

Committee 22

Economics of Urinary & Faecal Incontinence, and Prolapse

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CONTENTS

I. INTRODUCTION

II. BACKGROUND

1. PLACING ECONOMIC ANALYSIS OF CONTINENCE CONDITIONS INTO PERSPECTIVE
2. COUNTRY SPECIFIC ECONOMIC ISSUES
3. OTHER “FRAMEWORK” ISSUES

III. TYPES OF ECONOMIC ANALYSIS

1. OVERVIEW
2. DETAILS OF DECISION ANALYSIS
3. STATISTICAL ANALYSIS
4. BUDGET IMPACT ANALYSIS (BIA)

IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS IN THE CONTINENCE FIELD

1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES
2. “DO IT YOURSELF” - HOW TO CONDUCT A COST UTILITY ANALYSIS: THE COMMITTEE’S RECOMMENDATIONS

V. SUMMARY OF RECENT ECONOMIC ANALYSES

1. SURGICAL TREATMENT COST EFFECTIVENESS STUDIES
2. OUTPATIENT CONSERVATIVE THERAPIES
3. PHARMACOTHERAPY OF OVERACTIVE BLADDER
4. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING
5. LONGITUDINAL BURDEN OF DISEASE STUDIES
6. PROLAPSE TREATMENTS, COST IMPLICATIONS
7. ECONOMIC CONSEQUENCES OF FECAL INCONTINENCE

VI. SUMMARY AND FUTURE RESEARCH PRIORITIES

VII. APPENDIX – SEARCH STRATEGIES

REFERENCES

ABBREVIATIONS

ADLs	Activities of Daily Living	NCA	Nurse Continence Advisor
AF	Attributable Fraction	NICE	National Institute for Health and Clinical Excellence (UK)
BIA	Budget Impact Analysis	NIH	National Institutes of Health (USA)
CCA	Cost Consequence Analysis	OAB	Overactive Bladder
CBA	Cost Benefit Analysis	OR	Odds Ratio
CEA	Cost-effectiveness Analysis	PFMT	Pelvic Floor Muscle Training
CI	Confidence Interval	QALY	Quality Adjusted Life Year
COI	Cost of Illness	QOL	Quality of Life
CMA	Cost Minimisation Analysis	QWB	Quality of Well-Being Index
CUA	Cost-utility Analysis	RCT	Randomised Controlled Trial
DRG	Diagnostic Related Group	SD	Standard Deviation
EQ5D	EuroQoL 5 Dimension Health Status Measure	SF-36	Short Form – 36 Quality of Life Test
FI	Faecal Incontinence	SUI	Stress Urinary Incontinence
GDP	Gross Domestic Product	TTO	Time Tradeoff
HRG	Health Care Resource Group	TVT	Tension Free Vaginal Tape
HRQOL	Health Related Quality of Life	WTP	Willingness to pay
HUI	Health Utilities Index	UI	Urinary Incontinence
ICER	Incremental Cost-Effectiveness Ratio	UK	United Kingdom
ICI	International Consensus on Incontinence	USA	United States of America
IQR	Interquartile Range (25% - 75%)	UTIN	Urologic Treatment of Incontinence Network
MAU	Multi – Attribute Utility	VAS	Visual Analog Scale
MRC	Medical Research Council (of UK)		

Economics of Urinary & Faecal Incontinence, and Prolapse

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I. INTRODUCTION

Since the first publication of the ICI, which included a basic review of the economics of urinary incontinence, our knowledge about this subject has increased substantially. Initially, many publications in this field comprised simple Cost of Illness (COI) studies, in which the cost of managing incontinence conditions were tabulated, without measurement of the benefit of treatment outcomes. Since that time, continence clinicians have become increasingly aware that we need to balance the cost of the illness against the cost of a range of treatments, to yield the net benefit for the money spent. Also economic analysis should not just consider the objective reduction in leakage severity, but also consider the improvement in overall quality of life.

In the last decade, we have become increasingly aware that economic analysis of incontinence is somewhat dependant upon the condition to be studied. For example, stress incontinence can be readily cured by a range of surgical options, but the benefit may decay over time. Stress incontinence can also be cured by more time consuming physical therapies but these depend upon patient compliance with treatment over time.

On the other hand, pharmaceutical companies have provided an increasing array of anticholinergic treatments for the overactive bladder, but these may require prolonged administration with longstanding drug costs. Such pharmacotherapy needs to be accompanied by bladder training, which also requires patient compliance to achieve success. The benefit of surgery for Botox injections is well known to decline with time. Because of these individual characteristics of the subtype of incontinence, the blanket term of “the economics of incontinence” is less applicable, one should drill down into the relevant treatments of these aetiological subgroups. The present chapter takes account of these considerations, and is arranged according to incontinence subtype.

More recently, clinicians have become aware that

uterovaginal prolapse treatments require economic analysis, which have received little attention to date. As the population becomes increasingly elderly, prolapse will become more common. Resources allocated to this condition need to be spent prudently. Finally, the last taboo of faecal incontinence has come into the spotlight. As a wider range of conservative, surgical and neurostimulation treatments become available for this condition, our scientific community has realised that economic analysis of these treatments is becoming feasible and increasingly important. Thus for the first time a part of this chapter is dedicated to the economics of faecal incontinence.

In the first three monographs produced by the ICI, the broad context and some of the statistical methods of economic analyses were included. However, the range of mathematical treatments of these conditions has expanded so that a brief summary of newer methods is now included.

II. BACKGROUND

1. PLACING ECONOMIC ANALYSIS OF CONTINENCE CONDITIONS INTO PERSPECTIVE

When a patient with urinary or faecal incontinence (and to some extent prolapse) walks into a doctor’s office in any country, they will have already incurred some personal costs in managing the condition at home, such as pads or laundry expenses. He or she will then have a basic consultation, tests will probably be ordered, a range of outpatient conservative (including pharmacological) treatments may be prescribed, or a surgical procedure that may involve day-only stay or an inpatient stay may be recommended. At some stage, particularly in the elderly, the patient may suffer a urinary infection which may be associated with the incontinence/ cystocele, or may slip in their urine on the way to the toilet and have a fall. These are known as the direct personal and treatment costs of the condition, which are included in Cost of Illness (COI) studies.

The patient may have lost time off work, stopped heavy lifting, or had to retire early because of the condition. These are known as Indirect Costs, which are often included in COI studies. Finally, the patient is likely to have undergone pain (from urine excoriation on the perineum) or suffering (e.g. inability to go out of the house due to constant leakage and foul smell rendering them socially unacceptable) which are known as the Intangible Costs. These are seldom included in simple COI studies, but are considered if Quality of Life tests are included in the study.

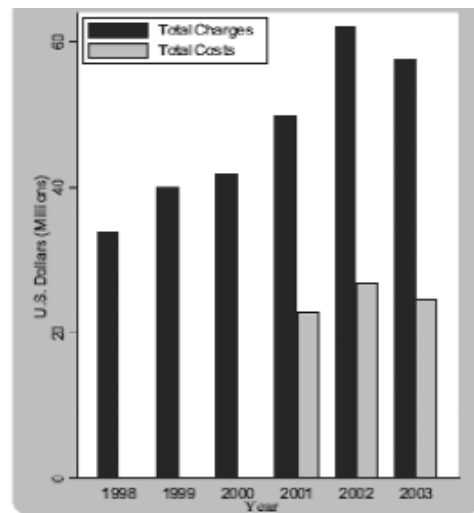
The way in which these various costs can be measured varies a great deal from country to country. Although all countries regulate health care to some degree, they do so in very different ways (e.g., the regulatory environment within which health care is provided, insurance, limitations on the building of hospitals, and control over health care costs such as drug prices [1]. Health care systems, as a nation, province, or health plan, can limit the treatments for which they will pay or set limits on the prices. This has implications for estimating costs, and places an even greater burden on researchers to describe explicitly where, when and how the costs were calculated.

Patients often observe very different “costs” for health care goods and services. Cost is the amount to produce the good, whereas a charge represents the amount on a bill, which often includes profit for the manufacturer. Therefore, different accounting systems can yield very different cost estimates.

Most of the hospital accounting systems in the U.S. focus on billing and payments. The charges listed on the bill usually overstate costs and are rarely paid in full by the payer. For example, in a recent study of the costs of surgery for female fecal incontinence (FI) in the US [2], hospital “charges” were defined as the amount that the hospital actually billed to the payer for the surgery etc, but the hospital “costs” were defined as the amount that the hospital actually received in payment! Only after understanding this definition can one make sense of the fact that hospital “charges” for FI surgery rose from \$48 million to \$57 million over 3 years, but the hospital “costs” increased only slightly from \$23 to \$24.5 million over the same 3 years (**Figure 1**).

In the U.S., researchers have developed imperfect methods for adjusting the charges with a hospital-specific ratio of costs to charges to better estimate costs [3]. Charges, however, are not always available. Integrated health care systems, including Canada and the U.K, do not routinely generate bills. For these systems, researchers have developed methods for generating pseudo-bills and cost estimates [4-6].

Many cost determination methods are used. Most analyses include a combination of “gross costing” and “micro costing” [7]. These terms are similar to



Bar graph demonstrates trends in hospital charges and costs associated with surgical management of FI. (Note: Cost data not available prior to year 2001).

Figure 1: Difference between hospital charges and costs, reproduced with permission of Elsevier (*Am J Obstet Gynecol*)

the phrases “top-down” and “bottom-up”. Accounting and billing systems use micro-costing methods, whereby detailed estimates of time and products (inputs) are combined with unit costs to estimate total costs. Micro-costing (or “bottom-up”) is challenging to perform because a single inpatient stay or outpatient procedure might have hundreds or thousands of inputs. Even when there is just a single input, such as a tablet, the cost can vary by location or the time of purchase if prices fluctuate. At the other end of the spectrum, gross cost methods (“top-down”) identify a limited number of important characteristics such as the Health Care Resource Group (HRGs) in the U.K., Diagnosis Related Groups (DRGs) in the U.S or Australia, and length of stay. These characteristics can then be combined using different techniques to estimate total costs.

Accounting systems are limited in that they always report the health care payer’s costs or charges. Since societal costs are of most interest [7, 8], one must distinguish between and include both provider-incurred costs and patient-incurred costs. This distinction is important for urinary incontinence, since most providers do not pay for routine care (e.g., pads and protection). These costs are usually incurred by individuals, and in 1995 the routine care costs in the U.S. represented at least 50% of the total cost of urinary incontinence [9, 10].

Thus the conclusion drawn by a researcher may be heavily dependant upon the completeness of their methodology. For example, a recent study from the USA [11] analysed Medicare claims for the treatment of urinary incontinence among women aged 65 or older for 3 years (1992, 1995, 1998) including outpatient, inpatient and emergency department visits.

Such Medicare claims nearly doubled over the time frame, from \$128 million to \$234 million, largely due to increased numbers of women treated by office visits and ambulatory (day only) surgery for items such as collagen injections. When the per capita changes were analysed, and inflation was considered, costs had actually declined by 15%. However, the editorial comment following this article points out that Medicare claims do not quantitate pad usage, and cannot record pharmacotherapy for urge incontinence. Since we know that overactive bladder is more common as age increases, such pharmacotherapy is likely to be increasingly important in the over 65 age group, so that the conclusion of a 15% drop in per capita Medicare expenditure are not likely to be valid in general. The editors pointed out that the article was mainly representative of patients with stress incontinence as a result. Such methodology issues are important.

In the example described above, the “**perspective**” that the researchers used was that of Medicare claims. In other words, Medicare was the “payer”, not the patient. This highlights the fact that costs can be evaluated from several different perspectives. The four most commonly used perspectives are (1) overall society costs, that include all aspects of care and treatment, (2) the payer, such as Medicare, (3) the provider, such as a hospital or managed care plan and (4) the patient.

In general, health economists prefer that a societal perspective (include all costs) is used [7,8]. This facilitates comparison of the cost of illness across different countries. The problem is that different countries use different frameworks for reimbursing some or all of the costs of various conditions, so that international comparison remains controversial.

2. COUNTRY SPECIFIC ECONOMIC ISSUES

From the perspective of a patient, large costs are often incurred when paying for routine care products, treatments, lost wages, and long-term care. These patient costs vary by country. For example, in Sweden and Spain, the government (tax based) health insurance does cover routine care products. In the UK, age-dependant patient subsidies are available for pads. In Germany and Spain, pad costs are reimbursed if prescribed by a doctor [12]. In Australia, low-income patients can apply for a subsidy to reimburse most of their routine care products, but more wealthy patients must pay all costs. In the USA, such products are not covered at all and can be very expensive.

From the patient’s perspective, out of pocket expenses for outpatient physiotherapy (pelvic floor muscle training) also varies considerably between countries. For example, a set number of physiotherapy visits (4-6) are free of charge in the UK and Spain, but patients in other European countries must give a co-payment that represents about one third to one tenth of the real cost (**Table 1** below).

The degree of government subsidy to the patient varies greatly by country. In the UK, most patients use the National Health Service (NHS) so that all office visits, tests, outpatient visits and surgical treatments are free to the patient. Pharmacotherapy does attract a small out of pocket payment for each drug. In Italy and Sweden pads are reimbursed, but not in Germany. Pads are not routinely subsidized, only at the discretion of the local Care Trust. In Australia, about 70% of patients only have government insurance, similar to the UK NHS, but 30% of patients

Table 1. Costs of PFMT as an example of out-of-pocket expenses in 2004 (from Monz et al [12]).

Country	Total costs	Description of program	Costs incurred by Health Care System	Out-of-pocket payment patient
France ^a	€ 94	One visit to urologist/gynaecologist/general practitioner for prescription and 10 visits to physiotherapist for training	€ 58	€ 36 unless additional complementary private health insurance
Germany ^b	€ 99	One visit to gynaecologist for prescription and six visits to physiotherapist for training	€ 81	€ 8 co-payment on physiotherapist, plus € 10 prescription charge
Spain ^c	€ 240	One visit to gynaecologist for prescription and six visits to therapist for training	€ 240	None
Sweden ^d	€ 467	One visit to gynaecologist and three visits to urotherapist	€ 400	€ 67 fees
United Kingdom ^e	£ 64	Four visits to continence nurse/physiotherapist in primary care	£ 64	None

^a Costs from <http://www.anaes.fr/>.

^b Costs from German Social Code Book V, 2004 [26] and EBM, 1999 [29].

^c Costs from Hospital Clinico, Universidad de Barcelona, Barcelona, Spain.

^d Costs for urotherapist from “Södra sjukvårdsregionen 2004”, for gynaecologist Linköping Hospital 2003, and patient fees from Stockholm 2004 <http://www.varldguiden.se/Article.asp?ArticleID=3796>.

^e Cost from PSSRU, 2003 [30].

also have private insurance so that inpatient treatments attract a rebate from their health fund. In the USA, adults over age 65 and those with a disability are covered by the Medicare program. This provides coverage for inpatient, outpatient and pharmacotherapy, although patients are generally responsible for sizable co-payments and nursing home care is capped. Those not covered by Medicare often have private insurance or Medicaid (a program for people with low incomes); nonetheless about 48 million Americans lack any insurance.

In the Netherlands, all legal residents are obliged to purchase a basic health policy (the purchase of a complementary policy covering extra health services remains voluntary). The choice of health insurer and type of health plan is free. The government establishes what is in the basic package and under what conditions people are entitled to care.

