

**PHUSE Single Day Events  
UCB Biosciences (RTP Campus)  
Dec-08-2023**

**Next Steps in Rare Diseases – Innovation, Standards and Opportunities!**

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# **Rare Diseases and Programming Challenges: A Programmer's Perspective**



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EPHICACY 

# Presentation Disclaimer

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The views and opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of Efficacy.

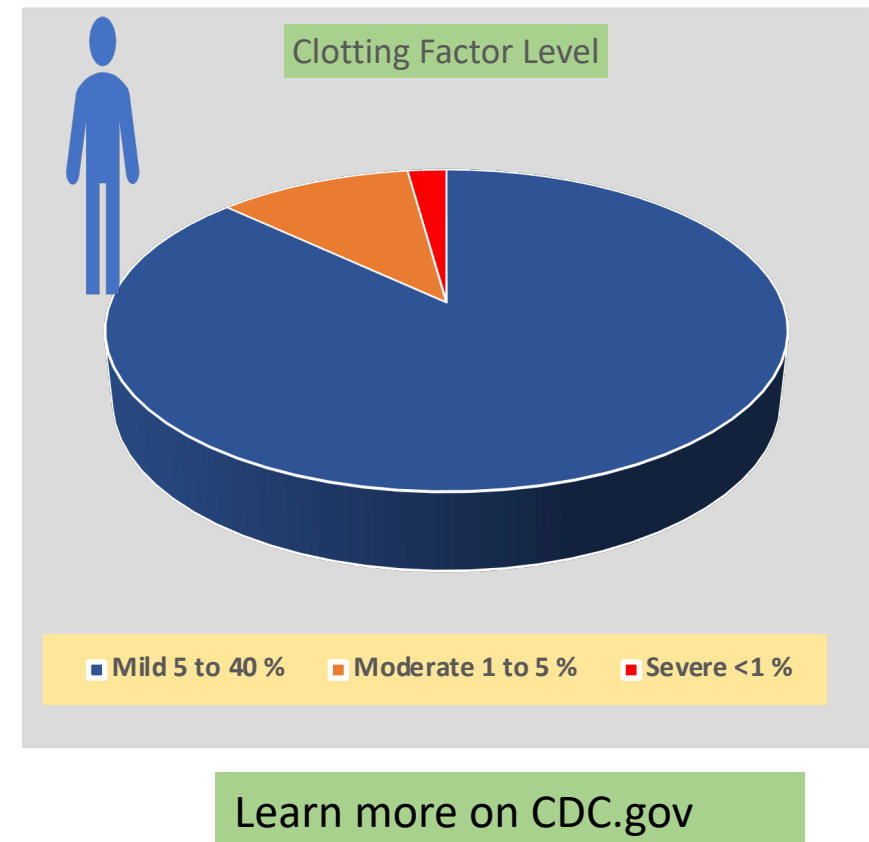
# Presentation Highlights

- Rare Disease – About Hemophilia
- Study Design
- Endpoint(s)
- Annualized Bleeding Rate
- Data Collection & Tabulation
- ADaM Dataset Dependencies
- ADABR Dataset Example
- Reports
  - Analysis of ABR
  - Factor Activity Measurements
- Challenges we overcame



