# Adherence to prophylactic treatment

## of patients with haemophilia A and B using the VERITAS-Pro in a population on the Colombian Caribbean Coast

*Adherencia al tratamiento profiláctico de pacientes con hemofilia A y B utilizando el VERITAS-Pro en una población de la Costa Caribe Colombiana*

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## Abstract

**Background:** Haemophilia is a disease that results in high costs worldwide, and whereby there is limited access to prophylactic treatment due to poor health conditions and difficultt in accessing healthcare; therefore, it becomes necessary to establish policies to improve the implementation or adherence of treatments in patients. **Methods:** An observational, cross-sectional, and prospective study was conducted, with the application of the VERITAS-Pro test, which was validated using Cronbach´s alpha. The adherence was determined using a scale-based on VERITAS-Pro. Previously, sociodemographic and clinical variables were collected in order to relate the data to a questionnaire. **Results:** 32 patients with haemophilia and prophylaxis treatment were included. They were divided into adults (>18 years-old) and minors (<18 years-old). The majority of participants evidenced haemophilia A (77.8% of adults and 64.3% of minors) and the majority of participants had severe haemophilia (77.8% of adults and 85.0% of minors). The internal consistency showed high reliability ($\alpha$= 0.811 in minors and $\alpha$= 0.858 in adults). The results showed that 66.7% of adults evidenced adherence while minors showed 50.0%. These results were compared with variables such as type of hemophilia, degree of hemophilia, presence of arthropathy, emergency admission, family history and inhibitors of coagulation factors. **Conclusions:** The VERITAS-Pro questionnaire showed high levels of consistency and reproducibility. The study population showed a high degree of adherence. It was therefore useful to evaluate the adherence of haemophiliac patients in the Colombian Caribbean.

**Keywords:** Haemophilia, VERITAS-Pro, Prophylaxis, Adherence, Colombian Caribbean Coast

## Resumen

**Antecedentes:** La hemofilia es una enfermedad que genera altos costos a nivel mundial, y por la cual existe un acceso limitado al tratamiento profiláctico debido a las malas condiciones de salud y a la dificultad de acceso a la atención médica; por lo tanto, se hace necesario establecer políticas para mejorar la implementación o adherencia de los tratamientos en los pacientes. **Métodos:** Se realizó un estudio observacional, transversal y prospectivo, con la aplicación del test VERITAS-Pro, que fue validado mediante el alfa de Cronbach. La adherencia se determinó mediante una escala basada en VERITAS-Pro. Previamente se recogieron variables sociodemográficas y clínicas para relacionar los datos con un cuestionario. **Resultados:** Se incluyeron 32 pacientes con hemofilia y tratamiento profiláctico. Se dividieron en adultos (>18 años) y menores (<18 años). La mayoría de los participantes presentaban hemofilia A (77,8% de los adultos y 64,3% de los menores) y la mayoría de los participantes tenían hemofilia grave (77,8% de los adultos y 85,0% de los menores). La consistencia interna mostró una alta fiabilidad ($\alpha$= 0,811 en los menores y $\alpha$= 0,858 en los adultos). Los resultados mostraron que el 66,7% de los adultos evidenciaron adherencia mientras que los menores mostraron un 50,0%. Estos resultados se compararon con variables como el tipo de hemofilia, el grado de hemofilia, la presencia de artropatía, el ingreso en urgencias, los antecedentes familiares y los inhibidores de los factores de coagulación. **Conclusiones:** El cuestionario VERITAS-Pro mostró altos niveles de consistencia y reproducibilidad. La población del estudio mostró un alto grado de adherencia. Por lo tanto, fue útil para evaluar la adherencia de los pacientes hemofílicos en el Caribe colombiano.

