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PhD THESIS

**POPULATIONAL STUDY OF THE SECONDARY MORBIDITY
IN HAEMOPHILIA AND ITS SOCIO-ECONOMICAL IMPACT**

S U M M A R Y

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INTRODUCTION

Hemophilia is a monogenic X-linked hereditary bleeding disorder, characterized by the deficiency of coagulation factor VIII (hemophilia A-HA) or IX (hemophilia B-HB), demanding for therapeutic control a lifelong replacement with these factors. Hemophilia, a rare diseases, is fortunately experiencing a continuously improving treatment, able today to ensure a “functional cure” with the hope of soonreacheable “genetic cure”. In the previous decades pharmaceutical companies registered significant progress, succeeding in bringing into use, beside safe plasma derived (pd) coagulation factor concentrates (CFC), other recombinant factors (rF). Successively, there were a first, second, third and fourth generation, followed today by extended half-life factors (EHLF) or recently non-factor products, paving the way for the “new golden era” of hemophilia. Regular prophylaxis for life is the key of a modern haemophilia care in the world

In Romania, the replacement therapy with CFC has begun rather late (1997), and on demand (OD) therapy has been performed with low dosages; only recently (2016-2017) we could register a turning point in our hemophilia care, with a significant increase (2.7 times more) of its dedicated budget. It allowed to start regular (RP) and intermittent prophylaxis (IP), OD treatment remaining the mostly used regimen (Tab.1).

Tab. Budgetary credits foe NHP for hemofilia (x 10³ mii Lei) and number of treated patients

Year	Budget (X 10 ³ mii Lei)	Nr.PwH treated/ year	Consumption UI/cap/ year	
			F VIII	F IX
2013	36.900			
2014	60.261		0,99	0,11
2015	72.550	1080	1,06	0,11
2016	79.408	1020	1,32	0,19
2017	202.288	1197	2,28	0,29
2018	188.897	1012	2,36	0,35
2019	159.046	1007	3,7	0,39

The advantage of prophylaxis versus OD therapy has been repeatedly proved in randomized controlled clinical studies. The secondary morbidity, especially the chronic hemarthropathy is depending on the replacement regimen, obviously striking severe for those with OD therapy. Despite the acceptance of the reality that prophylaxis is the standard of care, the high economic burden of missing it in the situation of limited resources is responsible for treating only 25-30% of persons with haemophilia (PwH) in the world Unfortunately, despite the increased budget dedicated to haemophilia in 2016/2017/,with our present consumption of less than 4 IU F VIII and 0.5 IU/capita/year respectively we continue to remain among the European countries with the lowest level of therapy, under our economical affordability

In this situation, we wanted to have an insight in the real life of PwH in our country; to evaluate the secondary morbidity of haemophilia and to see what is reasonable and achievable to be performed in order to give PwH similar opportunities for treatment as they have in rest of Europe. Confronted with the present situation with significant improvement of outcomes of PwH with RP, but also facing the high competition of hemophilia for the financial support with many other disorders, with the concern of losing the access to an appropriate therapy, we decided to undertake a cost-effectiveness study of hemophilia care aiming at exploring the societal economic burden in order to find a reasonable, affordable solution, based on the medical, humanitarian and socio-economic principles of medical care.

STUDY DESIGN

It is a populational, observational descriptive ,non-randomized,cross-sectional study of PwH and its related von Willebrand diseases (vWD), diagnosed and treated in 11 surrounding counties from the Western part of Romania, chosen for the better regional

communication in this period of COVID19 pandemics. It was performed based on the presently promoted studies a PRO (Patient reported outcomes) model.

AIM of THE STUDY

We wished to obtain an image of the real life of PwH in our condition of treatment in our country, to evaluate the avoidable costs for secondary morbidity and comorbidities and to establish the affordability of a modern therapy by calculating the ICER.

