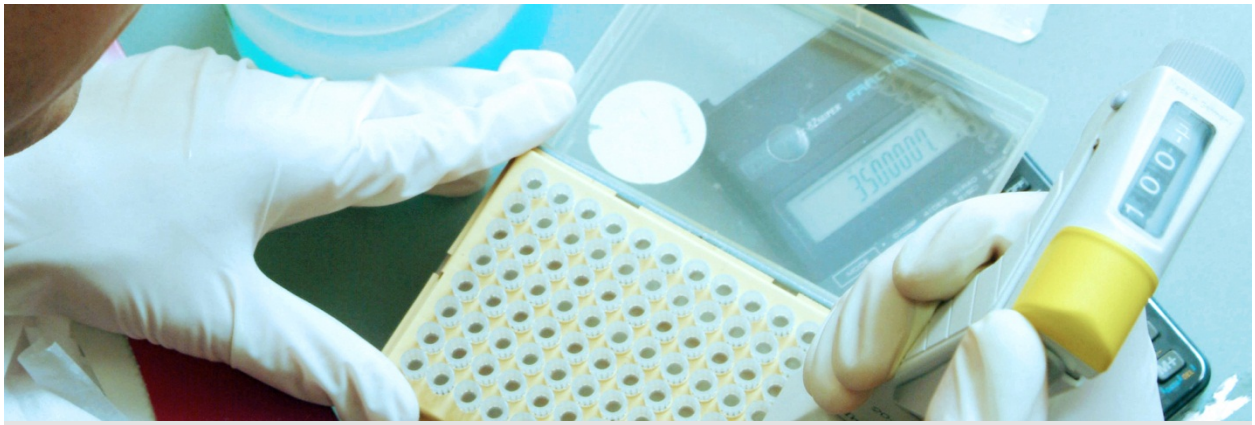
Robotic versus open surgery for radical prostatectomy

Robotic versus laparoscopic surgery for simple or radical hysterectomy



Project plan

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Contents

Abbreviations

AE	Adverse Event
CLS	Conventional Laparoscopic Surgery
FIGO	International Federation of Gynecology and Obstetrics
FSO	Federal Statistical Office
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
LRP	Laparoscopic Radical Prostatectomy
LYG	Life Years Gained
ORP	Open Radical Prostatectomy
PICO	Population Intervention Comparator Outcome
Post-OP	Post-operative
PSA	Prostate Specific Antigen
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RAH	Robot-assisted Hysterectomy
RARP	Robot-assisted Radical Prostatectomy
SAE	Serious Adverse Event

1 Background

Prostate and endometrial cancers are common cancer diseases in Switzerland. Between 2010 and 2014, there were 6 087 new prostate cancer cases and 1 350 deaths [Marquis et al. 2018]. Prostate cancer is the most common cancer in men and the second most common cause of death among men [Federal Statistical Office (FSO) 2016]. The proportion of all cancers cases, averaged from 2008 to 2012, was 29.9% [NICER 2016].

For endometrial cancer, there were 580 new cancer cases in Switzerland between 2008 and 2012 [FSO 2016]. Overall, 430 women died from it [FSO 2016]. Ninety percent of ovarian cancers are epithelial [Torre et al. 2018]. The FSO report mentioned that ovarian cancer accounts for 3.3% of all new cancer cases and for 6% of all cancer deaths.

1.1 Radical Prostatectomy

Treatment for **prostate cancer** is mainly dependent on the stage of the disease, histology (Gleason Score), serum prostate-specific antigen (PSA) levels, and life expectancy. Treatment options, according to the guideline of the European Association for Urology, range from watchful waiting and active surveillance (for localized low risk prostate cancer), over surgery and radiation, to hormonal therapy [Heidenreich 2013, Ontario HTA 2017].