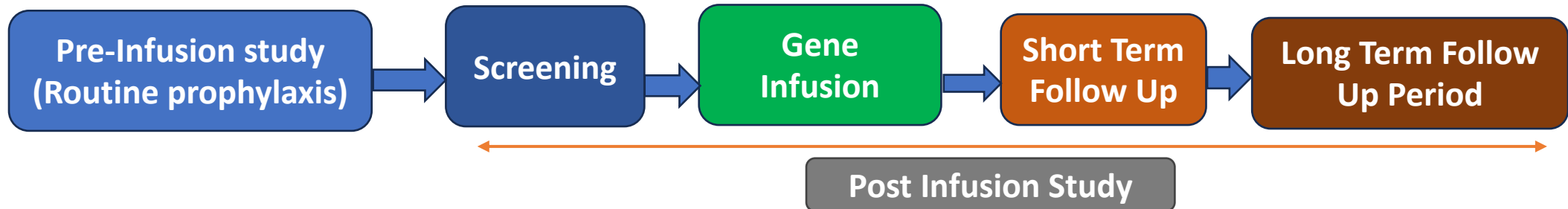
# About Hemophilia

- Hemophilia is rare **genetic bleeding disorder** caused by insufficient levels of a blood protein called **clotting factor VIII / FIX**. Without enough human factor VIII/FIX, the blood cannot clot properly to control bleeding.
  - **Hemophilia A** due to deficiency of clotting **factor VIII**.
  - **Hemophilia B** due to deficiency of clotting **factor IX**.
- Latest Rare diseases report :
  - Hemophilia A : 1 in 5,000 male births
  - Hemophilia B : 1 in 25,000 male births
- **Treatment options:**
  - Plasma-derived;
  - **Recombinant replacement factors;**
  - Fresh Frozen Plasma;
  - **Gene Therapy, latest.**



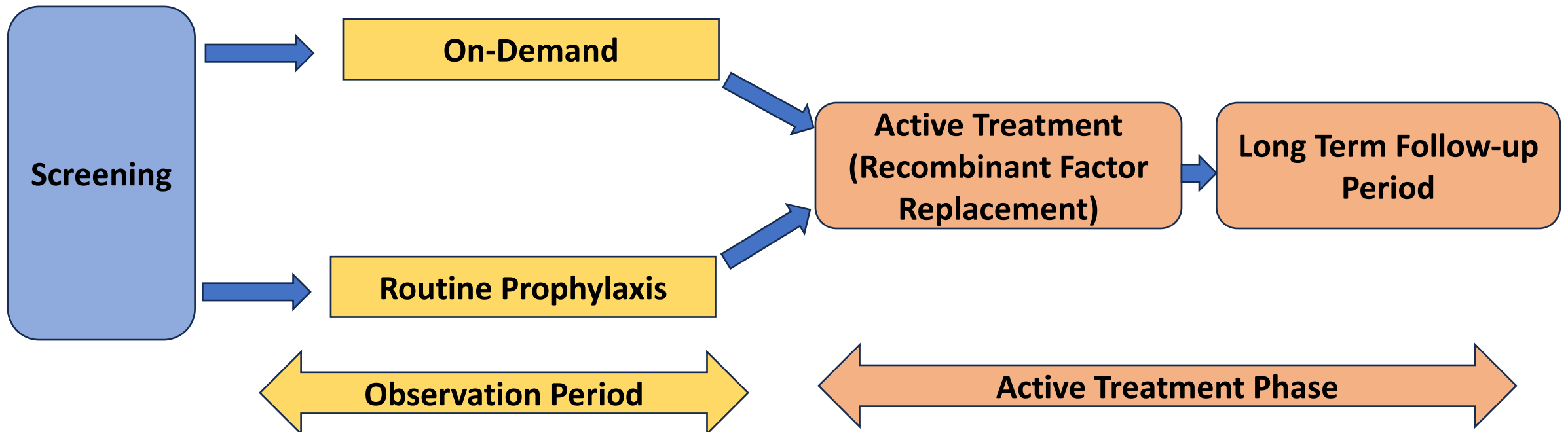
# Study Design 1

- Moderately Severe to Severe Hemophilia A/B.
- Evaluate the efficacy and safety of a gene-based drug therapy.



# Study Design 2

- Moderately Severe to Severe Hemophilia A/B.
- Comparing Standard Treatment with Active treatment.



# Study Design - Description

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## **Pre-infusion: (Lead-in)**

- Enrolling Routine Prophylaxis patients.
- Observing patients for 6 months and collected bleed & Infusion data.
- Serve as the control group after post infusion.
- Baseline dose stability to facilitate efficacy assessments
- Data for supportive endpoints.

## **Post-infusion :**

- Factor replacement therapy (Gene/Recombinant).
- Using same Routine Prophylaxis to prevent (or treat) bleeding during the interval from post- product administration to steady state factor levels.
- Target factor activity level or duration vs timing to discontinue factor prophylaxis.
- Assessment of ABR and durability of response.
- Assessment plan to correlate factor activity and bleeding rates.