**Palabras claves:** Hemofilia, VERITAS-Pro, Profilaxis, Adherencia, Costa Caribe Colombiana

## Introduction

Haemophilia is a condition inherited due a mutation in the genes encoding clotting factors, characterized by a low concentration of factor VIII (Haemophilia A) and factor IX (haemophilia B). This condition is linked to the X chromosome, which affects primarily men[1]. According to an annual global survey by the World Federation of Haemophilia, 393,658 people with bleeding disorders were reported, which consisted of 241,535 people with haemophilia[2]. Likewise, the World Federation of Haemophilia estimated that about 13.6/100,000 male births are related to hemophilia. In Colombia until 2020, 3,834 cases of haemophilia were dated[2]. Also, the incidence of haemophilia in Bolivar is 5/34,200 live male births[3].

Haemophilia is an orphan disease and results in high costs. It has been established that requires an investment of 70 million € annually per patient[4]. Equally, the increase in cost are associated to number cases of haemophilia A and B, due lack in access to the health system around to diagnosis and treatment[3,5]. In countries such as Colombia usually do not have access to treatments early prophylaxis; further, low socioeconomic status and high illiteracy lead to the minimum knowledge and understanding of the disease. On the other hand, the unqualified medical practitioners, conditions of little inherence to receive treatment, social stigma, interference in daily habits and limited family support affect the quality of life[6].

Thus, adherence is a determinant in the effectiveness of the treatment and essential to prepare corrective measures as poor adherence by these patients may induce significant medical problems, permanent disability due to hemarthrosis resulting in arthropathy and higher healthcare costs (orthopedic surgery, rehabilitation, physiotherapy)[7]. Thus, it is important to know the degree of adherence of the haemophiliac patients and the use of specified factors. This will allow the creation of tools to improve adherence, which will affect their quality of life in the long term with decreased bleeding episodes, also with decreasing hospital admissions and medical visits, both clinical consultations and emergency services[8].

Therefore, in this study was evaluated adherence to prophylactic treatment in patients with haemophilia in Cartagena and municipalities using VERITAS-Pro, which is a specific questionnaire for haemophilia.

## Methods

### Type of study, population and sample
An observational, analytical, and cross-sectional study was conducted in patients with haemophilia type A and B in Cartagena and municipalities. It was carried out between June and December 2018. The study included 32 male patients of ages 3-59 years-old with a diagnosis of deficiency of FVIII or FIX. The sample was divided into two groups, adults and minors, in order to allow more rigorous monitoring give that the management of an adult patient is different from the management of pediatric patients regarding the treatment approach[9,10]. Groups were formed by 14 patients ages 3-17 years-old and 18 patients ages 20-59 years-old. The sample did not include women as no homozygous available women were found.

### Instrument and Validation
VERITAS-Pro (Spanish version) was donated by doctor Natalie Duncan. The questionnaire was administered to each group set, consisting of 24 questions divided into six subscales, those being time, dose, plan, remember, skip, and communicated[11], which was validated by internal consistency based in a Cronbach´s alpha test. The measurement of adherence was performed using a scale adherence established by VERITAS-Pro (high, moderately-high, moderate, moderately-low, and low)[12]. Adult patients signed the informed consent document. In the case of minor patients, the legal representative signed the informed consent after their agreement. The legal representative was who completed the questionnaire (ages 3-17). Participants were assigned a unique identification number, were informed that all data related to the study would be stored confidentially, and were advised that they would be identified with unique ID rather than the patient's name or other identifying information. This questionnaire was applied to the individual with primary responsibility. Subsequently, the questionnaire was applied to 10 participants in each group was reevaluated in order to measure reproducibility.

### Ethical aspects
To carry out the study aspects referred to in Resolution 008430 of 1993 of Ministry of Health of the Republic of Colombia, and the ethical guidelines of the Council of Organizations of Medical Sciences and WHO, protection of privacy of the patient was taken into account through the informed consent and explaining in detail the purpose of the study, its benefits and risks.

