Diplôme en Economie et Administration de la Santé
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Eliciting Educated Preferences of Health Care Professionals

Cost-effectiveness and cost-benefit analysis

of Amphotericine B

Travail de mémoire de fin d'étude
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1. Introduction

Health care expenses are steadily increasing since the 60's. Advances in technology and treatment options have broadened since then, and life expectancy has risen substantially in the industrialised world.
Formerly rapidly fatal diseases like leukaemia and lymphoma are today treatable illnesses with the hope of long-term survival.

The usual treatment options for haemato-oncological diseases now include high dose chemiotherapy and bone marrow transplantation. These very aggressive treatments are not without important side effects, some of them life-threatening.

Systemic fungal infections are one of these feared complications. Treatment options for serious infections in the immunocompromised host are still very limited and not free from additional side effects.

A new generation of antifungal drugs recently entered the market with a lower side effect profile but also a much higher cost. In Switzerland the new liposomal Amphotericines did not obtain authorisation for reimbursement by health insurance companies, and if prescribed, are paid entirely by the hospital budget.

This particular situation, like many similar others, occurs at a time when hospital budgets are limited and not extensible any more. Therefore, choices need to be made on how to allocate these rare resources.

At our University Hospital, global budget put a major constraint on all departments and services. In this context, it happened that the division of infectious diseases experienced for several years important deficits in their drug budget, due to the use of systemic antifungal drugs.

Agreeing with the recommendation of federal authorities, new diagnostic and therapeutic procedures have to undergo a medical and economic evaluation process in our institution.

For this purpose, a cost-effectiveness analysis has been performed, in order to establish a valid policy about the use of available antifungal drugs.

The extraordinary price difference between the two drug formulations is not compensated by a difference in efficiency, but is justified by the pharmaceutical industry mainly because of a different side effect profile. Modulation of the incidence of side effects of the old drug was recently shown to be possible

The discussions we had with the medical and nursing team during the cost-effectiveness evaluation showed that they had clear drug preferences. We were therefore interested in investigating the problem of drug preferences and their impact on drug choices.

The best-established method for this purpose is the contingent valuation method, which uses the willingness to pay to elicit preferences in monetary terms. This economically sound method has been used mainly in areas others than health care, due to the obvious difficulty to value health in monetary terms. Despite this ancestral reticence, this method is attracting growing interest in the actual financial health care crisis.

In a pilot study we used the willingness to pay method to show the possibilities and limits of this method as a tool for evaluating educated preferences of health care professionals.

This study will, after an introductory part, present both the cost-effectiveness analysis and the cost-benefit analysis, which was based on the results of the previous study.

1.1 Local conditions

The University Hospital of Lausanne has a triple mission: it is a regional hospital for the city of Lausanne and a population of 300'000 inhabitants. It is also a secondary centre for the whole Canton including approximately 600'000 inhabitants; and it is a tertiary centre and a teaching hospital for the French speaking part of Switzerland for several health care professions, including doctors, nurses, physiotherapists, laboratory technicians and others (1).

This broad mission is reflected in the size of the hospital and its staff and equipment. (Annexe 1). The almost 800 beds show constantly a very high occupancy, especially in the medical specialties. (Annexe 2)

1.1.2 Hospital data

The 4000 employees of the hospital are state employees. The university hospital is the biggest employer in the canton and includes a great variety of professions. Employees from more than 100 different nations are working in the institutions. The turnover can be very high in some sectors, for example in the nursing field. Medical residents have very often a short-term contract for training, which explains the high rotation rate amongst them.

1.1.3 Hospital budget

The hospital budget is a fixed state subsidy of approximately about 50 % of the expenses, the other 50% being covered by the insurance companies. Every division has its own fixed envelope for running costs.

The pharmacy budget is likewise allocated to each division, service or department. It is important to mention, that neither the hospital administrative data, not the medical records do allow, to identify a single patient's drug consumption and expenses.

1.1.4 Haematological oncological diseases

The **incidence** of acute lymphoblastic and myeloblastic leukaemia is about 5-6 cases per 100'000 inhabitants per year. The disease consists in a monoclonal proliferation of early bone marrow cells with consequently disturbed production of all blood components. Patients are diagnosed very often with a bleeding disorder and an infection and are severely ill at admission. The immediate treatment of a newly diagnosed leukaemia is a medical emergency. The induction treatment aims at reducing the number of leukaemic cells and restoring the normal blood functions (2). After the induction treatment, according to the response to the first line therapy, patients receive another cycle of high dose chemotherapy, which is, in some indications, followed by bone marrow transplantation. The whole treatment from diagnosis to consolidation therapy can take as long as 2 years and sometimes even longer.

1.1.5 Complications during the treatment of hematological malignancies

The treatment of acute leukaemia is frequently associated with complications. The incidence of minor complications, like digestive disorders, anaemia and low grade fever are higher than 60%. Severe complications occur mainly during the phase of neutropenia. The risk increases in proportion with the length of neutropenia, which is in the case of acute leukaemia up to 20-30 days. High grade fever occurs in about 40% of the cases (2). The underlying cause is therefore extensively investigated, but the bacterial or fungal origin can be clearly diagnosed only in a small proportion of cases.

1.1.6 Leukemia treatment in the Infectious Diseases Unit

The Infectious Diseases Division is an isolation unit for respiratory, infectious or high risk diseases requiring isolation of the patient. Each of 13 single rooms is equipped with laminar flow and sas. The medical staff on this ward is composed of 2 residents, 16.1 FTE nurses and 3.9 FTE nursing aids.

Patients with haematological malignancies are the biggest patient population in this unit, with the longest hospital stay (Table 1).

Due to this particular patient population, the unit has developed a strong interrelationship with the division of Haematology. Patients are followed by both divisions on a regular basis. The residents are supervised by a senior fellow and by an attending doctor of both specialties.

Table 1
The Infectious Disease Unit

	1996	**1997**	**1998**	**1999**
Number of patients	241	223	259	256
Number of hospitalisation days	4'200	4'296	4'552	4'785
Occupancy (%)	82.0	84.1	89.1	93.6
Medium length of stay (days)	17.4	19.3	17.6	18.7
Number of Patients in isolation (protective)	**202**	**176**	**194**	**188**
Patients with hematological malignancies		**131**	**158**	**146**
from which				
• high dose chemiotherapy with autologous BMT		35	40	41
• from Geneva		13	19	15
• for leucopheresis		0	9	5
Patients with solid tumours		**42**	**36**	**36**
Number of hospitalisation days	3'706	3'874	3'760	3'880
Medium length of stay(days)	14.8	11.12	14.83	18.56
Patients hosted from the Department of Internal Medicine	**13**	**11**	**35**	**45**
Number of hospitalisation days	107	55	364	441
Medium length of stay (days)	8.2	5	10.4	9.8

2. Cost-Effectiveness analysis

Cost-effectiveness analysis is the most widely used pharmacoeconomic analysis in the medical literature. It compares clinical efficacy and costs of different alternative strategies. Because all cost effectiveness analyses are comparative, the cost and clinical outcome of health care technology must be compared to those associated with an alternative strategy for treating the same group of patients.

2.1 Aim of the study

In this study, we foresee to establish the cost and effectiveness of all available treatment options in case of suspected or diagnosed disseminated fungal infections in patients with neutropenic fever not responsive to broad-spectrum antibiotics, after high dose chemotherapy for leukaemia with or without autologous bone marrow transplantation.

2.2 Methods

2.2.1 Effectiveness measurements

- Description of available treatment options and their side effects.
- Literature review with the elements to define the effectiveness of the drugs in the case of suspected or proven fungal infection in the neutropenic host.
- A ten years review of the leukaemia patients in the CHUV (3,4)

2.2.2 Cost analysis

- The cost analysis takes the standpoint of the hospital finances.
- We determine the drug budget for the institution and different departments
- Main cost analysis is based on the acquisition costs of all available drugs.
- The analysis focuses on direct cost and is not considering indirect costs or intangible costs

2.3 Sensitivity analysis

2.3.1 Simulation of one drug costs

- Simulation of financial impact of one drug use on the drug budget

2.3.2 Simulation of variation in patient population

- Financial impact of increasing patient population on the drug budget

2.3.3 Data sources

- Medical literature is available through the hospital electronic library (medline).
- Medical records are taken into account in the 10 year analysis.
- Hospital pharmacy for drug data.
- Administrative data for admission and discharge data and diagnostic codes as well as the overall consumption of diagnostic tests and costs of care (nursing and physiotherapy, etc.).

3. Results

3.1 Literature review

Patients undergoing high dose chemotherapy experience a period of neutropenia and profoundly reduced immune functions. During this period they are at risk of developing any kind of infectious complications. The risk increases with the length of neutropenia and presents with fever, which is treated readily with broad spectrum antibiotics A fungal infection occurs in about 30 % of patients in neutropenia the mortality reaches 40-80% (5). The most common fungal infections are due to Candida albicans, the most invasive to Aspergillus fumigatus. Unfortunately, it is difficult to cultivate and isolate these infectious agents. In most of the cases the presumed diagnosis is based on a strong clinical suspicion. The treatment of fungal infections in neutropenic patients is therefore a real challenge for physicians.

In the following analysis we will use the commercial names for clarity purpose in distinguishing between the three formulations of Amphotericine.

3.1.1 Available drugs

Fungizone is the treatment of choice in suspected and proven systemic fungal infections since almost 40 years. The standard dose of Fungizone (0.6-1.25mg/kg/d) is administered over a 4-6 hour period. It is very a well established drug despite the fact that the majority of patients (79%) experience reactions while receiving the drug (6) from which 44% are due to Fungizone.

