Clinical Research and Adjudication

Rick Kuntz, MD, MSc
Chief Scientific, Clinical and Regulatory Officer
Medtronic, Inc.
Medical Device Unanswered Questions
Need for Surveillance

• **Device performance: Efficacy confirmation**
  – Does the device work as intended, confirming pre-market study expectations?

• **Long-term device efficacy**
  – Does the device have a sustainable effect, change the natural history of the disease, or improve the Standard-of-Care?

• **Device Effectiveness: Performance in the clinical practice**
  – What are the performance characteristics with average operators, broad health care systems, widened use patterns and performance?
  – What are the patient-reported outcomes (PROs) of interest?

• **Comparative effectiveness**
  – Where does the device fit with alternative choices?

• **Common and rare adverse events, predictability, surrogacy**
  – What are the device (machine) and patient adverse events?
  – What are their rates, are they deviated from expectations?
  – How do we communicate this data to stakeholders for best decisions?
Medical Device Lifecycle (TPLC)

Outcomes of Interest

- Pre-Market Pilot & Pivotal Evaluation
- FDA/Panel Analysis and Approval
- Post-Market Studies & Surveillance
- Next Gen Improvements & Obsolescence

Device Safety & Durability, Manufacturing Reliability

Safety and Efficacy for pre-defined discrete indication

Device Performance: Durability and Product Safety

Patient Outcomes: Rare Events, Efficacy for Broader Patient & Operator Population
Medical Device Lifecycle (TPLC)
Pathophysiology-Treatment Variables

Device Design

Bench Measurement

Pilot Pivotal Outcomes

Device performance

Real World Outcomes

Rare AE Long-term Effects

Ideas, Design, Bench & Mfg Validation

Pre-Market Pilot & Pivotal Evaluation

FDA/Panel Analysis and Approval

Post-Market Studies & Surveillance

Next Gen Improvements & Obsolescence
Device Surveillance Tools and Controls

• Voluntary AE reporting
  – FDA tools: MDR patient reports, MAUDE device summary report

• Health care data systems
  – Claims-based
  – Hospital, HMOs/Health Plan EHR Systems
  – National health care databases

• Prospective Studies
  – RCTs: masked/unmasked, placebo/sham controlled,
  – Registers: Medical Societies, Industry, FDA Sentinel initiative

• Device Generated Data
  – CareLink data network: ICDs, Pacemakers, Diabetic pumps…

• Patient Generated Data
  – Internet (Patients Like Me), Cell phone apps…
# Medical Device Surveillance
## Key Design Elements

<table>
<thead>
<tr>
<th>Design Element</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Capture at Entry</td>
<td>How is the patient captured for research: partial or complete?</td>
</tr>
<tr>
<td>Follow-up Method</td>
<td>Is the follow-up passive or active. Are “pertinent negatives” documented?</td>
</tr>
<tr>
<td>Endpoint Specificity</td>
<td>How specific are the endpoints to the device? Is the data from electronic health records, general research fields, or special “add-on” elements?</td>
</tr>
<tr>
<td>Follow-up Ascertainment</td>
<td>What is the completeness of follow-up and the minimization of missing data? Many studies show that &gt;95-98% follow-up is needed for reliability</td>
</tr>
<tr>
<td>Source for Inference</td>
<td>What is the research sample: random patients, all patients that consent, all patients at a designated hospital or clinic, all patients in the reference population (e.g., country)?</td>
</tr>
</tbody>
</table>
## Medical Device Surveillance Variations in Methodology and Reliability

<table>
<thead>
<tr>
<th>Level</th>
<th>Patient Entry Capture</th>
<th>Follow-Up</th>
<th>Data Specificity</th>
<th>Follow-up Ascertainment</th>
<th>Inference Source</th>
<th>Example</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>Passive Voluntary</td>
<td>High</td>
<td>Very Low</td>
<td>Reference population</td>
<td>FDA MAUDE</td>
<td>-Low Cost -Qualitative -Low biased rates</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>Active</td>
<td>Low</td>
<td>High</td>
<td>Reference population</td>
<td>US/UK National Death Index</td>
<td>-Low Cost -Reliable rates -Poor specificity</td>
</tr>
<tr>
<td>III</td>
<td>Low</td>
<td>Active</td>
<td>High</td>
<td>Low</td>
<td>Random patient sample</td>
<td>Most device registers</td>
<td>-Biased rates -Poor inference</td>
</tr>
</tbody>
</table>
## Medical Device Surveillance
**Variations in Methodology and Reliability (2)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Patient Entry Capture</th>
<th>Follow-Up</th>
<th>Data Specificity</th>
<th>Follow-up Ascertainment</th>
<th>Inference Source</th>
<th>Example</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>High</td>
<td>Active</td>
<td>High</td>
<td>High</td>
<td>Sample Clinical Sites</td>
<td>Post-approval network (PAN)</td>
<td>-Low Cost -Qualitative -Low biased rates</td>
</tr>
<tr>
<td>V</td>
<td>High</td>
<td>Active</td>
<td>Moderate</td>
<td>High</td>
<td>Reference Population</td>
<td>-UK NHS CPRD</td>
<td>-Reliable rates -Good inference on subsets</td>
</tr>
<tr>
<td>VI</td>
<td>High</td>
<td>Active</td>
<td>High</td>
<td>High</td>
<td>Reference Population</td>
<td>NHS National Joint Registry</td>
<td>-Reliable rates -Good inference on subsets -High specificity</td>
</tr>
</tbody>
</table>
Structured Clinical Trials and Adjudication

- Structured CRF, data dictionaries, standardization of endpoints, known consent pool, auditing

- Adjudication processes
  - Independent expert panel
  - Additional collateral data required
  - Academic processes: ARC, VARC, etc.
Patient-Reported Outcomes

- Unreliable, especially for rates
- Under- and Over-reporting of re-hospitalizations
- Most PROs are poorly structured

Barriers to the use of patient-reported outcomes in clinical care.

How Reliable are Patient-Reported Rehospitalizations?
Implications for the Design of Future Practical Clinical Studies
Krishnamoorthy, A; Peterson ED,; Knight JD, et al. J Am Heart Assoc
2016;5:2695
Completeness of Ascertainment

- Voluntary AE reports through the MDR process are vastly under-reported
- Rates do not equal reported AEs/Sales
- Incomplete ascertainment >20% can generate significant bias that make estimates unreliable

Value of Active Surveillance in Collecting Lead Adverse Event Data

Voluntary AE Reporting Biases
Medtronic Experience

- Substantial under-reporting for known AEs
- More reliable reporting for novel AEs.
Observational Registries
Real or Virtual

• Registry platform **is likely** the best platform for device surveillance
• The desire for frequent monitoring exists to take appropriate action and provide rapid design feedback
• Adequate adjudication will likely require adjunctive data outside the registry dataset
Adjudication for Clinical Research Using Unstructured Data Sources

• Fundamentals of reliable data sources must first be present: define the study sample, completeness of follow-up, standardized metrics

• Adjudication will not correct these fundamental flaws, especially incomplete ascertainment bias