COST-UTILITY ANALYSIS OF LAPAROSCOPIC VERSUS OPEN APPENDECTOMY IN CHILDREN

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

By

Sanskriti

Under the Supervision and Guidance of

Dr. Ashok Peepliwal

2024

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled "Cost-Utility Analysis of Laparoscopic Versus Open Appendectomy in Children" is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

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This is to certify that dissertation titled "**Cost-Utility analysis of Laparoscopic versus Open Appendectomy in Children**" is a record of the research work undertaken by **Ms. Sanskriti** in partial fulfillment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

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Acknowledgment

At the outset of my thesis, I would like to express my sincere gratitude to all the individuals who have assisted me with this research. Their strong leadership, participation, and encouragement have been instrumental in the completion of this work.

I am deeply indebted to my advisor, Mr. Anoop, for their unwavering guidance and support throughout the research process. Their insightful feedback and expertise have been invaluable.

I am also profoundly grateful to Mr. Saurabh Kumar, Associate Professor and Dean at School of Pharmaceutical Management, IIHMR University, for his exceptional direction and support. My deepest sense of gratitude also extends to Mr. Vinod Tejwani, Dean of Placements & Alumni Relations at IIHMR University, for his assistance and encouragement.

A special thanks to my faculty guide, Mr. Ashok Peepliwal, for his consistent guidance and valuable insights, which greatly contributed to the completion of this thesis.

Lastly, I would like to thank all my friends and family who, directly or indirectly, have supported me in completing this thesis. Any omission from this acknowledgment does not imply a lack of gratitude.

Thank you.

Sincerely,

Sanskriti
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TABLE OF CONTENT

ABBREVIATIONS

Abbreviation	Meaning
AA	acute appendicitis
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CUA	cost-utility analysis
ETI	endotracheal intubation
HRQoL	health-related quality of life ICER
	incremental cost effectiveness ratio
LAp	laparoscopic appendectomy
lpm	liters per minute
MCS	Monte Carlo simulation
MIS	minimally invasive surgery
OAp	open appendectomy
QALY	quality adjusted life year
QALM	quality adjusted life month
QoL	quality of life
SD	standard deviation
MIN	minimum value
MAX	maximum value

Abstract

Laparoscopic appendectomy is one of the most common minimally invasivesurgeries performed in children. Demonstrating its cost-utility concerning health-related quality of life (HRQoL) will support justifying the higher costs associatedwith this method.

Objective: To conduct a costutility analysis (CUA) comparing open appendectomy (OAp) and laparoscopic appendectomy (LAp).

Material and methods: To achieve this, we created a decision analytic model to calculate the cost effectiveness of LAp versus OAp. Our analysis included data from children who had undergone surgery for uncomplicated acute appendicitis and agreed to participate by completing a validated quality of life questionnaire. We calculated the total costs incurred for each patient undergoing either procedure. For the analysis, we set a cost-effectiveness threshold, or λ, at 20,000to 30,000 euros per quality-adjusted life year (QALY), which is a standard metric used to measure the value for money in healthcare.

Results: We included 53 patients in the study. The average cost for patients undergoing open appendectomy was 758.98 euros, while the cost for those undergoing laparoscopic appendectomy was significantly higher at 1,525.50 euros.Despite the higher cost, the incremental cost-effectiveness ratio (ICER) was calculated to be 18,000 euros per QALY, which falls within the acceptable threshold we established.

Discussion: Economic evaluation studies in pediatric surgery are rare and infrequently consider quality of life outcomes. This information is crucial for informed decision-making. Our findings support the use of laparoscopy in pediatric appendectomy to enhance the HRQoL of our patients.

Chapter 1: Background

Health economics has become an increasingly popular field of study. There is a growing interest in economic analyses within healthcare, as evidenced by the publication of more than 6,000 papers on the subject in 2019[1].This heightened focus is likely due to a greater recognition among healthcare professionals of the importance of understanding the economic implications of medical treatments and interventions.

Traditionally, the approach of a physician when a new medical intervention is introduced focuses primarily on evaluating its efficacy and associated complications. This involves making comparisons between two drugs or surgical techniques to ascertain which one yields better outcomes, boasts ahigher resolution rate, has fewer complications, or results in a shorter hospital stay. Clearly, this type of assessment is crucial and forms the foundation of medical practice.

However, it is imperative that we broaden our perspective and consider a more comprehensive evaluation. Once an intervention has been proven to be more effective in terms of clinical outcomes, we must delve deeper into understanding its broader implications. The medical community must recognize the necessity of taking into account the economic aspects of each intervention, especially in environments where resources are limited and during times of economic crisis.

In scenarios where a standard intervention is already well-established and delivers satisfactory results, demonstrating superior outcomes with a new intervention can be particularly challenging. This difficulty is often compounded in fields like Pediatric Surgery, where the number of patientsis smaller and the differences in outcomes between the new and standard interventions are often subtle. In such cases, the evidence supporting the superiority of a new intervention over the established standard may not berobust enough.

Therefore, beyond the clinical efficacy, it is essential to incorporate econo mic evaluations into our assessments. This involves analyzing the cost-effectiveness of new interventions in comparison to the standard ones,consideri ng the overall value they bring in terms of health outcomes and financial impact . By doing so, healthcare professionals can make more informed decisions that not only improve patient care but also ensure the optimal allocation of limited resources.

Economics as a science, investigates the best possible way to allocate a resour ce, as they are limited and could have many alternative uses[2]. This is esp ecially true in Health Economics. (Figure 1)

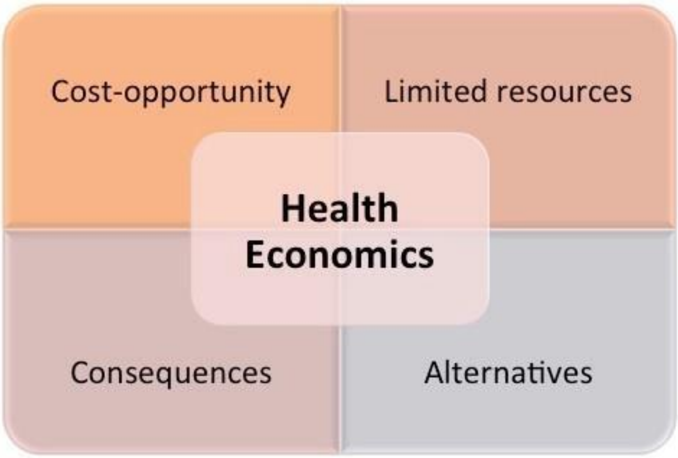


Figure 1: Scheme of Health Economics connecting the main concepts.

Every resource used in an intervention—whether it's healthcareprofessionals, equipment, or space—has an opportunity cost, meaning that these resources could potentially be use d elsewhere. Ideally, each resource should be allocated to its most beneficial us e[3].

Minimally invasive surgery (MIS) was developed to reduce surgical traum ato patients, thereby improving outcomes and speeding up recovery. The jour ney began in the early 20th century when the first laparoscopes were used on animals with the aid of pneumoperitoneum[4]. This method advanced si gnificantly throughout the century, especially with the

introduction of video technology in the 1960s. Gynecologists played a keyro le in its development, and its applications spread across various medical special ties. However, laparoscopy initially faced considerable skepticismand was not widely accepted right away. It wasn't until 1989 that the firstlaparoscopic c holecystectomy was formally recognized at the AmericanCollege of Surgeons meeting. Since then, the innovative concept of minimally invasive surgery has expanded across all surgical fields, including Pediatric Surgery[5].

