

# The cost-utility of Viagra<sup>®</sup> in The Netherlands

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Report number: 99.49

Dear readers,

This letter accompanied our research report "The cost-utility of Viagra® in The Netherlands", iMTA report number 99.49.

The report is meant as a detailed description of our investigation and is made directly after the data collection in order to allow for fast communication between the researchers who were directly involved in the investigation. Given the comprehensiveness of the report, the document is also used as the technical part of the economic dossier of Viagra as requested by the authorities of the national public health insurance (The Council of the Sick Fund).

Although the report will probably remain the most detailed description of our research effort, it must not be seen as the final interpretation of the results. The report now serves as an easy accessible collection of research data, on which basis we hope to write peer-reviewed articles. The original report will remain available on request, for those researchers who would like to have a detailed description of the research and the data.

Note that parts of the report still reveal the early thoughts and interpretations, the informal style, type and spellings errors which are characteristic for a first report written just after finishing the data collection. Although these characteristics may be annoying and sometimes even be charming, we have chosen not to change the original report for two reasons. First of all, so far we have not found any data that has been presented inadequate or major flaws in the interpretation. Secondly, we want to present our research as transparent as possible. We are therefore keen on avoiding any confusion or misinterpretation that can be caused when multiple versions of the same research document circulated in the public domain. We are therefore happy to share with you our data in detail and we would welcome your comment on our first interpretations.

On behalf of the researchers,

Jan van Busschbach

Rotterdam, April 1999

This publication can be ordered from MTA's secretariat



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## **General abstract**

### *Introduction*

In an economic evaluation, we estimated the cost-effectiveness of sildenafil (Viagra) in terms of costs per quality adjusted life year (QALY).

### *Methods*

A sample of 169 subjects of the general public and 106 patients valued question 3 and 4 of the International Index of Erectile Function (IIEF) in terms of Time Trade-Off (TTO). These questions were used as the primary outcome measures in the Viagra trial of Goldstein et al. (1998) to establish the efficacy of Viagra. Using the TTO-values, we could recalculate the trial results into QALYs. Costs were estimated from the societal perspective. We compared the cost-effectiveness of Viagra with Androskat, an intracavernosal injection therapy for erectile dysfunction, which is reimbursed in The Netherlands. Because the effects of Androskat on the IIEF are unknown, it was assumed that the effect size was valued the same as Viagra, which is a conservative assumption.

### *Results*

The cost price per QALY was NLG 13227.36 for Viagra and NLG 15745.55 for Androskat in the first year and NLG 8261.36 for Viagra and NLG 7587.82 for Androskat in each following year. The incremental cost-effectiveness ratio for Viagra as compared to Androskat was NLG 9750.80 for the first year and NLG 9098.52 for each following year.

### *Discussion*

The relatively low cost-effectiveness ratio of Viagra suggests that this is a cost-effective medicine.

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# 1. Introduction

## 1.1. *Erectile dysfunction and Viagra*<sup>®</sup>

On 15 September 1998 the European Agency for the Evaluation of Medicinal Products authorised the release of Viagra (sildenafil) in the European Union.<sup>1</sup> At the time of the authorisation of the release, the cost-effectiveness of Viagra was still unknown. This complicates decisions about a possible reimbursement, as the cost-effectiveness is seen as an important argument in this political decision. For this reason Pfizer BV, the marketing Authorisation Holder responsible for Viagra in the Netherlands, invited the institute for Medical Technology Assessment (iMTA) to perform a pharmaco-economic evaluation of Viagra, in order to estimate the cost-effectiveness of Viagra. This document is the report of the investigation of iMTA.

The active substance of Viagra is sildenafil. Sildenafil is indicated for the treatment of erectile dysfunction, which is the inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance.<sup>2</sup> Sildenafil is the first effective and tolerable oral therapy which is available in the Netherlands for the treatment of erectile dysfunction. Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). PDE5 is the predominant enzyme responsible for the degradation of cGMP in the corpus cavernosum. During a natural erection cGMP is triggered by the release of nitric oxide. In turn, cGMP is responsible for relaxation of the corpus cavernosum, which increases the blood flow to the penis and builds up intracavernosal pressure and penile erection.<sup>3</sup>

The extent of erectile dysfunction as a health problem is difficult to assess. Patients are ashamed for their erectile dysfunction, hence a lot of patients do not seek treatment.<sup>4</sup> It is expected that greater numbers of patients will seek treatment in the future, as awareness of the disorder and of successful non-invasive treatment like Viagra grows. Nevertheless, until now the prevalence and incidence of erectile dysfunction are still dark numbers. Estimates for the incidence and prevalence can be derived from the Massachusetts Male Aging Study.<sup>5</sup> The results of this study confirmed that the prevalence of erectile dysfunction is associated with age. Between the ages 40 to 70, the prevalence of complete erectile dysfunction tripled from 5 to 15%, while the probability of moderate impotence doubled from 17 to 34%.

Concepts about the etiology of erectile dysfunction have changed during the last decade. Until the 1970s, erectile dysfunction was regarded primary as a psychogenic disorder. Nowadays it is argued that the origin of most erectile dysfunction is multifactorial. It is now believed that most erectile dysfunction originates from organic causes (mostly neurological and vascular problems), though an emotional component is common, especially in younger men.<sup>6</sup>

## **1.2. Alternative therapies**

Besides Viagra there are several other medical interventions available for the treatment of erectile dysfunction. Possible alternatives are other oral agents, psychotherapy or behavioural therapy, vascular surgery, intracavernosal injections, vacuum constriction devices and prosthesis.<sup>2</sup> Only the last three therapies are assumed to be acceptable.<sup>7</sup> The others have low effect and/or low tolerability (f.i. Yohimbine, an oral agent or vascular surgery (recurrence of the problem)), which is in most cases also not adequately documented.<sup>2</sup> Psychotherapy is indicated for erectile dysfunction of psychologic origin or as adjunct to other therapies, however outcome data are also not well-documented.<sup>2</sup> Below we will describe the three acceptable therapies.

Intracavernosal injections (IC-injections) are injections of a vasoactive substance into the corpus cavernosum, which cause the muscles in the corpus cavernosum to relax. Various studies of IC-injections have demonstrated high initial success rates for producing erections. IC-injections have success rates of 60 to 70% for patients who have vasculogenic erection dysfunction, and 100% for patients with erectile dysfunction from neurogenic origin.<sup>6</sup> IC-injections are the most effective therapy in terms of rigid erections. However, despite the high efficacy for producing erections, studies have demonstrated generally low levels of patient/partner satisfaction, low levels of patient preference for IC-injections and high drop-out rates. Thirty to sixty percent of the patients who start with IC-injection therapy do not continue or report that they are not satisfied with the therapy.<sup>8, 9, 10</sup> In the Netherlands alprostadil (Caverject<sup>®</sup>) and the combination of papaverine and phentolamine (Androskat<sup>®</sup>) are authorised for the treatment of erectile dysfunction. There are some differences in effectiveness, though it is not possible to predict in advance which patients will profit most from which treatment. Only IC-injections with Androskat are reimbursed through the social health insurance system.

Vacuum constriction therapy can produce erections in every patient. They consist of a closed plastic cylinder fitted over the penis from which air is drawn with either a manual or battery powered pump in order to create a vacuum and cause the corpora to fill with blood. A tension band is applied at the basis of the penis to ensure the erection is maintained. These are highly efficacious devices. Complications include a cold penis and occasional petechiae associated with too great negative pressure. The rigidity of the erection is not always sufficient for sexual intercourse at the basis of the penis.<sup>6, 11</sup>

Another acceptable treatment is the penile prosthesis implantation.<sup>7</sup> Potential complications are infections, erosion and mechanical failure. Prosthesis are seen as the last resort because of irreversible damage.<sup>6, 8</sup>

Viagra has the potential to become the new treatment of choice for erectile dysfunction, given the good efficacy and the relative mild side effects. The overall clinical safety of oral sildenafil was evaluated in more than 3700 patients.<sup>3</sup> Long-term sildenafil treatment (up to 1 year) was received by 2199 patients. The most commonly adverse events were headache (16% sildenafil, 4% placebo), flushing (10% sildenafil, 1% placebo) and dyspepsia (7% sildenafil, 2% placebo) and they were predominantly transient and mild or moderate in nature. The rate of discontinuation due to adverse events was comparable in patients and placebo, respectively 2,5% and 2,3%.

### **1.3. Research questions**

Although Viagra has the potential to become the new treatment of choice for erectile dysfunction, whether or not Viagra is reimbursed is a political decision. The decision is political because the resources available for health care are limited and therefore the reimbursement of a new therapy has to be compared to all other possible allocations. An important argument in such deliberation is the magnitude of the effects compared to the costs of the different interventions. In other words, to convince health authorities that Viagra should be reimbursed through the social health insurance system, it would be necessary to show the relative cost-effectiveness of Viagra in comparison to other health care interventions in general and other treatment strategies for erectile dysfunction in particular. The present investigation is initiated to determine the costs and effects of Viagra. Thus the main research question can be formulated as follows: *What is the cost-effectiveness of Viagra?*

In line with the intention to compare the cost-effectiveness of Viagra with other possible health care interventions, the economic evaluation of Viagra is performed from a societal perspective. This societal perspective is the preferred perspective in health economics.<sup>12</sup> This perspective prescribes that all costs and effects must be measured, no matter who bears these costs or who receives the effects. With respect to the costs in the health care sector, a complete overview of costs in the different sectors is necessary in order to give insight into possible substitution effects. With respect to the effects, the societal perspective demands that the health effects should be valued by the general public.<sup>13</sup> This is in line with the “insurance principle” which dominates the financing structure of most health care systems.<sup>14</sup>

In contrast to the estimation of the effects, the estimation of the costs is relatively straightforward. The challenge of the investigation is the valuation of the effects from a societal perspective. The effects of Viagra have to be valued in such a way that comparisons with the benefits of other interventions in health care can be made.

Normally the values or the “utilities” of the effects of a therapy are measured alongside a clinical trial. During the clinical trial, generic quality of life questionnaires are given to the patients, like the EuroQol or the Health Utility Index. These questionnaires classify the patients in so called “health states”. The values of the general public for these health states have already been determined in large scale investigations in the general public. Unfortunately, these questionnaires have not been used in the Viagra trials. And even if one had included them in the trials, one could have doubts about the sensitivity of these questionnaires for problems related to erectile dysfunction. Instead, the outcomes of the Viagra trials were determined in terms of a disease specific questionnaire.<sup>15</sup> In this investigation, the challenge was to re-examine and modify the disease specific outcomes in such a way that they now give scores in terms of values (utilities) which can be used in economic appraisal. This strategy is advised by Brazier et al.<sup>16</sup> However, to our knowledge we are the first to apply this strategy. Therefore we examined the feasibility and validity of this strategy. The first additional research question formulated is therefore: *Is it possible to value the outcomes of a disease specific questionnaire of quality of life into utilities in a valid way?*

A major drawback in the assessments of the benefit of health care by the general public is that they lack the experiences of patients. In the societal perspective, the values of the general public are only valid when the respondents are “well-informed”.<sup>13</sup> This may especially be a problem when the general public is not exposed to the disease. Erectile

dysfunction may be such a disease, given the hidden suffering of the patients. Thus, the public may be unaware of the decrease in quality of life due to erectile dysfunction. When one can doubt the awareness within the general public, it may be informative to compare the values of the general public with values given by the patients. These patients' values also have a meaning on their own: they represent the values from a "patient perspective", also called the "clinical perspective". Outcomes from the patient perspective are informative to maximise the benefits in a patient population, which support medical decisions when costs are not an issue. When costs are an issue, the use of patients' values is dissuaded.<sup>14</sup> Nevertheless, these values can be used to get an indication of the validity of values of the general public. This is translated into the second additional research question: *To what extent differ values given by patients and the general public for health states associated with erectile dysfunction?*

We further anticipated that personal circumstances (such as having a partner) and personal characteristics (such as age, gender and the subjective enjoyment of sex) would moderate the impact of erectile dysfunction on quality of life considerable. This may not only be true for patients with erectile dysfunction, but also for the general public, when they value the effects of medical interventions which could improve erectile functioning. If the differences are substantial and meaningful from a policy perspective, it is advised to consider different cost-effectiveness analysis for these subgroups.<sup>13, page 102</sup> For this reason we formulated the last additional research question: *What are the systematic relations between the values for erectile dysfunction and the background variables in the general public?*

#### **1.4. Structure of this report**

Chapter 2, 3, and 4 address the main question of our investigation: the economic appraisal of Viagra. Chapter 2 accounts for the methodology. This chapter describes the study design, the treatment comparator and the analytical techniques we used. Chapter 3 presents the results of the economic evaluation. The presentation of the results consists of a presentation of all compounds of the estimation of the costs and effects separately, and of the outcomes aggregated into a cost per QALY. Chapter 4 contains the discussion of the results, the conclusions and the considering of the limitations of the study.

The first two appendices present details about the three additional research questions of this study: Appendix A, "Converting clinical outcomes into utilities: the valuation of International Index of Erectile Function (IIEF)" reports about the validation of the erectile dysfunction states. Appendix B, "Differences in the values given by the general public and patients to health states of erectile dysfunction" describes the influences of the background variables and the influence of the perspective: how are the values of patients related to the values of the general public. Finally, appendix C provides an overview of all persons who were involved in this study and their contribution.

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## **2. Methods**

### **2.1. Study design**

This study is performed from the societal perspective. This means that all costs are relevant no matter who is paying them.<sup>1</sup> Furthermore, the societal perspective demands that the health effects should be valued by the general public.<sup>2</sup> In order to meet these criteria, we tried to estimate all costs associated with the use of Viagra. Furthermore, we used values or “utilities” of the general public to value the established clinical effect of Viagra. The data regarding the clinical effect of Viagra were derived from the clinical trial described by Goldstein et al.<sup>3</sup> After weighing the clinical effects with the values of the general public, we converted the effects to Quality Adjusted Life Years, the preferred outcome measure in health economics.<sup>1, 2</sup> The methods we used to estimate the costs and effects are described below.

### **2.2. Effects**

Goldstein, Lue, Padma-Nathan et al. (1998) evaluated the efficacy of Viagra in two clinical trials; one dose-response study and one dose-escalation study. A full report of these clinical trials is published in the New England Journal of Medicine (vol. 338, issue 20, page 1397-1404). We used the data of the dose-escalation study to determine the effect of Viagra from a societal perspective. We chose this study for two reasons. In the first place because it is one of the largest clinical trials of Viagra that has been reported, and the one with the longest follow-up so far. Secondly, because future patients will try to find the most suitable dosage, the dose escalation study provides best insight in the usage of Viagra in practice.

The dose-escalation study performed by Goldstein et al. consisted of 329 men who were treated with placebo or Viagra. Depending on the dose, side effects occurred in 6 to 18% of the men, but only 2% withdrew because of treatment-related adverse effects. The mean numbers of successful intercourse attempts were 5.9 for the men receiving Viagra and 1.5 for those receiving placebo. The efficacy was assessed with the International Index of Erectile Function (IIEF). This is a disease specific questionnaire to quantify the degree of erectile dysfunction, which includes quality of life aspects. Two question of the

IIEF were use as primary endpoint in the assessment of the efficacy of Viagra: question 3 and 4 (Table 1).