As regards long term care benefits for those in residential care, considerable variation occurs. In the USA, Medicare and Medicaid benefits are time limited for re-imbursing to nursing homes and other assisted living facilities. Usually after several months benefits stop and payment must come from private insurance or the patient's pocket. In Australia, low income patients who have no private superannuation (pension fund) can receive the "old age pension" which covers fully funded long term care, albeit in lower-calibre facilities than would be chosen by those who could afford better (similar to the Netherlands system). In Japan, generous long term benefits are provided to long term institutional residents, so that out of pocket payments are reduced.

3. OTHER "FRAMEWORK" ISSUES

Another methodological issue that must be incorporated into any study is the **context of time framework**. As mentioned in the Introduction, many continence treatments are time dependant, ie their effect extinguishes over time. However, from an economic view, a standard methodology exists. First the author of any study must identify the year for which the costs were calculated. Some economic studies collect costs over many years and also make projections about the future. In this case, the costs should be adjusted so that they reflect a single year. Future costs should be discounted to represent the present value. Controversy exists about the appropriate discount rate [13-15] but most international studies use a discount rate of 3% per annum. See Adang et al. [16] for example.

Second, costs borne in past years should be expressed in the current year's dollars. In many countries, past and future costs can be adjusted by the Consumer Price Index or other appropriate indices for all urban consumers (e.g., www.stats.bls.gov). In the UK, the Health Service Cost Index or the Retail

Price Index, published by the NHS Executive, Leeds, UK, can be used to adjust the costs of health care services; other indices would be used to adjust other items, such as wages (www.statistics.uk.gov). Most countries track inflation using relatively standardized methods, thereby providing a method for inflating past costs.

Caution is needed because general inflation relates to the cost of a *consistent* set of goods over time, eg the goods must be of the same quality over time, and thus the costs observed five years ago can be observed today. If so, then the inflation index is informative. However, medical goods change rapidly. For example re-usable laparoscopic equipment has been replaced by disposable equipment which is usually more expensive, and the newer drugs for OAB are generally more expensive. This makes it difficult to determine whether any changes in price is due to inflation or due to improved quality. Thus, just inflating costs from many years ago can be misleading.

In summary, defining and measuring costs in health care can be difficult. Often there is large variability in costs. Given this uncertainty, researchers should use sensitivity analysis to investigate how different cost estimates can influence the results. By this we mean re-running the analysis with different input parameters. As we describe in the next section, explicitly describing these contextual issues is crucial for interpreting results.

III. TYPES OF ECONOMIC ANALYSIS

1. OVERVIEW

A typology of economic analysis for health and medicine has emerged over the past few decades. This section reviews these studies.

a) *Cost of illness (COI)*

As already described, COI studies summate the costs related to a condition for a given population. The costs are annualized for a given year (ie 2008). A COI is a descriptive analysis and is only as good as its assumptions and only as complete as current knowledge allows. However, COI studies provide little information to decision makers about how to allocate scarce resources for treating conditions, because there is no attempt to measure the "value" of the relevant treatments or health interventions.

b) *Cost minimization analysis (CMA)*

CMA compares the costs of alternative health care strategies, assuming that the benefits of the alternatives are equivalent. When the two treatments are truly equivalent in their risks, outcome, and an individual's preference for them, then a cost minimization analysis is sufficient; the cheapest intervention is to be preferred.

c) Cost consequence analysis (CCA)

CCA is a variation on cost-minimization analysis, which involves assessing whether a new treatment results in a greater decrease in health care utilization than another treatment. Thus costs of the intervention are compared to health care utilization, such as the cost per hospitalization averted. There is a naturally appealing rationale for conducting this analysis. Unfortunately, when examined in detail, this rationale boils down to an analysis of whether the new treatment saves money in comparison to the alternative treatment. Accordingly, a cost-utility or cost-benefit analysis provides many advantages over a cost consequence analysis.

d) Cost-effectiveness analysis (CEA)

CEA refers to the broad class of calculations where the effectiveness measure is a general health outcome. CEAs with narrowly focused health outcomes (e.g., incontinence episodes) have well-accepted limitations. Most notably, the use of narrowly focused health outcomes will miss other important effects. For this reason, there has been widespread agreement on the use of quality adjusted life years (QALYs) as the preferred health outcome in cost-effectiveness analysis.

e) Cost-utility analysis (CUA)

CUA refers to a CEA when QALYs are used as the outcome measure. Gold et al [7] and Drummond et al. [8] have published texts that discuss standard techniques for conducting a CUA. In health and medicine, the CUA is considered to be the gold standard. Utilities capture all potential benefits of an intervention and allow comparisons with other health conditions, making cost-utility analysis a powerful research tool.

Compared to other medical fields, we have minimal data on utilities in incontinence or on the effect of treatment or change in incontinence severity upon preferences, to date.

Data in a CEA and CUA are represented by an incremental cost-effectiveness ratio (ICER). The ICER represents the average cost of the intervention group minus the average cost of the control group. This amount is then divided by the average utility of the intervention group minus the average utility of the control group (see Section IV.2).

f) Cost benefit analysis (CBA)

involves measuring the benefits in dollars. When everything is measured in dollars, optimal choice can be easily found by addition and subtraction. However, it is difficult to measure benefits in dollars, and many researchers, policymakers and clinicians are averse to placing a dollar value on life. CBA is rarely used in health.

g) Summary

COI and cost-minimization analyses are simple, yet limited economic tools. Most new treatments offer additional benefits at an additional cost. The CBA, CUA and CEA were designed to determine how much money it costs to obtain another unit of effectiveness. Although the CUA is the preferred method, there are many challenges with calculating a QALY. We will discuss these issues in more depth because different methods for calculating QALYs can have a very profound effect on the interpretation of the CEA.

2. DETAILS OF DECISION ANALYSIS

Decision analysis is a tool that can be used to summarize effectiveness data, costs data, or combine both cost and effectiveness data in a CUA. The value of decision analysis is highlighted by a recent multi-site clinical trial by Albo and colleagues [17] that compared Burch colposuspension to fascial sling for stress incontinence. They concluded that the fascial sling yielded a higher rate of successful treatment, measured as a composite outcome, but also resulted in greater morbidity. Even in well-designed multi-site clinical trials, the results may be ambiguous. Decision analysis may be used to overcome this ambiguity. Decision analysis is a quantitative probabilistic tool for resolving problems when there is uncertainty with regards to treatment options.

There are two primary decision analytic methods (see below); each has its strengths and weaknesses. The starting point with any decision analysis is the delineation of a clinical question, such as how to treat women with stress urinary incontinence. The question should fully and fairly address the clinical question or questions. One might develop add on questions, such as how to treat women who had surgical failure, but it is often best to address these more specific questions as part of the broader decision analysis.

A benefit of decision analysis is that researchers can combine data from multiple clinical trials and marry that data to observational information (e.g., long-term follow-up data). Decision analytic tools are flexible and can be used to identify the treatment that maximizes quality of life. One can also use the same model to address issues of cost-effectiveness. Hence, one of the first tasks in the decision analysis is to identify the primary outcome. Outcomes such as quality adjusted life years (QALYs), that can reflect treatment and disease, are recommended. By using QALYs, one can overcome conflicting data—for example, the finding that vaginal slings have higher success rates but also greater morbidity. As is discussed elsewhere in this chapter, QALYs value all aspects of quality of life and combine that information with mortality. Next, the researcher must determine whether the model will include cost information or not. Some decision analytical models focus only on

outcomes, while others add cost data to address resource allocation questions.

By combining data from multiple sources, decision analysis' can be used to model lifetime costs and benefits. Researchers are often tasked with identifying the treatment(s) that maximizes lifetime benefits or lifetime cost-effectiveness. Randomized trials, while the gold standard for assessing causation, are time limited, often following participants for less than five years. Decision analysis can extend such data to consider future events, such as surgical failure rates, nursing home admission or life expectancy. Decision analysis can also be used to understand if the analysis differs by perspective. Payers, providers and patients all have different perspectives, and decision analysis makes it relatively easy to consider each of these perspectives and whether they differ from a society perspective. Frequently it is helpful to understand where the perspectives diverge as this can highlight conflicting incentives. Aligning incentives, when possible, is often seen as socially optimal for governmental regulations and programs.

a) Steps in a decision analysis

Decision analysis can be boiled down into five steps. The first step involves identifying the structure of the problem and this requires the listing of all decision alternatives, all clinical outcomes, and a sequence of events. Once step one is complete, then step two involves assigning probabilities to all chance events (e.g., death). Step three involves assigning outcome (e.g., QALYs) to all outcomes. The fourth step involves the mathematical calculation of expected utility for each strategy. Step four will often identify the preferred strategy. The final step involves identifying the robustness of the model and this is achieved by conducting sensitivity analysis.

Every decision model involves some assumptions. Frequently assumptions are needed to incorporate clinical trial data in the model. For example, a common assumption is that the effect shown in a clinical trial is generalizable to the broader population—treating women with Burch colposuspension will result in effects like those seen in Albo and colleague's [17] paper. Some assumptions may seem trivial, but it is best to delineate each assumption along the way. Published decision analysis should include a table of assumptions along with other data inputs; frequently this is the first table in the decision analysis.

The clinical question and the structure of the problem (step 1) should provide guidance on the decision model. Frequently decision trees are used because they address the question at hand. Decision trees are so named because they look like a tree with a trunk, branches and leaves.

While decision trees are easy to describe and conduct, it is hard to include time in the analysis. Diseases

often change over time and people may transition into and out of different health states. A strength of Markov models is their ability to include these time-related transitions. We will discuss decision trees first and then Markov models in more detail afterwards.

b) Decision Tree

In the decision tree, there is a distinction between a decision node and a chance node. A decision node is a point where a choice is made by the decision maker (typically a physician or patient). For example, for a woman with stress incontinence, the choice to operate (yes or no) would be represented with a decision node. A choice must have at least two options and more than two choices are permitted. However, each choice must be mutually exclusive. A patient cannot choose both operation and no operation. A chance node is a point where chance determines fate. For example, the decision maker chooses to operate or not operate, and hopefully the treatment is successful, but treatment success or failure is a chance node. Not only must chance nodes be mutually exclusive, but they must also be collectively exhaustive (one of the changes must happen and the sum of probabilities for all of the chances must add to 100%).

In addition to chance and decision nodes, there are terminal nodes. These nodes are the final outcome for the pathway taken. Sometimes understanding the nodes makes more sense when looking at the pictorial representation. Figure 2 shows a hypothetical decision tree for treating a patient with stress incontinence. In this hypothetical situation, we structure the model to have two options: surgery or drugs. It is overly simplistic in that we do not differentiate between drugs. Also the model is completely hypothetical in that a surgical death rate of 10% and a 10% cure rate are not realistic.

The main choice is surgery versus medical management. Surgery carries some risks—a small probability of operative death. The decision nodes are represented by squares while chance nodes are represented by circles. The terminal nodes are cure, no cure, operative death or non-adherence, which is the same as no cure. This is a hypothetical decision model, and most decision models are much more complex. Clearly this model could be expanded to include behavioral treatment and each decision node could be expanded to consider all relevant alternatives (sling, Burch colposuspension, tension-free vaginal tape) (**Figure 2**).

For the next step in the decision model, one must include probabilities at each chance node. We must identify the probability the disease is cured after operation. Researchers should review the published literature to find this probability and ideally some information about the distribution around this probability (e.g., probability= 58% with a 95% CI 51-68%).

After including probabilities, one must place values next

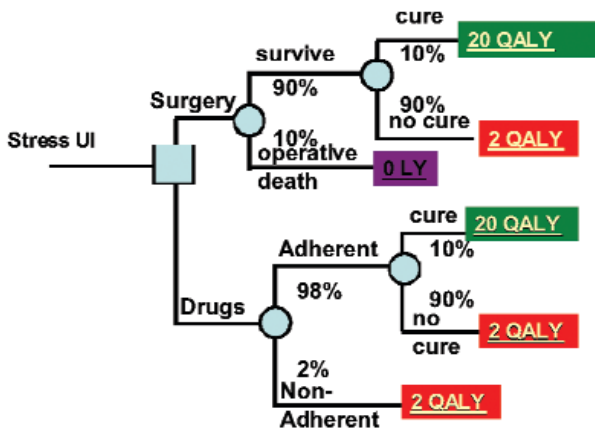


Figure 2 : A hypothetical decision tree for treatment of patients with stress incontinence. Squares = Decision nodes, Circles = Chance nodes and terminal nodes.

to the terminal nodes. These values must be a single outcome and QALYs are preferred, although life years are used for some diseases. With outcome and probabilities, one can then “run” the decision tree. Because there is one decision node with two options, we will be computing expected values for the two options. Running the model involves starting at each endnode and working left or backwards. The expected value for the surgical survival node is 3.8 QALYS (Figure 3).

The expected value for the surgical operative death node is 0. When we combined a 10% chance of operative death (0 QALYS) and a 90% chance of survival (3.8 QALYS), we find the expected value of surgery is 3.42 (Figure 4). If we do the math for the lower branch, we get the expected value for drug therapy is 3.76 QALYs. Because $3.76 > 3.42$, we would recommend surgery over drugs IF the sensitivity analysis shows this result to be robust. The decision tree in the example focuses on QALYs for UI treatment and it ignores and cost differences, but it could be easily modified to include cost information.

c) Markov Model

The decision tree, as shown above, assumes the chance of events is stable over time. Our knowledge about urinary incontinence suggests otherwise. A person, for example, could get surgery for stress incontinence, but over time we need to include the potential for surgical failure. Markov models are good for incorporating changes in health states over time. At their core, Markov models are mathematical techniques, derived from matrix algebra, that describe the transitions a cohort of patients make among a number of mutually exclusive health states over time. The model works by cycling to make new calculations for each period of time.

The pictorial depiction of a Markov model is typically shown as a decision state. Figure 5 shows a very basic three-state Markov model. At each period in time, a person has to be in one and only one of the

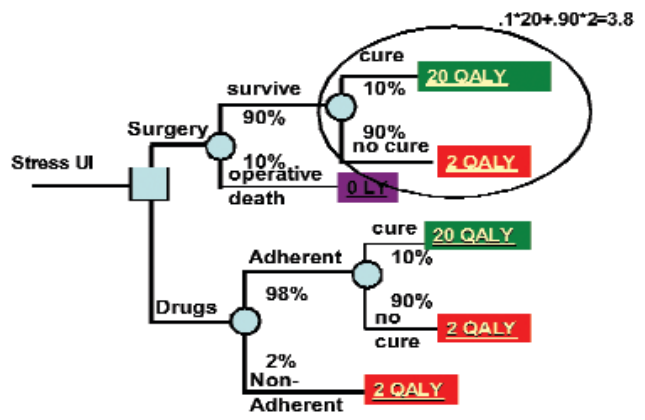


Figure 3 : Computation of expected QALY values for the two terminal nodes, after surgery survival.

