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## Psychosocial and medical determinants of long-term patient outcomes

Prihodová, Lucia

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# Chapter 9

## 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

Declan Noone, Brian O'Mahony, Jitse P van Dijk, Lucia Prihodova

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**ABSTRACT**

A number of studies have been published on the benefits of prophylactic treatment in adults with haemophilia. However, in many countries, it is considered as optional due to financial constraints. This survey was carried out to examine the long-term effects of prophylaxis and the continuing benefit of the treatment into adulthood. Self-assessed health-related data and the EQ-5D questionnaire measuring health utility were collected from 124 men ( $26.9 \pm 4.6$  years) from Canada (n=40), France (n=14), Ireland (n=17), the Netherlands (n=16), Poland (n=24) and the UK (n=13). The respondents were split into four groups: On-Demand, <50% life on prophylaxis,  $\geq 50\%$  life on prophylaxis, Prophylaxis. Overall, long-term prophylaxis results in lower presence of target joints ( $P \leq 0.001$ ), occurrence of serious bleeding episodes ( $p \leq 0.05$ ), recurring bleeding episodes ( $p \leq 0.01$ ) and requirement for surgical procedures ( $p \leq 0.05$ ). Furthermore, health utility ( $p \leq 0.01$ ) in the On-demand group was significantly lower ( $p \leq 0.01$ ) compared to the  $\geq 50\%$  life on prophylaxis and the Prophylaxis group. No significant differences between countries were found except between the Netherlands and Poland, with Poland showing the lowest health utility ( $p \leq 0.01$ ) and the most problems with mobility ( $p \leq 0.05$ ) and pain/ discomfort ( $p \leq 0.001$ ). The Netherlands showed the highest health utility (0.915) followed by Canada (0.791), Ireland (0.786), UK (0.768), France (0.687) and Poland (0.629). The results demonstrate consistently higher quality of life of individuals who are on long-term prophylactic treatment when compared to on-demand treatment or intermittent prophylaxis and on -demand treatment.

**KEYWORDS:**

EQ-5D, haemophilia, on-demand, prophylaxis

## INTRODUCTION

In haemophilia, prophylaxis for children with severe FVIII and FIX deficiencies is recognized as the optimum standard of care.<sup>1-3</sup> However, the continuation of prophylactic therapy into adulthood is still closely scrutinized. In many countries, the clinical benefit is acknowledged, although given the limited resources not everywhere provides prophylaxis into adulthood. A number of studies have been published demonstrating the benefits of prophylactic treatment in adults.<sup>4-6</sup>

This study was carried out to examine the long-term effects of prophylaxis and the continuing benefit of the therapy into adulthood. It is an expansion of the four-country survey reported in 2009.<sup>7</sup> Dutch patients with severe haemophilia have been treated with prophylaxis from childhood since the 1970s, although Ireland, France, the UK and Canada introduced prophylaxis for children in the mid-1990s and therefore the young adults in this survey from those countries would have had substantial exposure to on-demand therapy. Poland has introduced prophylaxis for children in the last 3 years with no adults having access to long-term prophylaxis. These differences enable us to further examine the inequalities in medical outcomes and quality of life in patients who had full access to prophylaxis from birth and those who received prophylaxis for a period as a child and then switched to on-demand as well as those who continued entirely with varying levels of on-demand therapy.

## METHODS

### SAMPLE

National Haemophilia organisations in Canada, France, Ireland, the Netherlands, Poland and the UK were asked to participate by randomly selecting 20 severe haemophilia patients, with FVIII/IX (levels <1 IUdL-1) aged 18–35 years and by asking them to complete a survey. This sample of young adults with severe haemophilia was chosen as at the age of 18, patients usually chose to continue on prophylaxis or change regimen. The age of 35 was chosen as this was the eldest possible age for a patient from the countries asked to participate to in the survey. Data on co-morbidities were not collected. Sweden and Romania that were also included in the study but did not reply. The data collection was performed by e-mail or phone interview in the period between October and November 2011.