Given the advanced technology and the increased operational times requir ed for minimally invasive surgery (MIS), these procedures tend to incur hi gher costs[6,7]. However, there is evidence from adult populations that the r educed hospital stays and quicker return to normal activities can offset these higher costs when considering the broader social and healthcare system p erspectives[8]. MIS has demonstrated its superiority over traditional open surgery in adults for procedures such as cholecystectomy, appendectomy, and colon su rgery[9,10,11]

In pediatric patients, however, justifying the use of MIS can be more challengi ng for several reasons. Firstly, many pediatric procedures are performed on a d ay-

case basis, and even in cases of acute uncomplicated appendicitis, children are t ypically discharged shortly after surgery. The recovery for a previously healt hy child following an open appendectomyis usually swift and uncomplicate d. When a specialized Pediatric Surgery team manages pediatric surgical con ditions, with established protocols and enhanced recovery pathways, outcomes are generally excellent, making further improvements difficult to achieve[12].

Additionally, obesity, a condition where MIS clearly shows advantages, is mu ch less common in children than in adults, making open surgery quicker and easier in small, thin patients[13]. Furthermore, complex and lengthy proc edures are less frequent in pediatric surgery compared to day-

case surgeries. This scarcity makes it difficult to complete the learning curve for advanced pediatric MIS and to accumulate enough cases to provide high-quality evidence of its benefits[14].

There are not many studies regarding the economical evaluation of pediatric MIS. Most of them are focused on comparing the costs of the laparoscopic procedure and the costs of the postoperative course or hospital stay without taking into account quality of life measurements[21,22]. It is important for healthcare professionals to understand the differences inmethodology of these kinds of studies, to analyze the data and assess the implications of our choices in the best possible way.

Drummond and cols defined economic evaluation in healthcare as"comparative analysis of alternative courses of action in terms of both their costs and consequences"23. In our case, we do so by evaluating cost-opportunity and health effects (consequences) of two different surgical approaches (open and laparoscopic). On the one hand, costs can be divided into three different categories:

- Direct costs: they are the ones directly derived from the intervention.They can be further divided into direct healthcare costs (such as hospital stay) and direct non-healthcare costs (such as transport to the hospital).
- Indirect costs: those are the ones related to the loss of productivity of the patient or in case of children, of the parents or caregivers.
- Intangible costs: they are related to psychological impact, or pain. They are subjective and therefore not usually considered in economicstudies as they cannot be easily measured.

On the other hand, consequences can be measured in different ways,defini ng different approaches to the economical analysis. There are four different wa ys to undertake this analysis depending on how the health effects or conse quences are measured[3]. (Figure 2)

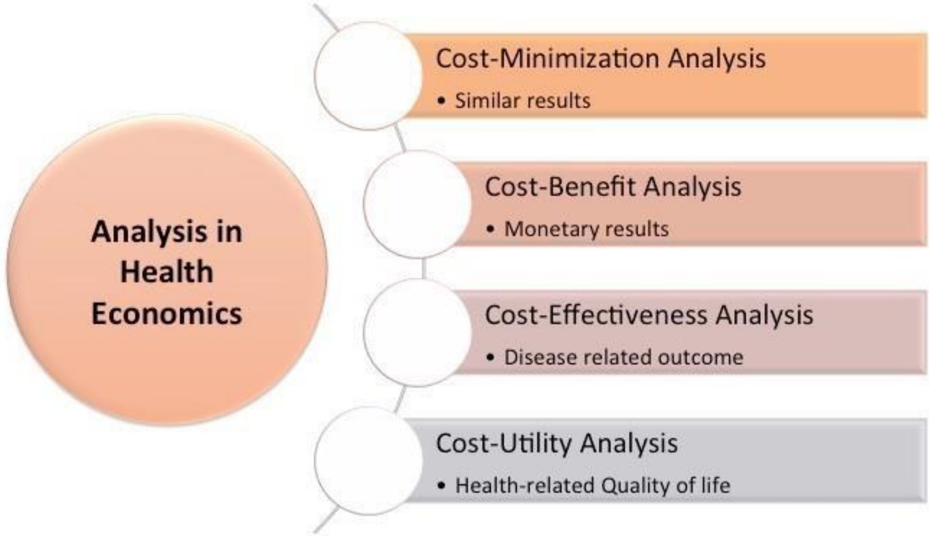


Figure 2: Different types of health economic studies.

The costeffective analysis (CEA) measures the health effect in terms of a physical outcome, general or disease-specific. The most common unit is life-years gained. In the case of pediatric MIS could be something else, for i nstance time to full feeds in open versus laparoscopic pyloromiotomy[24]. In this case we are measuring a direct positive consequence or health effect o f our intervention that directly benefits the patient.

Finally, one step ahead we have the costutility study (CUA). In this analysi s we measure the health effects in a way that takes into accountnot only the healthstate but the quality of this healthstate as well. This concept is calle d healthrelated quality of life (HRQoL). For instance, after appendectomy the h ealthstate will be "cured", but it is not definitely the same a cured child that have some residual discomfort and that takes more time to get back to schoo l or sports or social life, that a child that can do so right away. The unit we use to measure HRQoL is the quality-adjusted lifeyear or month (QALY or QALM)[25]. This measurement is estimated from the area under the curve of preferences regarding health status over time. (Figure 3).

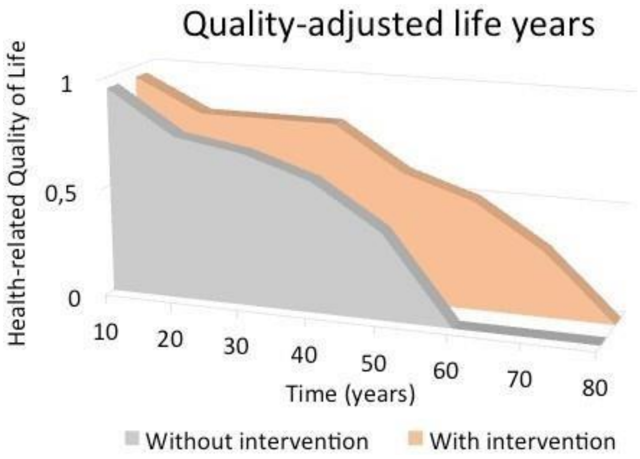


Figure 3. Example of Healthrelated quality of life in two hypotheticalscenarios with and without an intervention.

This curve depicts how we would like our health to be along a period oftime, where 0 represents death and 1 the best possible health. QALYS canbe obtained by many validated health questionnaires that can be disease specific or generic. There are also quality of life questionnaires specially developed for pediatric population that can be used for this purpose[26].

The main advantage of this measurement is that it takes into account both the quality and the length of life; therefore it overcomes the limitations ofsome other monetary or diseasespecific outcome measurements. QALYs can be compared between different conditions and interventions, as it is a generic measurement of the health effects or consequences.

Summing up, CBA would take into account only monetary measurements, whereas both CEA and CUA would take into account quality of life. The main difference between them is that CEA measures a disease-specific outcome and CUA a generic adjusted quality of life unit. As a consequence CUA results could be compared among different interventions, diseases and conditions. In order to represent the results in CEA and CUA we use a chart in which X-axis represents health effects and Y-axis represents costs. (Figure 4)

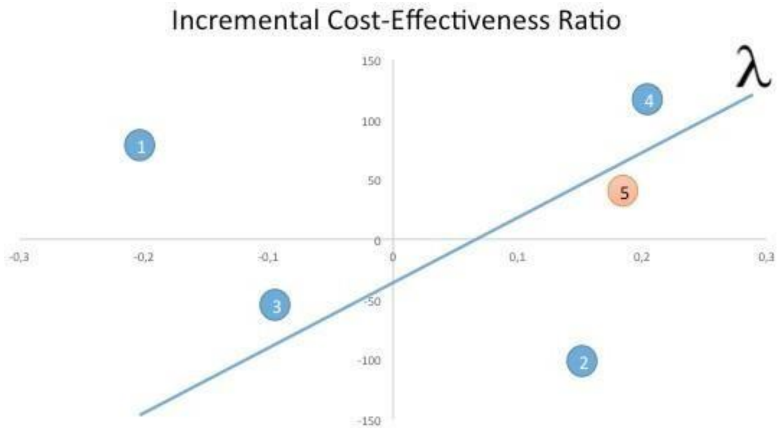


Figure 4: The graphic representation of the incremental cost-effectiveness ratio (ICER) in five different scenarios. In nº 1 the intervention is more expensive and it has less HRQoL. In nº 2 it is less expensive and has associated a better HRQoL. In point nº 3 is less expensive and it has also less HRQoL. In points nº 4 and 5, the intervention is more expensive but it provides better HRQoL. The difference is that nº 4 is over the threshold λ that we establish as the limit of what we would be willing to pay to improve HRQoL, and nº 5 is under it therefore it would be the best choice.

