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ORIGINAL ARTICLE

Haemophilia Utilization Group Study – Part Va (HUGS Va): design, methods and baseline data

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Summary. To describe the study design, procedures and baseline characteristics of the Haemophilia Utilization Group Study – Part Va (HUGS Va), a US multi-center observational study evaluating the cost of care and burden of illness in persons with factor VIII deficiency. Patients with factor VIII level ≤30%, age 2–64 years, receiving treatment at one of six federally supported haemophilia treatment centres (HTCs) were enrolled in the study. Participants completed an initial interview including questions on socio-demographical characteristics, health insurance status, co-morbidities, access to care, haemophilia treatment regimen, factor utilization, self-reported joint pain and motion limitation and health-related quality of life. A periodic follow-up survey collected data regarding time lost from usual activities, disability days, health care utilization and outcomes of care. HTC clinicians documented participants' baseline clinical characteristics and pharmacy dispensing records for 2 years. Between July 2005 and July 2007, 329 participants were enrolled. Average age was 9.7 years for children and 33.5 years for adults; two-thirds had severe haemophilia. The distributions of age, marital status, education level and barriers to haemophilia care were relatively consistent across haemophilic severity categories. Differences were found in participants' employment status, insurance status and income. Overall, children with haemophilia had quality of life scores comparable to healthy counterparts. Adults had significantly lower physical functioning than the general US population. As one of the largest economic studies of haemophilia care, HUGS Va will provide detailed information regarding the burden of illness and health care utilization in the US haemophilia A population.

Keywords: cost of illness, haemophilia, observational study, outcome, quality of life, utilization

Introduction

Haemophilia is a rare chronic inherited bleeding disorder affecting approximately 400 000 persons of all races worldwide and 20 000 in the United States [1–3]. Patients with haemophilia either lack or are deficient in clotting factors VIII or IX, which places them at high risk of bleeding into the joints, muscles and other hollow organs. Repeated haemorrhage into joints, especially in persons with severe haemophilia, can lead to the development of chronic arthropathy, which causes joint pain, reduction in joint range of motion (ROM), crippling musculoskeletal deformity and disability.

The availability of commercially available clotting factor has transformed haemophilia from a frequently fatal to a manageable disease. Since the 1960s, clotting factor concentrate has been used widely to treat haemophilia patients episodically [4]. Episodic treatment, administered after a bleed has occurred, is known to slow the progression of arthropathy, but not to reverse it. Clotting factors can also be infused prophylactically on a regular schedule to maintain the blood factor activity above 1%, especially in persons with

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severe haemophilia. Many clinical studies have shown that prophylaxis can significantly improve outcomes by decreasing the frequency of bleeding, thereby delay the onset of arthropathy and improve patients' quality of life [1,5–8]. In a recent randomized clinical trial, Manco-Johnson *et al.* [9] found that children who received primary prophylaxis had significantly greater reduction in the risk of joint damage detected by MRI and fewer joint bleeds compared with those on episodic treatment. Primary prophylaxis is recommended for children with severe haemophilia by many medical organizations, including the World Health Organization [10].

Clotting factors are very costly [between $100 000 and $300 000 per year for a person with severe haemophilia (9)] and haemophilia treatment is lifelong. Clotting factor consumption accounted for 72% of total costs, ranging from 45% for mild haemophilia to 83% for severe haemophilia. Prophylactic treatment requires two to three times more clotting factor than episodic treatment [11,12]. The amount is even higher in patients with inhibitors who receive immune tolerance therapy [13,14]. Optimal management of haemophilia care requires an understanding of the costs of illness, the outcomes associated with various treatment regimens, the risk factors associated with poor outcomes and the cost-effectiveness of various treatment strategies. Such information assists policy makers and those involved in the delivery of haemophilia services as they work to provide adequate care to chronically ill patients and to maximize their health status.

The Haemophilia Utilization Group Study (HUGS) was initiated in 1995 to quantify both the annual utilization of resources in haemophilia treatment and the burden of illness resulting from haemophilia. Clinical records and haemophilia care cost data were collected for 336 patients receiving treatment at one of five federally supported haemophilia treatment centres (HTCs) in California [15,16]. The study found that medical costs were significantly associated with prophylaxis, history of inhibitor and comorbid medical conditions, such as HIV and arthropathy. However, the initial HUGS data collection was completed more than one decade ago, and only included HTCs in California, thereby limiting its generalizability in identifying current trends in haemophilia care and treatment on a national level. Therefore, in 2005, the HUGS team launched a 2-year national observational study: HUGS Va. The current HUGS study was designed to: (i) examine health care utilization and cost of illness among persons with haemophilia A at several HTCs in the US, and (ii) link the patient characteristics and physician characteristics with clinically relevant haemophilia health outcomes, including arthropathy, quality of life, functional and work status. The objective of this article was to summarize the study design and data collection of HUGS Va, and to present the baseline characteristics of the study cohort.