OBJECTIVES

The *primary objectives* were:

- establishment of the prevalence and clinical profile of secondary morbidity
- assessment of its socio-economical impact and its significance for the quality of life

The *secondary objective* aimed:

- estimation of medical and non-medical, direct and indirect costs of haemophilia
- estimation of medical and non-medical, direct and indirect costs of secondary morbidities and of comorbidities
- comparison of the results of the two groups of patients
- evaluation of cost-effectiveness of treatment of haemophilia in our country.

PATIENTS

The study population was a cohort of 122 patients with severe (115) and moderate with severe phenotype (7) of HA (92), HB (16) and severe form of vWD (14). The sample was divided in 2 subgroups: subgroup 1, consisting of 39 patients born after 1997 with a history of replacement therapy since their early childhood, at present with RP (76.92%) or STP (15.38%) and subgroup 2 of 83 patients born before 1997, the year when replacement therapy was introduced in our country, lacking this treatment for a period, and at present predominantly (39.76%) with on-demand treatment (OD) (Tab.2).

Tab. 2. Patients in the study

Disease	Total	%
Hemofilia A- severe	87	94,57
-moderate	5	5,43
Hemofilia B -severe	14	87,50
-moderate	2	22,50
vW Disease -severe	13	92,86
-moderate	1	7,14
Total -severe	114	93,44
-moderate	8	6,56

METHODS

The study was based on a comprehensive questionnaire, administered to the patients, consisting of 56 items, for recording appropriate information on 4 domains: socio-demographic (9), medical (31), quality of health and life (10) and costs/ cost-effectiveness of treatment (6); a similar questionnaire without the medical information was administered to the control group.

For the *estimation of health quality* surrogate markers like annualized bleeding rate (ABR), annualized joint bleeding rate (AJBR), target joints, need of invasive orthopedic interventions and surgery for life threatening bleeds were used; for the evaluation of secondary morbidity much attention was dedicated to the impact of treatment: mainly on chronic hemarthropathy, an important driver of budget consumption, but also neutralizing inhibitors of F VIII or IX and bloodborne infections, like hepatitis C or B, and HIV infection

For the *economic evaluation*, the following parameters were considered for direct medical costs: specific medicines (CFC and by-passing agents-BPA), biological and imaging assessments (ultrasonography, magnetic resonance imaging, computed tomography, radiography) for diagnosis and monitoring, hospital admission and ambulatory

bleed related activity, whereas for indirect costs: healthcare transport, social support and services for handicap, sick leave, early medical retirement and labor productivity losses. All data regarding the real costs were sourced from the administrative departments of the treating clinics and from publicly available data; in order to be comparable with the dates from other countries we also established costs/capita/year, all expressed in national currency exchanged in Euro at the present rate (1 Euro=4.85 LEI)

For estimation of *quality of health*, quality of life (QoL) was evaluated using generic instruments, based on self-estimation, EQ-5D-VAS, aiming at receiving an insight in 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Additionally, the International Classification of Functioning (ICF) classification of WHO for the estimation of function and participation of our patients was used. The social impact (academic performance, familial, professional and social status) of hemophilia care was also analyzed in comparison with the control group

Special attention was dedicated for the evaluation of *cost-effectiveness* of treatment comparatively in the two subgroups, defined by their different treatment regimens, calculating the incremental costs, the incremental QALYs, costs/QALY and the ICER. For the ICER calculation we used a long-term perspective of 30 years and the present real-life expectancy for male persons in our country and discounted it by 15% for hemophiliacs under our treatment conditions. All the collected data have been analyzed, resulting in following:

- populational study of PwH
- populational study of secondary morbidities and comorbidities
- evaluation of the costs
- estimation of the quality of life and
- establishment of incremental cost-effectiveness ratio (ICER) in haemophilia care in Romania

Statistical analysis was performed using Microsoft Excel 2013 and SPSS 14.0 for Windows Evaluation Version, calculating average and standard deviation with significance at $p < 0.05$ and correlation coefficient significant when $r > 0.4$.