Abelcet is the first drug of the new generation of Amphotericins. It is described as a lipid complex. The appropriate dose varies between 3mg/kg/d and 5mg/kg/d given over several hours. No definite evidence in the literature favours either the higher or the lower dose. Abelcet has been extensively studied during the past decade.

Ambisome was the last drug to enter the market and is the only drug which is a true liposomal formulation. Many comparative studies with Fungizone have been undertaken mainly to compare their toxicities. The usual dose of Ambisome varies between 1mg/kg to 5mg/kg. The most used dosage is 3mg/kg. (6,7).

3.1.2 Effectivness

Effectiveness measures in antibiotic resistant neutropenic fever can be defined as:

- Survival of treatment and discharge alive
- Fever reduction despite neutropenia
- Absence of breakthrough fungal infections

The definition of effectiveness in the empirical treatment of febrile neutropenia is already a difficult task. Effectiveness indicators used in the literature are very different from each other and cannot be directly compared. A comparative study (8) between Fungizone and Ambisome showed a success rate of 50,1% for Ambisome and 49,4% for Fungizone. Fever reduction and reversed neutropenia were observed in both treatment groups in 58% of the cases.

The absence of systemic fungal infections could be confirmed in 90% of the cases; 85,7% of the patients could continue their treatment without delays in the Ambisome group and 81,4% in the Fungizone group.

Based on this study and others not to in this analysis, it can be concluded that both drugs can be considered as equally effective in treating suspected fungal infections in febrile neutropenic patients.

3.1.3 Toxicity

The toxicity can be measured in general symptoms and organ specific toxicities:

- Acute, infusion related toxicity, general symptoms (Chills, fever)
- Organ specific toxicity (Nephrotoxicity)
- Treatment interruption for toxic reasons

- Treatment switch for toxic side effects

As toxicity is the major criterion distinguishing the three drugs, a separate description will be provided of this aspect has been made for clarity.

The toxicity in the original and liposomal forms is essentially acute or perfusion related. It consists in chills, fever, hypotension, nausea and vomiting in decreasing order of frequency. These acute reactions abate for unknown reasons over the treatment course. Increasing with the length of treatment is nephrotoxicity, which is not perceived by the patient.

Fungizone treatment causes acute perfusion related side effects in 79% of the cases (renal function impairment) from which 44% are due to the drug (6). Hypotension might occur and mandates vital signs to be controlled frequently during the perfusion (9). Elevated creatinine levels are observed in different ranges in 50-80 % of the patients (8). This effect is dose related and occurs mainly after the 15th treatment day, or after a cumulative dose of 2000mg of Fungizone.

The renal toxicity is in general transient and reversible after stopping the drug administration. Only 6% of the patients presented a severe renal failure, if several pre-existing renal risk factors associated (other nephrotoxic drugs like cisplatine, and cyclosporine or pre-treatment renal impairment) (9). Renal acidosis and important potassium loss can complicate the treatment with Fungizone in 38% of the cases (10). Acute as well as cumulative side effects can be controlled up to a certain degree with an adequate premedication and hydration.

An important reduction of all side effects seems possible by extending the infusion time from 4 hours to 24 hours, as recently shown (11). This randomised study compared the acute and cumulative side effects in 67 patients. Patients receiving the 24 hours perfusion presented significantly less toxic side effects such as shivering ($p=0.0006$), and vomiting ($p=0.0037$). The perfusion or the treatment was significantly less often interrupted ($p=0.0001$) in the 24 hours infusion group. The 4 hours infusion group presented more frequently renal impairment, defined as a reduction of 25% in the creatinine clearance.

Abelcet has a small rate of minor effects, like chills, tachycardia and fever (6). Some rare cases of severe bronchospasms were described (12). At the usual doses the nephrotoxic effect was mild.

Ambisome is known for its low acute and cumulative toxicity. Infusion related fever occurs only in 9% of the cases, and only in case of high dosage (5mg/kg/d) (13).

3.2 Ten years review of antifungal drug use and outcome in the Infectious Disease Unit

A recent poster presented by A.K. Lapointe (4) reviewed the last ten years of antifungal treatment in the isolation unit. Table 2 shows the patient characteristics during this period. This table confirms that the great majority of patients who developed neutropenic episodes and were at risk for developing infectious complications were suffering from acute leukaemia. High dose chemotherapy led to the greatest risk for fungal infections.

Table 2

Patient characteristics of 861 non-allo BMT neutropenic episodes in adult cancer patients studied over the period 1990-1999

Patients treated with Amphotericine	**130**	
Age (years; median, range)	53	(17-78)
Underlying malignancy		
Acute leukaemia	107	(82%)
Lymphoma	12	(9%)
Others	11	(9%)
Neutropenic episodes treated with Amphotericine	**163**	
Myeloablative chemotherapy	143	(88%)
Auto-BMT	14	(8%)
No chemotherapy	6	(4%)
Duration of neutropenia (days; median, range)	26	(5-84)

.K.Lapointe et al, ICAAC 2000

Table 3 shows the number of patients treated during a period of 10 years and the treatment indication.
The majority of treatment indications (54%) were fever of unknown origin in a neutropenic patient (empiric indication). It represented 44 % of all treatment days. Aspergillosis, a very severe fungal infection, represented 25% of all episodes but 32% of the treatment days.

Table 3
Indications for Amphotericine treatment

Indication	Treatment episodes (%)		Treatment days (%)		Treatment days Median (range)		Total dosis (mg/kg) Median (range)	
Empiric	89	(54)	1027	(44)	9	(2-52)	6	(1-36)
Candidiasis[a]	24	(15)	438	(19)	16.5	(4-66)	12.5	(3-68)
Aspergillosis[b]	40	(25)	740	(32)	15.5	(2-85)	11.5	(1-126)
Others[c]	10	(6)	128	(5)	12	(4-33)	8.5	(2-28)
All	163	(100)	2333	(100)	11	(2-85)	7	(1-126)

A.K.Lapointe et al, ICAAC 2000

[a] 10 possible, 14 proven. [b] 27 possible, 5 probable, 8 proven. [c] 3 Invasive fungal infection (IFI), 7 suspected IFI not confirmed in follow-up. Treatment duration and total dosis for both most frequent IFI, candidiasis and aspergillosis, were significantly different from those of empiric treatment : $p<0.05$ and $p<0.0001$, respectively.

During the last 10 years the vast majority of patients were treated as first line therapy with Fungizone. It needs to be taken into account that the new antifungal drugs were only used very sporadically before 1996. This fact is reflected by the very low percentage of patients treated with the liposomal drugs (Table 4).

Table 4
Treatment days with the different forms of Amphotericine for the different indications

	Empiric		Invasive fungal infections		All Drugs	(%)
Fungizone	634	(90%)	850	(77%)	1'484	(82%)
Abelcet	13	(2%)	160	(14%)	173	(9%)
Ambisome	57	(8%)	102	(9%)	159	(9%)
TOTAL	**704**	**(100%)**	**1'112**	**(100%)**	**1'816**	**(100%)**

A.K.Lapointe et al, ICAAC 2000

This 10 year review also showed the side effects experienced by the 193 treatment episodes in table 5. It showed likewise that 26% of all Fungizone treatment episodes needed to be interrupted for toxic reasons.

Table 5
Treatment side effects (%) with the different forms of Amphotericine for the different indications

Side effects	Fungizone		Abelcet		AmBisome	
Treatment episodes (total 193)	**(n=159)**		**(n=17)**		**(n=17)**	
Nephrotoxicity	85	(53)	2	(12)[t]	1	(6) [t]
moderate	54	(34)[a]	2	(12)	1	(6)
severe	31	(19) [a]	0		0	
stop of treatment c	26	(16)	0		0	
residual	3/77	(4)	0		0	
Chills and fever	107	(67)	11	(65)	5	(29) [t]
stop of treatment [c]	10	(6)	2	(12)	1	(6)
Hypokaliemia	107	(67)	11	(65)[b]	7	(41)[b]
moderate	54	(34)	4	(24)	5	(29)
severe	53	(33)	7	(41)	2	(12)
stop of treatment [c]	2	(1)	0		0	
Renal acidosis	26/76	(34)	4/13	(31)	1/9	(11)
stop of treatment [c]	2	(1)	0		0	
Bronchospasm	3	(2)	1	(6)	0	
stop of treatment [c]	1	(1)	1	(6)	0	
Overall stop of treatment	41	(26)	3	(18)	1	(6) [t]

A.K.Lapointe et al, ICAAC 2000

[t] : P<0.06 if compared to Fungizone.

[a] : Concomitant nephrotoxic drugs were administered in 23/54 (43%) of episodes of moderate and in 12/31 (42%) of episodes of severe nephrotoxicity.

[b] : Due to Rx with Fungizone, hypokaliemia was already present before switch to Abelcet or Ambisome, respectively, in 7/17 and 11/17 episodes.

[c] : During neutropenia.

Table 6
Patient outcome after treatment with Fungizone

	Empiric Treatment (%)		Invasive fungal infection (%)	
Survival at discharge	72/75[a]	(96)	50/57[b]	(88)
Clinical response	49/72	(68)	41/57c	(72)
Patient who remained on Fungizone throughout Rx	54/75	(72)	35/57	(61)
Success	36/72	(50)	29/57	(51)

A.K.Lapointe et al, ICAAC 2000

[a] : 3 deaths. 1 Pt had autopsy : upper gastrointestinal hemorrhage (cause of death) and macroscopic oesophageal candidiasis (possible fungal breakthrough). The others 2 deaths were due to : encephalitis of unknown origin, intracranial hemorrhage (Invasive fungal infection not excluded in these 2 episodes).