Materials and methods

Study design

The HUGS Va is a 2-year multicenter observational cohort study conducted in six US HTCs that provide care to patients in seven geographically diverse states (California, Colorado, Indiana, Massachusetts, Montana, Texas and Wyoming). Data were collected prospectively from both patients and health care providers. Participation was voluntary, and informed consent was given by patients (or parents of minor children and assents by children) before recruitment. The University of Southern California (USC) served as the data and coordinating center. The study protocol was approved by the Institutional Review Boards of USC and of each participating HTC.

Eligibility and exclusion criteria

Patient selection was stratified by the level of factor VIII deficiency based on the Centers of Disease Control and Prevention (CDC) surveillance report of haemophilia population in each region, to ensure a representative proportion of mild, moderate and severe patients were recruited in each region [3]. Haemophilia severity levels were categorized as mild if the factor activity is 6–30%, moderate if 1–5% and severe if <1% of normal.

The inclusion criteria for patient participation in the study were: (i) ages 2–64 years, (ii) factor VIII level ≤30%, with or without a history of inhibitor, (iii) received at least 90% of their haemophilia care at the participating HTC, (iv) obtained HTC care within 2 years prior to study enrolment, and (v) English speaking. Individuals were excluded from participation in the study if they were determined to be cognitively impaired or had an additional bleeding disorder.

Patient survey data collection

A convenience sample patients were recruited in this study. A total of 1228 active patients diagnosed with haemophilia A were seen at one of the six HTCs during 2005. Among them, 95% were aged 2–64 and received at least 90% of their haemophilia care at the HTCs. Potentially eligible patients were identified by each centre, informed of the purpose of study and asked if they wished to participate. Patients were not contacted if they were non-English speaking, diagnosed with additional bleeding disorders, did not respond to mail or email contact or had psychological issues that make them unsuitable for participation. After ascertaining eligibility, informed consent was obtained.

A baseline survey was completed during an initial patient interview, which included the following items: socio-demographical characteristics, health insurance status, co-morbidities, access to care, haemophilia treatment regimen, factor utilization and self-reported arthropathy (joint pain and motion limitation). A periodic patient follow-up survey was used to collect data on time lost from work, school or usual activities, disability days, health care utilization and outcomes of care. Follow-up interviews were administered monthly in the first year and semi-annually in the second year. Based on preference, participant follow-up interviews were administered using either an automated telephone system or a commercial online survey system. Some follow-up data were obtained *via* telephone interviews conducted by health care providers, when participants were not responsive, had no internet access or had difficulties with the automated telephone survey system.

Participants were compensated a total of $90 for participation in the study. A $20 gift card or a $20 donation to a haemophilia-related charity (such as Haemophilia Camp) was given at initial interview; $60 was given at the end of first year follow-up and $10 for completion final survey.

Health-related quality of life

General health status and well being was measured using validated health-related quality of life (HRQoL) questionnaires, which were administered upon initial interview and every 6 months during the 2-year follow-up.

SF-12. Adult general HRQoL was assessed using the Short Form 12-item Health Survey version 1 (SF-12). This instrument is an abbreviated 12-item version of the widely used SF-36, and has been found to reproduce scores on the original SF-36 with considerable accuracy and less respondent burden [17]. The SF-12 assesses eight dimensions of HRQoL, which provide two summary scores, physical component summary (PCS) and mental component summary (MCS). The score in each dimension was calculated using the US scoring algorithm. The scoring methods were norm-based and standardized to the 1998 US population, so that the general population has a mean score of 50 and standard deviation of 10 for both scales. Scores above or below 50 can be interpreted as above or below the general population norm.

