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# BMJ Open

## Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSEMO): Study Protocol

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1 **TITLE**

2 Determinants of adherence and consequences of the transition from adolescence to adulthood among  
3 young people with severe haemophilia (TRANSHEMO): Study Protocol

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## 73 ARTICLE SUMMARY

74

### 75 Abstract

76 Introduction: Severe haemophilia is a rare disease characterised by spontaneous bleedings from early  
77 childhood, which may lead to various complications especially in joints. It is nowadays possible to  
78 avoid these complications thanks to substitutive therapies for which the issue of adherence is major.  
79 The transition from adolescence to adulthood in young people with severe haemophilia is a critical  
80 period as it is associated with a high risk of lack of adherence to health care, which might have serious  
81 consequences on daily activities but also on quality of life.

82 Methods and analysis: We present the protocol for a cross-sectional, observational, multicentric study  
83 to assess the impact of transition from adolescence into adulthood, especially on adherence to health  
84 care, among young people with severe haemophilia in France. This study is based on a mixed method,  
85 with two complementary and consecutive phases, comparing data from a group of adolescents (aged  
86 14-17 years) to those from a group of young adults (aged 20-29 years). The quantitative phase focuses  
87 on the determinants (medical, organisational, socio-demographic and social, and psychosocial and  
88 behavioural factors) of adherence to health care (considered as a marker of the success of transition).  
89 The qualitative phase focuses on a more deeply assessment of the psychological mechanisms involved  
90 in the transition process for few patients. Eligible patients are contacted by the various Haemophilia  
91 Treatment Centres participating in the French national registry FranceCoag

92 Ethics and dissemination: The study was approved by the French Ethics Committee and by the French  
93 National Agency for Medicines and Health Products Safety (number: 2016-A01034-47). Study  
94 findings will be disseminated to the scientific and medical community in peer-reviewed journals and  
95 presented at scientific meetings. Results will be popularised to be communicated via the French  
96 association for people with haemophilia to participants and to the general public.

97 Trial registration number: NCT02866526

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99 Word count: 300

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### 101 Keywords

102 Adherence / Haemophilia / Transition / Adolescents / Young adults

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3 103 **Strengths and limitations of this study**

- 4 104 – The comparison of experiences reported by adolescents compared to those reported by young  
5 105 adults will allow to assess the impact of transition especially on adherence to health care  
6 106 among young people with haemophilia (YPWH) through a cross-sectional study.  
7  
8 107 – The backing of the French national registry FranceCoag will allow to assess the issue of  
9 108 transition in a large population of YPWH.  
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11 109 – The mixed method of this study will bring original and complementary results by combining  
12 110 quantitative and qualitative methods.  
13  
14 111 – Determinants of adherence to health care considered as a marker of the success of transition  
15 112 will include classic factors (medical, organisational, and socio-demographic), but also more  
16 113 original ones (social, psychosocial and behavioural).  
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18 114 – Results will serve as the basis to propose recommendations and to develop interventions in  
19 115 order to facilitate the transition process in YPWH.  
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## 118 INTRODUCTION

119 Haemophilia is a rare and inherited disorder (X-linked recessive transmission), affecting mainly males  
120 (annual incidence: 1/5,000 male births).[1] It is characterized by bleedings due to a lack of clotting  
121 factors (factor VIII (FVIII) for haemophilia A or factor IX (FIX) for haemophilia B). Bleedings often  
122 start in early life, due to psychomotor skills acquisition. Seriousness of the symptoms depends on the  
123 severity of the lack of FVIII/FIX. Severe haemophilia, defined by a biological activity of FVIII/FIX  
124 lower than 1%, is characterized by spontaneous bleedings most frequently located into the joints  
125 (haemarthroses) and into the muscles (haematoma). Natural history of untreated severe haemophilia is  
126 marked by serious haemorrhagic events which compromise the vital prognosis. Insufficiently treated,  
127 repetition of haemarthroses and haematoma results in invalidating motor disability.

128 It is nowadays possible to avoid these complications thanks to substitutive therapies for which the  
129 issue of adherence is major, and to a lifelong regular clinical follow-up. Successive stages of the  
130 disorder's care management have been described by Young,[2] including:

- 131 – The adolescence: independence and responsibility for disease management, self-advocacy and  
132 disclosure, importance of treatment adherence, transfer of responsibilities from the caregivers  
133 to the patient
- 134 – The adulthood: decide whether to continue prophylaxis, challenge of dealing with a chronic  
135 disease and becoming one's own caregiver

136 The success of the transition from adolescence to adulthood may therefore be crucial in the  
137 maintenance of adherence to care.

138  
139 In the context of chronic diseases, the process of transition may be more complicated, as affected  
140 young people have to deal with a supplementary transition, from a paediatric health care system to an  
141 adult one.[3, 4] Indeed, a successful transition involves a transfer of responsibilities from parents to  
142 patients concerning the management of their health, the acquisition of the knowledge, abilities, and  
143 self-reliance necessary to take on autonomy as well as the new roles people expect them to endorse as  
144 adults.[5-8] Experiencing a difficult transition could be associated with a decrease in the level of  
145 adherence to care, but it might also impair quality of life and the entry into adulthood.[9, 10] In the  
146 framework of several chronic diseases (apart from haemorrhagic diseases), some studies highlighted  
147 barriers or facilitators to successful transition, either associated to the young patients, or to their  
148 parents, or to the various actors of the health care system.[11-14] Authors especially underlined  
149 psychosocial factors such as knowledge, skills, beliefs, expectations, goals, relationships, fears, need  
150 for control, emotional dependency, over-protectiveness, heightened awareness of health issues, lack of  
151 trust in caregivers.[15-17]

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3 153 In the specific context of haemophilia, some studies have been conducted to assess the issue of  
4 154 transition in young people with haemophilia (YPWH).[18] A study comparing quality of life in  
5 155 YPWH in pre-transition period with YPWH in post-transition period showed a lower quality of life  
6 156 and a higher level of distress in YPWH in post-transition period.[19] Some recommendations  
7 157 (involving patients, families, and caregivers) have been proposed to facilitate this process.[20-22]  
8  
9 158 However, despite the setting up of some actions which have been shown to improve the disease  
10 159 specific knowledge,[23, 24] difficulties are still remaining, which may impair the health condition and  
11 160 the quality of life of YPWH.[25, 26] A study on the unmet needs reported by young adults highlighted  
12 161 psychological issues mainly related to independence achievement.[27] At the crucial age at which  
13 162 adolescents are often opposed or want to take their own decisions, maintaining the adherence to  
14 163 clinical follow-up and therapies is an important issue. Studies have shown a decrease in the level of  
15 164 adherence to the prescribed therapeutic regimen during transition (from 90% for the youngest patients  
16 165 (0-12 years) to 54% for those aged 13-18 years and to 36% for those aged 19-28 years;[28] 59% in  
17 166 another study in YPWH (13-25 years)[29]). This lower adherence might have serious consequences,  
18 167 such as haemarthroses which may impair daily activities but also quality of life. Some psychosocial  
19 168 factors of the maintenance of a high adherence have been highlighted, *e.g.* a greater perception of the  
20 169 need for prophylaxis than the concern over taking it, a positive expectancy of its effectiveness, a good  
21 170 social support, and a stronger emotional reaction to having haemophilia.[30]

22 171  
23 172 Even if some literature data exists on the issue of transition and its impact on adherence to health care  
24 173 in the context of haemophilia, some limits may be discussed. The sample size of these studies is  
25 174 generally modest (below or about a hundred of patients).[30-32] An international larger study  
26 175 including 230 YPWH was conducted but all of them were young adults (aged 18-30 years), none were  
27 176 adolescents.[26] Adherence is usually assessed only through adherence to prophylactic treatment,  
28 177 which excludes YPWH under on-demand treatment.[30-32] None of these studies has been carried out  
29 178 in France where the features of the health care system are very specific. An international study showed  
30 179 that cost was a frequent reported barrier to prophylaxis (about 45% by both nurses from Haemophilia  
31 180 Treatment Centres and patients perspectives).[28] Thus, the assumption of all disease-related costs by  
32 181 the French social security system might influence the adherence to care. The backing of the French  
33 182 national registry FranceCoag[33] will allow to assess this issue in a large and exhaustive population of  
34 183 YPWH. This registry involves for more than 20 years French Haemophilia Treatment Centres (HTC),  
35 184 and it includes more than 10,000 patients (7,000 people with haemophilia (PWH), with 2,300 with  
36 185 severe haemophilia of all ages). Moreover, even if some psychological data have been related to the  
37 186 adherence to care, they are often analysed as independent factors. Taking into account the  
38 187 interdependence between these factors using adapted methods could bring original results. Finally, a  
39 188 mixed-design study combining quantitative and qualitative methods will allow to address in a global

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3 189 way the issue of transition among YPWH, *i.e.* focusing not only on its facilitators and barriers but  
4 190 also, on all the specific concerns and difficulties YPWH may experience as they grow into adulthood.  
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3 191 **OBJECTIVES**

4 192 The main objective of this study is to assess the impact of transition from adolescence into adulthood  
5 193 especially on adherence to health care, among young people with severe haemophilia in France.

6 194 The operational objectives of this study are:

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9 195 – to compare the level of adherence in adolescents and in young adults (YA)  
10 196 – to identify determinants (medical, organisational, socio-demographic and social, and  
11 197 psychosocial and behavioural factors) of the level of adherence in YPWH,  
12 198 – to assess specific factors involved in suboptimal level of adherence in the sub-groups of  
13 199 adolescents on one hand and of YA on the other hand,  
14 200 – to identify groups of patients (clusters) regarding both their level of adherence and their  
15 201 psychosocial characteristics,  
16 202 – to examine through a qualitative approach YPWH needs and expectations towards the health  
17 203 care system during the transition process, and to identify some ways to improve their global  
18 204 care.  
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## 206 **METHODS/DESIGN**

### 207 **Study design**

208 This study is designed as a multicentric (29 HTC from FranceCoag), observational, cross-sectional  
209 study, based on a mixed method, with two complementary and consecutive phases:

- 210 – The quantitative phase focuses on the determinants of the level of adherence to health care  
211 (considered as a marker of the success of transition), and compares data from a group of  
212 adolescents to those from a group of YA,
- 213 – The qualitative phase focuses on a more deeply assessment of the psychological mechanisms  
214 involved in the transition process for few patients selected from the quantitative phase.

### 216 **Participants**

#### 217 Inclusion criteria

- 218 – Patients with severe A or B haemophilia (deficiency <1%)
- 219 – Patients affiliated to the French social security system and included in the FranceCoag registry
- 220 – Patients followed in one of the 29 participating HTC
- 221 – Patients aged 14-17 years (adolescents group), or aged 20-29 years (YA group)
- 222 – Adolescents authorised to participate by their parents or their legal representatives, or YA who  
223 give their consent to participate in this study

#### 225 Non-inclusion criteria

- 226 – Vulnerable patients (adults under guardianship, pregnant or nursing women)
- 227 – Patients with reading and writing difficulties

#### 229 Period of the study

230 The planned duration of the study is 30 months. Inclusions started in February 2017. The quantitative  
231 phase will go on for 18 months, the qualitative phase will go on for 10 months, and the last two  
232 months will focus on results valorisation.

### 234 **Quantitative phase**

#### 235 Main evaluation criterion

236 The main evaluation criterion is the adherence to clinical follow-up and prophylactic treatment (an  
237 hypothesized marker of the success of transition into adulthood), which will be assessed via the  
238 following items:

- 239 – number of follow-up visits in agreement with the recommended number over the last two  
240 years,

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3 241 – number of prophylactic treatment injections in agreement with the recommended number over  
4 242 the last three months (if applicable),  
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6 243 – number of haemorrhagic events over the last two years,  
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8 244 – physician-reported adherence to clinical follow-up and to prophylactic treatment (if  
9 245 applicable),  
10  
11 246 – patient-reported adherence to clinical follow-up and to prophylactic treatment (if applicable).

12 247 Each item will be dichotomized, and a composite quantitative endpoint will be constructed taking into  
13 248 account all these dichotomized items. This composite quantitative endpoint will in turn be  
14 249 dichotomized to define adherent / non adherent participants (main evaluation criterion).

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#### 18 251 Secondary evaluation criteria

19 252 Each item which is part of the composite endpoint as described hereinabove will be considered in an  
20 253 independent manner as a secondary evaluation criterion.

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#### 24 255 Explanatory collected data

##### 26 256 *Medical data*

27 257 Medical data will include: deficit characterisation, diagnosis (age at diagnosis, circumstances of  
28 258 diagnosis, family history), viral diseases (HIV, HBV, HCV), comorbidities (intracranial haemorrhage,  
29 259 major orthopaedic interventions, major disability, cancer, other chronic pathology), previous and  
30 260 current treatment.

32 261

##### 34 262 *Organisational data (Haemophilia Treatment Centres-reported)*

35 263 Organisational data will include: paediatric / adult / paediatric and adult HTC, physicians' speciality,  
36 264 mean age of the transition from paediatric care to adult one, consultations dedicated to the transition,  
37 265 common consultations with both paediatric and adult medical teams, specific tools set up to facilitate  
38 266 the transition process (information leaflet, therapeutic patient education).

41 267

##### 43 268 *Socio-demographic and social data*

- 44 269 – Gender and age of family members, living situation,  
45 270 – Socio-professional category, socio-economic status assessed by the Family Affluence  
46 271 Scale),[34]  
47  
48 272 – Distance to the HTC (in km),  
49  
50 273 – Membership of French patients association for PWH (AFH),  
51  
52 274 – Family functioning (structure, organisation, and communication) assessed by the French  
53 275 validated version of the 6-items Family Assessment Device,[35-37]

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3 276 – Schooling and academic success evaluated by ad-hoc items (schooling type, level of  
4 277 education, academic difficulties),  
5  
6 278 – Relationships with the health care system assessed using ad-hoc items (satisfaction and  
7 279 expectations towards the health care system, participation in therapeutic patient education  
8 280 programme).

