# Adherence to prophylaxis and bleeding outcome in children and adolescents with severe haemophilia

Wife, C
5776953
Master Thesis: Final
Jun 28, 2018
Utrecht University, Master Clinical Health Science, Nursing science, UMC-Utrecht
Supervisor: Marlies Schrijvers
Study group teacher: Jacqueline van Dijk
Internship: Van Creveldkliniek, University Medical Centre, Utrecht
Intended magazine: Haemophilia - The Official Journal of the World Federation of Haemophilia
Amount of words: 3697
Criteria used for transparent reporting: STROBE statement
Amount of words Samenvatting: 285
Amount of words Abstract: 287

**ABSTRACT**

*Background*

Severe haemophilia can lead to spontaneous bleeds which can be prevented by the use of prophylaxis. In children and adolescents, several factors can influence adherence to the prescribed prophylaxis regime. They experience different kind of challenges, depending on their age. Now, children and adolescents receive comparable care although the need for guidance is likely to vary. To be able to provide tailored care, the relationship between adherence, age and bleeds should first be investigated.

*Aim*

The aim of this study was to explore adherence to prophylactic treatment and its association with age and frequency of bleeding events in children and adolescents with severe haemophilia.

*Methods*

A quantitative, cross-sectional survey was conducted, using existing data that was collected between 2011 and 2016 during outpatient visits in the Netherlands (Utrecht). The focus was on children and adolescents with severe haemophilia. During this study, demographic data and data of bleeding events were extracted from electronic patient medical records. A Spearman's rank correlation was conducted to analyze adherence to prophylaxis and its association with age and number of bleeds.

*Results*

In total, 68 patients (children and adolescents) were included whereafter data was analyzed. An adherence was found of median 84.9%. A significant correlation was found between the VERITAS-pro total score and an increasing age ($r_s = 0.37$; $P = 0.002$). No significant correlation was found between the VERITAS-pro total score and total bleeds or joint bleeds.

*Conclusion and Recommendation*

This study showed that patients were less adherent as they increased in age. No association was found between adherence and bleeds. Future research should focus on optimizing care, depending on age, to enable tailored care from physicians and nurses fitted to patients age.

*Keywords: adherence, prophylaxis, bleeds, severe haemophilia, minors*

**SAMENVATTING**

*Achtergrond*

Ernstige hemofilie kan leiden tot bloedingen en gewrichtsschade wat kan worden voorkomen door een juiste toediening van profylaxe. Verschillende factoren kunnen de therapietrouw van profylaxe bij kinderen en adolescenten beïnvloeden, afhankelijk van hun leeftijd. Nu ontvangen kinderen en adolescenten vergelijkbare zorg, hoewel de behoefte aan zorg waarschijnlijk varieert. Om zorg op maat aan te kunnen bieden moet eerst de relatie tussen therapietrouw, leeftijd en het aantal bloedingen worden onderzocht.

*Doel*

Het doel van deze studie was om de therapietrouw van profylaxe en de associatie met leeftijd en de frequentie van bloeding te onderzoeken bij kinderen en adolescenten met ernstige hemofilie.

*Methode*

Een kwantitatief, cross-sectioneel onderzoek werd uitgevoerd met behulp van bestaande gegevens die tussen 2011 en 2016 werden verzameld tijdens poliklinische bezoeken in Nederland (Utrecht). Kinderen en adolescenten met ernstige hemofilie waren geschikt voor inclusie. Tijdens dit onderzoek werden demografische gegevens en gegevens over bloedingen verzameld uit elektronische patiëntendossiers. De associatie tussen therapietrouw, leeftijd en het aantal bloedingen werd geanalyseerd middels de Spearman's rank correlatie.

*Resultaten*

In totaal werden 68 patiënten (kinderen en adolescenten) geïncludeerd, waarna de gegevens zijn geanalyseerd. Er werd een mate van therapietrouw gevonden van mediaan 84,9%. Een significante correlatie werd gevonden tussen de VERITAS-pro totale score en een toenemende leeftijd ($r_s$ = 0.37; P = 0.002). Er werd geen significante correlatie gevonden tussen de VERITAS-pro totale score en totale bloedingen of gewrichtsbloedingen.

*Conclusie en Aanbeveling*

Deze studie liet zien dat patiënten minder therapietrouw waren naarmate zij ouder werden. Er werd geen verband gevonden tussen therapietrouw en bloedingen. Toekomstig onderzoek moet zich richten op het optimaliseren van de zorg, afhankelijk van leeftijd, zodat artsen en verpleegkundigen zorg op maat kunnen bieden die is aangepast naar de leeftijd van de patiënt.

## INTRODUCTION

Haemophilia is an X-linked inherited bleeding disorder, caused by a lack or absence of clotting Factor VIII (haemophilia A) or Factor IX (haemophilia B)[1]. The prevalence of haemophilia is approximately 400.000 worldwide[2]. In the Netherlands, approximately 1.600 people are affected with haemophilia A or B[3]. There are three classifications: mild, moderate or severe. People with severe haemophilia have less than 1% of the normal clotting factor and experience spontaneous bleeds in joints, muscles or soft tissue[4-5]. To prevent bleeding, patients are treated with intravenous injections of factor concentrate. There are two types of treatment: on-demand, where medication is used to treat a bleed; or as prophylaxis, where medication is used to prevent bleeds[6]. For patients with severe haemophilia, prophylaxis is the standard therapy[7]. It is an invasive home treatment whereby patients are treated with prophylactic infusions approximately 3 to 3,5 times a week. This treatment commences after the first joint bleed and should be continued lifelong[2,8-9].