PedsQL. The PedsQL™ 4.0 generic core scales [18] were used to assess HRQoL of participants younger than 18. The PedsQL is a general, non-disease specific HRQoL instrument developed in the US for children and adolescents. The PedsQL has been shown to be valid, reliable and responsive [19,20]. Parents for participants aged 2–7 and participants aged 8–17 (or their parents) self administered the questionnaire in our study. The questionnaire consists of 23 items that contribute to a total score, and to four subscales of functioning: physical, emotional, social and school. The subscale physical functioning can be used to produce a single Physical Health Summary Scale, whereas the remaining three subscales can be combined to be used as a single Psychosocial Health Summary Scale to facilitate comparison with the adult HRQoL scales. Scales range: 0–100. The higher score represents better HRQoL.

Clinical data collection

Patient clinical data were collected by healthcare providers through chart and pharmacy dispensing record review using three standardized clinical data collection forms. Baseline clinical characteristics were documented when participants had initial interview. Information recorded in this form included: body weight and height, current and historical inhibitor levels, history of immune tolerance therapy, hepatitis virus serology, infusion method and treatment regimen at the time of the study. We were able to obtain clinically measured ROM for patients from three HTCs to compare with self-reported joint pain and motion limitation that was collected for all patients. Then 1-year clinical charts were reviewed to collect information on medical care utilization, changes in treatment regimen, inhibitor development, new medical conditions, emergency room visits and hospitalizations. A third dispensing data collection form was used to record the brand and amount of factor or other haemophilia-related products dispensed to participants each month in the 2-year study period.

HTC Information

To assess the variety of services offered during each comprehensive visit, we collected general information from each HTC regarding the services and providers involved. As patients from rural areas often face obstacles related to geographical distance and transportation when seeking health care, we identified whether each HTC provided an outreach clinic to serve these rural areas. Finally, we identified a variable called 'distance to HTC', which is the distance from the patients' home to their regular or outreach clinic, where participants received their usual care.

Statistical analysis

Participant age is calculated as of the date of initial interview. For some variables, such as marital status, education level, employment status, income and barriers to care, parents' status was used for participants

younger than 18. Descriptive statistics were calculated for all participants grouped by haemophilia severity or age. Comparisons of socio-demographical and clinical characteristics between (among) groups were calculated using chi-squared or Fisher Exact statistic for discrete variables. For the ROM measurement, a method suggested by Soucie *et al.* was employed to calculate the proportion of ROM limitation [21]. A higher percentage ROM limitation score indicates less joint movement. For HRQoL, one-way analysis of variance (ANOVA), followed by *post hoc* testing with the Scheffe multiple comparison procedure was performed to identify significant differences among the mean SF-12 and PedsQL score grouped by haemophilia severity. All analyses were performed using SAS version 9.1 statistical software (SAS Institute, Cary, NC, USA).

Results

Baseline socio-demographical and clinical characteristics

Between July 2005 and July 2007, 329 patients with haemophilia A were recruited into the HUGS Va study. One centre was not able to provide the number of patients who declined to participate. From the other centres, the rate of those who declined to participate in the study ranges from 2% to 10% of eligible patients in the five HTCs. The average age was 9.7(SD = 4.5) years for children and 33.5 (SD = 12.5) years for adults. The socio-demographical and clinical characteristics of the participants, stratified by disease severity, are shown in Table 1. More than 98% of participants were men. The proportions of persons with mild, moderate and severe haemophilia were 24.9%, 10.9% and 64.1% respectively. The vast majority (94%) of patients reported using factor VIII concentrates and 44% treated prophylactically. Sixteen percent had a history of inhibitors (antibody to factor VIII) and 4% had current inhibitors. Eighty percent of adults reported one or more co-morbidities. More than 70% of adults were antibody-positive for the HCV and 27% were HIV-positive. Mean ROM limitation was 5.2% (range: −10.1% to 38.7%).

The distributions of age, marital status, education level and barriers to HTC utilization were relatively consistent across haemophilia severity groups (Table 1). However, differences were found in participants' employment status and income. Participants with severe haemophilia were more likely to work part-time or be unemployed and have a lower income. Many clinical characteristics were also found to be associated with haemophilic severity. The greater the severity of haemophilia, the larger the proportion of participants with co-morbidities, prophylaxis use, a history of inhibitors and factor infusion by self or family members. The prevalence of HIV and HCV infection in adults was also significantly associated with haemophilic severity as a result of greater exposure to plasma-derived factor concentrates before the availability of high-purity, virus inactivated plasma factor VIII or recombinant products.