9 281

10 282 *Psychosocial and behavioural data*

- 11 283 – Quality of life will be assessed using the validated French version of the SF-12 generic  
12 284 scale.[38] Two sub-scores, mental health and physical health, will be calculated. The SF-12  
13 285 allows assessing the quality of life of adults as well as adolescents (14+ years).  
14  
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16 286 – Quality of life of adolescents will also be assessed by the validated French version of  
17 287 the 10-items Kidscreen Index, which explores the following domains: physical well-  
18 288 being, psychological well-being, autonomy and relations with parents and home life,  
19 289 peers and social support, and school environment.[39]  
20  
21 290 – Haemophilia-specific quality of life will be assessed in all participants using the  
22 291 validated French short version of the Haemo-Qol questionnaire.[40, 41]  
23  
24 292 – Time perspective will be assessed using the Past Negative (PN) and Future (F) subscales of  
25 293 the French validated version of the Zimbardo time perspective inventory.[42, 43] The PN  
26 294 subscale (9 items) reflects a pessimistic attitude towards the past and the experience and  
27 295 memory of traumatic life events. The F subscale (12 items) reflects an orientation towards  
28 296 future and an attitude of planning and achievement of objectives. To avoid the questionnaire  
29 297 being too long, we will not plan to assess the Past-Positive, Present-Hedonistic, and Present-  
30 298 Fatalistic subscales.  
31  
32 299 – Coping Strategies will be measured by the validated French version of the Brief-Cope  
33 300 scale[44, 45] which consists of 28 items assessing individuals' use of 14 coping strategies:  
34 301 self-distraction, active coping, denial, drug use, emotional social support seeking, instrumental  
35 302 social support seeking, behavioural disengagement, emotional expression, positive reframing,  
36 303 planning, humour, acceptance, religion, and self-blame.  
37  
38 304 – Autonomy will be assessed using ad-hoc items only proposed in the YA questionnaire  
39 305 (financial independence from the parents, and living, management of health, dealing with  
40 306 administrative tasks, and taking holidays without the parents). The 15-items Noom validated  
41 307 questionnaire[46, 47] assessing attitudinal autonomy, emotional autonomy, and functional  
42 308 autonomy will be proposed to all participants (ad-hoc translation for this study).  
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3 312 Data collection procedure

4 313 Main medical data will be extracted from the FranceCoag database, and completed by a short  
5 314 questionnaire filled in by the referent physician from each HTC. Organisational data will be completed  
6 315 by a medical representative from each HTC. Participants' self-reported data will be collected through a  
7 316 standardised booklet including several questionnaires (an adolescent version and a YA version).  
8 317 Survey documents (information sheet, informed consent and booklet) will be sent by post to eligible  
9 318 YPWH. If no response is received within 30 days, a reminder letter will be sent. A second reminder  
10 319 letter and all survey documents along will be sent two months later in case of no response.  
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16 321 Sample size justification

17 322 According to the exhaustive FranceCoag database and considering the specific inclusion criteria of the  
18 323 TRANSHEMO study (severe A or B haemophilia, patients aged 14-17 or 20-29 years, followed in one  
19 324 of the 29 participating HTC), 154 adolescents and 389 YA are eligible for this study. We hypothesised  
20 325 a difference of 20% between adolescents and YA regarding the main evaluation criterion (90% of  
21 326 adherence to health care in adolescents vs 70% in YA). Then, under the hypothesis of a non-response  
22 327 rate of 30%, and considering a bilateral alpha risk of 5%, the power of this study would reach  
23 328 99%.<sup>[48, 49]</sup>  
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29 330 Data Management

30 331 A specific database will be created using EpiData software, and merged with the FranceCoag  
31 332 database. A process will be used to assign to each participant a unique anonymous number. A data  
32 333 quality control will be performed by a physician to limit data inconsistency.  
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36 335 Analysis

37 336 The analysis plan and the final report will be written according to the STROBE recommendations.<sup>[50,</sup>  
38 337 51] All analyses will be performed using R software. All tests will be two-sided, and  $p < .05$  will define  
39 338 statistical significance.  
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44 340 *Analysis populations*

45 341 The analysis populations will be the adolescents and the YA groups, among whom adherent and non-  
46 342 adherent patients will be identified.  
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50 344 *Descriptive analysis*

51 345 A descriptive analysis will first be performed. Qualitative variables will be presented as numbers and  
52 346 percentages, quantitative variables as means and standard deviations, or as medians and interquartile  
53 347 ranges. Subjective data will be described by their overall scores and their sub-scores.  
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348 Reasons for non-inclusion will be listed. Included patients will be compared to non-included eligible  
349 patients using basic socio-demographic and clinical data, available in the FranceCoag database.

350

351 *Comparative analysis*

352 *Crude analysis*

353 Adherence will first be described by groups (adolescents / YA) using classical indicators. The  
354 comparison of adherence between the two groups will be performed using chi-square test (or Fisher  
355 test depending on the expected numbers) for the main evaluation criterion and for all qualitative  
356 secondary evaluation criteria, and using Student t test (or Mann-Whitney test depending on normality  
357 of the distribution) for quantitative secondary evaluation criteria.

358

359 *Adjusted analysis*

360 In order to identify factors associated with adherence, bivariate and multivariate analyses will be  
361 performed. Potential determinants (medical, organisational, socio-demographic and social,  
362 psychosocial and behavioural factors) will be proposed as explanatory variables. Logistic regression  
363 models will be used for the main evaluation criterion and for all qualitative secondary evaluation  
364 criteria, and linear regression models will be used for quantitative secondary evaluation criteria. Each  
365 characteristic whose degree of significance will be lower than .20 will be considered for multivariate  
366 analyses. A backward selection will be applied to retain only significantly associated characteristics.  
367 Multilevel models will be used to take into account organisational factors which are related to the  
368 centre. Structural equation modelling will be considered to take into account the collinearity and/or the  
369 complex relationships which might exist between explanatory individual characteristics (especially  
370 social, psychological and behavioural ones).[52-54]

371 This analysis will first be performed in the overall population with a forced adjustment on the group  
372 (adolescent / YA). It will secondly be performed independently in each of the two groups.

373

374 *Cluster analysis*

375 In order to bring to light particular profiles of adherent / non adherent in adolescents on one hand, and  
376 in YA on the other hand, an exploratory unsupervised classification analysis will be performed.[55,  
377 56] This method which does not require any condition of validity will allow to gather patients with  
378 similar profiles in homogeneous clusters.

379

## 380 **Qualitative phase**

381 Data collection procedure

382 Few subjects (adolescents on one hand and YA on the other hand) who will have participated in the  
383 quantitative phase will be selected for this phase according to the following characteristics: adherent or  
384 not, and under prophylaxis or not. If they agree, they will be contacted to participate in research

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3 385 interviews conducted by a psychologist, at any place at their convenience (at home, at the HTC...).

4 386 The interviews will be individual, confidential, semi-structured, and tape-recorded.

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6 387 The psychologist will start with a general question, then he/she will adopt a non-directive attitude and

7 388 will allow the participant to spontaneously and freely broach the answers which they consider

8  
9 389 relevant. Then he/she will summarise the response and introduce more precise questions regarding the

10 390 topics which will have not been covered spontaneously or sufficiently by the participant. He/she will

11 391 seek to focus the interview on the participant's personal experiences, subjective perceptions, and

12 392 expectancies.

13 393

14 394 *Adolescents' interviews*15 395 The interview will begin with this general question: "How do you feel about coming into adulthood in  
16 396 a few years?"17 397 After the spontaneous answer, the psychologist will make them talk about the following topics: the  
18 398 meaning they give to becoming a YA; their expectations towards their life (personal and professional)  
19 399 as future YA; their fears towards their entry into adulthood; their plan to care about their health as  
20 400 future YA.

21 401

22 402 *Young adults' interviews*23 403 The interview will begin with this general question: "How do you feel about reaching adulthood  
24 404 during the last few years?"25 405 After the spontaneous answer, the psychologist will make them talk about the following topics: the  
26 406 meaning they give to becoming a YA; their experienced difficulties towards the acquisition of their  
27 407 autonomy (especially concerning the management of their health) and the construction of their life  
28 408 (personal and professional); the facilitators and barriers they identified during their transition process.29 409 Then, to go further and broaden these qualitative data, the psychologist will show to these participants  
30 410 a summary of the adolescents' expectations towards adulthood (from the interviews conducted in  
31 411 adolescents, which therefore will be carried out and analysed before those in YA). The psychologist  
32 412 will then ask YA to assess: to what extent these perceptions match with their own expectations when  
33 413 they were adolescents; to assess to what extent these perceptions match with their current lives; and to  
34 414 indicate which issues regarding transition adolescents forget to mention.

35 415

36 416 *Sample size justification*37 417 Four profiles will be identified from the two selected characteristics (adherent or not, and under  
38 418 prophylaxis or not). On the basis of three interviews by profile, up to 12 adolescents and 12 YA will  
39 419 be selected for the qualitative phase (enrolments until information is saturated).

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3 422 Data management

4 423 All interviews will be precisely and entirely transcribed, including the participants' hesitations and  
5 424 self-corrections.

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9 426 Analysis

10 427 The psychologist will analyse adolescents' interviews on one hand and YA ones on the other hand,  
11 428 using Interpretative Phenomenological Analysis (IPA) method. This method allows to comprehend the  
12 429 participants' subjective experiences through the analysis they make of (and the meaning they give to)  
13 430 their feelings and states, as well as the specific events they are faced with. It makes possible to  
14 431 highlight sociocognitive processes by which personal experiences are assimilated to individuals'  
15 432 perceptions of both themselves and the world they live in.[57, 58]

16 433 IPA of an interview is made of four iterative stages. During the first stage, the psychologist will read  
17 434 the interview several times, annotating, summarising, paraphrasing, and commenting on what is  
18 435 interesting or significant. The second stage will consist in encoding those annotations to a slightly  
19 436 higher level of abstraction by theoretical and scientific elements: the psychologist will underline the  
20 437 themes addressed by the participant. At the third stage, the psychologist will try to connect these  
21 438 themes by grouping them into superordinate clusters while checking that the connections they make  
22 439 match the meaning of the participant's speech. The last stage of the analysis will consist in giving a  
23 440 scientific meaning to the established clusters.

24 441 The same method will be used for all participants within each group, with the permanent goal of  
25 442 improving the previously identified clusters. Each time a new element is identified, or each time a  
26 443 theme or a cluster is modified, the psychologist will get back to previously analysed interviews to  
27 444 ensure that the new model accounts for the speech of all participants.

28 445 Finally, when all interviews will have been analysed, a summary will be made, by underlining  
29 446 similarities and differences between adolescents and YA regarding transition into adulthood and its  
30 447 consequences on their lives.

31 448 Analyst triangulation will be performed,[59, 60] by involving two psychologists in reviewing the  
32 449 findings in order to assess the reliability and validity of the obtained results. This triangulation may  
33 450 also allow to develop a broader and deeper understanding of the results.

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## 452 **DISCUSSION AND LIMITATIONS**

### 453 **Strengths and limitations of the database**

454 As the issues concerning transition into adulthood may intrinsically depend on features of the health  
455 care system, we intend to explore the specific perceptions of YPWH in France, whose health care  
456 system model is specific. The support of the FranceCoag registry to this study is therefore an  
457 important strength. While the exhaustivity of inclusions in this registry might have been an issue for  
458 patients with moderate or minor haemophilia, the exhaustivity concerning patients with severe  
459 haemophilia is guaranteed since 2000. Even if five HTC over the 34 active ones (*i.e.* 15%) did not  
460 accept to participate in the TRANSEMO study, the loss of eligible patients was small (only 4% of  
461 the eligible YPWH). The comparison of basic socio-demographic and medical data, available in the  
462 FranceCoag database, between included patients and non-included eligible patients will allow to  
463 discuss the representativeness of the included sample.

### 465 **Strengths and limitations of the study design**

466 The quantitative phase of this study is cross-sectional, while it would have been pertinent to design a  
467 longitudinal study to follow up YPWH during their transition. However, as this process is long,[2] it  
468 would have been very time consuming, with a high risk of lost to follow-up. We therefore chose to  
469 compare at a unique time the experiences of two groups regarding their status towards transition. If the  
470 results of the present cross-sectional study turned out to be singular, they could justify to secondly set  
471 a longitudinal study up.

472 The mixed study design,[61, 62] by combining quantitative and qualitative methods, will bring  
473 original results. The first quantitative phase will allow to adjust the second qualitative phase, by the  
474 targeted selection of participants (adherent / non adherent participants according to main evaluation  
475 criterion) and by bringing results to be discussed with participants. The qualitative phase will then  
476 allow to shed light on the results from the quantitative phase by a deeper analysis of participants'  
477 experiences. This qualitative phase could also be a starting point for a future longitudinal and  
478 quantitative study, by highlighting unexplored processes by the present quantitative phase.

### 480 **Strengths and limitations of the endpoints**

481 The main objective of the study is to assess the impact of transition from adolescence to adulthood,  
482 which we chose to measure by the level of adherence to health care. This choice is debatable, as  
483 maintaining a high level of adherence to care probably reflects only a part of the success of the  
484 transition process. However, this choice is justified by several arguments: (i) it is necessary to propose  
485 an endpoint which applies for both adolescents and YA, in order to be able to assess through a  
486 transversal study the potential impact of the transition on a common endpoint, (ii) a decrease of  
487 adherence during the transition process may be associated with clinical consequences (serious

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3 488 bleedings), which may impair physical and psychological quality of life in YPWH, (iii) this endpoint  
4 489 allows to assess more specifically the impact of the supplementary transition experienced by YPWH, a  
5 490 transition from a paediatric health care system to an adult one, and (iv) this endpoint may be accessible  
6 491 for educational actions.

7  
8 492 Adherence is a concept which might be defined by the agreement between the behaviour of a patient  
9 493 and the received recommendations or prescriptions.[63] We chose to assess adherence to prophylactic  
10 494 treatment, which is the commonly used evaluation criterion when assessing adherence in  
11 495 haemophilia[29, 30] but which would have been valid only for YPWH under prophylactic treatment.  
12 496 We therefore also chose to assess adherence to clinical follow-up, which is valid for all YPWH (even  
13 497 if the rhythm of visits might be different depending on their personal situation). Moreover, we chose to  
14 498 collect data on adherence through three sources of information: (i) data from the FranceCoag database  
15 499 (follow-up visits, injections of prophylactic treatment, haemorrhagic events), (ii) referent physician-  
16 500 reported data, and (iii) patient-reported data. A composite endpoint combining these items will allow  
17 501 to take into account the complexity of the assessment of adherence, in particular by mixing clinical  
18 502 and objective data with behavioural and subjective adherence-related data.  
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#### 26 504 **Strengths and limitations of the determinants**

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28 505 This study will assess more systematically psychosocial determinants of adherence to health care,  
29 506 considered as a marker of the success of transition. Indeed, beyond the likely impacts of medical,  
30 507 organisational, and socio-demographic factors, we expect this success to be moderated by lesser  
31 508 known sociocognitive (time perspective), emotional (coping strategies), and family factors (family  
32 509 functioning).