*Table 1: Question 3, 4 of the International Index of Erectile Function (IIEF)*

IIEF Question 3	IIEF Question 4	Response level
<i>During the past 4 weeks, how often were you able to penetrate?</i>	<i>During the past 4 weeks, how often were you able to maintain the erection?</i>	
Almost never or never	Almost never or never	1
A few times	A few times	2
Sometimes	Sometimes	3
Most times	Most times	4
Almost always or always	Almost always or always	5

### *Converting the clinical effects of treatment with Viagra into utilities*

Our estimation of the utilities gained by Viagra treatment, is based on the effectiveness of Viagra in the clinical trial described above. We calculated the mean utility gained for the patients in the trial. To that end, we attribute utilities to the 25 health states that can be defined using questions 3 and 4 of the IIEF. These utilities were collected in a separate investigation in which a representative sample of the general public valued the 25 health states. Hundred and sixty nine subjects form the general public valued the 25 health states as defined IIEF with time trade-off. Time trade-off is one of the preferred valuation methods in health economics that are used to determine the values or “utilities” of health states.<sup>1</sup> The results of this study support the validity of the process of valuing the outcomes of disease specific questionnaires into utilities. This investigation is described in detail in appendix A.

Because it is possible that the awareness in the general public for erectile dysfunction is low and because of the subjective nature of the enjoyment of sex, we also collected patients’ values for the different health states of erectile dysfunction. We did this in the same way as we collected values from the general public. For this purpose the 25 health states of as defined by question 3 and 4 of the IIEF were valued by 106 patients who participated in a phase 4 trial of Viagra. This investigation is described in detail in appendix B. In a sensitivity analysis we investigated how the cost-effectiveness ratio is affected by the use of different values.

Besides making differences between patient values and values for the general public, one can also look at the possibility that subgroups within the patients or within the general public have different values. If the differences are substantial and meaningful from a policy perspective, Gold, Patrick & Torrance et al. (1996, page 102) advise to consider different cost-effectiveness analyses for these subgroups. In appendix B we investigated the influence of background variables like age, gender, availability of a partner, having children, sexual activity and sexual satisfaction.

### *Calculating QALYs*

We attributed the utilities of the general public to the health states of the individual patient, both before and after treatment. The difference between the mean utility before and after treatment is the mean gain of utility. This effect is compared with the effect in the placebo group and the differences between these two is used as the adjustment factor for the calculation of the final effect parameter, namely Quality Adjusted Life Years (QALYs). In a QALY analysis the remaining life years of an individual are adjusted for the quality of life during this period. In this way a QALY combines the two most important measures in health care: lifetime and quality of life. QALYs are the preferred effect parameter in health economics, as it makes the effects of different allocations in health care comparable.<sup>1, 2</sup>

## **2.3. Costs**

### *Cost identification*

In the societal perspective direct costs must be considered both inside and outside the health care sector. Also indirect costs could be recognised.<sup>4</sup> Below we describe these considerations for the economic appraisal of Viagra.

#### *Direct medical costs: within the health care sector*

In an economic evaluation of a health care program an analysis of the direct medical costs is always necessary.<sup>5</sup> These direct medical costs are specific to the therapy being investigated, and concern the resources used by a

health care program and consist of the costs of organising and operating the program.

*Direct non-medical costs: patient and family resources*

The treatment of erectile dysfunction involves patients' costs related to visits to a general practitioner and to the pharmacy. Both are normally within a few miles distance from the patients' homes, hence the direct non-medical costs are assumed to be negligible.

*Indirect medical costs: within the health care sector*

There is a low level of agreement whether these costs should be incorporated in economic analysis.<sup>6, 7</sup> However, in our study these costs play no role anyway: because erectile dysfunction is not a life threatening condition, it can be assumed that treatment of erectile dysfunction would not save any life years. Therefore treating erectile dysfunction would not yield additional medical costs in additional live years.

*Indirect non-medical costs: sectors outside the health care system*

Analyses of indirect non-medical costs are mostly focuses on costs of production losses. Because patients with erectile dysfunction are in most cases capable of performing their daily activities normally, the indirect non-medical cost are not of relevance either.

In sum, it can be concluded that in the cost price calculation of treatment for erectile dysfunction only the direct medical costs are of relevance. Estimating these costs, means measurement of the quantities of resource use and the assignment of unit cost prices to these resources. Both will be presented separately, in order to make the cost-price calculation as transparent as possible.

*The cost model*

Given the many elements that are usually involved in a cost price calculation, economists present their calculation in a cost model. Because such models are based on many elements, the model structure is usually presented in the result section of the

report. We will use this same lay out and present the details of the model along with the results in the next chapter. Below we only describe the basic elements of the cost model.

#### *Treatment regime*

Treatment for erectile dysfunction starts with a period in which the right dosage for a patient must be established. For a part of the patients the outcome is that the treatment has no effect or has too many side effects. After establishing the right dosage for patients who can be treated successfully, the costs remain constant. For that reason we calculate separately the costs of the first year (in which the costs of non-successfully treated patients are added to the costs of successfully treated patients) and the costs of each year in which therapy is continued.

#### *Treatment comparator*

To make the results applicable to the Dutch health care setting, we chose to compare the costs and effects of Viagra with the costs and effects of Androskat, a drug for erectile dysfunction that is reimbursed through the social health insurance system.<sup>8</sup> Androskat is indicated for the treatment of erectile dysfunction. It involves injection of the active substances papaverine and phentolamine in the corpus cavernosum of the penis. This causes relaxation of the muscles in the corpus cavernosum, and subsequently an erection. Side effects could be prolonged erections (4-5 hours), pain and fibrosis. The maximum number of injections is limited to 1 per week because of these side effects.

#### *The estimation of the cost and effects of Androskat*

We compare Viagra and Androskat with respect to both costs and effects. The estimation of costs of Androskat is based on the same assumption that only direct medical costs are of importance. The effects of Androskat were not measured with the IIEF, and no other investigations are reported which could be used to estimate the number of QALYs gained as a result of the use of Androskat. Therefore we assume that the utility gained by a patient who is successfully treated with Viagra is similar to the utility gain of a patient who is successfully treated with Androskat. Given the obvious differences in treatment and effects, this is a conservative assumption in the economic appraisal of Viagra as compared to Androskat.

### *Difference in effectiveness between Viagra and Androskat*

The different treatment effects of Viagra and Androskat become evident when one compares the effectiveness. An important difference between Viagra and Androskat is that for 30% of the patients with erectile dysfunction only oral therapy is acceptable.<sup>9</sup> For these patients the enjoyment of sex is decreased with injection therapy (or the use of vacuum devices), because this decreases the spontaneity of intercourse. This means that effectiveness of Androskat and Viagra not only depends on the opportunity to create an erection, but also on the acceptance of treatment. On the other hand, if Viagra yields no response, some patients will start to use Androskat. We control for this effect in our estimation of the costs and effects of both therapies.

### *The rationing of the treatment*

In our comparison of the costs and effects we also have to deal with the fact that the use of Androskat is rationed for medical reasons: too many erections can cause fibrosis in the penis. To enhance the comparability of the use of Androskat and Viagra, we compared both alternatives assuming the same frequencies of intercourse. However, the use of Viagra is not rationed for medical reasons; the maximum recommended dosing frequency is once a day. In the sensitivity analysis we will analyse how changes in frequency of intercourse with Viagra would influence the cost. In this context it should be noted that treatment of erectile dysfunction is valued as a relative increase of successful attempts of intercourse and not as an absolute increase in the frequency of intercourse. This means that we can not control for rationing the treatment in our effect analysis. However, to use the same values for Viagra in Androskat is a conservative approach with respect to the differences in costs and effects between Viagra and Androskat.

## **2.4. Cost-effectiveness**

The results will first be presented in costs per QALY for patients in the Viagra scenario Viagra and for patients in the Androskat scenario separately as compared to no treatment. Because Androskat is an alternative for Viagra and is currently being reimbursed, we will also present the results in the form of an incremental analysis: i.e. as the differences in the costs and effects between Viagra and Androskat. This is relevant because it is expected that Viagra will yield additional costs and additional effects, because a larger population of patients with erectile dysfunction will seek treatment.

## **2.5. Discounting**

Because there is no time preference in treatment for erectile dysfunction (both costs and effects are received at the same time) discounting of future costs is not necessary.

## **2.6. Time of the data collection**

The collection of data concerning the costs and effects of Viagra and Androskat, was done in the period between April 1998 and April 1999.

## **2.7. Sensitivity analysis**

We performed a sensitivity analysis to estimate the effect of uncertainty regarding different variables on the costs and effects. As indicated before, we will estimate how changing the frequency of the use of Viagra affects the costs. Furthermore, we will analyse how the use of different values influences the effects. However, the most important goal of our sensitivity analysis is to deal with the uncertainties regarding the quantities of resource use. This element of the sensitivity analysis is described below.

To calculate the costs and effects of Viagra we made a global estimate about the quantities and cost prices of resource use. This estimation is based on data regarding resource use in two different hospitals and on the suggested protocol for the treatment of erectile dysfunction, which has been developed in a round table conference about diagnosing and treating erectile dysfunction.<sup>10</sup> It can be assumed that the protocol is quite cautious in the sense that it prescribes more visits than will be made in daily practice. Furthermore, daily practice appears to be different in different institutions. In order to deal with the uncertainties regarding the quantities of resource use, we modelled the costs into three scenarios, representing a high estimation of the costs, a low estimation of the costs and a 'base' scenario, which includes our global estimate of the costs. All three scenarios will be presented in our estimation of resource use in the next chapter. The final estimation of cost-effectiveness of Viagra will be based on the base scenario; the sensitivity analysis will indicate how the different scenarios would affect the conclusions of our economic appraisal.

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### **3. Results**

This chapter presents the cost-utility analysis of Viagra. The effects of treatment with Viagra and of treatment with Androskat injections are reviewed in relation to the costs of treatment. The results of the valuation of the IIEF, the first additional research question are discussed in detail in appendix A. This chapter only presents the main outcomes of that investigation. The same applies for the values of the patients and the influences of the background variables on the values given by the general public. These results are discussed in detail in appendix B.

#### **3.1. Effects**

The estimation of the effect size of Viagra is based on the changes reported on the IIEF in the Viagra trial described by Goldstein, Lue, Padma-Nathan et al.<sup>1</sup> In the article only accumulated data are printed. We could not use these accumulated data, because for the calculation of the cost-utility, we cannot assume that this 5 level scale of item 3 and 4 of the IIEF has interval properties. Table 1 therefore describes the same data in non-accumulated form. For purpose of illustration, we printed in the same table the self-reported erectile dysfunction in our sample of men of the general public. Note that the figures in Table 1 only represent the men who had attempted intercourse in the 4 weeks prior to the IIEF administration.

A sample of 169 subjects of the general public valued the 25 possible health states of the IIEF with the use of time trade-off, the preferred valuation method in health economics. As described in detail in appendix A, the estimated values of “utilities” of the general public showed good content validity: the values were in the expected range and consistent with the ordinal structure of the health states. There were differences observed between some values of the group administration and the values of the individual administration, but there was no overall effect. Next to the sample of the general public, we also collected the patients’ values for the 25 health states of the IIEF, in 106 patients. Appendix B describes that the patients’ values were found to be higher than the values of the general public. The extent to which the mode of administration influences our results is analysed in the sensitivity analysis, as is the difference between patient values and the values of the general public.

Table 1: Frequency distribution over de different ED-states

IIEF question 3	IIEF question 4	Sildenafil group (N=163)		Placebo group (N= 166)		General public (N=78)
		At baseline	End-of-treatment	At baseline	End-of-treatment	
never	Never	49	19	36	45	2
	A few times	9	4	20	19	0
	Sometimes	5	0	9	5	1
	Most times	4	2	2	1	0
a few times	Always	4	1	1	2	0
	Never	0	0	1	1	0
	A few times	7	4	9	13	0
	Sometimes	5	4	2	5	0
Sometimes	Most times	5	2	3	4	1
	Always	0	0	2	1	0
	Never	0	0	1	0	0
	A few times	2	0	1	1	0
most times	Sometimes	13	5	11	4	1
	Most times	2	4	7	2	0
	Always	2	4	2	1	1
	Never	0	0	0	0	0
Always	A few times	1	0	0	0	1
	Sometimes	2	2	2	1	2
	Most times	2	11	2	4	3
	Always	1	9	5	7	1
Total	Never	0	0	0	0	0
	A few times	0	1	2	0	0
	Sometimes	0	1	0	0	0
	Most times	1	6	0	1	1
	Always	2	55	2	9	44
Total		116	134	120	126	58

In the general public, all but one of the background variables showed no statistical significant relation with the values given to health states of erectile dysfunction. The exception was that subjects with children gave higher values to the health states. In other words: subjects with children considered erectile dysfunction less of a problem than subjects without children did.

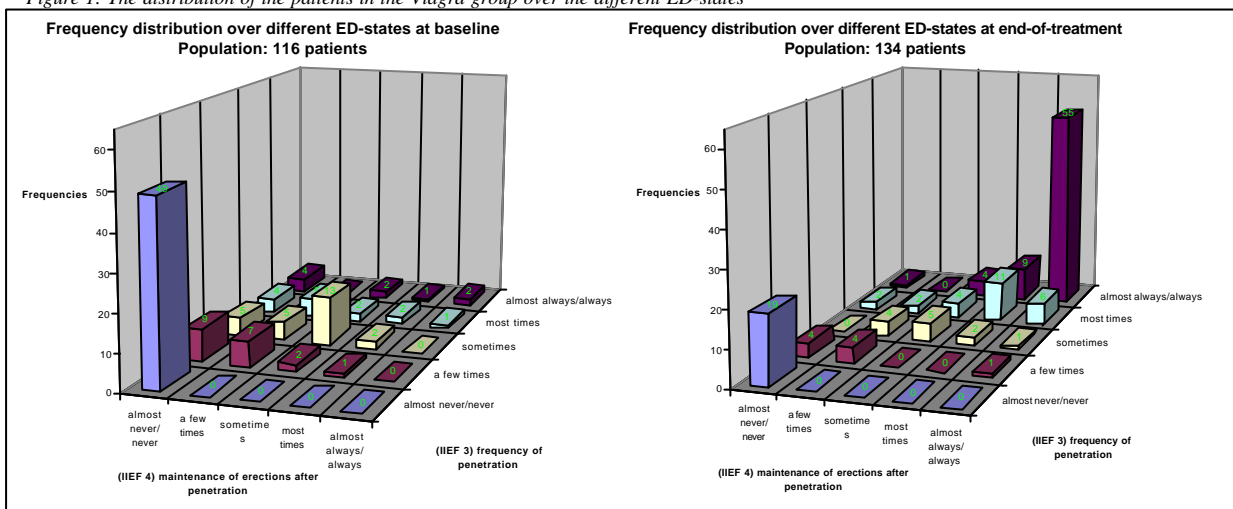
The utilities attributed to the different states of erectile dysfunction by the general public are presented in Table 2. There is no value elicited for normal erectile function, because this health states (normal health) is used as a reference point in time trade-off. The value for this state is set at 1.00.

