healing, mobilisation)†				x x x x x
Case costs				x
<b>Inflammatory markers</b>				
Length of hospital stay, surgical resection status, histological tumour classification, Fuhrmann grading		x	x	x x

\*Or at hospital discharge.

†Outcome assessment when meaningful (eg, length of stay at discharge, resection status dependent on pathology report).

CARE, Convalescence and Recovery Evaluation; EQ-5D-5L, 5-level version of EuroQol-5 Dimension; GDS, Geriatric Depression Scale; KDQOL-SF, Kidney Disease Quality of Life Short Form; QLQ-C30, Quality of Life Questionnaire C30; SCQ, Self-administered Comorbidity Questionnaire; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; WITT, warm ischemia time.

## DISCUSSION

There is currently no published data from RCTs comparing RAPN and OPN. A systematic review and meta-analysis of retrospective studies by Tsai *et al*<sup>61</sup> found lower blood loss, fewer transfusions, longer operative times, fewer postoperative complications, lower readmission rate, shorter length of stay and a lower estimated GFR decline for RAPN. Due to low quality of evidence and high heterogeneity, the authors concluded that RCTs are needed. Similar findings were reported in another meta-analysis by Cacciamani *et al*<sup>52</sup> who also compared minimally invasive approaches. Here, RAPN showed better results compared with laparoscopic PN for perioperative parameters (intraoperative complications, ischaemia time, conversion rate), oncological parameters such as positive margins as well as kidney function.<sup>52</sup> Furthermore, Cacciamani *et al*<sup>52</sup> published a series of meta-analyses focusing on the impact of host factors (eg, tumour complexity, patient comorbidities), hilar control and other factors such as length of hospital stay, readmissions and overall mortality when performing RAPN.<sup>53,54</sup> However, even retrospective studies with appropriate statistical methods cannot adjust for unknown group differences and baseline imbalances. This can only be achieved through randomisation.

Although results from retrospective studies seem promising for RAPN, Ramirez *et al*<sup>55</sup> presented negative results for robot assisted surgery in their prospective LACC trial concerning radical hysterectomy. According to their study, laparoscopic or robotic radical hysterectomy was associated with higher cancer recurrence rate and worse overall survival. Consequently, the trial was terminated early for futility. Therefore, randomised evidence is urgently needed to justify the worldwide surge in adopting RAPN to daily practice and to avoid patient harm.

In order to realise such an RCT, a feasibility trial should precede a phase III trial. The importance of conducting feasibility trials has been shown multiple times, with warning examples such as the PREFERE prostatic cancer trial.<sup>56</sup> The RCT was designed to show non-inferiority of active surveillance, external-beam radiotherapy and brachytherapy by permanent seed implantation to radical prostatectomy with a planned sample size of 7600 patients. However, the trial was stopped early due to poor accrual as only 459 patients agreed to participate within a time period between 2012 and 2016. The realisation of such a study requires the incorporation of all caretakers and patients with their relatives in the process of trial development due to the clinical equipoise and individual beliefs on both sites.<sup>57</sup> For example, the ORANGE II trial was conducted between January 2010 and July 2014 and recruited 24 patients in 8 study centres before it was terminated due to poor accrual.<sup>58</sup> Therefore, dedicated staff training including lectures and simulations should be implemented before commencement of the trial in order to optimised workflow and recruitment as done in recent urological feasibility RCTs.<sup>59</sup> Studies found that telephone reminders, financial incentives, open-trial

designs and opt-out procedures are helpful tools to improve accrual.<sup>60,61</sup>

As mentioned before, a shift in urological surgery towards the robotic approach must be supported and justified by clinical evidence, bearing in mind not only the costs, but also other significant aspects such as long-term oncological and functional outcomes along with patients' satisfaction and surgeons' performance. In addition to the ROBOCOP II trial, there are currently other RCTs comparing RAPN and OPN being conducted. The CONVERT trial (NCT04011891) is designed as feasibility trial and aims to include a total of 30 patients in Canada. Healthcare systems between different countries differ considerably, as a consequence such a trial is important to enable international trials and to confirm findings among different centres and systems. Furthermore, the phase III OpeRa trial (NCT03849820) is being conducted as a multicentre trial in Germany with industry funding. However, the investigators have reported challenges in recruiting patients. Thus, primary completion rate of the study was postponed from February 2021 to May 2023. Additionally, long-term outcomes were recently added as endpoints and are expected in March 2028. The detailed study protocol including sample size estimation and recalculation is yet to be published. Another trial willing to compare RAPN versus OPN for tumours with a RENAL score higher than seven was recently registered in Egypt (NCT04537247).

In summary, the ROBOCOP II trial is essential in order to evaluate whether an independent phase III RCT is realistic and to provide the basis for effect estimates and meaningful endpoints. Moreover, the trial will help to overcome well-known challenges of recruitment in surgical trials and to explore facilitators and barriers for participation for both, clinicians and patients. Last but not least, it will contribute to the evaluation of which surgical approach is superior, even though all endpoints are exploratory.

**Contributors** Academic authorship is based on international authorship criteria. Individuals who collaborated in the trial—yet not fulfilling authorship criteria—will be listed as 'cooperators'. All authors contributed to multiple of the following aspects: Study design: K-FK, MASA, MN, CMH, PN, NW and MCK. Data collection: KF-K, MASA and LE. Statistical planning: K-FK, MK, RK and FS. Statistical analysis: MK, RK and FS. Drafting of manuscript: K-FK, MASA, MN, LE, CMH and NW. Patient counselling: K-FK, MASA, NW and MCK. Operative Procedures: PH, PN and MCK. Critical review: M-SM, PH, PN and MCK. Supervision: M-SM, PN and MCK. Thus, all authors contributed significantly to the presented work. In detail, all author met the following criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work. Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published. 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.

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