Accepted: 24 April 2017

DOI: 10.1111/hae.13275

ORIGINAL ARTICLE

Clinical Haemophilia

WILEY Haemophilia

The effects of joint disease, inhibitors and other complications on health-related quality of life among males with severe haemophilia A in the United States

J. M. Soucie[1] | S. D. Grosse[1] | A.-E.-A. Siddiqi[1] | V. Byams[1] | J. Thierry[1] | M. M. Zack[2] | A. Shapiro[3] | N. Duncan[3] the Hemophilia Treatment Centers Network

[1]Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA

[2]Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

[3]Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA

Correspondence
J. Michael Soucie, PhD, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA.
Email: msoucie@cdc.gov

Introduction: Health-related quality of life (HRQoL) is reduced among persons with haemophilia. Little is known about how HRQoL varies with complications of haemophilia such as inhibitors and joint disease. Estimates of preference-based HRQoL measures are needed to model the cost-effectiveness of prevention strategies.

Aim: We examined the characteristics of a national sample of persons with severe haemophilia A for associations with two preference-based measures of HRQoL.

Methods: We analysed utility weights converted from EuroQol 5 Dimensions (EQ-5D) and the Short Form 6 Dimensions (SF-6D) scores from 1859 males aged ≥14 years with severe haemophilia A treated at 135 US haemophilia treatment centres in 2005-2011. Bivariate and regression analyses examined age-group-specific associations of HRQoL with inhibitor status, overweight/obesity, number of bleeds, viral infections, indicators of liver and joint disease, and severe bleeding at the time of the first HRQoL measurement.

Results: Overall mean HRQoL utility weight values were 0.71 using the SF-6D and 0.78 using the EQ-5D. All studied patient characteristics except for overweight/obesity were significantly associated with HRQoL in bivariate analyses. In a multivariate analysis, only joint disease was significantly associated with utility weights from both HRQoL measures and across all age groups. After adjustment for joint disease and other variables, the presence of an inhibitor was not significantly associated with HRQoL scores from either of the standardized assessment tools.

Conclusion: Clinically significant complications of haemophilia, especially joint disease, are strongly associated with HRQoL and should be accounted for in studies of preference-based health utilities for people with haemophilia.

KEYWORDS

haemophilia, health-related Quality of Life, inhibitors

1 | INTRODUCTION

Haemophilia is a rare coagulation disorder occurring in 1 in 10 000 births that results from the lack of either of two proteins, called factors, necessary for the formation of a normal blood clot. Deficiency of factor VIII (FVIII), called haemophilia A, is the most common form. Therapy involves the intravenous administration of clotting factor concentrate (CFC) either in response to a bleeding episode or prophylactically to prevent these episodes. In about 20%-30% of individuals, an antibody (referred to as an inhibitor) to the infused clotting factor

develops that renders treatment with CFC ineffective against bleeding.[1] Those with inhibitors have increased morbidity [2] and mortality,[3] and treatment for bleeding episodes with alternative CFCs called bypassing agents is extremely costly.[4, 5]

A number of studies have assessed the burden of haemophilia on health-related quality of life (HRQoL).[6, 7] A recent review summarized 18 studies of health status utility values (HSUVs) in haemophilia patients, most of which used the EuroQol EQ-5D or the SF-6D based on the Rand Short Form questionnaire; no study used both measures.[8] A previous analysis of HSUVs in 425 patients with severe haemophilia A from four European countries excluded patients who had an inhibitor.[9] SF-6D scores decreased with increasing age and with a combined measure of joint disease and frequency of bleeding. Only two studies reported HSUVs for males with an inhibitor relative to those with the same level of severity of haemophilia A but without an inhibitor.[10, 11]

The purpose of this study was to use EQ-5D and SF-6D data collected on males with severe haemophilia A to calculate utility weights adjusted for demographic and clinical characteristics and for the presence of complications such as bleeding and liver disease to determine the independent effect of joint disease and an inhibitor on preference-based HRQoL. Data collected from the same subjects using both instruments provided the opportunity to evaluate the consistency of the results between the instruments.