The average distance to HTC (primary clinic or local outreach clinic) was 45.3 miles (range: 1.2–460 miles). A total of 32 (9.7%) patients received their usual haemophilia care at a local outreach clinic affiliated with two HTCs. For these patients, the average distance to outreach was 47.8 miles compared with 271.2 miles if they attended the primary HTC clinic ($P < 0.0001$).

Detailed information regarding the insurance status of participants is shown in Table 2. Ninety percent of patients had insurance coverage for the entire year prior to enrolment and less than 10% had partial-year coverage. Almost one-fifth of the participants did not know their monthly out-of-pocket premium and 19% reported that they would pay a lower health insurance premium if they/their children did not have haemophilia. Among those insured, 33% had public insurance; 60% had private or commercial insurance; the remainder reported having both. Overall, 27% of the participants reported difficulty finding adequate coverage, 40% reported not having full coverage for haemophilia-related medical care and 42% did not have full coverage for prescription drugs. To obtain or retain their health insurance, 20% reported staying in a less desirable job, whereas 14% earned less to qualify for public insurance and 10% worked part-time to keep total income low.

Difference in baseline characteristics between children and adults

Additional analysis comparing the socio-demographical and clinical characteristics between children and adults is shown in Table 3. Most socio-demographical characteristics were similar between age groups, with the exception of insurance status. All children were insured, whereas 7% of adults did not have any insurance. The mean out-of-pocket monthly insurance premium was $208.90 (range: $0–$2,000) for children and $156.20 (range: $0–$1,273) for adults. Eighty-six percent of children with severe haemophilia were treated prophylactically, compared with only 42% of adults. Discrepancies were also found between children and adults in self-reported joint pain and motion limitation. Adults were more likely to report having barriers to care than were the parents of children with haemophilia (18.3% vs. 9.8%, $P = 0.03$).

HRQoL

The results of HRQoL measurements are shown in Table 4. Overall, children with haemophilia had quality of life scores that were similar to the population without

Table 1. Baseline socio-demographical and clinical characteristics of all participants.