RESULTS

Socio-demographic and clinical data of the study group

Tab. 3. Characteristics of subgroup I and II of PwH

Variabiles	Lot I (39)	Lot II (83)	Total (122)
Age (X \pm DS)	11,3 \pm 6,51	39,7 \pm 10,79	31,0 \pm 16,3
Body weght(X \pm DS)	38,87 \pm 27,02	79,91 \pm 17,98	66,79 \pm 21,5
Therapeutic regimen			
-OD	3 (7,69%)	33 (39,76%)	36 (29,51%)
-PI	6 (15,38%)	43 (51,81%)	49 (40,16%)
-PC	30 (76,92%)	7 (8,43%)	37 (30,33%)

Tab. 4. Age at initiation of replacement

Age (years)	Lot I	Lot II	p	Total
Average \pm DS	2,22 \pm 1,88	18 \pm 10,69	<0,01	12,91 \pm 11,53

In *PwH* the clinical expression :annual bleeding (ABR) and joint bleeding rate(AJBR), are presented comparatively in dependence on the therapy in the two groups of study in tables 5,6,7

Tab. 5. ABR and AJBR in PwH with RP

Variabiles	Lot I	Lot II	p
ABR	2,84 (2,56 – 2,97)	15,25 (14,95 – 15,55)	<0,001
AJBR	1,15 (1,15 – 1,25)	12,75 (12,15 – 13,05)	<0,001

Tab. 6. ABR and AJBR in PwH with IP

Variabiles	Lot I	Lot II	p
ABR	4,0 (3,5 – 4,5)	13,90 (13,50 – 14,50)	<0,001
AJBR	3,42 (2,95 – 3,92)	10,27 (9,90 – 10,95)	<0,001

Tab. 7. ABR and AJBR in PwH with OD

Variabiles	Lot I	Lot II	p
ABR	7,33 (6,55 – 7,95)	18,31 (17,90 – 18,95)	<0,001
AJBR	6,67 (6,05 – 7,05)	14,06 (13,56 – 14,67)	<0,001

Epidemiological and clinical data regarding secondary morbidity and comorbidities of hemophilia

The *secondary morbidity* with its comprehensive clinico-biological and imagistic assessments was very impressive: a very high prevalence and severity of chronic hemarthropthies, above all in subgroup 2 of patients, 69.88% of them with poliarticular involvement and 55,88% with more than 4 bleeds/joint in a time interval of 6 months. The inhibitors and blood borne infections constituted an additional burden for our PwH (Tab.8,9). They also have been associated with comorbidities, a special burden in lot II (Tab.10).

Tab. 8. Chronic arthropathy–main secondary morbidity of haemophilia

Variabiles	Lot I (39 PwH)	Lot II (83 PwH)	p	Global lot
Number of PwH with arthropathy	8(20.51%)	58(69.88%)	<0,01	66(54.10%)
Type and number of affected joint				
-hip				
-knee				
-ankle	0	10 (12,0%)	<0,01	10 (8,2%)
-elbow	6 (15,38%)	95 (11,4%)	<0,01	101 (82,3)
-shoulder	3 (7,69%)	84(10,1%)	<0,01	87 (71%)
-other	5(12,82%)	74(89,2%)	<0,01	79 (64,7%)
	1 (2,56%)	8 (9,64%)	<0,01	9 (7,47%)
	0	2 (2,41%)	0,04	2 (1.64%)
Nr.pf patients with affected joints	8(20,5%)	59(71,08%)	<0,01	67/54,92%
1	3 (7,69%)	1 (1,2%)	0,03	4 (3.27%)
2	3 (7,69%)	10 (12%)	<0,01	13 (10,6%)
3	2 (5,12%)	7 (8,4%)	<0,01	9 (7,37%)
≥4	0	41 (49,4%)	<0,01	41 (33,6%)
Number of patients with target joints	7(17.95%)	46(55.42%)	<0,01	53(43.44%)
Type of affected joints				
-hip				
-knee	0	3 (3,6)	0,04	3 (2,45%)
-ankle	5(12,8%)	46 (55,42)	<0,01	51 (41,8%)
-elbow	2 (5,12%)	30 (36,14)	<0,01	32 (26,2%)
-shoulder	4 (10,24%)	34 (40,96)	<0,01	38(31,14%)
-other	1 (2,56%)	2 (2,41)	0,14	3 (2,45%)
	0	0	0	0
Nr. of target joints				
1	4 (10,24%)	12(14,46%)	<0,01	16 (13,11%)
2	19 (2,56%)	17(20,48%)	0,04	18(14,75%)
3	2 (5,12%)	5 (6,02%)	0,01	7(5,73%)
≥4	0	12(14,46%)	<0,01	12 (9,83%)

