Non-Interventional Studies: From Data Collection to Reliable Insights

Workshop on the use of external controls for evidence generation in regulatory decision-making

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Non interventional Studies

Non-interventional study (NIS)

What is it?

A **NIS*** is a clinical study that does not fulfil any of the conditions defining a clinical trial (CT) in Article 2.2 of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Also known as **Observational study**, it is a type of study in which all participants receive routine clinical care and are not assigned per protocol to a specific treatment or health intervention.

Key Characteristics:

- Treatment and patient management follow **normal clinical practice.**
- No predefined assignment to a treatment group.
- Data is collected through **observational methods.**
- Contrast with clinical trials, which involve a pre-specified intervention.

Regulatory Context:

- EMA and national authorities recognize NIS as source of Real-World Evidence (RWE)
- Key guidelines: EMA Reflection paper on use of RWD in NIS for regulatory purposes
- Not subject to same approval process as interventional trials
- Must still adhere to strict ethical and scientific standards
- **Data quality is paramount for regulatory acceptance**

Ethical & Scientific Standards

Ethical Standards

Informed Consent: Patients must give informed and voluntary consent to have their data collected and used for research purposes

Ethics Committee Review: Most NIS require review and positive opinion from local or central ethics committee (IRB)

Data Protection: Must comply with regulations like EU's GDPR

Participant Rights: Ensure rights, safety, and well-being are protected

Scientific Standards

Rigorous Methodology: Clear research question, well-defined study population, robust statistical analysis plan to minimize bias

Data Quality Framework: Strong protocol with data validation, quality control checks, strategy for handling missing or inconsistent data

Transparency: Protocol and results publicly registered to ensure transparency and prevent selective reporting

Why Data Quality Matters

RWE from NIS is no longer “nice-to-have”—it’s a critical tool for regulatory decision-making

Informing Regulatory Decisions

Study medicine’s use in routine practice: long-term safety & effectiveness, broader patient populations (elderly, children, co-morbidities), benefit-risk profile in real world

Building Trust

Confidence in data for positive regulatory decisions (marketing authorization, label updates, safety measures). Poor quality data → misleading conclusions

Fit-for-Purpose Principle

Data quality must be high enough to support the specific regulatory question being asked

Common Challenges in NIS

Data Completeness & Consistency

Real-world data collected for clinical care, not research

Significant gaps (vital signs, lab tests, adverse events)

Doctor may not record if not clinically relevant

Bias & Confounding

Selection Bias: Non-random patient characteristics

Confounding: External factors (e.g., wealth → better care)

No randomization to balance groups

Data Source Complexity

Disparate sources (EHRs, claims, registries)

Different coding systems, or type of data collected

Complex harmonization required

Mitigation Strategies

📋 Robust Study Protocol

Foundation: clearly define research question, study population, variables to collect, statistical analysis plan. Anticipate challenges and outline handling of missing data or confounding

✓ Data Quality Framework

Formal procedures and tools: validation rules (for edit checks), quality control checks to identify outliers and inconsistent data points
Careful review

📊 Standardized Data Entry

Remove ambiguity and improve consistency. Eg. Use pre-defined drop-down lists and standardized codes

🔍 Proactive Planning

Anticipate challenges and build mitigation strategies directly into protocol from the start

An example : BH29768 study

NIS for patients with Hemophilia A

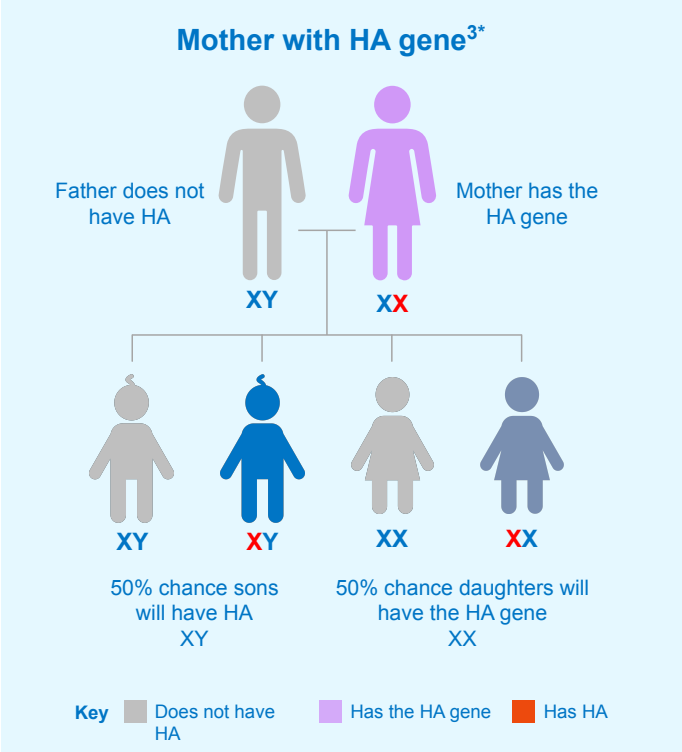
What is haemophilia A (HA)?