Table 2: Values of the general public for erectile dysfunction (N=148)

IIEF question 4	IIEF question 3									
	Never		a few times		Sometimes		Most times		Always	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Never	0.74	0.18	0.79	0.17	0.82	0.17	0.82	0.15	0.84	0.17
a few times	0.77	0.18	0.83	0.16	0.85	0.16	0.86	0.15	0.88	0.16
Sometimes	0.79	0.16	0.85	0.14	0.87	0.14	0.90	0.13	0.91	0.13
Most times	0.81	0.17	0.86	0.15	0.88	0.14	0.94	0.12	0.93	0.13
Always	0.82	0.17	0.87	0.15	0.91	0.13	0.94	0.11	1.00	

On basis of the clinical trial data and the values for the health states of erectile dysfunction, it is possible to estimate how much utility is gained as a result of Viagra treatment. To that end, the distribution of patients over the different health states at baseline and at end-of-treatment must be multiplied by the values of the general public for each health state. The distribution over the different health states of erectile dysfunction at baseline and at end-of-treatment of the patients in the Viagra group in the trial of Goldstein, Lue, Padma-Nathan et al. (1998) is illustrated in Figure 1.

Figure 1: The distribution of the patients in the Viagra group over the different ED-states



The mean utility in the sildenafil group is 0.80 at baseline and 0.91 at end-of treatment; the mean utility in the placebo group is 0.81 at baseline and 0.82 at end-of treatment. The mean utility gain must be controlled for the utility gain in the placebo group. This means that the utility gain is calculated as the utility gained in the Viagra group minus the utility gained in the placebo group:  $(0.91-0.80) - (0.82 - 0.81) = 0.11$  (rounded numbers).

The utility gain of Androskat could not be calculated in the same way as the utility gain of Viagra, because the effectiveness of Androskat has not been measured with the IIEF. We therefore had to assume that the mean utility gain of Androskat is similar to the mean utility gain of Viagra: 0.11.

### 3.2. Costs

The number of consults, the number of prescriptions, the prescription method and the frequency of use are the main elements of the total costs of treatment. We therefore analysed the resource use in these units and determined for each unit a cost price.

#### *Resource use*

In the treatment of erectile dysfunction three periods could be recognised, in which resource use is notably different:

- ◆ In establishing the effective dosage
- ◆ In the remaining part of the first year
- ◆ In each following year

For each period the resource use is separately presented in terms of the number of consultations, the number of prescriptions, the prescription method and the frequency of use.

#### *Establishing the effective dose*

When a patient presents himself with complaints about his erectile function, the physician executes an anamnesis. After the diagnosis is determined, a treatment must be chosen. In some cases an additional diagnostic consult is necessary to determine the therapy of choice. After the choice of treatment has been made the effective dosage of Androskat or Viagra has to be established. To that end each patient pays several visits to the physician, in which different dosages are tested and the efficacy and side-effects are evaluated. After a new dosage is tested an evaluative consult is planned. These data for Viagra and Androskat are summarised in Table 3.

*Table 3: resources used during establishing the effective dosage*

VIAGRA		Scenario		
		Low	Base	High
Consultations	<i>Duration anamnesis (minutes)</i>	7.5	10	12.5
	<i>Duration consult with partner</i>	12.5	12.5	12.5
	<i>(% receiving separate consult with partner)</i>	0%	10%	20%
	<i>Duration diagnostic consult</i>	12.5	12.5	30
	<i>(% receiving diagnostic consult)</i>	10%	18%	25%
	<i>Duration of evaluative consult</i>	7.5	7.5	7.5
	<i>(Mean number of evaluative consults)</i>	2	2.5)	3
	<i>Number of weeks before effective dose is established</i>	8	9	10
Medicine	Number of pills	8	10	12
Prescriptions	Number of prescriptions	2	2.5	3

Table 3: resources used during establishing the effective dosage

ANDROSKAT		Scenario		
		Low	Base	High
Consultations *	Duration anamnesis (minutes)	10	10	10
	Duration consult with partner	12.5	12.5	12.5
	(% receiving separate consult with partner	0%	10%)	20%
	Duration diagnostic consult	12.5	12.5	30
	(% receiving diagnostic consult	25%	33%)	40%
	Duration of evaluative consult (minutes)	7.5	10	12.5
	(Mean number of evaluative consults	2.4	2.3)	2.2
	Number of weeks before effective dose is established	14.4	9.4	4.4
Medicine	Number of injections	12	11.5	11
Prescriptions	Number of prescriptions	2.4	2.3	2.2

\* Note that all patients need a referral from the general practitioner to the urologist. This is not the case for treatment with Viagra, because the patients on Viagra treated by the urologists would have been treated by the general practitioner, when they would have used a normal entry point of health care for treatment of erectile dysfunction.

### The first year

Viagra is effective in about 65% of the patients. After successful establishment of the effective dose, the patients can continue to use Viagra as often as they want and can afford (up to a maximum of once a day). In Table 4 presents the resource use based on a frequency of intercourse of ones a week, in order to make comparisons with Androskat possible.

Table 4: Resources used during the first year

		Viagra scenario			Androskat scenario		
		Low	Base	High	Low	Base	High
Consultations	Number of routine controls	1	2	4	2	2	3
	Duration of routine controls	7.5	7.5	7.5	7.5	7.5	7.5
Medicine	Number of pills/ampuls** per week	1	1	1	1	1	1
	Number of weeks left year 1***	44	43	42	37.6	42.6	47.6
Prescriptions	Number of pills/ampuls per prescription	14.66	5.5*	5.5*	10	10	5
	Number of prescriptions	3	7.8	7.6	3.8	4.3	9.5

\* This is the mean number of pills per prescription in the first three months of Viagra use in The Netherlands<sup>2</sup> (source: Stichting Farmaceutische Kengetallen, 1999). For most patients it is too expensive to buy more pills at once. The number of pills might increase when Viagra would be reimbursed. The protocol provides for a prescription for 24 pills and for 3 prescriptions at a yearly basis Note that more pills per prescription lowers the costs.

\*\* The number of Androskat ampules is bound to a maximum because of the possibility that fibrosis develops in the penis.

\*\*\* The number of weeks are shorter in the high scenario, which is consistent with the high scenario in which the period to establish the effective dose was longer. Note that the costs are higher when the period to establish the effective dose is longer and remaining part of the first year is shorter than the other way around. The high and low costs scenarios therefore originate in the period to establish the effective dose.

### Each following year

The Viagra protocol provides for routine examination by the physician every three months. It is however likely that lesser visits to the physician will take place as long as patients are satisfied with the therapy. When necessary, there will be room to discuss problems when a patients contacts the physician for a new prescription (Table 5)

Table 5: Resources used during the first year

		Viagra scenario			Androskat scenario		
		Low	Base	High	Low	Base	High
Consultations	Number of routine controls	1	1,5	3	1	1,5	2
	Duration of routine controls	7.5	7.5	7.5	7.5	7.5	7.5
Medicine	Number of pills/ampules** per week	1	1	1	1	1	1
	Number of weeks left year 1	52	52	52	52	52	52
Prescriptions	Number of pills per prescription	12	5.5*	5.5	10	10	5
	Number of prescriptions	4.3	9.5	9.5	5.2	5.2	10.4

\* This is the mean number of pills per prescription in the first three months of Viagra use<sup>2</sup>. For most patients it is too expensive to buy more pills at once. The number of pills might increase when Viagra would be reimbursed. In that case the costs would be lower.

\*\* The number of Androskat ampules is bound to a maximum because of the possibility that fibrosis develops in the penis.

In our base scenario, we assumed the number of consults of patients treated with Viagra to be equal to the number of consults of patients treated with Androskat. The protocol of Viagra suggests more visits, probably because the long-term effects of Viagra are yet unknown.<sup>3</sup> Nevertheless, we assumed that it is not likely that patients on Viagra would need more visits than patients on Androskat do, because the treatment is less invasive and the side effects are only minor.

### Cost per unit

The number of consults, the number of prescriptions, the prescription method and the amount of medicine used are the main elements of the total costs of treatment. In the previous section we estimated the volumes of these units. In the next section we describe the cost prices for each unit (Table 6).

The costs of a consult with the general practitioner and the costs of a consult with an urologists, represent all costs involved with a consultation, such as personal, accommodation, and equipment. For the calculation a method is used in which the costs of a consult with the urologists are described in two pieces: costs of the capacity (which summarise all costs related to the hospital) and costs of the specialist, which are calculated on basis of the estimated duration of an out-patient visit.<sup>4</sup> Consultation costs of a visit to the general practitioner are described in a lump sum, referring to the mean costs of a short visit to the general practitioner.

Table 6: Cost prices for resources used in treatment with Viagra or Androskat in NLG (without VAT)

Viagra	Dose	25 mg	50 mg	100 mg
	Effective dosage	25%	62%	13%
	Blister pack containing 4 Viagra pills	51.89	62.88	76.32
	Mean cost price per pill *	15.47		
Androskat	Pack containing 5 ampules Androskat (2 ml)	63.35		
	Mean cost price per injection	12.67		
Consultations	General practitioner	36.85		
	Urologist**	60.00 + 4,60 per minute		
Prescriptions	Prescription rule***	11.20		

\* The mean cost price per pill is based the 'effective dose distribution' across the different strengths of Viagra.

\*\* This is an estimation of the weighted mean of the costs per consultation in University hospitals and peripheral hospitals.

\*\*\* There are no costs calculated for getting a prescription, because prescriptions are given during a visit, and can be repeated without a visit. The only prescription relate dcosts therefore are the costs of the 'prescription rule': this is a lump sum charge to refund pharmacy costs. This charge is independent of the prescribed medicine or the amount prescribed.

### Patient flows

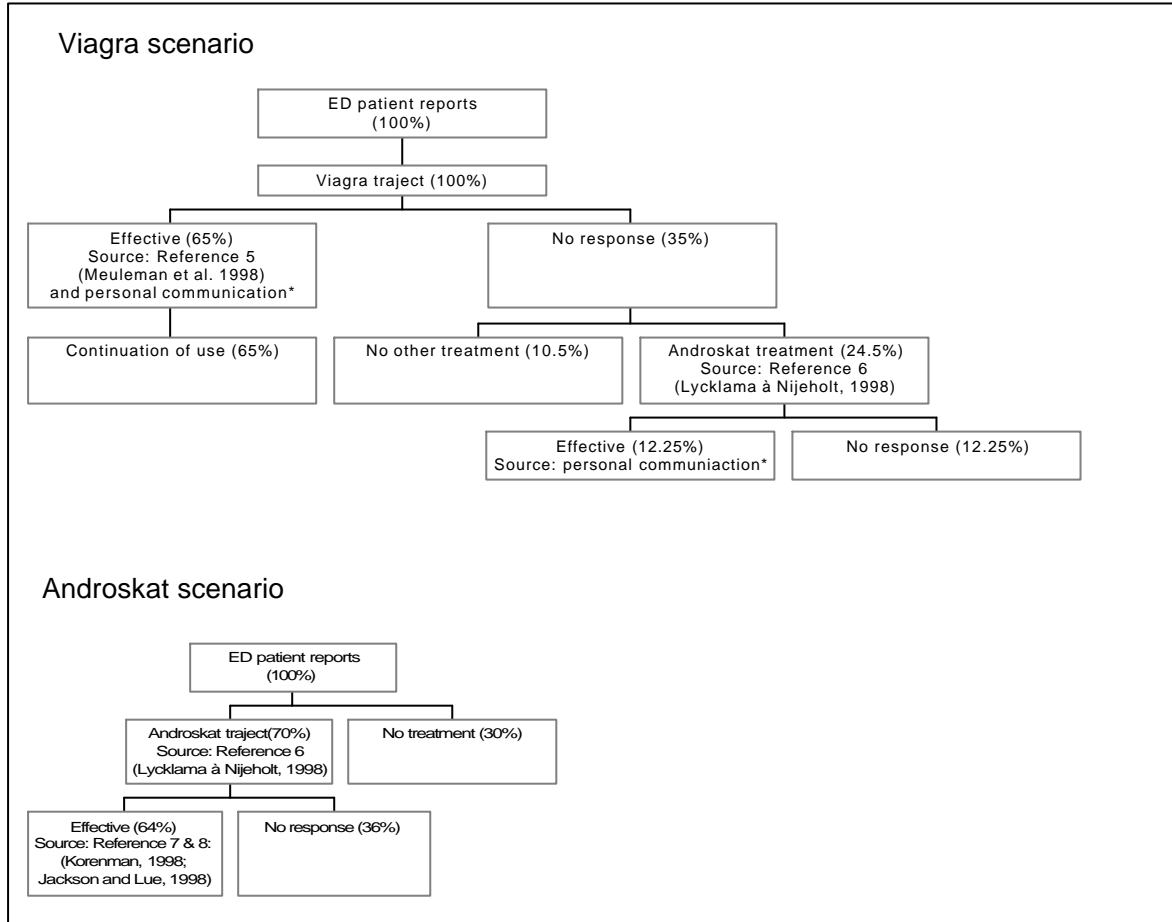
In this part of the cost analysis we compare the treatments Viagra and Androskat. In estimating the costs of both treatments, we created two scenarios: a) the Viagra scenario in which both Viagra and Androskat will be reimbursed, and b) the androskat scenario, in which only Androskat is reimbursed. This means that in the Viagra scenario it is possible to try Androskat when Viagra fails, but in the Androskat scenario the use of Viagra is not possible after Androskat fails (see figure 2).

In the first period after the release of Viagra, from October to December 1998 about 129,000 Viagra tablets have been sold.<sup>2</sup> The tablets were sold to men who had not received any prior treatment before, but also to patients who had received other treatments before, such as Androskat. This means that irrespective of reimbursement, Viagra has already become the preferred treatment for many patients. The patient flows in the Viagra scenario are therefore most likely the current patient flows and the Androskat scenario describes the patient flows before the release of Viagra.

Note that figure 2 only presents the patient flows in the first year. However, it is important to realise that after the first year 10% of the Viagra patients have ended treatment, whereas this number is 14% for the Androskat patients. The percentage of patients ending treatment will be the same for patients on Androskat and Viagra from the second year on: 5%. Our calculations are concerned with costs per patient, costs per QALY and costs per additional QALY. A similar dropout rate will not influence these

parameters. This means that these parameters are constant from the second year on. We therefore present the outcomes for the first year and for each following year.

Figure 2: Patients flows for the two different scenarios: The Viagra scenario or the Androskat scenario\*



\* This refers to personal communication with the clinicians cooperating in our study: E.J.H. Meuleman, MD, Ph.D. of the University Hospital St. Radboud in Nijmegen, urology department and M. Caffa, M.D. of the hospital St. Antoniushove in Leidschendam. Their estimates are based on their experiences with Viagra in the clinical trial but also in daily practice.

In the clinical trials with Viagra efficacy is assessed with a global efficacy question (“Did the treatment improve your erections?”), with a response of yes or no. The end points of the IIEF quantified the magnitude of the response.<sup>1</sup> In daily practice patients with a limited improvement in the erection might not continue the use of Viagra and also patients with side-effects might not continue the use of Viagra. This means that the effectiveness is lower than the efficacy. Therefore, we did not use the outcomes of the global efficacy question (which indicated efficacy of 78%) in the model of our patient flows, but we used the percentage of patients who continued treatment after establishing



the effective dose (based on estimates from the clinicians participating in this study: Viagra is estimated to be effective in 65% of the patients).

### *Cost calculations*

The calculation of treatment costs is based on the presented volumes of resource use, the costs per unit of the resources and the patient flows. In the determination of the treatment costs we first of all determined for each stage of treatment the volumes of resource used and the cost prices (see Table 4). For the calculation of total costs on basis of these figures it should be noted that 80% of the patients on Viagra are treated by the general practitioner, whereas this percentage is only 10% for Androskat users. The costs for referral to the specialist are included in the calculations. The treatment costs are summarised in Table 7.