2 | MATERIALS AND METHODS

From May 1998 through September 2011, people with haemophilia and other bleeding disorders receiving care in one of 135 haemophilia treatment centres (HTCs) in the USA were offered the opportunity to participate in the Centers for Disease Control and Prevention (CDC)'s Universal Data Collection (UDC) system.[12] The project was approved by Institutional Review Boards at each institution, and all patients (or parents of minor children) gave informed consent for participation.

2.1 | Data collection

HTC staff collected data at annual comprehensive clinic visits. Date of birth (used to calculate age at the time of the visit) and self-identified race and ethnicity data were collected at the initial UDC visit. For the analysis, a combined race/ethnicity variable was created with four levels: non-Hispanic white, non-Hispanic black, Hispanic, and other race ethnicities. Other sociodemographic data, including type of health insurance and whether the participant was employed or a student, were collected at each UDC visit. Clinical information collected during visits included measurements of height and weight; the type of treatment regimen (prophylaxis vs episodic); the highest inhibitor titre measured since the last UDC visit; whether the patient was on an immune tolerance treatment regimen; the number of joint, muscle or other bleeds experienced in the previous 6 months; the presence of signs or symptoms of liver disease (e.g, jaundice, ascites, varices), elevated liver enzymes, or evidence of previous infection with hepatitis B or C; the presence of a target joint (following the UDC definition as 4 or more bleeds in the same joint in the previous 6 months); the number of days missed from work or school due to a joint problem; use of a cane or other assistive device for ambulation; and self-reported current activity level. The presence of HIV infection was determined on the basis of blood testing performed at the CDC laboratory as part of the surveillance.[12]

2.2 | Data analysis

For the analysis, we converted height and weight to body mass index (BMI) by dividing weight by height squared and categorized body weight as normal (BMI<25 kg/m^2), overweight (BMI=25-29.9 kg/m^2) or obese (BMI≥30 kg/m^2) for patients aged ≥20 years or according to CDC BMI charts for patients aged <20 years.[13] Only patients who had a recent inhibitor titre >1 Bethesda Unit or who were on an immune tolerance treatment regimen at the time of the visit were defined as having an inhibitor for the study. Insurance type was collapsed into two categories: commercial vs any other type of insurance or none.

We created three indicators for the following outcomes based on the empirical distribution of the present data:

- Severe bleeding was defined as ≥5 joint or total bleeds in the previous 6 months or as having one or more target joints (a joint with ≥4 bleeds in the previous 6 months);
- Liver disease was defined as the presence of either signs/symptoms of liver disease, or elevated liver enzymes, or hepatitis B- or C-positive serologic status;
- Joint disease was defined as having a decreased activity level (either has limitations in or requires assistance with school/work, recreation and self-care), or ≥10 missed days of work or school due to a joint problem,[14] or continuous use of a cane or a wheelchair for ambulation.

Beginning in 2005, UDC participants aged ≥14 years could optionally complete a HRQoL questionnaire that incorporated the EQ-5D (EuroQol Group, Rotterdam, The Netherlands) and the SF-12v2® (QualiMetric, Lincoln, RI, USA) health surveys as well as the CDC HRQOL-04 "Healthy Days" (available at: https://www.cdc.gov/hrqol/hrqol14_measure.htm) instrument. The first completed questionnaire was used for those who completed more than one questionnaire, and data on other characteristics and outcomes were taken from the UDC visit at which the questionnaire was completed.

Conversion of the raw survey scores to HSUVs for each survey was accomplished using computer programs that applied country-specific weights to the survey question response levels. The EQ-5D HSUVs were derived using a US population value set [15] (using software authored by James W. Shaw and available at: https://www.ahrq.gov/professionals/clinicians-providers/resources/rice/ceoutc.html#EuroQol), whereas the SF-6D HSUVs were derived from the SF® health survey using the original UK. population value set [16] (using software licensed from Sheffield University Enterprises Ltd., Sheffield, UK) as a US value set was not available.