# Endpoint(s)

**Annualized Bleeding Rate (ABR)**



**Annualized Infusion Rate (AIR)**



**Factor VIII/XI activity level at steady state**



**Factor IX/VIII consumption**



**Annualized number of bleeding events**



**Frequency of target joint bleeds**



**Percentage of the participants without bleeds**



**Change in Hemophilia Joint Health Score**



**Hemophilia Quality of Life (Haem A QoL)**



**Hemophilia Activities List (HAL)**



**ABR for total bleeds of specific type by cause and by location**

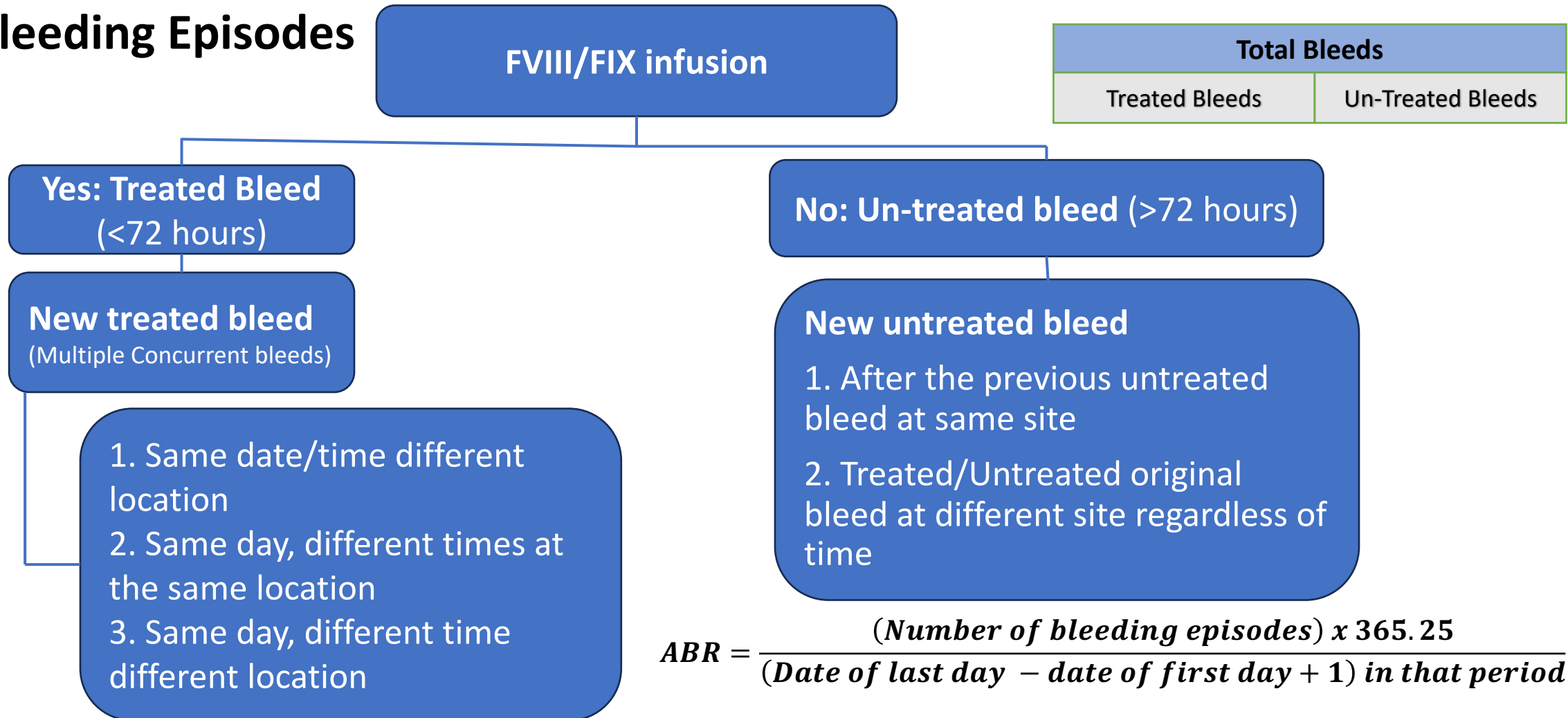