*Table 7: Costs in different treatment periods following the patient flows (in NLG)*

Scenario	Effective	Physician	Costs establishing effective dose	Costs remaining part first year	Costs for each following year
Viagra	Viagra is effective (Viagra)	General practitioner	321.81	786.67	908.24
		Urologists	565.31	901.97	977.47
		Weighted mean	370.51	809.73	922.09
	Viagra is not effective (Androskat)	General practitioner	308.73	555.47	772.36
		Urologists	621.85	699.59	841.58
		Weighted mean	590.54	685.18	834.66
Androskat	Androskat is effective	General practitioner	308.73	679.58	772.36
		Urologists	621.85	823.70	841.58
		Weighted mean	590.54	809.29	834.66

When these figures are combined with the patient flows presented in figure 2, the treatment costs of erectile dysfunction can be calculated in the two different situations: the Viagra scenario and the Androskat scenario. In these calculations the costs of patients in which treatment yielded no response are added to the costs of patients in which therapy was successful.

Some patients discontinue treatment during the first year, namely 10% for Viagra and 14% for Androskat. This dropout is not caused by a medical factor, and it is unknown when this dropout takes place. We modelled the costs assuming that each patient would continue to use treatment for a whole year, because it is unknown when this dropout takes place. Note that this modelling overestimates the costs.

### *The first year*

In the Viagra scenario 77.25% of the patients will be treated successfully: 65% with Viagra, and an additional 12.25% with Androskat. The mean costs of the 65% of patients in which Viagra is successful amounts NLG 1180.24. In the 12.25% patients in whom Androskat is successful, the mean costs amount NLG 2912.97 in the first year. This last figure is build up of the costs of establishing the effective dose of Viagra in the 35% in which Viagra failed, and the subsequent establishing of the effective dose of Androskat in 24,5% and continued use of Androskat in 12.25% for the first year. The mean costs per successfully treated patient in the Viagra scenario in the first year are estimated at NLG 1455,01 (weighted for use of Androskat and Viagra).

In the Androskat scenario, the mean costs per successfully treated patient are estimated at NLG 1732.01 in the first year. This means that Androskat is more costly in the first year, although the medicine is less costly. This can be explained by the high number of consultations with the specialist involved in establishing the effective dose; the costs of the general practitioner (80% in the Viagra scenario) are lower. Also the costs of non-successfully treated patients are therefore relatively high in the Androskat scenario. Together this explains the higher costs in the Androskat scenario in the first year. Androskat treatment would only be effective in 44.80% in the first year as compared to 77.25% in the Viagra scenario.

### *Each following year*

The next year starts with 10% less Viagra users and 14% less Androskat users. The number of patients using Viagra and Androskat decreases 5% per year from the second year on. For the Androskat the costs are NLG 834.66 for the second year, for Viagra the costs are NLG 922.09. This means that the mean costs in the Viagra scenario are NLG 908.75 (weighted for use of Androskat (10.5% in the second year) and Viagra (58.5% in the second year)). Note that all costs of non-successfully treated patients were accounted for in the first year figures of successfully treated patients. This means that from the second year on, the costs per successfully treated patient are constant (when the frequency of use remains constant). Therefore, the costs in each following year will be the same as the costs per successfully treated patient in the second year.

## Summary

In sum, the treatment costs in the Viagra scenario and the Androskat scenario were build up of the number of consults, the number of prescriptions, the prescription method and the amount of medicine used. The main cost-driver is the medicine itself, both for Androskat and Viagra. The cost price of Viagra is higher than the cost price of Androskat. However, in the Androskat scenario the consultation costs are higher. The number of prescriptions hardly influences the difference in costs. In the first year the Androskat scenario is more costly, but in the following years the costs per successfully treated patient are higher in the Viagra scenario (summarised in Table 8)

Table 8: Summary of costs of Viagra and Androskat (NLG)

	Viagra scenario	Androskat scenario
First year	1455.01	1732.01
Each following year	908.75	834.66

### 3.3. Cost-effectiveness

The utility gain of successful treatment for erectile dysfunction is estimated at 0.11 QALY. In the Viagra scenario the costs are estimated to be NLG 1455.01 in the first year and NLG 908.75 in each following year. The costs per QALY in the first year are:  $1455.01/0.11 = \text{NLG } 13227.36$  per QALY. In each following year the costs are 8261.36 per QALY. In the Androskat scenario the costs are estimated at NLG 1732.01 in the first year and on NLG 834.66 in each following year. The utility gain is assumed to be comparable, thus 0,11. This means that the costs per QALY in the first year are NLG 15745.55 and in each following year NLG 7587.82.

To analyse the additional costs and effects of Viagra scenario when compared to the Androskat scenario, we performed an incremental analysis. This means that the additional costs and additional effects of the Viagra scenario are compared. On basis of the prior reported results, this can be calculated with formula 1.

$$\text{Formula 1: } \frac{77.25 \times 1455.01 - 44.80 \times 1732.01}{77.25 \times 0.11 - 44.80 \times 0.11}$$

$$\text{Formula 2: } \frac{69.53 \times 908.75 - 38.53 \times 834.66}{69.53 \times 0.11 - 38.53 \times 0.11}$$

This would result in NLG 9750.80 per additional QALY in the Viagra scenario as compared with the Androskat scenario in the first year. For the second year the increment would be NLG 9098.52, as represented in formula 2.

So far we have used the artificial distinction between the first year and each following year. Below we explored what happens to the cumulative costs and effects when this distinction is not made. To that end we calculated the cumulative costs and effects of the Viagra and Androskat scenario for periods of multiple years. This means for example that the figures after 2 years are built up of the costs and effects of the 77.25 successfully treated patients in the first year and the costs and effects of the 69.53 successfully treated patients in the second year.

*Table 9: Cumulative costs and effects of Viagra and Androskat at long-term (costs in NLG per QALY)*

	Viagra scenario		Androskat scenario		Incremental costs per QALY
	% patients continuing treatment	Costs per QALY	% patients continuing treatment	Costs per QALY	
After 1 year	77.25	13227.36	44.80	15745.55	9750.80
After 2 years	69.53	10875.05	38.53	11973.41	9432.44
After 3 years	66.05	10063.90	36.60	10643.93	9326.63
After 4 years	62.75	9653.47	34.77	9950.24	9273.65
After 5 years	59.61	9405.90	33.03	9543.57	9242.07
After 6 years	56.63	9240.48	31.38	9255.76	9221.08
After 7 years	53.80	9122.27	29.81	9056.01	9206.12

As presented in table 9, the Viagra scenario is approximately effective in 20 to 30% more patients than the Androskat scenario is. Furthermore, the costs per QALY of the Viagra scenario are lower until the 7<sup>th</sup> year of treatment as compared to the Androskat scenario, despite the higher medication costs. The cost driver in the Androskat scenario is that Androskat is prescribed by the urologist, which means that also the costs of non-successfully treated patients are relatively high. These costs are added to the costs of successfully treated patients. Our figures show that the higher costs of the Androskat scenario in the first year have a strong impact on the cost-effectiveness of this treatment.

### **3.4. Sensitivity analysis**

We perform sensitivity analysis with respect to three subjects:

1. The frequency of intercourse
2. Different values for erectile dysfunction
3. The uncertainty with respect to the volumes of resource use.

These 3 subjects will be discussed separately.

### Frequency of intercourse

As indicated before, the use of Androskat is limited for medical reasons to once a week. This is not the case in Viagra, which can be used daily (but only one dose per day). Therefore we analysed how much the frequency of use affects the costs and the costs per QALY and how this affects the increment between the costs and effects of Androskat and Viagra. This is summarised in Table 10. One can see that the results are highly influenced by the frequency of use.

Table 10: Sensitivity of cost-effectiveness ratios in the Viagra scenario for frequency of intercourse (in NLG)

Frequency of use per week	First year			Each following year		
	Mean costs	Costs per QALY	Costs per additional QALY (%)	Mean costs	Costs per QALY	Costs per additional QALY (%)
1	1455.01	13227.36	9750.80 (100.00)	908.75	8261.36	9098.52 (100.00)
1.5	1754.96	15954.18	16242.22 (166.57)	1270.15	11546.82	17012.56 (185.10)
2	2054.92	18681.09	22733.86 (233.15)	1631.55	14832.27	24833.86 (270.19)

### Different values

The differences that occur because of the differences between values of the patients and values of the general public are presented in Table 11. Note that the higher values of the patients result in a better cost-effectiveness ratio.

Table 11: Sensitivity of cost-effectiveness ratios in the Androskat and in the Viagra scenario for different values (in NLG)

Source of Values	QALY gain	First year			Each following year		
		Costs per QALY Viagra	Costs per QALY Androskat	Costs per additional QALY (100%)	Costs per QALY Viagra	Costs per QALY Androskat	Costs per additional QALY (100%)
General public (group)	0.11	13227.36	15745.55	9750.80 (100.00)	8261.36	7587.82	9098.52 (100.00)
Students (group)*	0.11	13227.36	15745.55	9750.80 (100.00)	8261.36	7587.82	9098.52 (100.00)
Students (individual)*	0.12	12125.08	14433.42	8938.23 (91.66)	7572.92	6955.50	8425.31 (91.66)
Patients (individual)	0.14	10392.93	12371.50	7661.34 (79.57)	6491.07	5961.86	7221.70 (79.57)

\* Source: This report, appendix A<sup>9</sup>. Note that these data suggest that the QALY gain as assessed by the general public might have been higher when TTO would have been done individually instead of in groups.

These figures not only present a sensitivity analysis for the source of our values, but also for our method of time trade-off. As described in appendix A, the TTO in groups resulted in somewhat higher values for mild states of erectile dysfunction. When these values are combined with the frequency distribution over different health states, this resulted in a different utility gain: 0.11 in group sessions and 0.12 in individual TTO. Note that in groups the values for students and the general public are the same. Therefore it could be expected that individual TTO in the general public could yield the same result as individual TTO in students: 0.12.

### Uncertainty regarding resource use

The differences that occur because of different scenarios about resource use are presented in Table 12.

Table 12: Sensitivity of cost-effectiveness ratios in the Viagra scenario for uncertainty regarding resource use (in NLG)

Scenario	First year			Each following year		
	Mean costs	Costs per QALY	Costs per additional QALY (%)	Mean costs	Costs per QALY	Costs per additional QALY
Low	1320.65	12005.91	6843.02 (71.18)	860.84	7825.82	8154.40 (89.72)
Base	1455.01	13227.36	9750.80 (100.00)	908.75	8261.36	9098.52 (100.00)
High	1568.56	14259.64	12208.21 (125.20)	1015.92	9235.64	11510.59 (125.23)

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## 4. Discussion

### 4.1. Summary

In this investigation we demonstrated that the costs per QALY of Androskat are higher than the costs of Viagra in the first year (NLG 15745.55 versus NLG 112399.52). The costs of the Androskat scenario per successfully treated patient after establishing the effective dose are lower than the costs of the Viagra scenario (NLG 7587.82 versus NLG 8261.36). However, the high costs of establishing the effective dose in the Androskat scenario strongly influence the cost-effectiveness: the Androskat scenario yields higher costs per QALY until the 7<sup>th</sup> year. In the following years, Viagra is more costly, but is also more effective in the sense that more patients can be treated. For example after 7 years, 53.80% of the patients in the Viagra scenario is continuing treatment, whereas this is only 29.81% in the Androskat scenario. Note that these figures are relevant in an incremental analysis of the additional effects of Viagra as compared to Androskat. This incremental analysis shows that the higher costs of the Viagra scenario are in line with the higher effects; for example, the additional costs per additional QALY are estimated to be NLG 9206.12 in the 7<sup>th</sup> year.

It must be noted that these comparisons can only be made on the assumption that the effects and the frequency of use are the same for Viagra and Androskat, as is the impact on quality of life. The results of the sensitivity analyses show that the cost-effectiveness ratios are robust for differences between patients' values and values of the general public and for the uncertainties regarding the other assumptions in our model. All presented cost effectiveness ratios are favourable: as well the ratios for Androskat and Viagra therapy as the ratio of the increment between costs and effects in the Viagra and Androskat scenario.

In valuing disease specific outcomes we introduced two methodological novelties. The first is that we collected values for health states described in disease specific instead of generic terms. The second novelty is that we collected TTO values in groups. Therefore we analysed in appendix A the possibility to value the health states defined by the IIEF with TTO in groups. The validity of the methods we used, proved to be good (see appendix A).

The results of appendix B showed that both patients and the general public consider erectile dysfunction to have a substantial impact on quality of life. The values given to health states of erectile dysfunction by patients were lower than those of the general public were. Hence, when the patients value the effects, the cost-effectiveness of Viagra improves. This effect is shown in the sensitivity analysis, where the model is tested for the differences between values of patients and the general public.

Within the general public, values were not related to age, gender, the availability of a partner, sexual activity and sexual satisfaction. Only one background variable seems to have a relation with the values given: subjects without children gave lower values for health states of erectile dysfunction. This means that the cost-effectiveness of Viagra improves when used in subjects without children.

#### **4.2. Limitations**

In our comparison of the costs and effects, we had to deal with the fact that the use of Androskat is rationed for medical reasons: too many injections can cause fibrosis in the penis. To enhance the comparability of the use of Androskat and Viagra, we compared both alternatives by assuming the same frequencies of intercourse. However, the use of Viagra is less rationed for medical reasons. In the sensitivity analysis we analysed how changes in frequency of intercourse with Viagra influence the cost: the costs of treatment increase almost linearly if the frequency of use of Viagra increased. This also means that the cost-effectiveness is almost linearly related to the frequency of use. Because the use of Androskat is limited, this means that the costs per additional QALY rise exponentially when the frequency of use increases.

In this context it should be noted that treatment of erectile dysfunction is valued as a relative increase in successful attempts of intercourse, without restriction of the number of attempts of intercourse as is the case with Androskat. Furthermore, the TTO protocol for valuation of the health states of erectile dysfunction, provides for cure with oral treatment. It can be assumed that a protocol that provides for cure with an invasive treatment, such as injections with Androskat, would yield lower values. For instance the lower continuation rates for Androskat therapy after the first year might indicate that the quality of life effect of Androskat is lower. Thus, to use the same utility gain in Androskat and Viagra is a conservative approach in the incremental analysis of costs and effects of Viagra as compared with costs and effects of Androskat.



The trial design of Goldstein, Lue, Padma-Nathan et al. on which we based our estimate of the clinical effect, was analysed on an “intention to treat” basis.<sup>1</sup> That means that also patients who do not respond to Viagra remain in the trial. There is no doubt that an “intention to treat” design can demonstrate the efficacy very convincingly. However, such design may not be the most appropriate design for the estimation of the effect of Viagra in patients who continue to use the medication. In the estimation of the utilities gained, we summarised the effect in patients in which Viagra yielded sufficient response and in patients in which Viagra yielded no response (in 35% of the patients). This means that we underestimated the utility gain of patients who will continue treatment. The estimation of the effect of Viagra is also in that respect conservative.

We used the values of the general public. It is remarkable that the values of the general public were higher than values of patients, which means that the general public judges the impact on quality of life to be milder than patients do. In most research this is the other way around.<sup>2</sup> This means that in this case the “clinical selection bias” and the “strategic bias” are more dominant than the adaptation process. As explained in appendix B, this could be expected in a situation in which patients participate in a trial with an effective intervention. On the other hand, it could also mean that the awareness of the problems of erectile dysfunction in the general public is low. However, for our purposes it is not necessary to further investigate this difference, because the values of the general public will give a conservative estimate of health care interventions.