2.3 | Statistical analysis

Data from all UDC participants with severe haemophilia A completing at least one HRQoL questionnaire were included in the analyses. Because the HSUVs for participants were not normally distributed, Wilcoxon score comparisons using nonparametric regression analyses were used to assess differences in utility values between levels of the sociodemographic and clinical characteristics for statistical significance.

Multiple linear regression analyses were used to compare mean HSUVs for those with and without an inhibitor adjusted for other patient characteristics. Because the results of regression analyses using either the actual utility values (parametric) or the ranks of the utility values (nonparametric) were virtually identical, only the results of the parametric multiple linear regression analyses are reported. Collinearity diagnostics revealed no indication of multicollinearity between variables; however, statistical interaction between age and several of the variables was identified. Therefore, the results of regression analyses were stratified by three age groups: 14-20, 21-44 and 45+ years to allow for potential age differences in influences of the studied risk factors on HRQoL.

All analyses used SAS statistical software (SAS Institute, Cary, NC, USA), and *P*-values ≤.05 were considered statistically significant. Any differences in SF-6D scores <0.03 and differences in EQ-5D scores <0.04 were considered to be not "minimally important" and hence not of clinical significance. The minimally important difference (MID) for a patient-reported outcome measure is the smallest difference that a patient would be likely to perceive as beneficial.[17] In the case of multi-attribute utility instruments like the SF-6D and the EQ-5D, the MID is measured as the smallest difference in HSUV associated with a one-step change in the underlying health state classification system.[18] A US study that used that approach found that the mean MID was 0.027 for the SF-6D and 0.040 for the EQ-5D using the US preference function or value set.[18]

3 | RESULTS

The study population comprised 1859 males with severe haemophilia A with at least one completed HRQoL survey. One-third of patients were under age 21 years and one-half between 21 and 44 years old (Table 1). Compared to the US population,[19] Hispanic ethnicity was under-represented. One-half had commercial insurance, while one-third had public (Medicare or Medicaid) insurance. Two-thirds were employed or attended school. Nearly half were overweight or obese. Nearly 40% were on a prophylactic regimen, and 6.7% of the patients had a current inhibitor. About one-fourth were HIV-infected, two-thirds had an indicator of liver disease, and one-half had joint disease or severe bleeding (Table 1). The respondents represented 51.6% of the 3603 otherwise eligible patients during the same time period. Those who completed the questionnaire were somewhat younger, less likely to be a minority and less likely to be uninsured than the non-respondents. Respondents also less often had inhibitors than did non-respondents.

In bivariate analyses, sociodemographic, treatment and clinical characteristics except body adiposity were significantly associated with at least one of the two HSUVs (Table 1). The average HSUVs were generally higher for the EQ-5D measure than for the SF-6D, but the relative differences in average HSUVs among levels of the characteristics were similar. Average HSUVs decreased with age but increased for patients with commercial vs other types of insurance, those who were students or employed, those who were on prophylaxis, those who were not HIV-infected, and those without evidence of severe bleeding, joint disease or liver disease.

Average HSUVs were slightly lower for the SF-6D (0.04 lower) and EQ-5D (0.03 lower) measures in patients with a current inhibitor than in those without an inhibitor (Table 1). The magnitudes of both differences were of marginal clinical significance, although the difference in the SF-6D HSUV exceeds the MID, whereas the EQ-5D HSUV does not. All other differences in Table 1 that were statistically significant were of clinical significance, with differences ≥0.04 exceeding the MID for both measures.

One patient characteristic, a dichotomous variable for joint disease, was independently and negatively associated with HSUVs in multivariate analyses (indicated by negative values for the coefficients) across both measures and all three age groups (Table 2).