In total, 124 responses were received. The Netherlands provided 16 responses (one moderate, three inhibitors), Ireland 17 (one inhibitor), Poland 24 (two moderate, two inhibitors), the UK 13 (one moderate), France 14 (one inhibitor) and Canada 40 (four moderate, six inhibitors). Eight responders with moderate haemophilia were excluded from the analysis in spite of severe bleeding phenotype. Of 116 responders with severe disease 13 had a previous history of inhibitors

and were examined separately as the level of the inhibitor and current status was unknown. One non-inhibitor respondent did not provide information on his treatment regimen and was excluded from the therapy analysis.

## **MEASURES**

The data collected was sociodemographic data (age, country and work or college status), medical data and responses to the EQ-5D questionnaire. The medical data collected were, the type of haemophilia, severity, treatment regime (prophylaxis vs. on demand, length of time on each regimen, dose of each infusion and number of infusions per week), current regimen, history of inhibitors, bleeding episodes per year, target joints, serious bleeding episodes (head or soft tissue (e.g. iliopsoas, forearm) bleeding episodes, mobility, recurring bleeding episodes, surgery, pain and use of pain medication, and days missed from work due to haemophilia as total number of days missed from work per year. Primary prophylaxis was defined as having a preventive aim with infusion regularly several times a week during the whole year to prevent bleeding episodes from occurring. The respondents were asked to report the number of times per week prophylactic treatment was administered. On-demand was defined as when needed to treat a bleed. A target joint was defined as three or more bleeding episodes into the same joint in a consecutive 3-month period. Annual factor consumption was calculated on self-reported use.

## *UTILITY VALUE*

The responders were also asked to complete the EQ-5D questionnaire, a generic health-related utility value measure which has been previously used in haemophilia patients.<sup>6,8</sup> It is used to determine a utility value based on five dimensions of quality of life: Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety.<sup>9</sup> A higher score indicates a higher utility value. Cronbachs of the total EQ-5D in the present sample was 0.75.

## *STATISTICAL ANALYSES*

We analysed the number of bleeding episodes related to the time spent on prophylaxis. The sample was split into four groups: Always On-demand (N=26), <50% of their life on Prophylaxis (N = 26), ≥50% of their life on prophylaxis (N=35) and Always on Prophylaxis (N=15). We analysed the seriousness of bleeding episodes and utility values in these categories.

Then, we explored the utility value in these categories. We evaluated the differences regarding the seriousness of bleeding episodes, total factor consumption and the health utility values between the participating countries. ANOVA, correlation matrix and chi square were used to analyse the data in predictive analytic software (PASW) 18 ( $p \leq 0.05$ ).

## RESULTS

The average age was  $27 \pm 4.6$  years. A total of 106 patients (91.3%) had severe factor VIII deficiency, nine (8.5%) had factor IX deficiency and one (0.9%) had type 3 von Willebrand disease. In total, 103 non-inhibitor and 13 inhibitor patients were analysed. Respondents with FVIII deficiency administered prophylactic treatment one to seven times a week with the majority (77%) receiving prophylactic treatment two to three times per week. Factor IX and von Willebrand's Disease respondents received prophylaxis treatment two to three times per week.

### *COMPARISON OF GROUPS WITH REGARD TO THE TREATMENT REGIMEN*

In the analysis examining time spent on prophylaxis and the number of bleeding episodes per year, there was a strong correlation between the variables (Table 9.1). The Always On-demand group had significantly more bleeding episodes than the Always on Prophylaxis or the  $\geq 50\%$  of their life on Prophylaxis groups. The majority of the Always On-demand group (61%) reported more than 30 bleeding episodes per year. In the Always on Prophylaxis group, 53% of respondents reported less than three bleeding episodes year and no respondent reported more than seven bleeding episodes in the last year.