[b] : 7 deaths. Autopsy performed in 5 Pt identified a fungal cause of death (cerebral Aspergillosis, Mucor pneumonia, pulmonary Aspergillosis, disseminated fusariosis, disseminated Aspergillosis). The remaining 2 deaths were possibly due to an Invasive fungal infection (pulmonary Aspergillosis).

[c] : 16 failures: 7 deaths (see comment [d]), 9 non responses (2 of which in uncontrolled underlying malignancies) :1 documented Pseudoallescheria boydli, 4 proven Candiasis, 2 probable Aspergillosis, 2 possible Aspergillosis.

3.3 Cost analysis

The cost analysis is focusing only on direct costs and does not include indirect costs or intangible costs. The hospital standpoint is taken in account.

3.3.1 Drug budget

As briefly mentioned in the introduction, drugs have a special status in the hospital finances.
Table 7 and 8 show the evolution of the drug budget of our institution in relation to the infectious disease division.

It is at this point in time impossible to identify the drug cost of an individual patient unless the medical record is taken in account for every single patient. It would be very important be able to establish a cost per patient analysis. The attempt to do so has been made but did not lead to a reliable result without a system of analytical accounting.

Two considerations can be made even in the absence of our own data. The literature reports that the side effects due to Fungizone treatment do not increase the hospital stay. Our preliminary data show that the nursing workload (in PRN points) does not increase significantly for patients experiencing major complications.

Table 7 shows the drug budget for the institution over the last two 2 years. It also shows the actual expenses and the two-year variation. This budget is compared to the drug budget of the infectious disease unit and its actual expenses.

Table 7
Drug budget and actual expenses CHUV and Infectious disease division

	1998		**1999**		**Variation 1998/1999**	
Budget	13'096'700		13'329'412		232'712	
actual expenses	13'853'914		14'374'583		520'669	
Δ	**757'314**		**1'045'171**		287'857	
Infectious disease Haematology-Oncology (ID+HO)	**ID**	**HO**	**ID**	**HO**	**ID**	**HO**
Budget	501'150	278'500	502'600	325'000	1'450	46'500
actual (ID+HO)	534'089	324'745	663'070	331'150	128'981	6'405
Δ	**32'939/**	**46'245**	**160'470**	**6'150**	**127'531**	**40'095**
Budget ID + HO	779'650		827'600		47'950	
actual ID + HO	858'834		994'219		135'385	
Δ	**79'184-**		**166'619-**		**87'435**	
Percentage budget CHUV/ ID+HO Actual ID+HO	5,9% budget 6,2% actual budget		6,2% budget 6,9 % actual budget			
Δ Percentage of budget CHUV	10,5%		16,0 %		+5,5%	

Table 8 shows the drug expenses per patient in relation to the number of hospitalisation days and the number of hospitalised patients in different departments and divisions.

To evaluate the impact of very expensive drugs on the hospital drug budget, we established a drug cost per hospitalisation day for the whole institution and specifically for certain departments

considered to be heavy drug consumers, like the department of medicine and surgery and their specific intensive care divisions. We used actual drug costs, not the budgeted sum.

Table 8
Drug costs per hospitalisation day and per patient during 1999

1999	Number of patients	Hospitalis. days	Actual drug expenses 1999	Drugs expenses per hospitalis. day	Drugs expenses/ patient
CHUV	**26'860**	**274'727**	**14'374'583**	**53,32**	**535,16**
Infectious disease**	**256**	**4'785**	**994'219**	**207,77**	**3'883,66**
Internal medicine B	2'104	18'900	570'655	30,19	271,22
General Surgery	2'762	26'214	1'013'999	36,81	367,24
Medical Int. Care	999	5'014	1'017'739	202,85	1'018,75
Surgical intensive care/Burn Unit	1'383	5'666	1'086'269	191,71	785,44

**Included Haemato-oncology

This table shows quite impressively that the isolation unit has by far the highest drug expenses per patient compared to any other department of our institution.

3.3.2 Antifungal therapy

The costs of intravenous antifungal drugs were established with data from the central pharmacy. Costs are acquisition prices for our pharmacy and do not necessarily correspond to market prices.

The three drugs evaluated in the literature are considered here for cost analysis. We did not consider drugs which are currently under investigation or which cannot be considered as standard treatment.

3.3.3 Cost analysis of anti fungal drugs

Table 9 shows the drug acquisition costs per patient treatment day and per department.
It is easy to see that the difference in acquisition cost between the three drugs is 10 to 30 times the costs of original drug.

Table 9
Antifungal drug acquisition cost per unit of weight and per dosage and per average patient

Drug	Dosage	Cost per unit/kg	Cost per patient per 70kg
Fungizone	0,6 mg	0.408 Sfr	28.56 Sfr
	1,0 mg	**0.68 Sfr**	**47.60 Sfr**
Abelcet	1 mg	2.19 Sfr	153.30 Sfr
	3 mg	**6.57 Sfr**	**459.90 Sfr**
	5 mg	10.95 Sfr	766.50 Sfr
Ambisome	1mg	6.03 Sfr	422.10 Sfr
	3mg	**18.09 Sfr**	**1'266.30 Sfr**
	5mg	30.15 Sfr	2'110.50 Sfr

The following table 10 shows the total antifungal drug use in 1999 in the hospital. It highlights the fact that, intravenous antifungal drugs are used only in specialised departments. (Data provided from the hospital pharmacy).

Table 10
Acquisition costs of the different formulations of Amphotericine available in 1999

1999	Fungizone	Abelcet	Ambisome	Total
Infectious Disease Unit	9'659	61'709	63'599	**134'967**
Department of Medicine				
Intensive Care	2'818	8'815	15'003	**26 636**
Hospitalisation Internal Medicine	1'083	4'410		**5 493**
Department of Surgery				
Intensive care	418	11'024	6'445	**17 887**
Hospitalisation Surgery	2'809	2'203		**5 012**
Department of Paediatrics				
Intensive care and hospitalisation	2'227	4'410		**6 637**
Total 1999	**18'255**	**66'108**	**78'621**	**196'632**

3.3.4 Disease related drug costs

The three treatment indications for systemic antifungal drugs cover very different disease severity and treatment duration. The mere drug acquisition costs vary therefore very much according to the disease, the drug choice and dosage. Table 11 shows that the cost of an empirical treatment of neutropenic fever vary about 30 fold. As shown in our 10 year review, at least 54% of all treatments with antifungal drugs were started empirically.

Table 11
Disease related drug costs

		Cost per patient per treatment day (average)	Aspergillosis dissiminated	Candidosis dissiminated	Empirical treatment
Drug Formulation	**Dosage**	**Cost per average patient, weight 70 kg**	**Cost of 26,3 day treatment (Sfr)**	**Cost of 17,day treatment (Sfr)**	**Cost of 9,4 day treatment (Sfr)**
Fungizone	0,6 mg	28.56	751.12	502.56	268.46
	1,0 mg*	**47.60**	1'251.80	837.76	447.44
Abelcet	1 mg	153.30	4'031.79	2'698.08	1'441.02
	3 mg*	**459.90**	12'095.70	8'094.24	4'323.06
	5 mg	766.50	20'158.95	13'490.40	7'205.10
Ambisome	1mg	422.10	11'101.23	7'428.96	3'967.74
	3mg*	**1'266.30**	33'303.69	22'286.88	11'903.22
	5mg	2'110.50	55'506.15	37'144.80	19'838.70

* in black are the most frequently used dosages

This table shows all dosages used in clinic and considered safe as and valuable treatment options. The dosage most frequently used is highlighted in black.
It is clear that each treatment course using the expensive drug has an important impact on the division's drug expenses The cost evolution over the last three years in the infectious disease department is shown in table 12. This evolution explains the vast majority of the drug deficit in this division.

Table 12
Costs of Antifungal drugs in the Infectious Disease Unit

Infectious Disease Unit Cost evolution 1997-1999				
	Fungizone(%)	**Abelcet** (%)	**Ambisome** (%)	**Total** (100%)
1997	10'044 (33)	2'156 (7)	17'850 (60)	30'050
1998	10'082 (14)	37'235 (50)	27'132 (36)	74'449
1999	9'659 (7)	61'709 (46)	63'599 (47)	134'967

Table 13 shows that in 1998 the expensive drugs were rarely used as empiric treatment but limited to disseminated fungal infections (non empiric).

Table 13
Annual cost of antifungal treatment (treatment days) 1998

	Empiric (treatment days)	Non empiric (treatment days)	Total costs (treatment days)	% of costs
Fungizone	3'136 (66)	6'946 (146)	10'082 (212)	14%
Abelcet	3'239 (7)	33'996 (74)	37'235 (81)	50%
Ambisome	6'430 (5)	20'702 (16)	27'132 (21)	36%
Total	**12'805 (78)**	**61'644 (236)**	**74'449 (314)**	**100%**

3.4. Sensitivity analysis

The previous cost analysis could did show very clearly that the drug budget of the whole institution and particularly of the infectious disease unit is very sensitive to a rather small number of drug choices.

3.4.1 Simulation of Drug costs in the infectious disease Unit 1999

Treatment days for 1999 are not available but can be obtained indirectly through the drug expenses. The number of patients treated as well as the number of hospitalization days remained the same in 1998 and 1999. The number of treatment days inferred from the drug expenses shows that the treatment days had increased from 314 to about 387 (+18%). The acquisition cost of antifungal drugs had increased during the same period likewise from 74'449 Sfr to 134'967 Sfr (+55%.)
In table 14 we simulate the compulsory use of a single drug in the infectious disease unit during a one year period (data from 1999). The total Amphotericine cost can vary according to the drug choice significantly.