The only other characteristic that was significantly associated with HRQoL across both measures within two age groups was student/employment status. Among patients under age 45 years, being in school or employed was associated with significantly better HRQoL, with absolute adjusted differences of 0.04-0.07 in HSUVs. Having commercial insurance relative to any other insurance type was significantly positively associated with HRQoL among those aged 21-44 years. It was significantly associated with HRQoL in the other two age groups for only one of the two measures in each group. It was of clinical significance only in the older age group.

Among those aged 14-20 years, current use of prophylaxis was associated with statistically significantly higher EQ-5D HSUVs, although the difference was not clinically significant, and it was not statistically significantly associated with SF-6D HSUVs. The remaining variables did not have statistically significant associations with HRQoL. In particular, the presence of an inhibitor was not statistically significantly associated with HRQoL in any age group after adjustment for other factors (*P*=0.5-0.7).

The adjusted mean HSUVs are presented for patients with and without an inhibitor in Table 3. Although the mean EQ-5D HSUVs were uniformly higher than those from the SF-6D, differences were very small, and the HSUVs differed very little by inhibitor status or across age groups.

4 | DISCUSSION

Among a large group of patients with severe haemophilia A, we found relatively consistent effects on HRQoL associated with several sociodemographic and clinical characteristics as assessed by two preference-based HRQoL measures, the EQ-5D and SF-6D. Most importantly,

TABLE 1 Bivariate associations between sociodemographic and clinical characteristics of 1859 males with severe haemophilia A and HRQoL as measured by the SF-6D and the EQ-5D

Characteristic	n	%	Mean SF-6D	*P*	Mean EQ-5D	*P*
Age group						
14-20	608	32.7	0.77	<.001	0.85	<.001
21-44	970	52.2	0.69		0.76	
45+	281	15.1	0.66		0.70	
Race/Ethnicity						
Non-Hispanic white	1265	68.0	0.72	.06	0.78	.04
Non-Hispanic black	249	13.4	0.72		0.76	
Hispanic	190	10.2	0.69		0.77	
Other	155	8.4	0.71		0.82	
Insurance						
Commercial	939	50.5	0.74	<.001	0.82	<.001
Medicaid	443	23.8	0.70		0.75	
Medicare	255	13.7	0.64		0.68	
Other	170	9.0	0.70		0.81	
Uninsured	52	2.8	0.69		0.74	
Student or Employed						
Yes	1299	69.9	0.74	<.001	0.82	<.001
No	560	30.1	0.64		0.69	
Body Mass Index						
Normal	955	52.5	0.72	.8	0.78	.9
Overweight	500	27.5	0.71		0.78	
Obese	363	20.0	0.71		0.78	
Treatment type						
Episodic	1137	60.8	0.70	<.001	0.76	<.001
Continuous prophylaxis	722	38.8	0.74		0.82	
Current inhibitor						
Yes	125	6.7	0.68	.01	0.75	.02
No	1734	93.3	0.72		0.78	
HIV infection						
Yes	452	24.3	0.67	<.001	0.72	<.001
No	1407	75.7	0.73		0.80	
Liver disease						
Yes	1183	63.6	0.68	<.001	0.74	<.001
No	676	36.4	0.77		0.85	
Joint disease						
Yes	834	44.9	0.66	<.001	0.71	<.001
No	1025	55.1	0.75		0.84	
Severe bleeding						
Yes	992	53.4	0.70	<.001	0.76	<.001
No	867	46.6	0.73		0.81	

patients with indicators of joint disease had substantially decreased HRQoL within each age group. Adolescents and adults under age 45 who were students or were employed had significantly better HSUVs. Patients with commercial insurance generally had higher HSUVs than those with other forms of insurance but the association was too modest to be of clinical significance for those under age 45.[18]

The impact of joint disease on HRQoL is marked. Our results suggest that this risk factor alone is primarily responsible for the decreased HRQoL observed in persons with severe haemophilia. The adjusted and unadjusted impact of joint disease on EQ-5D HSUVs is virtually the same, about −0.13 (Tables 1 and 2). That is almost equal in absolute magnitude to the 0.15 difference in mean EQ-5D HSUVs