In children and adolescents, the diagnosis of severe haemophilia has a great impact on both parents' and patients' lives. Parents administer the prophylactic infusions to their children and must therefore be taught how. In addition, they need to be aware of the importance of adherence. Non-adherence can lead to irreversible damage in which only a single bleed in a joint or the central nervous system can lead to major motoric and cognitive disabilities[10-11]. Bleeding events are any bleeds requiring extra treatment with clotting factor concentrate (CFC)[12]. When prophylaxis is used correctly, no bleeds occur, which makes adherence vitally important[13-14]. For parents, injecting the prophylaxis can be seen as a burden and can be found difficult to cope with[10]. During the process of infusion, children often experience fear and anxiety, leading to resistance and fights[15]. For children, it can be hard to understand why prophylactic infusion is necessary and why this treatment gives more protection for them in their daily activities.

When children reach early adolescence ($\pm$ 12 years old) they learn to administer the prophylaxis by themselves. The exact age varies per child. Adolescents of around 14 years old take primary responsibility for their treatment[16]. In their teenage years, adolescents experience physical, cognitive and psycho-social changes. They are confronted with maintaining treatment and taking responsibility for their disease whilst at the same time evolving their own identity and becoming independent[17]. Lack of knowledge about the disease, teenage rebellion, interference with daily habits and little family support are factors that can lead to non-adherence[18-19].

Several factors are known that can influence the level of adherence in children and adolescents. They experience different kinds of challenges, depending on their age. Now, children and adolescents receive comparable care although the need for guidance is likely to vary. To be able to provide tailored care, the relation between adherence and age should first be explored. Several studies have examined adherence to prophylaxis and children and/or adolescents with (severe) haemophilia, but these studies were all somewhat limited. Some studies had a small sample size and used non-validated questionnaires that varied in their definition of adherence[6,20-21-22-23]. As a lower adherence could result in more severe disease outcomes, non-adherence to prophylaxis could be related to more frequent bleeding events[24]. This relation between adherence and bleeds should be further examined. The aim of this study was to explore adherence to prophylactic treatment and its association with age and frequency of bleeding events in children and adolescents with severe haemophilia.

## METHOD

### *Design*

A quantitative, cross-sectional survey was conducted, using existing data that was collected between 2011 and 2016 during standard care outpatient visits in the Netherlands (Utrecht). During this study, demographic data and data of bleeding events were analyzed with the adherence questionnaire. This design was chosen because the use of a validated questionnaire is currently the best reliable method to measure adherence[21].

### *Population*

A convenience sample was used at the National Haemophilia Treatment Center in the Netherlands (Utrecht) between the years 2011 and 2016. Patients, from birth to eighteen years old and diagnosed with severe haemophilia (Factor VIII or Factor IX deficiency) were eligible. These patients were required to practice prophylactic home infusion, administered by their parents or by themselves, for at least 1 year and at least once a week. A distinction was made between children and adolescents, depending on who administered the prophylaxis. This information was extracted from the electronic patient medical records. In children (approximately 0 to 12 year of age), parents administered the prophylaxis and therefore completed the questionnaire. When adolescents (approximately 12-18 years of age) administered the prophylaxis themselves, they completed the questionnaire. Patients needed to speak Dutch and the person who completed the questionnaire was required to read and write Dutch as well.

### *Data collection*

*Adherence*

Adherence to the prophylactic infusion was measured by the 'Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis' questionnaire (VERITAS-pro)[21]. The VERITAS-pro was developed and validated by Duncan et al. in the United States and the questionnaire was then translated and validated into a Dutch version by Lock et al.[21,25]. The VERITAS-pro evaluates the total and specific domains of adherence to the prophylactic regimes[21,25]. The six subscales, concerning a specific domain in haemophilia care are: Time, Dose, Plan, Remember, Skip and Communicate. Each subscale has four questions, leading to a total of 24 items[21]. Each item is quantified on a five-point Likert scale, ranging from 'Always' to 'Never' rating to a numeric score with the 'best' adherence score given one point and the 'worst' five points. A higher score reflects lower adherence[21]. The cumulative total-score ranges from 24 to 120 and the cumulative sub-scores from 4 to 20. It is a short (±10 minutes) questionnaire that is completed by the person who administered the prophylaxis (parent or adolescent)[21].

*Bleeding events*

Bleeding events were collected from the electronic patient medical records over the last three years, starting the moment the VERITAS-pro was completed. Bleeding events were updated during each outpatient visit. Bleeding events were categorized into: total bleeds, joint bleeds and target joints. The number of total bleeds and joint bleeds were identified per year. Target joints were defined as a joint with three or more bleeds within three months and were extracted form the number of joint bleeds in a 3-month period[26]. Bleeding events in case of surgery were excluded. The year a patient had a modified prophylactic regime and a bleeding event occurred was also excluded. These events were excluded because these circumstances increase the risk of a bleed, which is not particularly due to non-adherence. Bleeding events were defined as any bleed requiring extra treatment with clotting factor concentrate (CFC)[12].

*Patient characteristics*

The following baseline characteristics were collected from the hospital electronic patient medical records: date of birth (month and year), diagnosis of severe haemophilia: Factor VIII (haemophilia A), Factor IX (haemophilia B) or other factor deficiency disorders[27]. In addition, venous access (IV or CVAD), prescribed frequency and dose of CFC over the period of three months, frequency and/or dose change over the period of one year, and which person (parents or adolescents) administered the prophylactic infusion, were identified.