Congenital HA is a rare bleeding disorder characterised by a lack or deficiency of clotting factor FVIII[1]

- Being an X-linked recessive hereditary disorder, HA is far more common in males[2]
- Females can inherit HA when they have the gene in both of their X chromosomes (one from each parent)[3]

Haemophilia can cause frequent spontaneous and traumatic bleeding, typically into the joints, muscles and soft tissues[4]

- Recurrent bleeds, particularly into the joints, leads to long-term complications, such as debilitating haemophilic arthropathy and an overall reduced quality of life[5,6]



FVIII, factor VIII; HA, haemophilia A.

*Adapted from Zimmerman B & Valentino LA. Hemophilia: in review. *Pediatr Rev*. 2013;34(7):289–295.

1. Berntorp E, et al. *Nat Rev Dis Primers*. 2021;7(1):45; 2. Shoukat H, et al. *Cureus 2020;*12(10):e112164; 3. Miller CH, Bean CJ. *Haemophilia*. 2021;27(2):e164–e179; 4. Srivastava, A, et al. *Haemophilia*. 2020;26 (Suppl 6): 1–158; 5. Knobe K & Berntorp E. *J Comorb*. 2011;1:51–59; 6. Soucie JM, et al. *Haemophilia*. 2017;23:e287–e293.

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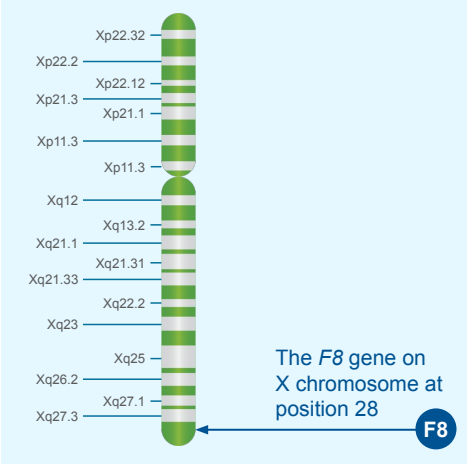
What causes haemophilia A?

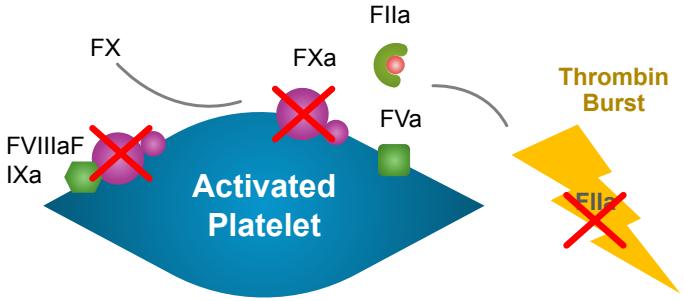
HA is caused by a mutation in the *F8* gene that results in FVIII deficiency[1]

- The type of mutation in *F8* determines the clinical sequelae of HA, with larger mutations associated with more severe phenotypes[2]



Coagulation factors, such as FVIII, are essential to blood clot formation[3]

- Absence or dysfunction of FVIII prevents activation of FX[4,5]
- Activated FX is needed to generate the thrombin burst[4–6]
- Without the thrombin burst, not enough thrombin is generated to create adequate fibrin, resulting in weak, leaky clots[4–6]



FVIII, factor VIII; FVIIIa, activated factor VIII; FX, factor X; HA, haemophilia A

Figure adapted from. Ho KM & Pavey W. Anaesth Intensive Care. 2017;45(2):166–176. 1. Berntorp E, et al. *Nat Rev Dis Primers*. 2021;7(1):45; 2. Castaman G & Matino D. *Haematologica*. 2019;104(9):1702–1709; 3. Barmore W, et al. *Biochemistry, Clotting Factors*. [Updated 2023 Feb 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507850. [Accessed November 3, 2023]; 4. Reyes M. In: Transfusion Medicine and Hemostasis: Clinical and Laboratory Aspects. 3rd ed. Elsevier; 2019:559–564; 5. Negrier C, et al. *Blood Rev*. 2019;38:1–8; 6. Ho KM & Pavey W. *Anaesth Intensive Care*. 2017;45(2):166–176.