TABLE 2 Multivariate associations between sociodemographic and clinical characteristics of 1859 males with severe haemophilia A and HRQoL as measured by the SF-6D and the EQ-5D

	Age 14-20 years				Age 21-44 years				Age 45+years			
	SF-6D		EQ-5D		SF-6D		EQ-5D		SF-6D		EQ-5D	
Characteristic	Coeff	*P* value	Coeff	*P* value	Coeff	*P* value	Coeff	*P* value	Coeff	*P* value	Coeff	*P* value
Age	−0.005	.1	−0.007	**.04**	−0.001	.07	−0.002	.1	0.003	**.01**	0.002	.1
White race	0.04	**.002**	0.014	.3	−0.01	.2	−0.02	.08	0.02	.4	0.06	**.02**
Commercial insurance	0.01	.2	0.03	**.02**	0.02	**.01**	0.03	**.02**	0.04	**.03**	0.05	.06
Student or employed	0.04	**.01**	0.07	**<.001**	0.05	**<.001**	0.07	**<.001**	0.02	.3	0.002	.9
Overweight/Obese	−0.01	.6	0.02	.2	0.01	**.05**	0.01	.4	−0.006	.7	0.001	.9
Prophylaxis use	0.004	.7	0.03	**.03**	0.001	.9	0.004	.7	0.02	.3	−0.04	.2
Inhibitor	−0.03	.2	−0.009	.7	0.003	.8	0.02	.5	−0.002	.9	−0.01	.7
HIV positive	−0.03	.7	−0.04	.7	0.005	.6	0.01	.4	0.001	.9	−0.006	.8
Severe bleeding indicator	−0.02	**.05**	−0.02	.2	−0.002	.8	0.005	.7	−0.01	.5	−0.04	**.05**
Liver disease indicator	−0.02	.2	−0.01	.5	−0.004	.7	−0.02	.2	−0.03	.5	−0.05	.5
Joint disease indicator	−0.07	**<.001**	−0.13	**<.001**	−0.09	**<.001**	−0.12	**<.001**	−0.08	**<.001**	−0.13	**<.001**

P-values ≤.05 appear in bold text in the table.

observed between the 14-20 and 45+ year age groups. An important implication is that the presence of joint disease should be accounted for in analyses of the effects of other variables on HRQoL among persons with haemophilia, especially when using the EQ-5D, which includes a mobility component.

Of interest was the finding that our severe bleeding indicator was not generally independently associated with HSUVs in multivariate analyses. A likely explanation is that individuals with more severe bleeding typically develop joint disease. After adjusting for the presence of joint disease, bleeding does not appear to have a significant direct impact on HRQoL. Rather, severe bleeding in haemophilia appears to primarily influence HRQoL indirectly through the development of joint disease.

The negative effect of an inhibitor on HRQoL was surprisingly modest. Although unadjusted HSUVs for people with an inhibitor differed statistically significantly from those without an inhibitor, HSUVs after accounting for other patient characteristics did not differ statistically between groups.

Several other characteristics, including liver disease, BMI and HIV infection, likewise were not independently associated with HRQoL. BMI had no association with HRQoL even without controlling for confounding, whereas persons with either liver disease or HIV had significantly worse HRQoL on average before controlling for confounding (Table 1). After controlling for other patient characteristics, though, neither factor had a significant association with HRQoL. In a preliminary multivariate regression analysis for the pooled sample, liver disease was strongly negatively associated with HRQoL (results not reported), but that association essentially disappeared when the analysis was stratified by age group (Table 2). One possible explanation is that liver disease is strongly associated with older age, particularly over age 45 years, among whom HRQoL is generally lower than that among individuals in the younger age groups. Within age groups, liver disease was not associated with HRQoL.