Assuming the traditional surgical technique or gold standard is at point (0, 0) the new one would have a variation in both costs and effects and this would be represented in 12 the chart as the incremental cost-effectiveness ratio (ICER) as shown in the following formula:

ICER= Cost A-Cost B/QALY A- QALY B

When the ICER is in the left upper quadrant of the chart on figure 4, thene w intervention is obviously worthless and it should not be implemented (it would mean it is more expensive and with less gain in quality of life). On the contrary, when it falls into the right lower quadrant it would be the best possible scenario, less expensive and better results, therefore it would be clearly considered to be implemented. The incertitude emerges when the I CER falls into the right upper quadrant and the left lower one.We would h ave to establish the threshold of the increase in costs that wewould be willing to accept in exchange for an improvement in patient's quality of life (willing -
topay) usually named λ[27,28]. If the ICER of our technique were situated below the threshold we would accept the new treatment as cost-effective.

ICER= Cost A-Cost B/QALY A-QALY B=Δ Cost Δ QALY≤ λ

Among all the possible procedures we could have chosen to evaluate, we ha ve decided to begin with appendectomy for the following reasons. Acute appen dicitis is the most frequent surgical emergency in children[30]. About
20 to 30% of all children that are referred for evaluation to the pediatric surge on for acute abdominal pain will turn out to have it[31]. The overall incidence is 5.7–
50 per 100,000 inhabitants per year with an overall lifetime risk of 8%[31,32].

Although acute appendicitis can present at any age, it has a peak of inciden ce between 10 and 18 years old, with a predominance of males[33]

The knowledge about this condition has incredibly increased in the past decad es and nowadays both its natural history and its management keeps on ge nerating controversy.

The traditional belief regarding the natural history towards perforation if untreat ed is also being revisited. There are reports of resolution without treatment, rela pses and even the socalled chronic appendicitis[36,37]. It has been postulated th at some specific immunological factors would predisposesome children to earl y perforation whereas some others would be more likely to have a self-limited course[38]. This is the reason why although the traditional approach for acute noncomplicated appendicitis isappendectomy , there is a trend in recent years towards nonoperative management[39]. It is com mon practice in many centers to avoid immediate surgery in the case of acute a ppendicitis when it is complicated with phlegmon or abscess formation. In th ese cases, a course of antibiotics followed by delayed appendectomy after 6 8 weeks is the standard of carein many Pediatric Surgery centers[40]. In re cent years after favourable resultsin adult population it has been proposed to adopt this strategy even in acute noncomplicated appendicitis, with appar ently favourable outcomes in published results[41]. The rationale of this approach is some evidence of a possible role of the appendix in the normal homeost asis of intestinal flora or an influence on immunological regulation of the int estinal barrier[42]. Although appendectomy is not clearly associated with any posterior condition that could be develop later in life, it is widely accepted that theappendix has a role to play and it is not completely a vestigial structure.

Regardless all these new trends, until enough strong evidence leads us to a generalized agreement on nonoperative management of acute appendiciti s, appendectomy remains the first line therapy in most Pediatric Surgery units a round the world[43]. As it is one of the most frequents procedures in pediatric population, it is constantly the subject of high quality research, randomize d controlled trials and metaanalysis. This is whyit provides us with strong e vidence, allowing us a more scientific and evidencebased approach[43].

First laparoscopic procedure in a pediatric patient was reported in 1971[44]. Sin ce then, many things have changed and nowadays almost 90% of all appendect omies are minimally invasive[31]. There are many techniques described for la paroscopic appendectomy, including single site surgery, with or without ext eriorization of the appendix and even roboticappendectomy. However the mo st widespread one is the three ports technique. Randomized controlled trial s have failed to prove any significant superiorityiofisingleisiteiappendectomyiovericlassicithree-portsiapproach,iandiapparentlyitheicosmeticiscoresitenditoibeisimilariasitimeipa sses[45,46]

In the first years, it seemed to be a trend towards an increased risk of postoperat ive abscess formation in complicated appendectomies but nowadays it is clea r that this is not the case. On the contrary, there is a decreased risk of would i nfection and less pain on the first postoperative day as it is reported in the most recent metaanalysis in Cochran Library[47]. Previous studies have evaluated the different approaches, open and laparoscopic, in terms of cost effectivenes s or costs of hospital stay but none has evaluated before in terms of health -related quality of life of patients after surgery[22].

As the last metaanalysis in the Cochrane Library states, CEA and CUA ar e lacking in pediatric appendectomy and this data should be analyzed aswell in order to have the 16 best possible evidence in all aspects, clinicaland ec onomical, of minimally invasive surgery for appendicitis inchildren[47]

Chapter 2: Review of Literature

Appendectomy is one of the most common surgical procedures performed on children worldwide, with acute appendicitis being a frequent cause of abdom inal pain necessitating surgery. There are two primary surgical techniques for appendectomy: laparoscopic appendectomy (LA) and open appendectomy (OA) . Each technique has its own advantages and disadvantages in terms of clin ical outcomes, cost, and utility. This literature review aims to explore the ex isting research on the costutility analysis (CUA) of laparoscopic versus open a ppendectomy in children, focusing on the comparative effectiveness, costs, a nd quality-adjusted life years (QALYs) associated with each procedure.

Clinical Outcomes

Laparoscopic Appendectomy (LA)

- **Advantages**: Several studies have reported that LA is associated withshort er hospital stays, reduced postoperative pain, faster recovery, and better c osmetic outcomes compared to OA. LA also has a lower risk of wound infe ctions and postoperative complications .
- **Disadvantages**: LA can be technically more demanding and mayhav e a higher initial cost due to the need for specialized equipment and longer operative times in some cases .

Open Appendectomy (OA)

- **Advantages**: OA is a well-established, simpler procedure that can be performed quickly and is less reliant on specialized equipment. It is often preferred in resource-limited settings .
- **Disadvantages**: OA generally has a longer recovery period, higher postop erative pain, and an increased risk of wound infections compared toLA .

Cost Analysis

Direct Costs

- **Laparoscopic Appendectomy**: The direct costs associated with LA include the cost of laparoscopic equipment, operating room time, anesthesia, and hospital stay. Several studies have shown that although LA may have higher initial costs, these can be offset by shorter hospital staysand faster recovery times .
- **Open Appendectomy**: OA tends to have lower direct costs in terms of equipment and operative time but may incur higher costs due to longerhospital stays and a potentially higher rate of postoperative complications .

Indirect Costs

- **Laparoscopic Appendectomy**: The indirect costs for LA, such as lost productivity of parents due to shorter recovery times, can be lower compared to OA .
- **Open Appendectomy**: OA may result in higher indirect costs due tolonger recovery times and increased parental absence from work .

Utility Analysis

Quality-Adjusted Life Years (QALYs)

- **Laparoscopic Appendectomy**: Studies suggest that LA may result in higher QALYs due to quicker return to normal activities, reduced pain, and better cosmetic outcomes .
- **Open Appendectomy**: OA may result in lower QALYs compared to LA due to longer recovery periods and higher incidence of complications, affecting the overall quality of life post-surgery .

Comparative Cost-

Utility AnalysisStudies and Finding

1. **Study by Chang et al. (2014)**: This study found that LA, despite higher initial costs, was more cost-effective in the long run due to reduced postoperative complications and shorter hospital stays, leading to higher QALYs .