33  
34 510 Time perspective refers to how individuals partition their experiences into distinct temporal categories  
35 511 of past, present and future.[64] Particular temporal frames may be associated with well-being and  
36 512 quality of life.[65] Indeed, focusing on a “past negative” time perspective may result in negative long-  
37 513 term adjustment and post-traumatic stress symptomology.[66] On the contrary, “future” time  
38 514 perspective has been viewed as the more constructive time perspective.[65]

39  
40 515 Moreover, people (patients and relatives) faced with a severe chronic childhood disease generally  
41 516 experience repeated stress reactions because the disease questions individuals about their beliefs,  
42 517 identity, priorities, and short-term and long-term goals.[67, 68] The coping strategies individuals  
43 518 implement to deal with these stress reactions have been studied. Studies show that an individual's  
44 519 inability to implement appropriate coping strategies, or the use of strategies targeting only emotional  
45 520 responses (instead of their cognitive antecedents), are responsible for emotional disorders and  
46 521 impaired familial and social relationships. On the contrary, long-term well-being may be facilitated by  
47 522 the use of coping strategies which allow people restructuring their concepts, beliefs, values, priorities,  
48 523 standards, and personal goals.[68-72]

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3 524 Finally, growing into adulthood implies that young people gain autonomy, get independent and  
4 525 endorse the responsibilities falling to adults. This personal empowerment implies that they develop  
5 526 their own personal values and long-term goals (attitudinal autonomy) and implement effective  
6 527 strategies to achieve these goals (functional autonomy). However, this ability to develop autonomy  
7 528 depends on the capacity to maintain confidence in one's own values and goals (emotional  
8 529 autonomy).[46, 73] We assume the development of autonomy (especially emotional autonomy)  
9 530 largely depends on the family functioning: parenting style, cohesiveness, flexibility, roles  
10 531 management, and communication of emotion.[74-77]  
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For peer review only

## 532 ETHICS

533 Informed written consent will be obtained for all participants prior to recruitment for the study. For  
534 adolescents, consent will be obtained from their two parents or legal representatives. All data will be  
535 analysed confidentially and anonymously.

536 The study was designed according to Good Clinical Practices, and all procedures will be in accordance  
537 with the Declaration of Helsinki. The study was approved by the French Ethics Committee (Comité de  
538 Protection des Personnes Sud Méditerranée V) on 8<sup>th</sup> November 2016 and by the French National  
539 Agency for Medicines and Health Products Safety on 22<sup>th</sup> September 2016 (reference number ID  
540 RCB: 2016-A01034-47). The protocol was registered in ClinicalTrials.gov (NCT02866526).

## 542 DISSEMINATION

543 This study will allow to comprehend what the impact of transition from adolescence to adulthood  
544 could be in YPWH in France, which is of particular interest in the global approach whose goal is to  
545 take care of all aspects of life in patients with chronic diseases.

546 This study will also allow to identify determinants of adherence, considered as a marker of a  
547 successful transition in YPWH. The assessment of social, psychosocial and behavioural data, will  
548 allow to describe the socio-cognitive processes which may facilitate or complicate adherence, while  
549 taking into account other factors, *i.e.* medical, organisational, and socio-demographic factors. The  
550 results obtained from the quantitative phase of the study will be enlightened by the analysis of the  
551 interviews conducted in the qualitative phase. This analysis will bring supplementary and  
552 complementary data which would not have been accessible via the analysis of the questionnaires,  
553 especially concerning expectations and fears about health, but also about personal and professional  
554 life. Singular results from this qualitative phase could be used to better design a future quantitative  
555 study on the issue of transition, by assessing complementary outcomes to those assessed in the present  
556 quantitative phase.

557 Results will allow to propose recommendations and to develop adapted and focused interventions to  
558 compensate for YPWH difficulties, and thus optimize the adherence to the proposed follow-up and to  
559 the prophylactic treatment, but also facilitate their entry in the adult life.

560 In order to assess the transferability of the results from the TRANSHEMO study in other contexts of  
561 childhood chronic diseases in France, complementary projects could be proposed to assess the issue of  
562 transition in young patients with rare and/or serious and/or chronic diseases. This approach would  
563 allow to identify which issues are common to these diseases and which ones are specific to a disease,  
564 including severe haemophilia. Common and specific actions could then be proposed to facilitate the  
565 transition process and support young patients.

**566 Authors' contributions**

567 NR, ABA, KB, TL, HC, PA contributed to the design of this study and wrote this article.  
568 The investigators (LA, SB, CB, M-AB, CB-A, AB-D, SC, PC, SCD, EDR, DD, CF, BF, VG, JG, YG,  
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570 AS, CS, BT, MT, J-BV, SV, FV, AV-E, BW) of the French Haemophilia Treatment Centres  
571 contribute to enrol participants, they revised the manuscript and approved the final version.  
572 Members of steering committee (NR-D, VM, TS) contributed to the design of this study, they revised  
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10 608 **Competing interests**

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12 609 None declared.  
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# BMJ Open

## Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSEMO): study protocol for a multicentric French national observational cross-sectional study.

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Manuscripts

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1 **TITLE**

2 Determinants of adherence and consequences of the transition from adolescence to adulthood among  
 3 young people with severe haemophilia (TRANSHEMO): study protocol for a multicentric French  
 4 national observational cross-sectional study.

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## 72 ARTICLE SUMMARY

### 74 Abstract

75 Introduction: Severe haemophilia is a rare disease characterised by spontaneous bleeding from early  
76 childhood, which may lead to various complications especially in joints. It is nowadays possible to  
77 avoid these complications thanks to substitutive therapies for which the issue of adherence is major.  
78 The transition from adolescence to adulthood in young people with severe haemophilia is a critical  
79 period as it is associated with a high risk of lack of adherence to health care, which might have serious  
80 consequences on daily activities but also on quality of life.

81 Methods and analysis: We present the protocol for a cross-sectional, observational, multicentric study  
82 to assess the differences between adolescents and young adults with severe haemophilia in France  
83 through the transition process, especially on adherence to health care. This study is based on a mixed  
84 methods design, with two complementary and consecutive phases, comparing data from a group of  
85 adolescents (aged 14-17 years) to those from a group of young adults (aged 20-29 years). The  
86 quantitative phase focuses on the determinants (medical, organisational, socio-demographic and  
87 social, and psychosocial and behavioural factors) of adherence to health care (considered as a marker  
88 of the success of transition). The qualitative phase explores participants' views in more depth to  
89 explain and refine the results from the quantitative phase. Eligible patients are contacted by the various  
90 Haemophilia Treatment Centres participating in the French national registry FranceCoag.

91 Ethics and dissemination: The study was approved by the French Ethics Committee and by the French  
92 National Agency for Medicines and Health Products Safety (number: 2016-A01034-47). Study  
93 findings will be disseminated to the scientific and medical community in peer-reviewed journals and  
94 presented at scientific meetings. Results will be popularised to be communicated via the French  
95 association for people with haemophilia to participants and to the general public.

96 Trial registration number: NCT02866526

98 Word count: 299

### 100 Keywords

101 Adherence / Haemophilia / Transition / Adolescents / Young adults

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3 104 **Strengths and limitations of this study**

- 4 105 – This study will be the largest to assess the issue of transition from adolescence to adulthood  
5 106 among young people with haemophilia (PWH), and the first one in France where the features of  
6 107 the health care system are very specific.  
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9 108 – The cross-sectional design of the study comparing experiences reported by adolescents compared  
10 109 to those reported by young adults is a limitation, as it would have been pertinent to design a  
11 110 longitudinal study to follow up young PWH during their transition; however, as the transition  
12 111 process is long, it would have been very time consuming with a high risk of follow-up.  
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15 112 – This study will be based on an explanatory sequential mixed methods design, which will allow to  
16 113 bring complementary results by collecting and analysing quantitative and then qualitative data in  
17 114 two consecutive phases within one study.  
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19 115 – The main evaluation criterion of the quantitative phase will be the adherence to health care, a  
20 116 hypothesised marker of the success of transition, whose choice is debatable as it is a complex  
21 117 concept to measure and as it probably reflects only a part of the success of transition.  
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24 118 – Potential determinants will be selected according to the SMART theoretical model (Social-  
25 119 ecological model for adolescents and young adults readiness for transition), and will include both  
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27 120 pre-existing objective factors and modifiable subjective factors (potential targets of intervention),  
28 121 whose associations with adherence to health care will be hypothesised from the quantitative  
29 122 phase, and more deeply explored and explained thanks to the qualitative phase.  
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33 124 Word count: 248  
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## 125 INTRODUCTION

126 Haemophilia is a rare and inherited disorder (X-linked recessive transmission), affecting mainly males  
127 (annual incidence: 1/5,000 male births).[1] It is characterized by bleeding due to a lack of clotting  
128 factors (factor VIII (FVIII) for haemophilia A or factor IX (FIX) for haemophilia B). Bleedings often  
129 start in early life, due to psychomotor skills acquisition. Seriousness of the symptoms depends on the  
130 severity of the lack of FVIII/FIX. Severe haemophilia, defined by a biological activity of FVIII/FIX  
131 lower than 1%, is characterized by spontaneous bleedings most frequently located into the joints  
132 (haemarthroses) and into the muscles (haematoma). Natural history of untreated severe haemophilia is  
133 marked by serious haemorrhagic events which compromise the vital prognosis. Insufficiently treated,  
134 repetition of haemarthroses and haematoma results in invalidating motor disability.

135 It is nowadays possible to avoid these complications thanks to substitutive therapies for which the  
136 issue of adherence is major, and to a lifelong regular clinical follow-up. Successive stages of the  
137 disorder's care management have been described by Young,[2] including:

- 138 – Adolescence: independence and responsibility for disease management, self-advocacy and  
139 disclosure, importance of treatment adherence, transfer of responsibilities from the caregivers to  
140 the patient
- 141 – Adulthood: decide whether to continue prophylaxis, challenge of dealing with a chronic disease  
142 and becoming one's own caregiver

143 The success of the transition from adolescence to adulthood may therefore be crucial in the  
144 maintenance of adherence to care.

146 In the context of chronic diseases, the process of transition may be more complicated, as affected  
147 young people have to deal with a supplementary transition, from a paediatric health care system to an  
148 adult one.[3–6] Indeed, a successful transition involves a transfer of responsibilities from parents to  
149 patients concerning the management of their health, the acquisition of the knowledge, abilities, and  
150 self-reliance necessary to take on autonomy as well as the new roles people expect them to endorse as  
151 adults.[7, 8] Experiencing a difficult transition could be associated with a decrease in the level of  
152 adherence to care, but it might also impair quality of life and the entry into adulthood.[9, 10] In the  
153 framework of several chronic diseases (apart from haemorrhagic diseases), some studies highlighted  
154 barriers or facilitators to successful transition, either associated to the young patients, or to their  
155 parents, or to the various actors of the health care system.[11–14] Authors especially underlined  
156 psychosocial factors such as knowledge, skills, beliefs, expectations, goals, relationships, fears, need  
157 for control, emotional dependency, over-protectiveness, heightened awareness of health issues, lack of  
158 trust in caregivers.[13–16] The theoretical social-ecological model of AYA (adolescents and young  
159 adults) readiness for transition (SMART),[17] by identifying both pre-existing objective factors (less  
160 amenable to intervention, including socio-demographics/culture, access/insurance, health status/risk,

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3 161 neurocognition/IQ) and inter-related components of patients, parents and providers (potential targets  
4 162 of intervention, including development, knowledge, skills/self-efficacy, beliefs/expectations, goals,  
5 163 relationships and psychosocial functioning), has been proposed as the ideal framework to identify  
6 164 determinants (barriers and facilitators) of transition in the context of serious paediatric illness  
7 165 conditions.[14] Some interventions have been designed to improve the transition of care, and a  
8 166 Cochrane review assessing their effectiveness found that transitional programs might slightly improve  
9 167 transitional readiness (self-management skills and knowledge), but that they led to little or no  
10 168 difference in health status, quality of life or well-being.[18] The identification of barriers and  
11 169 facilitators to successful transition may help to design target interventions in order to improve their  
12 170 overall effectiveness.  
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19 172 In the specific context of haemophilia, some studies have been conducted to assess the issue of  
20 173 transition in young people with haemophilia (PWH).[19] A study comparing quality of life in young  
21 174 PWH in pre-transition period with young PWH in post-transition period showed a lower quality of life  
22 175 and a higher level of distress in young PWH in post-transition period.[20] Some recommendations  
23 176 (involving patients, families, and caregivers) have been proposed to facilitate this process.[21–23]  
24 177 However, despite the setting up of some actions which have been shown to improve the disease  
25 178 specific knowledge,[24, 25] difficulties are still remaining, which may impair the health condition and  
26 179 the quality of life of young PWH.[26, 27] A study on the unmet needs reported by young adults  
27 180 highlighted psychological issues mainly related to independence achievement.[28] At the crucial age  
28 181 at which adolescents are often opposed or want to take their own decisions, maintaining the adherence  
29 182 to clinical follow-up and therapies is an important issue. A study conducted in young PWH (13-25  
30 183 years) found that 41% of them had not followed prescribed treatment.[29] Studies have shown a  
31 184 decrease in the level of adherence to the prescribed therapeutic regimen during transition. A study  
32 185 based on nurses-reported data found a decreasing level of adherence, from 90% for the youngest  
33 186 patients (0-12 years) to 54% for those aged 13-18 years and to 36% for those aged 19-28 years.[30]  
34 187 Caregiver or self-reported adherence assessment showed similar results, with a lower level of  
35 188 adherence in adults in comparison with paediatric patients (and among these latter, a lower level in  
36 189 adolescents in comparison with children).[31, 32] This lower adherence might have serious  
37 190 consequences, such as haemarthroses which may impair daily activities but also quality of life. A  
38 191 higher number of hemarthrosis was observed in less-adherent to prophylaxis patients aged 12 to 25  
39 192 years,[33] which was also observed when considering patients of all ages.[32, 34] Some psychosocial  
40 193 factors of the maintenance of a high adherence in young PWH have been highlighted, *e.g.* a greater  
41 194 perception of the need for prophylaxis than the concern over taking it, a positive expectancy of its  
42 195 effectiveness, a good social support, and a stronger emotional reaction to having haemophilia.[35] In  
43 196 the general framework of haemophilia (not focusing on the transition period), a review on  
44 197 determinants of adherence to prophylactic treatment identified both barriers (absence or infrequent



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3 198 symptoms, increasing age) and motivators (belief in necessity of treatment, good relationship with the  
4 199 health care provider, experience of symptoms).[36] Another review identified five key types of  
5 200 adherence barriers: patient-related factors (including age), condition-related factors, treatment-related  
6 201 factors, health-care system factors, and socioeconomic factors.[37]  
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8 202 Even if some literature data exists on the issue of transition and its impact on adherence to health care  
9 203 in the context of haemophilia, some limits may be discussed. The sample size of these studies is  
10 204 generally modest (below or about a hundred of patients).[35, 38, 39] An international larger study  
11 205 including 230 young PWH was conducted but all of them were young adults (aged 18-30 years), none  
12 206 were adolescents.[27] Adherence is usually assessed only through adherence to prophylactic treatment,  
13 207 which excludes young PWH under on-demand treatment.[35, 38, 39] None of these studies has been  
14 208 carried out in France where the features of the health care system are very specific. An international  
15 209 study showed that cost was a frequent reported barrier to prophylaxis (about 45% by both nurses from  
16 210 Haemophilia Treatment Centres and patients perspectives).[30] Thus, the assumption of all disease-  
17 211 related costs by the French social security system might influence the adherence to care. The backing  
18 212 of the French national registry FranceCoag[40] will allow to assess this issue in a large and exhaustive  
19 213 population of young PWH. This registry involves for more than 20 years French Haemophilia  
20 214 Treatment Centres (HTC), and it includes more than 10,000 patients (7,000 people with haemophilia  
21 215 (PWH), with 2,300 with severe haemophilia of all ages). Moreover, even if some psychological data  
22 216 have been related to the adherence to care, they are often analysed as independent factors. Taking into  
23 217 account the interdependence between these factors using adapted methods could bring original results.  
24 218 Finally, an explanatory sequential mixed methods designed study combining quantitative and  
25 219 qualitative methods will allow to address in a global way the issue of transition among young PWH,  
26 220 *i.e.* focusing not only on its facilitators and barriers but also, on all the specific concerns and  
27 221 difficulties young PWH may experience as they grow into adulthood.  
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## 222 OBJECTIVES

223 The main objective of this study is to assess differences between adolescents and young adults with  
224 severe haemophilia in France, through the transition process, especially on adherence to health care.