Radical prostatectomy is the surgery to remove the entire prostate and some of the tissue around it [National Cancer Institute]. Radical prostatectomy is recommended, in particular, for patients with low and intermediate risk localized prostate cancer (cT1a-T2b grade tumors, Gleason score ≤ 7 and PSA ≤20, and a life-expectancy >10 years) but is also an option for a variety of patients with different risk profiles [Heidenreich 2013]. It aims to remove the cancer while maintaining continence and erectile function if possible. Depending on tumor characteristics and the patient's sexual function, either nerve-sparing radical prostatectomy (to preserve erectile function) or non-nerve-sparing radical prostatectomy is commonly performed [Ontario HTA 2017]. Nearby lymph nodes may also be removed. In this case, pelvic lymphadenectomy is performed concurrently and is generally reserved for patients with a higher risk of lymph node involvement [Ontario HTA 2017].

Radical prostatectomy can be carried out in four different ways. There exist two different types of open surgical intervention and two minimally invasive techniques:

1. Open radical retropubic prostatectomy
2. Open radical perineal prostatectomy
3. Conventional laparoscopic radical prostatectomy
4. Robot-assisted laparoscopic radical prostatectomy

1.2 Hysterectomy for Benign and Malign Gynecological Disease

Hysterectomy is one of the most common surgeries in gynecology [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe 2015]. It is not only used for malignant disease (most importantly,

endometrial, cervical and ovarian cancer [Ludwig Boltzmann Institut (LBI) 2015]), but also for many benign or pre-malignant conditions such as fibroids, endometrial hyperplasia, adenomyosis, uterine prolapse, dysfunctional uterine bleeding, and cervical intraepithelial neoplasia [Papadopoulos 2010]. Only a small proportion of hysterectomies are performed for malignant disease [LBI 2015]. Alternative treatment methods for benign diseases consist in systemic or local hormonal therapy, operative hysteroscopy, uterine artery embolism or laparoscopic myomectomy [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe 2015].

Vaginal hysterectomy is performed as a total vaginal procedure (uses vaginal hysterectomy techniques only) [Fitch 2016]. An incision deep within the vagina is made. Laparoscopic hysterectomy can be performed in one of three ways: (1) as a total laparoscopic hysterectomy (using laparoscopic hysterectomy techniques only, with or without robotics); (2) as a laparoscopic-assisted vaginal hysterectomy (using both laparoscopic and vaginal hysterectomy techniques); or (3) as a laparoscopic supracervical hysterectomy (using laparoscopic techniques but with retention of the cervix) [Fitch 2016, Warren 2009]. In summary, the following five different ways have been deduced to perform a hysterectomy:

1. Open abdominal
2. Vaginal
3. Laparoscopic-assisted vaginal
4. Laparoscopic
5. Robot-assisted laparoscopic

1.3 Aim of this HTA

The aim of this report is to assess and evaluate the clinical and cost-effectiveness of

- robot-assisted radical prostatectomy (RARP) in comparison to open radical prostatectomy (ORP) for men with localized prostate cancer
- robot-assisted hysterectomy (RAH) in comparison to conventional laparoscopic hysterectomy (CLH) for women with benign or malignant gynecological disease at any stage

2 PICO

In this chapter, we described PICOs (Population, Intervention, Comparator, Outcomes) for radical prostatectomy in section 2.1 and for hysterectomy in section 2.2.

The part of the Cochrane Review for radical prostatectomy comparing robot-assisted versus open surgery forms the basis for the PICOs for prostatectomy [Ilic 2017]. (In its entirety, the Cochrane Review for prostatectomy compares laparoscopic and robot-assisted versus open radical prostatectomy for the treatment of localized prostate cancer).

The Targeted Update of the Cochrane Review for robot-assisted surgery in women undergoing hysterectomy forms the basis for the PICOs for hysterectomy [Cochrane Targeted Update 2018].

In both cases, the Assessment Team added health economic outcomes in line with the results of the scoping process. There may be no data for some of the health economic outcomes listed.