### *Procedures*

Data collection of the VERITAS-pro and other data (baseline characteristics and number of bleeds) already took place during outpatient visits as part of standard care between the years 2011 and 2016. The baseline characteristics and bleeding events were extracted from the electronic patient medical records by the researcher (CW). Bleeding events were collected retrospectively over the last three years, starting the moment the VERITAS-pro was completed. The completed questionnaires were collected and the baseline characteristics and data pertaining to the bleeding events were reported on a Case Report Form (CRF) before analysis.

### *Data analysis*

Missing data of the VERITAS-pro was identified as Missing Completely At Random (MCAR), Missing At Random (MAR) or Missing Not At Random (MNAR) by the researcher (CW). MNAR data were analyzed as to why they were MNAR and these patients were excluded. The Shapiro-Wilt test was used to test outcomes for normality[28]. Continuous data were presented by median and interquartile range (IQR) because of the skewed distribution. Dichotomous and categorical data were presented by frequencies and percentages. The VERITAS-pro score was analyzed for differences between children and adolescents reported outcome by the Mann-Whitney U test[29-30]. In case of no significant differences, children and adolescents were analyzed together. All outcomes were considered significant with a p-value of <0.05. Data processing and analyses were performed with IBM SPSS Statistics, version 24 (IBM Armork, New York, USA).

#### *Adherence*

Questions of the VERITAS-pro were reversed to determine the total and sub-scores. The total cumulative score of the VERITAS-pro ranges from 24 to 120 and was normalized into a 0 to 100% score range, where a higher score reflects a higher adherence. The VERITAS-pro was analyzed using continuous variables because this gives more insight into the data.

#### *Adherence and its association with age and bleeding outcome*

Descriptive analysis was made for adherence and age, using different age groups (3-6, 6-9, 9-12, 12-15 and 15-18). Similarly, adherence and total and joint bleeds were descriptive analyzed per number of bleeds. Adherence and its association with age and its association with bleeding outcome were analyzed using a Spearman's rank correlation with a separate analysis for the different bleeding outcome: total bleeds, joint bleeds and target joints. The Spearman’s rank correlation was chosen instead of the Pearson correlation because

bleeding events were likely to have a skewed distribution and because of the possible outliers in the level of adherence and bleeds[31-32].

*Additional analysis VERITAS-pro*

Although the VERITAS-pro was tested for reliability and validity, no analysis was performed to sharpen the questions for better reflection of adherence. To ascertain these sharpened questions, a Principal Componence Analysis (PCA) was conducted with varimax rotation and Kaiser method for factor retention[38-39-40].

### *Ethical issues*

This study was approved by the Medical Ethics Review Committee of University Medical Center (UMC) Utrecht (reference number: WAG/mb/18/001276). Although the VERITAS-pro was part of standard care, patients were informed that completing the questionnaire was completely voluntary. No additional informed consent form was needed and patients were aware that the return of the questionnaire was seen as consent.

## RESULTS

In this study, 68 patients (children and adolescents) were analyzed. In total, 70 patients were included which was a high response rate, with almost all eligible patients participating. Two patients were excluded because they did not complete one or more questions about the sub-scale 'skip' of the VERITAS-pro that was identified as MNAR. Because the Mann-Whitney U test showed no significant differences between the VERITAS-pro score of children and adolescents (P = 0.14), children and adolescents were analyzed together.

*Patient characteristics*

In this study, 42 children were injected by their parents and 26 adolescents injected themselves. The majority (83.8%) were diagnosed with haemophilia A with a median age of 12.2 years old. Patients received their infusion a median of 3 times per week with a median dose of 1000 IU. Patients experienced a median of 0.6 total bleeds per year and a median of 0.3 joint bleeds per year. Three patients (4.4%) had a target joint. Demographic characteristics are shown in Table 1.

*Adherence*

The VERITAS-pro total score showed a median of 84.9%, (min/max range 52%-99%). The sub-scales of the VERITAS-pro varied between 75%-100%, with the lowest adherence level for 'Plan' (median: 75%) and the highest adherence level for 'Dose' (median: 100%), which

was the highest adherence level possible. Both sub-scales ‘Time’ and Communication’ had a median of 81.3% and the sub-scale ‘Remember’ showed a median of 87.5%. The sub-scale ‘Skip’ showed a median of 93.6%. Details of adherence levels are shown in Table 2.

*Adherence and its association with age*

Children between the age of 3-6 years showed the highest adherence level of 93.2% where after the adherence level dropped to 83.3% for children between the age of 6-9 years. Children between the age of 9-12 showed a slightly higher adherence level of 86.5%, whereafter adherence dropped to 83.3% for adolescents between 12-15 years. Adolescents between the age of 15-18 years showed the lowest adherence level of 81.8%. Details of the normalized median adherence and age groups are shown in Figure 1. The Spearman’s rank correlation (Table 3) showed a weak but significant positive correlation between the VERITAS-pro total (unadjusted) score and an increasing age ($r_s$ = 0.377; P = 0.002). This indicates that when age increases, patients were overall less adherent. A moderate positive correlation was shown between the VERITAS-pro sub-scale ‘Remember’ and age ($r_s$ = 0.510; P < 0.000). The association between the sub-scale ‘Skip’ and age was also significant (P = 0.019) but with a weak positive correlation ($r_s$ = 0.284). This indicates that when patients increased in age, it became more difficult for them to remember to infuse their prophylaxis and they also skipped more prophylaxis. The other sub-scales of the VERITAS-pro (Time, Dose, Plan and Communicate) showed no significant associations with age.