Individuals using prophylaxis had significantly better average HRQoL than those who received on-demand factor, and prophylaxis status was slightly more strongly associated with HRQoL than was severe bleeding (Table 1). However, younger subjects were much more likely than older subjects to be on prophylaxis and to have higher HSUVs. After adjusting for patient characteristics, prophylaxis status was not associated with HRQoL past age 20 years. Prophylaxis was weakly positively associated with HRQoL in the youngest age group, but only for one measure, the EQ-5D. Cross-sectional associations of current prophylaxis status and HRQoL typically do not differ statistically significantly, but the profile of prophylaxis over time may be more important.[8] Primary prophylaxis, initiated before the onset of severe bleeds, greatly reduces the risk of joint disease, the primary predictor of HRQoL in patients with severe haemophilia.[20]

Comparisons of our findings on inhibitors and preference-based HRQoL with those of previous studies are complicated by differences in study design. Wasserman et al. [10] used a standard gamble approach to directly elicit HSUVs for hypothetical health states, one of which was having a lifelong inhibitor and chronic joint damage; it is not possible to separate out the effect of an inhibitor from that of joint damage.

TABLE 3 Adjusted[a] mean preference-based utility scores of 1859 males with severe haemophilia A as measured by the SF-6D and the EQ-5D for those with and without an inhibitor by age group

	Age 14-20		Age 21-44		Age 45+	
	SF-6D	Eq-5D	SF-6D	Eq-5D	SF-6D	Eq-5D
Inhibitor positive	0.68	0.74	0.68	0.75	0.67	0.71
Inhibitor negative	0.71	0.75	0.67	0.74	0.67	0.72

[a]Adjusted for all characteristics studied (Table 2).

Noone, et al. [11] reported a mean EQ-5D HSUV of 0.798 for 13 males with an inhibitor, which was higher than in our study, but the authors did not report a pooled HSUV for males without an inhibitor. Neufeld et al. [21] reported a mean EQ-5D HSUV of 0.72 for 18 US adults with an inhibitor that was intermediate between the adjusted values of 0.74 and 0.75 in the two younger age groups and the value of 0.71 among the oldest patients with an inhibitor in our study. However, HSUVs were not adjusted for other comorbidities.

Study limitations should be considered when interpreting our results. First, our results reflect the measurement of HRQoL at one point in time and may be influenced by short-term events occurring in the patient's life unrelated to the studied variables. Because we consider the possible influence of these other events on our findings to be random and non-differential, these events are unlikely to have systematically affected our results except to decrease statistical power in detecting differences among groups.

Second, because the completion of the questionnaire was voluntary, not all patients participated. Non-response bias in HRQoL surveys is often associated with less participation by people who are older, more socio-economically deprived and more likely to have comorbid conditions.[22] To the extent that non-responders in this survey may have had worse HRQoL, our results may overstate HRQoL overall. In particular, if those with inhibitors who did not respond had worse HRQoL, our findings may underestimate the effect of an inhibitor on quality of life.

Third, many of the patients that we studied with a more severe bleeding phenotype were likely to have chosen to utilize prophylaxis, which is readily available to patients in this clinical setting. Therefore, to the extent that subjects who chose not to use prophylaxis despite frequent bleeding were less concerned with this complication, we may have underestimated the effect of frequent bleeding episodes on HRQoL.

Finally, all of the patients participating in the surveillance receive care in the US HTC Network and have access to comprehensive haemophilia care and a variety of therapies including immune tolerance therapy treatment and bypassing products. It is possible that access to these therapies may have minimized any effects of inhibitors on HRQoL.

In conclusion, we found no consistent effect of an inhibitor on HRQoL after adjusting for the effects of other comorbid conditions, especially joint disease. The adjusted HSUVs we report may be useful in calculations of quality-adjusted life years (QALYs) for cost-effectiveness or cost-utility studies needed to assess improvements in health for people with haemophilia resulting from therapeutic strategies such as prophylaxis.