Table 14
Simulation of Drug costs in the infectious disease Unit 1999

1999	Fungizone	Abelcet	Ambisome	Total
Real drug consumption 1999	9'659	61'709	63'599	**134'967**
Presumable treatment days	*203*	*134*	*50*	***387***
Fungizone only (387 days)	*18'444*			***18'444***
Abelcet only (387 days)		*177'981*		***177'981***
Ambisome only (387 days)			*490'058*	***490'058***

3.4.2 Simulation of the financial impact of increasing the size of the patient population

The data from the Infectious Disease Unit showed that the patient population remained very stable over the last three years. It is however possible to envision an increase of patients referred for this very specialised treatment to our institution.
In the following table we simulate the financial impact of increasing patient population by 5, 10 or 20 per year.
The 41 patients treated in 1999 for acute leukaemia received presumably 387 days of antifungal drugs or 9,3 days per patient.
We did take into account that in the year 1999 antifungal treatment was given during 10% of the hospitalisation days for oncological diseases. We are unable to distinguish hospitalisation days of patients with acute leukaemia from those with other tumours as indicated in Table 1 The simulation is therefore potentially optimistic, as the complication rate of disseminated fungal infections is much lower for patients with solid tumours.

Table 15
Simulation of the financial impact of an increasing patient population

1999	**Number of patients**	**Hospitalisation days**	**Hospitalisation days with antifungal drugs (%)**	**Total Antifungal drug acquisition costs 1999 (%of total drug budget ID- HO)**
CHUV	**26'860**	**274'727**		
ID high dose chemotherapy patients	**146**	**3'880**	**387 (10%)**	**134'967 (16%)**
Additional patients	*Patient number*	***Total hospitalisation days***	***Marginal drug expenses per additional patients ID-HO***	
Number of patients (19 days, average hospitalisation days)	***5*** *(95)*	*3'975*	*19'738*	*154'705*
	10 *(190)*	*4'075*	*38'836*	*173'803*
	20 *(380)*	*4'260*	*77'673*	*212'640*

A rather small increase in the patient population has immediate important consequences on the drug budget, growing by 10% with an increase of 20 patients.

4.0 Conclusion of the cost-effectiveness analysis

Systemic fungal infections in febrile neutropenic patienst are still a feared complication with an important morbitiy and mortality. The three Amphotericine formulations evaluated previously have shown to be equally effective for the defined endpoint such as there are the survival at discharge, the absence of breakthrough fungal infections and the decrease of fever despite neutropenia.

The main difference between the three drugs remains the acute and cumulative side effects of Fungizone. The recent study from Zürich showed that it was feasible to considerably reduce these side effects of Fungizone by increasing the infusion rate from 4 to 24 hours (11). This very simple measure may change the cost benefit ration if liposomial formulations.

For our institution the conclusion from this analysis is that the liposomal formulations cannot be considered cost affective as first line therapy. However their use can be indicated and fully justified in case of Fungizone incompatibility or preexisting renal impairment.

Our conclusion has been very recently confirmed by the International Society of Infectious Diseases, which published a full set of guidelines on the treatment of fungal infections (14-16).

4.1 Motivation to go further and develop a cost benefit analysis

The previously described cost-effectiveness analysis showed the complexity of the medical and the economic situation, which has to be faced when very expensive drugs are required but not reimbursed by social security.

Drug price negotiation could be one of the solutions in this financial dilemma or at least be part of it. In this particular case, drug prices were determined by pharmaceutical industry marketing policy. The original drug does not benefit from any kind of marketing effort any more as it has been on the market for almost 40 years. In the recent literature, hardly any study has been published using Fungizone as the investigational drug, except the study by Eriksson, modulating its side effects (11).

The liposomal drugs benefit worldwide from a very aggressive marketing campaign in the first 5 to 10 years after their registration in the USA, including a very restrictive price strategy. Therefore the price negotiation solution did not solve the financial problem.

Budgets can only be kept if health care professionals are aware of costs and are motivated to acknowledge the budget constraint. This motivation is kept alive if their 'educated' preferences are taken into account and respected.
In this particular situation the medical and economic importance of every single treatment choice motivated us to investigate individual preferences of health care professionals, in a cost-benefit analysis, using the willingness to pay method. During several discussions we had realized that professionals expressed very clear preferences, which we wanted to know and understand better.

The review of the literature showed that only very few studies addressed the problem of preferences of health care providers (17), which gave us the chance to perform a pilot study on willingness to pay also for the first time in our institution.

5.0 Cost benefit analysis

5.1 The Theoretical Foundations of cost-benefit analysis

The welfare theory is the economic theoretical background of the cost benefit analysis (CBA). Welfare economics is a branch of economics that addresses normative questions because it embodies certain value judgements in contrast to most of economic evaluations, which make predictions without value judgements.
The principal value theory has been developed by V. Pareto in the nineteenth century. He assumed that individuals are the best judges of their own welfare (18). This theory describes that the benefit an individual derives from a service or an intervention is defined as his or her maximum willingness to pay for this service or intervention. The benefit of the intervention for the society is the sum of each individual's willingness to pay.

In the presence of budget constraints, CBA may allow decision makers to rank the net benefits per unit of budget expenditure for all possible interventions, and use this ranking to allocate the limited budget among competing expenditures. Income effects can likewise be taken in account and smoothen social differences

Since then, three different approaches have been developed within the cost benefit analyses, the human capital approach, the revealed preference studies and the contingent valuation method. We will focus in this analysis exclusively on the contingent valuation analysis or willingness to pay method.

5.2 Cost-benefit analysis in health care

Cost-benefit analysis (CBA) expresses all costs and benefits (or consequences) in monetary terms. As money is a universal good, health care programs can therefore be compared to programs in other economic areas. It also allows resource allocation in health care to be finally compared to other economic sectors.
The great perceived disadvantage of this particular approach in the field of health care is the fact that human lives and quality of life as well as medical ethics need to be expressed in monetary units (19). This explains why the cost-benefit approach has been used so little by health care professionals in the past. Mainly physicians find it difficult and even unethical to translate intrinsic medical values into money.
The term cost-benefit analysis has been widely used in the medical literature probably because of ethymologic reasons, but often inappropriately. It has been shown that 53% of the studies labeled as cost-benefit analysis were only cost-comparison analysis. Only 13% of the studies performed between 1991-1995 used the contingent valuation method and could be labeled rightly cost-benefit analysis. (20-22).
A 10 year review of the literature showed that the contingent valuation method was the most frequently used analysis amongst the different forms of cost-benefit analysis. The described studies are all small and very often do not go beyond the phase of a pilot study. However the literature shows that the contingent valuation method is a valid method in health care. Studies focusing on cost-benefit analysis of entire health care programs are very rare (23-28).

5.3 The contingent valuation method or 'Willingness to Pay' (WTP)

5.3.1. Description of the model

The contingent valuation method is a survey based method using hypothetical scenarios to determine monetary valuations of effects of health technologies and benefits (22).
Respondents are asked to think about the contingency of an actual 'market' for a health care program and to state the maximum they are willing to pay out of their own pocket to have the program or benefit. They are asked to consider their real financial possibilities when answering the bidding questions. The method implies that the consumer is willing to give up other activities or services to obtain the health service. In a way, the WTP analysis is trying to create a market situation where there normally is none.
The validity of the results of this method depends strongly on the choice of the area to be investigated and the way the scenarios are built. A very important aspect is the wording and the language used in the scenarios. In the following sections we will outline the different key aspects of the contingent valuation method.

5.3.2 The scenario and the questions

The contingent valuation scenarios describe a hypothetical situation and ask the respondent to situate himself/herself in that given situation for the duration of the questionnaire. The scenario has to give the necessary aspects and details of the health program to allow the respondent to determine his or her WTP in the scenario question. Direct and indirect questions are possible. Direct questions are the simplest method to ask individuals for their WTP. In this case the respondent has to identify himself his own WTP without any reference amount. This method requires a strenuous effort from the respondent and might lead to quit especially if the motivation to answer the questions is not enhanced by other means.
A higher participation can be obtained with the use of payment cards, which indicate a range of predetermined amounts from which the respondent has to choose one.
The WTP survey can be performed as a telephone interview, a direct interview, a computer based system or a mail survey. The cost of the survey varies considerably according to the method chosen, the most expensive being the computer based and the individual method. The mail survey is used frequently but risks a rather low response rate.
Every aspect of the contingent valuation scenarios is important and carries the potential for biases.

5.3.3 Potential Biases

The contingent valuation method allows a number of method-specific biases, which might jeopardise the validity of the method and need special consideration (29, 30).

1. **Implied value cues** represent a bias when information is contained in the contingent valuation scenarios, which implies a certain value for the good. An important and well-known example of the implied value cue bias is the **starting point bias.** This implies that the WTP can be influenced by the value of the first bid offered, such that a higher starting bid determines a higher WTP. The payment card system offering a range of monetary values, can be source of starting point bias as well as range bias due to the chosen bidding interval.

2. **Scenario misspecification** occurs frequently**,** when respondents do not answer correctly the contingent valuation question, often because the question is asked incorrectly.

3. A third category of biases might occur if the respondents have an **incentive to misrepresent responses** and to state their WTP a higher or a lower than what they would have given as the real value. This bias could occur if the privacy of the respondents is not protected or, if the results of the study is directly used by decision making authorities.

