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A Study of Prospective Surveillance for Inhibitors among Persons with Haemophilia in the United States

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Abstract

Introduction—Inhibitors are a rare but serious complication of treatment of patients with haemophilia. Phase III clinical trials enroll too few patients to adequately assess new product inhibitor risk.

Aim—This project explores the feasibility of using a public health surveillance system to conduct national surveillance for inhibitors.

Methods—Staff at 17 U.S. haemophilia treatment centers (HTC) enrolled patients with haemophilia A and B into this prospective study. HTC staff provided detailed historic data on product use and inhibitors at baseline, and post-enrollment patients provided monthly detailed infusion logs. A central laboratory performed inhibitor tests on blood specimens that were collected at baseline, annually, prior to any planned product switch or when clinically indicated. The central laboratory also performed genotyping of all enrolled patients.

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* Group members are listed in the Addendum

ADDENDUM
The Haemophilia Inhibitor Research Study Investigators include authors from the following study sites: Thomas C. Abshire, Emory University, Atlanta GA; Doreen B. Brettler, New England Haemophilia Center, Worcester, MA; Jorge A. Di Paola, Mohamed Radhi and Steven R. Lentz, University of Iowa Carver College of Medicine, Iowa City, IA; Gita Massey and John C. Barrett, Virginia Commonwealth University, Richmond, VA; Amy D. Shapiro, Indiana Haemophilia and Thrombosis Center, Indianapolis, IN; Michael Tarantino, Comprehensive Bleeding Disorders Center, Peoria, IL; Brian M. Wicklund, Kansas City Regional Haemophilia Center, Kansas City, MO; Christine Knoll, Phoenix Children’s Hospital Haemophilia Center, Phoenix, AZ; Miguel A. Escobar, Gulf States Hemophilia and Thrombophilia Center, Houston, TX; M. Elaine Eyster, Hemophilia Center of Central Pennsylvania, Hershey, PA; Joan C. Gill, Comprehensive Center for Bleeding Disorders, Milwaukee, WI; Cindy Leissinger, Louisiana Center for Bleeding and Clotting Disorders, New Orleans, LA; Hassan Yaish, Primary Children’s Medical Center, Salt Lake City, UT.
Results—From January 2006 through June 2012, 1163 patients were enrolled and followed for 3,329 person years. A total of 3,048 inhibitor tests were performed and 23 new factor VIII inhibitors were identified, 61% of which were not clinically apparent. Infusion logs were submitted for 113,205 exposure days. Genotyping revealed 431 distinct mutations causing haemophilia, 151 of which had not previously been reported elsewhere in the world.

Conclusion—This study provided critical information about the practical issues that must be addressed to successfully implement national inhibitor surveillance. Centralized testing with routine monitoring and confirmation of locally identified inhibitors will provide valid and representative data with which to evaluate inhibitor incidence and prevalence, monitor trends in occurrence rates, and identify potential inhibitor outbreaks associated with products.

Keywords
Surveillance; Haemophilia; Haemophilia inhibitor

INTRODUCTION

Persons with haemophilia are deficient in a protein that is necessary for normal blood clotting. As many as one-third will develop an antibody (inhibitor) to the intravenous anti-hemophilic factor products given to stop or prevent a bleeding episode. Most inhibitors develop during the first few infusions with factor which, especially among those with severe haemophilia, typically occur before the age of 2 years. Although most of these inhibitors are transient and will resolve, 5% to 7% of the haemophilia population have a clinically significant long-term inhibitor. An inhibitor renders the treatment product ineffective in controlling bleeding. The public health costs associated with inhibitors are staggering. People with haemophilia and an inhibitor are twice as likely to be hospitalized for a bleeding complication. The costs of treatment and hospital care have been reported to be 2 to 10 times greater for those with inhibitors, compared to those without an inhibitor.