**Incidence and severity of Aes.**



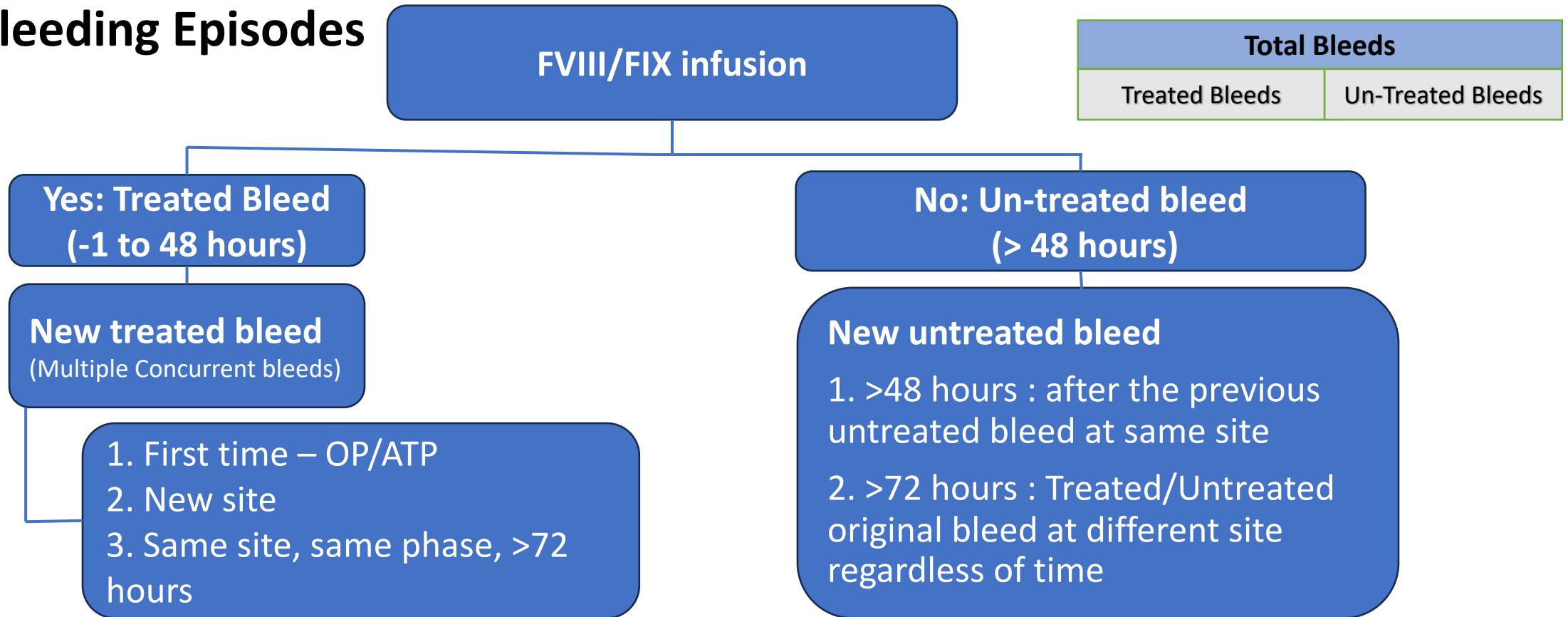
# ABR (Annualized Bleeding Rate)

## Bleeding Episodes



# ABR (Annualized Bleeding Rate)

## Bleeding Episodes



$$ABR = \frac{(Number\ of\ bleeding\ episodes) \times 365.25}{(Date\ of\ last\ day - date\ of\ first\ day + 1)\ in\ that\ period}$$

# Data Collection

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ABR data is collected in e-Diary and Bleeding CRF.