*Adherence and its association with bleeding outcome*

Patients experienced too few target joints to perform a reliable Spearman’s rank correlation. A trend was seen for patients who were more adherent when they experienced more (joint) bleeds. However, the Spearman’s rank correlation showed no significant correlation between the VERITAS-pro total score and total bleeds or joint bleeds (Total bleeds: $r_s$ = -0.106; P = 0.390; Joint bleeds: $r_s$ = -0.105; P = 0.393), (Table 4). Only the sub-score ‘Skip’ and total bleeding events showed a significant but weak negative correlation ($r_s$ = -0.280; P = 0.021). Patients who skipped more prophylaxis were also the ones who experienced less total bleeds. Figure 2 and 3 show a scatterplot between the normalized VERITAS-pro score and total or joint bleeds. Both total and joint bleeds show a comparable correlation with the normalized VERITAS-pro score. Only a few patients in this study experienced two or more bleeds per year.

*VERITAS-pro*

The PCA was conducted using 23 variables. The VERITAS-pro exist of 24 variables but one variable (question 6) had zero variance and was therefore excluded. The Kaiser-Meyer-Olkin (KMO) test showed that it was a moderate sample to perform a PCA (KMO = 0.72)[41]. Bartlett's test of sphericity was significant showing a sufficiently high correlation between the variables for a PCA. Seven components had eigenvalues above the Kaiser's criterion of 1. The first five components jointly explain 61.39% and the first seven components jointly explain 71.38% of the variance. Table 5 shows the factor loads of the seven components after rotation.

## DISCUSSION

*Main findings*

Both children and adolescents showed a high adherence to their prophylaxis (median 84.9%). A significant association was found between adherence and patients' age ($r_s$ = 0.37; P = 0.002). Patients became generally less adherent when they increased in age. When patients increased in age, they found it also more difficult to remember their prophylaxis and skipped more prophylactic infusions. No significant association was found between adherence and bleeds (total or joint bleeds).

*Compare findings with literature*

The high adherence in children and adolescents and its association with age is in line with earlier research which analyzed adherence using the VERITAS-pro as well[21-22,25,33]. Duncan et al. found an adherence level of 88.2% in children and adolescents and Miesbach et al. found an adherence level of 93.8% in children[25,33]. Lock et al. analyzed adherence in 60 children and adolescents between 1 and 18 years in three Dutch Haemophilia Treatment Centers and found a better adherence in children than in adolescents ($r_s$ = 0.27; P = 0.04)[21]. This was confirmed by Duncan et al. who analyzed 53 children and adolescents from the US who found a better adherence in children than for adolescents with a score of 88% vs. 82.5% (P < 0.05)[22]. Duncan et al. also showed a transaction point when patients changed from being infused to self-infused (12-14 years)[22]. The overall high adherence is also consistent with other studies who used a non-validated adherence questionnaire[6,23,34]. In this study, the high measured adherence for both children and adolescents with severe haemophilia is higher than other chronic diseases[35]. In chronic diseases it is generally accepted that 50% of the patients adhere to the prescribed medication[35]. Although the anticipated relationship between non-adherence and more frequent bleeds, no association was found between adherence and bleeding events. Other studies found inconsistent findings[6,36-37]. Schrijvers et

al. found a trend between joint bleeds and non-adherent children[36]. This trend was confirmed by Garcia-Daci et al. who found an significant association between increase of joint bleeds and a lower adherence in Spanish children[37]. This is in line with the anticipation that a lower adherence could result in more bleeds[24]. In contrast, Os et al. found fewer bleeds for non-adherent patients[6]. This can be explained by patients who are more adherent also may be more attentive to bleeding events than less adherent patients. Therefore, non-adherent patients might interpret symptoms less often as a bleed and experience more bleeds than reported[6]. A reason for the inconsistent findings of these studies can be explained due to the use of different adherence measurements and different reporting's of bleeding events[6,36-37].

*VERITAS-pro*

The VERITAS-pro provides a comprehensive view of adherence. In addition to its potential value for adherence research, the VERITAS-pro is an easy to use questionnaire and well-suited for clinic visits[25]. Although the VERITAS-pro was tested for reliability and validity, no analysis was performed to sharpen the questions for better reflection of adherence.
To optimize the use of the VERITAS-pro, a PCA was performed to sharpen these questions. This PCA showed that the last two components (component 6 and 7) of the VERITAS-pro only explained 9.9% more of the variance (component 1-5: 61.39%; component 1-7: 71.38%). The recommendation of this analysis is to sharpen the questions of components 6 and 7 (questions 5, 11 and 12) in order to enhance the interpret adherence reflection of the VERITAS-pro. Although question 3 is also in these components, no new question was recommended because it adequately reflects adherence. Table 6 represent the recommended new questions to optimize the use of the VERITAS-pro with a better reflection of adherence.

*Strengths & Limitations*

A strength of this study was the use of the validated VERITAS-pro, which is currently the best reliable method to measure adherence to prophylaxis. Because the VERITAS-pro was collected over a longer period of time (2011 to 2016), a high response rate was met, including almost all of the eligible patients of the National Haemophilia Treatment Center in the Netherlands (Utrecht). Some limitations of this study may be considered. Missing data of the VERITAS-pro was MNAR because patients did not complete one or more questions about the sub-scale 'skip'. These questions could either not have been applicable or patients may not have wished to give this information. Not completing the question or choosing to complete the question with an answer that does not reflect their adherence could lead to bias. The VERITAS-pro is collected at one point in time, reflecting the previous three months,

whereas a recall period of two weeks is considered as optimal due to reliability[42]. The number of bleeds were extracted from the electronic patient medical records which were verified and updated during each outpatient visit. Non-adherence patients may have reported less bleeding events (reporting bias). Patients could also forget to report bleeds during their visits to the clinic (recall bias). This could explain the fewer reported bleeds compared to other studies[36-37].