### Statistical analysis
In general, the variables were expressed in terms of frequencies and percentages. Statistical analysis of reliability and reproducibility was based on Cronbach´s alpha test in which values are obtained from the α coefficient for each variable and total score. Adherence to prophylactic treatment was established in terms of frequencies and percentages, respectively. Finally, were associated variables associated to hemophilic patients such as type of hemophilia, degree of hemophilia, emergency admission and inhibitors employed Chi-squared test ($\chi^2$). The results were considered significant at a level of $p < 0.05$.

## Results

The study clinical variables for which frequencies and percentages were determined such as type of haemophilia, degree of haemophilia, presence of inhibitors, presence of arthropathy, location and occurrence of arthropathy, pathology associated, emergency admission and family history are summarized in Table 1. All variables were described in both groups, except location and occurrence of arthropathy.

On the other hand, a review of the geographical location of patients with haemophilia condition in Cartagena and other municipalities of Bolívar (Figure 1) was conducted. 59.4% of patients were found in Cartagena and 40.6% were found in Villanueva, Turbaco, Arjona, Malagana, San Jacinto and Magangué (Figure 1A). In Cartagena, the haemophilic patients were identified in: Boquilla, Torices, Boston, Paraguay, Las Lomas, Tacarigua, India, Los Cerezos, Pozón, Bicentennial Garden City and Nelson Mandela (Figure 1B)[13–15].

The validation of the questionnaire was based on internal consistency analysis, whereby initially the total score showed accepted reliability (α= 0.811 in minors and α= 0.858 in adults) and the re-test (α= 0.836 in minors and α= 0.802 in adults) demonstrating that the Spanish version of VERITAS-Pro is a valid and reliable questionnaire for measuring adherence in the sample evaluated in this study (Table 2).

Furthermore, the internal consistency of the total score was comparatively low with the results obtained from the original questionnaire (α= 0.920 USA); however, the Brazilian sample (α= 0.737) were significantly more consistent and also showed consistency of samples from Spain (α= 0.820) (Table 3)[13,15]

**Fig. 1. A. Percentage of patients with haemophilia condition and its location geographic. B. Distribution of patients with haemophilia condition in Cartagena.**
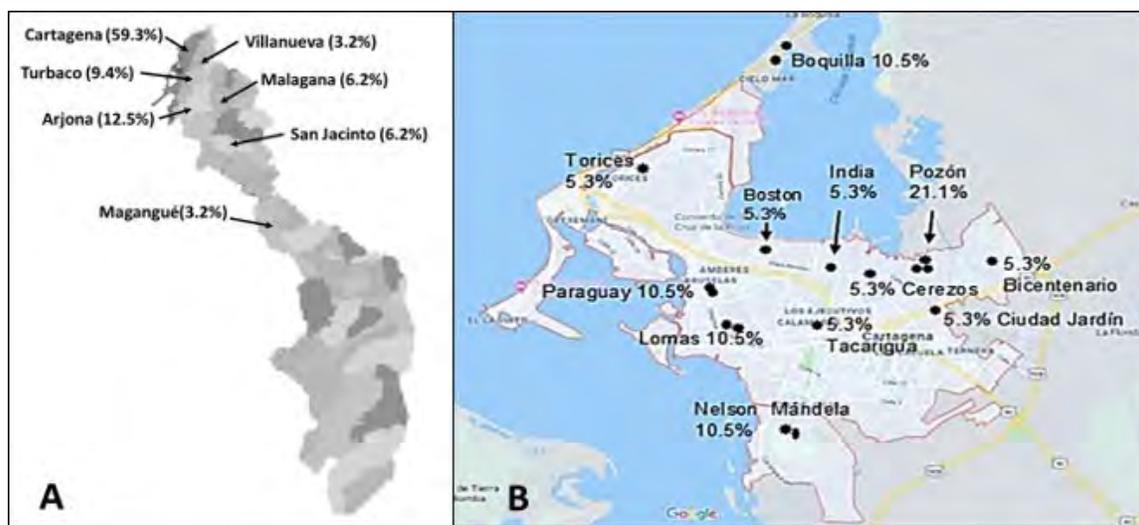