We found significant differences regarding a greater presence of target joints, greater occurrence of serious bleeding episodes, recurring bleeding episodes and surgical procedures in the Always On-demand group compared to the  $\geq 50\%$  of their life on Prophylaxis and the Always on Prophylaxis group (Table 9.1). The mean number of joints with reduced mobility as well as reported frequency of severe pain increased with less time on prophylaxis. The mean age of respondents who required surgical procedures as a result of their bleeding disorder was 29.6 years. Among the respondents that use pain medication there was a significant difference between the Always on Prophylaxis group and all other groups, with less pain medication used by this group. In relation to missing time off work due to their bleeding disorder, 23% of the Always On-demand group missed more than 30 days of work in the last year, 3% of  $< 50\%$  of their life on Prophylaxis, 0% of  $\geq 50\%$  of their life on Prophylaxis and 7% of the Always on Prophylaxis group. There was one respondent in the Always on Prophylaxis group who had significant health issues due to his bleeding disorder and as a result was an outlier in the group. There were significant differences in utility value (Fig. 9.1) with the Always On-demand group (0.619) having a significantly lower ( $p \leq 0.01$ ) utility value compared with the  $\geq 50\%$  of their life on Prophylaxis (0.812) and the Always on Prophylaxis group (0.866). The Always On-demand group had significantly more mobility problems than those with  $\geq 50\%$  of their life on Prophylaxis ( $p \leq 0.05$ ) and significantly more pain and discomfort than the  $\geq 50\%$  of their life on Prophylaxis ( $p \leq 0.05$ ) and the Always on Prophylaxis group ( $p \leq 0.001$ ). Results also showed that the  $< 50\%$  of their life on Prophylaxis group had significantly more pain than the

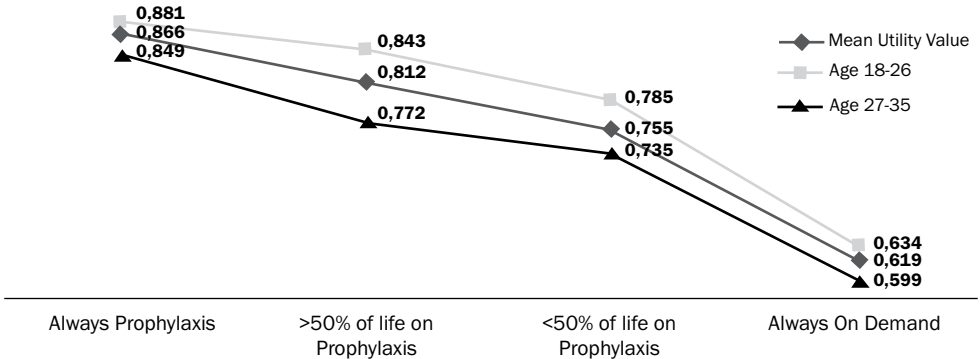
Always on Prophylaxis group ( $p \leq 0.01$ ). The results demonstrated a trend of increasing problems with self-care, usual activities and anxiety with less time on prophylaxis, but these were not statistically significant. In relation to factor consumption, the mean annual factor consumption for the Always On-demand group was 145 500 IU, <50% on of their life on Prophylaxis 298 000 IU,  $\geq 50\%$  of their life on Prophylaxis 251 000 IU and Always on Prophylaxis 263 000 IU. There were no statistically significant differences between the groups when the estimated annual consumption of factor was calculated.

**Table 9.1** Comparison of groups based on time spent on prophylaxis

		Always On-demand	<50% of life on Prophylaxis	≥50% of life on Prophylaxis	Always Prophylaxis	Inhibitors
<b>Number in Group (N)</b>		26	26	35	15	13
<b>Mean Age (Years)</b>		28	27	26	26	27.5
<b>Mean Health Utility (EQ-5D)</b>		0.619	0.755	0.812	0.866	0.798
<b>Mean Annual Factor Consumption (IU)</b>		145,500	298,700	251,000	263,000	326,000
<b>Number of bleeds over the last year</b>	0-3	0%	29%	28%	53%	38%
	4-7	4%	32%	22%	47%	15%
	8-10	4%	16%	25%	0%	8%
	10-15	4%	13%	13%	0%	8%
	15-30	26%	6%	6%	0%	23%
	>30	61%	3%	0%	0%	0%
<b>Reported a Target Joint</b>		87%	74%	50%	40%	77%
<b>Reported serious bleeds (head or soft tissue)</b>		74%	32%	53%	27%	46%
<b>Reported reduced mobility due to BD*</b>		65%	65%	53%	40%	77%
<b>Reported mobility reduced in any joints</b>		74%	61%	53%	40%	77%
<b>Mean No. of joints with reduced mobility</b>		2.6	1.27	0.8	0.5	1.33
<b>Currently experiencing any recurring bleeds in any joints</b>		65%	35%	28%	20%	69%
<b>Undergone surgery or other invasive procedure because of problems related to bleeds</b>		43%	23%	22%	0%	46%
<b>Experiences pain because of BD*</b>	Daily	35%	29%	22%	13%	31%
	Once a Week	30%	19%	16%	13%	8%
	Once a Month	13%	10%	16%	13%	8%
	<once a month	9%	26%	25%	33%	15%
	Never	13%	16%	16%	27%	31%
<b>Joint/muscle bleed requiring pain medication over last year</b>	No	30%	48%	31%	80%	46%
	Once	4%	6%	19%	0%	15%
	2-3 times	9%	23%	13%	13%	15%
	4-5 times	0%	3%	6%	7%	15%
	6-7 Times	4%	3%	0%	0%	15%
	>7 times	48%	16%	22%	0%	8%
<b>Employment</b>	Working FT <sup>a</sup>	52%	61%	59%	53%	69%
	Student FT <sup>a</sup>	26%	23%	22%	27%	15%
	Other	9%	16%	13%	13%	8%
	Early Retirement	13%	0%	0%	7%	8%
<b>Missed days from work/studies over last year because of BD*</b>	0 days	32%	52%	36%	43%	25%
	1-7 days	36%	28%	39%	50%	67%
	8-14 days	5%	14%	7%	0%	8%
	15-30 days	5%	3%	18%	0%	0%
	>30 days	23%	3%	0%	7%	0%