Tab. 9. Blood borne infection and inhibitors

	Lot I (39)	Lot II (83)	p	Total (122)
Infections				
-HIV	0	0	<0,01	0
-HBV	0	4 (4,82)	<0,01	4 (3,27%)
-HCV	0	38 (45,78)		38 (31,15%)
Inhibitors				
-low titre	1 (2,56%)	-	<0,01	1 (0,82%)
-high titre	5 (12,8%)	5 (6,02%)		10 (8,2%)
Total	6 (15,38%)	5 (6,02%)	<0,13	11 (9,02%)

Tab. 10. Comorbidities of Pch

	Lot I (39)	Lot II (83)	p	Total (122)
Subponderal IMC≤18,49	13(33,33%)	1 (1,20 %)	<0,01	14 (11,48%)
18,50-24,99	14(35,9%)	24 (28,92%)	<0.11<	35 (28,69%)
IMC 25-29,99	11(28.21%)	28(33,73%)	0,08	12 (22,95%)
Obesity gr.I	-	12 (14,46%)		3 (2,46%)
gr.II	-	3 (3,61%)		-
gr.III ≥40	1 (2,56%)	3 (3,61%)	<0,01	4 (3,28%)
Cardio-vasculaire	0	22 (26,5%)	<0,01	0
Coronar-artery disease	0	0		0
HTA	0	9 (10,84%)	<0,01	9 (7,38%)
Aquired valvulopathies	0	1 (1,20%)	0,11	1 (0,82%)
Anevriasm of aorta	0	1 (1,20%)	0,11	1 (0,82%)
Cardiac Insufficiency	0	5 (6,02 %)	<0,01	5 (4,1%)
Atrial Fibrilation	0	1(1,20%)	0,11	1 (0,82%)
Venous Insuficiency	0	2 (2,41%)	0,04	2 (1,64%)
Cerebro-vasculaire disease	0	2 (2,41%)	0,04	2 (1,64%)
Periferic Arteriopat	0	1 (1,20%)	0,11	1 (0,82%)
Diabetes	0	2 (2,4%)	0,04	2 (1,64%)
- Type 1		1 (1,2%)	0,11	1 (0,82%)
- Type 2		1(1,2%)	0,11	1 (0,82%)
Cancer	0			0
- yes		0		
- Type		0		
- No		0		
Supraponderability	0	24 (28,9%)	<0,01	30,33%
Obesity		13 (15,66%)	<0,01	
Osteoporosis	0	13 (15,66%)	<0,01	10,66%
Others				
- Epilepsy		1 (1,2%)	0,11	0,82%
- IRC		1 (1,2%)	0,11	0,82%
- Hypotiroidism		2 (2,4%)	0,04	1,64%
- Biliary litiasis		1 (1,2%)	0,11	0,82%
- Anxiety and depressionT		1 (1,2%)	0,11	0,82%
- Psoriasis		1 (1,2%)	0,11	0,82%
- Chronic Hepatitis		1 (1,2%)	0,11	0,82%

Direct and indirect costs of haemophilia care

What concerns the economic evaluation, our results were correlated with patient characteristics, mainly focused on the treatment history, specific for each subgroup, looking for the distribution of direct and indirect costs(11,12), expressed also in Euro, and also adjusted to the body weight of group II of patients (13,14)

Tab.11. Distribution of our real direct costs/patient/year (EUR)