There were no relevant systematic differences in absolute values between the individual and the group administration of the TTO. There were however some small differences at the level of the individual health states: the better erectile dysfunction states were valued lower in TTO in groups than in individual TTO. Though this only applies to 4 states of erectile dysfunction, there is an effect on the utility gain in the patient population; the utility gain is 8.3% higher when assessed with individual TTO as compared with TTO in groups. The same difference between TTO in groups and individual TTO could also be expected in the general public. That means that the costs per QALY and the costs per additional QALY could be expected to be 8.3% lower when assessed with individual TTO. Given that we used group sessions for the evaluation of erectile dysfunction, we made again a conservative estimation of the cost-effectiveness.

One can argue that we only established a validity test of the group sessions in students, and therefore we are still uncertain about the validity of group sessions in the general public. However, we do think that the results of the student investigation can be validly

generalised to the general public for two reasons. First of all, the group sessions in the general public were not more difficult to administer than in students. A second reason is that the differences between our group protocol hardly differed from an individual administration. Comprehension of the valuation task is tested on an individual level, and as soon as the investigator notes signs of misinterpretation of the task, an intervention at an individual level takes place.

We did not present the influence of the background variables in patients. Given the homogeneous composition of this group in terms of the background variables, we did not expect that the statistical power of the investigation would be strong enough to detect any influence. We indeed could not detect any significant relation in the patient population.

The sample of the general public was not completely representative in terms of the distribution of age categories. However we did not want to stratify the results for this observation, because age did not have significant influences on the values of the health states.

#### ***4.3. Implication for theory***

A specific implication of our research is that we now are able to recalculate the outcomes of the Viagra trial of Goldstein, Lue & Padma-Nathan et al. (1998) into QALYs. A more general implication is that this means that we have proceeded in the application of QALY-theory: we have demonstrated that it is possible to attribute utilities to health states as defined by a disease specific questionnaire and that this can be done in a cost-effective way. This enlarges the area of application of QALY-analysis. It seems even possible to recalculate disease specific outcomes of trials to QALYs. Furthermore, the enhanced validity of the group sessions open up the possibility for researchers to quickly assess the utility of different scenarios, which will facilitate model studies in health sciences.

It seems that the relations between the values for health states of erectile dysfunction and background variables are restricted to having children and being a patient with erectile dysfunction or not. The robustness of values of hypothetical health states for the influences of social economic variables has been reported several times. Handbooks and literature studies report that the influences of these variables seem limited.<sup>2, 3</sup> The lack of influence of background variables on the values of the general public indicates

that in that respect there is no need for different cost-effectiveness ratio for different subgroups. An exception might be for the couples who have trouble getting children because of the erectile dysfunction. In these couples the cost-effectiveness of Viagra is better: the costs per QALY gained are lower.

We did not determine different cost-effectiveness ratios for different patients groups on the basis of differences in efficacy. We could not do this, because such differential efficacy data is lacking. If such differential data becomes available in terms of outcomes of the IIEF, adaptation of our estimates of the cost-effectiveness are easily made. Given that the placebo effect can be expected to be negligible (Goldstein, Lue, Padma-Nathan et al., 1998), it must not be very difficult to obtain this information.

#### **4.4. Policy implication**

We estimated the cost-effectiveness of Viagra and compared this in a conservative way with the cost-effectiveness of Androskat, which is already reimbursed in The Netherlands. Compared in that way, the cost-effectiveness of both products is about the same. Furthermore, the cost-effectiveness ratio of Viagra lies at the favourable end of the scale when compared with interventions in health care for other diseases.<sup>4</sup> Given the outcomes of these comparisons, reimbursement of Viagra should be considered.

If reimbursement of Viagra is considered, the rationing of the medication should be a focus point of the distribution, because the frequency of use is the major cost driver of Viagra. That means that the allocation of resources to Viagra can be controlled by rationing or by a partial reimbursement of the medication.

If the reimbursement of Viagra is considered, monitoring the effects in terms of the IIEF and frequency of use *per subgroup can be considered*. Both variables are the major determinants of the cost-effectiveness, and therefore essential parameters in determination of an allocation strategy per subgroup based on cost-effectiveness arguments.

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## **Appendix A: Converting clinical outcomes into utilities: the valuation of International Index of Erectile Function (IIEF)**

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### ***Key words***

Economic evaluation, quality of life, time trade-off, erectile dysfunction

## **Abstract**

### *Introduction*

Health economists have a preference to measure quality of life in terms of utilities, because this offers the possibility to integrate this outcome with life expectancy into QALYs. These utilities are often collected with the use of standardised questionnaires like the EuroQol or the HUI. These questionnaires are said to have a low sensitivity, as compared to specific questionnaires. An alternative would be to value the outcome of disease specific questionnaires in terms of utilities. To our knowledge, we are the first to apply and describe this strategy. For the valuation of disease specific outcome we used time trade-off (TTO) in both standard individual interviews and group sessions, in order test the possibilities of a more cost-effective administration.

### *Methods*

169 subjects from the general public and 117 students valued 28 health states as defined by the International Index of Erectile Function (IIEF) with TTO. All members of the general public and half of the students valued the states in a group session. The other half of the students valued the states in individual sessions.

### *Results*

There were small differences between the values of the group administration and the individual administration, but there was no overall effect. The factor structure was also similar. The values showed good content validity.

### *Conclusions*

The results support the validity of the proposed process of valuing the outcomes of disease specific questionnaires into utilities. The administration of TTO can be done in group sessions, which reduces the costs of the administration.

## **Introduction**

Quality of life can be measured with disease specific questionnaires, generic questionnaires and in terms of utilities. Health economists have a clear preference for utilities, because these outcomes can be integrated with life expectancy into “Quality Adjusted Life Years” (QALYs). Normally, health economists collect the values or utilities for health states with the use of standardised questionnaires like the EuroQol or the Health Utility Index. Typically, these instruments are generic questionnaires: they can be used in all kinds of patient populations. This generic entity enlarges the area of application, but at the same time lowers the sensitivity of the instrument, because the questionnaire may not contain items directly related to specific aspects of the illness. Brazier and Dixon (1995) therefore suggest to adapted disease specific quality of life questionnaires for the measurement of the utilities. So far, such efforts have been scarce and the methodology has not been thoroughly described. In this manuscript we describe such valuation process in which the general public attributes utilities to the health states defined by the International Index of Erectile Function (IIEF).

Doubts about the sensitivity of generic quality of life questionnaires in general and of utility measurement in particular are widespread.<sup>1</sup> For instance, Kantz, Harris & Levitsky et al.<sup>2</sup> Spectus, Winder, Dewhurst et al.<sup>3</sup> and Gliklich & Hilinski<sup>4</sup> all concluded that their disease-specific instrument was more sensitive than the SF-36 survey. A similar opinion exists for utility measurements.<sup>5, 6</sup> Brazier & Dixon<sup>7</sup> begin their article with the statement: “...*There is increasing concern over the use of health utility measures in economic appraisal for valuing health. These measures have been criticised for not capturing all relevant aspects of a condition (Hall, Gerard & Salkeld, 1992), being insensitive to lower levels of perceived ill-health (Brazier, Jones & Kind, 1993), and for the general failure on the part of economists to test the relevance of their measure for the intervention and condition being evaluated (Carr-Hill & Morris, 1991)...*”.

Because of these drawbacks, health economists have tried to adapt their generic measures to the specific circumstances of the illness. In the past, several ad hoc methods were used, like for instance using “experts” to attribute values to patients in the trial.<sup>8</sup> Others followed the instructions of Gold, Patrick & Torrance et al.<sup>9</sup> and mapped the outcomes of disease specific measure “afterwards from behind the desk” into utility instruments like the EuroQol and the Rosser Index.<sup>10, 11, 12</sup>

A more structural solution is to generate a small number of holistic scenarios, which are disease specific and adequately describe the main differences between patient subgroups. The scenarios are then valued in a separate investigation.<sup>13, 14</sup> By classifying the patients in these scenarios, the researcher can attribute utilities to the patients in the trial. A major disadvantage of such approach is that only a small number of scenarios can be generated. Therefore these scenarios mean a significant reduction of clinical information. This reduces the sensitivity for small changes in health. So in this approach the health states descriptions may be specific, but they are also rigid and limited in number.

To overcome these problems there have been attempts to make disease specific classification systems suitable for the calculation of utilities or to make generic instruments more sensitive to disease specific problems. For instance Mohide, Torrance & Streiner et al.<sup>15</sup> attempt to make a disease specific classification system for the health states of caregivers. Krabbe, Stouthard & Essink-Bot et al.<sup>16</sup> tried to adapt the EuroQol EQ-5D, a questionnaire already suitable for the calculation of utilities. They tested the effect of adding a cognitive dimension to the 5 dimensions of the EuroQol EQ-5D. In both cases, the authors conclude that their new system adequately classified their patient group. However, the problem remained that utilities could only be attributed to some of the health states, because the recourses did not allow for a complete valuation of the classification system.

Of course one could overcome all these problems by asking the patients in the trial to value their own health with the use of utility measures like standard gamble and time trade off. However, there are several drawbacks for this design.

First of all the approach is extremely labour intensive, as the measurement has to be done within an interview session by specially trained personnel. Especially when one would like to measure several times during the trial, costs can be mounting.

Furthermore, many quality of life researchers have been experiencing reservations in clinicians to use interview techniques like standard gamble and time trade-off in patients, like we did.<sup>7, 17</sup> Although justification of such reservations is not given in the literature, resistance can be insuperable. In that case the only remaining direct utility measurement by patients is a visual analogue scale. However, the performance of a visual analogue scale as a utility instrument in the economic evaluation of health care is low.<sup>9</sup>

A third argument against the use of direct utility measures by patients is the issue of the perspective of the measurement. In the economic appraisal of health care the preferred



perspective is the societal.<sup>18</sup> If one chooses to value the health states by patients, one is changing the perspective of this part of the analysis from a societal perspective to a patient perspective. The patient perspective is not necessarily wrong in other evaluations (for instance, it makes good sense in a clinical perspective), but as soon as the costs are calculated from a societal perspective, it has been recognised that it makes most sense to value the effects from the same perspective.<sup>9, 19</sup> In appendix B, we elaborate on the choice of the perspective in economic appraisal of health care.<sup>20</sup>

To come to a conclusion: the sensitivity of generic instruments - capable of attributing utilities to health states - has been questioned. A good solution would be to validate disease specific instrument in such a way that they would also be capable to attribute utilities to health states. In the present manuscript we tested the validity of such valuation process. In this investigation the general public attributed utilities to the health states defined by the International Index of Erectile Function (IIEF).

The strategy above has been followed before<sup>15, 16</sup>, but it has not been fully explored, given the costs constrains. Therefore it would be helpful if this process is further investigated, and directed towards more inexpensive research designs. For this reason we added an additional research question, aimed at reducing the costs of such effort: can one collect the data validly in a group session, as compared to the usual face-to-face interview. This additional research question was investigated in a student population.

## **Methods**

### *International Index of Erectile Function (IIEF).*

To generate utilities for erectile dysfunction, we converted disease specific outcomes into utilities. The valuation method was time trade-off (TTO).

The health states valued were based on question 3, 4 and 7 of the International Index of Erectile Function (IIEF). This is a 15-item questionnaire to assess sexual functioning.<sup>21</sup> Prior to the development of the IIEF, the National Institutes of Health pointed out the need for a symptom scoring sheet necessary to aid in standardisation of patient assessment and treatment outcome. Furthermore they pointed out the need to develop a staging system to permit quantitative and qualitative classification of erectile dysfunction.

The IIEF was developed in response to these needs. The IIEF is currently the preferred disease specific questionnaire for several reasons: it is valid and psychometrically sound, it can be used across different cultures and it contains the two primary end points of erectile dysfunction treatment as defined by the National Institutes of Health: the ability to penetrate and to maintain an erection.<sup>22</sup>

The IIEF has been used in the clinical trials in which the efficacy of Viagra was demonstrated.<sup>23</sup> If we are able to value the IIEF in terms of utilities, we are also able to translate the outcome of the trial into utilities. The primary end points in this clinical trial were question 3 and 4; thus the same questions as used in this investigation.

By addressing the ability to attain and maintain an erection, the IIEF has the sensitivity and specificity to detect treatment-related changes in patients with erectile dysfunction.<sup>21</sup>

Because these two primary end points have each five response levels, they define (5 x 5) 25 unique health states (table 1). Question 7 is about the satisfaction of the intercourse in general, without making a direct reference to erectile functioning (table 1). The 4 health states as defined by question 7 were valued independently. The subject valued the total of 28 health states using “time trade-off”. The best health state (no erectile dysfunction) was not valued, because normal health is a reference point in TTO.

*Table 1: Question 3, 4 and 7 of the IIEF*

IIEF Question 3	IIEF Question 4	IIEF Question 7	Response level
<i>During the past 4 weeks, how often were you able to penetrate?</i>	<i>During the past 4 weeks, how often were you able to maintain the erection?</i>	When you attempted sexual intercourse, how often was it satisfactory for you	
Almost never or never	Almost never or never	Almost never or never	1
A few times	A few times	A few times	2
Sometimes	Sometimes	Sometimes / Most times	3
Most times	Most times	Almost always or always	4
Almost always or always	Almost always or always		5

### *Valuation method (TTO)*

Time trade-off (TTO) is, next to standard gamble, one of the preferred valuation methods in health economics that are used to determine the values or “utilities” of health states. The methodology of this interview technique is described in detail in Drummond, O'Brien & Stoddart et al. (1997). Based on this standard work, one has to make some methodological choices to be able to operationalise the method for the specific research question. These methodological choices are motivated below.

As usual in this kind of valuation tasks, the subjects had to value the health states “for a person like themselves”. Thus the subjects had to imagine that they had an erectile

dysfunction as described by the 25 health states. This means for example that older subjects gave values from an ageing perspective, while persons without a sexual active partner could incorporate this circumstance in their values. The only exception was gender: women had to imagine that they were men with erectile dysfunction.

The health states of erectile dysfunction were assumed to be chronically. This means that the subjects had to assume that they were in the health states for the rest of their lives, other things being equal to their own present and further situation.

The trade-off in time was measured relative to the life expectancy of the subjects. The subjects had to assume that they would reach their life expectancy in “normal health for that age”.

The health states were presented on cards in random order. Subjects were allowed to reshuffle the cards. They were also allowed to go back to a former response, if they had changed their mind during the interview. Because of the large number of states that had to be valued and because of the intimacy of the subject, it was chosen to let the respondents record the answers on an answer form instead of letting the interviewer record the responses. The cards had numbers that corresponded to the answer form. The answer forms consisted of lines representing the life span of the respondent. The respondents indicated on this line the so called “indifference point”. This point indicates that a loss of years to gain full health for which the respondents have no preference for living shorter as indicated on the line in full health or living their complete life span in the health state described on the card. This adaptation of the TTO administration was based on the work of Bleichrodt & Johannesson.<sup>24, 25</sup>

### *Interview protocol*

The interview protocols for individual interviews and for the TTO administration in groups were designed to be as similar as possible.

Both protocols began with a general introduction after which the subjects practise with TTO using the health state “sitting in a wheelchair” as an example. In the group sessions this health states was valued by a volunteer from the group, and had the form of an individual administration of TTO, using the typical “ping-pong interview technique”. After this example, the group was invited to discuss the results and was encouraged to ask questions about the procedure if they did not fully comprehend the administration. In both the individual and the group protocol, we tested the ability to perform the task by

valuing 3 generic EuroQol EQ-5D health states (states 11211, 11122 and 21232) with TTO.<sup>26</sup> In both protocols the answers were checked and discussed. If there were signs of misinterpretation, the protocol was explained again. In the groups sessions this check and the additional explanation was done on an individual basis.