Characteristics, *N* (%)	Total (*N* = 329)	Haemophilia severity			*P*-value*
		Mild *N* = 82 (24.9%)	Moderate (*N* = 36) (10.9%)	Severe *N* = 211 (64.1%)	
Socio-demographical characteristics					
Age	–	–	–	–	0.39
Child (2–17 years old)	165 (50.2)	36 (43.2)	20 (55.6)	109 (51.7)	–
Adult (18+ years-old)	164 (49.8)	46 (56.1)	16 (44.4)	102 (48.3)	–
Male	325 (98.8)	79 (96.3)	36 (100)	210 (99.5)	0.06
Married/with a partner†	193 (58.7)	57 (69.5)	19 (52.9)	117 (55.5)	0.07
Employment status†	–	–	–	–	0.04
Full-time	150 (45.6)	49 (59.8)	14 (38.9)	87 (41.2)	–
Part-time	74 (22.5)	11 (13.4)	8 (22.2)	55 (26.1)	–
Not employed	105 (31.9)	22 (26.8)	14 (38.9)	69 (32.7)	–
Education >12 years†	226 (69.5)	57 (70.4)	24 (66.7)	145 (69.7)	0.92
Annual household income†,‡	–	–	–	–	0.05
Below $20,000	54 (18.1)	7 (9.3)	3 (9.7)	44 (22.8)	–
$20,001–$40,000	75 (25.1)	15 (20.0)	11 (35.5)	49 (25.4)	–
$40,001–$75,000	73 (24.4)	22 (29.3)	7 (22.6)	44 (22.8)	–
$75,001 and above	97 (32.4)	31 (41.4)	10 (32.2)	56 (29.0)	–
Race/ethnicity‡	–	–	–	–	<0.0001
White/non-hispanic	213 (65.7)	53 (65.4)	23 (67.6)	137 (65.6)	–
Black/non-hispanic	16 (4.9)	2 (2.5)	7 (20.6)	7 (3.3)	–
Hispanic	59 (18.2)	21 (25.9)	3 (8.8)	35 (16.7)	–
Other§	36 (11.2)	5 (6.2)	1 (2.9)	30 (14.4)	–
HTC location**	–	–	–	–	<0.01
UMASS	54 (16.4)	15 (18.3)	0 (0)	39 (18.5)	–
CHOC	49 (14.9)	11 (13.4)	12 (33.3)	26 (12.3)	–
UCD	62 (18.8)	18 (22.0)	3 (8.3)	41 (19.4)	–
CHLA	50 (15.2)	15 (18.3)	4 (11.1)	31 (14.7)	–
IHTC	56 (17.0)	7 (8.5)	9 (25.0)	40 (19.0)	–
GSHTC	58 (17.6)	16 (19.5)	8 (22.2)	34 (16.1)	–
Barriers to care†	46 (14.1)	12 (14.8)	3 (8.3)	31 (14.8)	0.57
Clinical characteristics					
Co-morbidities (1 or more)¶	132 (80.5)	30 (65.2)	12 (75.0)	90 (88.2)	<0.01
HCV	113 (72.0)	20 (47.6)	12 (75.0)	81 (81.8)	<0.001
HIV/AIDS	44 (26.8)	2 (4.3)	1 (6.3)	41 (40.2)	<0.0001
Self-reported joint pain‡	–	–	–	–	<0.0001
Have no pain	87 (26.5)	42 (51.9)	11 (30.6)	34 (16.1)	–
Only when bleeding	95 (29.0)	13 (16.0)	13 (36.1)	69 (32.7)	–
Some of the time	73 (22.3)	11 (13.6)	7 (19.4)	55 (26.1)	–
Most of the time	51 (15.5)	10 (12.4)	4 (11.1)	37 (17.5)	–
Severe pain all the time	22 (6.7)	5 (6.2)	1 (2.8)	16 (7.6)	–
Self-reported motion limitation‡	–	–	–	–	<0.0001
No limitation	114 (35.0)	50 (61.7)	14 (38.9)	50 (23.9)	–
Only when bleeding	102 (31.3)	19 (23.5)	14 (38.9)	69 (33.0)	–
Affects activities	95 (29.1)	12 (14.8)	7 (19.4)	76 (36.4)	–
Severe limitation	15 (4.6)	0 (0)	1 (2.8)	14 (6.7)	–
Use factor VIII	305 (93.8)	68 (85.0)	32 (88.9)	205 (98.1)	0.0001
Use of prophylaxis	144 (43.8)	4 (4.9)	3 (8.3)	137 (64.9)	<0.0001
History of inhibitors	51 (15.5)	3 (3.7)	1 (2.8)	47 (22.3)	<0.0001
Current inhibitors	13 (4.0)	2 (2.4)	0 (0)	11 (5.2)	0.24
Primary infusion method	–	–	–	–	<0.0001
Self	160 (49.2)	26 (33.3)	9 (25.0)	125 (59.2)	–
Parent/family	91 (28.0)	10 (12.8)	8 (22.2)	73 (34.6)	–
Clinic staff	37 (11.4)	19 (24.4)	12 (33.3)	6 (2.8)	–
Emergency room	23 (7.1)	17 (21.8)	5 (13.9)	1 (0.5)	–
Visiting nurse	14 (4.3)	6 (7.7)	5 (5.6)	6 (2.8)	–

HTC, haemophilia treatment centre; HCV, hepatitis C virus; HIV/AIDS, acquired immunodeficiency syndrome/human immunodeficiency virus.
*Data are presented as frequency (column percentage); *P*-values of 0.05 or less indicate that the levels of the characteristic differ significantly across haemophilia severity based on chi-squared or Fisher Exact statistic.
†For patient or parent for age <18 years.
‡Data do not add up to *N* = 329 because of missing data.
§Other races include: American Indian, Alaskan Native, Asian/Pacific Islander and other;
¶Applied to adults only, *N* = 164.
**UMASS, Worcester, Massachusetts; CHOC, Orange County, California; UCD, Denver, Colorado; CHLA, Los Angeles, California; IHTC, Indianapolis, Indiana; GSHTC, Houston, Texas.

Table 2. Insurance status of all participants.

