CDISC Implementation on Haemophilia Trial Data

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Disclaimer

The information contained in this presentation is provided for informational purposes only. And is based on Larix’s SDTM approach of handling Haemophilia data.
AGENDA

- About Haemophilia
- Introduction to Haemophilia trial data
- Our approach to implementing CDISC models on this trial data
- Challenges and important considerations around data structure / mapping
- Conclusion
- Haemophilia is a group of hereditary genetic disorders that impairs the body's ability to control blood clotting.
- Haemophilia is carried on the X chromosome and is called an X linked genetic disorder and occurs more commonly in males than in females.
- Mutations in the FVIII gene cause Haemophilia A. Mutations in the FIX gene cause Haemophilia B.

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Cause</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A</td>
<td>X linked recessive</td>
<td>Factor VIII</td>
<td>80%</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>X linked recessive</td>
<td>Factor IX</td>
<td>15%</td>
</tr>
</tbody>
</table>
Management and Treatment

No cure for Haemophilia.

But a number of treatments exist.

- Plasma and whole blood transfusions
- Factor replacement (Prophylaxis or On-demand) – Intravenous infusions of the deficient clotting factor
- Gene therapy: Replacement of/Addition to a defective gene sequence with a corrected version to eliminate disease for the lifetime of the patient
- Preventive exercises
Introduction to Haemophilia trial data – an Example

Trial data consists of general data
- Demographics (DM),
- Inclusion/Exclusion criteria (IE),
- Exposure (EX),
- Surgical history (MH),
- Adverse events (AE),
- Vital signs (VS) etc.
but in addition to this we also encounter (}
Haemophilia Joint Health Score (HJHS)
Factor Gene mutation and gene sequencing analysis (FGM)
Haemophilia history
Degree of factor deficiency and inhibitors
Bleeding episodes
Target Joints
Prophylactic or On-demand factor Replacement Therapy
Tapering of prophylactic replacement therapy
History and Status of factor medication and Bleeding
Diagnosis and Laboratory data
Stages and processes – Screening and Inclusion

Subject

- participates in

Diagnostic process

- includes one or more

Haemophilia history

Bleeding history

Status of factor medication

- Blood tests like Complete Blood count (CBC), APTT Tests, PT test, Fibrinogen test, Clotting Factor IX assay
- HJHS assessment etc

Getting results like

- Haemophilia Joint Health Score
- Degree of factor deficiency and inhibitors
- Gene mutation and DNA rearrangements
- Target Joint data

Subject participates in Diagnostic process which results in Haemophilia history, Bleeding history, and Status of factor medication. The diagnostic process includes blood tests and HJHS assessment. Getting results includes Haemophilia Joint Health Score, Degree of factor deficiency and inhibitors, Gene mutation and DNA rearrangements, and Target Joint data.
Stages and processes - Treatment

Subject administration

Followed by

- Bleeding episodes
- Prophylactic factor replacement therapy
  - On-demand factor replacement therapy
- Tapering of factor replacement therapy
- Blood sampling
An approach of mapping Haemophilia data to SDTM

### Haemophilia Data

**Bleeding History**
A physician administered standard questionnaire for history taking and bleeding score assignment

**Examples:** Number of episodes, Duration, Spontaneous?, Location, Type of Bleeding

**Haemophilia disease related History**
Questions related to disease diagnosis history prior to the trial participation

**Examples:** Diagnosed date, Factor activity level, Degree of deficiency, Any of family members has factor inhibitors? etc

### SDTM

**Questionnaires Domain (QS)** when QSCAT="BLEEDING HISTORY"
QRS controlled terminology does not cover some of the above questionnaires, hence used the custom terminology for QSTESTCD, QSTEST, QSORRES

**Custom Domain (XH)** for Haemophilia History based on *Findings* observation class. We followed SDTM IG rules for creating custom domain.
**Haemophilia Data**

**Status of factor medication and Bleeding**
Medication prior to Trial start.

**Examples:** Treatment, Form, Frequency, Start date, Stop date, Ongoing, Dose, Number of treatment requiring bleeding episodes

**Target Joint data**
Target joint is the joint having four bleeds into the same joint in a six-month time period.

**Examples:** Any Target joints?, Location, Laterality etc

**SDTM**

**CM, MH and Supplementary domains**
Factor medication data placed into CM, SuppCM e.g. with CMCAT = "PRIOR FACTOR MEDICATION" and CMSCAT = XXXX.