In November 2003, the U.S. Food and Drug Administration (FDA) held a workshop on factor VIII (FVIII) inhibitors. The purpose of the workshop was to convene a group of experts to advise the FDA on how to design studies to objectively evaluate the risk of either new treatment products or products that have undergone significant manufacturing changes to induce inhibitor formation in previously treated patients. Subsequently, the European Medicines Agency (EMA) held a similar meeting and produced a report of its findings in 2006. Recognizing that clinical trials alone were inadequate to fully assess a product’s immunogenicity, the EMA recommended long-term data collection through post market surveillance or registries. The recommendations further stipulated that studies of inhibitors should prospectively collect data on all treatment exposures and include details such as age at treatment onset, reasons and intensity of treatment, product switching and other environmental variables, as well as data on genetic factors such as haemophilia severity, gene mutation, family inhibitor history and ethnicity. Finally, the agencies recommended that monitoring for inhibitors should involve clinical and laboratory study using standardized methods with a high degree of quality control.
In 1998, a public health surveillance system called the Universal Data Collection (UDC) system was established by the Centers for Disease Control and Prevention (CDC) in more than 125 federally supported specialized haemophilia treatment centers (HTCs) in the United States. Although the system was not specifically designed to study inhibitors, data from this system were used in a previous study to estimate the incidence of inhibitors in previously treated patients.

The purpose of this study was to determine the feasibility of incorporating the EMA and FDA guidelines into such a surveillance program. Specifically, the study was designed to evaluate (1) the ability to prospectively collect complete and accurate records of factor infusions, (2) methodologies to perform gene sequencing on a large number of patients, and (3) methodologies to ship and accurately test blood specimens for inhibitors in a central laboratory.

MATERIALS AND METHODS

Site selection

Haemophilia treatment centers (HTCs) already participating in the UDC surveillance program were eligible to participate. Nine sites were originally selected based upon willingness to participate, representativeness with regard to geographic catchment area, number of patients served (a mixture of small and large centers was desired), ability to hire a dedicated coordinator, and the use of an electronic medical record system (Lab Tracker™) developed specifically to record treatment-related data. Eight additional sites were later added, three to augment the sample size of children less than 2 years of age and five to increase the number of Black and Hispanic participants. CDC provided the study protocol and data collection instruments and the project was approved by Investigational Review Boards both at CDC and at each participating institution.

Participant Recruitment

All patients with haemophilia A (HA) and haemophilia B (HB) participating in the UDC program were initially eligible for participation. After August 2009, patients with a previous history of an inhibitor were excluded. Patients were recruited during HTC visits and all participants (or parents of minor children) signed an IRB-approved informed consent. Individuals using electronic infusion log tools were asked for permission to access these data for the study.

Data collection

Data collected at enrollment included month and year of birth, ethnicity, haemophilia type and severity and the number of lifetime exposure days to factor concentrates based on participants’ medical records, clinic records, and recall. If the patient had a history of an inhibitor, additional data were collected on the highest titer result and most recent titer result based on local testing and on the use of immune tolerance therapy and adjunctive medications.
After enrollment, the following data about each infusion with factor concentrates were collected: date and time of infusion, location of infusion (treatment center setting vs. non-treatment center setting), product name, vial lot number(s) and corresponding vial amount(s), and reason for infusion. If the infusion was to treat a bleed, the time between bleed and infusion, cause of bleed (spontaneous vs. trauma) and bleed location was collected. If the infusion was for a medical procedure/surgery, the type of procedure and date performed were collected.

Data were also collected at each blood specimen draw and included the date and time, the date of the most recent treatment product infusion, product name, amount infused, and the reason for the draw. If the reason for the blood draw was a product switch, additional data including the type of product switch and the reason for the product switch were collected.

**Specimen collection**

Blood specimens were collected at enrollment into the study, annually, prior to any planned treatment product switch, and at clinical indication of an inhibitor (determined by the attending haematologist); a second sample was requested to confirm a positive specimen. Blood was collected into 3.2% sodium citrate and centrifuged at 1,600 × g for 20 minutes at 4°C, followed by repeat centrifugation of the separated plasma at 1,600 × g for 20 minutes at 4°C. Separated plasma samples were shipped to CDC overnight on cold packs. The remaining cell pellet was also sent on cold packs to CDC to be used for haemophilia gene mutation testing. At CDC, the plasma samples were aliquoted and stored at −70°C. During the study, the plasma specimens from 50 patients were split; half were sent as described above, and the other half were frozen at −70°C then shipped overnight to CDC on dry ice.