Characteristics, *N* (%)	Total (*N* = 329)	Haemophilia severity			*P*-value*
		Mild (*N* = 82)	Moderate (*N* = 36)	Severe (*N* = 211)	
Health insurance	–	–	–	–	0.98
Not covered	12 (3.7)	4 (4.9)	1 (2.9)	7 (3.4)	–
Less than 12 months	19 (5.9)	5 (6.2)	2 (5.9)	12 (5.8)	–
Entire 12 months	280 (90.3)	72 (88.9)	31 (91.2)	187 (90.8)	–
Insurance type†	–	–	–	–	<0.01
Private	189 (60.0)	59 (75.6)	24 (68.6)	106 (52.5)	–
Public	104 (33.0)	16 (20.5)	9 (25.7)	79 (39.1)	–
Both public and private	22 (7.0)	3 (3.9)	2 (5.7)	17 (8.4)	–
Insurance limiting HTC visit†	–	–	–	–	0.04
Yes	7 (2.3)	0 (0.0)	0 (0)	7 (3.5)	–
No	267 (85.9)	62 (80.5)	29 (85.3)	176 (88.0)	–
Don't know/refused	37 (11.9)	15 (19.5)	5 (14.7)	17 (8.5)	–
Pay less premiums if no haemophilia†	–	–	–	–	0.05
Yes	59 (19.0)	11 (14.3)	5 (14.3)	43 (21.6)	–
No	217 (69.8)	55 (71.4)	22 (62.9)	140 (70.4)	–
Don't know/refused	35 (11.3)	11 (14.3)	8 (22.9)	16 (8.0)	–
Insurance coverage to haemophilia medical cost	–	–	–	–	0.04
Not covered	10 (3.1)	3 (3.9)	1 (2.8)	6 (2.9)	–
More than half	119 (37.3)	25 (32.9)	16 (44.4)	78 (37.7)	–
All	173 (54.2)	39 (51.3)	16 (44.4)	118 (57)	–
Don't know/refused	17 (5.3)	9 (11.8)	3 (8.3)	5 (2.4)	–
Insurance coverage to haemophilia drug cost	–	–	–	–	<0.01
Not covered	14 (4.4)	4 (5.3)	1 (2. 9)	9 (4.3)	–
More than half	119 (37.2)	28 (36.8)	16 (47.1)	75 (35.7)	–
All	170 (53.1)	34 (44.7)	14 (41.2)	122 (58.1)	–
Don't know/refused	17 (5.3)	10 (13.2)	3 (8.8)	4 (1.9)	–
Difficulty in finding insurance‡	–	–	–	–	0.56
Yes	88 (27.0)	23 (28.8)	10 (27.8)	55 (26.2)	–
No	229 (70.2)	53 (66.3)	26 (72.2)	150 (71.4)	–
Don't know/refused	9 (2.8)	4 (5.0)	0 (0)	5 (2.4)	–
Things you had to do to get or maintain your health insurance?‡	–	–	–	–	–
Work part-time	34 (10.3)	6 (7.3)	2 (5.6)	26 (12.3)	0.25
Stay in less desirable job	64 (19.5)	13 (15.9)	4 (11.1)	47 (22.3)	0.36
Spend savings	14 (4.3)	3 (3.7)	1 (2.8)	10 (4.7)	0.83
Earn less	44 (13.4)	10 (12.2)	5 (13.9)	29 (13.7)	0.97
Change marital status	5 (1.5)	1 (1.2)	1 (2.8)	3 (1.4)	0.87
Others	17 (5.2)	4 (4.9)	0 (0)	13 (6.2)	0.56

HTC, haemophilia treatment centre.

*Data are presented as frequency (column percentage); *P*-values of 0.05 or less indicate that the levels of the characteristic differ significantly across haemophilia severity based on chi-squared or Fisher Exact statistic.

†Applied to those with insurance only (*N* = 317).

‡For patient or parent for age <18 years.

medical diagnoses [22]. In our sample of haemophilic children, the mean total PedsQL score was 85.9 (SD = 13.8) compared with 82.7 for healthy children. The subscale for physical functioning was 89.5 (SD = 15.2) for children with haemophilia versus 84.5. The psychosocial functioning subscales were 84.1 (SD = 15.4) and 81.7 respectively. Adult patients had significantly lower PCS than the general US population. The mean haemophilic adult SF12-PCS was 43.4 (SD = 10.7), whereas the mean SF12-MCS was 50.9 (SD = 10.1). Despite having a serious chronic disease, adult individuals with haemophilia had a relatively normal mental score compared with the general population. Both adults and children with severe haemophilia had significantly lower physical health scores compared with those with mild haemophilia ($P = 0.01$ and $P = 0.02$ respectively).