After this check, the subjects were introduced into the health problems associated with erectile dysfunction. Female subjects were asked to imagine themselves to be men when valuing the problems associated with erectile dysfunction. After the introduction, the subjects were asked to value the health states of erectile dysfunction with the use of TTO. It was explained that some health states may appear illogical, namely states that describe that penetration is (almost) never possible, but that patients are able (sometimes, most times or always) to maintain the erection. Although these health states may seem odd, inquiry about the data set published by Goldstein et al. showed that all 25 states were represented but one: "almost never being able to penetrated, but always able to maintain the erection after penetration".<sup>27</sup> Because it is technically possible for patients with erectile dysfunction to classify themselves in all states, subjects were encouraged to value this state as well.

Twenty eight health states of erectile dysfunction as defined by question 3, 4 and 7 of the IIEF, were printed on cards and presented randomly. During both the individual and the group sessions the interviewer checked the responses, and if there were signs of misinterpretation, the subjects was interviewed on an individual basis, until the subject could perform the task independently. For this reason, if there were more than 6 subjects in the group session, the interviewer in the group session was assisted with one or two fellow researchers.

### *Invalid responses*

Invalid responses were excluded from the analysis. Invalid responses were defined according to three criteria: A) when a respondent trades more years than possible in his life expectancy; B) when there are too many missing values (>4); and C) when subjects did not make any trade-off during the administration of the three EuroQol health states. Criteria A and B control for task comprehension. Criteria C refers also to "lexicographic responders". A lexicographic responder is defined as a subject who is not prepared to make any trade-off for any health state, not even for a very bad health state like for instance the EuroQol health state 21232. Lexicographic means that when a respondent

is faced with an option, he or she will always choose for one particular alternative, no matter how favourable the other might be. Of course, no trade-off on EuroQol state 21232 could also mean that the subject still did not understand the task. In both cases (did not understand or a lexicographic response) the responses on time trade-off questions becomes meaningless. When the interviewer observed such response, both options were checked. If the respondent still did not understand the task, the task was explained again. If the responder seemed to act in a lexicographic way, an even more extreme health state than 21232 was proposed. If the subject maintained in his or her lexicographic response mode, or when it was not feasible to explain the task, the responses of the subject were excluded.

Note that the exclusion of lexicographic responders was only based on the responses on the EuroQol health states and not on the responses on the 28 health states of erectile dysfunction. If a respondent did not made any trade-off in case of the health associated with erectile dysfunction, the responses were judged to be valid, as long as the subject made a trade-off on the EuroQol states, and as long as it was clear that the respondent understood the task.

### *Subjects*

We tested our valuation methods in three subject groups, namely a pilot group, students and the general public. First we piloted both the individual and the group protocol in a group of 25 colleagues and students. The results of this “corridor investigation” were encouraging and the protocol was refined on the basis of these experiences.

Prior to the data collection in the general public, we performed TTO interviews in a sample of students. To test the validity of the TTO administration in groups, we divided the student population in two parts: half of them were individually interviewed and half of them were interviewed in a group session. Subjects were recruited using posters at the university. The poster mentioned an interview task about health state valuation. It was not mentioned that the health states being investigated were associated with erectile dysfunction. We paid the students NLG 25,- (similar to 11,- Euro). An effort was made to match the student in the individual sessions and the group sessions in respect to gender and age.

Blauw Call Centre, a marketing research bureau, recruited a representative sample of the general public from a random sample of the telephone directory. The sample was

based on quota sampling, and stratified on the basis of sex, age and education. In this process, we allowed oversampling of the men aged 40-70 years, because this group is the target group of Viagra. If applicable, the results could be weighted for differences in gender and age between our sample and the national statistics. This stratification would be done if the differences from national data were substantial and if a relationship was found with the dependent variable of this investigation, namely the value attached to health states of erectile dysfunction. The subjects were interviewed at the university. The subjects were paid NLG 30,- (similar to 14,- Euro) and got a refund of their travelling expenses. Also the sample of the general public was not notified in advance that the health problem being examined was erectile dysfunction. Instead the study objective was described as the valuation of some health states.

### *Analysis*

The analysis aimed to answer two questions: “is it valid to convert clinical outcomes of erectile dysfunction into utilities?”, and - serving this question: “is it valid to administer TTO in groups?”. We have tried to answer these questions in terms of content validity, criterion validity and construct validity.

#### Content validity

The analysis of the validity of responses was first of all done on the basis of content validity: do the responses make sense in terms of absolute value and are they consistent within the ordinal structure of the 25 health states of erectile dysfunction as defined by question 3 & 4 of the IIEF. Deviations were expected at the less logical health states like “almost never being able to penetrate, but always able to maintain the erection after penetration”.

#### Criterion validity

The analysis of the validity of the group session was primarily based on the convergence between the answers recorded in individual measures and in groups. As time trade-off is usually performed in a face-to-face setting, the individual sessions were seen as the criterion for the group responses. The analysis was done with a ‘MANOVA repeated measure’ analysis. The effects are tested both multivariately and univariately. If statistical significant differences occur, the relevance of the differences was tested in a

population of patients with erectile dysfunction (baseline data Goldstein, Lue & Padma-Nathan et al., 1998).

#### Construct validity

It was recognised that the construct validity of the group sessions would be supported if the resulting factor structure in the group data would be closely related to the factor structure of the data of the individual sessions. For instance if the response on question 3 was more important than question 4, during the individual sessions, then this should also be visible in the data of the group sessions. Introducing question 3 and 4 as two “within-subjects-factors” in the MANOVA tested the factor structure. A similar factor structure should result in small or non significant interaction effects between the mode of administration (individual of group) and the two within-subjects factors (question 3 and 4).

Furthermore it was also expected that the mode of administration would influence the comprehension of the valuation task. It was therefore expected that more censoring of data was necessary during the group sessions. Given the complexity of the task, it was also expected that censoring would be a function of age.

## **Results**

#### Respondents

A sample of 117 students was recruited, of which 54 were interviewed in groups, and 63 were interviewed individually. In the TTO in groups female students were overrepresented with 40 females to 14 males. In the individual sessions the man and female were matched: 32 males and 31 females participated. The mean age for respondents of TTO in groups was 24 year, the mean age of the respondents of individual TTO was 22 year ( $p = 0.000$ ). One of the students discontinued the interview (individual session) after the health problem ‘erectile dysfunction’ was introduced. Responses of one of the others students – a male- were excluded (due to criteria B: too many missings).

We interviewed 169 subjects of the general public. The responses were valid in 148 subjects of the general public (88%). Most exclusion (48%) was based on the second

criterion: no trade-off for any of the EuroQol states. The mean age of subjects of the general public with valid responses was 45.5 years (SD 15.2).

Table 2 describes the sample of the general public. The oversampling of male respondents between 40 and 70 years was not that successful as expected. We hoped for an over sampling of 100%, but we only succeeded to oversample this group with about 30%. This resulted in a sample in which the gender distribution is close to the expected distribution, but the distribution over age is somewhat different from the distribution in the general population, according to the national statistics.<sup>28</sup>

Table 2: Representativeness of the sample of the general population with valid responses

Age group	Males		Females		Total		Reference
	N	%	N	%	N	%	%
18 to 39	24	45.3	29	54.7	53	35.8	42.0
40 to 54	25	55.6	20	44.4	45	30.4	24.0
55 to 70	28	58.3	20	41.7	48	32.4	21.0
71 to 79	1				1	0.70	8.5
>79	0		1		1	0.70	4.0
Total	78	100.0	70	100.0	148	100.0	100.0

### Content validity

Figure 1 and table 3 present the mean values of the students (group and individual sessions combined) and of the general public. Note that the value of the best health state (no erectile dysfunction) is not measured, but based on theory: 1.00.

Figure 1: Visual representation of the utilities of students and the general public for the 25 erectile dysfunction states defined by IIEF question 3 and 4

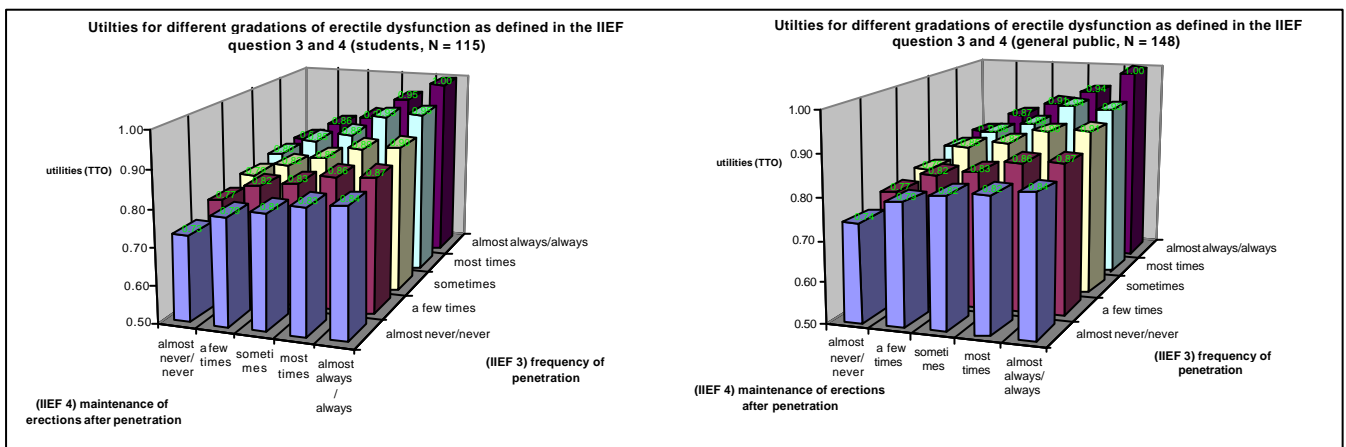




Table 3: Values for three EuroQol states and 28 erectile dysfunction states

Health state		General public		Students				Sig. of the difference
				TTO in groups (N=13)		TTO individual (n=57)		
		Mean	SD	Mean	SD	Mean	SD	
EuroQol	11211	0.95	0.09	0.94	0.07	0.91	0.10	0.33
	11122	0.90	0.11	0.90	0.08	0.87	0.11	0.43
	21232	0.68	0.17	0.75	0.11	0.67	0.15	0.08
IIEF q3	IIEF q4							
(almost) never	Never (almost)	0.74	0.18	0.73	0.14	0.73	0.11	0.71
	A few times	0.77	0.18	0.78	0.12	0.76	0.12	0.62
	Sometimes	0.79	0.16	0.80	0.13	0.78	0.11	0.27
	Most times	0.81	0.17	0.80	0.12	0.81	0.10	0.88
	Always (almost)	0.82	0.17	0.80	0.14	0.81	0.10	0.64
A few times	Never (almost)	0.79	0.17	0.78	0.13	0.79	0.11	0.73
	A few times	0.83	0.16	0.81	0.12	0.82	0.10	0.61
	Sometimes	0.85	0.14	0.83	0.10	0.82	0.10	0.53
	Most times	0.86	0.15	0.85	0.13	0.86	0.09	0.48
	Always (almost)	0.87	0.15	0.86	0.11	0.87	0.08	0.57
Sometimes	Never (almost)	0.82	0.17	0.79	0.13	0.82	0.10	0.20
	A few times	0.85	0.16	0.82	0.12	0.84	0.09	0.28
	Sometimes	0.87	0.14	0.86	0.10	0.85	0.10	0.79
	Most times	0.88	0.14	0.86	0.11	0.89	0.08	0.12
	Always (almost)	0.91	0.13	0.88	0.10	0.89	0.08	0.54
Most times	Never (almost)	0.82	0.15	0.81	0.13	0.85	0.12	0.15
	A few times	0.86	0.15	0.84	0.12	0.88	0.08	0.07
	Sometimes	0.90	0.13	0.87	0.11	0.90	0.08	0.12
	Most times	0.94	0.12	0.91	0.10	0.95	0.06	*0.01
	Always (almost)	0.94	0.11	0.93	0.09	0.96	0.05	*0.03
Always (almost)	Never (almost)	0.84	0.17	0.83	0.13	0.85	0.11	0.38
	A few times	0.88	0.16	0.84	0.14	0.89	0.09	*0.04
	Sometimes	0.91	0.13	0.88	0.13	0.91	0.08	0.16
	Most times	0.93	0.13	0.93	0.09	0.97	0.05	*0.00
	Always (almost)	1.00		1.00		1.00		
IIEF q7	Never (almost)	0.75	0.18	0.75	0.16	0.76	0.13	0.90
	A few times	0.83	0.16	0.82	0.12	0.83	0.11	0.80
	Sometimes	0.88	0.14	0.88	0.09	0.88	0.09	0.91
	Most times	0.95	0.11	0.94	0.10	0.96	0.06	0.05
	Always (almost)	1.00		1.00		1.00		

\* Significant ( $p < .05$ )

The responses do make sense given their absolute values: health states associated with erectile dysfunction have a utility below 1.0, but extreme low average values were not given. The values are also in line with an investigation of the World Health Organization (WHO). As part of the “Global Burden of Disease Project” a panel of “health workers” valued erectile dysfunction.<sup>29</sup> This panel valued the decrease in quality of life caused by erectile dysfunction on a utility scale between 12 and 24%.

The values are consistent with the ordinal structure of the question 3 and 4 of the IIEF. The expected deviations at the less logical health states are absent. These observations support the content validity of the valuation process.

#### Criterion validity

There were no differences in values given by male or female students ( $p = 0.646$ ). This was also true in the general public ( $p = 0.101$ ). Furthermore, age was not related with the utilities (students:  $p = 0.225$ ; general public:  $p = 0.896$ ). This means that it was not necessary to weight the results for difference in gender and age.

The multivariate analysis shows that there is no main group effect for the mode of administration: the utilities obtain in the group session were on average the same as in the individual sessions ( $p = 0.421$ ). There was however an interaction effect between the health states and the mode of administration. That means that although there is no overall effect, there are some health states that were valued differently in a group session than in an individual session. This is shown in table 3, which presents the univariate results: 4 relatively good health states are valued higher by the students in the group session than by the students who were interviewed individually ( $p < .05$ ). The relevance of these statistical significant differences is modest. The mean utility of the follow up data of Goldstein, Lue & Padma-Nathan et al. (1998) increased from .902 to .914. The mean utility at baseline of this investigation was unaffected, as the differences occur only in the health states with a relative high utility.

#### Construct validity

As could be expected from the results above, the mode of administration had a limited, but significant influence on the factor structure of the valuation space as defined by question 3 & 4 of the IIEF. The respondents in the group sessions valued the ability to maintain an erection slightly lower than the subjects in the individual sessions did. In both the responses from group and the individual sessions it appears that the ability to penetrate was more important than the ability to maintain an erection.

The amount of invalid responses was minimal both in individual and in group sessions. Within the general public, exclusion was related to age in the expected direction: half of the respondents older than 70 years gave invalid responses.

## ***Discussion***

In this investigation we tested the possibility to value the health states defined by a disease specific questionnaire with TTO. The absolute values showed good content validity and the results were consistent in terms of the ordinal structure of the questionnaire. There were no relevant systematic differences in absolute values between the individual and the group administration. The group sessions did not increase the amount of invalid data.

