Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.
What is Medical Device?

“An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article.”*

*: Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act
Device Classification

Class I  Class II  Class III

Risk

Low  High
Regulatory Pathway

Pre-clinical Studies → Clinical Trials/Studies → Pre-market Application → Post-market

Real World Evidence
Randomized Clinical Trials (RCT)

**Study Design**
Protocol, Statistical Analysis Plan, Case Report Form

**Trial Implementation**
Patient enrollment, data collection,

**Data Analysis**
Report efficacy and safety results
Real World Evidence (RWE)
Use of RWE in the Regulatory Decision-making

Expand the labelling

Control group

Post-approval and post-market surveillance studies

Supplementary data
 Benefit Risk Analysis

**Benefits**
- Type of benefit(s)
- Magnitude of benefit(s)
- Likelihood of benefit
- Duration of effects
- Patient perspective on benefit
- Doctor perspective
- Medical necessity

**Risks**
- Severity of harm
- Likelihood of risk
- False-positive or false-negative results
- Patient tolerance of risk
- Risk factors for healthcare professionals or caregivers
Precision Medicine

**In-vitro Diagnostic (IVD)**
- Companion Diagnostic
- Microarray Assay
- Molecular Profiling (IHC, FISH, NGS, PCR)
- Digital Pathology

**Data Mining Challenges**
- Few Data Points
- Large Dimension Spaces
- Reproducibility
- Sample Availability
- Analytical Validation
- Clinical Validation
Type I and Type II Errors

Type I error (false positive)

Type II error (false negative)

Image source: Effect size FAQs
Medical Device Reporting (MDR)

- Mandatory Reporting
  - Manufacturer
  - Importer
  - User Facility

- Voluntary Reporting
  - MedWatch
National Evaluation System for Health Technology Coordination Center (NESTcc)

Nestcc.org

Innovative Analytical Tool for NEST
PI: Xu, Tiwari, 2017-2019
Signal Detection

Patients’ Adverse Events (AE)

Device stops intermittently

Devices’ Problems
Signal Detection

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<th>AE</th>
<th>Device</th>
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<td>l</td>
<td>$n_{l1}$</td>
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</table>

An AE is a **signal** if its observed count $>>$ its expected count.

Signal Detection Methods

- MGPS: Multi-item Gamma Poisson Shrinker
- PRR: Proportional Reporting Rate
- BPCNN: Bayesian confidence propagating neural network
- LRT: Likelihood Ratio Test
Likelihood Ratio Test (LRT)

For $i^{th}$ AE and $j^{th}$ device

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<th>AE</th>
<th>Devices</th>
<th>Row total</th>
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<td>Col total</td>
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Likelihood Ratio Test (LRT)

\[ n_{ij} \sim \text{Pois}(n_i p_i) \]

\[ n_{-i,j} \sim \text{Pois}(n_{-i} \times q_i) \]

\[ H_0 : p_i = q_i = p_0 \]

\[ H_a : p_i > q_i \]

\[ LR_i = \frac{L_a \left( \hat{p}_i, \hat{q}_i \right)}{L_0(p_0)} = \frac{\left( \frac{n_{ij}}{n_i} \right)^{n_{ij}} \left( \frac{n_{-i,j}}{n_{-i}} \right)^{n_{-i,j}}}{\left( \frac{n_{.j}}{n_{..}} \right)^{n_{.j}}} \]

- LR for every AE
- Find maximum likelihood ratio (MLR)
- Monte Carlo Simulation

Case study: HeartMate II
Case study: HeartMate II
## Case study: HeartMate II

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<tr>
<th>Type of AE</th>
<th>Reported AE Counts</th>
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<th>All LVAD</th>
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Safety Signals Over Time – Cumulative Year Total

- Early signal detected by LRT in 2013
- NEJM report in 2013
- FDA Safety Comm. in 2015
Bioresearch Monitoring (BIMO)
Site Selection
Image source: Pharmaceutical Manufacturing
BIMO Site Selection

Multi-Center Clinical Trials
BIMO Site Selection – A hypothetic example

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<th>Sample Size</th>
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BIMO Site Selection

Statistical test for each variable and p-value generation from statistical tests by variable

**Combination of p-values in a p-value Matrix**

**Site ranking**

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Conclusion

Thank you!
Acknowledgement

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