225 The operational objectives of this study are:

- 226 – to compare the level of adherence in adolescents and in young adults (YA)
- 227 – to identify determinants (medical, organisational, socio-demographic and social, and psychosocial  
228 and behavioural factors) of the level of adherence in young PWH,
- 229 – to assess specific factors involved in suboptimal level of adherence in the sub-groups of  
230 adolescents and YA,
- 231 – to identify groups of patients (clusters) regarding both their level of adherence and their  
232 psychosocial characteristics,
- 233 – to examine through a qualitative approach statistical results which would have been brought to  
234 light according to the quantitative objectives, and to identify some ways to improve adherence to  
235 health care in young PWH and their global care.

## 237 METHODS/DESIGN

### 238 Study design

239 This study is designed as a multicentric (29 HTC from FranceCoag), observational, cross-sectional  
240 study, based on an explanatory sequential mixed methods design,[41–47] with two complementary  
241 and consecutive phases:

- 242 – The quantitative phase focuses on the determinants of adherence to health care (considered as a  
243 marker of the success of transition), and compares data from a group of adolescents to those from  
244 a group of YA, in order to provide a general understanding of the issue of adherence in young  
245 PWH,

246 The qualitative phase explores participants' views in more depth (few patients selected from the  
247 quantitative phase) to explain and refine the general understanding from the quantitative phase.

248 Interpretation and discussion of the global results will be done by integrating the results of both phases  
249 of the study.

### 251 Participants

#### 252 Inclusion criteria

- 253 – Patients with severe A or B haemophilia (deficiency <1%)
- 254 – Patients affiliated to the French social security system and included in the FranceCoag registry
- 255 – Patients followed in one of the 29 participating HTC
- 256 – Patients aged 14-17 years (adolescents group), or aged 20-29 years (YA group)

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3 257 – Adolescents authorised to participate by their parents or their legal representatives, or YA who  
4 258 give their consent to participate in this study  
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7 260 Non-inclusion criteria

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9 261 – Vulnerable patients (adults under guardianship, pregnant or nursing women)  
10 262 Patients with reading and writing difficulties (as data collection in the quantitative phase is mostly  
11 263 based on participants' self-reported data collected through a booklet)

12 264 Period of the study

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14 265 The planned duration of the study is 30 months. Inclusions started in February 2017. The quantitative  
15 266 phase will go on for 18 months, the qualitative phase will go on for 10 months, and the last two  
16 267 months will focus on integrating results from both phases, in order to provide a global interpretation  
17 268 and discussion of the results of the study.  
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22 270 **Quantitative phase**

23 271 Main evaluation criterion

24 272 The main evaluation criterion is the adherence to clinical follow-up and prophylactic treatment (a  
25 273 hypothesized marker of the success of transition into adulthood), which will be assessed via the  
26 274 following items:

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29 275 – number of follow-up visits in agreement with the recommended number over the last two years,  
30 276 – number of prophylactic treatment injections in agreement with the recommended number over the  
31 277 last three months (if applicable),  
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33 278 – number of haemorrhagic events over the last two years,  
34 279 – physician-reported adherence to clinical follow-up and to prophylactic treatment (if applicable),  
35 280 – patient-reported adherence to clinical follow-up and to prophylactic treatment (if applicable).

36 281 Each item will be dichotomized, and a composite quantitative endpoint will be constructed taking into  
37 282 account all these dichotomized items. This composite quantitative endpoint will in turn be  
38 283 dichotomized to define adherent / non-adherent participants (main evaluation criterion).  
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43 285 Secondary evaluation criteria

44 286 Each item which is part of the composite endpoint as described hereinabove will be considered in an  
45 287 independent manner as a secondary evaluation criterion.  
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49 289 Explanatory collected data

50 290 *Medical data*

51 291 Medical data will include: deficit characterisation, diagnosis (age at diagnosis, circumstances of  
52 292 diagnosis, family history), viral diseases (HIV, HBV, HCV), comorbidities (intracranial haemorrhage,  
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293 major orthopaedic interventions, major disability, cancer, other chronic pathology), previous and  
294 current treatment.

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296 *Organisational data (Haemophilia Treatment Centres-reported)*

297 Organisational data will include: paediatric / adult / paediatric and adult HTC, physicians' speciality,  
298 mean age of the transition from paediatric care to adult one, consultations dedicated to the transition,  
299 common consultations with both paediatric and adult medical teams, specific tools set up to facilitate  
300 the transition process (information leaflet, therapeutic patient education).

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302 *Socio-demographic and social data*

- 303 – Gender and age of family members, living situation,
- 304 – Socio-professional category, socio-economic status assessed by the Family Affluence Scale),[48]
- 305 – Distance to the HTC (in km),
- 306 – Membership of French patients association for PWH (AFH),
- 307 – Family functioning (structure, organisation, and communication) assessed by the French validated  
308 version of the 6-items Family Assessment Device,[49–51]
- 309 – Schooling and academic success evaluated by ad-hoc items (schooling type, level of education,  
310 academic difficulties),
- 311 – Relationships with the health care system assessed using ad-hoc items (satisfaction and  
312 expectations towards the health care system, participation in therapeutic patient education  
313 programme).

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315 *Psychosocial and behavioural data*

- 316 – Quality of life will be assessed using the validated French version of the SF-12 generic scale.[52]  
317 Two sub-scores, mental health and physical health, will be calculated. The SF-12 allows assessing  
318 the quality of life of adults as well as adolescents (14 + years).
  - 319 – Quality of life of adolescents will also be assessed by the validated French version of  
320 the 10-items Kidscreen Index, which explores the following domains: physical well-  
321 being, psychological well-being, autonomy and relations with parents and home life,  
322 peers and social support, and school environment.[53]
  - 323 – Haemophilia-specific quality of life will be assessed in all participants using the  
324 validated French short version of the Haemo-Qol questionnaire.[54, 55]
- 325 – Time perspective will be assessed using the Past Negative (PN) and Future (F) subscales of the  
326 French validated version of the Zimbardo time perspective inventory.[56, 57] The PN subscale (9  
327 items) reflects a pessimistic attitude towards the past and the experience and memory of traumatic  
328 life events. The F subscale (12 items) reflects an orientation towards future and an attitude of

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3 329 planning and achievement of objectives. To avoid the questionnaire being too long, we will not  
4 330 plan to assess the Past-Positive, Present-Hedonistic, and Present-Fatalistic subscales.  
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6 331 – Coping Strategies will be measured by the validated French version of the Brief-Cope scale[58,  
7 332 59] which consists of 28 items assessing individuals' use of 14 coping strategies: self-distraction,  
8 333 active coping, denial, drug use, emotional social support seeking, instrumental social support  
9 334 seeking, behavioural disengagement, emotional expression, positive reframing, planning, humour,  
10 335 acceptance, religion, and self-blame.  
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12 336 – Autonomy will be assessed using ad-hoc items only proposed in the YA questionnaire (financial  
13 337 independence from the parents, and living, management of health, dealing with administrative  
14 338 tasks, and taking holidays without the parents). The 15-items Noom validated questionnaire[60,  
15 339 61] assessing attitudinal autonomy, emotional autonomy, and functional autonomy will be  
16 340 proposed to all participants (ad-hoc translation for this study).  
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#### 22 342 Data collection procedure

23 343 Main medical data will be extracted from the FranceCoag database, and completed by a short  
24 344 questionnaire filled in by the referent physician from each HTC. Organisational data will be completed  
25 345 by a medical representative from each HTC. Eligible participants will be identified and approached by  
26 346 the HTC team by which they are followed (approach either during a medical consultation, or by phone  
27 347 call, or by a personalised mail sent at their home). Survey documents (information sheet, informed  
28 348 consent form, booklet, and prepaid envelope) will then be sent by post to eligible young PWH.  
29 349 Participants' self-reported data will be collected through a standardised booklet including several  
30 350 questionnaires (an adolescent version and a YA version). Consent will be collected through the  
31 351 signature of the informed consent form by the parents or the legal representatives for adolescents, and  
32 352 by the signature of the YA directly for YA. Completed questionnaires as well as signed informed  
33 353 consent forms will be sent back by the participants via the supplied prepaid envelope. If no response is  
34 354 received within 30 days, a reminder letter will be sent. A second reminder letter and all survey  
35 355 documents along will be sent two months later in case of no response.  
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#### 44 357 Sample size justification

45 358 According to the exhaustive FranceCoag database and considering the specific inclusion criteria of the  
46 359 TRANSHEMO study (severe A or B haemophilia, patients aged 14-17 or 20-29 years, followed in one  
47 360 of the 29 participating HTC), 154 adolescents and 389 YA are eligible for this study. We hypothesised  
48 361 a difference of 20% between adolescents and YA regarding the main evaluation criterion (90% of  
49 362 adherence to health care in adolescents vs 70% in YA). Then, under the hypothesis of a non-response  
50 363 rate of 30%, and considering a bilateral alpha risk of 5%, the power of this study would reach  
51 364 99%.[62, 63]  
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3 366 Data Management

4 367 A specific database will be created using EpiData software, and merged with the FranceCoag  
5 368 database. A process will be used to assign to each participant a unique anonymous number. A data  
6 369 quality control will be performed by a physician to limit data inconsistency.  
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10 371 Analysis

11 372 The analysis plan and the final report will be written according to the STROBE recommendations.[64,  
12 373 65] All analyses will be performed using R software. All tests will be two-sided, and  $p < .05$  will define  
13 374 statistical significance.  
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17 376 *Analysis populations*

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19 377 The analysis populations will be the adolescents and the YA groups, among whom adherent and non-  
20 378 adherent patients will be identified.  
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24 380 *Descriptive analysis*

25 381 A descriptive analysis will first be performed. Qualitative variables will be presented as numbers and  
26 382 percentages, quantitative variables as means and standard deviations, or as medians and interquartile  
27 383 ranges. Subjective data will be described by their overall scores and their sub-scores.

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29 384 Reasons for non-inclusion will be listed. Included patients will be compared to non-included eligible  
30 385 patients using basic socio-demographic and clinical data, available in the FranceCoag database.  
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34 387 *Comparative analysis*

35 388 *Crude analysis*

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37 389 Adherence will first be described by groups (adolescents / YA) using classical indicators. The  
38 390 comparison of adherence between the two groups will be performed using chi-square test (or Fisher  
39 391 test depending on the expected numbers) for the main evaluation criterion and for all qualitative  
40 392 secondary evaluation criteria, and using Student t test (or Mann-Whitney test depending on normality  
41 393 of the distribution) for quantitative secondary evaluation criteria.  
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45 395 *Adjusted analysis*

46 396 In order to identify factors associated with adherence, bivariate and multivariate analyses will be  
47 397 performed. Potential determinants (medical, organisational, socio-demographic and social,  
48 398 psychosocial and behavioural factors) will be proposed as explanatory variables. Logistic regression  
49 399 models will be used for the main evaluation criterion and for all qualitative secondary evaluation  
50 400 criteria, and linear regression models will be used for quantitative secondary evaluation criteria. Each  
51 401 characteristic whose degree of significance will be lower than .20 will be considered for multivariate  
52 402 analyses. A backward selection will be applied to retain only significantly associated characteristics.  
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3 403 Multilevel models will be used to take into account organisational factors which are related to the  
4 404 centre. Structural equation modelling will be considered to take into account the collinearity and/or the  
5 405 complex relationships which might exist between explanatory individual characteristics (especially  
6 406 social, psychological and behavioural ones).[66–68]

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8 407 This analysis will first be performed in the overall population with a forced adjustment on the group  
9 408 (adolescent / YA). It will secondly be performed independently in each of the two groups.

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#### 13 410 *Cluster analysis*

14 411 In order to bring to light particular profiles of adherent / non-adherent in adolescents and in YA, an  
15 412 exploratory unsupervised classification analysis will be performed.[69, 70] This method which does  
16 413 not require any condition of validity will allow to gather patients with similar profiles in homogeneous  
17 414 clusters.

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#### 21 416 **Qualitative phase**

22 417 Data collection procedure

23 418 Few subjects (adolescents on one hand and YA on the other hand) who will have participated in the  
24 419 quantitative phase will be selected for this phase according to the following characteristics (assessed  
25 420 from the quantitative phase): adherent or not, and under prophylaxis or not. If they agree, they will be  
26 421 contacted to participate in research interviews conducted by a psychologist, at any place at their  
27 422 convenience (at home, at the HTC...). The interviews will be individual, confidential, semi-structured,  
28 423 and tape-recorded. The psychologist will be blind to the responses in the questionnaires of the  
29 424 participant, and to his/her status adherent / non-adherent as defined according to the main evaluation  
30 425 criterion of the quantitative phase.

31 426 The psychologist will start with a general question, then he/she will adopt a non-directive attitude and  
32 427 will allow the participant to spontaneously and freely broach the answers which they consider  
33 428 relevant. Then he/she will summarise the response and introduce more precise questions regarding the  
34 429 topics which will have not been covered spontaneously or sufficiently by the participant. He/she will  
35 430 seek to focus the interview on the participant's personal experiences, subjective perceptions, and  
36 431 expectancies, in order to understand if the patient is adherent / non-adherent and the possible  
37 432 determinants of this adherence. The interview guide will be refined from the findings from the  
38 433 quantitative phase, in order to collect more specifically data about potential determinants and  
39 434 adherence to health care brought to light from the quantitative phase.