## Table 1. Clinical variables of patients diagnosed with hemophilia prophylaxis regimen in minors and adults.

| VARIABLES | Adults (n=18) | Minors (n=14) |
|---|---|---|
| **Type of hemophilia** | | |
| Hemophilia A | 14 (77.8) | 9 (64.3) |
| Hemophilia B | 4 (22.2) | 5 (35.7) |
| **Degree of Hemophilia** | | |
| Moderate hemophilia | 4 (22.2) | 2 (14.3) |
| Severe hemophilia | 14 (77.8) | 12 (85.7) |
| **Presence of inhibitors** | | |
| Yes | 4 (22.2) | 5 (35.7) |
| No | 14 (77.8) | 9 (64.3) |
| **Presence of arthropathy** | | |
| Yes | 15 (83.3) | 2 (14.3) |
| No | 3 (16.7) | 12 (85.7) |
| **Location of arthropathy** | | |
| Knee and others | 15 (83.3) | NR |
| None | 3 (16.7) | NR |
| **Occurrence arthropathy** | | |
| Before of prophylactic treatment | 11 (61.1) | NR |
| After of the prophylactic | 2 (11.1) | NR |
| Not register | 5 (27,8) | NR |
| **Pathology associated** | | |
| Yes* | 1 (5.6) | 1 (7.1) |
| No | 17 (94.4) | 13 (92.9) |
| **Family history** | | |
| Yes | 11 (61.1) | 6 (42.9) |
| No | 7 (38.9) | 8 (57.1) |
| **Emergency admission** | | |
| Yes | 4 (22.2) | 2 (14.3) |
| No | 14 (77.8) | 12 (85.7) |

## Table 2. Internal consistency reliability by Cronbach alpha test and Re-test by subscale and total score.

| Veritas pro-subscales | Adults | | Minors | |
|---|---|---|---|---|
| | Cronbach´s | Re-test | Cronbach´s | Re-test |
| Time | 0.639 | 0.613 | 0.443 | 0.690 |
| Dose | 0.670 | 0.826 | 0.640 | 0.585 |
| Plan | 0.644 | 0.698 | 0.671 | 0.766 |
| Remember | 0.502 | 0.682 | 0.781 | 0.624 |
| Skip | 0.778 | 0.657 | 0.544 | 0.532 |
| Communicate | 0.721 | 0.746 | 0802 | 0.789 |
| **Total** | 0.858 | 0.802 | 0.811 | 0.836 |

## Table 3. Comparative validation with other studies using analysis of internal consistency (Cronbach's alpha).

| Veritas Pro-Subscales | Adults | Minors | Sample USA [12] | Sample Spain [15] | Sample Brazil [13] |
|---|---|---|---|---|---|
| Time | 0.639 | 0.443 | 0.840 | 0.510 | 0.589 |
| Dose | 0.670 | 0.640 | 0.660 | 0.610 | 0.656 |
| Plan | 0.644 | 0.671 | 0.650 | 0.500 | 0.514 |
| Remember | 0.502 | 0.781 | 0.880 | 0.550 | 0.843 |
| Skip | 0.778 | 0.544 | 0.910 | 0.830 | 0.864 |
| Communicate | 0.721 | 0.802 | 0.870 | 0.550 | 0.826 |
| **Total** | 0.858 | 0.811 | 0.920 | 0.820 | 0.737 |

According to the scale of adherence, 50.0% of patient minors were highly adherent, 42.9% have moderately high ad-

herence and 7.1% showed moderate adherence. In the adult group, 66.7% was found with high adherence and the remaining presented a moderately high adherence (Table 4). However, neither adults nor caregivers of children presented a result of low adherence to factor treatment after applying the questionnaires.