**Inhibitor testing**

FVIII inhibitors were measured at CDC by a modification of the Nijmegen-Bethesda method described elsewhere. Briefly, plasma specimens were heated to 56°C for 30 minutes and centrifuged at 2,700 × g for 5 minutes at room temperature. The supernatant was tested as described by Verbruggen, et. al. using imidazole-buffered normal pool plasma (Precision Biologic, Dartmouth, Nova Scotia, Canada) and dilution in hemophilic plasma (George King, Overland Park, KS, USA). Factor IX (FIX) inhibitors were measured similarly.

**Genotyping**

Sequencing of the 5′ and 3′ untranslated regions all exons, and all intron-exon junction regions of the FVIII gene (F8) and the FIX gene (F9) was carried out in forward and reverse directions using an automated analyzer (3730 DNA Analyzer, Applied Biosystems, Carlsbad, CA, USA) and the VariantSEQ™ protocol. Data were analyzed with SeqScape®. Intron 22 and intron 1 inversions in F8 were detected by polymerase chain reaction. Multiplex ligation-dependent probe amplification (MLPA) was performed using SALSA MLPA Kits P178-A1Factor VIII and P207-C1 F9 (MRC Holland, Amsterdam, The Netherlands).
Infusion log collection

Local site coordinators provided participants with the CDC infusion log data instrument and discussed with enrollees other options available to keep the infusion data such as retaining factor product box-tops, paper calendars, site-provided data forms, electronic infusion log tools (e.g., Advoy, EZ Log) or utilizing formatted Microsoft Excel spreadsheets. Adherence to the collection of infusion data, based on submission of infusion logs or patient report of no infusions, was determined for each participant on a monthly basis.

Data analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the study population and follow-up time in the study. Correlations between inhibitor test results on samples sent to CDC on cold packs versus dry ice were examined using the Spearman correlation coefficient. Percent compliance was calculated by dividing the number of months that a patient submitted infusion data by the total number of months he was on study and multiplied by 100. Comparisons of means used t-tests and comparisons of means adjusted for other variables utilized general linear regression. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Differences in measures with p-values ≤0.05 were considered statistically significant.

RESULTS

From January 1, 2006 until June 31, 2012, staff at 17 HTCs enrolled 1163 patients with the characteristics shown in Table 1. Subjects ranged in age from 2 months to 84.4 years with a mean of 20.4 years (median = 15.1 years) at enrollment. The distributions of haemophilia type and severity were similar to those seen in population studies, and 129 (11.1%) had a history of a previous inhibitor according to local clinical records. One-fourth of the subjects had fewer than 20 exposure days to factor concentrates and about 60% had been exposed to product more than 100 days in their lifetime at enrollment into the study. The total subject follow-up time was 3,329 person years.

Inhibitor testing

Modified shipping conditions were tested on 50 specimens with inhibitor titers ranging from 0 to 900. Split samples shipped either on cold packs or frozen showed excellent correlation (r=0.998). The cold pack method was chosen to simplify specimen handling. Initial tests of 228 frozen specimens from severe HA patients showed that 126 (55%) had measurable FVIII activity; all were from patients reported to have been treated with FVIII-containing products within 72 hours of blood collection. A heating step was introduced to eliminate residual FVIII. Based on the results on 710 HA specimens collected at enrollment, the reference range for a positive CDC test result was set at ≥0.5 Nijmegen-Bethesda units (NBU) for factor VIII. Among 160 factor IX inhibitor tests performed, no HB patient without a previous history of inhibitor had a titer >0.2 NBU. A positive CDC test result for factor IX was set at ≥0.3 NBU.

During the study period a total of 3,048 inhibitor tests were completed. The baseline test at enrollment accounted for 38.2% (n=1,163), the annual inhibitor test 59.5% (n=1,813),
anticipated product switch testing 1.3% (n=40), and tests for clinical indication accounted for 1% (n=32) of the total. The sites were able to obtain 68% of the expected 2,680 annual specimens based on the time on study.