**e-Diary:** An electronic hand-held device given to the patients to log all the bleeding episodes and infusion records.

- **Bleed Type:** Spontaneous, Traumatic, Procedural
- **Bleed Treatment Type:** No Treatment, Treating with clotting Factor Replacement other than the study drug
- **Joint Bleed :** Yes or No
- **Bleed Start date and time:** ddmmmyyyy:hh:mm:ss
- **Bleeding site (40+ possible sites):** Elbow\_R, Elbow\_L, Ankle\_R, Ankle\_L, Thigh\_R, Thigh\_L....etc

# Sample Data

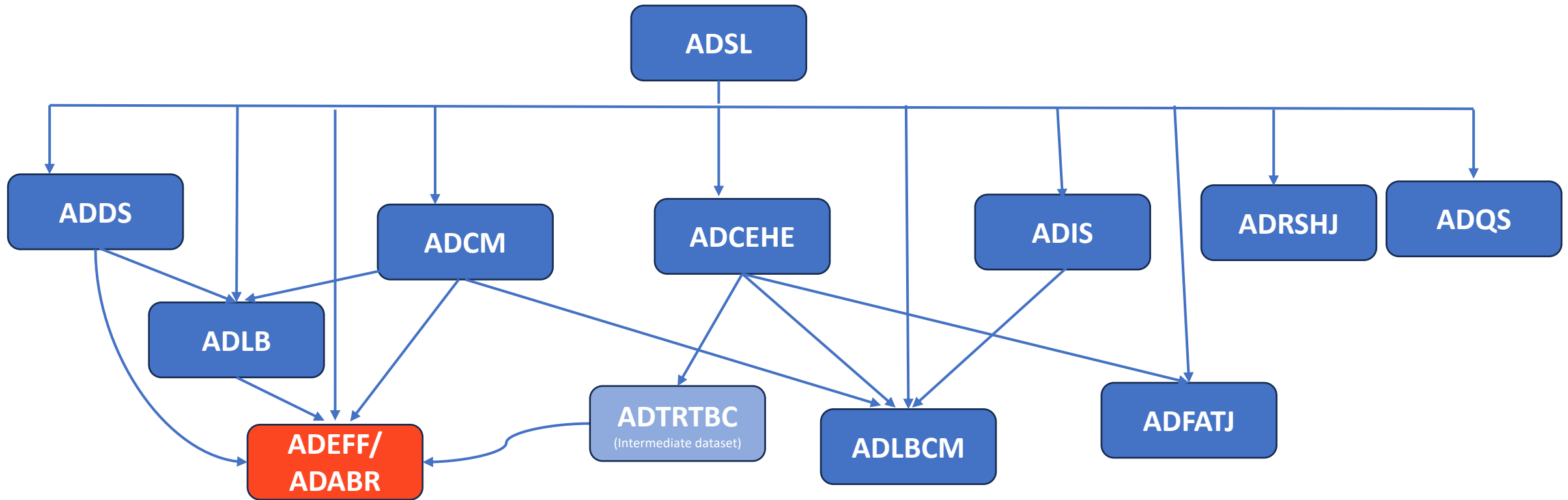
The study can have subjects with one bleeding episode to several hundred (350+) bleeding episodes. The below example data is for one subject to demonstrate how the data is collected. Only Important variables are presented, and the data is mocked up.