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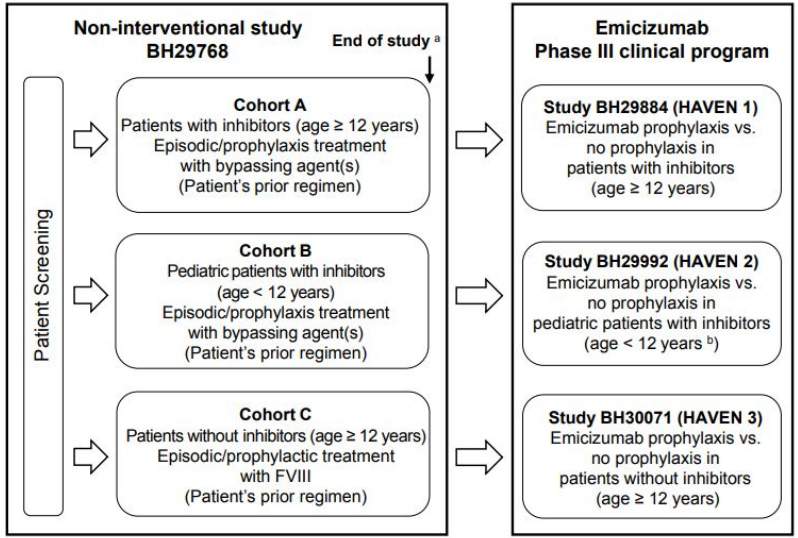
Case Study : The BH29768 Trial

This non-interventional study (NIS) was conducted to prospectively collect **bleed and bleed medication information** in patients with hemophilia A.

- The first prospectively conducted NIS, collecting **high-quality data** on the entire spectrum of relevant outcomes in this patient population.
- The **robust and complete data collected** from this NIS contrast with the non-standardized nature of data collection in routine clinical practice, the latter of which likely underrepresents the true burden of this disease.
- This study was conducted to:
  - inform the design and facilitate the interpretation of results from the emicizumab interventional studies,
  - provide data to allow for **true intra-patient comparisons** (controlling for confounding factors) within the emicizumab Phase III studies,
  - provide new and rigorous scientific information of high relevance for the hemophilia community.

Study Design



Notes: The total number of patients enrolled into the episodic or prophylactic groups in the non-interventional study was fixed by the study design and does not reflect the real-life distribution of patients across countries. Patients who were compliant with Study BH29768 could proceed to enroll in the emicizumab Phase III studies as soon as these opened for enrollment, provided they fulfilled the inclusion criteria. Eligibility criteria were similar among the NIS cohorts and respective Phase III studies in order to maximize the number of patients eligible to transition to the Phase III studies.

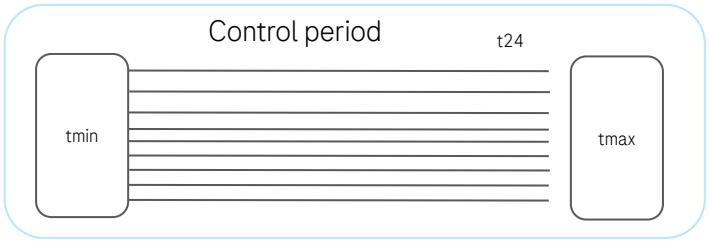
[a] The end of study was the last patient last assessment, which was the later of the following: Last patient was followed for 6 months (3 months if the last patient is 0 – 2 years of age) or switched to one of the emicizumab interventional studies.

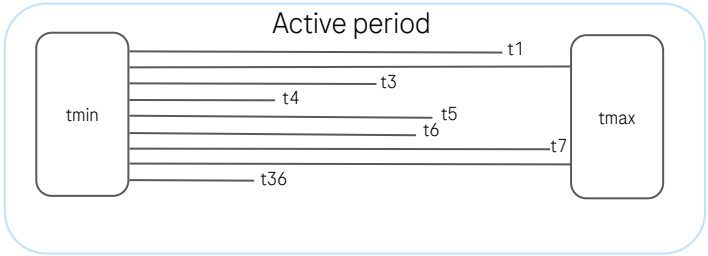
[b] Patients ≥ 12 years who weighed < 40 kg, could also participate in HAVEN 2.