2.1 PICO Radical Prostatectomy

Population

Adult men with localized prostate cancer

Intervention

Robot-assisted radical prostatectomy (RARP)

Comparator

Open radical prostatectomy (ORP)

Outcomes

We considered the following clinical and health economic outcomes:

1) <u>Clinical Outcomes</u>

a) <u>Primary Clinical Outcomes</u>

- Prostate cancer-specific survival
- Urinary quality of life
- Sexual quality of life

b) <u>Secondary Clinical Outcomes</u>

- Biochemical recurrence free survival
- Overall survival
- Overall postoperative surgical complications

- Serious postoperative surgical complications
- Postoperative pain
- Hospital stays
- Blood transfusions (after surgery)

2) <u>Health Economic outcomes</u>

- Costs (total and by category)
- Quality-adjusted life-years (QALYs), life-years gained (LYG)
- Incremental cost-effectiveness ratio (ICER; expressed as cost per QALY gained or cost per LYG)
- Medical resource use (where robotic and open surgery may differ)

2.2 PICO Hysterectomy

Population

Women requiring hysterectomy for benign and malignant gynecological disease at any age

Intervention

Robot-assisted hysterectomy (RAH)

Comparator

Conventional laparoscopic surgery (CLS)

Outcomes

1) <u>Clinical Outcomes</u>

- Intra- and post-operative complications combined
- Intraoperative complications (*injury to the bladder, ureters, bowel, blood vessels and nerves*)
- Postoperative complications (*vascular (e.g. hemorrhage, deep vein thrombosis), wound (e.g. infection, wound breakdown), gastrointestinal (e.g. bowel obstruction due to fibrous adhesions, paralytic ileus due to paralysis of intestinal muscles, incisional hernia (a swelling caused by tissue poking through a surgical wound)), neurological, respiratory (e.g. pneumonia, embolism (blood clot in a lung blood vessel)) and urinary complications (e.g. acute urinary retention)*
- Total operating time (from skin incision to closure)
- Overall hospital stay

- Mortality
- Blood transfusion (during surgery)
- Quality of life
- Postoperative pain
- For cancer surgery: Disease-free survival

2) <u>Health Economic Outcomes</u>

- Costs (total and by category)
- QALYs, LYG
- ICER (expressed as cost per QALY gained or cost per LYG)
- Medical resource use (where robotic and open surgery may differ)

3 Methods

3.1 Clinical Part

The Cochrane Review for radical prostatectomy [Ilic 2017] and the Targeted Update of the Cochrane Review for hysterectomy [Cochrane Targeted Update 2018] will form the basis of the clinical part of this assessment. The Targeted Update of the Cochrane Review for hysterectomy is an update of the original 2014 Cochrane review of robot-assisted surgery in gynecology [Liu 2014]. The update was commissioned by the Swiss Medical Board and focused on the comparison of robot-assisted surgery versus conventional laparoscopic surgery as well as on specific endpoints. In addition to the Cochrane Reviews, an HTA conducted by the Ludwig-Boltzmann Institute (LBI) in 2015 has been considered for this report. It covered the use of robotic surgery for various indications, including prostatectomy and hysterectomy [Ludwig Boltzmann Institut 2015].

Since all above-mentioned reports are very recent, a *de-novo* assessment or an update of the clinical effectiveness of the compared interventions will not be conducted. Thus, the clinical effectiveness part of this assessment will summarize and describe the main results of the above-mentioned Cochrane review and the Targeted Update [Ilic 2017, Cochrane Targeted Update 2018]. The clinical outcomes from the Cochrane Reviews will then be compared with the clinical outcome of the LBI report. In case of discrepancies with regard to the results of the LBI report, differences will be highlighted and discussed. Only endpoint results with an evidence strength (GRADE score) of higher or equal to “low” will be presented for derivation of conclusions for this HTA.

3.2 Health Economic Part

The health economic assessment consists in a systematic review of the currently published literature and a *de novo* cost analysis and budget impact analysis.

The systematic review will primarily focus on economic evaluations reporting results in terms of cost per QALY or cost per LYG. In addition, we will review cost studies to populate the model for the *de novo* cost analysis.

In the scoping, considered options include a *de novo* cost-effectiveness analysis for Switzerland or a cost analysis with a potentially relatively short time horizon, depending on data availability. We plan a budget impact analysis in any case. Given the limited evidence with regard to longer-term clinical differences, we might choose a cost analysis instead of cost-effectiveness analysis for this HTA.