	Total Group (122)		Subgroup 1 (39)		Subgroup 2 (83)	
	Sum	Per capita	Sum	Per capita	Sum	Per capita
Specific medication	8,284,770.31	67,907.95	3,054,449.48	78,319.21	5,230,320.82	63,015.91
Diagnosis and monitoring	26,802.06	219.68	8,615.46	220.90	18,186.00	219.11
Hospitalization	91,231.30	747.79	29,912.00	766.90	61,319.38	738.78
Total costs	8,402,803.67	68,875.42	3,092,876.94	79,307.09	5,309,826.20	63,973.81

Tab. 12. Distribution of our real indirect costs/patient/year (EUR)

	Total Group (122)		Subgroup 1 (39)		Subgroup 2 (83)	
	Sum	Per capita	Sum	Per capita	Sum	Per capita
Transport	43,772.37	358.78	18,058.55	463.04	25,713.80	309.80
Social support	18,321.60	150.14	3,112.50	79.81	15,209.00	183.24
Loss of productivity	586,587.00	4,808.09	20,582.00	527.74	566,005.00	6,819.33
Total costs	648,680.97	5,317.01	41,753.05	1,070.59	606,927.80	7,312.37

Additionally, in order to have an insight into the potential future costs of patients, now belonging to subgroup 1, reaching the age of adolescents and adults, we also calculated beside real life costs the BW adjusted costs for medication (Table 13), for total direct and indirect costs (Tables 14 and 15).

Tab. 13. Distribution of the BW-adjusted direct costs/patient/year (EUR)

	Total group (122)		Subgroup 1 (39)		Subgroup 2 (83)	
	Sum	Per capita	Sum	Per capita	Sum	Per capita
Specific medication	11,491,942.25	94,196.25	6,261,621.43	160,554.38	5,230,320.82	63,015.91
Diagnosis and monitoring	26,802.06	219.68	8,615.46	220.90	18,186.00	219.11
Hospitalization	91,231.30	747.79	29,912.00	766.90	61,319.38	738.78
Total costs	11,609,975.61	95,163.72	6,300,148.89	161,542.18	5,309,826.20	63,973.81

Tab. 14. Distribution of BW-adjusted direct and total costs/patient/year (EUR)

	Total Group (122)		Subgroup 1 (39)		Subgroup 2 (83)	
	Sum	Per capita	Sum	Per capita	Sum	Per capita
Direct costs	11,609,975.61	95,163.72	6,300,148.89	161,542.18	5,309,826.20	63,973.81
Indirect costs	648,680.97	5,317.01	41,753.05	1,070.59	606,927.80	7,312.37
Total costs	12,258,656.58	100,480.73	6,341,901.94	162,612.77	5,916,754.00	71,286.18

Tab. 15. Comparative distribution of the real and the BW-adjusted direct and indirect costs/patient/year and their proportion from the total costs (EUR)

	Total group (122)		Subgroup 1 (39)		Subgroup 2 (83)	
	Real	BW Adjusted	Real	BW Adjusted	Real	BW Adjusted
Direct costs (Euro)	68,875.4	95,163.72	79,307.00	161,542.18	63,973.8	63,973.8
%	92.83	94.71	98.67	99.34	89.74	89.74
Indirect costs (Euro)	5,317.00	5,317.00	1070.6	1070.6	7312.4	7312.4
%	7.17	5.29	1.33	0.66	10.26	10.26
Total costs (Euro)	74,192.4	100,480.73	80,377.6	162,612.77	71,286.2	71,286.2

The largest costs consumption was dedicated for the specific replacement therapy consisting of CFC including BPA (Table 16).

Tab. 16. Real and BW-adjusted costs of medication/patient/year and their proportion from direct and total costs (EUR)

	Cost CFC	Cost direct	%	Cost total	%
Real cost	67,907.95	68,875.42	98.58	74,192.40	91.52
BW adjusted costs	94,196.25	95,163.72	98.98	100,480.73	93.74
Subgroup 1					
-real cost	78,319.21	79,307.09	98.75	80,377.60	97.43
-BW adjusted costs	160,554.38	161,542.18	99.38	162,612.77	98.73
Subgroup 2					
-real cost	63,015.91	63,973.81	98.5	71,286.20	88.39
- BW adjusted cost	63,015.91	63,973.81	98.5	71,286.20	88.39

The financial impact of orthopedic interventions for chronic pain, disabling chronic hem-arthritis, expression of the principal hemophilia therapy-related secondary morbidity, is illustrated in Table 17. Inhibitors, the other considered most important secondary morbidity, is high budget consuming, as it is evident also on the same table, containing also BW-adjusted CFC costs (mentioning that the only subject with inhibitors undergoing surgery was a child with cheilognathopalatoschisis with a BW of 7 kg) (Tab.18,19).