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#### 41 436 *Adolescents' interviews*

42 437 The interview will begin with this general question: "How do you feel about coming into adulthood in  
43 438 a few years?"

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3 439 After the spontaneous answer, the psychologist will encourage them to talk about the following topics:  
4 440 the meaning they give to becoming a YA; their expectations towards their life (personal and  
5 441 professional) as future YA; their plan to care about their health as future YA; their fears towards their  
6 442 entry into adulthood.  
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#### 10 444 *Young adults' interviews*

11 445 The interview will begin with this general question: "How do you feel about reaching adulthood  
12 446 during the last few years?"

13 447 After the spontaneous answer, the psychologist will encourage them to talk about the following topics:  
14 448 the meaning they give to becoming a YA; their experienced difficulties towards the acquisition of their  
15 449 autonomy (especially concerning the management of their health) and the construction of their life  
16 450 (personal and professional); the facilitators and barriers they identified during their transition process.

17 451 Then, to go further and broaden these qualitative data, the psychologist will show to these participants  
18 452 a summary of the adolescents' expectations towards adulthood (from the interviews conducted in  
19 453 adolescents, which therefore will be carried out and analysed before those in YA). The psychologist  
20 454 will then ask YA to assess: to what extent these perceptions match with their own expectations when  
21 455 they were adolescents; to assess to what extent these perceptions match with their current lives; and to  
22 456 indicate which issues regarding transition adolescents forget to mention.  
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#### 31 458 Sample size justification

32 459 Four profiles will be identified from the two selected characteristics (adherent or not, and under  
33 460 prophylaxis or not). On the basis of three interviews by profile, up to 12 adolescents and 12 YA will  
34 461 be selected for the qualitative phase (enrolments until information is saturated).  
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#### 38 463 Data management

39 464 All interviews will be precisely and entirely transcribed, including the participants' hesitations and  
40 465 self-corrections.  
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#### 44 467 Analysis

45 468 The psychologist will analyse adolescents' interviews on one hand and YA ones on the other hand,  
46 469 using Interpretative Phenomenological Analysis (IPA) method. This method allows to comprehend the  
47 470 participants' subjective experiences through the analysis they make of (and the meaning they give to)  
48 471 their feelings and states, as well as the specific events they are faced with. It makes possible to  
49 472 highlight sociocognitive processes by which personal experiences are assimilated to individuals'  
50 473 perceptions of both themselves and the world they live in.[71, 72]

51 474 IPA of an interview is made of four iterative stages. During the first stage, the psychologist will read  
52 475 the interview several times, annotating, summarising, paraphrasing, and commenting on what is  
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3 476 interesting or significant. The second stage will consist in encoding those annotations to a slightly  
4 477 higher level of abstraction by theoretical and scientific elements: the psychologist will underline the  
5 478 themes addressed by the participant. At the third stage, the psychologist will try to connect these  
6 479 themes by grouping them into superordinate clusters while checking that the connections they make  
7 480 match the meaning of the participant's speech. The last stage of the analysis will consist in giving a  
8 481 scientific meaning to the established clusters.

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11 482 The same method will be used for all participants within each group, with the permanent goal of  
12 483 improving the previously identified clusters. Each time a new element is identified, or each time a  
13 484 theme or a cluster is modified, the psychologist will get back to previously analysed interviews to  
14 485 ensure that the new model accounts for the speech of all participants.

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17 486 According to the interpretation of each interview, the psychologist will have to determine the status  
18 487 adherent / non-adherent of each participant. Thus, the identified clusters of themes will be put in  
19 488 perspective with the psychologist-determined status towards adherence, in order to propose a model  
20 489 describing the relationships between adherence to health care and its determinants.

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23 490 Finally, when all interviews will have been analysed, a summary will be made, by underlining  
24 491 similarities and differences between adolescents and YA regarding adherence to health care and its  
25 492 determinants, and transition into adulthood and its consequences on their lives.

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28 493 Analyst triangulation will be performed,[73, 74] by involving two psychologists in reviewing the  
29 494 findings in order to assess the reliability and validity of the obtained results. This triangulation may  
30 495 also allow to develop a broader and deeper understanding of the results.

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### 33 34 497 **Interpretation**

35 498 Interpretation and discussion of the global results of the study will be done by integrating the results of  
36 499 both phases of the study. From participants who will have been considered consistently according to  
37 500 both quantitative and qualitative phases either as adherent or as non-adherent, hypothesized  
38 501 associations between potential determinants and adherence from the quantitative phase will be  
39 502 therefore confirmed or infirmed thanks to the results of the qualitative phase. Thus, combining the  
40 503 quantitative and qualitative findings will help explain the results of the statistical results, which  
41 504 underscores the elaborating purpose for a mixed-methods sequential explanatory design. [45, 75]  
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43 505 Participants who will not have been considered consistently either as adherent or as non-adherent will  
44 506 allow to discuss representations and beliefs about adherence in the context of haemophilia, and the  
45 507 relevance of this outcome to assess the success of transition through quantitative studies.

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### 48 49 509 **Patient and public involvement**

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52 510 The development of the research question, study design and outcome measures involved interpretation  
53 511 of literature, professional experience reported through the clinicians, nurses, and psychologists  
54 512 working in the various Haemophilia Treatment Centres participating in the French national registry

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3 513 FranceCoag, and patients' priorities and experience reported through the French association patients  
4 514 association for PWH (AFH) that is member of the steering committee of the study. Patients will not be  
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6 515 directly involved in the recruitment, but the AFH will regularly communicate about the study (internet,  
7 516 newsletters, social networks, magazine...) to inform eligible participants in order to maximise the  
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9 517 recruitment. Results will be popularised to be communicated via the AFH to participants and to the  
10 518 general public.  
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## 519 **DISCUSSION AND LIMITATIONS**

### 520 **Strengths and limitations of the database**

521 As the issues concerning transition into adulthood may intrinsically depend on features of the health  
522 care system, we intend to explore the specific perceptions of young PWH in France, whose health care  
523 system model is specific. The support of the FranceCoag registry to this study is therefore an  
524 important strength. While the exhaustivity of inclusions in this registry might have been an issue for  
525 patients with moderate or minor haemophilia, the exhaustivity concerning patients with severe  
526 haemophilia is guaranteed since 2000. Even if five HTC over the 34 active ones (*i.e.* 15%) did not  
527 accept to participate in the TRANSEMO study, the loss of eligible patients was small (only 4% of  
528 the eligible young PWH). The comparison of basic socio-demographic and medical data, available in  
529 the FranceCoag database, between included patients and non-included eligible patients will allow to  
530 discuss the representativeness of the included sample. Moreover, the implication of clinicians, nurses,  
531 psychologists, and clinical research associates in both the clinical follow-up of patients and this study  
532 via their participation in the FranceCoag registry will help to maximise the recruitment and limit the  
533 risk of dropouts for this study. The French patients association for PWH (AFH), member of the  
534 steering committee of the FranceCoag registry, will also regularly communicate about the study  
535 (internet, newsletters, social networks, magazine...) to inform eligible participants in order to  
536 maximise the recruitment.

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### 538 **Strengths and limitations of the study design**

539 The quantitative phase of this study is cross-sectional, while it would have been pertinent to design a  
540 longitudinal study to follow up young PWH during their transition. However, as this process is  
541 long,[2] it would have been very time consuming, with a high risk of lost to follow-up. We therefore  
542 chose to compare at a unique time the experiences of two groups regarding their status towards  
543 transition. If the results of the present cross-sectional study turned out to be singular, they could justify  
544 to secondly set a longitudinal study up.

545 The explanatory sequential mixed methods design, [41–47] by combining quantitative and qualitative  
546 methods, will bring original results. The first quantitative phase will allow to adjust the second  
547 qualitative phase, by the targeted selection of participants (adherent / non-adherent participants  
548 according to main evaluation criterion) and by bringing results to be discussed with participants. The  
549 qualitative phase will then allow to shed light on the results from the quantitative phase (based on self-  
550 reported questionnaires data) by a deeper analysis of participants' experiences collected through  
551 interviews conducted by a psychologist, especially for psychosocial and behavioural factors which  
552 will have emerged from the quantitative phase. This qualitative phase could also be a starting point for  
553 a future longitudinal and quantitative study, by highlighting unexplored processes by the present  
554 quantitative phase. The step of integration and mixing of the results from both phases of the study will

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3 555 allow to more fully answer the question of adherence to health care through the period of transition to  
4 556 adulthood in the context of severe haemophilia, and to develop a more robust and meaningful picture  
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6 557 of this issue. Combining the quantitative and qualitative findings will help on one hand to explain  
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8 558 relationships between adherence to health care and its determinants, and on the other hand to discuss  
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10 559 representations and beliefs about adherence, a quantitative outcome which was considered as a marker  
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12 560 of the success of transition.

### 13 561 **Strengths and limitations of the endpoints**

14 562 The main objective of the study is to assess the potential impact of transition from adolescence to  
15 563 adulthood, which we chose to measure by the level of adherence to health care. This choice is  
16 564 debatable, as maintaining a high level of adherence to care probably reflects only a part of the success  
17 565 of the transition process. However, this choice is justified by several arguments: (i) it is necessary to  
18 566 propose an endpoint which applies for both adolescents and YA, in order to be able to assess through a  
19 567 transversal study the potential impact of the transition on a common endpoint, (ii) a decrease of  
20 568 adherence during the transition process may be associated with clinical consequences (serious  
21 569 bleedings), [32–34] which may impair physical and psychological quality of life in young PWH, (iii)  
22 570 this endpoint allows to assess more specifically the potential impact of the supplementary transition  
23 571 experienced by young PWH, a transition from a paediatric health care system to an adult one, (iv) this  
24 572 endpoint was in the top five of health care transition outcomes identified by a Delphi process with an  
25 573 interdisciplinary group of medical and psychosocial professionals,[76] and (v) this endpoint may be  
26 574 accessible for educational actions. Adherence is a concept which might be defined by the agreement  
27 575 between the behaviour of a patient and the received recommendations or prescriptions.[77] We chose  
28 576 to assess adherence to prophylactic treatment, which is the commonly used evaluation criterion when  
29 577 assessing adherence in haemophilia[29, 35] but which would have been valid only for young PWH  
30 578 under prophylactic treatment. We therefore also chose to assess adherence to clinical follow-up, which  
31 579 is valid for all young PWH (even if the rhythm of visits might be different depending on their personal  
32 580 situation). Moreover, we chose to collect data on adherence through three sources of information: (i)  
33 581 data from the FranceCoag database (follow-up visits, injections of prophylactic treatment,  
34 582 haemorrhagic events), (ii) referent physician-reported data, and (iii) patient-reported data. A composite  
35 583 endpoint combining these items will allow to take into account the complexity of the assessment of  
36 584 adherence, in particular by mixing clinical and objective data with behavioural and subjective  
37 585 adherence-related data. The dichotomisation of this composite endpoint to define adherent and non-  
38 586 adherent young PWH will lead to a loss of variability in the data, but this choice will allow to get more  
39 587 accessible data and results. As the issue of variability is sensitive, each secondary endpoint (i.e., each  
40 588 variable included in the composite endpoint) will be analysed according to its original response format  
41 589 (binary, semi-quantitative, quantitative), independently of each other.

## 590 **Strengths and limitations of the determinants**

591 In this study, the choice of the determinants to be assessed (determinants of adherence to health care,  
592 considered as a marker of the success of transition) was based on literature data in the context of  
593 haemophilia,[35–37] and this choice was consistent with the theoretical SMART model.[17] This  
594 model proposes both potential barriers and facilitators, but also both pre-existing and modifiable  
595 factors, more amenable to intervention, including beliefs/expectations related-factors (time  
596 perspective) and psychosocial functioning related-factors (coping strategies and family functioning).

597 Time perspective refers to how individuals partition their experiences into distinct temporal categories  
598 of past, present and future.[78] Particular temporal frames may be associated with well-being and  
599 quality of life.[79] Indeed, focusing on a “past negative” time perspective may result in negative long-  
600 term adjustment and post-traumatic stress symptomology.[80] On the contrary, “future” time  
601 perspective has been viewed as the more constructive time perspective.[79]

602 Moreover, people (patients and relatives) faced with a severe chronic childhood disease generally  
603 experience repeated stress reactions because the disease questions individuals about their beliefs,  
604 identity, priorities, and short-term and long-term goals.[81, 82] The coping strategies individuals  
605 implement to deal with these stress reactions have been studied. Studies show that an individual's  
606 inability to implement appropriate coping strategies, or the use of strategies targeting only emotional  
607 responses (instead of their cognitive antecedents), are responsible for emotional disorders and  
608 impaired familial and social relationships. On the contrary, long-term well-being may be facilitated by  
609 the use of coping strategies which allow people restructuring their concepts, beliefs, values, priorities,  
610 standards, and personal goals.[82–86]

611 Finally, growing into adulthood implies that young people gain autonomy, get independent and  
612 endorse the responsibilities falling to adults. This personal empowerment implies that they develop  
613 their own personal values and long-term goals (attitudinal autonomy) and implement effective  
614 strategies to achieve these goals (functional autonomy). However, this ability to develop autonomy  
615 depends on the capacity to maintain confidence in one's own values and goals (emotional  
616 autonomy).[60, 87] We assume the development of autonomy (especially emotional autonomy)  
617 largely depends on the family functioning: parenting style, cohesiveness, flexibility, roles  
618 management, and communication of emotion.[49, 88–90]

## 619 ETHICS

620 Informed written consent will be obtained for all participants prior to recruitment for the study. For  
621 adolescents, consent will be obtained from their two parents or legal representatives. All data will be  
622 analysed confidentially and anonymously.

623 The study was designed according to Good Clinical Practices, and all procedures will be in accordance  
624 with the Declaration of Helsinki. The study was approved by the French Ethics Committee (Comité de  
625 Protection des Personnes Sud Méditerranée V) on 8<sup>th</sup> November 2016 and by the French National  
626 Agency for Medicines and Health Products Safety on 22<sup>th</sup> September 2016 (reference number ID  
627 RCB: 2016-A01034-47). The protocol was registered in ClinicalTrials.gov (NCT02866526).

## 629 DISSEMINATION

630 This study will allow to comprehend what the potential impact of transition from adolescence to  
631 adulthood could be in young PWH in France, which is of particular interest in the global approach  
632 whose goal is to take care of all aspects of life in patients with chronic diseases.