Table 5 indicate the association between adherence to the prophylactic treatment with some variables, where the minors showed statistically non-significant for all comparisons. These variables do not show an association directly with a consistent adherence with the reports established by questionnaires, which are classified as high and moderately high. Also, adults are observed with emergency admission, family history and inhibitors (Table 5).

### Table 4. Frequency and Percent of adherence of adults and minors according to Veritas-Pro

| Classification | High | | Moderately high | | Moderate | | Moderately low | | Low | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Adults | Minors | Adults | Minors | Adults | Minors | Adults | Minors | Adults | Minors |
| Time | 14 (77.8) | 6(42.9) | 3(7.16) | 6() | 1(5.5) | 2() | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Dose | 17 (94.4) | 12(85.7) | 1(5.5) | 2(14.3) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Plan | 11 (61.1) | 4(28.6) | 4(22.2) | 4(6.26) | 1(5.5) | 2(14.3) | 2(11.1) | 3(21.4) | 0(0.0) | 1(7.1) |
| Remember | 14 (77.8) | 12(85.7) | 3(7.16) | 1(7.1) | 1(5.5) | 1(7.1) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Skip | 14 (77.8) | 10(71.4) | 3(7.16) | 3(21.4) | 1(5.5) | 1(7.1) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Communicate | 14 (77.8) | 7(50.0) | 3(7.16) | 3(21.4) | 1(5.5) | 0(0.0) | 0(0.0) | 3(21.4) | 0(0.0) | 1(7.1) |
| **Total** | 12(66.7) | 7(50.0) | 6(33.3) | 6(42.9) | 0(0.0) | 1(7.1) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |

Frequency (Percent's). Adults (n= 18) and minors (n=14)

### Table 5. Comparison of adherence level and variables associated to individuals with hemophilia.

| Classification | Adults (n=18) | | | | Minors (n=13) | | | |
|---|---|---|---|---|---|---|---|---|
| | High | | Moderately high | | High | | Moderately high | |
| Type of hemophilia | A | B | A | B | A | B | A | B |
| | 9 (50.0) | 3 (16.67) | 5 (27.78) | 1 (5.55) | 3 (23.07) | 4 (30.77) | 5 (38.46) | 1 (7.69) |
| | p = 0.688 | | | | p = 0.135 | | | |
| Degree of Hemophilia | Moderate | Severe | Moderate | Severe | Moderate | Severe | Moderate | Severe |
| | 4 (22.22) | 8 (44.44) | 0 (0.0) | 6 (33.33) | 2 (15.38) | 5 (38.46) | 0 (0.0) | 6 (46.15) |
| | p = 0.109 | | | | p = 0.155 | | | |
| Pathology reported | None | Others | None | Others | None | Others | None | Others |
| | 12(66.67) | 0 (0.0) | 5 (27.78) | 1 (5.55) | 7 (53.85) | 0 (0.0) | 5(38.46) | 1 (7.69) |
| | p = 0.146 | | | | p = 0.261 | | | |
| Presence of arthropathy[†] | Yes | No | Yes | No | Yes | No | Yes | No |
| | 10 (55.56) | 2 (11.11) | 5 (27.78) | 1 (5.55) | 0 (0.0) | 7 (53.85) | 2 (15.38) | 4 (30.77) |
| | p = 1.00 | | | | p = 0.097 | | | |
| Inhibitors[†] | 3 (16.67) | 9 (50.0) | 1 (5.55) | 5 (27.78) | 2 (15.38) | 5 (38.46) | 3 (23.07) | 3(23.07) |
| | p = 0.688 | | | | p = 0.429 | | | |
| Emergency admission[†] | 2 (11.11) | 10 (55.56) | 2 (11.11) | 4 (22.22) | 1 (7.69) | 6 (46.15) | 1 (7.69) | 5 (38.46) |
| | p = 0.432 | | | | p = 0.906 | | | |
| Family history[†] | 7 (38.89) | 5 (27.78) | 4 (22.22) | 2 (11.11) | 3 (23.07) | 4(30.77) | 3 (23.07) | 3 (23.07) |
| | p = 0.732 | | | | p = 0.797 | | | |