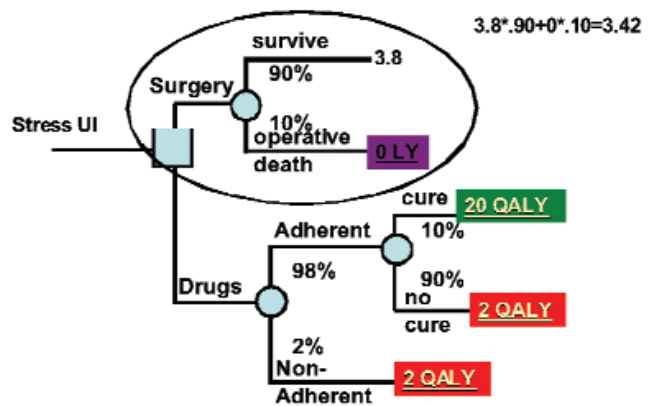


Figure 4 : Computation of expected QALY values after surgery for stress incontinence.

states. But with each change in time (cycle), the person can move to another state, shown with arrows, depending on the possible states and a probability. If the person dies, they are shown to enter the death state. The person cannot leave this state.

Some aspects of the Markov model construction are similar to a decision tree and some are different. Setting up the model is quite similar. One must identify the health states and the transition probabilities. What is quite different is that one must determine the cycle length—the rate at which you allow people to change states. The cycle length should be a clinically meaningful period of time and this choice is also frequently affected by the availability of data. There may be publications showing annual failure rates for surgery and so one could choose an annual cycle or choose a monthly cycle, making a correction to the probabilities so that the sum of twelve months is equivalent to the annual data.

For a Markov model, one needs to know the value for each state. Again, QALYs is the preferred metric. When the model runs, the program keeps track of the amount of time each person spends in each state.

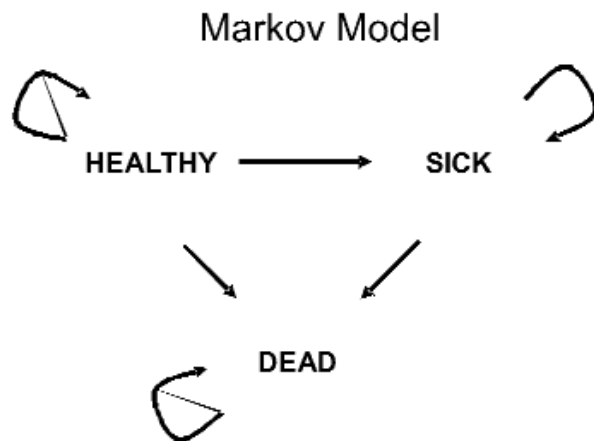


Figure 5 : A basic three-state Markov Model.

Transitions to other states are handled by transition probabilities, and decisions, such as the decision to get treatment, can affect transition probability. Models can use cohort simulations where a large hypothetical cohort of patients is run through the model. This does not provide information on the distribution of expected values. Monte Carlo simulations run each patient through the model a large number of times (e.g., 10^4). In doing so, this provides a distribution and variance information on patients.

With Markov models, sensitivity analyses remain a crucial step to test the robustness of the model. Recent advances in sensitivity analyses and in the graphical presentation of data general require the use of specific software. Although some people program Markov models into a spreadsheet, such as Excel, both Tree Age and Decision Maker software are well known for their ability to streamline decision analysis and provide many advanced features that would be very difficult in Excel.

3. STATISTICAL ANALYSIS

One of the tasks of data analysis is to provide answers to the research questions being studied. When a study examines the relationship or association between two variables, such as the frequency of incontinence and the cost of incontinence care, then a bivariate correlation is useful. The **correlation coefficient** measures a linear relationship between these two variables to show the degree of association ranging from 0 (no relationship) to 1.0 (a perfect positive relationship) or -1.0 (a perfect negative relationship). When there is more than one factor that can explain the variation of the cost of treating incontinence, such as the age of the patient, other illness conditions, and employment status, a **multivariate regression** analysis is required. For instance, in a study by Birnbaum and others [18] to examine the costs of stress of urinary incontinence, their **log-linear regression** model indicated that patients with surgery would cost more than those without surgery, and

patients with other co-morbidities would cost more than those without. To test the statistical significance of these covariates, a **standard error of the coefficient** of these variables is needed, for which a t-test can be used. The predicted log-linear dependent variable can be transformed into a nominal value.

Another useful application of multivariate regression model using a **dummy variable** may occur when a cost-effectiveness analysis of a particular intervention (clinical trial), is desired. For instance, in a randomized clinical trial of a behavioral therapy to reduce urinary incontinence in nursing homes Hu et al. [19] used a Dummy Variable (a value of 1 for treatment group and zero for the control group) that the treatment group's wet episodes have been reduced by 26% over the baseline while the control group remained the same after the 22-week follow-up period. When comparing cost differences between two conditions or two programs, (e.g. [18]), the study used the dummy variable (stress incontinence equals 1 and non-stress incontinence is '0') in the regression model to show that the added cost (incremental cost) for stress incontinence patients was 30% higher than non-stress incontinence costs, after controlling for other covariates.

When incontinence episodes have a **discrete probability distribution**, the probability of either having an incontinent episode or not having one episode is random, these events can be analyzed by a negative binomial distribution. Under this distribution, a mean of a given time period (such as the weekly number of episodes of urinary incontinence), and variance of the incontinence can be estimated. For example Hughes and Dubois [20] used such a **negative binomial distribution** to compare the cost-effectiveness of extended-release formulations of oxybutynin and Tolterodine for treatment of OAB.

With discrete value and skewed distribution, negative binomial distributions can also be used for the regression model, instead of using a linear regression model. In the statistical literature, the **Poisson distribution** is a special case of binomial distribution. In this case, the variable takes a value of 0, 1, 2, 3, ..., n. Poisson regression is an extension of the negative binomial regression.

4. BUDGET IMPACT ANALYSIS (BIA)

Providers and payers often have priorities that are not directly addressed by a cost-effectiveness analysis from a societal perspective. The budget impact analysis (BIA) was developed to inform a decision maker on how alternative technology will affect their budget. A BIA will often focus on the decision maker's costs and over a short time frame (e.g., 1-3 years). Other parameters in the model, such as patient characteristics or input costs, can also be tailored specifically for the decision maker. Making decision based solely on a BIA can lead to suboptimal social

results. Hence, scientists advocate that a BIA be done in conjunction with a CEA so that decision makers are informed about the broader social implications of their decision. The International Society for Pharmacoeconomics and Outcomes Research (www.ispor.org) has created guidelines for conducting a BIA and these can be found on their website.

IV. PRACTICAL ASPECTS OF ECONOMIC ANALYSIS IN THE CONTINENCE FIELD

1. HEALTH OUTCOME MEASURES SUITABLE FOR USE IN ECONOMIC ANALYSES

There are a number of health outcomes that are used in economic evaluations of incontinence. These include disease-specific outcomes, health status and health value (e.g., QALY). Each is discussed in turn.

a) *Incontinence specific outcomes*

Cost-Effectiveness in Health and Medicine [7] recommends using QALYs as the effectiveness measure in the CEA. However, the panel also notes that analysts can use a clinical outcome measure. For incontinence, clinical outcome measures include 24-hour pad test, a voiding diary, or urodynamics. These outcomes are attractive for clinicians because they often use these measures in clinical practice.

Clinical outcomes can be very valuable in identifying when a treatment is efficacious. However, using clinical outcomes in a CEA yields results that are limited in scope. A treatment might have improved a person's quality of life, but had little effect on the clinical outcome measure. In this case, the results would be biased. In addition, a CEA with a clinical outcome measure might not be comparable to another CEA with a different clinical outcome measure. A clear advantage of cost utility analysis is that QALYs can be generalized beyond incontinence. For this reason, QALYs and CUAs are the gold standard.

b) *Health Status and Quality of Life Measures*

There are a number of frequently used and highly regarded general health status measures, such as the SF-36, the Sickness Impact Profile and the Nottingham Health Profile, which describe a person's current health state. Instruments that assess how a person perceives or feels about their health state are called quality of life (QOL) measures.

Chapter 5 in this book reviews generic and disease – specific quality of life measures, which are useful for understanding the effects of a treatment. However, because they cannot be used to create QALYs they are of limited value in economic analysis. The exception is the SF-36 for which Brazier et al. [21] have created a rudimentary utility scoring system.

c) *Health value*

Although there are several ways of measuring the value of a health state, the most common are willingness to pay (WTP, [22]) and the quality-adjusted life year (QALY). We focus on QALYs as they represent the current standard for measuring health value.

QALYs denote the relationship between the value of a given health state and the length of time a person lives in that health state. The value of a given health state is measured in 'utilities', where 'utilities' represent preferences for a given health state.

To understand utilities, consider the following. Most people would prefer to be healthy over a given time rather than suffer constant urinary or fecal incontinence. Utility measurement refers to valuing these preferences on a life-death scale with endpoints of 1.00 and 0.00, where 1.00 is perfect quality of life (best imaginable) and 0.00 is death equivalent quality of life. For example, the measured utility for urinary incontinence may be 0.60. If treatment improves this to 0.70, then the value of the treatment is $0.70 - 0.60 = 0.10$. If this utility gain is maintained over time, say for 10 years, then the gain is $0.10 \times 10 = 1.00$ QALY. Because utilities fall on the life-death scale, they are (in theory) common across all health states and therefore can be used to compare the effect of interventions in different health fields, or different interventions within the same field. For example, the QALYs gained from treatment for incontinence could be compared with those gained from treatment for depression. Where treatment costs (including costs to the patient) are known, the treatment providing the lowest cost-per-QALY gained is preferred as this ensures society gains the greatest benefit from the health care dollar.

Direct and indirect methods have been used to elicit utilities [23]. The most common direct elicitation methods for valuation include time trade off (TTO), standard gamble (SG), and the visual analog scale (VAS). For description of these methods, see our previous chapter in this ICI Monograph series [24].

1. INSTRUMENTS MEASURING UTILITIES SUITABLE FOR QALY CALCULATION

Multi-attribute utility (MAU) instruments can be used instead of the direct elicitation methods. Simply, a MAU-instrument decomposes HRQoL into health domains (e.g., mobility and emotions). Respondents provide estimates for each of the parts, which are then 'valued' and recomposed back into a utility. The three most commonly used MAU instruments are QWB, HUI and EQ5D (as reviewed by Hawthorne & Richardson [25]).

2. QUALITY OF WELL-BEING INDEX (QWB)

The QWB has three dimensions (Mobility, Physical Activity, and Social Activity), with 3–5 levels each,

and 27 illness symptoms. [26]. The QWB requires trained interview administration (15–35 minutes), although a shorter version is available; a self-report version is under development. The upper boundary is 1.00, lower boundary is 0.00

3. HEALTH UTILITIES INDEX (HUI)

The HUI uses 12 items that measure 8 domains (Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain). The upper boundary is 1.00, lower boundary is –0.36.

4. EQ5D

The EQ5D was developed by the Euroqol team from 7 European countries [27, 28]. It has 5 items measuring Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression. The upper boundary is 1.00, lower boundary is –0.59.

5. SF6D

Although two different algorithms have been published for deriving preference-based values from the SF-36, only the second is described here [21]. Whenever SF-36 raw scores are available, SF6D utilities can be computed. The SF6D measures physical functioning, bodily pain, mental health, physical role, emotional role, social functioning, and vitality. The endpoints for the SF6D are 1.00, and 0.30 for the worst possible health. .

6. OTHER MAU INSTRUMENTS

The Assessment of Quality of Life (AQoL) includes five dimensions: Illness (not used in utility computation), Independent Living, Social Relationships, Physical Senses and Psychological Well-being [29]. The upper boundary is 1.00, lower boundary is –0.04. The Rosser Index has two dimensions measuring disability and distress, and measured 29 health states. Values (magnitude estimation) were from a convenience sample of 70 respondents [30]. A revised version in the early 1990s included discomfort as an additional dimension [30]. Administration requires a trained interviewer. The upper boundary is 1.00, and the lower boundary –1.49, which means that health states worse than death are permitted. The 15D was created in Finland. It has 15 items, measuring Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Elimination, Usual Activities, Mental Function, Discomfort & Symptoms, Depression, Distress, Vitality and Sexual Function [27]. The upper boundary is 1.00, lower boundary is +0.11.

For a full review of cost utility analysis up to 2004, see our previous chapter [24]. For subsequent studies, see Section V of this chapter.

One final note about collecting utilities is warranted. Many people with incontinence are not cognitively able to complete a MAU or go through a standard utility elicitation process. Some of the MAUs, such

as the HUI 3, have been validated for use with proxies. Although not always possible, if proxies are expected then proxies should be gathered for all cases, even those patients who complete the utility measure themselves, so that the method is applied in a standard fashion.

2. “DO IT YOURSELF” - HOW TO CONDUCT A COST UTILITY ANALYSIS: THE COMMITTEE’S RECOMMENDATIONS

The cost utility analysis (CUA) now represents the gold standard for medical decision making. Therefore, the remainder of this section highlights ten key issues that must be addressed in a CUA. These ten principles, summarized below, comprise an appropriate minimum standard for performing and reporting cost utility analyses. The principles were identified from guidelines established by the Panel on Cost-Effectiveness in Health and Medicine convened by the United States Public Health Service [7] Each principle should be explicitly addressed in every study.

1. The **Research Question** must be clearly stated. All CUAs must compare at least two different treatments or interventions. One of these should include the current standard practices. For example when comparing surgeries for stress incontinence, one of the comparators should be a longstanding method; avoid comparing two new methods side by side.
2. The **Time Frame** over which costs and benefits are measured should be long enough to capture the economic impact of an intervention and future health outcomes. Pharmacology studies of 12 weeks duration give very little real economic information, and surgical complications/ failures seldom emerge in less than 1-2 years.
3. **Perspective:** The choice of perspective should be clear. Total society perspective (all payers) is the gold standard. Other perspectives, such as the payer or patient perspective, may be useful but must be stated clearly.
4. **Probabilities** are needed for each “chance” event, such as chance of cure or chance of an adverse event. The best sources of probabilities come from meta-analyses of randomized clinical trials, or if not available use data from individual clinical trials.
5. **Costs:** Units of expense and unit costs should be described in detail. Information on the source (e.g., charges, payments) and year of the cost data should be presented. If the costs were inflated and/or converted from another currency, then this must be described.
6. **Outcome Measure:** Measures of effectiveness depend on the type and objectives of analysis. Quality adjusted life years are the gold standard, as described previously in this chapter.
7. **Analytic Model:** Each intervention being assessed

must be described and possible courses of events identified, including the expected course of disease, treatments, complications, and outcomes. This may be performed using a spreadsheet/clinical trial path, or Decision Tree, or Markov Model.

8. **Discounting:** Since the value of both costs and benefits may decrease over time, discounting is used to calculate the present value of money and health states that will occur in the future. Future costs and utilities should be discounted to present value; 3 % per year is a recommended starting point.
9. **Incremental Analysis:** The purpose of a CUA is to describe the relative value of one health care strategy compared to another. An **incremental cost-effectiveness ratio (ICER)** is the incremental cost divided by the incremental effectiveness of intervention a compared to intervention b, and is calculated as follows.

$$\text{ICER} = \frac{\begin{array}{c} \text{Average Cost} \\ \text{intervention A} \end{array} - \begin{array}{c} \text{Average Cost} \\ \text{intervention B} \end{array}}{\begin{array}{c} \text{Average Utility} \\ \text{intervention A} \end{array} - \begin{array}{c} \text{Average Utility} \\ \text{intervention B} \end{array}}$$

Averages should be used rather than other measures of central tendency, such as medians, because it is important to include the effect of outliers. The leverage of the outliers should be tested in a sensitivity analysis.