Discussion

The HUGS Va is one of the largest economic studies of haemophilia care conducted in the United States. Over the past 10 years, HUGS has successfully collected the healthcare utilization history of patients with factor VIII deficiency from retrospective chart reviews and developed a model of predictors associated with higher utilization and cost of care [15,16]. The new HUGS study uses prospective data collection to ensure more accurate and comprehensive measures of outcomes, utilization and cost of haemophilia care. Understanding

Table 3. Baseline socio-demographical and clinical characteristics between children and adults

Characteristics	Children (N = 165)	Adults (N = 164)	P-value*
Age in years, mean (standard deviation)	9.7 (4.5)	33.5 (12.5)	–
Haemophilia severity	–	–	0.39
Mild	36 (21.8)	46 (28.0)	–
Moderate	20 (12.1)	16 (9.8)	–
Severe	109 (66.1)	102 (62.2)	–
Insurance status	–	–	<0.01
None	0 (0)	12 (7.4)	–
Private	101 (61.2)	88 (54.0)	–
Public	51 (31.1)	53 (32.5)	–
Both public and private	12 (7.3)	10 (6.1)	–
Insurance coverage	–	–	<0.0001
Not covered	0 (0)	12 (7.5)	–
More than 12 months	2 (1.2)	17 (10.7)	–
Entire 12 months	160 (98.8)	130 (81.8)	–
Co-morbidities	–	–	<0.0001
No	127 (77.0)	32 (19.5)	–
Yes (1 or more)	38 (23.0)	132 (80.5)	–
Joint pain	–	–	<0.0001
Have no pain	72 (43.6)	15 (9.2)	–
Only when bleeding	59 (35.8)	36 (22.1)	–
Some of the time	24 (14.5)	49 (30.0)	–
Most of the time	9 (5.5)	42 (25.8)	–
Severe pain all the time	1 (0.6)	21 (12.9)	–
Motion limitation	–	–	<0.0001
No limitation	88 (54.0)	26 (15.9)	–
Only when bleeding	59 (36.2)	43 (26.4)	–
Affects activities	14 (8.6)	81 (49.7)	–
Severe limitation	2 (1.2)	13 (8.0)	–
Barriers to care	16 (9.8)	30 (18.3)	0.03
Use factor VIII	154 (93.3)	151 (92.1)	0.66
Severe patients only	109 (100)	96 (94.1)	0.01
Use of prophylaxis	97 (57.8)	47 (28.7)	<0.0001
Severe patients only	94 (86.2)	43 (42.2)	<0.0001
Primary infusion method	–	–	<0.0001
Self	30 (18.5)	130 (79.8)	–
Parent/family	83 (51.2)	8 (4.9)	–
Clinic staff	20 (12.4)	17 (10.4)	–
Emergency room	19 (11.7)	4 (2.4)	–
Visiting nurse	10 (6.2)	4 (2.4)	–

*P-values of 0.05 or less indicate that the levels of the characteristic differ significantly between children and adults based on chi-squared or Fisher Exact statistic.

Table 4. Descriptive statistics for health-related quality of life.

	N	Mean (SD)	Median	Minimum	Maximum
Adult: SF-12					
SF12-PCS	157	43.4 (10.7)	45.3	14.3	60.7
SF12-MCS	157	50.9 (10.1)	54.1	24.3	67.2
Child: PedsQL					
Total score	164	85.9 (13.8)	90.2	22.8	100
Physical functioning	163	89.5 (15.2)	93.8	6.3	100
Psychosocial health	164	84.1 (15.3)	87.9	31.7	100
Emotional functioning	165	82.2 (19.1)	85.0	20.0	100
Social functioning	164	87.7 (16.8)	95.0	25.0	100
School functioning	151	81.6 (17.3)	85.0	35.0	100

SD, standard deviation; SF-12, Short Form 12-item Health Survey; PCS, physical component summary; MCS, mental component summary.

the burden and cost of haemophilia and the associated variables will expand the knowledge base regarding the impact of haemophilia on society, inform important health policy decisions related to haemophilia care and treatment and will support appropriate decision-making for public and private insurance programs.

Several limitations need to be considered when interpreting the results of this study. First, this cohort of haemophilia A patients had a higher proportion of patients with severe disease compared with the proportion in the United States reported by the CDC's UDC project [1]. This difference might limit the generalizability of the results of the study. However, this problem will be minimized in future analyses of the cost of haemophilia care by adjusting for severity. A second limitation is that haemophilia-related arthropathy is self-reported by patients or their parents. Different experiences and expectations in health status may lead patients to understand and respond to a given question in different ways [23]. In addition, parents, as a proxy, may have a different perception of health status than the children themselves. To account for this issue, we abstracted clinically measured ROM in a subsample and will compare the self-reported joint pain and motion limitation with the clinical measurement in the future study. Thirdly, the prospective data collection methodology also limited our ability to assess patients' treatment patterns and utilization prior to the study. Because of haemophilia's chronicity, and the progressive nature of joint disease, it is important note that current outcomes, such as arthropathy and HRQoL, can be attributed in part to historical utilization patterns and behaviours, not solely to current utilization and behaviours. Finally, our cohort includes only patients who received care in the network of more than 130 of federally supported HTCs [24] and the results therefore are applicable only to those receiving HTC care. Approximately 30% of persons with haemophilia in the US do not receive care through this nationwide network [21]. The characteristics, especially outcomes, of those patients may be different than those found in this study cohort.