| Subject Identifier | Bleeding Site                                    | Bleed Type  | Bleed Sub Type 1 | Bleed Sub Type 2   | Treatment Type                                    | Analysis Start Date/Time |
|--------------------|--------------------------------------------------|-------------|------------------|--------------------|---------------------------------------------------|--------------------------|
| 1001               | Knee_R,Ankle_R,Thigh_R,Foot_R,Gluteus            | SPONTANEOUS | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 07Jul2025:10:00:00       |
| 1001               | Knee_R                                           | SPONTANEOUS | JOINT            |                    | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 10Jul2025:10:00:00       |
| 1001               | Knee_R,Ankle_R,Thigh_R,Gluteus                   | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 13Jul2025:08:46:00       |
| 1001               | Knee_R,Knee_L,Thigh_R,Hamstring_R,Hamstring_L,G  | SPONTANEOUS | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 14Jul2025:17:00:00       |
| 1001               | Knee_L                                           | SPONTANEOUS | JOINT            |                    | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 17Jul2025:06:00:00       |
| 1001               | Knee_R                                           | SPONTANEOUS | JOINT            |                    | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 18Jul2025:23:00:00       |
| 1001               | Knee_R,Thigh_R,Hamstring_R                       | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 19Jul2025:21:24:00       |
| 1001               | Knee_R,Hip_R,Thigh_R,Hamstring_R,Gluteus         | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 24Jul2025:10:26:00       |
| 1001               | Knee_R,Ankle_R,Thigh_R,Hamstring_R,Foot_R,Gluteu | SPONTANEOUS | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 01Aug2025:17:02:00       |
| 1001               | Knee_R,Ankle_R,Thigh_R,Hamstring_R,Foot_R,Gluteu | SPONTANEOUS | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 05Aug2025:13:01:00       |
| 1001               | Elbow_L,Wrist_L,Finger_L                         | TRAUMATIC   | JOINT            |                    | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 08Aug2025:13:00:00       |
| 1001               | Knee_R,Ankle_R,Thigh_R,Hamstring_R,Foot_R,Gluteu | SPONTANEOUS | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 09Aug2025:03:00:00       |
| 1001               | Shoulder_L,Elbow_L,Wrist_L,Finger_L,Thigh_R      | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 11Aug2025:09:00:00       |
| 1001               | Thigh_R,Gluteus                                  | TRAUMATIC   |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 12Aug2025:10:00:00       |
| 1001               | Knee_R,Ankle_R,Thigh_R,Foot_R                    | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 20Aug2025:16:00:00       |
| 1001               | Thigh_R,Gluteus                                  | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 22Aug2025:09:00:00       |
| 1001               | Ankle_R,Thigh_R,Foot_R,Gluteus                   | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 30Aug2025:14:00:00       |
| 1001               | Hip_R,Thigh_R,Gluteus                            | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 01Sep2025:01:00:00       |
| 1001               | Hip_R,Thigh_L,Back Lower,Gluteus                 | TRAUMATIC   | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 01Sep2025:11:00:00       |
| 1001               | Thigh_R,Hamstring_R,Gluteus                      | TRAUMATIC   |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 03Sep2025:08:00:00       |
| 1001               | Thigh_R,Hamstring_R,Gluteus                      | TRAUMATIC   |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 06Sep2025:09:00:00       |
| 1001               | Hamstring_R                                      | TRAUMATIC   |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 08Sep2025:08:00:00       |
| 1001               | Thigh_R,Hamstring_R,Gluteus                      | SPONTANEOUS |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 17Sep2025:21:10:00       |
| 1001               | Thigh_R,Hamstring_R,Gluteus                      | SPONTANEOUS |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 25Sep2025:08:00:00       |
| 1001               | Thigh_R,Hamstring_R,Gluteus                      | SPONTANEOUS |                  | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 12Oct2025:11:30:00       |
| 1001               | Knee_R,Thigh_R,Hamstring_R,Gluteus               | SPONTANEOUS | JOINT            | SOFT TISSUE/MUSCLE | CLOTTING FACTOR REPLACEMENT OTHER THAN STUDY DRUG | 25Oct2025:05:28:00       |