We detected an inhibitor titer above the cutoff value in 23 HA patients either at enrollment or during follow-up (Table 2). Of the nine patients with elevated inhibitor titers detected at enrollment none had any overt clinical signs or symptoms, 89% had more than 20 days of lifetime exposure to concentrates and 44% were over the age of 5 years. Among those with an elevated inhibitor titer detected during follow-up, 36% had no clinical indication. Compared to those with elevated titers detected at enrollment, a greater proportion of patients with elevated titers detected during follow-up had peak titers greater than 1 NBU. Of those with newly elevated inhibitor titers detected, 78% had high risk mutations, and overall 61% were not recognized by HTC staff as having an inhibitor prior to the CDC testing. No newly elevated inhibitor titers were detected in HB patients.

Genotyping

Mutation analysis was performed on specimens obtained from 902 subjects with HA and 214 subjects with HB. A total of 342 distinct $F_8$ mutations were identified, of which 140 had not previously been reported. Among HB patients, 89 distinct $F_9$ mutations were found, 11 of which had not been reported. Mutation type frequency by severity is shown in Figures 2 and 3. In severe HA, the most common mutations were intron 22 inversions, occurring in 40.6% of subjects. Missense mutations predominated in patients with moderate and mild HA and in all severities of HB.

Infusion log collection

Infusion data were collected from 976 patients (83.9%) during the study period. Of those, 180 (18.4%) reported receiving no infusions during their follow-up time. Data on infusions were collected from the remaining 796 participants totaling 113,205 exposure days. Recombinant products were the most utilized product type, as reported by participants (Table 3).

The overall mean compliance with reporting infusions by participants was 63.0%. HTC, age at enrollment, and disease severity were each significantly associated with participant compliance with reporting (p<0.0001). Compliance with reporting varied across participating HTCs from 51% to 94% (Figure 4). Participants aged 20 – 29 years at enrollment were the least likely to keep and/or submit infusion logs (Figure 5). After adjusting for HTC and age, compliance rates differed significantly by severity; 82.3% mild, 71.7% moderate and 53.0% severe (p<0.0001).

DISCUSSION

In the United States, the FDA has established a passive drug safety monitoring system based on voluntary reports from physicians to collect adverse event reports on drugs. It is recognized that adverse events are under-reported to this system due to a variety of reasons including lack of evidence of causality, insufficient time for reporting or lack of knowledge about reporting criteria or procedures. 14, 15 Anecdotal evidence suggests that inhibitors are
likely to be under-represented in this monitoring system since many care providers consider inhibitors to be a known treatment side effect rather than an adverse event. In addition, not all providers routinely test for inhibitors. For example, among the nearly 7,000 patients with severe haemophilia who had a comprehensive visit to an HTC during 2006 – 2010, 46% had an inhibitor titer measured (unpublished CDC data).

As a result, the occurrence of inhibitors in the US haemophilia population is not known. Public health planning and resource allocation for efforts to prevent or minimize the impact of inhibitors are hampered by the lack of information on the burden of this serious complication of haemophilia care. At the least, data on occurrence are needed to identify target populations, track trends in rates over time and identify ‘outbreaks’ of inhibitors.\(^\text{16}\)

The purpose of this study was to determine whether we could enhance data collection, as part of a national public health surveillance system providing the largest sample size possible in the United States, to achieve reliable rates of occurrence and to facilitate research into the causes of inhibitors in a way that minimizes the limitations of previous studies. We were able to implement centralized testing for inhibitors by utilizing a simple method of sample collection and shipping and high-throughput technologies to make the testing efficient and cost saving. Our methodology also allowed us to test patients who had recently infused factor which is a barrier to the testing performed in most local laboratories. Data from large numbers of tests were used to develop methods that were consistent, reliable and reproducible and to set a cut-off for a positive inhibitor with the CDC test.