2. **Study by Lee et al. (2016)**: The study highlighted that while OA had lower immediate costs, LA provided better long-term outcomes and was associated with higher patient and parental satisfaction, thereby yielding a better cost-utility ratio

3. **Meta-Analysis by Li et al. (2018)**: A comprehensive meta-analysis indicated that LA generally results in better health outcomes and is more costeffective compared to OA when considering both direct and indirect costs, as well as QALYs.

The literature indicates that laparoscopic appendectomy is generally more cost-effective compared to open appendectomy in children when considering both direct and indirect costs as well as qualityadjusted life years. While LA may have higher initial costs, these are often offset by the benefits of shorter hospital stays, quicker recovery, and lower complication rates. Future research should continue to refine these analyses with larger sample sizes and consider varying healthcare settings to generalize these findings more broadly.

Chapter 3: Materials and Methodology

1. Type of study and population included.

This is a retrospective analytic economical study type cost-utility.

We have included pediatric patients between 8 and 15 years old diagnosedwit h acute non-complicated appendicitis operated in two Pediatric Surgical Centers over the pe riod between September 2017 and August 2020.

Criteria to define uncomplicated appendicitis are less than 2 days of sympto ms and no clinical or radiological findings of phlegmon, intraabdominal absc ess or peritonitis.

The inclusion and exclusion criteria are summarized in table 1.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Between 8- and 15-year-old	Previous physical condition
Uncomplicated appendicitis	More than 2 days
Agreed to Participate	Evidence of phlegmon, abscess peritonitis

Table 1. Inclusion and exclusion criteria of the study population.

2. Protocols for non-complicated appendicitis and details of intervention.

The protocol followed in both centers is the same.

2.1 Treatment at admission.

All patients are admitted with nil-per-oral, intravenous fluids, intravenous analgesics and all of them receive a preope rative prophylactic dose of intravenous amoxicilin-clavulanic acid (gentamicin + metronidazole in case of allergy to beta-lactamases).

2.2 Surgery

Surgery is undertaken within the next hours, when the patient is fasting fo rat least 6 hours and there is availability of the surgery theatre.

Patients undergo open or laparoscopic surgery depending on surgeon's choi ce and availability of the equipment.

2.2.1. Laparoscopic Appendectomy

After anesthetic block with bupivacaine and lidocaine, we enter the periton eal cavity by open technique, positioning the first port (a 11 mm one) thro ugh an infraumbilical incision. We purge the tubes first and then connect to the trocar and start insufflation with low flux at 2 litres per minute (lpm) until we reach a maximum pressure of 10-12 mmHg. Weuse a 5 mm-30º lens. We inspect the peritoneal cavity and then position two additional 5 mm ports at the left iliac fossa and at hypogastric area under direct lapar oscopic vision and after infiltration with local anesthetics.Mesoappendix and ap pendix are dissected with either electrocautery, or endo-sealer depending on the characteristics of each case and surgeon's preference. T he appendix is transected by endo- stapler or sectioning between endo-loops. We extract the appendix through the umbilical trocar.We close the fas cia with interrupted 2/0 polyglactine stitches at the umbilicus and we clos e subcutaneous tissue with 3/0 polyglactine stitches in all ports. Skin is clos ed with interrupted absorbable intradermic 5/0 polyglactine stitches.

2.2.2 Open Appendectomy

For the open technique, after abdominal wall block with bupivacaine and lidocai ne, we make a transverse incision at the level of the McBurney point[30]. We keep it as limited as possible. The fascia is opened with scissors and mu scles are separated and preserved. Appendix is localized and brought out of the incision with the minimum possible manipulation. Mesoappendix is dissect ed ligating appendicular vascular branches and appendix is transected betwee n ligatures. The stump is inverted by means of a purse-string suture. We aspirate fluids in the peritoneal cavity when present. We clos e the incision in layers, with a running 3/0 polyglactine suture in the perito neum, interrupted 2/0 polyglactine stitches toapproximate muscular layers and a running 2/0 polyglactine suture in the fascia. Subcutaneous tissue is approxi mated by interrupted 3/0 polyglactine suture and skin is closed by means of a running intradermic 5/0 polyglactine absorbable suture.

2.3 Postoperative management

2.3.1 Antibiotic

Antibiotic prophylaxis is discontinued when the appendix turns out to be flemon ous. If it has some degree of gangrene or necrosis with purulent intraperitoneal fluid, postoperative antibiotherapy is started with either intravenous cefotaxime plus metronidazole or piperacilin-tazobactam alone for 5 to 7 days (until the child is afebrile, feeding normall y and normalization of analytical parameters). In the intermediate cases w ith some evidence of localized gangrene without purulent fluid a short cou rse of amoxicilin-clavulanic acid plus gentamicin or cefotaxime plus metronidazole is establish ed for 48 hours.

2.3.2 Oral intake

Oral intake is re-established 4-6 hours after surgery and intravenous fluids discontinued before 12 hours unl ess vomiting appears. Diet is progressedas tolerated.

2.3.3. Postoperative pain

Postoperative pain is controlled with both metamizole scheduled every 6 or 8 hours and acetaminophen alternating for the first 24 hours at standard dos es. For the following days only metamizole is scheduled, leaving acetaminophe n as rescue. In patients older than 12 years, dexketoprophen is sometimes used as a rescue if needed.

2.3.4 Hospital stay

Patients are discharged when they are tolerating, with good pain control and once the antibiotic course, if needed, has finished. Usually the hospital stay is 1 to 2 days for flemonous appendicitis and 2 to 7 days ofgangrenous appendicitis.

3. Decision model

We constructed a decision analytic (Markov) model in order to comparethe two approaches[23]. We calculated the probabilities of each branch ofthe flowchart according to previous published data[47]. We took as reference OAp technique, as the traditional standard of care, and compared the results with those of LAp.

4. Cost estimation

It was decided to include only the direct costs of the interventions[48,49]. Both indirect and intangible costs such as days that the parents did not go to work or psychological impact were not taken into account because of the difficulty to accurately estimate them.Intraoperative costs, hospital stay and postoperative followup appointmentswere included. Information on costs was provided by the two centers participating on this study.

The intraoperative costs were calculated for each patient including theitems listed in table 2.

Item
Laparoscopic Hardware including light source, screen, insufflator and camera
Optics 5 mm 30º
Light cable
Reusable laparoscopic instruments 5 mm
Silicone tubes
Open surgery instruments
Trocar 5 mm
Trocar 11 mm
Polydioxanone ties
Other sutures
Endo-sealer
Endo-stapler

Table 2. Items considered in costs estimation for LAp

For laparoscopic hardware and reusable instruments, we considered a lifespan of 10 years. We calculated the mean number of times they are used per year and an equivalent cost was estimated for each patient, dividing the total amount per 10 years (approximate life span) and per patients-per-year.

Regarding operating room consumables, such as maintenance, sterilization of the instruments, anesthetics and so on, we considered them to be similar between both groups, as well as healthcare professionals workingon theatre.

We documented analgesics and antibiotics consumption and calculated theprices according to the doses received during hospital stay for each patient.

The price of each day at the hospital was calculated from standard hospital statistics that already include salaries of nurses and staff and other expenses. The total cost of hospital stay was calculated multiplyingthe day price by the days each patient was at the hospital.

The price of each outpatient visit was considered as well, it wascalculated from general hospital statistics and costs.

All costs are presented in Euros (exchange rate 2019).

5. Health-related quality of life.

We measured children's quality of life with the validated general questionnaire KIDSCREEN-10. The KIDSCREEN questionnaires are a series of instruments developed and normalized to assess health-related quality of life in children[50]. They are generic, not disease-specific, whichmeans they can be used for different researches, in a variety of conditions and in previously healthy children. There are three versions o fthe KIDSCREEN questionnaires, with 52, 27 and 10 items (short version)[51,52,53]. They all have been validated in different languages including Span ish[54]. We have chosen the KIDSCREEN-10 because it has been previously reported its extrapolation to QALYs, which is the standard measure of HRQoL[55] in CEA and CUA. (Figure 5)

HRQoL ranges from 0 to 1, being 0 death and 1 perfect health.