*Statistically significant (p<0.05)
[†] Parameters related with haemophiliac patients

## Discussion

The number of people with haemophilia selected in the overall study was 32 patients, who were localized in Cartagena and municipalities of Bolivar, which in the comparison with those reported by a report constitute about 29.8% of indicated by DADIS and DASALUD for Bolivar. In the report entitled *The situation of haemophilia in Colombia* for the year 2018, 104 patients were reported with haemophilia in Bolivar with a prevalence rate of 4.6/100,000[3]. This indicates the prevalence to be similar to the established reported average in the Colombian population, which is 4.5/100,000. However, the prevalence in our study tends to be smaller according to global reports that establish a prevalence of about 1/5,000 (haemophilia A) and 1/30,000 (haemophilia B)[16]. Therefore, it is considered to be a representative sample to study the degree of adherence of prophylactic treatment in Bolivar and the Colombian Caribbean based on epidemiological data previously[17].

All patients were classified as moderate or severe haemophilia, with a predominance of severity in both adults and children. Likewise, according to the report's impact of high cost, 88 cases of severe haemophilia were recorded in Bolívar, and the degree of adherence to prophylaxis in the study was assessed as 36.4% of patients registered in Bolivar[3]. However, in the study is notable that use of inhibitors for avoid the development of the disease evidenced low percent in both population; while that the presence of arthropathy was identified majority in adults, which is compared with Chang et al., 2017, where have been evidenced those adult individuals with diagnosed of hemophilia and severe arthropathy in six joints studied increased after 30 years of age. Additionally, in < 20 years of age, it was shown that the prevalence

of hemophilic arthropathy was lower; as well as mild ankle arthropathy was more predominant[18]. As well as, variables established as emergency admission not showed optimal clinical outcomes despite adherence results. However, it is important to note that the natural history of the disease could play a preponderant role[19,20], since most of the complications occur in adults in contrast to minors, as highlighted in Table 1.

Moreover, according to the geographical information in the study population, it is indicated that the geographic and economic access can be a completely decisive barrier in the course of the disease, because r transportation to places of care could lead an inefficient system, resulting in a decrease in daily work practices[10,21]. Also, in terms of quality of life, there should be a commitment to health conditions despite therapy with coagulation factors, something that may affect attendance at the institutions providing health service, conditioned by the complexity of transport of patients who live in places difficult to access, and even if they come from rural areas[22].

The validation of the questionnaire results in considerable reliability in the subscales planning and communication and dosing in both groups (minors and adults); also, the subscales timing and skipping reflected a suitable coefficient of validity in the adult group, whereas in the group of children was minimally accepted; subscale remembering showed very good reliability was in the minor's group and was minimally good in the adults group. However, the overall validation of the VERITAS-Pro questionnaire indicated an internal strength that statistically contributed to its implementation, and which was independent of the number of individuals and yielded sustainable results[13,15].

In the study population, minors had lesser adherence compared to adults, this could be due to the complexity of the treatment and to changes in the patients' usual activities of daily living. Moreover, at this stage (≥ 12 years) the patient is already able to understand and assimilate the complexity of disease and consequences of inadequate adherence, but could find it difficult to understand the chronicity of the condition, and especially maintaining adequate knowledge of treatment guidelines. On the other hand, conflicting feelings related to the disease appear and patients usually react by stopping the prophylaxis to feel "normal"[23]. The results of the association between adherence and some variables analyzed indicate that therapies based at clotting factors don´t have the same effect on the entire study population. Despite high adherence, it is presumed that therapeutic failures exist that could be related to aspects like the natural history of the disease, immunotolerance, complications in the patient, iatrogenic elements, and genetic factors[24,25]. In this case, patients identified with haemophilia A with mutations on gene encoding factor VIII would possibly be linked to the presence of inhibitors in some patients according to shown in the study. Also, these aspects are substantiated by Duncan and Thornburg in 2017[11], who reported that adherence barriers are not only related to difficulties to prophylactic treatment or low socioeconomic conditions, otherwise also linked to clinical and natural environmental conditions. Additionally, despite the high degree of adherence reported in this study, some subscales were low, which might also explain emergency admissions and the development of inhibitors to patients being adherent to treatment in most subscales[25].