In this article we did not analyse in full the differences between the response of the students and of the general public. Moreover, we also did not fully analyse the differences in responses related to background variables like the availability of a partner, having children, sexual activity and sexual satisfaction. These items are evaluated elsewhere, in combination with the valuation of the IIEF from a patient perspective.<sup>20</sup> In the present article we restricted ourselves to a general introduction into measuring utilities by disease specific instruments and to the possibilities of group administrations in order to reduce costs.

The sample of the general public was not completely representative in terms of the distribution across the age categories and gender. However we did not stratify the results for this observation, because age and gender did not have a significant influence on the values of the health states.

There were no relevant systematic differences in absolute values between the individual and the group administration. There were however some small differences at the level of the individual health states. These differences account for an 8.3% larger effect of Viagra using individual data, compared to group data. This means that in the case of Viagra the use of group data would give a conservative estimate of the cost-effectiveness.

One can argue that we only established a validity test of the group sessions in students, and therefore we are still uncertain about the validity of group session in the general public. However, we do think that the results of the student investigation can be validly generalised to the general public for two reasons. First of all, the group sessions in the general public were not more difficult to administer than in students. A second reason is that the differences between our group protocol hardly differed from an individual administration. Comprehension of the valuation task is tested on an individual level, and as soon as the investigator notes signs of misinterpretation of the task, an intervention at

an individual level takes place. Note that this remark does not apply to so call “voting systems” as has been reported in the past<sup>30</sup>, as these mass administrations hardly allow for individual interventions.

The IIEF contains more questions than the questions 3, 4 and 7 that were used in this investigation. In this investigation we combined question 3 and 4 in order to define 25 health states. When a third question would have been added, not 25 but 125 health state would be defined. This would make it almost impossible to value all health states empirically. In that case one has to value a sample of these health state, and estimate the remaining values on the basis of parametric models.<sup>31</sup> Because intercourse is generally seen as the primary endpoint to measure the effect of treatment for erectile dysfunction, we considered the values for the 25 states defined by question 3 and 4 to be good estimates of the quality of life effect of erectile dysfunction.

Our results suggest that one can validly value health states of disease specific questionnaires for the estimation of utilities. This facilitates the use of QALY-analyses. It would be interesting to test if this approach is consistent with an approach in which generic classifications systems are used, like the EuroQol and the HUI. Of course this can only be done if one could expect that these generic questionnaires would validly pick up the symptoms of the illness. For this reason we could not test the new approach in that respect, because it was not expected that the EuroQol or the HUI would be sensitive for erectile dysfunction.

Our results further suggest that one can validly administer TTO in groups. Such group sessions have been done before<sup>24, 25</sup>, but a comparison between group and the standard individual examination has not been reported before.

A specific implication of our research is that we now are able to recalculate the outcomes of the Viagra trial of Goldstein, Lue & Padma-Nathan et al. (1998) into QALYs. The resulting cost-effectiveness analysis is described elsewhere in this report.

One of the general implications of our research is that we have proceeded in the application of QALY-theory: we have demonstrated that it is possible to attribute utilities to health states as defined by disease specific questionnaires. Furthermore we demonstrated the validity of a cost-effective group administration of TTO. This enlarges the area of application of QALY-analysis. It seems even possible to recalculate disease specific outcomes of trials to QALYs. Furthermore, the enhanced validity of the group sessions open up the possibility for researcher to quickly assess the utility of different health states and scenarios, which will facilitate model studies in health sciences.

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## **Appendix B: Differences in the values given by the general public and patients to health states of erectile dysfunction**

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### ***Key words***

Erectile dysfunction, economic evaluation, quality of life, social economic states, time trade-off

## ***Abstract***

### Introduction

It is anticipated that personal circumstances and the subjective enjoyment of sex moderate the impact of erectile dysfunction on quality of life. This may not only be true for patients with erectile dysfunction, but also for the general public, when they judge the effectiveness of medical interventions which could improve erectile functioning. Therefore we explored whether the general public can validly attribute values to the health effects of treatment for erectile dysfunction.

### Methods

Twenty eight health states of the International Index of Erectile Function (IIEF) were valued using time trade-off (TTO) by 106 patient with erectile dysfunction and a representative sample of 169 individual of the general public. The patients participated in a phase 4 trial of Viagra.

### Results

The results show that both patients and the general public consider the impact on quality of life of erectile dysfunction to be substantial. The values given by patients were lower than those of the general public, but the factor structure of the valuation space was the same. Within the general public, values were not related to age, gender, the availability of a partner, sexual activity and sexual satisfaction. Only having children seems to be related to the values given. The factor structure of the valuation space was not influenced by the background variables mentioned.

### Discussion

With the use of the values give in this investigation one can use the IIEF as a utility measurement which can be used to estimated QALYs. The utility assessment can be performed from the societal perspective.

## ***Introduction***

One can anticipate that personal circumstances and the subjective enjoyment of sex moderate the impact of erectile dysfunction on quality of life. This may not only be true for patients with erectile dysfunction, but also for the general public when valuing the effects of medical interventions which improve erectile functioning. In this investigation we assess the impact of background variables on elicited values of both patients and the general public given to health states of erectile dysfunction, in order to determine whose values should be used in an economic evaluation of treatments for erectile dysfunction.

In economic evaluation of health care the preferred perspective is the societal.<sup>1</sup> Bearing the costs for an accessible health care system is seen as a societal responsibility. Consequently, insurance characteristics dominate the financing structure of health care.<sup>2</sup> The societal responsibility for an accessible health care system relieves the patient of the responsibility to pay the bill; typically, the general public pays most costs. Given that the general public pays the bulk of the costs in health care, not only patients' preferences should count when allocating resources in health care, but also the preferences of the general public which consists of possible future patients. It can even be argued that the preferences of the general public are more suitable than the preferences of patients are, because preferences change after the occurrence of a negative event (such as suffering from a disease). This is not in line with the insurance characteristics of the health care market. For that reason, health economists have strong preferences to measure the effects of health care by the values of the general public.<sup>3</sup>

In health economics the preferences of the general public are preferably measured in terms of Quality Adjusted Life Years (QALYs).<sup>1</sup> In a QALY-analysis a single outcome measure is created to allow for comparisons across different health care interventions. Morbidity and mortality are being combined in QALYs by correcting the remaining life years for the quality of life. This correction factor is often called the 'utility' of the health state. In line with the societal perspective and the insurance principle, this utility preferably reflects the value that the general public attributes to the quality of life a health state. Thus, if one wants to make an economic evaluation in terms of QALYs, one has to know the values of the general public for the health states under examination.

A major drawback in the assessment of the benefits of health care by the general public is that they lack the experiences of patients. In the societal perspective, the values of the

general public are only valid when the general public is “well-informed”.<sup>3</sup> This may be a problem when the general public is unaware of the patients suffering from a disease and subsequently of the consequences of this disease on the quality of life. Erectile dysfunction may be such disease, given the hidden suffering of the patients. When one can doubt the awareness within the general public, it may be informative to compare the values of the general public with values given by the patients. These patients’ values have a meaning on their own: they represent the values from a “patient perspective”, also called the “clinical perspective”. As argued before these values differ from societal values because values of patients do not refer to the costs of treatment. For that reason patients’ values are not suitable for appraising the effects of health care interventions. Nevertheless, the patients’ values could be of use in economic appraisal; knowledge about what constitutes the differences between patients’ values and values of the general public is building, hence patients’ values could be used to assess the validity of the values of the general public. Below it is discussed which elements constitute values for health states.

From an economic point of view and given the insurance principle, the patient is often characterised as acting according to rational strategies in order to maximise his or her own benefit. From this perspective it is predicted that patients will find any treatment worth trying, because they do not bear the costs. Therefore, health economists have argued that patients’ values suffer from a “strategic bias”: patients will respond in such a way, that the cost-effectiveness of the intervention would be favourable: “... [The difference in values between the general public and patients are] ... *quite consistent with the action of voluntary health organizations and other special interest groups who seek to influence governments to expand specific treatment programs*.”<sup>4</sup>, page 703 In the present situation, this would mean that patients would value the health of erectile dysfunction low, so that the cure would result in a great benefit.

Although this strategic bias is still one of the main motivations for the use values of the general public, it is nowadays recognised that patients values are perhaps more influenced by coping or adaptation mechanisms than by strategic motivations.<sup>5, 6</sup> Adaptation can be described as a process of interpreting past, present and future circumstances such that an acceptable level of well-being is achieved.<sup>7</sup> In general, patients tend to value the quality of life of their own health states higher than the general public. This is most strongly applies to chronic health states; as soon a patient is cured, the value given to the prior chronic health states (thus retrospectively) drops

dramatically.<sup>8, 9, 10</sup> These lower values can be explained by the loss of the necessity of the adaptation process to maintain a certain level of emotional well-being. It is likely that patient populations in a trial will reflect such post-treatment preferences, as soon as they anticipate an effective solution for their health problem.

Besides strategic bias and adaptation, values for health states are also influenced by factors related to the subjective way in which health is experienced. Besides making differences between patients' values and values of the general public, one can also look at the possibility that subgroups within the patients or the general public have different values. If the differences are substantial and meaningful from a policy perspective, Gold, Patrick & Torrance et al. (1996, page 102) advice to consider different cost-effectiveness analyses for these subgroups.

The remark above applies to both the patient perspective and the societal perspective. Different patients groups may have different values. This might for instance also be the case in erectile dysfunction, given the subjective nature of the enjoyment of sex. Hence, it may well be that some patients with erectile dysfunction may not experience their erectile dysfunction as a (big) problem, whereas others do. This might lead to "clinical selection bias": because erectile dysfunction has been a taboo subject for a long time, this suggests that patients who do not find erectile dysfunction a big health problem will not present themselves to a doctor. Therefore our sample of patients may not be representative for all patients with erectile dysfunction, as the patients who do not perceive erectile dysfunction as a problem, will not be present in this or study. It can be expected that the patients in this investigation will give relatively low values to health states associated with erectile dysfunction. This clinical selection bias may even be enhanced if the patients use these preferences to express their motivation to participate in a clinical trial. For this reason, the values of health states given by patients in clinical trials, can expected to be lower than the average within the whole patient group.

Within the general public there might also exist subgroups whose values are systematically different. Expected differences in the values for erectile dysfunction may occur between groups that differ in general demographic background variables such as age. For instance it may be expected that older subjects are less interested in sex than young subjects.<sup>11, 12, 13</sup> Another variable may be gender, for two reasons. First of all, women may have a different attitude towards health states related to sexual functioning. Secondly, they may have difficulties to imagine the problems associated with erectile dysfunction. Other background variables that could influence values for erectile

dysfunction are (for obvious reasons): availability of a partner, having children, sexual activity and sexual satisfaction.

In order to determine whose values should be used in an economic evaluation of erectile dysfunction, we applied the theory described above to the values of patients and the general public for erectile dysfunction. To that end we examined which variables constitute the values for erectile dysfunction. First we explored the relationship between the values of patients and the general public for health states of erectile dysfunction. We expected the values of the patients to be higher when coping mechanisms are dominant. The values of patients will be lower if: 1) the patients attribute values in a strategic way; 2) the awareness of the problems in the general public is low; or 3) the group of patients is a specific subgroup of patients for who sex is more important than it is on average in the general population. Furthermore we explored whether other background variables such as age, gender, availability of a partner, having children, sexual activity and sexual satisfaction are related to the value of health states of erectile dysfunction.

## ***Methods***

### *Respondents*

We interviewed patients with erectile dysfunction patients and a sample of the general public to value the health states related to erectile dysfunction.

Patients were recruited in two hospitals that participated in a phase 4 clinical trial of Viagra: the University Hospital St. Radboud in Nijmegen and the St. Antoniushove Hospital of Leidschendam. Both hospitals included 75 patients. From a random sample of the telephone directory we recruited a sample of the general public. The sampling was based on quota sampling, and stratified on the basis of sex, age and education. In this process, we especially aimed at recruiting a substantial sample of the men aged 40-70 years, because this group is the target group of health care interventions concerning erectile dysfunction. The results would be weighted, if 1) substantial difference in gender and age between the sample and the national statistics occurred, and 2) gender and age were indeed related to the dependent variable of this investigation, namely the value attached to health states of erectile dysfunction.

Respondents of the general public were not notified in advance that the health problem being examined was erectile dysfunction. Instead the study objective was described as the valuation of health states. The subjects were invited at the University. They were paid NLG 30,- (about 14,- Euro) and got a refund of their travelling expenses.

### *International Index of Erectile Function*

The health state descriptions that had to be valued were based on question 3, 4 and 7 of the International Index of Erectile Function (IIEF). This is a 15 item questionnaire to assess sexual functioning.<sup>14</sup> Use of this questionnaire is advisable, for several reasons: it is valid and psychometrically sound, it can be used across different cultures and it contains the two primary end points of erectile dysfunction treatment as defined by the National Institutes of Health.<sup>15</sup>

*Figure 1: Question 3, 4 and 7 of the IIEF*

IIEF Question 3	IIEF Question 4	IIEF Question 7	Response level
<i>During the past 4 weeks, how often were you able to penetrate?</i>	<i>During the past 4 weeks, how often were you able to maintain the erection?</i>	<i>When you attempted sexual intercourse, how often was it satisfactory for you?</i>	
Almost never or never	Almost never or never	Almost never or never	1
A few times	A few times	A few times	2
Sometimes	Sometimes	Sometimes	3
Most times	Most times	Most times	4
Almost always or always	Almost always or always	Almost always or always	5

The IIEF has been used in the clinical trial in which the efficacy of Viagra was demonstrated.<sup>16</sup> The primary end points in this clinical trial were also question 3 and 4, thus the same questions as used in this investigation. These items deal with the ability to penetrate and the ability to maintain the erection after penetration. By addressing the ability to attain and maintain an erection separately, the IIEF has the sensitivity and specificity to detect treatment-related changes in patients with erectile dysfunction.<sup>14</sup> Because these two primary end points have each five response levels, they define (5 x 5) 25 unique health states (Figure 1). Question 7 is about the satisfaction of the intercourse in general, without making a direct reference to erectile functioning (figure 2). The 4 health states as defined by question 7 were valued independently. The subject valued the total of 28 health states using “time trade-off”. The best health state (no erectile dysfunction) was not valued, because normal health is a reference point in TTO.

### *Valuation method (TTO)*

Time trade-off (TTO) is, next to standard gamble, one of the preferred valuation methods in health economics that are used to determine the values or “utilities” of health states. The methodology of this interview technique is described in detail in Drummond, O'Brien & Stoddart et al. (1997). Based on this standard work, one has to make some methodological choices to be able to operationalise the method for the specific research question. These methodological choices are motivated below.

### *Hypothetical health states*

As usual in this kind of valuation tasks, the subjects had to value the health states “for a person like themselves”. Thus the subjects had to imagine that they had an erectile dysfunction as described by the 28 health states. That means that older subjects gave values from an ageing perspective, while persons without a sexual active partner, could incorporate this circumstance in the values given. The only exception was gender: women had to imagine that they were men with erectile dysfunction.

The health states of erectile dysfunction were assumed to be chronically. This means that the subjects had to assume that they were in the health states for the rest of their lives, other things being equal to their own present and future situation.

The trade-off in time was measured relative to the life expectancy of the subjects. The subjects had to assume that they would reach their life expectancy in “normal health for that age”.