6. Sensitivity analysis and acceptability curve.

We followed the principles for reporting results published in the Consolid ated Health Economic Evaluation Reporting Standards (CHEERS)statement extended for non- pharmacological trials[56].

The sensitivity analysis was used to transfer the uncertainty of different esti mations to the outcomes of our model, comparing them with differentpossib le values. A probabilistic multivariate sensitivity analysis was done with 5 ,000 Monte Carlo Simulations (MCS). MCS is a statistical tool that al lows us to do stochastic analysis by generating random samples and ca lculating a result for each of them. We calculated the 95% confidence i nterval of the results of this sensitivity analysis.

We used a costeffectiveness plane to show each pair of costs andoutcom es of the model.We established a costeffectiveness acceptability line to determine the LApcost effectiveness to OAp with a reasonable level of willingness-to-pay.

We established a 20,000 to 30,000 euro-per-QALY threshold (λ) for cost-effectiveness as it is widely accepted in literature and it is a frequently used value in many healthcare cost-effectiveness analysis[57].

A 3% discount rate per year was applied for the estimation of costs andQAL Ys, following current health economic guidelines[58].

We calculated the incremental costeffectiveness ratio (ICER) of LAp inrelation with OAp. If the ICER of LAp were not to exceed the threshold limit established it would be considered cost-effective.

Although we consider that the perspective of the society it is the most appropriate because it takes into account all aspects of the medical intervention[29], we decided to undertake our analysis under the perspectiveof the health-provider due to the difficulties to estimate the social costs of the condition.

7. General statistics

For statistical analysis, we used the IBM SPSS Statistics version 23.0(IBM Corporation, Armonk, NY)In order to compare the two study groups, we performed a statistical analysis for independent samples. We run a KolmogorovSmirnov test foreach variable to check for normality. We compared basal characteristics of both groups.

For general descriptive statistics, quantitative data are expressed as mean and standard deviation or median and minimum and maximum values in variables that do not follow normal distribution. Categorical data are expressd as frequencies with percentage (%). Nonparametric test were used for analysis. Continuous data were assessed with MannWhitney Utests. Multivariable linear regression models were developed using the Spearman test.

A p value of less than 0.05 was considered statistically significant.

Chapter 4: Results

Fiftythree patients meet the inclusion criteria and agreed to participateanswer ing to the KIDSCREEN-10 questionnaire.

None of the data gathered followed a normal distribution according to there sults of the Kolmogorov-Smirnov test.

There were 37 (69.8%) boys and 16 (30.2%) girls. Age ranged between 8 and 14 years old with a median of 10 years. At the time of surgery, in 77.4% of the cases, the appendix was macroscopically flemonous an d in 22.6% it was gangrenous. Regarding the approach, there were 27 OAp and 26 LAp. Characteristics of each group are summarized in table 3.

	OAp	LAp	Total
n	27	26	53
Gender			
Male	19	18	37
Female	8	8	16
Median Age (min-max)	10 (8-13)	12 (8-14)	10 (8-14)
Type of appendix at surgery			
Flemonous	20	21	41
Gangrenous	7	5	12
Median hosp. stay (min-max)	1 (1-6)	2 (1-5)	2 (1-6)
Complications			
Wound infection	0	0	0

Table 3. Demographic and general data.

Both groups OAp and LAp were homogeneous without differences in gen der and type of appendicitis. The median age was lower in the OApgroup (10 vs. 12) being this difference statistically significant (p=0.008) (figure 6).

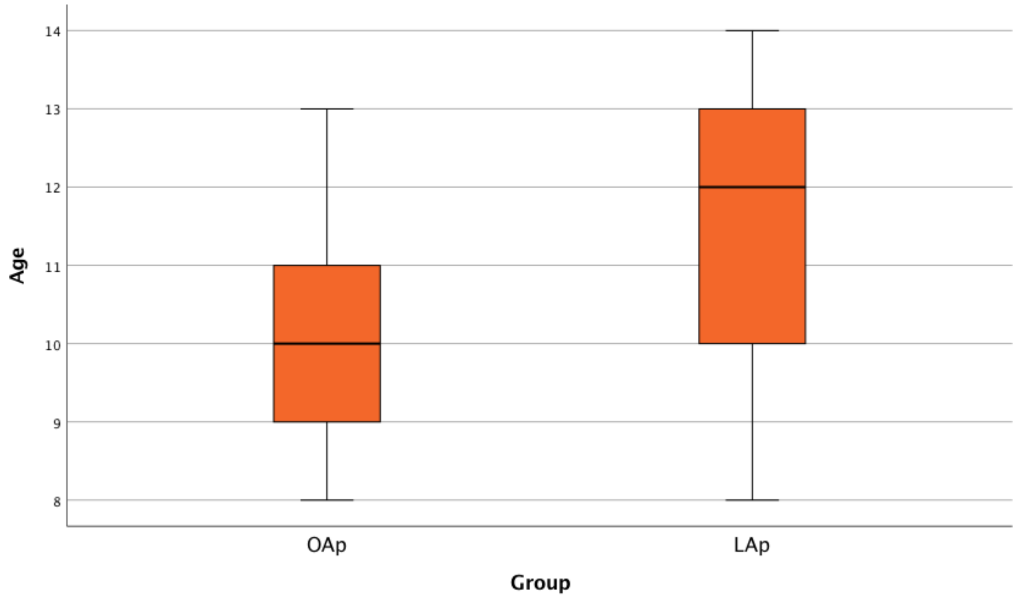


Figure 6. Box plot showing differences in age between the two groups.

We did not detect any significant difference in hospital stay. The median valu e in the OAp group was 1 and in the LAp 2. In both groups the hospital sta y for flemonous appendicitis was between 1 and 3 days (mostof them 2 day s) and for gangrenous appendicitis 3 to 6 days (most frequent value 2 days).

There were no complications in any group.

The cost of each item considered in the estimation is summarized inta ble 4.

Item	Price (in euros)
Laparoscopic Hardware (amortization per patient)	18.88
Optics 5 mm (amortization per patient)	2.3
Light cable (amortization per patient)	1.13
Laparoscopic instruments 5 mm (amortization per patient)	5.8
Silicone tubes (amortization per patient)	0.21
Open surgery instruments (amortization per patient)	1.6
Trocar 5 mm (x2)	58.54
Trocar 11 mm	46.43
Polydioxanone ties (x2)	13.17
Other sutures	12.72
Endo-sealer	702
Endo-stapler	399
Hospital Stay per day	323.28
Intravenous fluids 500 cc	0.88
Acetaminophen per dose	0.52
Metamizol per dose	0.51
Dexketoprofen per dose	0.26
Amoxicilin-clavulanic per dose	0.95
Metronidazol per dose	0.58
Cefotaxime per dose	0.6
Piperacilin-tazobactam per dose	2.26
Gentamicin 40 mg	0.58
Gentamicin 240 mg	2.09
Postoperative follow up outpatient visit	72.34