4. **The hypothetical nature of the scenario** might represent a bias. Studies showed that the hypothetical WTP is in general significantly overestimated compared to the real WTP. Calibration methods to reduce or to eliminate these biases are currently developed (31).

6.0 Pilot study to elicit educated preferences from health care professionals for high cost antifungal drugs

6.1 The aim

This study aims at eliciting drug preferences of health care professionals for high cost antifungal drugs in the same setting as described in the cost-effectiveness analysis**.** We wanted to assess their WTP in relation to the previous study and understand whether their preferences agree with the conclusion of the cost-effectiveness analysis. Our aim is also to assess the value given to drug side effects.
Preferences and value statements might differ according to the level of specific knowledge and training. We foresee to elicit preferences from trained health care professionals and consider them as 'educated' preferences. A group of non medically trained health care professionals is included as general population (29).

This first pilot study in our institution was also for us the beginning of the methodological validation process of the contingent valuation method in health care. It gave us a preliminary view of the method its limits and possibilities. It would allow us also to gain a first experience with the potential biases, known to be linked to this method.

6.2 The hypothesis

It becomes more and more important to allocate scarce resources according to the real value of a treatment or of a service. Educated preferences and value statements from professionals and instructed lay person could be considered close to the real value of a health good if expressed appropriately. These educated preference statements could participate in the decision making process, on a local level as well as on a bigger scale. They could also indicate whether administrative decisions are supported by professional values.

The study population were doctors and nurses from the division of infectious diseases and from the general internal medicine ward. The general population was represented by social workers and nursing aids. We chose this study population because of their specific knowledge in this special setting and because they potentially express preferences from slightly different standpoints.

We suppose that **doctors** in charge of these high-risk patients would express their preferences in full knowledge of the consequences. The fact that we asked for their personal preferences, if the disease affected themselves, might alter the answers. We expected them to be willing to pay for the new drug up to the real value of the drug.

Nurses are in contact with a patient on a daily basis in a very privileged way. They are very sensitive to patients complaints and well-being. Their profession makes them take care of any complaints at first, before the doctor.
The nursing profession is essentially based on the present medical situation of a patient. A prospective view of the disease and the evaluation of long-term risks are not necessarily taken in account by the nurses. This point of view might influence the value nurses give to the new drug and its benefits, in a way that they express a certain WTP for the new drugs.

The choice of t**he general population** was made for practical as well as policy reasons.
Nursing aids have in general no professional training in the medical field. They are informed at the beginning of their activity and mainly trained on the job. No specific knowledge on the disease or on its outcome can be expected from them. Their main task is to help the qualified nurses in basic nursing, like assistance in personal hygiene and feeding. This allows the nursing aid to have a very intimate contact with patients, without necessarily understanding entirely the medical condition. We

expected nursing aids to hesitate in the bidding process, giving importance to the new treatment but not entirely. They might present some problems in understanding the questions.

Social workers are very in very close contact to the different functions and professions in the hospital. Without a specific training in the medical field, they are for many aspects the link between the patient and the different medical professions. They are aware of the patient's personal and financial situation as well as the possibility to obtain additional subsidies. Social workers feel strongly about the patients needs, but they do understand the possibilities and limits of the financial resources in society.
We expect social workers to give importance to the new treatment.

We did not include patients in this preliminary study. The main reason was the critical situation in which these patients are once they are hospitalised. In addition, a research protocol needs to be approved by the ethical committee to include presently affected patients or former patients.

6.2.1 The scenarios

An introduction letter described the method and the aim of the study to the respondents assuring complete confidentiality. Three scenarios described likely situations in the infectious disease division. The respondent was requested to consider suffering from leukaemia for the duration of the study and answering the following questions:

Scenario 1:

How much are you willing to pay to avoid the risk of a major complication ?

Scenario 2:

Thank you for indicating us how much you are willing to pay put of your own pocket for the drug, which gives less side effects (for a complete treatment course of at least 10 days)

Scenario 3:

How much are you willing to pay out of your pocket for the new drug if we reduce the side effects of the original drug by half (for a complete treatment course) ?

6.2.2 The bidding

We used a ***payment card system*** with 9 increasing and decreasing ranges randomly allocated to each professional category. The bidding interval had been selected between nothing and more than 32'000Sfr. Using doubling steps allowed a wide range of possible willingness to pay.

Bidding ranges in Swiss Francs

Nothing

0-499

500-999

1'000-1'999

2'000-3'999

4'000-7'999

8'000-15999

16'000-31'999

more than 32'000

Blank

6.2.3 The difficulty

An evaluation of the perceived difficulty was requested with the following answer possibilities :

1. was difficult to answer the question
2. was difficult to understand the question
3. was difficult to determine the WTP
4. was or was not a pertinent question
5. was easy to answer the questions

6.2.4 Demographic data

Personal data concerning the age, the profession and the health insurance status as well as the respondents own health status were recorded. A question about the family members health status was included to evaluate the influence of personal experience with oncological diseases.

6.2.5 Data analysis

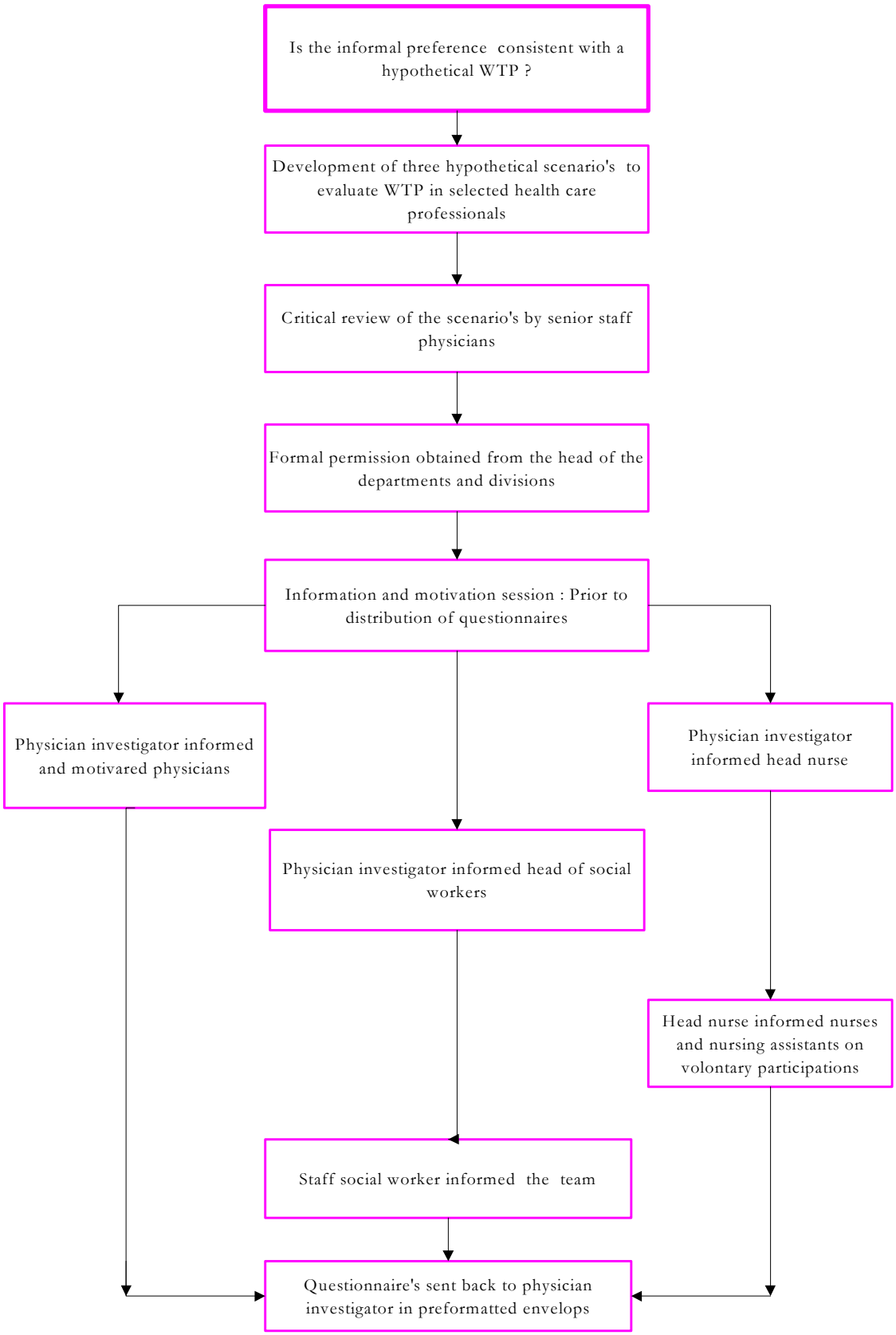
In this preliminary study we will limit our data analysis to descriptive statistics. A further econometric evaluation will be performed.

6.2.6 The review process and the motivation sessions

The internal validation process through peer review was considered important in a pilot study using a new method in our institution. Prior to the study the preliminary questionnaires were sent for internal peer review and authorisation.

Pre-study information sessions were organised for all 4 professional categories. The aim of the study was either directly explained to the respondent by the physician investigator (doctors and social workers) or indirectly through a senior staff member (nurses). The original questionnaire can be found in annexe 3. The study process is resumed in table 14.

Table 16
Process : Establishing a questionnaire using the contingent valuation method



7.0 Results:

7.1 Personal characteristics of respondents

We included 153 health care professionals. We obtained 97 answers, from which 1 invalid answer and 4 protest answers, which were excluded from the statistical evaluation.