10. **Sensitivity Analysis:** A sensitivity analysis should allow the reader to understand whether the conclusion of the analysis would hold true if either the Costs or the Probabilities (of cure or complications) were to vary substantially. For example if one treatment costs 5,000 Euro and has a cure rate of 90%, and the second treatment costs 2,000 Euro with a cure rate of 80%, then the ICER will assess whether the resultant benefit in QALY/ Quality of Life makes the first treatment worthwhile.

Having reached this conclusion, the researcher should then vary the costs and the cure rates in the model, to see how much variation in real life would be allowed yet still maintain a valid conclusion.

Documenting these boundaries helps define the conditions under which a treatment is preferred. Researchers are developing innovative methods for conducting sensitivity analyses.

Probabilistic models that use simulations are becoming more common, although they can be computationally complex.

V . SUMMARY OF RECENT ECONOMIC ANALYSES

Note: the Committee strongly recommends that all studies of economic analyses should publish the timeframe in which the study was actually performed (because the date of publication is often months to years later), and that the currency employed be stated for that year/timeframe. This is essential for accurate discounting of costs over time, and for comparing economic analyses of treatments performed in different years.

1. SURGICAL TREATMENT COST EFFECTIVENESS STUDIES

a) *Is treating incontinence cost-effective?*

Since the last ICI meeting in 2004, several cost-effectiveness analyses of surgical interventions for stress incontinence have been published. These analyses systematically compare costs and outcomes of surgical treatments for stress urinary incontinence. The largest number of cost-effectiveness analyses were done comparing less to more invasive procedures – tension-free vaginal tape (TVT) vs. alternative surgeries for stress incontinence and laparoscopic vs. open procedures. These are inherently appropriate for CEA since the less invasive approach is more likely to be less costly (both direct costs of surgery, hospitalization and indirect costs of shorter recovery time) yet may be less effective, be associated with more adverse events and/or result in lower health-related quality of life.

b) *TVT vs. Other procedures*

Several studies compared the cost and cost-effectiveness of incontinence surgeries, supporting the finding that tension free vaginal tape (TVT) is more likely to be cost-effective compared with the other surgical procedures. However, there is a need for longer-term follow-up data from methodologically rigorous randomized trials to provide a better data to estimate the relative benefits and cost implications.

Cody and colleagues [31] evaluated the effectiveness and cost-effectiveness of tension-free vaginal tape (TVT) compared to standard surgical interventions for stress incontinence [31, 32]. Effectiveness and cost (2001 pounds Sterling £) estimates came from a systematic review of studies published from 1966 to 2002 that compared TVT with any alternative surgical or injectable agent therapy and utilities were estimated using the EQ5D in a surgical trial [33]. A Markov model was developed to estimate costs and quality-adjusted life-years for up to 10 years following surgery. They found that open colposuspension, laparoscopic colposuspension and traditional slings have similar cure rates to TVT, whereas injectable

agents have lower cure rates. In economic modeling, TVT dominated open colposuspension (lower cost and same QALYs) within 5 years after surgery. The range of outcome measures used to define “cure” were not described, which may affect the accuracy of these conclusions.

However, there were no randomized controlled trial (RCT) data beyond 2 years post-surgery, and long-term effects could not be ascertained. TVT was more likely to be cost-effective compared with the other surgical procedures. Increasing the absolute probability of cure following TVT increased the likelihood that TVT would be considered cost-effective. The likelihood of TVT being cost-effective was 86% if decision-makers are willing to pay up to £ 30,000 per additional QALYs. In sensitivity analyses, TVT’s dominance depended on the assumption that retreatment open colposuspension has lower cure rates than a first colposuspension and the rate of retreatment. In the short- to medium-term the effectiveness of the TVT is similar to alternative procedures and TVT is less costly. Yet, they concluded that the long-term performance of TVT for effectiveness and adverse effects is unknown.

Wu and colleagues [34] performed a methodologically excellent cost-effectiveness analysis of Burch colposuspension compared with TVT for stress incontinence. They developed a Markov decision model to compare costs (2005 US dollars) and QALY’s (on Health Utilities Index) over 10 years from a health care system perspective. Probabilities, costs and utilities were estimated by literature review and used generalizable measures. After surgery, outcomes included cure, persistent stress incontinence followed by second surgery, and persistent stress incontinence and mesh erosion after tension-free vaginal tape. In their base-case, the Burch strategy cost more than TVT (\$9320 vs \$8081) but was slightly more effective (7.260 vs 7.248 QALY’s), with an incremental cost-effectiveness ratio of \$98,755 per QALY. The model was most sensitive to cost difference between the strategies, utility, probability of mesh erosion and the relative risk of a cure. The incremental cost-effectiveness ratio was less than \$50,000 per QALY when the relative risk of cure after Burch vs. TVT was greater than 1.09. In this well done study using state-of-the-art methods, Burch colposuspension was not cost-effective compared with TVT. However, if the tension-free vaginal tape failure rate was to increase over time, Burch may become cost-effective, reinforcing the need for long-term follow-up in surgical trials and cohorts.

Manca et al. [33] assessed the cost-effectiveness at 6 months of TVT compared with open Burch colposuspension as a primary treatment for urodynamic stress incontinence in 344 women in a multicentre RCT at 14 centres in the UK and Ireland. Resource use included length of hospital stay, time in

theatre and management of complications and was based on UK unit costs at 1999-2000 prices. They collected primary data on QALYs with the EQ-5D health questionnaire. At 6 months TVT dominated colposuspension: TVT had lower mean costs and higher mean QALY’s. TVT resulted in a mean cost saving of £ 243 (95% CI £ 341, £ 201) compared with colposuspension and differential mean QALYs per patient (TVT - colposuspension) of 0.01 (95% CI - 0.01 to 0.03). In sensitivity analyses, the probability of tension-free vaginal tape being, on average, less costly than colposuspension, was 100%, and the probability of tension-free vaginal tape being more cost-effective was 95% if the decision-maker was willing to pay £ 30,000 per additional QALY. Over six months, TVT was a cost effective alternative to colposuspension. The study was limited, however, by short follow-up.

Moreno et al. [35] performed a cost-minimization analysis of ambulatory surgery compared with inpatient surgery for TVT in a public hospital in Spain. They used activity-based (micro) costing of surgery, emergency service and admissions to hospital immediately following surgery. They observed that the mean cost for patients in the ambulatory group was 42% lower than that for the hospitalized patients and that ambulatory surgery had equal efficacy to the surgical intervention.

c) Open vs. laparoscopic colposuspension

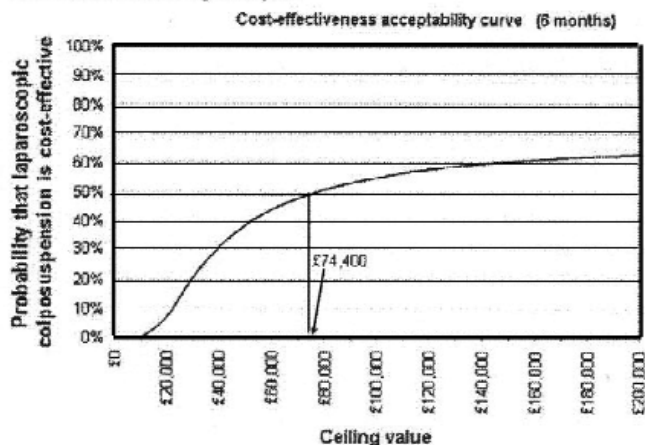
A methodologically excellent study by Dumville et al. [36] compared the cost-utility of laparoscopic versus open colposuspension to treat female urinary stress incontinence at 6 months. Cost utility analysis was performed alongside a RCT at 6 centres within the UK. Data on costs (£) and generic health-related quality of life (EQ-5D) were collected and patient-specific quality-adjusted life years (QALYs) calculated. Healthcare costs over 6-month follow up were higher for the laparoscopic arm than for the open arm (£ 1805 vs. £ 1433; differential mean cost £ 372; 95% CI 274, 471) due to increased theater costs. QALYs were slightly higher in the laparoscopic arm relative to the open arm (0.005; 95% CI -0.012, 0.023).

The ICER was £ 74,400 at 6 months. At 24 months, higher mean QALY’s persisted in the laparoscopic arm and modeling showed the ICER was reduced to £ 9300 (see **Figure 6** below). Limitations include few longer-term data on efficacy of the laparoscopic approach. While laparoscopic colposuspension was not cost effective compared with open colposuspension during the first 6 months following surgery, it may be cost effective over 24 months.

d) Injectable agent therapy

A cost- effectiveness and cost-consequence analysis found that urethral injection therapy is likely cost-effective compared to surgery to treat recurrent stress

Six months follow up analysis



24 month follow up analysis

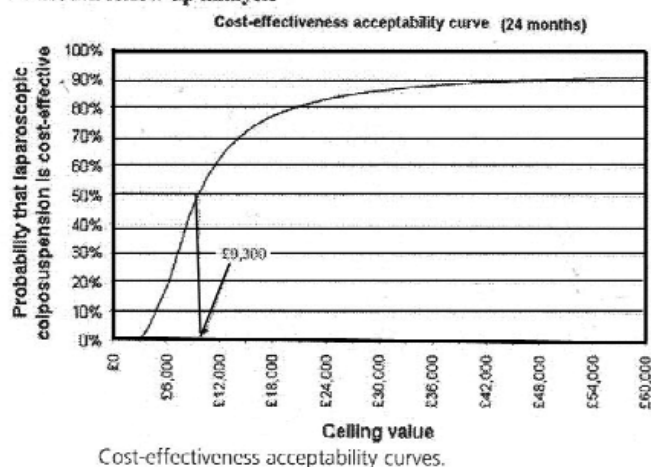


Figure 6 : Changes in the ICER from 6 months to 24 months when comparing laparoscopic versus open colposuspension (reproduced with permission from BJOG).

urinary incontinence. However, the study was limited by lack of long-term data and choice of outcome measures. Oremus et al. [37] performed a cost-effectiveness analysis to compare each of three surgeries (retropubic suspension, transvaginal suspension, sling procedures) with collagen injection therapy to treat female stress urinary incontinence after the failure of initial surgical treatment. The analysis used decision-modeling from the Canadian health care system perspectives using probabilities from a literature review and generalizable Canadian cost data. While the treatment with the lowest average cost was collagen (2718 Canadian dollars), the surgeries had higher probabilities of success (defined as 'cure'). The ICERs for all treatment comparisons indicated that the cost to cure an additional patient with surgery could range from 1824 - 6814 Canadian dollars in Ontario and 1388 - 3008 Canadian dollars in Quebec. These ratios were sensitive to changes in the mean number of injections for collagen patients and to a reduction in the length of hospital stay for surgery to 1 day. Each of the surgeries has a relatively small additional cost per cure for stress incontinence compared to collagen injections. Collagen injection

may be cost-effective as a follow-up treatment to initial surgical failure when the number of injections is kept to a minimum and hospital stays after surgery are relatively lengthy.

Tierney et al. [38] performed a "bottom up" study of the costs of performing TVT, open colposuspension and collagen injections in Scotland but only short term hospital costs were considered.

Kobelt and Fianu-Jonasson [39] performed a cost-consequence analysis including resource utilization and utility of a urethral injection therapy (the Zuidex system of prefilled syringes of non-animal stabilised hyaluronic acid/dextranomer (NASHA/Dx) gel) compared to TVT for stress incontinence. Utility was measured using the EQ-5D in 82 patients undergoing injections, and cost data were collected prospectively in a 12-month efficacy study of injections and retrospectively for TVT (n = 77). Injection therapy provided utility benefits that were similar to those previously reported for TVT (0.05 at 3 months and 0.01 at 12 months) and was associated with similar or lower overall costs in the short-term (€ 2200 at 3 months and € 3100 at 12 months for injection vis. € 4200 at 6 months for TVT). From an economic perspective, NASHA/Dx gel could be considered at least as favourable as TVT, pending the availability of long-term effectiveness data.

Kalsi et al. [40] performed a cost-consequence analysis of resource utilization and health benefits of intradetrusor injections of botulinum neurotoxin-A at 16 weeks in 101 patients with intractable overactive bladder (OAB) enrolled in a research protocol in the UK. The cost of therapy was quantified based on NHS resources used from the perspective of the UK NHS. After 16 weeks, 65% of patients showed $\geq 25\%$ improvement and 53% at least a 50% improvement in \geq two out of five OAB parameters (**Figure 7**). Therapy cost pounds 826 per patient, with a cost-effectiveness ratio of £ 617 per patient-year with $\geq 25\%$ clinical improvement. The investigators concluded that there is a role for botulinum toxin injection. However, the study was severely limited by using an outcome measure that is not generalizable and has minimal value ($>25\%$ clinical improvement), by short term follow-up and by having no comparison with a standard alternative therapy.

e) Conclusions

Current data on the cost-effectiveness of surgical treatment for stress incontinence show minimally invasive surgery (TVT, injectable therapy) vs. more invasive surgeries like the Burch colposuspension are likely cost-effective. However, the studies are limited by poor longer-term data on the effectiveness of less invasive procedures. In addition, these cost-effectiveness and cost-utility analyses are limited by lack of primary and/or generalizable data on costs,

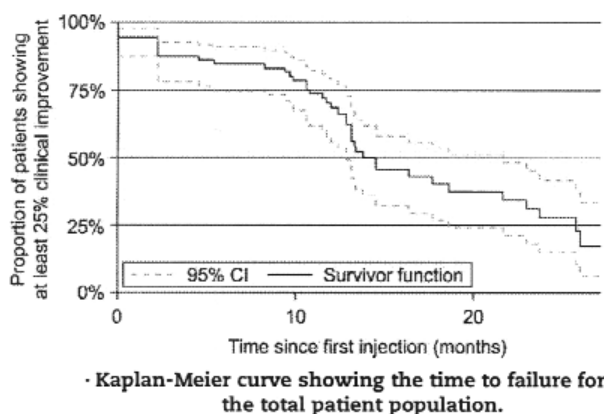


Figure 7 : Decline in percentage benefit over time after Botulinum toxin injection for intractable OAB

clinical outcomes and utilities and not using a accepted and generalizable outcome (cost per QALY or cost per “cure”). Further, few have primary data to perform analyses over a longer timeframe. Further research suggestions include unbiased assessments of longer term performance from follow-up of controlled trials or population-based registries, more data from methodologically sound RCTs using standard outcome measures, use of accepted standards for selecting outcome measures and for decision modeling, and a surveillance system to detect longer term complications.

2. OUTPATIENT CONSERVATIVE THERAPIES

a) Prospective studies of conservative therapy costs

Neuman et al. [41] calculated the physiotherapy treatment costs for 274 women with stress incontinence in Australia. A median of 5 (IQR 4-6) treatments were given, for a median cost of 250\$ (IQR 206-295). When cost of a GP visit was added, with MSU total cost of 302 AuD (in 2000). In the 208 women who completed therapy, weekly leakage episodes declined from 5 (IQR 3 -11) to 0 (IQR 0-2 leaks). Using intention to treat analysis, 64% of patients were dry on a stress test (or 84% of those who actually completed therapy). Improvement was observed using the Kings Health Questionnaire, but utilities were collected. This appears to be the first prospective study of physiotherapy costs for stress incontinence.