We therefore plan to:

a) perform a *de-novo* cost analysis from several perspectives (to the extent that data is available for each perspective)
    a. 'KVG perspective' (considering the direct medical costs of all health care services covered by the Swiss statutory health insurance irrespective of the actual payer, e.g. robot costs, home visit community nurse costs)

b. ‘Societal perspective’ (all medical and non-medical costs including time off work)
c. ‘Hospital perspective’ (hospital costs including robot costs ; to capture the difference between real costs of service provision and reimbursement; primarily based on DRG reimbursement)

b) conduct a budget impact analysis based on the results of the cost analysis in combination with the number of surgeries performed in Switzerland

The economic models for prostatectomy and hysterectomy will be developed as much as possible in parallel. Where differences arise, they will be highlighted.

The clinical outcomes from the Cochrane Reviews that will show to differ between the robotic and non-robotic surgical interventions will be selected. They will then be compared with the results of the LBI report and combined with clinical and economical parameters of relevance according to the results of the economic systematic literature review. Endpoints related to life expectancy and quality of life (i.e. LYG, QALYs, cost per LYG or QALY gained) will not be estimated since there was no available evidence on longer-term quality of life after the surgical interventions and a difference between the interventions under investigation. Published information about these endpoints has shown to be particularly scarce. The resulting list of outcomes and parameters will serve as input parameters into the health economic models.

The Targeted Update for hysterectomy also looked at total costs (including equipment costs, theatre costs and hospital stay). RAS showed possibly higher total costs compared with CLS (low certainty) for benign cases. We will compare the cost results of the Targeted Update of the Cochrane review with the cost results of the de novo cost analysis.

3.2.1 Systematic Literature Review

A systematic review of the current economic literature has been undertaken. The aim was to identify literature on the costs and cost-effectiveness of

- RARP compared to ORP for patients with prostate cancer
  and
- RAS compared to CLS for women requiring hysterectomy for benign or malignant endometrial cancer.

All types of economic evaluation studies have been considered and checked for relevant content: cost-effectiveness analyses, cost-benefit analyses, cost-utility analyses and cost-minimization analyses.

In addition, we will review cost studies to identify important input variables and unit costs for the planned *de novo* analysis.

3.2.1.1 Literature search strategy

We developed a search strategy to identify all relevant literature in the following electronic databases: Medline and Embase databases including abstracts by using OvidSP (including Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily Update, Embase), the Cochrane Library and the Centre for Review and Dissemination (CRD) database including the Database of Abstracts of Reviews of Effects (DARE), Cochrane

reviews, Health Technology Assessments (HTA) and the Economic Evaluation Database from the UK National Health Service (NHS EED).

The search string was obtained by integrating and combining a search string recently developed for two Cochrane systematic reviews [Ilic 2017, Cochrane Targeted Update 2018] and published search strings for health economic analyses from the InterTASC Information Specialists' SubGroup (ISSG) website (www.york.ac.uk/inst/crd/intertasc). The following filters, described as highly sensitive in Ovid MEDLINE and EMBASE, were included: The National Health Service Economic Evaluation Database (NHS EED) filter, the NHS Quality Improvement Scotland filter and the Royle filter published in 2003 [Royle 2003]. Additional filters such as the Scottish Intercollegiate Guidelines Network (SIGN) filter (www.sign.ac.uk/methodology/filters.html), the McKinlay et al. filter, the Wilczynski et al. filter, and the Sassi et al. filter were also included [McKinlay 2006, Wilczynski 2004, Sassi 2002]. Unspecific abbreviations such as CUA or CBA were not used.

We performed the search between the first and the sixth of March 2018 for prostatectomy and between the eight and eleventh of March 2018 for hysterectomy.

3.2.1.2 Screening of the search results

The screening of the literature was divided into three phases. In the first phase, all results of the literature search were screened by title. Titles containing relevant keywords such as prostatectomy, hysterectomy, robotic surgery, open surgery, laparoscopic surgery, costs, value, cost-effectiveness, cost-benefit, cost-utility, health technology assessment, quality of life, and burden were considered as potentially relevant.

All papers with potentially relevant titles then proceeded to the second phase, the screening by abstract. In this phase, abstracts were screened for relevant quantitative results (e.g. costs, LYG, QALYs, or ICERs) or for sentences suggesting potentially relevant content in the full text version.