Tab. 17. Global direct cost in PwH and surgery

Variables		Global lot		lotul I		lotul II	
		sum	per capita	sum	per capita	sum	per capita
Specific medication	lei	2,371,186.30	169,370.45	167,091.50	83,545.75	2,204,094.80	183,674.57
	euro	488,904.39	34,921.74	34,451.86	17,225.93	454,452.54	37,871.04
Diagnosis /monitoring	lei	39,185.00	2,798.93	5,315.00	2,657.50	33,870.00	2,822.50
	euro	8,079.38	577.10	1,095.88	547.94	6,983.51	581.96
Hospital care	lei	134,345.00	9,596.07	24,735.00	12,367.50	109,610.00	9,134.17
	euro	27,700.00	1,978.57	5,100.00	2,550.00	22,600.00	1,883.33
Total	lei	2,544,716.30	181,765.45	197,141.50	98,570.75	2,347,574.80	195,631.23
	euro	524,683.77	37,477.41	40,647.73	20,323.87	484,036.04	40,336.34

Tab. 18. Average costs for medication /PwH/year (Lei) in invasive interventions

Variables	Costs/ pacient/ intervention	P
Costs for PwH without inhibitors	181.765,47 ±104,235.33	0.62
Costs for PwH with inhibitors	168.613,49 ±111.16	
Costs allocated in NHP	315.000	

Tab. 19..Distribution of the real costs in invasive procedures patient/year (EUR) in invasive surgery and the impact on costs of inhibitors development

	Costs for investigations	Costs for Factor Concentrate/ Intervention	Costs for Medical Devices/ Intervention	Total cost/ Patient/ intervention
PwH without inhibitors	2798.93 503.2	169,370.45 104,235.33	9.596.07 6,985.8	181,765.45
PwH with inhibitors (real costs)	2,878.00	155,732.9	10,002.59	168,613.49
PwH with inhibitors (BW adjusted cost)	28,780.00	1,557,329.0	100,025.90	1,686,134.9

The third hemophilia treatment-related secondary morbidity is represented by blood-borne infections; the proportion of HBV (3.27%) and HCV (31.15%) was high in subgroup 2, fortunately without HIV contamination. Missing the costs of their diagnosis, monitoring and treatment, we could not introduce them in our costs calculations.

Regarding the proportion of indirect costs, a meaningful issue reflecting additional costs mainly generated by all the hemophilia-related secondary morbidity above-mentioned was 7.17% for the whole group of patients, reaching in contrast to subgroup 1 (1.33%) 10.26% in subgroup 2, as presented in Table 15.

Life Quality in PwH

The important differences between parameters of lot I and II reflecting quality of life are evident (Tab. 20,21,22).