Williams et al. [42] of the Leicestershire UK MRC Incontinence Study Team undertook a large RCT of conservative therapy. Personal and treatment costs were measured (year 2001). Of the 29,039 men and women who leaked several times per month and had frequency, urgency and nocturia, 6,207 agreed to participate in a home interview, of whom 3,746 were randomised. They were allocated in a 4:1 ratio to either treatment by a specialist nurse continence

advisor (who provided conservative treatments and urodynamic testing) or access to routine continence care by their GP and local continence nurse. Cure at 6 months occurred in 28% versus 19% [95%CI5-13, $p < 0.001$].

The intervention costs at 6 months (252 £, IQR 234-268) were greater than the routine costs (73 £, IQR 53-93). Cost effectiveness was calculated by dividing the between-group differences in the costs by the mean difference in outcome i.e. number of symptoms resolved. The incremental cost per additional symptom alleviated was 488 £ at 6 months: although of interest this is not a standard calculation in economic analyses.

Female participants in this study then were offered a more detailed treatment program [43]. A RCT of the effectiveness of three treatments for women age >40 with urodynamic stress or mixed incontinence was undertaken. Of the 238 women randomised between 1998 and 2001, 79 were allocated to control therapy (a brochure about pelvic floor muscle training (PFMT) followed by fortnightly visits to a continence nurse for 3 months), 79 were randomised to detailed personal PFMT by a continence nurse for 3 months, and 80 were randomised to vaginal cone weight therapy for three months.

The costs of the intervention were gathered by an interviewer-administered questionnaire (no further details), and from local and national cost data [44]. These comprised 287 £ for controls, 338 £ for PFMT, and 305 £ for vaginal cone weight therapy. There were no statistically significant differences between intervention groups (6%, 4% and 5% were cured, with 34%, 30% and 30% satisfied).

Subak et al. [45] prospectively ascertained the personal “routine care” costs of incontinence in 293 women age over 40 who had stress or urge leak more than 3 times per week, wanted help, but had not been treated in the previous 3 months. A self-report questionnaire asked about pad and laundry usage was given, quality of life was tested by Health Utilities Index Mark 3 and Willingness to Pay for incontinence was determined.

The mean annual cost (in 2005 dollars) of routine care was 492 US\$ (SD 898), which increased with the severity of incontinence. The costs for those with urge leak and mixed leak were greater than those with stress leak. For the first time, it was found that the costs were 2.4 fold higher for African Americans than for white women. There was no association between household income and incontinence costs. The quality of life (on HUI) was poorer as the frequency of incontinence increased, but not as the severity increased. Women were willing to pay \$70 per month for 100% reduction in the frequency of incontinence. Willingness to pay increased 2.3 fold in the highest income bracket compared to the lowest. Because

willingness to pay for improvement exceeded the routine care costs by 3-7 fold, effective continence treatment is likely to be economically feasible.

Ho et al. [46] performed a “bottom up” study of the short and long-term direct costs of conservative and surgical management of childbirth-related stress and mixed urinary incontinence (UI). A cohort of 150 women, who presented with post-childbirth incontinence during an eight-year period (1992-1999) were evaluated. Costs for treatment episodes during conservative and surgical management were calculated and related to cure. At 6-13 years follow up, personal and treatment expenditure was measured using a postal questionnaire.

During active treatment in the Unit, patients with stress UI treated conservatively incurred a median cost of AU\$658 per capita (IQR 476 – 1191 AU\$) compared to a median cost of \$6,870 per capita for surgical treatment (IQR 6,320 – 7508 AU\$). Similar cost difference was seen for the two treatment options in patients with mixed incontinence. Of regular clinic attendees, 39% of conservatively treated and 78% of surgically treated patients were cured.

At 6-13 years follow up, there were 82 women with a known address, of these, 43 (52%) responded to the survey, of whom 46% remained cured. The median treatment cost for the total group of postnatal incontinence (irrespective of continence status) was 885.80 per capita per annum (IQR 338- 2,589).

Foote and Moore [47] studied an RCT of Nurse Continence Advisor (NCA) therapy (N = 73) versus Urogynaecologist therapy (N = 72.) Both had significant improvements in leaks per week and incontinence score. QOL improvement was also similar (1.5% vs 1.2%). The economic data found a similar improvement in pad usage costs (\$A2.90 vs \$A3.52). The clinician costs were significantly lower for the NCA group (\$A60.00 vs \$A105.00, P < 0.0001). The cost per QALY was significantly lower for the NCA group (\$A28,009 vs \$A35,312, P = 0.03). Both groups had significant improvements in pad testing and leaks per week. The cure/improvement rates were also similar at three months (100% vs 89%).]

b) Retrospective studies of conservative and surgical therapy costs

Kinchen et al. [48] from Eli Lilly Research Laboratories (USA) undertook a retrospective analysis of private insurance and Medicare claims for stress incontinence in 8,126 women who had at least 12 months of claims data. Patients who were in “capacitated insurance cover” (i.e. managed care) were excluded because charges for their services were often “negotiated down”. Of the remaining 6,672 women, a mean of 0.4 inpatient care days and 1.6 incontinence related outpatient service days occurred, and 3.5 incontinence-related prescriptions were given.

The mean (SD) annual incontinence related expenditures per person, including inpatient and outpatient services (with pharmaceutical costs) was a total of 1,382 US\$. Patients who had surgery had a mean total expenditure of \$3620 (SD 3958) which was about ten fold greater than those who had non-surgical services (\$350, SD 724). Only 10% of patients in the study group were age over 65, so the sample was not representative of the total population but only of those with private insurance.

A more detailed study of 3 different costing methodologies, also using health care claims data, was performed by Birnbaum et al. [49], also from the Eli Lilly Company (see also Statistical Analysis section). They used individual claims data from over 100,000 women aged 18- 64 who were in a managed health care plan. A sample of 1006 women with stress urinary incontinence (SUI) were compared to 6475 continent women. The three economic analyses were as follows:

1. **Costs of Treatment of stress incontinence** were summated from the all claims data for this condition. Of the incontinent women, 14% had surgery, 23% had medical claims, the average costs was 606\$ per patient per annum (in 1998 dollars).
2. **The Incremental Cost of an SUI patient** was calculated by summing the total costs of patients with SUI versus the total costs of patients without SUI.). The average direct medical costs of SUI was 134% greater than that for a non-SUI patient. The indirect costs were 163% higher.
3. **The Incremental Cost of SUI Illness** were calculated by measuring the costs of SUI and the costs of treating conditions that may be causally related to SUI, such as obesity, chronic cough, diabetes and menopause. The average direct medical cost of SUI was \$5,642 per person per annum. The indirect workplace cost of SUI was calculated to be \$4,208 (but little methodology was provided). For patients who underwent surgery, the average direct medical costs were \$9,985 versus \$5,024 for those treated without surgery.

Kinchen et al. [49] also from Eli Lilly published an analysis of the direct costs of SUI among women enrolled in Medicaid. The authors pointed out that because of the “predominantly female population served by Medicaid”, it was important to undertake this particular analysis. Claims were recorded from Jan 1999 to Dec 2002, converted to 2002 dollars, in 4 states of the USA. The use of services one year before and after diagnosis of SUI or mixed incontinence was compared. Surgical procedures and a large list of surgical complications were examined. Co-existent prolapse, and prescriptions for anticholinergic drugs, were also tabulated. Comorbidities such as hyper-

tension, irritable bowel syndrome, cancer, diabetes and depression were noted. In the 4 year period, there were 48,160 Medicaid claims for urinary incontinence in general, of whom 28% had a SUI diagnosis, 5% were mixed incontinence, 6% were urge incontinence and 61% were unspecified incontinence (suggesting general practitioner claims without a precise diagnosis). Of those with SUI diagnosis, 36% were also Medicare eligible.

About half of the claimants in all the states were aged less than 40 years. In the SUI group, about 30% received anticholinergic drugs. Surgery was performed in 13%, of these about 8% had prolapse surgery as well. Looking at the pre-diagnosis 12 months versus the post SUI diagnosis year, in those who underwent surgery the total health care costs increased by 53% (from \$8,400 to \$12,900). In those who did not have surgery, the total costs increased by 3% (from \$11,200 to \$11,600). After analysing incontinence specific costs, the surgical expenditure (\$3,200) was almost tenfold greater than the nonsurgical expenses (\$420). For the 4 states included in the analysis, approximately 1% of females had a diagnosis of SUI during 2002. Average total spending accounted for by incontinence related care for the SUI patients was less than 0.1% of total Medicaid spending.

More recently, Turner and colleagues [50] estimated the cost of clinically significant stress and urge incontinence for the UK to be £536 million for the NHS and a further £207 million paid for by individuals (1999/2000 UK pounds Sterling).

3. PHARMACOTHERAPY OF OVERACTIVE BLADDER

a) Economics of pharmaceutical therapies

Drug developers must show that a new drug is safe and efficacious prior to approval and marketing. Requirements for economic studies, such as whether the new drug is cost-effective compared to standard treatment, vary considerably by regulatory agency. The U.S. Food and Drug Administration does not require any economic data in its review of a new drug. Instead it leaves economic questions to the purchasers (e.g., insurance companies, government purchasers or individuals). In the UK, however, the National Institute for Health and Clinical Excellence (NICE) requires economic review. They have denied approvals for new drugs that have an incremental cost effectiveness ratio greater than 30,000 pounds per QALY.

In response to the regulatory requirements, drug developers routinely conduct economic evaluations. In the UK, such efforts are done as part of the NICE review. In the US, developers present economic data to purchasers for post approval marketing. Many purchasers have formularies, or lists of medications that they are willing to pay for, and the economic

evaluation is frequently part of the request to place the new drug on the formulary.

In the next sections, we review the existing literature on the economics of drugs for incontinence and overactive bladder. We then outline drugs that are under development, and suggest methods to enhance their economic evaluations.

1. APPROVED MEDICAL TREATMENTS

There are five commonly used medical treatments for incontinence and overactive bladder: tolterodine (Detrol), darifenacin (Enablex), trospium (Sanctura), solifenacin (Vesicare), and oxybutynin (Ditropan). These drugs are predominantly used for urge incontinence or overactive bladder and work as antimuscarinic targeting M2 and M3 receptors. There are currently no commonly used medications for fecal incontinence, although there are some medications to treat its side effects. Surgical and behavioral treatments are common for stress incontinence, although there is some recent research on duloxetine, (widely used as an antidepressant), for stress incontinence.

Many economic evaluations are funded by drug developers and compare the investigational drug to placebo or to an older compound that has known problems with side effects (e.g., immediate release oxybutynin). With independent funding, Ko et al. [51] conducted an economic evaluation of five antimuscarinic drugs in eight treatment formats for the treatment of overactive bladder. They compared immediate-release oxybutynin, extended-release oxybutynin, transdermal oxybutynin, immediate-release tolterodine, extended-release tolterodine, trospium, solifenacin, and darifenacin. Their analysis concluded that solifenacin had the lowest costs and highest effectiveness in the treatment of OAB. However, their analysis faced many limitations. It did not meet common standards set forth for cost-effectiveness analysis [7, 8]. It focused on the payer's perspective (rather than a societal perspective), had a very limited time frame of 3 months (rather than lifetime costs and benefits), and used complete continence as the main effectiveness measure (rather than QALYs). Given these limitations, these results must be interpreted cautiously. We believe that additional studies using standard methods would be beneficial.

Most of the economic work in this area compares oxybutynin to tolterodine. Guest et al. [52] compared the cost-effectiveness of oxybutynin immediate release, oxybutynin extended release and tolterodine. They created a 6-month decision model from the payer's perspective and used short-term clinical endpoints (daily incontinence episodes and daily micturations). They concluded that extended release oxybutynin appears to be the most cost-effective of the three treatments. Getsios and colleagues [53, 54]

conducted two economic evaluations comparing oxybutynin extended release to tolterodine, and found that evidence suggesting that oxybutynin extended release may be cost-effective to tolterodine. Hughes and Dubois [55] created a CEA model but were very cautious in their interpretation, given the data limitations.

O'Brien and colleagues [56] conducted a cost effectiveness analysis using a 1 year Markov model. They attempted to determine the cost-effectiveness of tolterodine for patients who discontinued oxybutynin, using the payer perspective. They concluded that, "The incremental cost per QALY was Can \$9,982 [year of costs not stated] and appeared to be robust to alternative model parameter assumptions."

In 2005, Getsios and colleagues [57] published a review of the economic studies for overactive bladder, highlighting many of the limitations including a lack of comparisons of drugs to behavioral training. The UTIN group, which published a paper describing its trial design [58], is currently conducting a clinical trial comparing behavioral treatments to medications for urge incontinence. This high-quality study will measure costs and utilities, and through a NIH-funded substudy, separate researchers will conduct the economic evaluation of this trial.

There have been a handful of studies involving secondary data. Nitz et al. [59] analyzed secondary data from a large US health plan to assess the association between types of OAB treatment and health care costs in 2001 and 2002. They found that differences in health care costs were associated with type of treatment. Their analysis, while interesting, had a number of limitations including relatively old data (old in terms of OAB) and use of data from a single health plan. They also do not control for some economic issues and it is unclear how they handle people who change their medications. A cleaner analysis would have been to identify new claims for OAB treatment and then followed these patients, using an intent-to-treat analysis plan.

Darkow et al. [60] conducted a statistical analysis of secondary data to assess the additional cost of having OAB. They found that people with OAB had higher medical care costs, controlling for age and many comorbid medical conditions. Their results may be confounded by a number of issues because people with OAB are different from people without OAB in many ways that are not observable to researchers. Grocela and colleagues [61], reviewed the literature to determine how the introduction of pharmacy benefits for Medicare beneficiaries would affect the OAB market.

1. DARIFENACIN HYDROBROMIDE (ENABLEX)

Darifenacin was approved by the FDA in 2004, based on Phase II and III controlled clinical trials with over

8,800 patients. Short term efficacy (12 week) as well as longer term effects (24 and 52 week) were evaluated [62]. Few patients discontinued taking the drug in either the darifenacin arm (3.3%) or the placebo arm (2.6%). Patients assigned to darifenacin experienced decreased incontinence and voids/day, increased bladder capacity, and decreased urgency. Results were evident at 2 weeks and were sustained through the year endpoints.

Abrams and colleagues [63] found that darifenacin was associated with significant improvements in quality of life as measured by the King's Health Questionnaire at 12 weeks relative to placebo. Chancellor et al. [62] found that darifenacin and darifenacin combined with a behavioral modification plan both resulted in improvements in symptoms and quality of life, as measured by the Overactive Bladder Questionnaire (OAB-q), but there were no differences between the two groups. Unfortunately, neither the Abrams nor the Chancellor study measured utilities, so it is hard to gauge the magnitude of these quality of life effects. Besides the Ko [51] article discussed above, there is little data on the cost-effectiveness of darifenacin.

2. TROSPIMUM CHLORIDE (SANCTURA)

Approval was based on two Phase III double-blind, placebo-controlled trials comparing the reduction in the frequency of urination and the reduction in urge urinary incontinence episodes at 12 weeks with over 600 patients. The trials selectively identify high risk patients (e.g., those who had 10 or more toilet voids per day) to increase the power of detecting a significant result. This, however, makes it hard to generalize the findings to other patients. Patients treated with trospium chloride experienced significant improvement in number of voids per day and number of incontinent events at the end of the 12-week trial, compared to patients on placebo. Besides the Ko [51] article discussed above, there is little published data on the cost-effectiveness of trospium chloride.