However, there are some limitations to this study, such as a small sample size as it is an orphan disease of low prevalence in populations, it can generate a preliminary contribution for these types of patients and their treatments. Likewise, it can generate contributions within the framework of hematological institutions or organizations for the care and improvement of their quality of life, leading to the establishment of more updated databases at the national level.

## Conclusions

The VERITAS-Pro had high levels of internal consistency and reproducibility; this measurement tool can be applied to evaluate the degree of adherence in haemophiliac patients in the Colombian Caribbean. The study population showed a high degree of adherence. However, in some subscale's adherence was low, which could explain emergency admissions and the appearance of inhibitors in patients despite adherence to treatment in most subscales. In addition to these results, we could conclude that as well as conclusions in previous reports, where adherence barriers were determined not only to be the fault of prophylactic treatment regimens but of socioeconomic conditions, adherence is also related to the patient and associated clinical conditions

**Contribution of the authors**
**Antistio Alvíz-Amador:** Design, performed, analysis and write of the manuscript; **Neyder Contreras-Puentes:** Analysis and write of manuscript; **Jorge Gutiérrez-Cuesta:** Design, read and approved manuscript. **Antonio Diaz-Caballero:** Analysis, read and approved manuscript; and **Arnulfo Taron-Dunoyer:** Read, correction and approved manuscript.

analysis.

**Compliance with ethical standards**
**Conflict of Interest:** No conflict of interest was declared by the authors.

**Ethical Considerations.**
Authors declared the information of patients with hemophilia at guidelines based **in** Resolution 8430 of 1993 of the Ministry of Health of the Republic of Colombia. Helsinki Report was also accepted as an ethical benchmark in this research.

**Data availability.**
The information of the present study is saved in Excel database, condensed date of each patient, this personal information fulfils the principle of confidentiality according to the Colombian regulations Resolution 8430 of 1993.

## References

1. Muñoz-Grass LF, Palacios-Espinosa X. Calidad de vida y hemofilia: Una revisión de la literatura. CES Psicol. 2015;8(1):169–91.

2. World Federation of Hemophilia. Report on the Annual Global Survey 2020 [Internet]. Montréal, Canada; 2021. Available from: https://wfh.org/data-collection/#ags

3. Fondo Colombiano de Enfermedades de Alto Costo. Situación de la hemofilia en Colombia 2018. 2018. p. 1–238.

4. Bogotá-Pizarro D, Galeano-Pizarro CF. Determinación de costos médicos directos del tratamiento de la hemofilia tipo B sin inhibidores en Colombia. 2019.

5. Fuenmayor Castaño A, Jaramillo Restrepo M, Salinas Durán F. Calidad de vida en una población con hemofilia: estudio de corte transversal en un centro de tratamiento de hemofilia TT - Quality of life in a population with haemophilia: a cross-sectional study from a single haemophilia treatment centre. Rev Colomb Reumatol [Internet]. 2017;24(1):18–24. Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0121-81232017000100018&lang=pt%0Ahttp://www.scielo.org.co/pdf/rcre/v24n1/0121-8123-rcre-24-01-00018.pdf

6. Cassis F. Atención psicosocial para personas con hemofilia. 2007. p. 1–13.

7. Garre Andreo RS, Garre Andreo P, Giménez Fernández M, García Serrano JM, García Ruiz BM. Adherencia al tratamiento profiláctico en pacientes hemofílicos A severos. Eur J Child Dev Educ Psychopathol. 2017;5(1):5–20.