Tab. 20. Life Quality in PwH

	Lot I (37)	Lot (43)	p
EQ-5D, VAS	0,84±0,19	0,63±0,14	0.01

Tab. 21. Social impact of hemophilia

Variabiles	Lot I	Lot II	Lot total	Lot control	p
Age X±DS	11.91±6.82	40±10.69	30.94±16.29	37±14.38	<0,01
Location					
-rural	21 (53.8%)	38(45.78%)	59(48.36%)	-	
-urban	18(46.16%)	45(54.22%)	63(51.64%)	-	
Pathology					
HA -mild	0	0	0	-	
-moderate	1(2.56%)	4(4.82%)	5(4.10%)		
-severe	25(64.10%)	62(74.70%)	87(71.31%)		
HB -moderate	1(2.56%)	1(1.21%)	2(1.64%)	-	
-severe	7(17.95%)	7(8.43%)	14(11.47%)		
wWD	5(12.82%)	9(10.84%)	14(11.47%)	-	
Educational status					
elementary school	17 (43,59)	7 (8,43)	24 (19,6 %)	6 (4,44 %)	<0,01
professional school	6 (15,38)	12 (14,46)	18 (14,75 %)	9 (6,67 %)	<0,01
high school	5 (12,82)	22 (26,51)	27 (22,13 %)	50(37,04%)	<0,01
faculty	1 (2,56)	22 (26,51)	23(18,85 %)	67(49,63%)	<0,01
preschool	9 (23,08)	0 (0)	9 (7,38 %)	1 (074%)	<0,01
other	0 (0)	2 (2,41)	2 (1,64 %)	2 (1,48 %)	0,5
illiterate	1 (2,56)	0 (0)	1 (0,82 %)	1 (0.74%)	0,5
Marital status					
Married	0	31 (37,35)	31 (25,41 %)	82 (60,74 %)	<0,01
Divorced	0	29 (34,94)	29 (23,77 %)	7 (5,19 %)	<0,01
Single	8	4 (4,82)	12 (9,84 %)	36 (26,67%)	<0,01
Other	31	0	31 (25,41 %)	4 (2.96%)	<0,01
Widower	0	0	0	2 (1,48 %)	0,04

Tab. 22. Distribution of patients

	Lotul I 39 b (%)	Lotul II 83 b (%)	p
Deficiency	8 (20,5%)	34 (40,96)	0.01
Disability		30 (36,14)	0,001
Handicap		20,84	0.001

Cost-effectiveness of haemophilia care

We considered the evaluation of cost-effectiveness to be very important for our analysis. The comparative evaluation of the increment of QoL and its consequence, the QALYs and the increment of costs in the two subgroups, was the support for calculation of the ICER on a time horizon of 30 years. The ICER resulted was in favor of the subgroup 1. However, in order to exclude the bias related to the important discordance of the BW of patients in the two groups, we calculated the costs of CFC also for the BW adjusted consumption. In real life, but at the same time also in the scenario with adjusted costs to BW, we assessed an ICER (1082.30 and 10,878.10, respectively), with values that are

under the threshold for reimbursement, being less than one GDP/capita/year for our country. The reimbursement with ICER < 2–3 GDP/capita/year is generally considered acceptable. Consequently, we can conclude that maintenance of prophylactic regimen is affordable for the patients from subgroup 1 even later, in their adulthood (Tables 23,24).

Tab. 23. Cost/QALYs and parameters of cost-effectiveness evaluation with our present real costs/patient/year (EUR)

			Incremental	Incremental		
	Total costs	QALYs	Costs	QALYs	Cost/QALYs	ICER
Subgroup 2 (83)	71,286.2	25.2			2828.88	
Subgroup 1 (39)	80,377.49	33.6	9091.29	8.4	2392.19	1082.30

Tab. 24. Parameters of cost-effectiveness evaluation with BW adjusted costs/patient/year (EUR)

			Incremental	Incremental		
	Total costs	QALYs	Cost	QALYs	Cost/QALYs	ICER
Subgroup 2 (83)	71,236.18	25.2			2826.83	
Subgroup 1 (39)	162,612.77	33.6	91,376.59	8.4	4839.67	10,878.10

DISCUSSION

Revolutionary innovative changes have been achieved in the treatment of haemophilia. We reached the “golden era”, which assures the ‘functional cure’ of the disease. All these have happened at the expense of a considerable increase of the costs.

At the same time, in the real life of the majority of PwH in the world, it became evident that lack of an optimal, adequate replacement therapy implies a great burden of secondary morbidity, morbidity that also generates high costs in the detriment of the quality of life. That is also the situation in our patients, especially in group II with more neglected replacement.