3. SOLIFENACIN SUCCINATE (VESICARE)

Solifenacin succinate was evaluated in 12-week, randomized, placebo-controlled phase III clinical trials with more than 3000 OAB patients. US and European studies found solifenacin succinate was statistically superior to placebo in terms of micturition frequency, nocturia, volume voided, pad use, urgency episodes and incontinence episodes. Long term data suggest that the effects are maintained at 1 year. Besides the Ko [51] article discussed above, there is little published data on the cost-effectiveness of solifenacin succinate.

4. TOLTERODINE (DETROL)

Tolterodine has been extensively tested in controlled clinical studies against placebo. Newer clinical trials have combined tolterodine with tamsulosin (Flomax) and found that the combination of drugs provides

greater benefits than tolterodine alone in terms of lower urinary tract symptoms [64]. Tolterodine has also been tested against oxybutynin, with results favoring tolterodine in terms of tolerability (e.g., dry mouth, constipation). A number of studies have assessed the cost-effectiveness of tolterodine and in comparison to oxybutynin and we reviewed these results above.

5. EXTENDED RELEASE OXYBUTYNIN:

Patients treated with extended release oxybutynin showed significant improvements with total continence and improvements in OAB symptoms. Extended release oxybutynin was well tolerated by most patients, with more than 90 percent of patients reporting satisfaction with therapy, yet moderate-to-severe dry mouth was reported by a quarter of the patients.

6. OTHER MEDICATIONS

Brunenberg [65] conducted a Markov model to assess the cost-effectiveness of duloxetine, a serotonin and norepinephrine reuptake inhibitor, for stress incontinence. The model was designed to compare two strategies: duloxetine alone and duloxetine after inadequate response to pelvic floor muscle training [PFMT] compared with PFMT or no treatment for women 50 years of age or older.

The results showed the incremental cost per incontinence episode, but a major challenge with interpreting this paper is that it is narrowly focused on a pharmacotherapy +/- PFMT and does not include other treatments for stress incontinence (e.g., surgery).

Das Gupta and colleagues [66] developed a cost effectiveness model to assess the cost-effectiveness of duloxetine for moderate to severe SUI. Their model, however, was limited in that they assumed that drug treatment was fully effective. Even so, their results were highly sensitive to the time frame of the analysis.

7. THE RESEARCH AND DEVELOPMENT PIPELINE

Although governments vary in their desire to see economic analyses with an investigational new drug application, we believe that gathering evidence in clinical trials is the best way to conduct high quality economic evaluation. Therefore, we searched the World Health Organization and the National Institute of Health's clinical trial registry (www.clinicaltrials.gov) to learn about completed and ongoing studies for urinary incontinence and overactive bladder (search date 1/30/2008).

We found 64 drug trials and Table 2 summarizes the results. Each trial is listed once and there were four trials in which one drug was compared to another. In these cases, we listed the trial under the first drug listed in the registry. The greatest number of trials was on tolterodine (22 of 64)[51]. The drug with the most active number of trials was solifenacin, with 10

ongoing trials or trials that are about to start recruiting.

Of all the trials, 89% were industry funded with others being funded by US, UK and Israeli governments. The clinical trial registry includes information on the phase of the trial and the primary and secondary outcomes. Outcomes are "text fields" and there was considerable variability in how people entered data for the trials. Some trials provided the specific outcome measures, while other trials just mentioned urinary incontinence frequency and urgency. Quality of life was mentioned 18 times (28%); discussion of utilities or quality adjusted life years (QALYs) or economic outcomes (e.g., lost productivity or costs) was extremely rare (Table 2).

In 2007, the Cochrane Collaboration reviewed anticholinergics for the treatment of overactive bladder and urge incontinence [67]. The Cochrane authors reviewed twelve clinical trials and found "inadequate evidence to assess whether or not available alternative drugs are better or worse than anticholinergics in the management of people with symptoms of overactive bladder syndrome." In their recommendation section, they conclude that "larger randomised controlled trials versus anticholinergics and conducted in clinical settings are required to further establish the role of these other medications in the management of overactive bladder."

We agree with this statement and believe that better economic evaluations start with collecting the right information in high-quality clinical trials. We applaud the use of disease specific quality of life measures in clinical trials, but would also like to see the addition of utility measures, such as the Health Utilities Index that is being used in the UTIN network BE-DRI trial [68].

In addition, we believe that clinical trials need to include resource use questions to identify medical care use as well as routine care at home (e.g., use of pads or additional laundry). Dowell et al. [69] and Subak [45] created questionnaires for such data collection. Finally, we believe that it is easy to bias a cost-effectiveness analysis by focusing on a few treatment options, on a specific perspective, or with a limited time horizon. Therefore, while the clinical trials are the building blocks for the economic analysis, the economic analysis needs to embrace the societal perspective and lifetime costs and benefits.

4. COST IMPLICATIONS OF INCONTINENCE IN NURSING HOME SETTING

Two key aspects of cost of care for nursing homes are (1) cost of nursing home admissions attributable to urinary incontinence, and (2) the direct treatment cost of urinary incontinence.

Additional nursing home admissions cost is often a major component in the total cost of urinary incon-

Table 2. Registered Clinical Trials for Urinary Incontinence and Overactive Bladder

	tolterodine	darifenacin	trospium	solifenacine	oxybutinin	Total
Number of trials	22	10	2	16	14	64
Completed	12	8	0	6	10	36
Recruiting	8	2	2	7	3	22
terminated	1	0	0	0	0	1
Not yet recruiting	1	0	0	3	1	5
Industry funded	19 86%	10 100%	2 100%	14 88%	12 86%	57 89%
Phase						64
Phase IV	12	6	2	8	6	34
Phase III	5	2	0	5	6	18
Phase II	4	1	0	3	1	9
Phase I	1	1	0	0	1	3
QOL Outcome	9	4	0	2	3	18
QALY Outcome	0	0	0	0	1	1
economic outcome	0	0	0	0	1	1

tinence. In a 2001 study [70] the cost estimate was \$2.4 billion in 1995 dollars. In a 2004 study [71], the cost estimate was \$4.0 billion in 2000 dollars. In a recent update by Morrison and Levy [72], the attributable fraction (AF) statistics from published data was shown to be \$6.0 billion in 2004 dollars. The Attributable Fraction (AF) statistics are obtained by using incontinence prevalence rates for those admitted to nursing homes, as compared to those who were not admitted to nursing homes. It shows that reimbursement for treatment of UI in the community might help or delay institutionalization and offset some costs of staying in nursing homes. The AF method has been used in the economic cost of mental illness, smoking, and cancer diseases. The new estimated magnitude shows that reimbursement for treatment of UI in the community might help or delay institutionalization and offset some costs of staying in nursing homes.

Holroyd-Leduc, et al. [73] used a population-based prospective cohort study from 1993-1995 to determine whether UI is an independent prediction of death, nursing home admission, and decline in activities of daily living (ADLs). Over 6,500 elderly (>age70) were included in the study. It was found that after adjusting for confounders, UI was not an independent predictor for death, nursing home admission, or functional decline.

Within nursing homes, labor costs are a major component of caring for incontinent patients. These costs are studied via time/motion observation, correlated with severity and type of incontinence. In 49 long-term care facilities in North Carolina, USA, it

was found that the incremental labor costs (per shift) were \$3.31 for patients with occasional UI and \$5.61 for patients with frequent UI [74].

Bliss et al. [75] addressed the cost/effectiveness of incontinence-related treatment of skin condition in 16 US nursing homes. Care of perineal skin is crucial to incontinent persons in nursing homes. Four regiments of different moisture barriers were applied. Time and motion measurements included skin products and time spent. It was found that using acrylate barrier film spray achieved cost savings of between \$854 to \$1,862 per resident, with better skin protection than the use of an ointment or cream.

Bates-Jensen et al. [76] examined the effect of an exercise and incontinence intervention upon skin health outcomes in nursing home residents. However, no cost data was actually provided. A review [77] on perineal skin care protocols and skin barrier product use has been reported, but no cost data was mentioned.

In contrast to the nursing home/long care facility, Morris, et al. [78] undertook a "bottom-up" costing of both urinary (UI) and faecal incontinence (FI) in the Sub-Acute Care setting, which provides short term rehabilitation of acute physiological insults in the elderly. They costed 3,621 occasions of care in 29 consecutive incontinence patients for up to 3 weeks. Pure UI occurred in 97%, with pure FI in 62%. The median per capita incremental cost of these conditions was 49 AUD (IQR 36-59) per 24 hours (in 2003). On average, 2 hours per 24 hours were dedicated to

continence management. The incontinence costs on the “night shift” were almost as great as those for the day shift. Hence because of reduced night staffing, continence management comprised a heavy load at night.

5. LONGITUDINAL BURDEN OF DISEASE STUDIES

For the first time in this ICI report, we find a number of studies that attempt to measure the cost of incontinence over the long-term time frame. As pointed out by Birnbaum et al. [79] the study of “the lifetime cost of illness” is a rather recent area of research. These authors combined case-control methods (to calculate annual medical costs of stress incontinence, cardiac disease and diabetes) with knowledge of the incidence of the conditions, assuming “steady state conditions” of the costs, to project the lifetime costs of each disorder. Using a dataset of medical claims covering 1996-1998 for 931 women with stress incontinence who were under 65 at that time, they extrapolated the lifetime costs base on “published government statistics”. The prevalence rate for women >65 was assumed to be the same for women < age 65, which is probably an incorrect assumption. The authors calculated an annual treatment cost for stress incontinence of 15,000\$USD per woman, and gave a lifetime cost of 58,000\$. Treatment methods and lifetime expectancies were not given, so that the study was largely a hypothetical model with insufficient characterization of the model parameters. Nevertheless such attempts at modeling the lifetime costs do need to be performed in greater detail in the future.

As regard the Overactive Bladder (OAB) a study that reported “longitudinal” costs of medication actually reported data of 275 patients in North Carolina age >65 years receiving antimuscarinic drugs for 1-3 years [80]. The study calculated that a 10% increase in adherence to the prescribed OAB medication was

associated with a decline in overall health costs of 5.6%.

As regard the impact of incontinence upon employed women, Fultz et al. [81] sent a postal questionnaire to 5130 American households, yielding 3364 female replies (age 18-60). Of the 2326 employed women, 37% had leaked urine in the past month, severity was judged by Sandvik index. Severity was slight 52%, moderate 40%, severe 8%. The impact of incontinence upon ability to concentrate, performance of physical activities, self confidence, and ability to complete tasks without interruption increased with the severity of the leak and affected nearly 75% of all those with severe leak status.

Similarly, Wu et al. [82] focused upon the work loss burden of women with OAB. The number of days absent was 15% higher among 3077 OAB employees compared to 6154 controls. Multivariate analysis showed that OAB subjects had 4.4 more days off work than non-OAB subjects, yielding an annual excess cost of \$1220 per OAB employee.

Finally, Reeves et al. [83] employed a theoretical model based upon a large prevalence study of OAB [84] to derive the future cost burden for OAB in five European countries (Figure 8). They calculated an annual per capita expense of Euro 269-706 per annum.

A more detailed analysis of OAB costs in Germany [85] that included psychiatric costs of OAB-related depression, and nursing care, indicated an annual per capita expense of €609-1170 per annum.

6. PROLAPSE TREATMENTS, COST IMPLICATIONS

Despite the high prevalence of pelvic organ prolapse and frequency of surgery for prolapse, there are minimal data on costs or cost-effectiveness of medical care for this condition. One COI study estimated the annual direct cost of surgery for pelvic organ prolapse in the U.S. using national data. [86]. Direct costs of

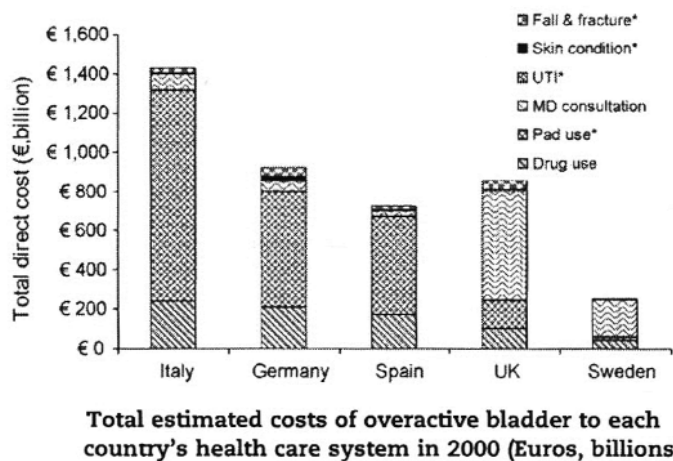
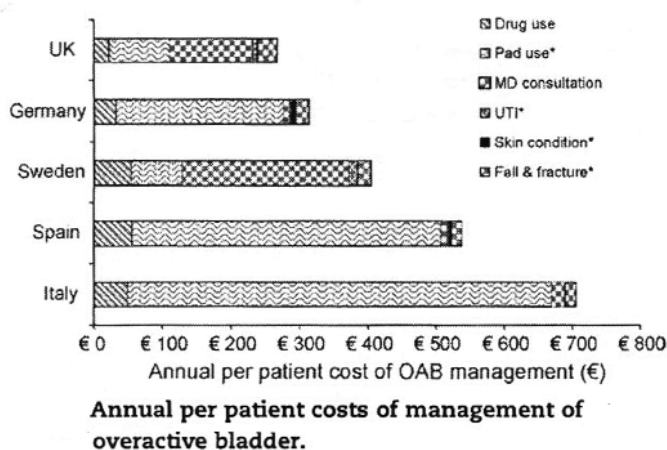


Figure 8 : Per capita and total estimated costs of OAB management in 5 European countries

pelvic organ prolapse surgery were US\$1,012 million (1997 dollars; 95% CI US\$775, US\$1,251 million), including US\$499 million (49%) for vaginal hysterectomy, US\$279 million (28%) cystocele and rectocele repair, and US\$135 million (13%) abdominal hysterectomy. Hospitalization accounted for a majority of the total cost (71%) with the remainder being physician services (29%). Twenty-one percent of pelvic organ prolapse operations included urinary incontinence procedures (US\$218 million). The annual direct costs of operations for pelvic organ prolapse are substantial and similar to other surgical interventions for women (breast cancer, gynecologic cancer, urinary incontinence).

A recent Cochrane review of surgeries for the management of pelvic organ prolapse (Maher et al) emphasized the importance of CEA and CUA [87]. They observed that abdominal sacrocolpopexy is associated with a lower rate of recurrent vault prolapse and dyspareunia than the vaginal sacrospinous colpopexy yet these benefits must be balanced against a longer operating time, longer time to return to activities of daily living and increased cost of the abdominal approach. Similarly, the use of mesh or graft inlays at the time of prolapse repair may reduce the risk of recurrence and the addition of a continence procedure to a prolapse repair operation may reduce the incidence of postoperative urinary incontinence. Yet, these benefits need to be balanced against possible differences in costs and adverse effects, which have not been assessed and, like surgical treatment for stress incontinence, are inherently appropriate for CEA since there may be differences between procedures in costs, clinical outcome and health-related quality of life.

Maher et al performed a randomized trial of abdominal sacral colpopexy vs. vaginal sacrospinous colpopexy to treat vaginal vault prolapse among 95 women [88]. Secondary outcomes included the impact on cost (measured as Australian bed and operating theater costs) and general- and incontinence-specific quality of life. Two years after the operation, the subjective and objective success rates were similar between groups. The abdominal approach was associated with a longer operating time, a slower return to activities of daily living, and a greater cost than the sacrospinous colpopexy ($P < .01$). Both surgeries significantly improved the patient's quality of life ($P < .05$). These data suggest that formal cost-utility analysis would be beneficial to further compare these two common procedures for pelvic organ prolapse. Additional data with generalizable costs and utility measures and long-term efficacy outcomes are needed.