*Conclusion*

This study explored adherence of prophylactic treatment and its association with age and bleeding events in children and adolescents with severe haemophilia. Children and adolescents showed a high adherence (median 84.9%). A significant association was found between adherence of prophylactic treatment and age. Overall, patients were less adherent when they increased in age. No association was found between adherence of prophylactic treatment and bleeding events (total or joint bleeds).

*Implications for clinical practice and future research*

Both children and adolescents received comparable care although this study showed that patients were less adherent when they increased in age. Future research should focus on optimizing care, depending on age, so physicians and nurses can provide tailored care that is fitted to patients age and challenges[18-19]. No association was found between adherence and bleeding events although the anticipated relationship between non-adherence and more frequent bleeds[24]. Due to the method of collecting bleeding events in this study and the inconsistent findings with other studies[6,36-37]. Future research should assess self-reported bleeds instead of collecting bleeds during outpatient visits to better understand the association between adherence and bleeding events. Additionally, adherence should be measured on different time points.

**REFERENCE LIST**


1. Bolton-Maggs PHB, Pasi KJ. Haemophilias A and B. Lancet. 2003 May;361(9371):1801–9.
2. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013 Jan 1;19(1):e1–4
3. Hemofilie. Nederlandse Vereniging voor Hematologie. 2016. [Internet]. Available from: https://www.hematologienederland.nl/hemofilie. [cited 2017 Oct 12].
4. Severity of hemophilia - World Federation of Hemophilia. 2012. [Internet]. Available from: https://www.wfh.org/en/page.aspx?pid=643. [cited 2017 Oct 7].
5. White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 2001 Mar;85(3):560.
6. Van Os SB, Troop NA, Sullivan KR, Hart DP. Adherence to prophylaxis in adolescents and young adults with severe haemophilia: A quantitative study with patients. PLoS One 2017;12(1):1–18.
7. Thornburg CD, Duncan NA. Treatment adherence in hemophilia. Haemophilia 2017 Jan;1677–86.
8. Delivery of Treatment for Haemophilia Human Genetics Programme. Management of Noncommunicable Diseases World Health Organization Human Genetics Programme. 2002. [Internet]. Available from:http://apps.who.int/iris/bitstream/10665/67792/1/WHO_WFH_ISTH_WG_02.6.pd. [cited 2017 Oct 5];
9. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). J Thromb Haemost. 2011 Apr;9(4):700–10.
10. Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, de Kleijn P, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. Blood. 2002 Apr 1;99(7):2337–41.
11. Nijdam A, Foppen W, van der Schouw YT, Mauser-Bunschoten EP, Schutgens REG, Fischer K. Long-term effects of joint bleeding before starting prophylaxis in severe haemophilia. Haemophilia. 2016 Nov;22(6):852–8.
12. MASAC Recommendations Regarding Doses of Clotting Factor Concentrate in the Home | National Hemophilia Foundation [Internet]. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-

Regarding-Doses-of-Clotting-Factor-Concentrate-in-the-Home. [cited 2017 Dec 9].
13. Fischer K, Steen Carlsson K, Petrini P, Holmström M, Ljung R, van den Berg HM, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. Blood. 2013 Aug 15;122(7):1129–36.
14. Rocino A, Franchini M, Coppola A. Treatment and Prevention of Bleeds in Haemophilia Patients with Inhibitors to Factor VIII/IX. J Clin Med. 2017 Apr 17;6(4).
15. Furmedge J, Lima S, Monagle P, Barnes C, Newall F. 'I don't want to hurt him.' Parents' experiences of learning to administer clotting factor to their child. Haemophilia. 2013 Mar;19(2):206–11.
16. Lindvall K, Colstrup L, Wollter I-M, Klemenz G, Loogna K, Grönhaug S, et al. Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia. Haemophilia. 2006 Jan;12(1):47–51.
17. Warner DE, Hauser ST. Behavioral Approaches to Chronic Disease in Adolescence. New York: Springer; 2009. p. 15–28.
18. Kyngäs H. Compliance of adolescents with chronic disease. J Clin Nurs. 2000 Jul;9(4):549–56.
19. De Moerloose P, Urbancik W, Van Den Berg HM, Richards M. A survey of adherence to haemophilia therapy in six European countries: results and recommendations. Haemophilia. 2008 Sep;14(5):931–8.
20. Fischer K, Collins P, Astermark J, Blanchette VS, Bjorkman S, Oh M, et al. Internal and External Determinants of Bleeding Patterns on Prophylaxis for Severe Haemophilia A. Blood. 2007;110(11).
21. Lock J, Raat H, Duncan N, Shapiro A, Beijlevelt M, Peters M, et al. Adherence to treatment in a Western European paediatric population with haemophilia: reliability and validity of the VERITAS-Pro scale. Haemophilia. 2014 Sep;20(5):616–23.
22. Duncan N, Shapiro A, Ye X, Epstein J, Luo MP. Treatment patterns, health-related quality of life and adherence to prophylaxis among haemophilia A patients in the United States. Haemophilia. 2012;18(5):760–5.
23. Geraghty S, Dunkley T, Harrington C, Lindvall K, Maahs J, Sek J. Practice patterns in haemophilia A therapy - global progress towards optimal care. Haemophilia. 2006 Jan;12(1):75–81.
24. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. N Engl J Med. 2007 Aug 9;357(6):535–44.
25. Duncan N, Kronenberger W, Roberson C, Shapiro A. VERITAS-Pro : a new measure of adherence to prophylactic regimens in haemophilia. Haemophilia. 2010;247–55.