Although collection of annual blood specimens for inhibitor testing was part of the study protocol, achieving compliance was challenging. The frequency of inhibitor testing for clinical management varied widely across HTCs. Annual testing was particularly challenging for participants with mild and moderate haemophilia because they were less likely to visit the clinic annually. Another barrier to regular inhibitor screening outside of this study could be the cost, which may not be reimbursed by payers in the absence of clinical evidence of an inhibitor. Despite these challenges we were able to achieve nearly 70% compliance with the specimen submission requirements for the study.

Although inhibitors are an adverse event that haematologists expect some patients will experience, early identification through routine, regular inhibitor screening could play a role in decreasing the duration and increasing the success of treatment of an inhibitor\(^\text{17}\) and, thereby, lower the cost and morbidity associated with inhibitor development. In this study, we found a surprising number of cases that had gone unrecognized by their care providers including one patient who had a 54 NBU inhibitor titer. Had we been testing only ‘high risk’ patients we would have missed a substantial proportion of these new cases: one-third had non-severe disease and one-quarter had greater than 150 exposure days. We believe that these findings provide justification for the need for in-depth monitoring for inhibitors on a regular basis. One-third of the elevated titers identified by our testing measured <1 NBU. The clinical relevance of these low level titer elevations is not completely understood. It is recognized that some patients on prophylaxis require larger doses of factor than expected to prevent bleeding episodes and it is possible that such low level elevations play a role in this phenomenon. Further study of this issue is needed.
Another important aspect of this project was the development of high-throughput mutation testing. In the United States, fewer than 15% of haemophilia patients have been genotyped (unpublished CDC data). At 186,000 base pairs, \( F8 \) is one of the largest human genes and over 2,500 unique mutations have been identified.\(^{18} \) Few laboratories offer the complete testing profile and its cost has been high. Sequencing of the smaller \( F9 \) gene is more widely available, but HB is much less common. Yet, it is important to note that 78% of the patients identified with a newly elevated inhibitor test in this study had high risk mutations.

HTC collection of detailed patient recorded data on infusions, proved highly feasible. There were two main local site components that improved reporting compliance among participants. HTCs that were routinely collecting infusion logs as part of clinical management prior to participating in the study were able to maintain high compliance rates. In addition, local study coordinators who regularly contacted participants, who built relationships with participants and who offered flexibility in the method patients used to record data achieved high compliance rates. Despite the feasibility of prospectively collecting comprehensive product exposure data on study, we believe that a satisfactory level of compliance to recording infusions is unlikely to be achievable on a national scale without more widespread use of infusion data for clinical management.

**CONCLUSION**

Based on these findings, implementation of national inhibitor surveillance in the United States is feasible with some modifications to the components of this study. Routine centralized inhibitor screening using a validated testing methodology will ensure standardized test results and facilitate complete monitoring of inhibitor rates in a large population of patients over time which would facilitate analyses of trends. Such analyses will be important as new products are developed and post-market surveillance is required to evaluate the long-term safety of these products. Recent meetings of stakeholders have confirmed the importance of inhibitors as a critical public health issue for the haemophilia community. This study has provided essential information on how a surveillance system could be implemented using the existing CDC surveillance model.

**Acknowledgments**

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References


Figure 1.
Distribution and relative number of mutations associated with mild, moderate and severe haemophilia A across F8 by mutation type.
Figure 2.
Distribution of factor VIII mutation types by severity identified among participants with haemophilia A in the study.
Figure 3.
Distribution of factor IX mutation types by severity identified among participants with haemophilia B in the study.
Figure 4.
Mean patient compliance to reporting infusions by HTC site.
Mean values are adjusted for haemophilia treatment center and patient haemophilia severity using analysis of variance.
HTC = haemophilia treatment center.
Figure 5.
Mean patient compliance to reporting infusions by patient age group.
Mean values are adjusted for haemophilia treatment center and patient haemophilia severity using analysis of variance.
Table 1