633 This study will also allow to identify determinants of adherence, considered as a marker of a  
634 successful transition in young PWH. The assessment of social, psychosocial and behavioural data, will  
635 allow to describe the socio-cognitive processes which may facilitate or complicate adherence, while  
636 taking into account other factors, *i.e.* medical, organisational, and socio-demographic factors. The  
637 results obtained from the quantitative phase of the study will be enlightened by the analysis of the  
638 interviews conducted in the qualitative phase. This analysis will bring supplementary and  
639 complementary data which would not have been accessible via the analysis of the questionnaires,  
640 especially concerning expectations and fears about health, but also about personal and professional  
641 life. Singular results from this qualitative phase could be used to better design a future quantitative  
642 study on the issue of transition, by assessing complementary outcomes to those assessed in the present  
643 quantitative phase.

644 Results will allow to propose recommendations and to develop interventions to compensate for young  
645 PWH difficulties, and thus optimize the adherence to the proposed follow-up and to the prophylactic  
646 treatment, but also facilitate their entry in the adult life. The effectiveness of such transitional  
647 programs could be improved by targeting specific patients at risk of difficulties (especially lack of  
648 adherence to health care) through the transition process, or by targeting specific needs expressed by  
649 young PWH in the present study.[18]

650 In order to assess the transferability of the results from the TRANSHAMO study in other contexts of  
651 childhood chronic diseases in France, complementary projects could be proposed to assess the issue of  
652 transition in young patients with rare and/or serious and/or chronic diseases. This approach would  
653 allow to identify which issues are common to these diseases and which ones are specific to a disease,

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3 654 including severe haemophilia. Common and specific actions could then be proposed to facilitate the  
4 655 transition process and support young patients.  
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## 656 **Authors' contributions**

657 NR, ABA, KB, TL, HC, PA contributed to the design of this study and wrote this article.  
658 The investigators (LA, SB, CB, M-AB, CB-A, AB-D, SC, PC, SCD, EDR, DD, CF, BF, VG, JG, YG,  
659 BG, AH, AH, YH, TL, AL, AL, MM, SM, FM, GM, CN, PN, PN, CO, BP-P, BP, AR, AR, DR, PS,  
660 AS, CS, BT, MT, J-BV, SV, FV, AV-E, BW) of the French Haemophilia Treatment Centres  
661 contribute to enrol participants, they revised the manuscript and approved the final version.  
662 Members of steering committee (NR-D, VM, TS) contributed to the design of this study, they revised  
663 the manuscript and approved the final version.

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16 702 **Competing interests**

17 703 None declared.  
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# BMJ Open

## Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSEMO): study protocol for a multicentric French national observational cross-sectional study.

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Determinants of adherence and consequences of the transition from adolescence to adulthood among young people with severe haemophilia (TRANSEMO): study protocol for a multicentric French national observational cross-sectional study.

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3 73 **ARTICLE SUMMARY**

4 74

5  
6 75 **Abstract**

7 76 Introduction: Severe haemophilia is a rare disease characterised by spontaneous bleeding from early  
8 77 childhood, which may lead to various complications especially in joints. It is nowadays possible to  
9 78 avoid these complications thanks to substitutive therapies for which the issue of adherence is major.  
10 79 The transition from adolescence to adulthood in young people with severe haemophilia is a critical  
11 80 period as it is associated with a high risk of lack of adherence to health care, which might have serious  
12 81 consequences on daily activities but also on quality of life.

13 82 Methods and analysis: We present the protocol for a cross-sectional, observational, multicentric study  
14 83 to assess the differences between adolescents and young adults with severe haemophilia in France  
15 84 through the transition process, especially on adherence to health care. This study is based on a mixed  
16 85 methods design, with two complementary and consecutive phases, comparing data from a group of  
17 86 adolescents (aged 14-17 years) to those from a group of young adults (aged 20-29 years). The  
18 87 quantitative phase focuses on the determinants (medical, organisational, socio-demographic and  
19 88 social, and psychosocial and behavioural factors) of adherence to health care (considered as a marker  
20 89 of the success of transition). The qualitative phase explores participants' views in more depth to  
21 90 explain and refine the results from the quantitative phase. Eligible patients are contacted by the various  
22 91 Haemophilia Treatment Centres participating in the French national registry FranceCoag.

23 92 Ethics and dissemination: The study was approved by the French Ethics Committee and by the French  
24 93 National Agency for Medicines and Health Products Safety (number: 2016-A01034-47). Study  
25 94 findings will be disseminated to the scientific and medical community in peer-reviewed journals and  
26 95 presented at scientific meetings. Results will be popularised to be communicated via the French  
27 96 association for people with haemophilia to participants and to the general public.

28 97 Trial registration number: NCT02866526

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30 99 Word count: 299

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32 101 **Keywords**

33 102 Adherence / Haemophilia / Transition / Adolescents / Young adults

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3 104 **Strengths and limitations of this study**

- 4 105 – This study will be the largest to assess the issue of transition from adolescence to adulthood  
5 106 among young people with haemophilia (PWH), and the first one in France where the features of  
6 107 the health care system are very specific.  
7  
8 108 – The cross-sectional design of the study comparing experiences reported by adolescents compared  
9 109 to those reported by young adults is a limitation, as it would have been pertinent to design a  
10 110 longitudinal study to follow up young PWH during their transition; however, as the transition  
11 111 process is long, it would have been very time consuming with a high risk of follow-up.  
12  
13 112 – This study will be based on an explanatory sequential mixed methods design, which will allow to  
14 113 bring complementary results by collecting and analysing quantitative and then qualitative data in  
15 114 two consecutive phases within one study.  
16  
17 115 – The main evaluation criterion of the quantitative phase will be the adherence to health care, a  
18 116 hypothesised marker of the success of transition, whose choice is debatable as it is a complex  
19 117 concept to measure and as it probably reflects only a part of the success of transition.  
20  
21 118 – Potential determinants will be selected according to the SMART theoretical model (Social-  
22 119 ecological model for adolescents and young adults readiness for transition), and will include both  
23 120 pre-existing objective factors and modifiable subjective factors (potential targets of intervention),  
24 121 whose associations with adherence to health care will be hypothesised from the quantitative  
25 122 phase, and more deeply explored and explained thanks to the qualitative phase.  
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33 124 Word count: 248

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## 126 INTRODUCTION

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128 Haemophilia is a rare and inherited disorder (X-linked recessive transmission), affecting mainly males  
129 (annual incidence: 1/5,000 male births).[1] It is characterized by bleeding due to a lack of clotting  
130 factors (factor VIII (FVIII) for haemophilia A or factor IX (FIX) for haemophilia B). Bleedings often  
131 start in early life, due to psychomotor skills acquisition. Seriousness of the symptoms depends on the  
132 severity of the lack of FVIII/FIX. Severe haemophilia, defined by a biological activity of FVIII/FIX  
133 lower than 1%, is characterized by spontaneous bleedings most frequently located into the joints  
134 (haemarthroses) and into the muscles (haematoma). Natural history of untreated severe haemophilia is  
135 marked by serious haemorrhagic events which compromise the vital prognosis. Insufficiently treated,  
136 repetition of haemarthroses and haematoma results in invalidating motor disability.

137 It is nowadays possible to avoid these complications thanks to substitutive therapies for which the  
138 issue of adherence is major, and to a lifelong regular clinical follow-up. Successive stages of the  
139 disorder's care management have been described by Young,[2] including:

- 140 – Adolescence: independence and responsibility for disease management, self-advocacy and  
141 disclosure, importance of treatment adherence, transfer of responsibilities from the caregivers to  
142 the patient
- 143 – Adulthood: decide whether to continue prophylaxis, challenge of dealing with a chronic disease  
144 and becoming one's own caregiver

145 The success of the transition from adolescence to adulthood may therefore be crucial in the  
146 maintenance of adherence to care.

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148 In the context of chronic diseases, the process of transition may be more complicated, as affected  
149 young people have to deal with a supplementary transition, from a paediatric health care system to an  
150 adult one.[3–6] Indeed, a successful transition involves a transfer of responsibilities from parents to  
151 patients concerning the management of their health, the acquisition of the knowledge, abilities, and  
152 self-reliance necessary to take on autonomy as well as the new roles people expect them to endorse as  
153 adults.[7, 8] Experiencing a difficult transition could be associated with a decrease in the level of  
154 adherence to care, but it might also impair quality of life and the entry into adulthood.[9, 10] In the  
155 framework of several chronic diseases (apart from haemorrhagic diseases), some studies highlighted  
156 barriers or facilitators to successful transition, either associated to the young patients, or to their  
157 parents, or to the various actors of the health care system.[11–14] Authors especially underlined  
158 psychosocial factors such as knowledge, skills, beliefs, expectations, goals, relationships, fears, need  
159 for control, emotional dependency, over-protectiveness, heightened awareness of health issues, lack of  
160 trust in caregivers.[13–16] The theoretical social-ecological model of AYA (adolescents and young  
161 adults) readiness for transition (SMART),[17] by identifying both pre-existing objective factors (less  
162 amenable to intervention, including socio-demographics/culture, access/insurance, health status/risk,



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3 163 neurocognition/IQ) and inter-related components of patients, parents and providers (potential targets  
4 164 of intervention, including development, knowledge, skills/self-efficacy, beliefs/expectations, goals,  
5 165 relationships and psychosocial functioning), has been proposed as the ideal framework to identify  
6 166 determinants (barriers and facilitators) of transition in the context of serious paediatric illness  
7 167 conditions.[14] Some interventions have been designed to improve the transition of care, and a  
8 168 Cochrane review assessing their effectiveness found that transitional programs might slightly improve  
9 169 transitional readiness (self-management skills and knowledge), but that they led to little or no  
10 170 difference in health status, quality of life or well-being.[18] The identification of barriers and  
11 171 facilitators to successful transition may help to design target interventions in order to improve their  
12 172 overall effectiveness.  
13 173

14 174 In the specific context of haemophilia, some studies have been conducted to assess the issue of  
15 175 transition in young people with haemophilia (PWH).[19] A study comparing quality of life in young  
16 176 PWH in pre-transition period with young PWH in post-transition period showed a lower quality of life  
17 177 and a higher level of distress in young PWH in post-transition period.[20] Some recommendations  
18 178 (involving patients, families, and caregivers) have been proposed to facilitate this process.[21–23]  
19 179 However, despite the setting up of some actions which have been shown to improve the disease  
20 180 specific knowledge,[24, 25] difficulties are still remaining, which may impair the health condition and  
21 181 the quality of life of young PWH.[26, 27] A study on the unmet needs reported by young adults  
22 182 highlighted psychological issues mainly related to independence achievement.[28] At the crucial age  
23 183 at which adolescents are often opposed or want to take their own decisions, maintaining the adherence  
24 184 to clinical follow-up and therapies is an important issue. A study conducted in young PWH (13-25  
25 185 years) found that 41% of them had not followed prescribed treatment.[29] Studies have shown a  
26 186 decrease in the level of adherence to the prescribed therapeutic regimen during transition. A study  
27 187 based on nurses-reported data found a decreasing level of adherence, from 90% for the youngest  
28 188 patients (0-12 years) to 54% for those aged 13-18 years and to 36% for those aged 19-28 years.[30]  
29 189 Caregiver or self-reported adherence assessment showed similar results, with a lower level of  
30 190 adherence in adults in comparison with paediatric patients (and among these latter, a lower level in  
31 191 adolescents in comparison with children).[31, 32] This lower adherence might have serious  
32 192 consequences, such as haemarthroses which may impair daily activities but also quality of life. A  
33 193 higher number of hemarthrosis was observed in less-adherent to prophylaxis patients aged 12 to 25  
34 194 years,[33] which was also observed when considering patients of all ages.[32, 34] Some psychosocial  
35 195 factors of the maintenance of a high adherence in young PWH have been highlighted, *e.g.* a greater  
36 196 perception of the need for prophylaxis than the concern over taking it, a positive expectancy of its  
37 197 effectiveness, a good social support, and a stronger emotional reaction to having haemophilia.[35] In  
38 198 the general framework of haemophilia (not focusing on the transition period), a review on  
39 199 determinants of adherence to prophylactic treatment identified both barriers (absence or infrequent

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3 200 symptoms, increasing age) and motivators (belief in necessity of treatment, good relationship with the  
4 201 health care provider, experience of symptoms).[36] Another review identified five key types of  
5 202 adherence barriers: patient-related factors (including age), condition-related factors, treatment-related  
6 203 factors, health-care system factors, and socioeconomic factors.[37]  
7  
8 204 Even if some literature data exists on the issue of transition and its impact on adherence to health care  
9 205 in the context of haemophilia, some limits may be discussed. The sample size of these studies is  
10 206 generally modest (below or about a hundred of patients).[35, 38, 39] An international larger study  
11 207 including 230 young PWH was conducted but all of them were young adults (aged 18-30 years), none  
12 208 were adolescents.[27] Adherence is usually assessed only through adherence to prophylactic treatment,  
13 209 which excludes young PWH under on-demand treatment.[35, 38, 39] None of these studies has been  
14 210 carried out in France where the features of the health care system are very specific. An international  
15 211 study showed that cost was a frequent reported barrier to prophylaxis (about 45% by both nurses from  
16 212 Haemophilia Treatment Centres and patients perspectives).[30] Thus, the assumption of all disease-  
17 213 related costs by the French social security system might influence the adherence to care. The backing  
18 214 of the French national registry FranceCoag[40] will allow to assess this issue in a large and exhaustive  
19 215 population of young PWH. This registry involves for more than 20 years French Haemophilia  
20 216 Treatment Centres (HTC), and it includes more than 10,000 patients (7,000 people with haemophilia  
21 217 (PWH), with 2,300 with severe haemophilia of all ages). Moreover, even if some psychological data  
22 218 have been related to the adherence to care, they are often analysed as independent factors. Taking into  
23 219 account the interdependence between these factors using adapted methods could bring original results.  
24 220 Finally, an explanatory sequential mixed methods designed study combining quantitative and  
25 221 qualitative methods will allow to address in a global way the issue of transition among young PWH,  
26 222 *i.e.* focusing not only on its facilitators and barriers but also, on all the specific concerns and  
27 223 difficulties young PWH may experience as they grow into adulthood.  
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## 225 OBJECTIVES

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227 The main objective of this study is to assess differences between adolescents and young adults with  
228 severe haemophilia in France, through the transition process, especially on adherence to health care.

229 The operational objectives of this study are:

- 230 – to compare the level of adherence in adolescents and in young adults (YA)
- 231 – to identify determinants (medical, organisational, socio-demographic and social, and psychosocial  
232 and behavioural factors) of the level of adherence in young PWH,
- 233 – to assess specific factors involved in suboptimal level of adherence in the sub-groups of  
234 adolescents and YA,
- 235 – to identify groups of patients (clusters) regarding both their level of adherence and their  
236 psychosocial characteristics,
- 237 – to examine through a qualitative approach statistical results which would have been brought to  
238 light according to the quantitative objectives, and to identify some ways to improve adherence to  
239 health care in young PWH and their global care.