\*BD - Bleeding disorder; <sup>a</sup>FT - Full-time



**Figure 9.1** Comparison of health utility value by the time spent on prophylaxis

### COUNTRY COMPARISON

We found no significant differences between countries except between the Netherlands and Poland, with Poland showing the lowest health utility ( $p \leq 0.01$ ) and the most problems with mobility ( $p \leq 0.05$ ) and pain ( $p \leq 0.001$ ) in comparison with the Netherlands. The Netherlands had the lowest rate of target joints, serious bleeding episodes, mobility issues, problems with recurring bleeding episodes and lowest rate of daily pain, with no patients requiring invasive surgical procedures. Based on the reported factor consumption by each patient for the past year both Poland and the Netherlands had a mean factor consumption of 169 000 IU per patient. Poland had the highest rate of early retirement due to bleeding problems with 15% of the group retiring at an average age of 32 years; compared to 2.2% with an average retirement age of 30 years in the rest of the group, but this difference was not statistically significant. Regarding the health utility values, the Netherlands had the highest health utility value with a mean of 0.915 followed by Canada (0.791), Ireland (0.786), UK (0.768), France (0.687) and Poland (0.629) (Table 9.2). The majority of the French respondents are currently on-demand treatment 62% compared to Canada 13%, Ireland 20%, the Netherlands 8% and the UK 8%. This may explain why the health utility value in the French cohort is closer to Poland where 79% are on-demand.

### INHIBITORS

A total of 13 respondents (mean age  $27.5 \pm 4.6$  years) had a previous history of an inhibitor, with 10 on primary prophylaxis, two with on-demand and one with secondary prophylaxis. All patients have had access to immune tolerance induction (ITI). The calculated factor consumption per year was 326 000 IU. The group reported a large number of target joints, serious bleeding episodes, reduced joint mobility, recurrent bleeding and requirement for surgical procedures. The mean utility value of the inhibitor cohort was 0.798.