HTA agencies in cooperation with caregivers and decision makers started to evaluate, in a proper manner, the cost-effectiveness and cost-utility of PR, the only modality of long-term control of the disease for restoring health over a long period of time. A new vision of evaluation of cost-effectiveness, taking in account also the patient's perspective over the whole life (at least 30 years), suggested that “treatment for life-prophylaxis in hemophilia is more effective than on demand in a cost-utility model”.

These were the reasons to undertake this PRO model observational survey aiming at receiving a snapshot of information about the medical, psychosocial condition of our patients, their treatment and economic impact; we compared our results with correspondent outcomes from other European countries.

Our total real annual costs per patients were 74,192.4 €; they were lower than those reported in the EU 5 countries with highest economic performances (France-196,117.00, Germany-319,024.00, Italy-220,344.00, Spain-173,771.00, and UK-129,363.00 €). Our direct medical costs represented 92.83% of the total costs, lower than in Germany (97.80%), Italy (96.3%), and France (95.80%). The main cost drivers were the expenses for CFC, representing in the whole group 98.58% of the direct costs and 91.5% of the total costs. Comparing the data of the two subgroups, it is evident that in subgroup 2 only 88.39% vs. 97.43% in subgroup 1 represented CFC costs; that means that secondary costs were 2 times higher in subgroup 2. The indirect non-medical costs (7.17%) were significantly higher than in EU 5 countries (1.59–5.5%), but also higher than in Hungary and Bulgaria, expressing the high burden of costs due to secondary, hemophilia treatment related morbidity.

ICER, highly linked to QoL parameters and dependent on the QALYs, with its value in the present situation of our GDP, highly supports the affordability of continuing prophylactic replacement in all severe forms of hemophilia, in patients of more than 18 years of age. It matches with the results of the comprehensive analysis performed on world level by Stonebraker and in Europe by O'Mahoney assessing our country on the last position in EU under our economic affordability. In a scenario based on the correction of CFC costs, adjusting them to BW, the data are revealing significantly higher CFC costs, however the

assessment of ICER proved that the available prophylactic replacement of our present subgroup 1 will be affordable also in a time when it reaches adulthood.

Our results underscore the wide variety of costs that accompany a rare disease like hemophilia and the substantial economic burden carried by patients, caregivers, healthcare systems and economic potential of the country. The gold standard for evidence generating data for health interventions is represented by the randomized controlled trials, however, these are very difficult to be undertaken in the field of rare disorders; the limited size of patient population becomes even lower in the situation of multiple alternative therapeutic measures, like in the case of hemophilia]. We are aware that cost-effectiveness evaluations are confronted with many limitations, subject of disputes and controversies. Therefore, beside the real costs, we also calculated BW adjusted costs for CFC for more accurate comparative parameters in order to have a prediction of the affordability for the maintenance of prophylaxis for subgroup 1 in their adulthood.

Despite of all these precautions, our study has some limits. The source of bias in the interpretation of the results in the subgroups 1 and 2 is the important difference between age of the patients, treatment history, body weight, all impacting the dosage and implicitly the costs of medication, the differences of the distribution of HA, HB and vWD, with differential burden of disease and non-inclusion of blood-borne infections, hepatitis B and C, both with considerable budget consumption. Translating our costs/capita/year on national level could overestimate the global consumption in the country, as in our region a comprehensive multi-institutional approach of patients is set in place with the largest orthopedic and surgery centers for hemophilia, where PwH from all over the country are addressed

CONCLUSIONS

In the heterogenous condition of PwH in our country from the point of view of their secondary morbidity and the therapeutical approach, it was possible to highlight the high burden of avoidable morbidity due to undertreated disease and its impact on the quality of life and socio-professional integration. In the group of patients with unsatisfactory replacement therapy with the missing coagulation factor it was generated a significantly higher indirect costs (10,26 vs 0,66)

Our study also supported the cost-effectiveness of a correct prophylactic replacement in hemophilia. It proved that the prophylactic approach dominant in lot I is affordable to be extended also to group II in adulthood. The early introduction will prevent the secondary joint morbidity with all its deleterious consequences; but also the late introduction will slow down the dramatic evolution of already installed arthropathy with medical risks and social burden.