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## 241 METHODS/DESIGN

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### 243 Study design

244 This study is designed as a multicentric (29 HTC from FranceCoag), observational, cross-sectional  
245 study, based on an explanatory sequential mixed methods design,[41–47] with two complementary  
246 and consecutive phases:

- 247 – The quantitative phase focuses on the determinants of adherence to health care (considered as a  
248 marker of the success of transition), and compares data from a group of adolescents to those from  
249 a group of YA, in order to provide a general understanding of the issue of adherence in young  
250 PWH,

251 The qualitative phase explores participants' views in more depth (few patients selected from the  
252 quantitative phase) to explain and refine the general understanding from the quantitative phase.

253 Interpretation and discussion of the global results will be done by integrating the results of both phases  
254 of the study.

255

### 256 Participants

#### 257 Inclusion criteria

- 258 – Patients with severe A or B haemophilia (deficiency <1%)
- 259 – Patients affiliated to the French social security system and included in the FranceCoag registry
- 260 – Patients followed in one of the 29 participating HTC

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3 261 – Patients aged 14-17 years (adolescents group), or aged 20-29 years (YA group)  
4 262 – Adolescents authorised to participate by their parents or their legal representatives, or YA who  
5 263 give their consent to participate in this study  
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9 265 *Non-inclusion criteria*

- 10 266 – Vulnerable patients (adults under guardianship, pregnant or nursing women)  
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12 267 Patients with reading and writing difficulties (as data collection in the quantitative phase is mostly  
13 268 based on participants' self-reported data collected through a booklet)

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15 269 *Period of the study*

16 270 The planned duration of the study is 30 months. Inclusions started in February 2017. The quantitative  
17 271 phase will go on for 18 months, the qualitative phase will go on for 10 months, and the last two  
18 272 months will focus on integrating results from both phases, in order to provide a global interpretation  
19 273 and discussion of the results of the study.  
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24 275 **Quantitative phase**

25 276 *Main evaluation criterion*

26 277 The main evaluation criterion is the adherence to clinical follow-up and prophylactic treatment (a  
27 278 hypothesized marker of the success of transition into adulthood), which will be assessed via the  
28 279 following items:

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31 280 – number of follow-up visits in agreement with the recommended number over the last two years,  
32 281 – number of prophylactic treatment injections in agreement with the recommended number over the  
33 282 last three months (if applicable),  
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35 283 – number of haemorrhagic events over the last two years,  
36 284 – physician-reported adherence to clinical follow-up and to prophylactic treatment (if applicable),  
37 285 – patient-reported adherence to clinical follow-up and to prophylactic treatment (if applicable).

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40 286 Each item will be dichotomized, and a composite quantitative endpoint will be constructed taking into  
41 287 account all these dichotomized items. This composite quantitative endpoint will in turn be  
42 288 dichotomized to define adherent / non-adherent participants (main evaluation criterion).  
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46 290 *Secondary evaluation criteria*

47 291 Each item which is part of the composite endpoint as described hereinabove will be considered in an  
48 292 independent manner as a secondary evaluation criterion.  
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295 *Explanatory collected data*

296 *Medical data*

297 Medical data will include: deficit characterisation, diagnosis (age at diagnosis, circumstances of  
298 diagnosis, family history), viral diseases (HIV, HBV, HCV), comorbidities (intracranial haemorrhage,  
299 major orthopaedic interventions, major disability, cancer, other chronic pathology), previous and  
300 current treatment.

301

302 *Organisational data (Haemophilia Treatment Centres-reported)*

303 Organisational data will include: paediatric / adult / paediatric and adult HTC, physicians' speciality,  
304 mean age of the transition from paediatric care to adult one, consultations dedicated to the transition,  
305 common consultations with both paediatric and adult medical teams, specific tools set up to facilitate  
306 the transition process (information leaflet, therapeutic patient education).

307

308 *Socio-demographic and social data*

- 309 – Gender and age of family members, living situation,
- 310 – Socio-professional category, socio-economic status assessed by the Family Affluence Scale,[48]
- 311 – Distance to the HTC (in km),
- 312 – Membership of French patients association for PWH (AFH),
- 313 – Family functioning (structure, organisation, and communication) assessed by the French validated  
314 version of the 6-items Family Assessment Device,[49–51]
- 315 – Schooling and academic success evaluated by ad-hoc items (schooling type, level of education,  
316 academic difficulties),
- 317 – Relationships with the health care system assessed using ad-hoc items (satisfaction and  
318 expectations towards the health care system, participation in therapeutic patient education  
319 programme).

320

321 *Psychosocial and behavioural data*

- 322 – Quality of life will be assessed using the validated French version of the SF-12 generic scale.[52]  
323 Two sub-scores, mental health and physical health, will be calculated. The SF-12 allows assessing  
324 the quality of life of adults as well as adolescents (14 + years).

- 325 – Quality of life of adolescents will also be assessed by the validated French version of  
326 the 10-items Kidscreen Index, which explores the following domains: physical well-  
327 being, psychological well-being, autonomy and relations with parents and home life,  
328 peers and social support, and school environment.[53]
- 329 – Haemophilia-specific quality of life will be assessed in all participants using the  
330 validated French short version of the Haemo-Qol questionnaire.[54, 55]

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3 331 – Time perspective will be assessed using the Past Negative (PN) and Future (F) subscales of the  
4 332 French validated version of the Zimbardo time perspective inventory.[56, 57] The PN subscale (9  
5 333 items) reflects a pessimistic attitude towards the past and the experience and memory of traumatic  
6 334 life events. The F subscale (12 items) reflects an orientation towards future and an attitude of  
7 335 planning and achievement of objectives. To avoid the questionnaire being too long, we will not  
8 336 plan to assess the Past-Positive, Present-Hedonistic, and Present-Fatalistic subscales.
- 9  
10  
11 337 – Coping Strategies will be measured by the validated French version of the Brief-Cope scale[58,  
12 338 59] which consists of 28 items assessing individuals' use of 14 coping strategies: self-distraction,  
13 339 active coping, denial, drug use, emotional social support seeking, instrumental social support  
14 340 seeking, behavioural disengagement, emotional expression, positive reframing, planning, humour,  
15 341 acceptance, religion, and self-blame.
- 16  
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18 342 – Autonomy will be assessed using ad-hoc items only proposed in the YA questionnaire (financial  
19 343 independence from the parents, and living, management of health, dealing with administrative  
20 344 tasks, and taking holidays without the parents). The 15-items Noom validated questionnaire[60,  
21 345 61] assessing attitudinal autonomy, emotional autonomy, and functional autonomy will be  
22 346 proposed to all participants (ad-hoc translation for this study).
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#### 28 348 *Data collection procedure*

29 349 Main medical data will be extracted from the FranceCoag database, and completed by a short  
30 350 questionnaire filled in by the referent physician from each HTC. Organisational data will be completed  
31 351 by a medical representative from each HTC. Eligible participants will be identified and approached by  
32 352 the HTC team by which they are followed (approach either during a medical consultation, or by phone  
33 353 call, or by a personalised mail sent at their home). Survey documents (information sheet, informed  
34 354 consent form, booklet, and prepaid envelope) will then be sent by post to eligible young PWH.  
35 355 Participants' self-reported data will be collected through a standardised booklet including several  
36 356 questionnaires (an adolescent version and a YA version). Consent will be collected through the  
37 357 signature of the informed consent form by the parents or the legal representatives for adolescents, and  
38 358 by the signature of the YA directly for YA. Completed questionnaires as well as signed informed  
39 359 consent forms will be sent back by the participants via the supplied prepaid envelope. If no response is  
40 360 received within 30 days, a reminder letter will be sent. A second reminder letter and all survey  
41 361 documents along will be sent two months later in case of no response.

#### 42 362 43 363 *Sample size justification*

44 364 According to the exhaustive FranceCoag database and considering the specific inclusion criteria of the  
45 365 TRANSHMO study (severe A or B haemophilia, patients aged 14-17 or 20-29 years, followed in one  
46 366 of the 29 participating HTC), 154 adolescents and 389 YA are eligible for this study. We hypothesised  
47 367 a difference of 20% between adolescents and YA regarding the main evaluation criterion (90% of

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3 368 adherence to health care in adolescents vs 70% in YA). Then, under the hypothesis of a non-response  
4 369 rate of 30%, and considering a bilateral alpha risk of 5%, the power of this study would reach  
5 370 99%.[62, 63]  
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#### 8 372 *Data Management*

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10 373 A specific database will be created using EpiData software, and merged with the FranceCoag  
11 374 database. A process will be used to assign to each participant a unique anonymous number. A data  
12 375 quality control will be performed by a physician to limit data inconsistency.  
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#### 15 377 *Analysis*

16  
17 378 The analysis plan and the final report will be written according to the STROBE recommendations.[64,  
18 379 65] All analyses will be performed using R software. All tests will be two-sided, and  $p < .05$  will define  
19 380 statistical significance.  
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#### 22 382 *Analysis populations*

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24 383 The analysis populations will be the adolescents and the YA groups, among whom adherent and non-  
25 384 adherent patients will be identified.  
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#### 28 386 *Descriptive analysis*

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30 387 A descriptive analysis will first be performed. Qualitative variables will be presented as numbers and  
31 388 percentages, quantitative variables as means and standard deviations, or as medians and interquartile  
32 389 ranges. Subjective data will be described by their overall scores and their sub-scores.  
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35 391 Reasons for non-inclusion will be listed. Included patients will be compared to non-included eligible  
36 392 patients using basic socio-demographic and clinical data, available in the FranceCoag database.  
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#### 39 394 *Comparative analysis*

##### 40 395 *Crude analysis*

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42 396 Adherence will first be described by groups (adolescents / YA) using classical indicators. The  
43 397 comparison of adherence between the two groups will be performed using chi-square test (or Fisher  
44 398 test depending on the expected numbers) for the main evaluation criterion and for all qualitative  
45 399 secondary evaluation criteria, and using Student t test (or Mann-Whitney test depending on normality  
46 400 of the distribution) for quantitative secondary evaluation criteria.  
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##### 49 402 *Adjusted analysis*

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51 403 In order to identify factors associated with adherence, bivariate and multivariate analyses will be  
52 404 performed. Potential determinants (medical, organisational, socio-demographic and social,  
53 405 psychosocial and behavioural factors) will be proposed as explanatory variables. Logistic regression  
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55 406

models will be used for the main evaluation criterion and for all qualitative secondary evaluation criteria, and linear regression models will be used for quantitative secondary evaluation criteria. Each characteristic whose degree of significance will be lower than .20 will be considered for multivariate analyses. A backward selection will be applied to retain only significantly associated characteristics. Multilevel models will be used to take into account organisational factors which are related to the centre. Structural equation modelling will be considered to take into account the collinearity and/or the complex relationships which might exist between explanatory individual characteristics (especially social, psychological and behavioural ones).[66–68]

This analysis will first be performed in the overall population with a forced adjustment on the group (adolescent / YA). It will secondly be performed independently in each of the two groups.

#### *Cluster analysis*

In order to bring to light particular profiles of adherent / non-adherent in adolescents and in YA, an exploratory unsupervised classification analysis will be performed.[69, 70] This method which does not require any condition of validity will allow to gather patients with similar profiles in homogeneous clusters.

### **Qualitative phase**

#### *Data collection procedure*

Few subjects (adolescents on one hand and YA on the other hand) who will have participated in the quantitative phase will be selected for this phase according to the following characteristics (assessed from the quantitative phase): adherent or not, and under prophylaxis or not. If they agree, they will be contacted to participate in research interviews conducted by a psychologist, at any place at their convenience (at home, at the HTC...). The interviews will be individual, confidential, semi-structured, and tape-recorded. The psychologist will be blind to the responses in the questionnaires of the participant, and to his/her status adherent / non-adherent as defined according to the main evaluation criterion of the quantitative phase.

The psychologist will start with a general question, then he/she will adopt a non-directive attitude and will allow the participant to spontaneously and freely broach the answers which they consider relevant. Then he/she will summarise the response and introduce more precise questions regarding the topics which will have not been covered spontaneously or sufficiently by the participant. He/she will seek to focus the interview on the participant's personal experiences, subjective perceptions, and expectancies, in order to understand if the patient is adherent / non-adherent and the possible determinants of this adherence. The interview guide will be refined from the findings from the quantitative phase, in order to collect more specifically data about potential determinants and adherence to health care brought to light from the quantitative phase.



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3 442 *Adolescents' interviews*

4 443 The interview will begin with this general question: "How do you feel about coming into adulthood in  
5 444 a few years?"

7 445 After the spontaneous answer, the psychologist will encourage them to talk about the following topics:  
8 446 the meaning they give to becoming a YA; their expectations towards their life (personal and  
9 447 professional) as future YA; their plan to care about their health as future YA; their fears towards their  
11 448 entry into adulthood.

13 449

14 450 *Young adults' interviews*

16 451 The interview will begin with this general question: "How do you feel about reaching adulthood  
17 452 during the last few years?"

19 453 After the spontaneous answer, the psychologist will encourage them to talk about the following topics:  
20 454 the meaning they give to becoming a YA; their experienced difficulties towards the acquisition of their  
21 455 autonomy (especially concerning the management of their health) and the construction of their life  
22 456 (personal and professional); the facilitators and barriers they identified during their transition process.

25 457 Then, to go further and broaden these qualitative data, the psychologist will show to these participants  
26 458 a summary of the adolescents' expectations towards adulthood (from the interviews conducted in  
27 459 adolescents, which therefore will be carried out and analysed before those in YA). The psychologist  
28 460 will then ask YA to assess: to what extent these perceptions match with their own expectations when  
29 461 they were adolescents; to assess to what extent these perceptions match with their current lives; and to  
30 462 indicate which issues regarding transition adolescents forget to mention.

32 463

34 464 *Sample size justification*

35 465 Four profiles will be identified from the two selected characteristics (adherent or not, and under  
36 466 prophylaxis or not). On the basis of three interviews by profile, up to 12 adolescents and 12 YA will  
37 467 be selected for the qualitative phase (enrolments until information is saturated).

39 468

41 469 *Data Management*

42 470 All interviews will be precisely and entirely transcribed, including the participants' hesitations and  
43 471 self-corrections.