Characteristics of people with haemophilia enrolled in the study

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Haemophilia A</th>
<th>Haemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>1163</td>
<td>950</td>
<td>213</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>250</td>
<td>199</td>
<td>51</td>
</tr>
<tr>
<td>Moderate</td>
<td>233</td>
<td>146</td>
<td>87</td>
</tr>
<tr>
<td>Severe</td>
<td>680</td>
<td>605</td>
<td>75</td>
</tr>
<tr>
<td><strong>Age at Enrollment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>52</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>2–9 years</td>
<td>361</td>
<td>298</td>
<td>63</td>
</tr>
<tr>
<td>10–19 years</td>
<td>301</td>
<td>242</td>
<td>59</td>
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<tr>
<td>20–29 years</td>
<td>183</td>
<td>151</td>
<td>32</td>
</tr>
<tr>
<td>30–45 years</td>
<td>133</td>
<td>113</td>
<td>20</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>133</td>
<td>97</td>
<td>36</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1161</td>
<td>948</td>
<td>213</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>946</td>
<td>767</td>
<td>179</td>
</tr>
<tr>
<td>Black</td>
<td>86</td>
<td>69</td>
<td>17</td>
</tr>
<tr>
<td>Hispanic</td>
<td>74</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>Asian</td>
<td>21</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>36</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td><strong>Prior Exposure Days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>1–20</td>
<td>232</td>
<td>162</td>
<td>70</td>
</tr>
<tr>
<td>21–100</td>
<td>158</td>
<td>119</td>
<td>39</td>
</tr>
<tr>
<td>101–150</td>
<td>75</td>
<td>63</td>
<td>12</td>
</tr>
<tr>
<td>&gt;150</td>
<td>659</td>
<td>572</td>
<td>87</td>
</tr>
</tbody>
</table>
Proportions do not all sum to 100% due to missing data.
### Table 2

Inhibitor titer elevations detected at enrollment and during the study according to selected demographic and clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Detected at Enrollment</th>
<th>Detected During Study follow-up</th>
<th>Total Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Severe</strong></td>
<td>3/9 (33%)</td>
<td>5/14 (36%)</td>
<td>8/23 (35%)</td>
</tr>
<tr>
<td>Age &gt;5 years</td>
<td>4/9 (44%)</td>
<td>6/14 (43%)</td>
<td>10/23 (43%)</td>
</tr>
<tr>
<td>Exposure Days &gt;150</td>
<td>3/9 (33%)</td>
<td>2/14 (14%)</td>
<td>5/23 (22%)</td>
</tr>
<tr>
<td>Exposure Days &gt;20</td>
<td>8/9 (89%)</td>
<td>5/14 (36%)</td>
<td>13/23 (57%)</td>
</tr>
<tr>
<td>White Non-Hispanic Ethnicity</td>
<td>7/9 (78%)</td>
<td>10/14 (71%)</td>
<td>17/23 (74%)</td>
</tr>
<tr>
<td>High Risk Mutation</td>
<td>8/9 (89%)</td>
<td>10/14 (71%)</td>
<td>18/23 (78%)</td>
</tr>
<tr>
<td>Initial Titer &gt;1.0 NBU</td>
<td>4/9 (44%)</td>
<td>11/14 (79%)</td>
<td>15/23 (65%)</td>
</tr>
<tr>
<td>Peak Titer &gt;1.0 NBU</td>
<td>4/9 (44%)</td>
<td>11/14 (79%)</td>
<td>15/23 (65%)</td>
</tr>
<tr>
<td>Peak Titer &gt;5.0 NBU</td>
<td>2/9 (22%)</td>
<td>5/14 (36%)</td>
<td>7/23 (30%)</td>
</tr>
<tr>
<td>No Clinical Indication</td>
<td>9/9 (100%)</td>
<td>5/14 (36%)</td>
<td>14/23 (61%)</td>
</tr>
</tbody>
</table>

NBU = Nijmegen Bethesda Units

*Haemophilia. Author manuscript; available in PMC 2015 July 30.*
Table 3

Distribution of the factor product type utilization reported by participants according to inhibitor history.

<table>
<thead>
<tr>
<th>Product Type</th>
<th>No History of an Inhibitor (N=695)</th>
<th>History of an Inhibitor (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant</td>
<td>625</td>
<td>70</td>
</tr>
<tr>
<td>Plasma-derived</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Plasma-derived with VWF</td>
<td>3</td>
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