Table 4. Costs per item

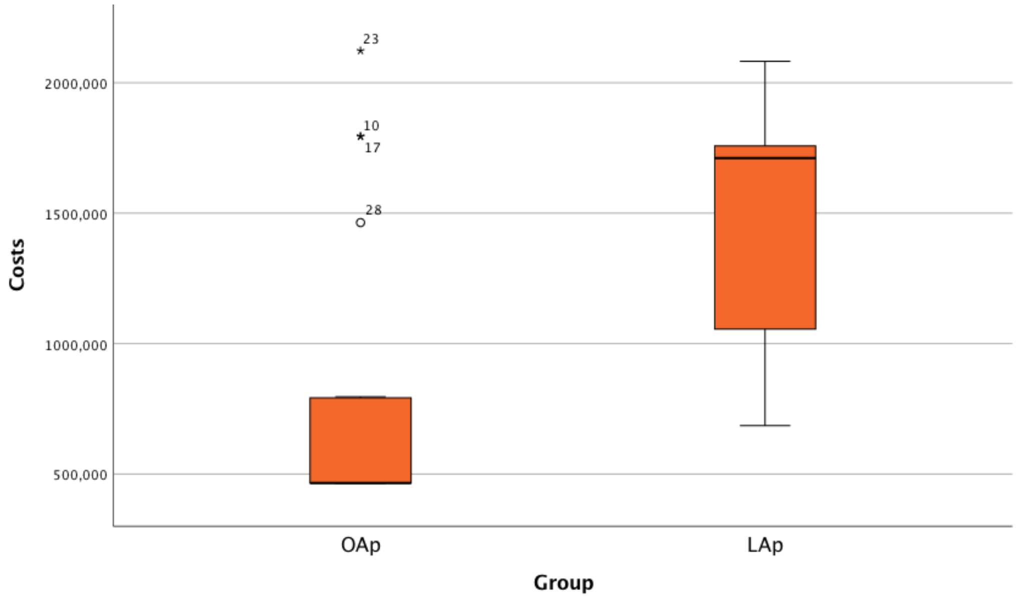
The costs of LAp ranged from 685.53 to 2082.53 euros with a median value of 1711.25 euros for patient, considering the items mentioned in

table 4. This range is explained by the use or not of the endo-
sealer orthe endo-
stappler and the length of hospital stay. The costs for OAp ranged betw
een 465.03 to 2122.99 euros with a median value of 465.91euros. These va
riations depended only on hospital stay, with an outlier value of 2122.99
euros due to a hospital stay of 6 days in one patient. LAp represented a
n increase in costs with a difference between the median values of 124
5.34 euros.

This difference is statistically significant ($p<0.001$) (figure 7)

Figure 7: Box plot showing differences in costs betweenth
e two groups.

Regarding the KIDSCREEN questionnaire results, patients from the OApgro
up scored better in one general item related to emotional wellbeing. Wherea
s in the LAp group, scores were significantly better in items related to th
e specific areas of relationship with friends and family and



in those related to performance and getting back to school. In the rest ofite
ms there were no statistically significant differences.

When considering the QALYs, the median value in the OAp group was 0.75 (0.67-0.82) and in the LAp group 0.77 (0.66-0.88), without reachingthis difference statistical significance (p=0.816) (figure 8)

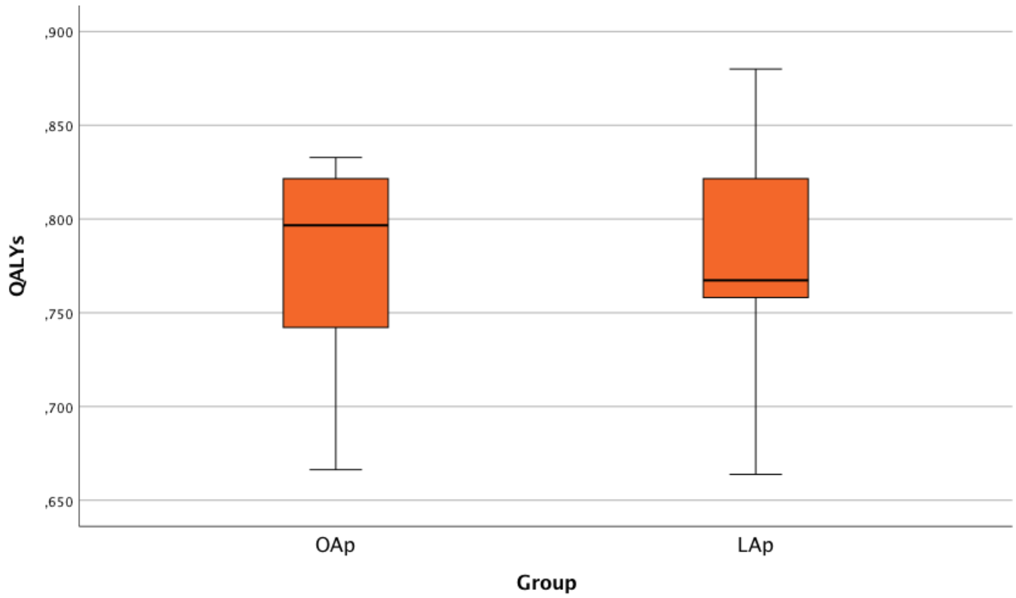


Figure 8: Box plot showing the distribution of QALYs in each group

The multivariate analysis considering the rest of the variables apart from the group LAp or OAp showed no significant correlation with QALYs.

	OAp (n=27)			**LAp (n=26)**		
	Mean (€)	**Confidence Interval 95%**		**Mean (€)**	**Confidence Interval 95%**	
		Lower	Upper		Lower	Upper
Costs (€)						
Mean Total Cost	758.98 €	572.09 €	945.88 €	1,525.50 €	1,353.66 €	1,697.34 €
Utility						
QALYs	0.7390587	0.7249066	0.7532107	0.7813543	0.759565399	0.8031433
Incremental Results						
Incremental Cost (€)	---	---	---	766.51 €	751.46 €	781.57 €
Incremental Utility (Qaly)	---	---	---	0.0422957	0.04993257	0.0346588
ICER (€/Qaly)	---	---	---	18,122.73 €	15,049.51 €	22,550.30 €

Table 5. Summary of the cost-utility analysis.

The acceptability curve for LAp over OAp, represents the probability that LAp is cost-
effective according to the values that we set as threshold for willingne ss to pay. Here we can se where our threshold of 20,000 to30,000 euros/Q ALYs is located. (Figure 9)

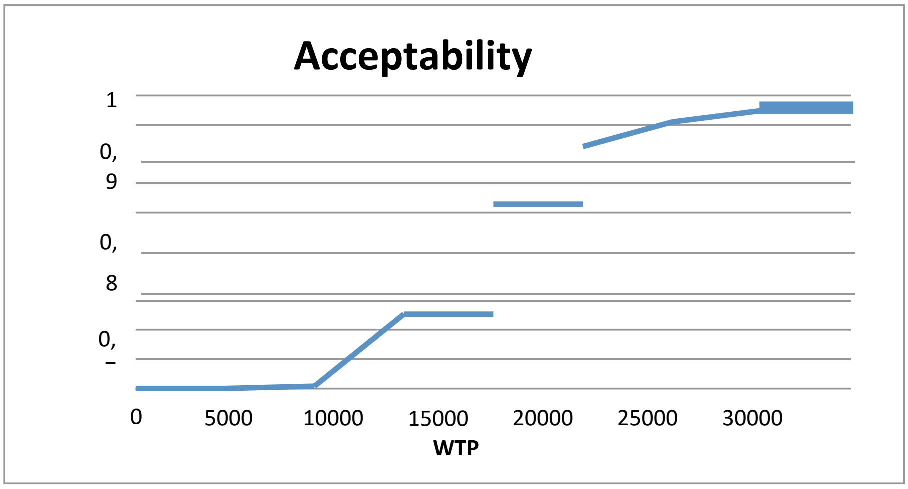


Figure 9: Acceptability curve. (WTP = willingness to pay

The incremental cost-
effectiveness ratio of choosing LAp over OAp was18,122.73 euros/QALY, which is just below of the established costeffectiveness threshold λ set at 20, 000 to 30,000 euros/QALY.

In figure 10 we can see the graphical representation of the probabilistic simu lations generated to prove our model. As it is depicted in the figure,most of the simulations are under the threshold of cost-effectiveness.