Weber and Walters [89] compared the cost-effectiveness of preoperative urodynamic testing vs. basic office evaluation in women with prolapse and stress incontinence, using a theoretical decision-analytical model. Costs were obtained from US

government data and effectiveness of urinary incontinence surgery was based on published literature (in 2000). The strategies of basic office evaluation and urodynamic testing had the same cure rate of urinary incontinence (96%) after initial and secondary treatment. The incremental cost-effectiveness of urodynamic testing was \$328,601 for single extra cure of urinary incontinence. In sensitivity analyses, basic office evaluation was more cost-effective than urodynamic testing when the prevalence of pure detrusor instability was $< 8\%$ or when the cost of urodynamic testing was $> \$103$. Urodynamic testing was not cost-effective before surgery for prolapse and stress urinary incontinence symptoms. However the current routine use of sling procedures for stress incontinence limit the broad applicability of the study

Segal et al. [90] compared the feasibility and cost of local anesthesia with IV sedation versus general anesthesia for vaginal correction of pelvic organ prolapse (N=40). "Costs" were recorded as hospital charges. Mean operating room, anesthesia, and surgical time, use of postoperative medication, postoperative verbal numerical pain scores and length of hospital stay were similar between the two groups. However, mean recovery room and total hospital charges were significantly lower in the local anesthetic group. These data suggest that local anesthesia with IV may be less costly for vaginal surgery to correct pelvic organ prolapse. Data on effectiveness are needed.

7. ECONOMIC CONSEQUENCES OF FECAL INCONTINENCE

a) *Cost of illness*

A prevalence study [91] in a long-term care hospital (457 patients) showed a prevalence of fecal incontinence of 46% (defined as at least one incontinent episode per week). The prevalence rate of urinary incontinence was 62% and combined incontinence 44%. The total annual cost of incontinence (urine plus fecal) per patient was \$9771. Of the total costs, 83% was associated with nursing time, and 13% with laundry.

A study in the Netherlands published in 2005 calculated the costs of fecal incontinence in outpatients [92]. Total costs were estimated to be €2169 per fecal incontinent patient per year. Production losses in paid and unpaid work accounted for more than half of the total costs and costs of health-care visits accounted for almost a fifth of total costs. Costs associated with protective material (partially reimbursable and not reimbursable) formed only one-tenth of total costs, while incontinence medication was responsible for only 5% of total costs.

b) *Prevention*

To date it is not completely clear what the causes are

of fecal incontinence, therefore primary prevention is difficult. Pelvic floor exercises before and after vaginal delivery could help to prevent incontinence. One study investigated in a decision analysis the effect of elective cesarean section for macrosomic infants to prevent maternal fecal incontinence [93]. It appeared that for every 100,000 deliveries, the policy of elective C-section resulted in 185.7 fewer cases of fecal incontinence, and cost savings of \$3,211,000. According to the authors, this policy would prevent one case of fecal incontinence for every 539 elective C-sections performed.

c) Hospital costs

Treatment and follow-up costs for fecal incontinence are identifiable. However, economic assessment is difficult because of the lack of uniform study populations, variation in techniques, reimbursements systems and regional costs. There is a limited number of studies that systematically compare costs and outcomes of fecal incontinence treatments.

Mellgren et al followed up 63 patients with FI and estimated that the average lifetime cost associated with treatment and follow-up was \$17,166 per patient in 1996, with average facility charges associated with sphincteroplasty to be \$8555 per procedure [94].

Sung et al. [2] showed that in the US total charges associated with surgical treatment for fecal incontinence increased from \$34 million in 1998 to \$57.5 million in 2003, translating to a total cost of \$24.5 million in 2003. Variables associated with increased costs included number of procedures per admission, length of stay, patient age, and race

Different surgical options are available. In a study by Adang and colleagues performed in 1998, the costs of dynamic graciloplasty were compared with costs of colostomy and conservative treatment [16]. The costs of all activities were calculated, inside and outside the hospital, for all three alternatives. Costs were based on real prices, not on charges. A distinction was made between direct and indirect costs. For conventional therapy, direct costs outside the hospital were counted, such as diapers, enemas, tissues, and diets [16]. Hetzer et al. [95] compared the costs of Sacral Nerve Stimulation (SNS) and sphincter repair. The SNS cost analysis was performed on an intention-to treat basis. The analysis was performed from a hospital perspective; therefore only direct medical costs were assessed. These authors also transformed the results of the Adang study to 2005 Euro's to be able to compare both studies. In **figure 9** the estimated long-term costs per patient for each treatment are shown.

In a Markov model, Tan et al. [96] compared the cost-effectiveness of artificial bowel sphincter (ABS), dynamic graciloplasty (DG) and permanent end stoma (ES) for the treatment of fecal incontinence. It appeared

that over the 5-year time horizon, ES gave a QALY gain of 3.45 for 16,280 £, giving an ICER of 4719 £/QALY. The ABS produced a gain of 4.38 QALYs for 23,569 £, giving an ICER of 5387 £/QALY. The DG produced a gain of 4.00 QALYs for 25,035 £, giving an ICER of 6257 £/QALY. The authors concluded that all three procedures were cost-effective. The ES was most cost-effective over 5 years, while the ABS was most cost-effective in excess of 10 years.

Finally, the direct and indirect costs of transanal irrigation for neurogenic faecal incontinence +/- obstructed defecation were compared with routine conservative management. Using micro costing over a very short time frame, transanal irrigation was more efficacious and slightly less expensive, but no QALYs were employed [97].

d) Consequences of Incontinence

The most frequently cited and most costly consequences of incontinence include admission to a nursing home or long-term care facility, and dermatitis. No study was found focusing solely on the effects of fecal incontinence, but many on the costs for urine incontinence and/or fecal incontinence. These results are described earlier.

VI. SUMMARY AND FUTURE RESEARCH PRIORITIES

In the four years since the last ICI consensus conference, several high quality economic analyses of stress incontinence treatments have been published. The Committee notes that evidence regarding cost

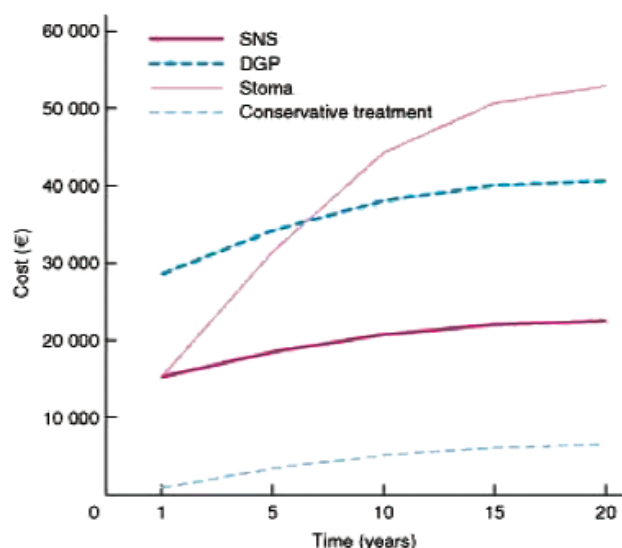


Figure 9 : Estimated long-term costs per patient for each treatment: sacral nerve stimulation (SNS), dynamic graciloplasty (DGP), stoma and conservative treatment after 1, 5, 10, 15 and 20 years. Costs are in euros and discounted to present values at a 5 per cent rate [16].

utility of outpatient therapies for stress incontinence remains very limited. However the economic analysis of therapy for overactive bladder syndrome requires greater effort, to encompass longer time frames and wider use of QALYs that can yield cost utility analysis (CUA). The Committee was disappointed to find that only 2 of the 64 currently registered clinical trials for OAB drug therapy included QALYs as an outcome measure.

In our previous Committee report, we provided a table giving international comparisons of the per annum expenditure from European countries, the USA and Australia, so as to provide a **“global summary”** of the costs of urinary incontinence. Similar data are here provided for OAB in our Table 8b [83], ranging from 200 – 1400 Billion Euros per annum. The data from Birnbaum et al [79] allow estimates to be made for per annum stress incontinence costs in the USA. However, no recent comparative studies have been published to allow us to give a global summary of all urinary incontinence costs at the present time. Indeed, with our increasing awareness of the human suffering costs arising from urinary fistulae in the developing nations, the Committee felt that it would be inappropriate to construct such a table that would include only patchy data from developed countries.

In the field of prolapse, it is not yet known whether any currently available QALYs are sensitive to treatment benefit, so that CUA may still not be feasible in this area. As regards faecal incontinence, research into Cost of Illness remains rather preliminary, so that broader more long term studies are needed. More data about Cost Utility in Faecal Incontinence is urgently needed.

The Committee commends the recent emergence of studies into the Burden of Disease for all continence conditions. The impact of both faecal and urinary incontinence upon costs in the nursing home or subacute care are becoming more fully understood but still require greater study.

As regards methodology, researchers need to consider carefully how they construct the model parameters for Decision Tree Analysis and Markov Models, so that “real life” assumptions are made. The gold standard remains Cost Utility Analysis in parallel with Randomized Controlled Trials, and we urge all clinicians to consider costs as an important outcome measure.

VII. APPENDIX – SEARCH STRATEGIES

We performed a comprehensive computerized medical literature search (PubMed) for the years 1966 through 2008 to identify all economic, health-related quality of life and cost-effectiveness analyses published on urinary incontinence, fecal incontinence or pelvic organ prolapse.

Our initial search strategy was very broad and meant to be very sensitive but not specific. We performed a search for the following Medical Subject Headings (MeSH) and keywords: cost-effectiveness analysis, health care costs, quality-adjusted life years, costs and cost analysis, sickness impact profile, or utilities and urinary incontinence, overactive bladder, fecal incontinence, anal incontinence, uterine prolapse or pelvic and prolapse. The initial searches were reviewed to identify articles appropriate for more detailed evaluation.

The literature was reviewed for studies describing costs associated with fecal incontinence. The costs for FI can be differentiated to costs for the disease of FI itself and for costs associated with the treatment of FI. Systematic searches of electronic databases were conducted, including National Library of Medicine (Medline), Cochrane economic evaluation database, Embase. The years included in the searches were 1970 – April 2008.

We combined the search terms (incontinen* AND (fecal or faec* or anus* or anal*)) or fecal incontinence [MeSH] with cost-effectiveness OR Health Care Costs [MeSH] OR “Costs and Cost Analysis [MeSH].

Inclusion criteria were: fecal incontinence as primary disease, data on costs available. Studies were excluded when they were a review, case-report or focused solely on urinary incontinence. 159 manuscripts were retrieved (Medline: n=70; Cochrane economic evaluation: n=82; Embase: n=7), of which 19 were duplicates.

The remaining 140 manuscripts were assessed for eligibility by reading title and abstract. This resulted in 24 potentially eligible citations. When full citations were obtained 19 studies could not be included. Two cost of illness studies, null on prevention studies, three on hospital cost studies and null on the consequences of incontinence

REFERENCES

- Kanavos P and Reinhardt U. Reference pricing for drugs; is it compatible with US health care? *Health Aff (Millwood)* 22 2003; 16-30.
- Sung VW, Rogers ML, Myers DL, Homayoon MA, Clark MA. National trends and costs of surgical treatment for female fecal incontinence. *Am J Obstet Gynecol* 2007; 197: 652.e1 - 652.e5
- Schwartz M, Young DW and Siegrist R. The ratio of costs of charges: how good a basis for estimating costs? *Inquiry* 32 (1995) 476-481.
- Wagner, TH, Chen S and Barnett PG. Using average cost methods to estimate encounter-level costs for medical-surgical stays in the VA. *Med Care Res Rev* 60 (2003) 15S-36S.
- Barnett PG. Research without filling data. Econometric estimation of patient-specific costs. *Med Care* 35 (1997) 553-563.
- Jacobs P and Roos NP. Standard cost lists for healthcare in Canada. Issues in validity and inter-provincial consolidation. *Pharmacoeconomics* 15 (1999) 551-560.
- Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. Oxford: Oxford University Press; 1996.
- Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Second Edition ed. Oxford: Oxford University Press; 1997.
- Wagner T and Hu T. Economic costs of urinary incontinence in 1995. *Urology* 51 (1998) 355-361.
- Wilson L, Brown JS, Shin GP, Luc KO and Subak LL. Annual direct cost of urinary incontinence. *Obstet Gynecol* 98 (2001) 398-406.
- Anger JT, Saigal CS, Madison R, Joyce G, Litwin MS. Urologic Diseases of America Project. Increasing costs of urinary incontinence among female Medicare beneficiaries. *Journal of Urology* 176 (2006) Jul; 247-51; discussion 251.
- Monz B, Hampel C, Porkes S et al. A description of health care provision and access to treatment for women with urinary incontinence in Europe- a five country comparison. *Maturitas* 2005; 52S, S3 – S12
- Krahn M and Gafni A. Discounting in the economic evaluation of health care interventions. *Med Care* 31 (1993) 403-418.
- Ganiats TG, Carson RT, Hamm RM, Cantor SB, Summer W, Spann SJ, Hagen MD and Miller C. Population based time preferences for future health outcomes. *Med Decis Making* 20 (2000) 263-270.
- Olsen JA. On what basis should health be discounted? *J Health Econ* 12 (1993) 39-53.
- Adang EM, Engel GL, Rutten FF, Geerdes BP, Baeten CG. Cost-effectiveness of dynamic graciloplasty in patients with fecal incontinence. *Dis Colon Rectum* 1998; 41:725-733.
- Albo, ME , et al. Burch Colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med* 2007; 356:2143-55.
- Birnbaum HG, Leong SA, Oster EF, Kinchen K, Sun P. Cost of stress urinary incontinence: a claims data analysis. *Pharmacoeconomics*. 2004; 22:95-105.
- Hu TW, Kaltreider DL, Igou J. Incontinence products: which is best? *Geriatr Nurs* 19 (1989) 184-186.
- Hughes DA, Dubois D. Cost-effectiveness analysis of extended-release formulations of oxybutynin and tolterodine for the management of urge incontinence. *Pharmacoeconomics* 2004;22(16):1047-59.
- Brazier J, Roberts J and Deverill M. The estimation of preference-based measure of health from the SF-36. *Journal of Health Economics* 21 (2002) 271-292.
- Johannesson M, O'Connor RM, Kobelt-Nguyen G and Mattiasson A. Willingness to pay for reduced incontinence symptoms. *Br J Urol* 80 (1997) 557-562.
- Torrance G. Measurement of health state utilities for economic appraisal: a review. *Journal of Health Economics* 5 (1986) 1-30.
- Hu TW, Wagner TH, Hawthorne G, Moore KH, Subak L. "Economics of Incontinence". Report of World Health Organisation, Editors: Abrams P, Cardozo L, Koury S, Wein A. 2005;2:75-95. Health Publications Ltd., Plymouth.
- Hawthorne G and Richardson J. "Measuring the value of program outcomes: a review of utility measures. *Expert Review of Pharmacoeconomics Outcomes Research* 1 (2001) 215-228.
- Kaplan R, Anderson J and Ganiats T. The Quality of Well-Being Scale: rationale for a single quality of life index. In Walker S and Rosser R eds *Quality of Life Assessment: Key Issues in the 1990s*. Dordrecht: Kluwer Academic Publishers. 1993.
- Sintonen H and Pekurinen M. A fifteen-dimensional measure of health-related quality of life (15D) and its applications, in Walker S and Rosser R eds *Quality of Life Assessment: Key Issues in the 1990s*. Dordrecht: Kluwer Academic Publishers. 1993.
- Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQoL Group. *Annals of Medicine* 33 (2001) 337-343.
- Hawthorne G, Richardson J and Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health related quality of life. *Quality of Life Research* 8 (1999) 209-224.
- Rosser R. A health index and output measure, in Walker S and Rosser R. eds. *Quality of Life Assessment: Key Issues in the 1990s*. Dordrecht: Kluwer Academic Publishers. 1993.
- Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, McCormack K, Vale L, Grant A. Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. *Health Technol Assess*. 7(21):iii (2003); 1-189. Review.
- Kilonzo M, Vale L, Stearns SC, Grant A, Cody J, Glazener CM, Wallace S, McCormack K. Cost effectiveness of tension-free vaginal tape for the surgical management of female stress incontinence. *Int J Technol Assess Health Care*. 20 (2004) ; 455-63.
- Manca A, Sculpher MJ, Ward K, Hilton P. A cost-utility analysis of tension-free vaginal tape versus colposuspension for primary urodynamics stress incontinence. *BJOG* 2003; 110; 255-262.
- Wu JM, Visco AG, Weidner AC, Myers ER. Is Burch colposuspension ever cost-effective compared with tension-free vaginal tape for stress incontinence? *Am J Obstet Gynecol* 2007; 197-62.e1-62.e5.
- Moreno K, Montesino M. Economic impact of tension-free vaginal tape surgery for urinary incontinence in an ambulatory regimen compared with hospital admission: a study of the minimization of costs of a public hospital in Spain. *Scand J Urol Nephrol*. 2007;41(5):392-7. Epub 2007 Feb 4. PMID: 17853045.
- Dumville JC, Manca A, Kitchener HC, Smith AR, Nelson L, Torgerson DJ. COLPO Study Group. Cost-effectiveness analysis of open colposuspension versus laparoscopic colposuspension in the treatment of urodynamics stress incontinence. *BJOG*. 113 (2006) 1014-22.
- Oremus M, Collet JP, Shapiro SH, Penrod J, Corcos J.