Potentially relevant abstracts proceeded to the third phase, in which full texts were screened. Articles were then classified as being potentially relevant or as potentially providing important information.

- Relevant articles needed to meet the following criteria:
    - The article reported a full-scale incremental cost-effectiveness analysis, ideally but not necessarily with an endpoint of cost per QALY gained or cost per life year gained.
    - The 'PIC' of the PICO corresponded to the one defined in the scoping document and used in the systematic review part of this HTA report.
    - The analysis was performed for a jurisdiction with broadly similar socioeconomic characteristics as Switzerland (e.g. North, Central and Western European countries, the USA, Canada, Australia and New Zealand).
- Study potentially providing important information were defined as not meeting the criteria for the 'relevant' category but potentially containing useful additional information concerning effectiveness or costs, and thus being 'partially relevant'. Depending on the quality and quantity of information available from relevant articles, some partially relevant articles were used as an additional source of information and for comparison.

3.2.1.3 Synthesis of findings

We synthesized the resulting different pieces of information. This necessarily involved an element of interpretation, but it has been an explicit aim to make all related assumptions transparent. Comparisons of the assumptions and of the data used by the various cost-effectiveness analyses were made. The discussion included a critical review of possible sources of uncertainty.

3.2.1.4 Additional cost data collection for cost analyses and budget impact analyses

De novo health economic modelling (see section 3.2.2) requires the best possible input parameter values. Depending on the availability of Swiss cost data, it may be necessary to extract information from international cost studies that are not full-scale health economic evaluation studies, and thus 'partially relevant' studies according the definition provided in section 3.2.1.2.

Next steps: for the above-mentioned reason, cost studies identified through the systematic literature search will be further analysed. Only recently published studies (not older than 10 years) reporting cost information for both robotic and open/laparoscopic surgery will be considered. Studies without adjustment for potential confounders will be excluded.

Transferability of the findings to Switzerland and implications for Switzerland will be discussed. For better comparison, numerical adaptation to Switzerland will be considered.

3.2.2 Cost Analyses

De-novo cost analyses for radical prostatectomy and hysterectomy will be performed for Switzerland. A patient cohort will be modelled for each indication and followed for a defined time horizon postoperatively. The two cost models (for prostatectomy and hysterectomy) will be developed in Microsoft Excel 2016® (Redmond, WA). The model populations will correspond to the populations as stated in the PICOs. The model will cover surgery costs, follow-up treatment costs, AEs costs, and, if possible, indirect costs due to time off work. Efficacy differences translating into resource use differences will mainly be derived from the Cochrane Reviews and the LBI report. Costs differences between treating strategies will be highlighted and discussed in detail. Determined cost components derived from the economic literature review will be broken down and Swiss costs listed.

To verify the validity of the models, uncertainty analyses (univariate sensitivity analyses, scenario analyses and probabilistic sensitivity analyses) will be performed as appropriate.

3.2.2.1 Time horizon

The time horizons for the cost analyses need to be longer than the duration of the primary hospital admission in order to capture the clinical and economic differences during the post-operative period. Specifics depend on how long differences have been observed or are expected by clinical experts. As of today, a time horizon of 3 months is anticipated due to the lack of robust studies with long-term clinical outcomes. *[NB: The currently chosen time horizon of 3 months post-surgery may be extended to 1 year]*

3.2.2.2 Discounting
Due to the short time horizon, discounting can be neglected except for the depreciation of the costs for the da Vinci robot.

3.2.2.3 Endpoints
Health economic endpoints of interest include total costs, sub-categories of total costs as well as their drivers. Drivers include e.g. immediate surgery costs, operating time, surgeon experience, estimated blood loss, number of blood transfusions, rates of conversion to open surgery, duration of total hospital stay, resource use for intra- and post-operative complications like e.g. incontinence treatment, hospital readmissions, and re-operations.
Unless the additional literature research for cost studies will reveal important differences in oncological outcomes based on observational studies, oncological outcomes will not be considered in the health economic assessment. The evidence of observational study results is likely to be low due to the methodological limitations of many of such studies.