# Data Collection and Tabulation

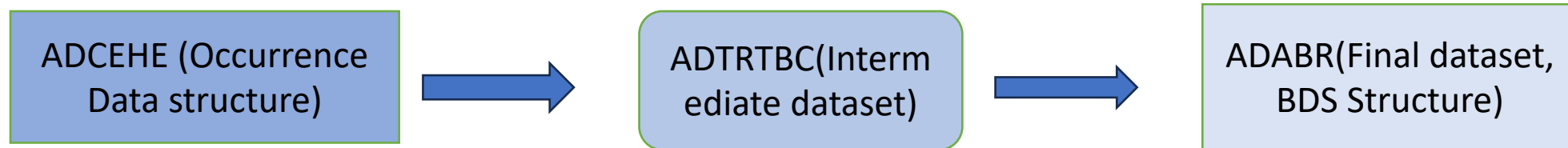
| CRF                                                                                                                                                                 | SDTM             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| <ul style="list-style-type: none"><li>• PRIOR AND CONCOMITANT MEDs</li><li>• PRIOR THERAPY MAINTENANCE</li><li>• FVIII/FIX ROUTINE PROPHYLAXIS RESUMPTION</li></ul> | CM               |
| <ul style="list-style-type: none"><li>• LIVER ULTRASOUND</li><li>• XRAY</li></ul>                                                                                   | MO               |
| <ul style="list-style-type: none"><li>• LIVER ELASTOGRAPHY</li><li>• MRI - JOINT</li><li>• NON-DRUG TREATMENTS/SURGERIES</li></ul>                                  | PR               |
| <ul style="list-style-type: none"><li>• MEDICAL HISTORY</li></ul>                                                                                                   | MH               |
| <ul style="list-style-type: none"><li>• CENTRAL LAB SAMPLE COLLECTION</li><li>• LABORATORY DATA - HEMATOLOGY</li></ul>                                              | LB               |
| <ul style="list-style-type: none"><li>• BLEED EVENT - NOT TREATED WITH STUDY DRUG</li></ul>                                                                         | CEHE             |
| <ul style="list-style-type: none"><li>• HEMOPHILIA JOINT HEALTH SCORE</li></ul>                                                                                     | RSHJ             |
| <ul style="list-style-type: none"><li>• IMMUNOGENICITY – CENTRAL LAB</li></ul>                                                                                      | ISBP, ISMV, COMV |

# ADaM Dataset Dependencies



# ABR - Data Flow

From the occurrence data structure(ADCEHE) to the final BDS structure, an intermediate dataset is created, which contains the processes bleeding episodes with New\_treated\_bleed and New\_untreated\_bleeds Flags.



ADCEHE: Has same number of records as that precursor SDTM Dataset

ADTRTBC (Intermediate Dataset) : Has less records than ADCEHE, after processing the dataset only record per event irrespective of the multiple sites. The Infusion missing time is imputed with that bleeding time and added new variables like last\_infusion\_time, new\_treated\_bleed flag and New\_untreated\_bleed flag.

# ABR Processing - Treated Bleeds

| Subject ID | Site               | Start Date/Time      | Last Infusion Date/Time | Treated | Phase | New_Treated |
|------------|--------------------|----------------------|-------------------------|---------|-------|-------------|
| 1001       | Knee_R             | Jan-01-2023:12:10:00 | Jan-01-2023:12:20:00    | Y       | OP    | Y           |
| 1001       | Knee_R             | Jan-02-2023:13:20:00 | Jan-02-2023:12:30:00    | Y       | OP    | N           |
| 1001       | Knee_R             | Jan-05-2023:12:31:00 | Jan-05-2023:12:50:00    | Y       | OP    | Y           |
| 1001       | Knee_R,<br>Ankle_L | Jan-06-2023:12:20:00 | Jan-06-2023:12:20:00    | Y       | OP    | Y           |
| 1001       | Knee_R             | Jun-07-2023:12:10:00 | Jun-07-2023:12:11:00    | Y       | ATP   | Y           |
| 1001       | Knee_R             | Jun-08-2023:12:10:00 | Jun-08-2023:12:11:00    | Y       | ATP   | N           |
| 1001       | Knee_R             | Jun-09-2023:12:10:00 | Jun-09-2023:12:11:00    | Y       | ATP   | N           |
| 1001       | Knee_R             | Jun-10-2023:12:15:00 | Jun-10-2023:12:20:00    | Y       | ATP   | Y           |
| 1001       | Knee_R             | Jun-11-2023:12:15:00 | Jun-11-2023:12:18:00    | Y       | ATP   | N           |
| 1001       | Knee_R             | Jun-12-2023:12:15:00 | Jun-12-2023:12:19:00    | Y       | ATP   | N           |
| 1001       | Knee_R             | Jun-13-2023:12:25:00 | Jun-13-2023:12:30:00    | Y       | ATP   | Y           |

First Instance  
of site

Time Diff  
< 72 hrs.

> 72 hrs.