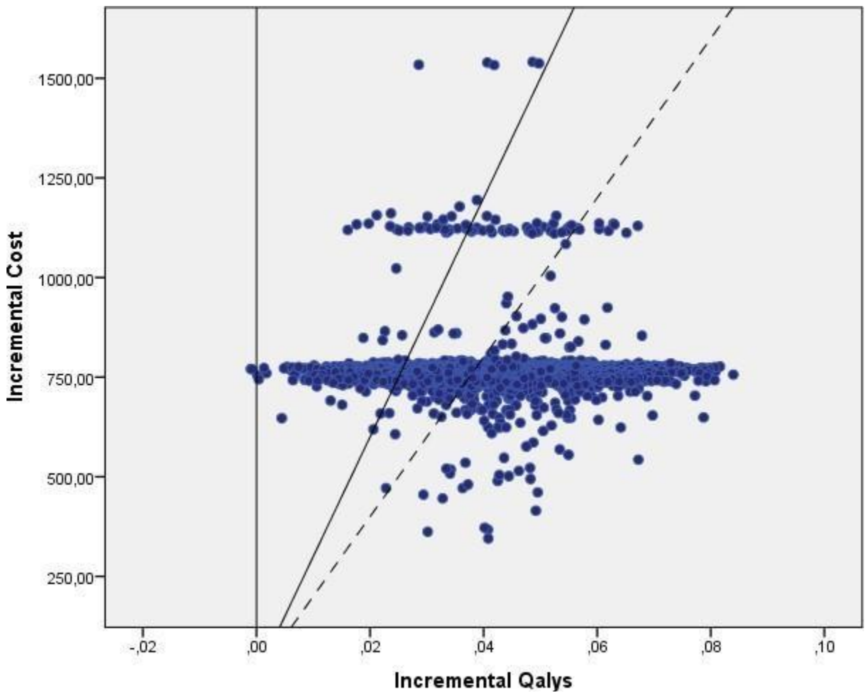


Figure 10. Incremental costeffectiveness plane. The continuous line is thethr eshold λ of 20,000 euro /QALY and the dotted line is the 30,000 euro/QAL Y one.

Chapter 5: Discussion

Surgery as a whole is much more than the single act that takes place i nthe surgery theatre. From the indication of the intervention at the outp atient visit or at the ER to the surgery theatre and beyond during the follow up. This is especially true in children, in which the implications and the consequences in the future, may be even more important than in the adult patient. Response to stress, psychological impact, and particul arities of anesthetics in the pediatric patient are all examples of how the su rgical procedure on a child is complex and delicate. It is also essential to take into account the role of the team-

work around the surgical procedure. Nurses, anesthetists and pediatrician s are all implicated in the care of the surgical patient along with the su rgeon. And in all this net of interactions, there is also a place for the soc ial perspective, the economic aspects and the responsibility of using wisel y the available resources when they are limited as in a public healthcare system. (Figure 11).

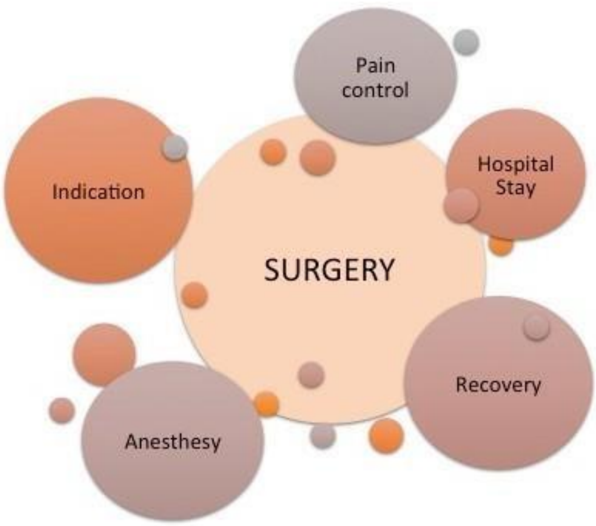


Figure 11: Representation of different aspects of the surgical intervention .

If we want pediatric MIS to evolve and take the place that it deserves amongst all the Pediatric Surgery centers, especially small centers such asours, we have a commitment to prove its less invasiveness in all aspects and especially that what it costs is worth, not in monetary terms, but in quality of life of our patients.

All the achievements that have led to the present development of MIShave been progressive and have involved different areas. Besides technical advancements, a favorable and supportive environment is needed. Both the society and the policy makers have to be convincednot only of its safety and efficacy, but also of its cost- effectiveness.

This is why the economic analysis of healthcare is important not only for the provider and governmental policy makers, but also for surgeons, all health-care professionals and even for patients.

In addition, when an economic study is well designed, it can also serve for the decisionmaking process of all the professionals implicated in the care of a child. This is also one reason for which surgeons should be more implicated in the development of the decision analysis tree of economic health studies. Decision analysis could be defined as the process of making a calculated and balanced choice under circumstancesof incertainty[23].

The decision analytic model is both useful and easy to work with, once we have come familiar with the general concepts. (Figure 12)

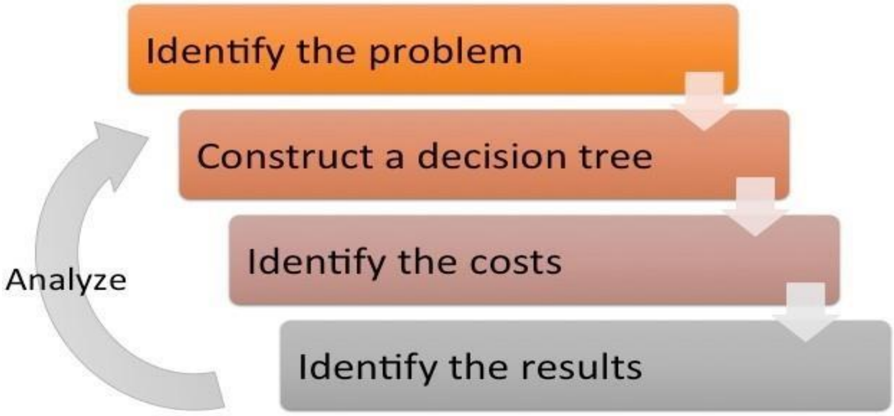


Figure 12: Steps to take to make the decision analytic model.

Once the decision analysis tree has ben designed, the economical study s hould proceed ideally in a prospective way. In our case, we decided to de sign our study retrospectively because there is no any other study regard ing HRQoL in pediatric MIS and we wanted to have a pilot experience to explore general data and to determine on what to build ourfuture resear ch.

When designing our study, we encountered challenges due to the lack ofinstrume nts to assess HRQoL in previously healthy pediatric patients.
Existing instruments often cater to specific conditions like cancer or diab etes, making general assessments difficult. The KIDSCREEN questionnaires , developed by an international team of health professionals,aim to address these limitations. They provide agespecific measures of HRQoL for childre n, teenagers, and parents, validated across more than30 languages. KIDSCR EEN is widely used in public health and clinicalmedicine for its simplicity and comprehensive coverage of physical, mental, and social well-being.

When applied to the surgical pediatric patient, items such as the relatio nship with their mates and the activities at school would be relatedwith t he return to normal activities after surgery and items regarding physical wellbeing could reflect issues regarding pain or scars. Therefore this kin d of instruments could allow us to evaluate the results of a surgical intervention in terms of patient's satisfaction, until more accuratea nd specific instruments could be developed.

However, as most of the HRQoL questionnaires specifically developed forchil dren, it is not suitable to be used directly for a cost- utility analysis. The reason is because an instrument that could generate Q ALYs, has to have the potential to both "measure" and "value" health statu s by incorporating the individual preferences. Chen and cols developed a ma thematical model to extrapolate the values of QALYs out of the results of the KIDSCREEN- 10 questionnaire opening the door to the use of this simple and accurat e instrument for cost-utility analysis in children[55].