26. Ota S, Mclimont M, Carcao MD, Blanchette VS, Graham N, Paradise E. Definitions for haemophilia prophylaxis and its outcomes: The Canadian Consensus Study. Haemophilia. 2007 Jan;13(1):12–20.
27. Other Factor Deficiencies | National Hemophilia Foundation [Internet]. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies. [cited 2017 Dec 9].
28. Ghasemi A ZS. Normality Tests for Statistical Analysis: A Guide for Non-Statisticians. I. Int J Endocrinol Metab.; 2012. 10(2):486–9.
29. Jones MP, Beath A, Oldmeadow C AJ. Understanding statistical hypothesis tests and power. Med J. 2017;(Aug;207(4):148–50).
30. Mann H WD. On a test of whether one of two random variables is stochastically larger than the other. 1947. [Internet]. Available from: www.jstor.org.proxy.library.uu.nl/stable/2236101. [cited 2017 Dec 9].
31. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012 Sep;24(3):69–71.
32. J. E. Straightforward statistics for the behavioral sciences. Pacific Grove, CA: Brooks/Cole Publishing; 1996. 10(2):486–9.
33. Miesbach W, Kalnins W. Adherence to prophylactic treatment in patients with haemophilia in Germany. Haemophilia [Internet]. 2016 Sep [cited 2018 May 17];22(5):e367–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27353213
34. Pérez-Robles T, Romero-Garrido JA, Rodriguez-Merchan EC, Herrero-Ambrosio A. Objective quantification of adherence to prophylaxis in haemophilia patients aged 12 to 25 years and its potential association with bleeding episodes. Thromb Res. 2016 Jul;143:22–7
35. De Geest S, Sabaté E. Adherence to Long-Term Therapies: Evidence for Action. Eur J Cardiovasc Nurs. 2003 Dec 22;2(4):323–323.
36. Schrijvers LH, Lock J, Marjon H, Schuurmans MJ. Adherence to prophylaxis and bleeding outcome in haemophilia : a multicentre study. Haemophilia. 2016 April;454–60.
37. García-Dasí M, Aznar JA, Jiménez-Yuste V, Altisent C, Bonanad S, Mingot E, et al. Adherence to prophylaxis and quality of life in children and adolescents with severe haemophilia A. Haemophilia. 2015 Jul;21(4):458–64.
38. Norris M, Lecavalier L. Evaluating the Use of Exploratory Factor Analysis in Developmental Disability Psychological Research. J Autism Dev Disord. 2010 Jan 17;40(1):8–20.
39. How to Reduce Number of Variables and Detect Relationships, Principal Components

and Factor Analysis [Internet]. Available from: http://www.statsoft.com/Textbook/Principal-Components-Factor-Analysis. [cited 2018 Jun 19].

40. Kaiser-Meyer-Olkin (KMO) Test for Sampling Adequacy [Internet]. Available from: http://www.statisticshowto.com/kaiser-meyer-olkin/. [cited 2018 Jun 19].
41. Hutcheson G, Sofroniou N. The multivariate social scientist: introductory statistics using generalized linear models. Sage Publications; 1999. 276 p.
42. Jerant A, DiMatteo R, et al. Self-Report Adherence Measures in Chronic Illness. Med Care. 2008 Nov;46(11):1134–9.

## TABLES

*Table 1. Patient characteristics*

| | *Children (parent-reported)* N = 42 | *Adolescents (self-reported)* N = 26 | *Total* N = 68 |
|---|---|---|---|
| Age, yrs. (med, IQR) | 10.1 (7.7-11.7) | 14.7 (14.1-16.4) | 12.2 (9.3-14.6) |
| Diagnosis (n, %) | | | |
| Haemophilia A | 36 (85.7) | 21 (80.8) | 57 (83.8) |
| Haemophilia B | 3 (7.1) | 4 (15.4) | 7 (10.3) |
| Other | 3 (7.1) | 1 (3.8) | 4 (5.9) |
| Venous access (n, %) | | | |
| IV | 36 (85.7) | 26 (100) | 62 (91.2) |
| CVAD | 6 (14.3) | 0 (0) | 6 (8.8) |
| Frequency of prophylaxis‡ (med, IQR) | 3.0 (3.0-3.0) | 3.0 (3.0-3.5) | 3.0 (3.0-3.5) |
| Prophylaxis dose, IU (med, IQR) | 875 (750-1000) | 1000 (938-1125) | 1000 (750-1000) |
| Frequency and/or dose change (n, %) | 13 (31) | 4 (15.4) | 17 (25) |
| Joint bleeds (med, IQR) | 0.3 (0.0-1.0) | 0.0 (0.0-1.0) | 0.3 (0.0-1.0) |
| Total bleeds (med, IQR) | 0.6 (0.0-1.1) | 0.6 (0.0-1.0) | 0.6 (0.0-1.0) |
| Target joint, yes (n, %) | 2 (4.8) | 1 (3.8) | 3 (4.4) |