3.2.2.4 Cost components
The LBI report about robotic surgery based on the da Vinci® surgical system forms the basis for the specification of the cost components for the different surgical systems, their equipment and consumables [LBI 2017]. We plan to add also information from selected cost publications. For prostatectomy, three publications [Burgess 2006, Hohwü 2010, Scales 2005] reporting cost comparisons between robotic and open radical prostatectomy as mentioned in the UK HTA [Ramsey 2012, p. 49], will also be considered. With regard to procedure costs, the UK HTA report cites two additional publications estimating US costs through a retrospective patient cohort and a hypothetical costing exercise for prostatectomy [Bolenz 2010, Lotan 2004]. Both publications will be considered for the identification of cost components.

The following costs endpoints for the surgical systems will be investigated in the above-mentioned studies (the listing may currently not be complete):

a) Costs for the robot and its yearly maintenance
b) Costs for the surgical equipment for open, laparoscopic and robotic surgery
c) Costs for consumables for the different surgery types under investigation
d) Costs for manpower for the different surgery types under investigation
e) Costs for the operating theatre

Depending on the perspective under investigation, we will explore number and costs of follow-up treatments, AEs, outpatient follow-up visits, home visit by community nurse, and productivity loss. If possible, also indirect costs related to time off work will be investigated to provide an estimation of the total costs of the interventions from a societal perspective.

A preliminary literature review indicated that the number of robotic operations per surgeon per year may have an impact on the duration of surgery. Surgeon experience may also impact on surgical outcomes and the number of adverse events (AEs) and serious AE (SAEs). Surgeon learning curve and related consequences will be investigated further through literature review, expert opinion and a possible analysis of data from the University Hospital Basel.

Cost sources

In general, we will obtain the required elements of the economic analysis through

- The results of the literature review of cost studies
- Input from Swiss clinical experts
- Swiss Hospital Statistics of the Swiss Federal Statistical Office (SFSO): e.g. published statistics of the "Schweizerische Eidgenossenschaft" (Medizinische Statistik der Krankenhäuser 2013, http://www.portal-stat.admin.ch/sgb2012/files/de/02f.xml, https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit.html?dyn_pageIndex=0)
- Diagnosis-related case costs statistics ("Statistik diagnosebezogener Fallkosten") of the SFSO
- The National Institute for Cancer Epidemiology and Registration (NICER) and the Swiss Cancer League
- Possibly an anonymized retrospective analysis of patient data from the University Hospital Basel
- The Intuitive Surgical Incorporated website for costs with regard to the da Vinci robot and its equipment (http://investor.intuitivesurgical.com/phoenix.zhtml?c=122359&p=irol-IRHome)
- Additional sources that may be identified during the research process

Costs will be inflated to 2017 values using the Swiss consumer price index. If required, we will derive unit costs for drugs with relevant Anatomical Therapeutic Chemical Classification System (ATC) from the SFOPH, Spezialitätenliste (http://www.spezialitaetenliste.ch/).

In summary, we will perform the approach to find suitable evidence to populate the models and to identify input parameters related to costs for radical prostatectomy and hysterectomy:

- The systematic review of the economic literature already mentioned above. The number of identified cost studies will be reported
- Additional targeted searches, complemented with hand-searches of the grey literature and the world wide web (non-systematic) will also be completed in order to identify manuscripts for event rates, health resource use and costs that will not be available from the above-mentioned literature reviews

Real-world evidence sources might also be used with regard to prevalence and robotic surgery in radical prostatectomy and hysterectomy.

3.2.3 Budget Impact Analyses

Budget impact analyses will be performed to compare robotic surgery with open/laparoscopic surgery in terms of their cost impact on the Swiss health care system.
It may be challenging to obtain valid estimates for the number of da Vinci Robots in Switzerland, the number of Swiss surgeries per robot and clinic and year (robot/clinic/year) as well as the number of Swiss surgeries per surgeon per year. The stakeholder list presented in the appendix will be utilized to find the necessary information.
A base case scenario representing the current use of robotic surgery in Switzerland will be estimated through the available literature, Swiss data (e.g. Swiss Hospital Statistics) and expert

opinions. Information on the yearly number of surgeries in Switzerland will be combined with the estimated costs from the cost analysis. Different scenarios for the development of the number of robotic surgeries in Switzerland will be analysed and presented.

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