ACKNOWLEDGEMENTS

The authors wish to thank the staff of the United States Hemophilia Treatment Center Network comprised of 135 clinical centres located throughout the country for recruiting patients into the UDC surveillance project and collecting the data. We also thank the patients and their families for their participation.

AUTHOR CONTRIBUTION

JMS designed research, analysed data and wrote the paper; SDG designed research, analysed data and wrote the paper; A-E-AS contributed to the design of the study and writing the paper; VB contributed to the design of the study and writing the paper; JT contributed to the design of the study and writing the paper; MMZ contributed to the design of the study, the analysis and writing the paper; AS contributed to the design of the study and writing the paper; and ND contributed to the design of the study and writing the paper.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

REFERENCES

1. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia*. 2003;9:418-435.
2. Soucie JM, Symons J, Evatt B, Brettler D, Huszti H, Linden J. Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia. *Haemophilia*. 2001;7:198-206.
3. Walsh CE, Soucie JM, Miller CH; United States Hemophilia Treatment Center Network. Impact of inhibitors on hemophilia A mortality in the United States. *Am J Hematol*. 2015; 90:400-405.
4. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008. *Haemophilia*. 2012;18:268-275.
5. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Health care expenditures for Medicaid-covered males with haemophilia in the United States, 2008. *Haemophilia*. 2012;18:276-283.
6. Fischer K, van der Bom JG, van den Berg HM. Health-related quality of life as outcome parameter in haemophilia treatment. *Haemophilia*. 2003;9(Suppl 1):75-81.
7. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. *Haemophilia*. 2015;21:578-584.

8. Grosse SD, Chaugule SS, Hay JW. Estimates of utility weights in hemophilia: implications for cost-utility analysis of clotting factor prophylaxis. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15:267-283.
9. Lippert B, Berger K, Berntorp E, et al. Cost effectiveness of haemophilia treatment: a cross-national assessment. *Blood Coagul Fibrinolysis*. 2005;16:477-485.
10. Wasserman J, Aday LA, Begley CE, Ahn C, Lairson DR. Measuring health state preferences for haemophilia: development of a disease-specific utility instrument. *Haemophilia*. 2005;11:49-57.
11. Noone D, O'Mahony B, van Dijk JP, Prihodova L. A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18-35-year old men with severe haemophilia in six countries. *Haemophilia*. 2013;19:44-50.
12. Soucie JM, McAlister S, McClellan A, Oakley M, Su Y. The universal data collection surveillance system for rare bleeding disorders. *Am J Prev Med*. 2010;38:S475-S481.
13. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics*. 2002;109:45-60.
14. National Survey of Children with Special Health Care Needs 2005-2006. www.chscndata.org.
15. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. *Med Care*. 2005;43:736-749.
16. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. 2004;42:851-859.
17. Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. *Health Qual Life Outcomes*. 2006;4:70.
18. Luo N, Johnson JA, Coons SJ. Using instrument-defined health state transitions to estimate minimally important differences for four preference-based health-related quality of life instruments. *Med Care*. 2010;48:365-371.
19. Humes KR, Jones NA, Ramirez RR. Overview of Race and Hispanic Origin: 2010. U.S. Census Bureau, March 2011. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf (Accessed 2/7/2017).
20. 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;357:535-544.
21. Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value Health*. 2012;15:916-925.
22. Coste J, Quinquis L, Audureau E, Pouchot J. Non response, incomplete and inconsistent responses to self-administered health-related quality of life measures in the general population: patterns, determinants and impact on the validity of estimates - a population-based study in France using the MOS SF-36. *Health Qual Life Outcomes*. 2013;13:11-44.

How to cite this article: Soucie JM, Grosse SD, Siddiqi A-E-A, et al. The effects of joint disease, inhibitors and other complications on health-related quality of life among males with severe haemophilia A in the United States. *Haemophilia*. 2017;23:e287–e293. https://doi.org/10.1111/hae.13275