Study Design

Repeated counts from control (NIS) and active (interventional) for each patient

- Repeated counts/bleeds from patients (control & active period)
  - Each patient is his/her own control
- Patients must first enrol in a **control period** lasting 24 weeks
- Duration of **active period** varies between patients
- Intra-patient comparison (ABR-control vs ABR-active)





Data Collection

The BMQ

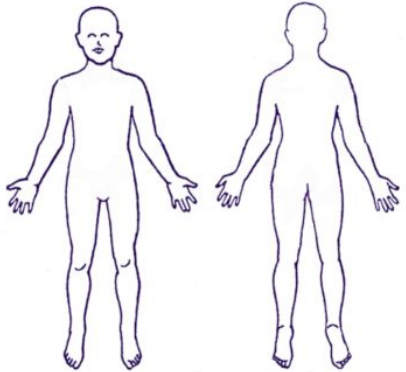
Data collection and data granularity ⟶ a Key issue in observational studies

Standardization of the data collection:

Creation of a **validated** ePRO questionnaire : **Bleed and Medication Questionnaire** (BMQ) was born !

The exact same data and with the **same granularity** were collected in both studies (the NIS and the interventional) and allowed us to properly compare data from both and as the patient was his own control.

3.1	Where did this bleed occur?	ZA.ZATEST='Where Did This Bleed Occur' ZA.ZATESTCD='CLAD006'



ZA.ZAORRES

Forehead Left cheek/Face Nose Mouth Throat Right cheek/Face Left eye Right eye Left ear Right ear	Top of the head Back of the head Neck	Left chest Right chest Left upper abdomen Right upper abdomen Left lower abdomen Right lower abdomen Left side Right side Genitals	Left upper back Right upper back Left middle back Right middle back Left lower back Right lower back Left buttock Right buttock	Left arm Left forearm Left wrist Left palm Left fingers/thumb	Left hip Left thigh Left knee Left shin Left ankle Left foot Left toes
Right arm Right forearm Right wrist Right palm	Right hip Right thigh Right knee Right shin	Left shoulder Back of left upper arm Left elbow Back of left forearm	Left hamstring Left calf Left sole/heel Back of left knee	Right shoulder Back of right upper arm Right elbow Back of right forearm	Right hamstring Right calf Right sole/heel Back of right knee

Data Quality

In routine clinical practice, patients with hemophilia A are managed in a home therapy setting that allows them to get immediate access to optimal early treatment.

Bleeds are treated primarily by the patient (or patient's legally authorized representative).

- the protocol did not mandate additional face-to-face clinic visits on a regular basis

- BUT, at least monthly interactions by telephone were requested (more frequent interactions may be needed [e.g., in case of non-compliance, sites received alerts via e-mail in case patients did not enter data into the ePRO device for more than 72 hours and must follow up with the patient]).

- The Study team invest an incredible amount of time reviewing the data weekly to check
  - Patient compliance
  - Data quality

Strong and validated Comparator arm

NIS data have been included in both EU and US labels

The intra-patient comparisons have been published in key scientific journals

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

In the HAVEN 3 intra-patient analysis, HEMLIBRA prophylaxis resulted in a statistically significant ($p < 0.0001$) reduction (68%) in bleed rate for treated bleeds compared with previous FVIII prophylaxis collected in the NIS prior to enrollment (see Table 6).

Table 6 Intra-Patient Comparison of Annualized Bleed Rate with HEMLIBRA Prophylaxis versus Previous FVIII Prophylaxis

Endpoint	HEMLIBRA 1.5 mg/kg once every week (N = 48)	Previous FVIII Prophylaxis (N = 48)
Median Observation Period (weeks)	33.7	30.1
Treated Bleeds		
ABR (95% CI) [a]	1.5 (1, 2.3)	4.8 (3.2, 7.1)
% reduction (95% CI) p-value	68% (48.6%, 80.5%) < 0.0001	
% patients with 0 bleeds (95% CI)	54.2 (39.2, 68.6)	39.6 (25.8, 54.7)
Median ABR (IQR)	0 (0, 2.1)	

ABR = annualized bleed rate; CI = confidence interval; 75th percentile.

[a] Based on negative binomial regression model.