- Abstract. Surgery versus collagen for remale stress urinary incontinence: economic assessment in Ontario and Quebec. *Can J Urol*. 2003 Aug;10:1934-44.
38. Tierney JP, Robins JB, Anthony GS, Bjornsson S, Orr G. Abstract. A costed profile audit of the surgical management of female stress incontinence. *Scott Med J*. 2004; 49:133-6.
 39. Kobelt G, Fianu-Jonasson A. Treatment of stress urinary incontinence with non-animal stabilised hyaluronic acid/dextranomer (NASHA/Dx) gel. An analysis of utility and cost. *Clin Drug Investig*. 2006; 26:583-91.
 40. Kalsi V, Popat RB, Apostolidis A, Kavia R, Odeyemi IA, Dakin HA, Warner J, Elneil S, Fowler CJ, Dasgupta P. Abstract. Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. *Eur Urol*. 2006; 49:519-27. Epub 2005 Dec 22.
 41. Neumann PD, Grimmer KA, Grant RE, Gill VA. The costs and benefits of physiotherapy as first-line treatment for female stress urinary incontinence. *Aust N Z J Public Health*. 2005; 29:416-21.
 42. Williams KS, Assessa RP, Cooper NJ, Turner DA, Shaw C, Abrams KR, Mayne C, Jagger C, Matthews R, Clarke M, McGrother CW and the Leicestershire MRC Incontinence Study Team. Clinical and cost-effectiveness of a new nurse-led continence service: a randomised controlled trial. *British Journal of General Practice* 2005; 55:696-703.
 43. Williams KA, Assassa RP, Gillies CL, Abrams KR, Turner DA, Shaw C, Haslam J, Mayne C, McGrother CW; Leicestershire MRC Incontinence Study Team. Abstract. A randomized controlled trial of the effectiveness of pelvic floor therapies for urodynamics stress and mixed incontinence. *BJU Int*. 2006; 98:1043-50.
 44. Netten, A, Curtis I. Unit costs of health and social care. Personal Social Services Research Unit. Canterbury; University of Kent, 2000.
 45. Subak LL, Brown JS, Kraus SR, Brubaker L, Lin F, Richter HE, Bradley CS, Grady D. Diagnostic Aspects of Incontinence Study Group. The "costs" of urinary incontinence for women. *Obstetrics & Gynaecology*. 107 (2006) 908-16.
 46. Ho T, Eastwood A, Kuteesa W, Short A, Moore KH. Incontinence after childbearing; Longitudinal analysis of direct costs of conservative and surgical therapy. *Neurourol & Urod*. 25 (2006); 513-514.
 47. Foote AJ, Moore KH. The cost of urogynaecological treatments: which are more cost-effective? *Aust N Z J Obstet Gynaecol*. 2007; 47:240-6.
 48. Kinchen KS, Long S, Orsini L, Crown W, Swindle R. A retrospective claims analysis of the direct costs of stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;14:403-11. Epub 2003 Nov 25.
 49. Kinchen KS, Long S, Chang S, Gurts TK, Panos B. The direct costs of stress urinary incontinence among women in a Medicaid population. *Am J Gyne* 2005; 193:1936-44.
 50. Turner DA, et al. The cost of clinically significant urinary storage symptoms for community dwelling adults in the UK. *BJU Int* 2004; 93:1246-1252.
 51. Ko Y, Malone DC, Armstrong EP. Pharmacoeconomic evaluation of antimuscarinic agents for the treatment of overactive bladder. *Pharmacotherapy*. 2006; 26:1694-702.
 52. Guest JF, Abegunde D, Ruiz FJ. Cost Effectiveness of Controlled-Release Oxybutynin Compared with Immediate-Release Oxybutynin and Tolterodine in the Treatment of Overactive Bladder in the UK, France and Austria. *Clin Drug Investig* 2004; 24:305-21.
 53. Getsios D, Caro JJ, Ishak KJ, et al. Oxybutynin extended release and tolterodine immediate release : a health economic comparison. *Clin Drug Investig* 2004; 24:81-8.
 54. Getsios D, Caro JJ, Ishak KJ, El-Hadi W, Payne K. Canadian economic comparison of extended-release oxybutynin and immediate-release tolterodine in the treatment of overactive bladder. *Clin Ther* 2004; 26:431-8.
 55. Hughes DA, Dubois D. Cost-effectiveness analysis of extended-release formulations of oxybutynin and tolterodine for the management of urge incontinence. *Pharmacoeconomics* 2004;22:1047-59.
 56. O'Brien BJ, Goeree R, Bernard L, Rosner A, Williamson T. Cost-Effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin: a Canadian perspective. *Clin Ther* 2001;23:2038-49.
 57. Getsios D, El-Hadi W, Caro I, Caro JJ. Pharmacological management of overactive bladder : a systematic and critical review of published economic evaluations. *Pharmacoeconomics* 2005;23:995-1006.
 58. UTIN Study Group. Design of the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) study. *Contemp Clin Trials* 2007;28:48-58.
 59. Nitz NM, Jumadilova Z, Darkow T, Frytak JR, Bavendam T. Medical costs after initiation of drug treatment for overactive bladder: effects of selection bias on cost estimates. *Am J Manag Care*. Jul 2005;11(4 Suppl):S130-139.
 60. Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy*. Apr 2005;25:511-519.
 61. Grocela JA, Kanji A, Ternullo J. Prediction of Medicare drug formulary drugs for treatment of overactive bladder. *J Urol*. Jul 2006;176:252-255; discussion 255-256.
 62. Chancellor MB, Kianifard F, Beamer E, et al. A comparison of the efficacy of darifenacin alone vs. darifenacin plus a Behavioural Modification Programme upon the symptoms of overactive bladder. *Int J Clin Pract* 2008;62:606-13.
 63. Abrams P, Kelleher C, Huels J, Quebe-Fehling E, Omar MA, Steel M. Clinical relevance of health-related quality of life outcomes with darifenacin. *BJU Int*. 2008;102:208-13.
 64. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006;296:2319-28
 65. Brunenberg DE, Joore MA, Veraart CP, Berghmans BC, van der Vaart CH, Severens JL. Economic evaluation of duloxetine for the treatment of women with stress urinary incontinence: a Markov model comparing pharmacotherapy with pelvic floor muscle training. *Clin Ther* 2006;28:604-18.
 66. Das Gupta R, Caiado M, Bamber L. An evaluation of the cost-effectiveness of duloxetine as a treatment for women with moderate-to-severe stress urinary incontinence. *Journal of Medical Economics*. 2006;9:1-25.
 67. Roxburgh C, Cook J, Dublin N. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. *Cochrane Database Syst Rev* 2007:CD003190.
 68. Design of the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) study. *Contemp Clin Trials*. 2007;28:48-58.
 69. Dowell CJ, Bryant CM, Moore KH, Simons AM. Calculating the direct costs of urinary incontinence: a new test instrument. *BJU Int* 1999; 83:596-606.
 70. Wilson I, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. *Obstet Gynecol* 2001; 98:398-406.
 71. Hu TW, Wagner TH, Bentkover JD, Leblanc K, Zhou SZ, Hunt T. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology* 2004; 63:461-465.

72. Morrison A, Levy R. Fraction of nursing home admissions attributable to urinary incontinence. *Value Health*. 2006; 9:272-4.
73. Holroyd-Leduc JM, Mehta KM, Covinsky KE. Urinary incontinence and its association with death, nursing home admission, and functional decline. *J Am Geriatr Soc*. 52 (2004); 712-8.
74. Shih YT, Hartzema AG, Tolleson-Rinehart S. Labor cost associated with incontinence in long-term care facilities. *Adult Urology* 62 (2003) 442-446.
75. Bliss DZ, Zehrer C, Savik K, Smith G, Hedblom E. Abstract. An economic evaluation of four skin damage prevention regimens in nursing home residents with incontinence: economics of skin damage prevention. *J Wound Ostomy Continence Nurs*. 2007; 34:143-52; discussion 152.
76. Bates-Jensen BM, Alessi CA, Al-Samarrai NR, Schnelle JF. The effects of an exercise and incontinence intervention on skin health outcomes in nursing home residents. *J Am Geriatr Soc*. 51 (2003); 348-55.
77. Nix D, Emermer-Seltun J. A review of perineal skin care protocols and skin barrier product use. *Ostomy Wound Manage*. 2004; 50:59-67. Review.
78. Morris AR, Ho MT, Lapsley H, Walsh J, Gonski P, Moore KH. Costs of managing urinary and faecal incontinence in a sub-acute care facility: a "bottom-up" approach. *NeuroUrol Urodyn*. 2005; 24:56-62.
79. Birnbaum H, Leong S, Kabra A. Lifetime medical costs for women: cardiovascular disease, diabetes, and stress urinary incontinence. *Womens Health Issues*. 2003; 13:204-13.
80. Balkrishnan R, Bhosle MJ, Camacho FT, Anderson RT. Predictors of medication adherence and associated health care costs in an older population with overactive bladder syndrome: a longitudinal cohort study. *J Urol*. 2006;175(3 Pt 1):1067-71; discussion 1071-2. Erratum in: *J Urol*. 2006; 175(5):1967.
81. Fultz N, Girts T, Kinchen K, Nygaard I, Pohl G, Sternfeld B. Abstract. Prevalence, management and impact of urinary incontinence in the workplace. *Occup Med (Lond)*. 2005; 55:552-7.
82. Wu EQ, Birnbaum H, Marynchenko M, Mareva M, Williamson T, Mallett D. Employees with overactive bladder: work loss burden. *J Occup Environ Med*. 2005 47:439-46.
83. Reeves P, Irwin D, Kelleher C, et al. The current and future burden of cost of overactive bladder in five euro countries. *Eur Urol* 2006; 50:1050-1057.
84. Milsom I, Abrams P, Cardozo L, Roberts RG, Theuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001; 87: 760.
85. Klotz T, Bruggenjurgen B, Burkart M, Resch A. The Economic costs of overactive bladder in Germany. *European Urology* 2007; 51: 1654-1663.
86. Leslee L. Subak , L. Elaine Waetjen, Stephen van den Eeden, David H. Thom, Eric Vittinghoff and Jeanette S. Brown. Cost of pelvic organ prolapse surgery in the United States. *Obstets and Gynec*. 2001; 98; 646-651.
87. Maher C, Baessler K, Glazener CM, Adams EJ, Hagen S. Surgical management of pelvic organ prolapse in women. *Cochrane Database Syst Rev*. 2007 Jul 18;CD004014.
88. Maher CF, Qatawneh AM, Dwyer PL, Carey MP, Cornish A, Schluter PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. *Am J Obstet Gynecol*. 2004 Jan; 190:20-6.
89. Weber AM, Walters MD. Cost-effectiveness of urodynamic testing before surgery for women with pelvic organ prolapse and stress urinary incontinence. *Am J Obstet Gynecol*. 2000 Dec; 183:1338-46; discussion 1346-7.
90. Segal JL, Owens G, Silva WA, Kleeman SD, Pauls R, Karram MM. A randomized trial of local anesthesia with intravenous sedation vs general anesthesia for the vaginal correction of pelvic organ prolapse. *Int Urogynecol J Pelvic Floor Dysfunct*. 2007 Jul; 18:807-12. Epub 2006 Nov 21.
91. Borrie MJ, Davidson HA. Incontinence in institutions: costs and contributing factors. *CMAJ* 1992; 147:322-328.
92. Deutekom M, Dobben AC, Dijkgraaf MG, Terra MP, Stoker J, Bossuyt PM. Costs of outpatients with fecal incontinence. *Scand J Gastroenterol* 2005; 40:552-558.
93. Culligan PJ, Myers JA, Goldberg RP, Blackwell L, Gohmann SF, Abell TD. Elective cesarean section to prevent anal incontinence and brachial plexus injuries associated with macrosomia—a decision analysis. *Int Urogynecol J Pelvic Floor Dysfunct* 2005; 16:19-28.
94. Mellgren A, Jensen LL, Zetterstrom JP, Wong WD, Hofmeister JH, Lowry AC. Long-term cost of fecal incontinence secondary to obstetric injuries. *Dis Colon Rectum* 1999; 42:857-865.
95. Hetzer FH, Bieler A, Hahnloser D, Lohlein F, Clavien P-A, Demartines N. Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. *British Journal of Surgery* 93(11)(pp 1411-1417), 2006 Date of Publication: Nov 2006 2006;1411-1417.
96. Tan EK, Vaizey C, Cornish J, Darzi A, Tekkis PP Surgical strategies for faecal incontinence - a decision analysis between dynamic graciloplasty, artificial bowel sphincter and end stoma. *Colorectal Dis*. 2008; 10:577-86. Epub 2007 Nov 12.
97. Christensen P, Bazzocchi G, Coggrave M, Abel R, Hultling C, Krogh K, Media S, Laurberg S. Treatment of faecal incontinence and constipation in patients with spinal cord injury – a prospective, randomised, controlled, multicentre trial of transanal irrigation vs conservative bowel management. *Neurourology & Urodynamics* 2006; 25: 594-595.