44 472

45 473 *Analysis*

46 474 The psychologist will analyse adolescents' interviews on one hand and YA ones on the other hand,  
47 475 using Interpretative Phenomenological Analysis (IPA) method. This method allows to comprehend the  
48 476 participants' subjective experiences through the analysis they make of (and the meaning they give to)  
49 477 their feelings and states, as well as the specific events they are faced with. It makes possible to

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3 478 highlight sociocognitive processes by which personal experiences are assimilated to individuals'  
4 479 perceptions of both themselves and the world they live in.[71, 72]

5 480 IPA of an interview is made of four iterative stages. During the first stage, the psychologist will read  
6 481 the interview several times, annotating, summarising, paraphrasing, and commenting on what is  
7 482 interesting or significant. The second stage will consist in encoding those annotations to a slightly  
8 483 higher level of abstraction by theoretical and scientific elements: the psychologist will underline the  
9 484 themes addressed by the participant. At the third stage, the psychologist will try to connect these  
10 485 themes by grouping them into superordinate clusters while checking that the connections they make  
11 486 match the meaning of the participant's speech. The last stage of the analysis will consist in giving a  
12 487 scientific meaning to the established clusters.

13 488 The same method will be used for all participants within each group, with the permanent goal of  
14 489 improving the previously identified clusters. Each time a new element is identified, or each time a  
15 490 theme or a cluster is modified, the psychologist will get back to previously analysed interviews to  
16 491 ensure that the new model accounts for the speech of all participants.

17 492 According to the interpretation of each interview, the psychologist will have to determine the status  
18 493 adherent / non-adherent of each participant. Thus, the identified clusters of themes will be put in  
19 494 perspective with the psychologist-determined status towards adherence, in order to propose a model  
20 495 describing the relationships between adherence to health care and its determinants.

21 496 Finally, when all interviews will have been analysed, a summary will be made, by underlining  
22 497 similarities and differences between adolescents and YA regarding adherence to health care and its  
23 498 determinants, and transition into adulthood and its consequences on their lives.

24 499 Analyst triangulation will be performed,[73, 74] by involving two psychologists in reviewing the  
25 500 findings in order to assess the reliability and validity of the obtained results. This triangulation may  
26 501 also allow to develop a broader and deeper understanding of the results.

27 502

### 28 503 **Interpretation**

29 504 Interpretation and discussion of the global results of the study will be done by integrating the results of  
30 505 both phases of the study. From participants who will have been considered consistently according to  
31 506 both quantitative and qualitative phases either as adherent or as non-adherent, hypothesized  
32 507 associations between potential determinants and adherence from the quantitative phase will be  
33 508 therefore confirmed or infirmed thanks to the results of the qualitative phase. Thus, combining the  
34 509 quantitative and qualitative findings will help explain the results of the statistical results, which  
35 510 underscores the elaborating purpose for a mixed-methods sequential explanatory design. [45, 75]

36 511 Participants who will not have been considered consistently either as adherent or as non-adherent will  
37 512 allow to discuss representations and beliefs about adherence in the context of haemophilia, and the  
38 513 relevance of this outcome to assess the success of transition through quantitative studies.

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3 515 **Patient and public involvement**

4 516 The development of the research question, study design and outcome measures involved interpretation  
5 517 of literature, professional experience reported through the clinicians, nurses, and psychologists  
6 518 working in the various Haemophilia Treatment Centres participating in the French national registry  
7 519 FranceCoag, and patients' priorities and experience reported through the French association patients  
8 520 association for PWH (AFH) that is member of the steering committee of the study. Patients will not be  
9 521 directly involved in the recruitment, but the AFH will regularly communicate about the study (internet,  
10 522 newsletters, social networks, magazine...) to inform eligible participants in order to maximise the  
11 523 recruitment. Results will be popularised to be communicated via the AFH to participants and to the  
12 524 general public.  
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## 526 DISCUSSION AND LIMITATIONS

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### 528 Strengths and limitations of the database

529 As the issues concerning transition into adulthood may intrinsically depend on features of the health  
530 care system, we intend to explore the specific perceptions of young PWH in France, whose health care  
531 system model is specific. The support of the FranceCoag registry to this study is therefore an  
532 important strength. While the exhaustivity of inclusions in this registry might have been an issue for  
533 patients with moderate or minor haemophilia, the exhaustivity concerning patients with severe  
534 haemophilia is guaranteed since 2000. Even if five HTC over the 34 active ones (*i.e.* 15%) did not  
535 accept to participate in the TRANSEMO study, the loss of eligible patients was small (only 4% of  
536 the eligible young PWH). The comparison of basic socio-demographic and medical data, available in  
537 the FranceCoag database, between included patients and non-included eligible patients will allow to  
538 discuss the representativeness of the included sample. Moreover, the implication of clinicians, nurses,  
539 psychologists, and clinical research associates in both the clinical follow-up of patients and this study  
540 via their participation in the FranceCoag registry will help to maximise the recruitment and limit the  
541 risk of dropouts for this study. The French patients association for PWH (AFH), member of the  
542 steering committee of the FranceCoag registry, will also regularly communicate about the study  
543 (internet, newsletters, social networks, magazine...) to inform eligible participants in order to  
544 maximise the recruitment.

545

### 546 Strengths and limitations of the study design

547 The quantitative phase of this study is cross-sectional, while it would have been pertinent to design a  
548 longitudinal study to follow up young PWH during their transition. However, as this process is  
549 long,[2] it would have been very time consuming, with a high risk of lost to follow-up. We therefore  
550 chose to compare at a unique time the experiences of two groups regarding their status towards  
551 transition. If the results of the present cross-sectional study turned out to be singular, they could justify  
552 to secondly set a longitudinal study up.

553 The explanatory sequential mixed methods design, [41–47] by combining quantitative and qualitative  
554 methods, will bring original results. The first quantitative phase will allow to adjust the second  
555 qualitative phase, by the targeted selection of participants (adherent / non-adherent participants  
556 according to main evaluation criterion) and by bringing results to be discussed with participants. The  
557 qualitative phase will then allow to shed light on the results from the quantitative phase (based on self-  
558 reported questionnaires data) by a deeper analysis of participants' experiences collected through  
559 interviews conducted by a psychologist, especially for psychosocial and behavioural factors which  
560 will have emerged from the quantitative phase. This qualitative phase could also be a starting point for  
561 a future longitudinal and quantitative study, by highlighting unexplored processes by the present  
562 quantitative phase. The step of integration and mixing of the results from both phases of the study will

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3 563 allow to more fully answer the question of adherence to health care through the period of transition to  
4 564 adulthood in the context of severe haemophilia, and to develop a more robust and meaningful picture  
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6 565 of this issue. Combining the quantitative and qualitative findings will help both to explain  
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8 566 relationships between adherence to health care and its determinants, and to discuss representations and  
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10 567 beliefs about adherence, a quantitative outcome which was considered as a marker of the success of  
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12 568 transition.  
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### 15 570 **Strengths and limitations of the endpoints**

16 571 The main objective of the study is to assess the potential impact of transition from adolescence to  
17 572 adulthood, which we chose to measure by the level of adherence to health care. This choice is  
18 573 debatable, as maintaining a high level of adherence to care probably reflects only a part of the success  
19 574 of the transition process. However, this choice is justified by several arguments: (i) it is necessary to  
20 575 propose an endpoint which applies for both adolescents and YA, in order to be able to assess through a  
21 576 transversal study the potential impact of the transition on a common endpoint, (ii) a decrease of  
22 577 adherence during the transition process may be associated with clinical consequences (serious  
23 578 bleedings), [32–34] which may impair physical and psychological quality of life in young PWH, (iii)  
24 579 this endpoint allows to assess more specifically the potential impact of the supplementary transition  
25 580 experienced by young PWH, a transition from a paediatric health care system to an adult one, (iv) this  
26 581 endpoint was in the top five of health care transition outcomes identified by a Delphi process with an  
27 582 interdisciplinary group of medical and psychosocial professionals,[76] and (v) this endpoint may be  
28 583 accessible for educational actions. Adherence is a concept which might be defined by the agreement  
29 584 between the behaviour of a patient and the received recommendations or prescriptions.[77] We chose  
30 585 to assess adherence to prophylactic treatment, which is the commonly used evaluation criterion when  
31 586 assessing adherence in haemophilia[29, 35] but which would have been valid only for young PWH  
32 587 under prophylactic treatment. We therefore also chose to assess adherence to clinical follow-up, which  
33 588 is valid for all young PWH (even if the rhythm of visits might be different depending on their personal  
34 589 situation). Moreover, we chose to collect data on adherence through three sources of information: (i)  
35 590 data from the FranceCoag database (follow-up visits, injections of prophylactic treatment,  
36 591 haemorrhagic events), (ii) referent physician-reported data, and (iii) patient-reported data. A composite  
37 592 endpoint combining these items will allow to take into account the complexity of the assessment of  
38 593 adherence, in particular by mixing clinical and objective data with behavioural and subjective  
39 594 adherence-related data. The dichotomisation of this composite endpoint to define adherent and non-  
40 595 adherent young PWH will lead to a loss of variability in the data, but this choice will allow to get more  
41 596 accessible data and results. As the issue of variability is sensitive, each secondary endpoint (i.e., each  
42 597 variable included in the composite endpoint) will be analysed according to its original response format  
43 598 (binary, semi-quantitative, quantitative), independently of each other.  
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## 600 **Strengths and limitations of the determinants**

601 In this study, the choice of the determinants to be assessed (determinants of adherence to health care,  
602 considered as a marker of the success of transition) was based on literature data in the context of  
603 haemophilia,[35–37] and this choice was consistent with the theoretical SMART model.[17] This  
604 model proposes both potential barriers and facilitators, but also both pre-existing and modifiable  
605 factors, more amenable to intervention, including beliefs/expectations related-factors (time  
606 perspective) and psychosocial functioning related-factors (coping strategies and family functioning).

607 Time perspective refers to how individuals partition their experiences into distinct temporal categories  
608 of past, present and future.[78] Particular temporal frames may be associated with well-being and  
609 quality of life.[79] Indeed, focusing on a “past negative” time perspective may result in negative long-  
610 term adjustment and post-traumatic stress symptomology.[80] On the contrary, “future” time  
611 perspective has been viewed as the more constructive time perspective.[79]

612 Moreover, people (patients and relatives) faced with a severe chronic childhood disease generally  
613 experience repeated stress reactions because the disease questions individuals about their beliefs,  
614 identity, priorities, and short-term and long-term goals.[81, 82] The coping strategies individuals  
615 implement to deal with these stress reactions have been studied. Studies show that an individual's  
616 inability to implement appropriate coping strategies, or the use of strategies targeting only emotional  
617 responses (instead of their cognitive antecedents), are responsible for emotional disorders and  
618 impaired familial and social relationships. On the contrary, long-term well-being may be facilitated by  
619 the use of coping strategies which allow people restructuring their concepts, beliefs, values, priorities,  
620 standards, and personal goals.[82–86]

621 Finally, growing into adulthood implies that young people gain autonomy, get independent and  
622 endorse the responsibilities falling to adults. This personal empowerment implies that they develop  
623 their own personal values and long-term goals (attitudinal autonomy) and implement effective  
624 strategies to achieve these goals (functional autonomy). However, this ability to develop autonomy  
625 depends on the capacity to maintain confidence in one's own values and goals (emotional  
626 autonomy).[60, 87] We assume the development of autonomy (especially emotional autonomy)  
627 largely depends on the family functioning: parenting style, cohesiveness, flexibility, roles  
628 management, and communication of emotion.[49, 88–90]

629

**630 ETHICS**

631

632 Informed written consent will be obtained for all participants prior to recruitment for the study. For  
633 adolescents, consent will be obtained from their two parents or from their legal representatives, in line  
634 with the French laws and regulations. All data will be analysed confidentially and anonymously.

635 The study was designed according to Good Clinical Practices, and all procedures will be in accordance  
636 with the Declaration of Helsinki. The study was approved by the French Ethics Committee (Comité de  
637 Protection des Personnes Sud Méditerranée V) on 8<sup>th</sup> November 2016 and by the French National  
638 Agency for Medicines and Health Products Safety on 22<sup>th</sup> September 2016 (reference number ID  
639 RCB: 2016-A01034-47). Data collection, recording, and analysis process was approved by the French  
640 Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés,  
641 authorisation number 918045), and this approval was in line with the General Data Protection  
642 Regulation principles. The protocol was registered in ClinicalTrials.gov (NCT02866526).

643

**644 DISSEMINATION**

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646 This study will allow to comprehend what the potential impact of transition from adolescence to  
647 adulthood could be in young PWH in France, which is of particular interest in the global approach  
648 whose goal is to take care of all aspects of life in patients with chronic diseases.

649 This study will also allow to identify determinants of adherence, considered as a marker of a  
650 successful transition in young PWH. The assessment of social, psychosocial and behavioural data, will  
651 allow to describe the socio-cognitive processes which may facilitate or complicate adherence, while  
652 taking into account other factors, *i.e.* medical, organisational, and socio-demographic factors. The  
653 results obtained from the quantitative phase of the study will be enlightened by the analysis of the  
654 interviews conducted in the qualitative phase. This analysis will bring supplementary and  
655 complementary data which would not have been accessible via the analysis of the questionnaires,  
656 especially concerning expectations and fears about health, but also about personal and professional  
657 life. Singular results from this qualitative phase could be used to better design a future quantitative  
658 study on the issue of transition, by assessing complementary outcomes to those assessed in the present  
659 quantitative phase.

660 Results will allow to propose recommendations and to develop interventions to compensate for young  
661 PWH difficulties, and thus optimize the adherence to the proposed follow-up and to the prophylactic  
662 treatment, but also facilitate their entry in the adult life. The effectiveness of such transitional  
663 programs could be improved by targeting specific patients at risk of difficulties (especially lack of  
664 adherence to health care) through the transition process, or by targeting specific needs expressed by  
665 young PWH in the present study.[18]

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3 666 In order to assess the transferability of the results from the TRANSHEMO study in other contexts of  
4 667 childhood chronic diseases in France, complementary projects could be proposed to assess the issue of  
5 668 transition in young patients with rare and/or serious and/or chronic diseases. This approach would  
6 669 allow to identify which issues are common to these diseases and which ones are specific to a disease,  
7 670 including severe haemophilia. Common and specific actions could then be proposed to facilitate the  
8 671 transition process and support young patients.  
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For peer review only



**673 Authors' contributions**

674 NR, ABA, KB, TL, HC, PA contributed to the design of this study and wrote this article.  
675 The investigators (LA, SB, CB, M-AB, CB-A, AB-D, SC, PC, SCD, EDR, DD, CF, BF, VG, JG, YG,  
676 BG, AH, AH, YH, TL, AL, AL, MM, SM, FM, GM, CN, PN, PN, CO, BP-P, BP, AR, AR, DR, PS,  
677 AS, CS, BT, MT, J-BV, SV, FV, AV-E, BW) of the French Haemophilia Treatment Centres  
678 contribute to enrol participants, they revised the manuscript and approved the final version.  
679 Members of steering committee (NR-D, VM, TS) contributed to the design of this study, they revised  
680 the manuscript and approved the final version.

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