EMICIZUMAB IN HEMOPHILIA A WITHOUT INHIBITORS

Table 2. Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group D), as Compared with Events in the Same Participants during Prophylactic Factor VIII Treatment Previously in the Noninterventional Study.*

Variable	Group D in Current Trial: Emicizumab Prophylaxis (N=48)	Noninterventional Study: Factor VIII Prophylaxis (N=48)
Median duration of efficacy period (range) — wk†	33.7 (20.1–48.6)	30.1 (5.0–45.1)
Annualized rate of bleeding events, model-based (95% CI)‡	1.5 (1.0–2.3)	4.8 (3.2–7.1)
Rate ratio vs. control (95% CI)	0.32 (0.20–0.51)	—
Percent difference vs. control	−68§	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Percent of participants with 0 bleeding events (95% CI)	54 (39–69)	40 (26–55)
Percent of participants with 0–3 bleeding events (95% CI)	92 (80–98)	73 (58–85)

* Data are shown for 48 participants in group D who had participated in an earlier noninterventional study of factor VIII prophylaxis. In group D, these participants received emicizumab at a once-weekly dose of 1.5 mg per kilogram.
† The efficacy period for the noninterventional study group was defined as the time between the day of handheld-device activation and either the date of study withdrawal or completion, whichever occurred first.
‡ The annualized bleeding rate was calculated with the use of a negative binomial-regression model.
§ P<0.001 for the comparison with the noninterventional study.

Table 7 HAVEN 1: Intra-patient comparison of Annualised Bleed Rate (treated bleeds) with Hemlibra prophylaxis versus previous bypassing agent prophylaxis (NIS patients)

Endpoint	Arm C$_{NIS}$: previous bypassing agent prophylaxis	Arm C: Hemlibra 1.5 mg/kg weekly
	N=24	N=24
Treated bleeds		
ABR (95% CI)	15.7 (11.08; 22.29)	3.3 (1.33; 8.08)
% patients with 0 bleeds (95% CI)	12.5 (2.7; 32.4)	70.8 (48.9; 87.4)
Median ABR (IQR)	12.0 (5.73; 24.22)	0.0 (0.00; 2.23)
% reduction (RR), p-value	79% (0.21), 0.0003	

Rate ratio and confidence interval (CI) comes from negative binomial regression (NBR) model and p-value from Stratified Wald test, comparing ABR between specified arms.
Intra-patient comparator data from the NIS.
Only patients who participated in the NIS and in study HAVEN 1 are included.
Includes data before up-titration only, for patients whose dose was up-titrated.
Treated bleeds = bleeds treated with bypassing agents.
Bleed definitions adapted based on ISTH criteria.
ABR= Annualised Bleed Rate; CI= confidence interval; RR= rate ratio; IQR=interquartile range, 25th percentile to 75th percentile

EMICIZUMAB PROPHYLAXIS IN HEMOPHILIA A WITH INHIBITORS

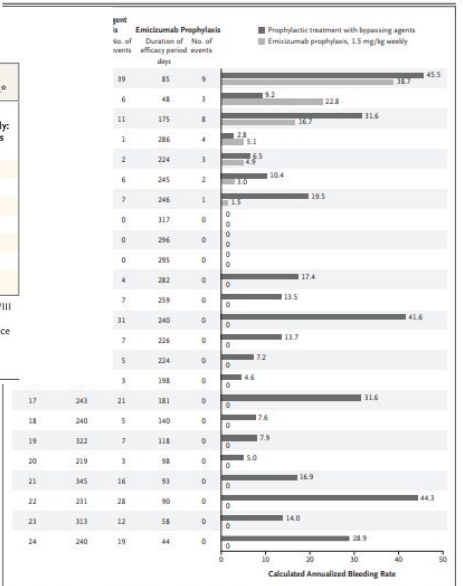


Figure 2. Intraindividual Comparison of Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group C) versus Previous Prophylactic Treatment with Bypassing Agents before Trial Entry.
Shown are data for the 24 participants in group C who had participated in the noninterventional study. Data are sorted according to the annualized bleeding rate with emicizumab prophylaxis in descending order and then according to descending duration of efficacy period with regard to emicizumab prophylaxis.

Conclusion

Conducting the NIS as an Interventional Study

To maximize the value and validity of a non-interventional study, it is key to adopt the rigorous standards of an interventional study.

Actionable Takeaways:

- Data **Quality**: Collect data that are appropriate for the research objectives and purposes.
- Data **Reliability**: Ensure all data are complete, trustworthy, and credible.
- Data **Relevance**: Collect data at the same granularity as the interventional study to ensure comparability.

Acknowledgment

The patients that took part in the study and the hemophilia community

The colleagues who have worked on these studies

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Doing now what patients need next