**Table 9.2** Individual Country Comparison

		Poland	France	UK	Ireland	Canada	The Netherlands
<b>Number in Group (N)</b>		20	13	12	16	30	12
<b>Mean Age (Years)</b>		28	26	26	27	27	27
<b>Mean Health Utility (EQ-5D)</b>		0.629	0.687	0.768	0.786	0.791	0.915
<b>Mean Annual Factor Consumption (IU)</b>		169000	273600	325000	195000	297600	169000
<b>Number of bleeds over the last year</b>	0-3	5%	23%	25%	20%	37%	42%
	4-7	5%	8%	8%	47%	43%	33%
	8-10	10%	23%	25%	13%	7%	25%
	10-15	5%	8%	33%	13%	3%	0%
	15-30	20%	8%	8%	7%	3%	0%
	>30	45%	31%	0%	7%	7%	0%
<b>Reported a Target Joint</b>		90%	62%	67%	87%	60%	25%
<b>Reported serious bleeds (head or soft tissue)</b>		80%	46%	42%	27%	57%	25%
<b>Reported reduced mobility due to BD*</b>		65%	54%	67%	67%	50%	50%
<b>Reported mobility reduced in any joints</b>		75%	54%	67%	73%	47	50%
<b>Mean No. of joints with reduced mobility</b>		3	1.33	1	1.61	0.73	0.5
<b>Currently experiencing any recurring bleeds in any joints</b>		80%	15%	17%	47%	27%	25%
<b>Undergone surgery or other invasive procedure because of problems related to bleeds</b>		35%	46%	42%	13%	23%	0%
<b>Experiences pain because of BD*</b>	Daily	40%	0%	33%	20%	37%	8%
	Once a Week	35%	23%	17%	27%	10%	17%
	Once a Month	5%	31%	17%	7%	17%	0%
	<Once a month	10%	31%	33%	40%	7%	50%
	Never	10%	15%	0%	7%	30%	25%
<b>Joint/muscle bleed requiring pain medication over last year</b>	No	45%	15%	33%	40%	63%	58%
	Once	5%	0%	8%	0%	13%	25%
	2-3 times	15%	8%	17%	33%	13%	8%
	4-5 times	0%	0%	8%	20%	0%	0%
	6-7 Times	5%	8%	0%	0%	0%	0%
	>7 times	30%	54%	33%	13%	10%	8%
<b>Employment</b>	Working FT <sup>a</sup>	55%	38%	83%	53%	73%	83%
	Student FT <sup>a</sup>	30%	38%	0%	27%	10%	8%
	Other	0%	23%	8%	27%	10%	8%
	Early Retirement	15%	0%	8%	0%	3%	0%
<b>Missed days from work/studies over last year because of BD*</b>	0 days	33%	38%	55%	8%	43%	55%
	1-7 days	39%	38%	9%	38%	37%	45%
	8-14 days	0%	8%	27%	23%	7%	0%
	15-30 days	6%	8%	9%	15%	10%	0%

\*BD – Bleeding disorder; <sup>a</sup>FT – Full-time**DISCUSSION**

The aim of this study was to further examine the differences in medical outcomes and health utility values in respondents who had full access to prophylaxis from birth and those who received

prophylaxis for varying periods through their lives and those who continued entirely with varying levels of on-demand therapy. The results show, that long-term prophylaxis results in less bleeding, less damage to joints, less serious bleeding episodes, lower number of recurrent bleeding episodes, lower haemophilia-related work absence and higher utility value.

#### *COMPARISON OF GROUPS WITH REGARD TO THE TREATMENT REGIMEN*

Our findings support the view that prophylaxis started at a young age and continued into adulthood is an extremely effective treatment for patients with severe haemophilia, similar to other studies.<sup>3, 5-7, 10</sup> The differences in the number of bleeding episodes, requirement for surgical procedures, reduced mobility, absence from work and overall health utility demonstrate the clear benefits of long-term prophylaxis over on-demand therapy. It is not surprising that the highest utility values were found in the patients from the Netherlands as prophylaxis has been available continuously since early childhood. When comparing the Always On-demand group with the Always on Prophylaxis group, the most significant differences in EQ-5D dimensions were found in mobility problems and higher pain/discomfort. A number of studies on cost effectiveness<sup>11-13</sup> have reported the difference in utility values between prophylaxis and on-demand of 0.03 and 0.08. Our results and previous study 7 suggest that the benefit of prophylaxis continued into adulthood increased the utility value more significantly, dependent on the level of on-demand treatment available, and could range from 0.16 to 0.247. In relation to mean annual factor consumption per patient it may be reasonable to postulate that for many adults, factor consumption may be less if an individual remains on long-term prophylaxis rather than on-demand or switching from on-demand to prophylaxis periodically as bleeding episodes may be more frequent and severe and require more intensive treatment.