Table 17
Personal characteristics of respondents

	Frequency	
	N	**%**
	96	**100**
Gender		
male	32	**33**
female	64	**67**
Age : mean (range)	34,5 (20-61)	

Profession		
Resident	12	12,5
Junior Staff	10	10.0
Senior Staff	8	8.0
Social worker	11	11,4
Registered nurse	34	34,4
Staff nurse	10	10,4
Nursing aide	11	11,4
Total	**96**	

Country of origin		
Switzerland	58	60
Europe	25	26
America/Canada	11	11
Missing data	2	2
	96	**100**

Insurance status		
Basic package	54	56
Private insurance	40	42
Missing data	2	2
	96	**100**

Health Status		
Perfect 95-100%	71	74
Slightly reduced 80-94%	25	26
Moderately reduced 70-79%	0	0
Seriously reduced < 70	0	0
		100

Household income (before tax) average	50'000-100'000	

Family status		
Live alone	38	**41**
Live in couple or married	32	**34**
Live with children and or married	21	**23**
Live with parents	2	**2**

Despite thorough information and motivation sessions, varied the response rates amongst professions very much as it is outlined in table18. Due to the rather low response rate of physicians it was impossible to evaluate separately the staff from the infectious disease unit. It was likewise impossible to distinguish the response rate of the registered nurses, the staff nurses and the nursing assistants as they all received the same envelope. The very high response rate amongst the nursing profession could be explained by their work in a team, compared to the more individualistic approach of physicians.

Table18
Response rate of different professions

Response rate		
Profession	**No. responses**	%
Residents	12	24%
Junior Staff	10	59%
Senior Staff	8	43%
Social worker	11	55%
Registered nurse	34	
Staff nurse	10	80%
Nursing aide	11	
Overall response rate	96	**61%**

Table 19 shows the response rate in relation to the questionnaires. We only received one invalid answer and 4 protest answers with some missing data. Other questionnaires had hand written comments, which will be resumed in table 20

Table 19
Response rate and questionnaires

Number of questionnaires		
Sent	157	
Response	97	Response rate 62%
Invalid	1	
Protest answers	4	Protest answers : 4 %
Valid questionnaires	96	
Questionnaire		
Top down 32'000-0 Sfr.	53	**55%**
Bottom up 0-32'000 Sfr.	43	**45%**
	96	**100%**

The personal comments in table 20 reflect the difficulty of the willingness to pay method in health care. They confirmed the importance of broad and thorough information about the method and its potential goals as well as its limitations.
These pertinent comments are an expression of the suspicion health care professionals express when monetary values are put on health issues.

Table 20
Personal comments of the respondents concerning the willingness to pay means

1. This approach leads to a two class medicine
2. The questionnaire seems to be a bad marketing strategy
3. It is unacceptable to estimate cost of life
4. Fear about the use of the study results
5. Health is not a merchandise
6. Life does not have a monetary value

7.2 Scenario results

The evaluation of the scenarios will be analysed at first for the entire study population and subsequently by other variables like profession, health state and perceived difficulty.

7.2.1 Total population Willingness to pay

Table 21 shows the median WTP for the three scenarios. The 9 bids on our payment card can be divided into different categories: The clear expression of a 'non WTP' (1), the moderate WTP of up to 1'000 Sfr. (2 and 3) and high WTP (4 and 5) and the very high WTP (6-9). Table 21 shows the number of respondents for each bid and the cumulative percentage (in brackets). The total median WTP shows that the first scenario is valued very highly, the second moderately and the third expresses clearly the non-WTP for a new drug which differs only in some side effects from the original drug.

Table 21
Total population Willingness to pay
Distribution of answers and cumulative percentage

Bidding ranges	WTP Swiss francs	Scenario 1 (cumulative%)	Scenario 2 (cumulative %)	Scenario 3 (cumulative%)
1	Nothing	19 (21)	28 (30)	46 (50)
2	0-499	1 (22)	13 (45)	12 (63)
3	500-999	5 (27)	12 (58)	4 (67)
4	1'000-1'999	2 (29)	8 (68)	5 (73)
5	2'000-3'999	7 (37)	7 (74)	14 (88)
6	4'000-7'999	12 (50)	13 (88)	3 (91)
7	8'000-15999	17 (68)	8 (97)	5 (97)
8	16'000-31'999	10 (79)	1 (98)	1 (98)
9	more than 32'000	19 (100)	2 (100)	2 (100)
0	Blank	4	4	4
		96	**96**	**96**
TOTAL	**Median WTP**	**4'000-7'999**	**500-999**	**nothing**

7.2.2 Professional status and WTP

We evaluated whether there were differences amongst professionals in the WTP. Table 22 shows that scenario 1 is valued highly by all professional groups participating in the study. Professional differences can be seen mainly for scenario 1. To explain the differences professional and economic aspects need further to be taken into account.

Physicians value very highly the first scenario, because they understand that the absence or presence of an infectious complication represents the major risk reduction. The willingness to pay for the scenario 2 in which side effects play the major role is valued rather modestly by knowledgeable physicians in the department of internal medicine. Their willingness to pay for a treatment episode is only 10% of the drug cost. The scenario 3 in which the side effects of the old drug have been attenuated have clearly no willingness to pay.

Nurses WTP showed the same trend as physicians. They valued highly the risk of complication and moderately side effects. The difference in monetary value needs a closer evaluation in relation to salary and working experience.

The general population or social workers and nursing assistants repeated the same pattern in WTP as nurses and physicians, except for scenario 3 for which they expressed a WTP in the low range. It is very difficult for non-medically trained professionals to evaluate the importance of specific side effects and their consequences. The expressed WTP of 0-499 Sfr. for both scenarios 2 and 3 reflects the difficulty to give a clear value of the side effects. We presume that some uncertainty is due to the lack of specific knowledge.

Table 22
Professional differences in willingness to pay

Profession	**Scenario 1**	**Scenario 2**	**Scenario 3**
WTP for	**Risk of complication**	**Side effects**	**Comfort and some side effects**
Physicians N=30	16'000-31'999	1'000-1'999	Nothing
Nurses N=44	2'000-3'999	0-499	Nothing
Social workers/nursing aid N=22	2'000-3'999	0-499	0-499
Median WTP Total N=96	**4'000-7'999**	**500-999**	**nothing**

7.2.3 Salary adjusted willingness to pay

The contingent valuation method asks the WTP from the own pocket. It is therefore important to evaluate an income adjusted WTP, which is outlined in table adjustment for income is important, it is outlined in table 21.
The average working experience amongst professionals was quite uniform, but with a large standard deviation. No valid analysis can therefore be made about the impact of working experience. A subdivision in more homogeneous groups would be too small to be significant.

Table 23
Willingness to pay as percentage of average salary

Professions	Scenario 1	Scenario 2	Scenario 3
Physicians	32%	2%	0%
Nurses	7%	0,8%	0%
Social workers/ Nursing assistants	7%	0,8 %	0,8%
Average % salary	15,3%	1,2%	0%

7.2.4 The starting point bias

The payment card system used in our study required the evaluation of a potential starting point bias. In table 24 the WTP of our study population is evaluated in correspondence to the value of the first bid on the questionnaire.

In scenario 1 the difference in WTP is of two ranges or by 4'000- to 12'000 Sfr. The questionnaires with the highest bid on the top of the payment card system had a two range higher WTP than those respondents who answered the low starting range. This observation is valid for all three scenarios but is the highest for the first scenario with a difference of 4'000-12'000Sfr. amongst the two scenarios.

Table 24
Evaluation of starting point bias

	Scenario 1		Scenario 2		Scenario 3	
WTP TOTAL POPULATION N=96	**4'000-7'999 Sfr**		**500-999 Sfr**		**Nothing**	
Questionnaire	**Bottom up** N=43	**Top down** N=53	**Bottom up** N=43	**Top down** N=53	**Bottom up** N=43	**Top down** N=53
SFR	**0-32'000**	**32'000-0**	**0-32'000**	**32'000-0**	**0-32'000**	**32'000-0**
Median WTP	2'000-3'999	8'000-15'999	0-499	500-999	Nothing	0-499
Δ	**4'000-12'000**		**0-499**		**0-499**	

7.2.5 The influence of the insurance status on the willingness to pay for expensive drugs

The possible impact of insurance status on the WTP was investigated. The distribution of insurance status by profession is shown in table 25. It shows also that the insurance status is evenly distributed amongst the professions and represents about 50% basic insurance and 50% private insurance. Amongst the registered nurses the percentage of private insurance is the lowest, they present also the youngest group with the shortest professional experience.

The median willingness to pay of the whole study population has been compared to the two insurance groups and showed no difference in willingness to pay between the two insurance states.

Table 25
Insurance status by profession

	Total	Basic insurance package (%of population)	Private insurance (%of population)
Total n=96			
Physicians	30	16 (53)	14 (47)
Nurses	42	27 (64)	15 (36)
Nursing assistant/ social worker	22	11 (50)	11 (50)

7.2.6 The influence of own health status and family member health status in the determination of WTP

The impact of personal experience with altered health status on the willingness to pay for an expensive drug was taken into account in the following tables. We will distinguish the WTP of respondents with a perfect health status and those with a slightly diminished health. Respondents declaring to have at least one family member suffering from cancer will be taken into account separately, and in a second approach jointly.