### *Response mode*

The health states were presented on cards in random order. Subjects were allowed to reshuffle the cards. They were also allowed to go back to a former response, if they had changed their mind during the interview. Because of the large number of states that had to be valued and because of the intimacy of the subject, it was chosen to let the respondent record the answers on an answer form instead of letting the interviewer record the responses. The cards had numbers that corresponded to the answer form. The answer forms consisted of lines representing the life-span of the respondent. The respondents indicated on this line the so called “indifference point”. This point indicates no preference for as much shorter as indicated on the line in full health or living their complete life span in the health state described on the card. This adaptation of the TTO administration was based on the work of Bleichrodt & Johannesson.<sup>17, 18</sup>



### *Interview protocol*

The interview protocols for the patients and the people of the general public were designed to be as similar as possible. One of the differences was that the general public was interviewed during a group session, while the patients were interviewed individually. Prior to this investigation, the results of group sessions were compared with individual session. In that investigation, no relevant differences in the values of the health states were found between the two modes of administration. Details about this investigation are described in appendix A of this report.<sup>19</sup>

### *General instruction concerning valuing health states*

Both protocols began with a general introduction after which the subjects practiced TTO using the health state “sitting in a wheelchair” as an example. During the group sessions, this health states was valued by a volunteer from the group, and had the form of an individual administration of TTO, using the “ping-pong interview technique”. After this example, the group was invited to discuss the results and was encouraged to ask questions about the procedure if they did not fully understand the task. In both the individual TTO and the TTO in groups, we tested the ability to perform the task by valuing 3 generic EuroQol EQ-5D health states (states 11211, 11122 and 21232) with TTO.<sup>20</sup> In both situations the answers were checked and discussed as indicated by the standard instruction for TTO.<sup>1</sup> If there were signs of misinterpretation, the protocol was explained again. In the groups sessions these checks and additional explanations were done on an individual basis.

### *Specific instructions concerning erectile dysfunction*

After practicing with the 3 EuroQol EQ-5D states, the members of the general public was introduced into the health problems associated with erectile dysfunction. This introduction was skipped in patients. Female subjects of the general public were asked to put themselves in the position of men, when valuing the problems associated with erectile dysfunction.

After this introduction, the subjects were asked to value the health states of erectile dysfunction with the use of TTO. It was explained that some health states may appear illogical, for instance “almost never being able to penetrated, but always able to maintain the erection after penetration”. Although these health states may seem odd, patients with

erectile dysfunction classify themselves in these states.<sup>21</sup> Therefore, the subjects were encouraged to value these states too.

#### *The valuation process*

During the validation of the health states of erectile dysfunction, the interviewer checked the responses. If there were any signs of misinterpretation, the subjects were interviewed on an individual basis, until the subject could perform the task independently. For this reason, if there were more than 6 subject in the group session, the interviewer was assisted with one or two fellow researchers.

#### *Background variables*

After the valuation task the members of the general public filled in questions about the availability of a partner, age, having children, the frequency of intercourse and the satisfaction of the intercourse in general without making a direct reference to erectile functioning (question 7 of the IIEF).

#### *Invalid responses*

Some subjects did not make any trade-off during the administration of the three EuroQol health states, even with the worse state (21232). This could mean that they still did not understand the task. It could also mean that the respondent was a so called "lexicographic responder". This means that when a respondent is faced with an option, he or she will always choose for one particular alternative, no matter how favourable the other might be. In both cases the responses on time trade-off questions become meaningless. When the interviewer observed such response, both options were checked. If the respondent still did not understand the task, the task was explained again. If the responder seemed to act in a lexicographic way, an even more extreme health state was proposed. If the subject maintained in his or her lexicographic response mode, or when it was not feasible to explain the task, the responses of the subject were excluded. Note that the exclusion of lexicographic responses was only based on the responses on the EuroQol health states and not on the responses on the health states of erectile dysfunction. If a respondent did not make any trade-off in case of the health associated with erectile dysfunction, the responses were judged to be valid, as long as the subject made a trade-off on the EuroQol states, and it was clear that the respondent

understood the task. Responses were also excluded when a respondent traded off more life years than he or she had left and when the respondent has more than 4 missing values in the assessment of the 28 health states.

### *Analysis*

Differences between subject groups and background characteristics were tested using MANOVA repeated measure analyses. In these analyses the differences between subjects were entered as 'between subject' variables.

Besides testing the overall effect, we also examined the interactions of the between subjects variables and the factor structure of the valuation space as defined by question 3 & 4 of the IIEF. For instance if women found that the response levels of question 3 were more important than those of question 4, then we would check if this preference also is present in the data of the male subjects. For this purpose, question 3 & 4 were labelled as two 'within subjects' factors in the repeated measure MANOVA. A similar factor structure should result in small or non-significant interaction effects between the subgroups and the two 'within subjects' factors (question 3 and 4).

### **Results**

#### Respondents

Of the 150 patients in the clinical trial, 106 were interviewed. Most of the patients who were not interviewed, had already stopped the phase 4 trial before we were able to interview them. Most of them stopped because they did not experience a substantial effect of Viagra. In the 106 interviews, we collected 93 valid responses (88%). Forty of them were interviewed at the University Hospital St. Radboud in Nijmegen and 64 at the St. Antoniushove Hospital of Leidschendam. The mean age of these patients was 56.71 (SD 11.39) year.

We interviewed 169 subjects of the general public. The responses were valid in 148 subjects of the general public (88%). Most exclusion (48%) was based on the second criterion: no trade-off for any of the EuroQol states. The mean age of subjects of the general public with valid responses was 45.52 years (SD 15.24). Age was a predictor of

the validity of responses: half of the respondents older than 70 years gave invalid responses.

Table 1 describes the sample of the general public. The oversampling of male respondents between 40 and 70 years was not as successful as hoped for. We hoped for an over sampling of 100%, but we only succeeded to oversample this group with about 30%. This resulted in a sample in which the gender distribution is close to expected, but the distribution over age is somewhat different from the distribution in the general population according to the national statistics.<sup>22</sup>

*Table 1: Representativeness of sample of the general population with valid responses*

Age group	Males		Females		Total		Reference
	N	%	N	%	N	%	%
18 to 39	24	45.3	29	54.7	53	35.8	42.0
40 to 54	25	55.6	20	44.4	45	30.4	24.0
55 to 70	28	58.3	20	41.7	48	32.4	21.0
71 to 79	1				1	0.70	8.5
>79	0		1		1	0.70	4.0
Total	78	100.0	70	100.0	148	100.0	100.0

### Differences between patients' values and values of the general public

Both patients and the general public considered erectile dysfunction to have a substantial effect on quality of life. For the 24 erectile dysfunction states defined by IIEF question 3 and 4, the values of the public range from 0.74 to 0.93, while values of patients range from 0.68 to 0.91 (see Table 2). The mean difference between patients' values and values of the general public is 0.06 ( $p < .000$ ). The values for question 7 range from 0.75 to 0.95 in the general public and from 0.68 to 0.91 in patients.

The repeated measure analysis showed that both patients' values and values of the general public had the same factor structure given the valuation space as defined by question 3 & 4 of the IIEF ( $p \geq 0.10$ ). That is to say, there was no significant interaction between the 'within subjects' variables (question 3 & 4) and the 'between subjects' variables (patients versus general public).

In the general public, all but one of the main effects and interactions effects showed a statistical significant relation with the values given to health states of erectile dysfunction. The exception was that subjects with children gave higher values to the health states ( $p$

= 0.009). In other words: subjects with children considered erectile dysfunction less a problem than subjects without children did.

Table 2: Values of patients and the general public for erectile dysfunction

The International Index of Erectile Function (IIEFF)		General public (N=123)		Patients (N=93)	
Question 3	question 4	Mean	SD	Mean	SD
never	never	0.74	0.18	0.68	0.26
	a few times	0.77	0.17	0.70	0.26
	Sometimes	0.79	0.16	0.71	0.25
	most times	0.80	0.16	0.73	0.24
	Always	0.82	0.16	0.74	0.25
a few times	never	0.80	0.16	0.73	0.25
	a few times	0.83	0.15	0.76	0.24
	Sometimes	0.85	0.13	0.78	0.22
	most times	0.86	0.14	0.80	0.23
Sometimes	Always	0.87	0.14	0.81	0.22
	never	0.81	0.15	0.75	0.22
	a few times	0.85	0.16	0.79	0.22
	Sometimes	0.86	0.14	0.81	0.23
most times	most times	0.88	0.14	0.85	0.21
	Always	0.91	0.13	0.85	0.18
	never	0.82	0.15	0.77	0.24
	a few times	0.86	0.15	0.81	0.22
Always	Sometimes	0.90	0.13	0.84	0.19
	most times	0.94	0.12	0.91	0.16
	Always	0.94	0.12	0.91	0.17
	never	0.84	0.15	0.79	0.22
IIEF question 7	a few times	0.89	0.14	0.84	0.20
	Sometimes	0.91	0.13	0.87	0.18
	most times	0.93	0.13	0.91	0.16
	Always	1.00	0.12	1.00	0.17
	never	0.75	0.18	0.68	0.25
	a few times	0.83	0.16	0.77	0.25
	Sometimes	0.88	0.14	0.85	0.20
	most times	0.95	0.11	0.91	0.15
	Always	1.00	0.12	1.00	0.17

## Discussion

Our results show that both patients and the general public consider erectile dysfunction to have a substantial impact on quality of life. The values given by patients to health states of erectile dysfunction were lower than those of the general public, but the factor structure of the valuation space was the same in patients and the general public. Within the general public, values were not related to age, gender, the availability of a partner, sexual activity and sexual satisfaction. Only one background variable seems to have a relation with the values given: subjects with children gave higher values. The factor structure of the valuation space was not influenced by the other background variables mentioned.

With respect to background variables, it is noted that the sample of the general public was not completely representative in terms of the distribution of age categories. However

we did not need to stratify the results for this observation, because age did not have significant influence on the values of the health states. We did not present the influence of the background variables in patients. Given the homogeneous composition of this group in terms of the background variables, we did not expect that the power would be strong enough to detect any influence. We indeed could not detect any significant relation in the patient population.

We analysed our to determine whether it is possible to use values of the general public in the utility assessment of erectile dysfunction. The validity of these values could be doubted, because of the subjective nature of sexual functioning and because of the fact that the general public might be unaware of the effects that erectile dysfunction has on quality of life. In order to test the validity we therefore analysed the sensitivity of the values for background characteristics and we compared the values of the general public with those of patients. Our results were remarkable.

First of all it was surprising that the values attributed to erectile dysfunction are robust for the influence of social economic variables. Although these results may have been anticipated on the basis of the literature<sup>3, 24</sup>, it is still surprising to see that this also holds for something as subjective as sexual functioning. After all, these results suggest that there is a high level of public agreement about the importance of treating erectile dysfunction. However, the importance of sexual activity has been a taboo subject for a long time. Can these findings be explained?

A stereotype assumption is that older people are less interested in sex than younger people. However, this was not observed in the values for the erectile dysfunction. Of course, it could be that the power of our design was too low to pick up the differences. However we did pick up the difference between patients and the general public, and the power was enough to pick up the difference between respondents who had children and those without. Therefore, our results seem to suggest that the stereotype assumption about declining interest in sex with age may not be as obvious as anticipated. Nevertheless, our results seem to be in line with other studies.

Although studies show that sexual activity decreases with age, research also shows that current physical and social factors play an overriding role in interest in and frequency of sexual intercourse: having mobility problems was found to be highly correlated to lack of sexual activity, as was marital status.<sup>11, 25</sup> Richardson et al. examine reasons for ending sexual activity: 30% of the respondents reported lack of a partner. Poor health was cited by 19 % of both men and women as the reason they ended sexual activity: 15% of the

men reported inability to perform as a reason. For women the second most reported reason was lack of interest: 28%.<sup>12</sup> In populations older than 60 years, about 60% of the men are sexually active and 30% of the women.<sup>11, 12, 25</sup> Marsiglio et al. show that in a population of 76 years and over, 26% is sexually active.<sup>13</sup>

We also expected differences in values of men and women. Remarkably was the finding that women seemed to use the same value system as the male subjects did. This could be explained because we explicitly asked the female subjects picture themselves as men, and to value the health states of erectile dysfunction from that perspective. An alternative explanation for our findings could be that women are well aware of the value system of men, and they are capable to respond like men when asked to. It could also mean that men and women have the same value system for sexual functioning.

Furthermore, we expected that characteristics about someone's sexual engagements would influence his or her values for erectile dysfunction. We expected that the people would value the health states of erectile dysfunction to be less severe when they had no partner or when they would not have intercourse or only on rare occasions. We expected the same for subjects with a low satisfaction of their intercourse. We hypothesised that the responses of these subject would show signs of adaptation or coping. This would result in higher values for the health states of erectile dysfunction. Much to our surprise this assumption could not be confirmed in the data analysis. There may be several explanations for this observation.

For instance, it could be noted that erectile dysfunction not only disturbs the sexual relationship with the partner. A man with erectile dysfunction can not achieve any erection at all, thus the patient is not capable of getting an erection during any sexual activity, including intercourse, but also caressing, foreplay, masturbation and other sexual stimulation. Therefore, not only the ability to have sexual intercourse is limited, but also the ability to be involved in other satisfactory sexual activity. Another explanation is that people without a sexual active partner anticipate to the time when a sexual partner will be present. In order words, people have a strong believe that things will change for the best, and therefore they do not adapt to their illness as patients with chronic diseases do. It is also possible that erectile dysfunction is seen as a handicap in getting a partner. Therefore erectile functioning may be even more important for a man without a partner than for a man who has a long standing relation.

Nevertheless, the fact that erectile dysfunction is considered generally an important health problem could be found surprising in itself. In this respect, our results could be

reflecting a social change. Given that the importance of sexual activity has been a taboo subject and that no non-invasive therapy was available, men did not come out with their problem. This veiled the magnitude of the problem. The availability of a non-invasive medicine for erectile dysfunction, could have give cause to this change. The media attention for Viagra, has made the public aware of the incidence and prevalence of this problem, which in turn could have made patients less ashamed of their problem.

Another remarkable finding was that the values of the general public were higher than values of patients. In most research this is the other way around.<sup>3</sup> This could mean that the awareness of the problems of erectile dysfunction in the general public is low. However, the values found in this investigation are in line with an investigation of the World Health Organization (WHO). As part of the “Global Burden of Disease Project” a panel of “health workers” valued erectile dysfunction.<sup>23</sup> This panel valued the decrease in quality of life caused by erectile dysfunction on a utility scale between 12 and 24%. Furthermore, the similar factor structure in values of patients and of the general public suggest that the general public used the same value system as patients did. This means that in this case the clinical selection bias and the strategic bias are dominant over adaptation in the patients’ values. As explained in the introduction, this could be expected in a situation in which patients participate in a trial with an effective intervention.

In sum, we conclude that the values of the general public can be validly used in economic evaluation of treatments for erectile dysfunction. It could be argues that the general public still is not enough aware of the problems caused by erectile dysfunction, becavuse patient give lower values. However, then the values of the general public will give a conservative estimate of health care interventions in patients with erectile dysfunction.

An important implication of this study is that we can use the IIEF as a utility measurement for the assessment of intervention in erectile dysfunction, based on the values given in table 2. These utilities can be used to estimate QALYs. When the values of the general public are used, these QALY-analyses will be ideal for the use in economic appraisal of health care interventions. When the values of the patients are used, the utilities are suitable for clinical decision analysis. Note that the values of question 7 can also be used for interventions which involve other aspects of sexual functioning than erectile dysfunction. The values could even be used for health care interventions exclusive for women.



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