IV, intravenous; CVAD, central venous access device
‡number per week

*Table 2. Overview of adherence to prophylaxis in Children and Adolescents*

| | *VERITAS-pro (24-120)‡ unadjusted* | *VERITAS-pro (0-100%) normalized* |
|---|---|---|
| Total scale | 38.5 (34.3-44.0) | 84.9 (79.2-89.3) |
| Time | 7.0 (5.0-8.0) | 81.3 (75.0-93.8) |
| Dose | 4.0 (4.0-6.0) | 100.0 (87.5-100.0) |
| Plan | 8.0 (5.3-9.0) | 75.0 (68.8-92.2) |
| Remember | 6.0 (4.0-9.0) | 87.5 (75.0-100.0) |
| Skip | 5.0 (4.0-8.0) | 93.6 (75.0-100.0) |
| Communicate | 7.0 (5.0-9.0) | 81.3 (68.8-93.8) |

Values are reported as median (interquartile range)
‡Sub-scales had a range of: 4-20

*Table 3. Correlation between VERITAS-pro and Age*

| | *Age* | |
|---|---|---|
| *VERITAS-pro* | *r* | *P* |
| Total scale | 0.377* | 0.002 |
| Time | 0.201 | 0.100 |
| Dose | 0.130 | 0.290 |
| Plan | 0.081 | 0.512 |
| Remember | 0.510* | 0.000 |
| Skip | 0.284* | 0.019 |
| Communicate | 0.218 | 0.074 |

*Correlation is significant at the 0.05 level

*Table 4. Correlation between VERITAS-pro and Total bleeds and Joint bleeds*

| | *Total bleeds* | | *Joint bleeds* | |
|---|---|---|---|---|
| *VERITAS-pro* | *r* | *P* | *r* | *P* |
| Total scale | -0.106 | 0.390 | -0.105 | 0.393 |
| Time | -0.144 | 0.240 | -0.098 | 0.427 |
| Dose | -0.075 | 0.546 | -0.019 | 0.880 |
| Plan | 0.115 | 0.349 | 0.064 | 0.602 |
| Remember | -0.107 | 0.387 | -0.149 | 0.226 |
| Skip | -0.280* | 0.021 | -0.226 | 0.063 |
| Communicate | -0.003 | 0.978 | -0.012 | 0.920 |

*Correlation is significant at the 0.05 level

*Table 5. Principal Componence Analysis of the VERITAS-pro*

| | Components | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1. I do prophylaxis infusions on the scheduled days. | .448 | .712 | | | | | |
| 2. I infuse the recommended number of times per week. | .520 | .664 | | | | | |
| 3. I do prophylaxis infusions in the morning as recommended. | | | | | | .518 | .427 |
| 4. I do infusions according to the schedule provided by the treatment center. | .414 | .720 | | | | | |
| 5. I use the doctor-recommended dose for infusions. | | | | | | | .849 |
| 7. I increase or decrease the dose without calling the treatment center. | | | | | .780 | | |
| 8. I use the correct number of factor boxes to total my recommended dose. | | .771 | | | | | |
| 9. I plan ahead so I have enough factor at home. | | | | .827 | | | |
| 10. I keep close track of how much factor and how many supplies I have at home. | | | | .787 | | | |
| 11. I run out of factor and supplies before I order more. | | | | | | -.853 | |
| 12. I have a system for keeping track of factor and supplies at home. | | | | .444 | | .543 | |
| 13. I forget to do prophylaxis infusions. | .759 | | | | | | |
| 14. Remembering to do prophylaxis is difficult. | .796 | | | | | | |
| 15. I remember to infuse on the schedule prescribed by the treatment center. | | .401 | | .564 | | | |
| 16. I miss recommended infusions because I forget about them. | .846 | | | | | | |
| 17. I skip prophylaxis infusions. | .882 | | | | | | |
| 18. I choose to infuse less often than prescribed. | .642 | .508 | | | | | |
| 19. If it is inconvenient to infuse, I skip the infusion that day. | .567 | | | | | | |
| 20. I miss recommended infusions because I skip them. | .748 | | | | | | |
| 21. I call the treatment center when I have questions about haemophilia or treatment. | | | .818 | | | | |
| 22. I call the treatment center when I have haemophilia-related health concerns or when changes occur. | | | .845 | | | | |
| 23. I make treatment decisions myself rather than calling the haemophilia center. | | | | | .760 | | |
| 24. I call the treatment center before medical interventions, such as dental extractions, colonoscopies, visits to the emergency room or hospital stays. | | | .786 | | | | |

Rotation method: varimax rotation with Kaiser normalization

*Table 5. Recommended questions of the VERITAS-pro*

| *Old questions* | *Recommended new questions* |
|---|---|
| 5. I use the doctor-recommended dose for infusions. | I use the doctor-recommended dose for standard infusions. |
| 11. I run out of factor and supplies before I order more. | I make sure that I always have sufficient factor and supplies at home. |
| 12. I have a system for keeping track of factor and supplies at home. | |