Prior bleeding episodes data are placed into MH, SuppMH with MHCAT/MHSCAT = XXX/YYY. If relevant: Link episodes with medications in RELREC

**FINDINGS**

**Findings About Domain (FA)**
NOTE: Custom terminology for FATESTCD, FATEST
**Haemophilia Joint Health Score**

The HJHS is a physical examination assessment tool sensitive enough to pick up the subtle early signs of joint damage.

**Examples of HJHS data:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Left Elbow</th>
<th>Right Elbow</th>
<th>Left Knee</th>
<th>Right Knee</th>
<th>Left Ankle</th>
<th>Right Ankle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
</tr>
<tr>
<td>Duration (swelling)</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
</tr>
<tr>
<td>Muscle Atrophy</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
</tr>
<tr>
<td>Crepitus on motion</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
</tr>
<tr>
<td>Flexion Loss</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
</tr>
<tr>
<td>Extension Loss</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
<td>□ NE</td>
</tr>
<tr>
<td>Strength</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
<td>□ NF</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sum of Joint Totals</strong></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Global Gait Score</strong></td>
<td>□ NE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NE included in Gait items)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HJHS Total Score</strong></td>
<td>=</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Haemophilia Data**

**Bleeding episodes**
Patient evaluation of treatment for a bleeding in e-diary

*Examples*: Start date, time of Bleed, Stop date, time of bleed, Location, Circumstances of bleed, Action taken, Treatment, Severity of Bleeding etc

**Prescribed factor replacement therapy**
Replacement therapy may be administered through on-demand or prophylaxis regimens.

*Examples*: Medication name, dose, units, frequency, Start, Stop date, On-going

**SDTM**

**EVENTS**

**CE, SuppCE** when CECAT = “BLEEDING EPISODE”

**INTERVENTIONS**

**CM, SuppCM** when CMCAT = “PRESCRIBED FACTOR REPLACEMENT THERAPY DURING TRIAL”
**Tapering of replacement therapy**
Gradually reducing the amount of a drug when stopping it abruptly would cause unpleasant withdrawal symptoms.

**Examples:** Did tapering start? If No, reason for not tapering; Date of initiating the tapering; Reason for the date chosen

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**Prophylactic factor Replacement Therapy and On-demand factor Replacement Therapy data**
Subject filled information about taking the factor infusions relating to the Bleeding episodes or Regular medications

**Examples:** Name of infusion product, dose, form, Start date and time etc

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**SDTM**

**SuppCM** in relation to prescribed factor replacement therapy records in CM

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**CM and SuppCM** when
CMCAT="PROPHYLACTIC INFUSION" or CMCAT = “ON-DEMAND INFUSION”
**Diagnosis and Laboratory data**

Factor activity, Factor inhibitors, CBC, aPTT, PT, Clotting factor assays, mutations and DNA rearrangements etc, other than general Chemistry, Hematology, Urinalysis data

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**SDTM**

**LB and SuppLB**

**NOTE:** SDTM controlled terminology doesn't cover the some of the Lab test names, hence used the custom terminology for LBTESTCD, LBTEST
Challenges and important considerations

- Handling the Haemophilia disease related history data
  Will it go into FA or SUPPMH or XH (custom) ????
- Handling the Bleeding history data
  Will it go into QS or SUPPMH or XB (custom)????
- Tapering of factor replacement dose
  Will it be placed in SUPPCM or any (custom) domain????
- Handling disease related Laboratory tests as they are not part of controlled terminology.
Conclusion

Haemophilia could be considered as candidate for a Therapeutic Area Standards User Guide development.

Overall, these are exciting times for Haemophilia clinical trials and likelihood of further clinical successes in the near future.

A day will come when a person with haemophilia will go to a treatment center and leave without haemophilia.
References

- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2408641/
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4039643/
- http://www.cdc.gov/ncbddd/hemophilia/data.html
Thank You For Your Support!!