8. van Os S, Troop N, Ryder N, Hart DP. Adherence to prophylaxis in adolescents and young adults with severe haemophilia A, a qualitative study with patients. Heal Psychol Behav Med. 2018;6(1):277–300.

9. Giordano P, Franchini M, Lassandro G, Faienza MF, Valente R, Molinari AC. Issues in pediatric haemophilia care. Ital J Pediatr. 2013;39(1):1–5.

10. Allen KN, Kachalsky E. Aging with hemophilia: Implications for social work practice. Soc Work Health Care. 2010;49(4):327–44.

11. Thornburg CD, Duncan NA. Patient Preference and Adherence Dovepress Treatment adherence in hemophilia. Patient Prefer Adherence [Internet]. 2017;11–1677. Available from: http://dx.doi.org/10.2147/PPA.S139851

12. Duncan NA, Kronenberger W, Roberson C, Shapiro A. VERITAS-Pro: A new measure of adherence to prophylactic regimens in haemophilia. Haemophilia. 2010;16(2):247–55.

13. Ferreira AA, Leite ICG, Duncan NA. Validation of the Brazilian version of the VERITAS-Pro scale to assess adherence to prophylactic regimens in hemophilia. Hematol Transfus Cell Ther. 2018;40(1):18–24.

14. Thornburg CD, Duncan NA. Treatment-adherence-in-hemophilia. Dovepress. 2017;1677–86.

15. Cuesta-Barriuso R, Torres-Ortuño A, Galindo-Piñana P, Nieto-Munuera J, Duncan N, López-Pina JA. Validation of the VERITAS-Pro treatment adherence scale in a Spanish sample population with hemophilia. Patient Prefer Adherence. 2017;11:653–60.

16. Jandial A, Mishra K, Sandal R, Jindal N, Goni D, Lad D, et al. Hemophilia in the developing world: Transforming lives through international collaboration. Blood Adv. 2018;2:39–41.

17. Alvíz-Amador A, Taron-Dunoyer A, Diaz-Caballero A. Quality of life of hemophiliac patients and satisfaction with their prophylactic treatment in Colombia. Arch Venez Farmacol y Ter. 2022;40(9):895–901.

18. Chang CY, Li TY, Cheng SN, Pan RY, Wang HJ, Lin SY, et al. Prevalence and severity by age and other clinical correlates of haemophilic arthropathy of the elbow, knee and ankle among Taiwanese patients with haemophilia. Haemophilia. 2017;23(2):284–91.

19. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. HSS J. 2010;6(1):37–42.

20. McMillan C, Shapiro S, Whitehurst D, Hoyer L, Rao A, Lazerson J. The natural history of factor VIII:C inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. Blood. 1988;71(2):344–8.

21. Goto M, Takedani H, Yokota K, Haga N. Strategies to encourage physical activity in patients with hemophilia to improve quality of life. J Blood Med. 2016;7:85–98.

22. Zhou Z, Riske B, Forsberg AD, Ullman M, Baker JR, Koerper MA, et al. Self-reported barriers to hemophilia care in people with factor VIII deficiency. Am J Prev Med [Internet]. 2011;41(6 SUPPL.4):S346–53. Available from: http://dx.doi.org/10.1016/j.amepre.2011.09.003

23. Honorato J. Adherencia al tratamiento farmacológico. Med Respir. 2015;8(1):47–52.

24. Porras-Moreno A, Ugalde-Solera D. Immunotolerance induction in a pediatric hemophilic patient in Costa Rica. Acta Med Costarric. 2018;60(3):139–41.

25. Coppola A. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med. 2010;1:183–95.