On the whole, the final extrapolated QALYs value did not reflect these variat ions and although it was higher in the LAp group (0.77 vs. 0.75) this dif ference was not statistically significant.

As we can see in our results, the ICER for laparoscopic appendectomy was 18,122.73 euros/QALY, right under the threshold of 20,000 to 30, 000 euros/QALY that we had established as the amount of money that we would pay for a quality life- year. This means that even though the expenses in the LAp group wer e significantly higher, they are justified, as they were associated with an i ncrease in HRQoL and at thesame time they remained under the λ thresh old.

Our study suggests that the increase in HRQoL with laparoscopic appendect omy could be underestimated due to non- random patient selection, potentially favoring less invasive procedures for younger and thinner patients, which may have skewed results towards small er HRQoLimprovements.

We are convinced that pediatric MIS is the future of Pediatric Surgery, especially for long complex procedures that require larger incisions and have a more painful postoperative recovery. However to reach this pointwith advanced surgeries, we have to implement the use of MIS in bothelective and routine procedures first, and reach standards of quality of care in all centers despite their volume of patients or their funding.

Laparoscopic appendectomy in children offers advantages such as easierdissection in challenging appendix locations, avoiding blind dissection, improved visualization for complicated cases, and aiding in differential diagnoses like ovarian conditions in girls.

After some controversy at the beginning of its use, it has finally been stated a lower rate of complications such as abscess formation and wound infection after laparoscopic surgery[47].

For all these reasons, we consider LAp is probably the best first line therapy for pediatric appendectomy, although OAp should not be discouraged in highly selected patients. We have seen that the results in the KIDSCREEN questionnaire and the QALYs were also good in the OAp group, only slightly under those of the LAp group, which means that in a specific subset of young and thin patients, with non-complicatedappendicitis, OAp might still play a role.

Moreover, we could keep on working to improve the costs to try toreach an even more favorable ICER in many different ways.

Pediatric Surgeons could team up with the rest of surgical specialists with special interest in MIS to share the equipment and hardware. This could be particularly useful in low-volume Pediatric Surgery Centers. Thereason is that when we share the most expensive MIS technology, the number of cases a year increases and the proportional total costs per patient decreases. We consider it is important to work in coordination with general surgeons, urologists and gynecologist for instance to try to have the best possible hardware and opt imize its use and the costs by

sharing it, compensating the initial costs, making technology available for all and improving the cost-effectiveness of our procedures.

Regarding the use of instruments, mechanical devices have failed to prove superiority over endo-loops for ligating the appendix in non-complicated appendicitis, and the latter are much cheaper[63]. Similarly, in favorable cases, dissection of the mesoappendix can be safely done by electrocautery, diminishing the costs considerably by avoiding the use of endo-sealer.

Regarding the single port appendectomy, there are studies that prove itscost-benefit, however some others question their real effectiveness, considering the overstretching of the umbilicus, with the consequent postoperative pain and concerns regarding the scars[45, 46]

We have not measured the operative time in this study, but as we have explained previously, time has also a cost-opportunity. The extra time wespend doing a longer MIS procedure is time we could be doing something else. Therefore, it is important to reduce the operative times, first of all for the patient safety, reducing time under general anesthesia, and secondly it will improve our cost-effectiveness as well.

Postoperative hospital stays after laparoscopic procedures are often longer for children than adults. Some centers keep children hospitalized for supervision post-MIS. Ideally, MIS should allow same-day discharge, especially for procedures like hernia repair or orchidopexy. As techniquesimprove and experience grows, shorter stays and procedures without endotracheal intubation should become common.[9,11,67,68,69.]

Our study is limited by its retrospective nature and the absence of prior research on pediatric MIS and HRQoL, leading to a small sample size focused on non-complicated appendicitis in older children. Although we avoided expanding the sample back in time to mitigate parental recall bias, our findings were supported by Markov Chain Simulation (MCS) analysis. Randomized selection between open and laparoscopic appendectomy would have enhanced accuracy, and future research shouldconsider baseline HRQoL comparisons for better insights. Despite these limitations, our study provides valuable insights into the economic and social impacts of pediatric MIS on children's quality of life.

Chapter 6: Conclusion

1. Cost-Utility Analysis in Pediatric Minimally Invasive Surgery

Cost-utility analysis (CUA) is an analytical method used to evaluate the economic value of medical interventions by comparing their costs to thehealth benefits they provide, often measured in terms of quality-adjustedlife years (QALYs). In the context of pediatric minimally invasive surgery (MIS), CUA is particularly important for several reasons:

- **Assessing Value:** CUA helps determine whether the benefits of pediatric MIS procedures justify their costs. By translating health outcomes into QALYs, CUA provides a standardized way to compare thevalue of different surgical approaches.
- **Health-Related Quality of Life (HRQoL):** Pediatric MIS procedurescan lead to significant improvements in HRQoL by reducing pain, minimizing recovery time, and lowering the risk of complications. CUA quantifies these improvements, providing robust evidence to support the use of MIS in pediatric surgery.
- **Justifying Use:** If CUA shows that pediatric MIS procedures offer substantial health benefits relative to their costs, this evidence can justifytheir broader adoption in clinical practice. This is particularly important in healthcare systems focused on delivering high-quality, cost-effective care.

2. Cost-Effectiveness of Laparoscopic Appendectomy (LAp) VersusOpen Appendectomy (OAp)

Laparoscopic appendectomy (LAp) has been found to be cost-effective compared to open appendectomy (OAp) for non-complicated appendicitisin children. This finding is supported by several key factors:

- **Shorter Hospital Stays:** LAp typically results in shorter hospital sta ys, which can reduce overall healthcare costs and allow children to return to their normal activities more quickly.

- **Reduced Postoperative Pain:** Children undergoing LAp often experien ce less pain after surgery, which can lead to a quicker and morecomfortable re covery process.

- **Quicker Recovery Times:** The minimally invasive nature of LApusu ally means that children can recover faster and resume their daily activities sooner than with OAp.

- **Fewer Complications:** LAp is associated with a lower risk of postoperati ve complications, which can further reduce healthcare costs andimprove outco mes for pediatric patients.

These advantages make LAp a more cost-effective and patient-friendly option for non-complicated appendicitis in children, supporting its use asthe preferred su rgical approach in these cases.

3. Development of Quality of Life Assessment Tools

To accurately assess the impact of pediatric MIS on quality of life, it is essenti al to develop specific tools designed to measure QoL in pediatric surgical pati ents. Such tools would enable healthcare providers to:

- **Capture Unique Experiences:** Pediatric patients have different needsan d experiences compared to adults. Tailored QoL assessment tools can capture these differences and provide a more accurate picture of how surgical inter ventions affect children's lives.

- **Quantify Impact:** Reliable QoL measures allow clinicians to quanti fy the benefits of MIS procedures, providing data that can be usedto info rm clinical decisions and improve patient care.

- **Guide Decision-Making:** With accurate QoL data, healthcareproviders can make more informed decisions about which surgical

approaches are most beneficial for pediatric patients, ensuring that interventio ns are aligned with the goal of maximizing patient well-being.

4. Future Research Directions

To further support the use of pediatric MIS, future research should focus on exploring its application in various indications and settings. Key areas f or research include:

- **Different Surgical Indications:** Investigating the effectiveness andQo L outcomes of MIS for a wide range of pediatric surgeries beyond appende ctomy. This could include procedures for conditions such as hernias, cong enital abnormalities, and gastrointestinal issues.
- **Diverse Patient Populations:** Studying the impact of MIS in diffe rent pediatric populations, including those with varying health condition s, ages, and socio-economic backgrounds. This would help ensure that MIS benefits are w idely applicable and understood.
- **Varied Healthcare Settings:** Assessing how pediatric MIS performs in different healthcare environments, from large urban hospitals to smallerrur al clinics. This research can help identify any setting-specific challenges or advantages, ensuring that MIS can be effectively im plemented across diverse healthcare systems.

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