New Site

# ADABR Dataset

| Subject ID | Parameter           | Phase | Aval | Period | ABR  |
|------------|---------------------|-------|------|--------|------|
| 1001       | Primary             | OP    | 29   | 180    | 58.8 |
| 1001       | Primary             | ATP   | 10   | 365    | 10.0 |
| 1001       | Spontaneous bleeds  | OP    | 20   | 180    | 40.5 |
| 1001       | Spontaneous bleeds  | ATP   | 10   | 350    | 10.4 |
| 1001       | Target Joint bleeds | OP    | 30   | 180    | 60.8 |
| 1001       | Target Joint bleeds | ATP   | 15   | 300    | 18.2 |
| 1001       | Total bleeds        | OP    | 40   | 180    | 81.1 |
| 1001       | Total bleeds        | ATP   | 50   | 365    | 20.0 |

The above example data is for one subject to demonstrate how the final dataset is expected. Only Important variables were presented, and the data is mocked up.

# Analysis of ABR

|                                               |                   | FVIII/FIX Prophylaxis<br>(N=xx) | Active Drug<br>(N=xx)   |
|-----------------------------------------------|-------------------|---------------------------------|-------------------------|
| Number (%) of participants without any bleeds |                   | xx (xx.x)                       | xx (xx.x)               |
|                                               |                   |                                 |                         |
| Number of bleeds                              | n                 | xx                              | xx                      |
|                                               | Mean (SD)         | xx.x (xx.xx)                    | xx.x (xx.xx)            |
|                                               | Median (Min, Max) | xx.x (xx, xx)                   | xx.x (xx, xx)           |
|                                               | (Q1, Q3)          | (xx.x, xx.x)                    | (xx.x, xx.x)            |
|                                               |                   |                                 |                         |
| Annualized bleeding rate (ABR)                | n                 | xx                              | xx                      |
|                                               | Mean (SD)         | xx.xx (xx.xxx)                  | xx.xx (xx.xxx)          |
|                                               | Median (Min, Max) | xx.xx (xx.x, xx.x)              | xx.xx (xx.x, xx.x)      |
|                                               | (Q1, Q3)          | (xx.xx, xx.xx)                  | (xx.xx, xx.xx)          |
|                                               |                   |                                 |                         |
| Model derived ABR                             | Estimate (95% CI) | xx.xx (xx.xx, xx.xx)            | xx.xx (xx.xx, xx.xx)    |
|                                               |                   |                                 |                         |
| Treatment difference                          |                   |                                 |                         |
|                                               | Estimate (95% CI) |                                 | xxx.xx (xxx.xx, xxx.xx) |
|                                               | P-value           |                                 | x.xxxx                  |
|                                               |                   |                                 |                         |
| Percentage reduction                          |                   |                                 |                         |
|                                               | Estimate (95% CI) |                                 | xxx.xx (xxx.xx, xxx.xx) |
|                                               | P-value           |                                 | x.xxxx                  |

# Factor Activity Measurements

- By different Lab assays - One stage clotting (OC) and chromogenic substrate (CS).
  - Discrepancies in factor activity measurements between the OC and CS methods.
  - Discrepancies between OC assays using different OC reagents.
- Endpoint : Vector derived Factor VIII/ activity level at steady state.

| Active Drug                 |                                            |                       |
|-----------------------------|--------------------------------------------|-----------------------|
| Factor VIII/IX Activity (%) | One-stage Assay<br>(Different OC reagents) | Chromogenic Assay     |
| n                           | xx                                         | xx                    |
| Mean (SD)                   | xxx.xx (xx.xxx)                            | xxx.xx (xx.xxx)       |
| Median (Min, Max)           | xxx.xx (xxx.x, xxx.x)                      | xxx.xx (xxx.x, xxx.x) |
| (Q1, Q3)                    | (xxx.xx, xxx.xx)                           | (xxx.xx, xxx.xx)      |
| 95% CI                      | xxx.xx, xxx.xx                             | xxx.xx, xxx.xx        |
| p-value                     | x.xxx                                      | x.xxx                 |

# Challenges we overcame

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**Disease  
Complexity**



**End points**



**Data  
Collection &  
Tabulation**



**Analysis**



**Adhocs**



**Trainings**



# Thank you

ANY QUESTIONS?

Contact us @ [latha.donapati@ephicacy.com](mailto:latha.donapati@ephicacy.com)  
[chandrashaker.vanampally@ephicacy.com](mailto:chandrashaker.vanampally@ephicacy.com)