## FIGURES

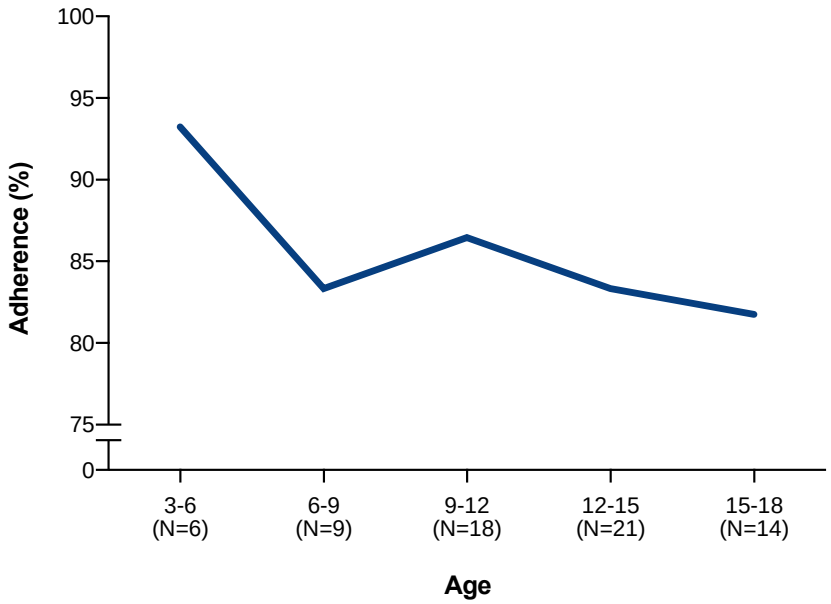


*Figure 1.* Total adherence (by the normalized VERITAS-pro score, 0-100%) according to age, presented by age groups. Values are in medians.

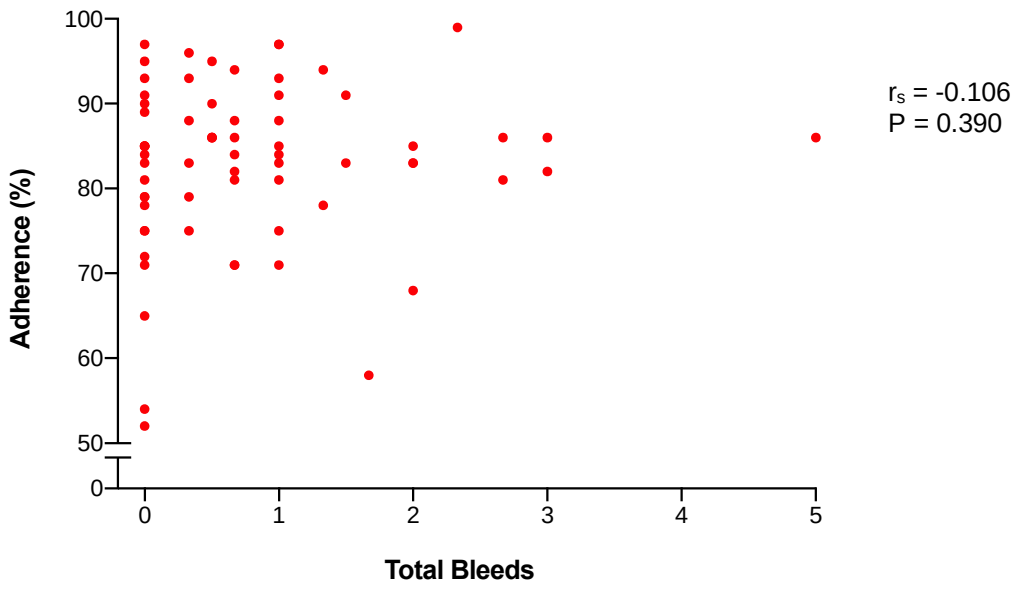


*Figure 2.* Total adherence (by the normalized VERITAS-pro score, 0-100%) according to total bleeds (number/year).

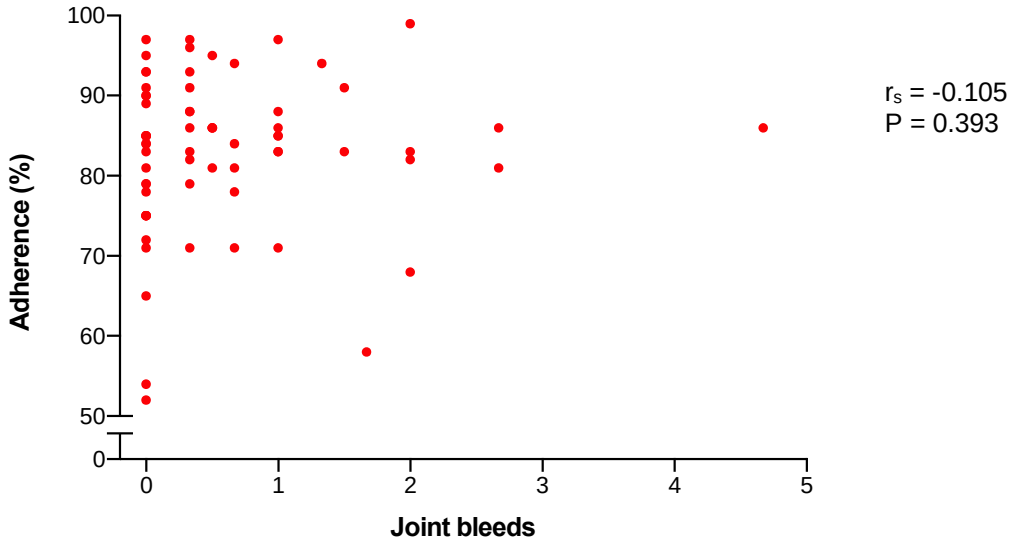


*Figure 3.* Total adherence (by the normalized VERITAS-pro score, 0-100%) according to joint bleeds (number/year).