In summary, the HUGS Va study provides detailed information regarding the burden of illness and health care utilization in patients with haemophilia. It is our hope that these data will contribute to a better understanding of the economic impact of this rare, chronic and expensive condition and will assist both policymakers and health care providers in making optimal decisions regarding the use of finite health care resources.

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References

1 Royal S, Schramm W, Berntorp E *et al.* Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia* 2002; **8**: 44–50.
2 World Federation of Hemophilia. Available at http://www.wfh.org. Accessed July 10, 2010.
3 The Centers for Disease Control and Prevention: Hemophilia Data and Statistics. Available at http://www.cdc.gov/ncbddd/hemophilia/data.html. Accessed July 10, 2010.
4 Teitel JM, Barnard D, Israels S, Lillicrap D, Poon MC, Sek J. Home management of haemophilia. *Haemophilia* 2004; **10**: 118–33.
5 Stobart K, Iorio A, Wu JK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. *Cochrane Database Syst Rev* 2006; CD003429.
6 Szucs TD, Offner A, Kroner B *et al.* Resource utilisation in haemophiliacs treated in Europe: Results from the European Study on Socioeconomic Aspects of Haemophilia Care. *Haemophilia* 1998; **4**: 498–501.
7 Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med* 1994; **236**: 391–9.
8 Fischer K, van der Bom JG, Molho P *et al.* Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia* 2002; **8**: 745–52.
9 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.
10 Berntorp E, Boulyjenkov V, Brettler D *et al.* Modern treatment of haemophilia. *Bull World Health Organ* 1995; **73**: 691–701.
11 Bohn RL, Avorn J, Glynn RJ, Choodnovskiy I, Haschemeyer R, Aledort LM. Prophylactic use of factor VIII: an economic evaluation. *Thromb Haemost* 1998; **79**: 932–7.
12 Miners AH, Sabin CA, Tolley KH, Lee CA. Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease. *J Intern Med* 1998; **244**: 515–22.
13 Gringeri A, Mantovani LG, Scalone L, Mannucci PM. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; **102**: 2358–63.
14 Auerswald G, von Depka Prondzinski M, Ehlken B *et al.* Treatment patterns and cost-of-illness of severe haemophilia in patients with inhibitors in Germany. *Haemophilia* 2004; **10**: 499–508.
15 Globe DR, Curtis RG, Koerper MA. Utilization of care in haemophilia: a resource-based method for cost analysis from the Haemophilia Utilization Group Study (HUGS). *Haemophilia* 2004; **10**(Suppl. 1): 63–70.
16 Globe DR, Cunningham WE, Andersen R *et al.* The Hemophilia Utilization Group Study (HUGS): determinants of costs of care in persons with haemophilia A. *Haemophilia* 2003; **9**: 325–31.
17 Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**: 220–33.
18 Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001; **39**: 800–12.
19 Varni JW, Seid M, Smith Knight T, Burwinkle T, Brown J, Szer IS. The PedsQL in pediatric rheumatology: reliability, validity, and responsiveness of the Pediatric Quality of Life Inventory Generic Core Scales and Rheumatology Module. *Arthritis Rheum* 2002; **46**: 714–25.
20 Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003; **3**: 329–41.
21 Soucie JM, Cianfrini C, Janco RL *et al.* Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. *Blood* 2004; **103**: 2467–73.
22 Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007; **5**: 2.
23 Salomon JA, Tandon A, Murray CJ. Comparability of self rated health: cross sectional multi-country survey using anchoring vignettes. *BMJ* 2004; **328**: 258.
24 Baker JR, Crudder SO, Riske B, Bias V, Forsberg A. A model for a regional system of care to promote the health and well-being of people with rare chronic genetic disorders. *Am J Public Health* 2005; **95**: 1910–6.