When comparing the 2009 survey data from Sweden to the current data, the number of bleeding episodes per year in the Always on Prophylaxis group was zero to three compared to the current study of four to seven bleeding episodes per year.<sup>7</sup> There was also a higher prevalence of target joints in this survey in the Always on Prophylaxis group (26.5% in 2009 vs. 40% in 2011) as well as a reduction in the health utility value for the Always on Prophylaxis group between the current survey (0.87) and the 2009 survey (0.88), which may be a result of the difference between the Dutch and the Malmö regimens. There was a reduction in the health utility value in the Always On-Demand group from 0.72 in 2009 to 0.619 in 2011, possibly due to the relative lack of organisation of haemophilia care and lack of resources for haemophilia in Poland in the past. The use of a long-term prophylaxis as implemented in the Netherlands shows a clear benefit over all other countries in the survey as the respondents had the lowest rate of target joints (40%), serious bleeding episodes (25%) and problems with recurring bleeding episodes (25%) compared to

all countries. It is the only country with no patients requiring invasive surgical procedures and has a mean of 0.5 joints that are reported as having reduced mobility. In comparison the respondents from Poland, had a twofold higher presence of target joints, a 3.2-fold higher occurrence of serious bleeding episodes and recurrent bleeding and a fivefold increase in presence of daily pain as a result of their bleeding disorder and a six-fold increase in joints with reduced mobility. The Polish health utility value (0.624) was lower by 31% and 20% compared with the Netherlands and Ireland respectively. The Polish utility value is lower than that which has previously been found in 60 year old patients with cancer.<sup>14</sup> Although not statistically significant, Poland has the highest rate of early retirement due to bleeding problems at 15% of the group with a mean age at retirement of 32 years, clearly demonstrating that the lack of prophylactic treatment available to the Polish respondents in childhood has had a significant long-term impact on the quality of their lives, especially when compared to the Dutch group. Despite the significant differences between the two groups, the reported mean factor consumption for both countries in the last year (September 2010–September 2011) was the same at 169 000 IU per patient suggesting that long-term prophylaxis may not only improve the quality of life but may also be cost effective in the long term. As a result of many target joints, the Polish respondents use similar quantities of treatment for on-demand therapy as the Netherlands respondents do for prophylaxis based on a relatively low-dose regimen. The difference between health utility values reported by Ireland, France, UK and Canada is minimal, which may be due to the later introduction of prophylaxis in comparison to the Netherlands. The effect of introducing prophylaxis in the mid-1990s can be seen in a reduction of presence of target joints, serious bleeding episodes, recurrent bleeding and prevention of further joint damage slowly moving towards the levels observed in the Netherlands.

### *INHIBITORS*

All respondents in the inhibitor group come from countries with well-established or improving haemophilia care and all had access to immune tolerance induction (ITI). It is encouraging to note that patients who previously had an inhibitor and have had access to ITI report similar health utility values as those with severe haemophilia and no inhibitors. There may also be a psychological factor. Successful ITI may impact the quality of life as the perceptions of their health state would have improved.

### *STRENGTHS, LIMITATIONS AND PRACTICE IMPLICATIONS*

This study comprises data from six countries of young adult men with varying access to haemophilia treatment and thus enabling a better understanding of effects of long-term prophylaxis. These surveys were self-reported so respondents may have some recall bias. The sample was defined

by only two criteria – age and severity of the haemophilia. Future studies should also consider alternative factors, such as comorbidities. The main limitations of this study are associated with the use of the UK-specific EQ-5D value set, due to unavailability of the value sets specific for other participating countries. The EQ-5D is based on the health state at time when the respondent is completing the survey; a coinciding bleed or other co-morbidities could impact the resulting health utility value. In future data on coinciding bleeding episodes and co-morbidities of respondents may benefit the analysis. It has also been suggested that the EQ-5D may not adequately describe the health of people with disabilities.<sup>15</sup> However, as the EQ-5D is the preferred utility measurement questionnaire for agencies carrying out Health Technology Assessments (HTA) such as the National Institute for Clinical Excellence (NICE, UK) and the Scottish Medicines Consortium (SMC, Scotland) it was considered an adequate tool to utilize in terms of health utilities and quality of life. Haemophilia patient organisations and clinicians need to develop a greater understanding of these economic concepts and their possible utilization in decision-making in relation to therapy.<sup>16</sup>

#### *CONCLUSION*

Prophylaxis started at an early age and continued into adulthood results in less bleeding, less damage to joints, less serious bleeding episodes and less recurrent bleeding episodes. Prophylaxis reduces problems with mobility and reduces pain and discomfort. As a result, people with severe haemophilia who have been on prophylaxis for their entire lives to date are reporting a quality of life much closer to their peers without haemophilia. It would also be instructive to extend the survey to countries which use low levels of FVIII per capita to assess what may well be, in effect, a baseline utility figure.

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