Table 26
Respondents declared health status

Health Status	Number of respondents	%
Perfect (95-100%)	81	84
Slightly reduced (80-94%)	12	12
Moderately reduced (70-79%)	0	0
Seriously reduced (< 70%)	0	0
Blank	3	**4**
		100%

We evaluated the WTP for respondents with a slightly reduced health status compared to the group in perfect health. We evaluated whether the impact of a personal physical impairment could possibly increase the willingness to pay. We tested this hypothesis by representing all respondents who had **no** willingness to pay for any of the three scenarios (n=17) according to their health state. Surprisingly 33% (n=4) of the respondents with some physical impairment had no WTP compared to 16% (n=13) of respondents in perfect health.

We explored further the coincidence of the respondents own health status with the family health status. Only one respondent had a reduced health state and family members suffering from cancer. The 4 respondents with family members suffering from leukemia are likewise in perfect health.
This fact allowed us to consider the family health status independently from the own health status in our study population.

The median WTP for respondents with cancer patients in the family does not differ from the WTP of the general population. These results show that there seems to be little influence from personal and family experience on the WTP for a very specific treatment.

7.2.7 Evaluation of questionnaires

The willingness to pay method was used for the first time in our institution and caused some surprise and difficulties for the respondents. We evaluated the difficulty to answer the scenario questions. Only 17% of the respondents thought that it was easy to answer the questions; 71% found it either difficult to answer the question or difficult to determine their willingness to pay.

It is not surprising to find the majority of respondents had difficulties with the investigation tool. Table 27 shows the perceived difficulty with the scenarios, by professional category. Due to the rather small number of respondents by profession no significant difference could be detected.

Tableau 27
Difficulty for the different professions to answer the scenarios

		Difficulty answering the scenarios					
Profession	**Blanc**	**Yes**	**to understand**	**to determine WTP**	**not pertinent**	**Easy to answer**	**Total population**
Physicians (%)	0	2 (7)	4 (13)	17 (57)	1 (3)	6 (20)	**30**
Nurses (%)	4 (9)	11 (25)	1 (2)	24 (55)	0 (0)	4 (9)	**44**
Nursing assistants/social workers (%)	1 (5)	4 (18)	1 (5)	10 (45)	0 (0)	6 (27)	**22**
Total (%)	**5 (5)**	**17 (18)**	**6 (6)**	**51 (53)**	**1 (1)**	**16 (17)**	**96 (100)**

How much the personal perception of the difficulties influenced the willingness to pay is evaluated. No difference in WTP could be detected between the respondent who found easy or difficult to answer the scenarios.

8.0 Conclusion:

This study aimed at eliciting drug preferences from healthcare professionals for high cost antifungal drugs. This first cost-benefit analysis using the contingent valuation method in our institution included three groups of health care professionals (physicians, nurses, social workers) from the department of internal medicine and the division of infectious diseases. Three scenarios were given, asking for the willingness to pay for: a) a risk reduction (infectious complication), b) a new drug with fewer side effects and c) a new drug if the side effects of the original drug had been reduced.

We have reached an acceptable response rate of 61% for this unusual survey analysis in our institution. The influence of motivation sessions became very clear with a variation in response rate from 24% to 80%.

The descriptive results showed that the respondents valued a) the risk reduction highly and b) the side effects moderately while c) there was no willingness to pay once the side effects were reduced for the original drug. Some professional differences in the willingness to pay can be attributed to professional knowledge.

The salary adjusted median WTP showed that physicians valued the highest the total risk reduction for a complication (32% of their salary). For the other scenarios the difference between the three professional groups was just marginal. Other possible factors influencing the willingness to pay were evaluated to improve the method and understand potential biases.

The literature on the contingent valuation method in health care mentions a number of potential biases, which represent an important aspect for its validity. In this study we addressed particular attention to these biases.

The real value of the three different drugs can be easily obtained from health care professionals and can potentially represent an **implied value cue bias**. Some physicians are supposed to know the acquisition costs of the drugs, which is not the case for nursing aids and social workers. This might explain at least partly the observed difference.

The importance of the first bid on the payment card on the WTP has been shown. The WTP was significantly higher in the group who had received the top down questionnaire. We could confirm the presence of a **starting point bias** in our study. The bias needs therefore to be addressed systematically in every study especially if the payment card system is used.

Scenario misspecification is difficult to evaluate quantitatively if parameters are not clearly set at the moment of the study design. In our study we counted on the 4 protest answers, which were given because the respondents did not understand the goal of the hypothetical scenarios and they interpreted it exactly the contrary of what it was designed for. Misspecification is well expressed in the hand written comments resumed in table 20. This bias influenced our study by a maximum of 10% of the respondents.

In a further study this bias will need to be addressed systematically at the moment of the study design and a quantitative evaluation method of misspecification should be integrated in the study. Establishing a structured peer review prior to the study could allow reducing this bias considerably. The information and motivation sessions could participate in keeping the misspecification bias low.

As the study was designed it seems difficult to imagine that employed health care professionals have a strong self-interest in stating their willingness to pay higher or lower than their real preferences. The possibility of an immediate impact of their WTP is not given in this study. We presume that this first pilot study was not incline to have a significant **incentive bias** to misrepresent the WTP.

The hypothetical nature of the scenarios was a completely new experience for health care professionals. Overstatement or understatement of WTP could be possible but was not addressed in this study. This aspect of potential biases will need to be addressed in further studies using more sophisticated econometric analysis.

Other potential influences were evaluated but did not, to our surprise, show significant differences; for example the **insurance status** and the personal and the family health status did not play a role in the WTP. These results need to be confirmed in a bigger study to validate the important result that the insurance status is independent from willingness to pay.

One would also expect that close experience with a **family member** suffering from an oncological disease could motivate the respondent for a higher willingness to pay. This was not the case in our study. These results, of potential long-term importance, need to be confirmed through a multicentre study including actual, past and future patients.

The **validation question** about the perceived difficulty to answer the questionnaires seemed to be essential at the end of the scenarios, because we could confirm the difficulty of this new tool for the population (80%) and we were able to specify the difficulties encountered. The determination of WTP presented for 53% of the respondents a hurdle. We understand hereby that only the careful preparation of the study population can keep them interested in this new approach.

8.1 Did we meet the aims of our study ?

We succeeded in conducting the first contingent valuation study in our institution with a significant response rate. We could elicit educated drug preferences from different professional backgrounds.
The respondents expressed differentiated preferences and even if the question was directly asked, their preferences do not seem to be in contradiction with the conclusion of the cost effectiveness analysis. We obtained in scenario 2 a value given to side effects which can be compared to drug costs.

We are satisfied with the participation of the nursing population and especially with the effort the nursing assistants had made to participate in the study (no missing data !)

The methodological evaluation of the tool showed the number of potential and confirmed biases, which need further studies to validate the results. We can consider our first experience with this tool is a positive one.

8.2 Limits of the performed pilot study

The study design had a number of first evaluation problems. The study population chosen was appropriate but the motivation and information strategy not sufficient. The clarity of the questionnaires needs to be enhanced in further studies to reduce the number of respondents who declared that it was difficult for them to answer the question.

A statistical and econometric evaluation needs to be established, allowing a far more detailed analysis of the results, which can increase the validity of the study and the tool.
The first struggles with the database did not facilitate data analysis and need to be enhanced in a further study.

8.3 Where to go from here ?

We just experienced through this first pilot study the potential of a very powerful and important tool. The possibility to use a universal language (money) to express intrinsic human and health care values is a thrilling experience. We have to get more and more familiar with the instrument and its limitations to be able to use the results of the contingent valuation studies in many different areas.

In a rather small impact study we tried to understand whether the conclusions of the cost effectiveness study were supported by professionals, knowing that unsupported administrative decisions risk having little success. We could imagine motivating health care professionals to use the contingent valuation method as 'loudspeaker' of their preferences and intrinsic values.

Decision makers on a local level as well as on a larger scale might benefit from this type of analysis. Cost-benefit analysis could be for example part of drug price negotiation and express educated preferences and value statements.

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Annexe1
Personnel in the CHUV

	1998	**1999**
Physicians	494.6	510
Nurses	1'352.8	1'442.7
Medical–technical staff	473.3	481.5
Logistics	722.1	738
Administratif	415.2	413.1
Others	46.2	47.4
Total	**3'504.2**	**3'632.8**

Annexe 2

Number of beds and treatment days per division

Beds and bed occupation	Beds 1998	Median occ. 1998	Beds 1999	Median Occ. 1999
Medicine	278	93,2	267	95.8%
Surgery	308	80,2	309	83.3%
Gynecology and Obst.	72	64,1	72	74.5%
Pediatrics	78	84,5	78	79.2%
Total	**734**	**84,0**	726	86.6%

Patient treated	1997	1998	1999
Hospitalisations	25'206	25'670	25'840
Semi hospitalisations	11'934	12'747	13'576
Total	37'140	38'417	39'416

Days	1997	1998	1999
Hospitalisations	226'571	232'817	238'441
Semi hospitalisations	11'934	13'333	14'402
Total	238'505	246'150	252'843

Annexe 3
WTP questionnaire

CENTRE HOSPITALIER UNIVERSITAIRE VAUDOIS

Direction médicale

CH-1011 Lausanne
Tél. : 021 / 314 11 11

Tél. direct : 021 / 314.18.02
Télécopieur : 021 / 314.18.18

Lausanne, le 7 février 2006

Madame, Monsieur,

Comme vous le savez, les budgets des hôpitaux sont limités et ne peuvent plus être augmentés. Nous nous trouvons donc toujours plus fréquemment dans des situations où nous devons faire des choix. Il est cependant primordial d'avoir des éléments objectifs et pertinents qui facilitent ces choix.

Les professionnels de la santé comme vous sont les personnes les plus aptes à fournir ces éléments nécessaires pour prendre des décisions. Il est donc souhaitable que vous puissiez exprimer vos opinions et vos préférences. Cette étude a pour but de mettre en évidence la valeur que vous attribuez à un traitement particulier en tant que professionnel de la santé. Plus spécifiquement, nous vous présentons des situations concernant des traitements particulièrement chers et non remboursés par les caisses maladie. Pour cela, nous utilisons comme approche une technique appelée « méthode de contingence» ou « willingness to pay», basée sur un questionnaire.

Quelques questions personnelles et sur votre parcours professionnel complètent le questionnaire dans la mesure où ils peuvent influencer les réponses.

Trois scénarios décrivent un certain risque associé à un état de santé. Nous aimerions savoir quelle valeur vous donnez à ce risque et combien vous seriez prêt(e)s à payer pour l'éviter. Nous vous demandons de cocher la somme maximale que vous envisagez de payer pour réduire le risque de maladie et ses conséquences.

De manière à permettre d'affiner l'analyse des résultats, nous vous remercions vivement de répondre au plus près de votre conscience en tenant compte de vos ressources financières réelles. Les prix que nous vous indiquons sont des prix et des valeurs réels.

Laissez-vous guider à travers ce questionnaire. Cela nous aidera à donner une réelle valeur à vos préférences. Nous assurons bien entendu la complète confidentialité de toutes les données. Les résultats seront analysés de manière à ne pas permettre d'identifier les participants à l'étude. Les résultats globaux vous seront fournis sur demande.

Nous vous remercions de bien vouloir participer à cette étude. Votre contribution nous est précieuse.

En restant à votre disposition pour tout renseignement que vous pourriez souhaiter, nous vous adressons, Madame, Monsieur, nos salutations les meilleures.

Dresse K. von Bremen
Chef de clinique adjointe

Dr J.-B. Wasserfallen
Adjoint au Directeur médical

SCENARIOS

Scénario 1

Considérez pour la durée de cette étude que vous avez une leucémie aiguë (sorte de cancer du sang). Vous savez que vos chances de survie durant les 5 prochaines années sont de 40% si vous êtes traité par chimiothérapie à haute dose. Vous savez également que le traitement intensif coûte cher (entre Sfr 60'000 et Sfr 100'000). Ce traitement comporte un risque de complications mineures dans 60% des cas, et de complications sérieuses dans 30% des cas, chaque fois que vous êtes exposé à une chimiothérapie. Les complications sérieuses augmentent votre risque de décès de 50% dans les semaines suivantes. Si la complication est traitée avec succès, vos chances de survivre ne changent pas, c'est-à-dire que vous disposez toujours de 40% de chance les 5 prochaines années.

Quelle somme seriez-vous d'accord de payer pour éviter le risque de complication majeure (maladie en plus de la leucémie) ?

- Rien ☐
- 0-499 Sfr ☐
- 500-999 Sfr ☐
- 1'000-1'999 Sfr ☐
- 2'000-3'999 Sfr ☐
- 4'000-7'999 Sfr ☐
- 8'000-15'999 Sfr ☐
- 16'000-31'999 Sfr ☐
- plus de 32'000 Sfr ☐

Scénario 2

Admettons que votre traitement de chimiothérapie à haute dose est compliqué par une infection fongique (à champignon) grave. Si elle n'est pas traitée, cette infection est fréquemment mortelle. Le traitement consiste en un traitement antibiotique intraveineux d'une durée d'au moins 10 jours.

- Un seul médicament efficace existe pour traiter votre infection, mais sous deux formes pharmacologiques différentes.
- Le médicament original est connu depuis 40 ans, et le deuxième est disponible seulement depuis quelques années.
- Ces médicaments peuvent guérir votre infection dans plus de 60% des cas. Cela signifie que vous avez encore au maximum 40% de risque de mourir de votre infection.
- Les deux médicaments sont égaux en efficacité, ce qui signifie que vos chances de survivre sont exactement les mêmes avec les deux médicaments.
- La seule différence entre les deux médicaments est que l'original peut causer des effets secondaires.
- Ces effets secondaires sont essentiellement de la fièvre, des frissons et des nausées lors des premières perfusions et une atteinte du fonctionnement du rein qui peut, dans quelques cas, nécessiter l'arrêt du traitement. Vous pourriez donc vous sentir encore moins bien. Les infirmières viendront plus souvent vous surveiller et prendre votre pression.
- Le nouveau médicament donne nettement moins d'effets secondaires et vous aurez moins d'attention de la part des infirmières.
- A la longue, il n'y a pas de différence majeure entre les médicaments : aussitôt que vous arrêtez de les prendre, les effets secondaires disparaissent. Vous n'aurez pas des complications à vie dues au médicament original.
- *La plus grande différence entre les deux médicaments est leur prix :* Le médicament original est relativement bon marché et le nouveau beaucoup plus cher.

- Le médicament original est remboursé par votre caisse-maladie, contrairement au nouveau qui n'est pas remboursé, ce qui signifie que vous devez le payer de votre poche si vous le préférez.

Merci d'indiquer quelle somme vous êtes d'accord de payer de votre poche pour avoir le médicament qui donne le moins d'effets secondaires ?
(prix pour le traitement complet, au moins10 jours)

- Rien ☐
- 0-499 Sfr ☐
- 500-999 Sfr ☐
- 1'000-1'999 Sfr ☐
- 2'000-3'999 Sfr ☐
- 4'000-7'999 Sfr ☐
- 8'000-15'999 Sfr ☐
- 16'000-31'999 Sfr ☐
- plus de 32'000 Sfr ☐

Scénario 3

Maintenant, nous allons explorer une nouvelle situation. Vous présentez à nouveau une complication infectieuse suite à votre chimiothérapie à haute dose pour lutter contre la leucémie (comme dans le scénario nr 2).

Des études récentes ont montré que les effets secondaires du médicament original peuvent être diminués si l'on change la durée d'administration. Si la durée de perfusion passe de 4 heures à 24 heures, cette simple mesure réduit la gravité des effets secondaires du médicament original de 50%, à moyen et à long terme. Cela signifie que vous pouvez encore subir quelques effets secondaires mais mineurs, dus au médicament original.

Comme par cette nouvelle application nous avons pu changer les effets toxiques du médicament original, et qu'avec cette mesure les deux médicaments se ressemblent maintenant de plus en plus, nous aimerions à nouveau connaître vos préférences.

Quelle somme êtes-vous d'accord de payer de votre poche pour le nouveau médicament si nous réduisons les effets secondaires de l'original de moitié ?
(prix pour le traitement complet)

- Rien ☐
- 0-499 Sfr ☐
- 500-999 Sfr ☐
- 1'000-1'999 Sfr ☐
- 2'000-3'999 Sfr ☐
- 4'000-7'999 Sfr ☐
- 8'000-15'999 Sfr ☐
- 16'000-31'999 Sfr ☐
- plus de 32'000 Sfr ☐

5) Avez-vous trouvé difficile de répondre aux questions des scénarios ?

a) oui ☐

si oui, pourquoi :

I) difficulté de comprendre les questions ☐

II) difficulté de déterminer votre volonté de payer ☐

III) le sujet ne signifie rien pour vous ☐

c) c'était facile de répondre aux questions ☐

MERCI BEAUCOUP D'AVOIR PRIS LE TEMPS DE REPONDRE A CES QUESTIONS

Maintenant, nous souhaitons vous poser quelques questions personnelles et sur votre expérience professionnelle, puisque ces deux facteurs peuvent influencer vos réponses. Merci de bien vouloir y répondre aussi.

Numéro ☐° Date °☐☐☐

Questionnaire

1.1 Age ☐ Sexe Femme ☐ Homme ☐

1.2 Nombre d'années d'expérience professionnelle (années complètes) ☐

1.3 Pays d'origine :_____

1.4 Depuis combien d'années vivez-vous en Suisse ? ☐

1.5 Situation familiale :

a) Vit seul(e) ☐ b) Marié(e) ou vit en couple ☐
c) Vit avec des enfants ☐ d) Vit avec des personnes plus âgées ☐

1.6 Quelle assurance avez-vous ?

a) Assurance de base ☐
b) Assurance complémentaire/privée/semi privée ☐

1.7 Y a-t-il des membres de votre famille qui souffrent d'une leucémie ou un d'un lymphome ?

a) oui ☐ b) si oui, combien ☐
c) non ☐

1.8 Y a-t-il des membres de votre famille qui présentent d'autres types de cancer?

a) oui ☐ b) si oui, combien ☐
c) non ☐

1.9 Comment jugez-vous votre état de santé actuel ?

a) parfait (95-100%) ☐
b) légèrement compromis (80-94%) ☐
c) modérément compromis (70-79%) ☐
d) sérieusement compromis (< 70%) ☐

2.0 Avez-vous été hospitalisé(e) pour plus de 24 heures durant ces deux dernières années ?

a) oui ☐ b) si oui, combien de fois ☐
c) non ☐

2.1 Quelle est votre profession ?

Médecin assistant(e) ☐ Chef de clinique (CDCA) ☐ Médecin cadre ☐
Assistant(e) sociale ☐ Infirmier(ière) ☐ ICS / ICUS ☐
Aide soignant(e) ☐

Questions pour les médecins

2.2 Quel est votre secteur d'activité professionnelle actuel (plusieurs réponses possibles) ?

a) clinique ☐ d) gestion de santé ☐
b) recherche ☐ e) politique de santé ☐
c) enseignement ☐ f) assurance ☐

2.3 Quels sont vos projets professionnels pour l'avenir ?

a) pratique privée ☐ c) autres ☐
b) hôpital ☐