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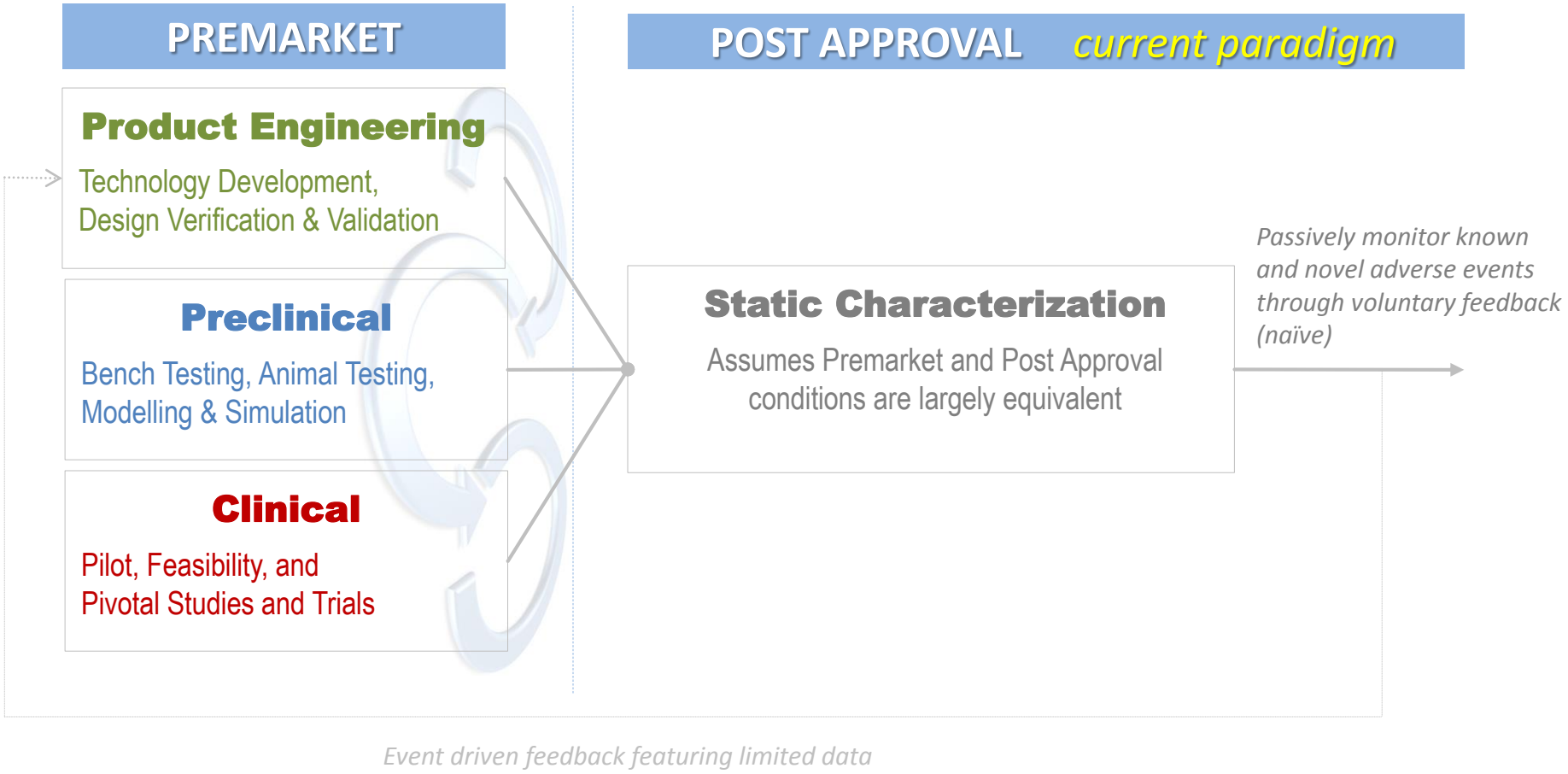
POSTMARKET SURVEILLANCE

RICK KUNTZ
MEDTRONIC

Problem Statement

- Compared with pre-market product development and evaluation processes, the post-market processes are less standardized and less quantified
  - Pre-market product evaluation processes:
    - Principal focus: Testing and characterizing the target population and product for distribution and application based on pre-market determined clinical, health economic and use characteristics
    - Methods: Pro-active, uniform and robust product design, development, verification/validation/DRM, clinical (+/- economic) evaluation and claims support
    - Assumptions: Performance, economic, safety and use characteristics are static
  - Post-market product evaluation processes:
    - Principal focus: Marketing and selling product features, established in pre-market evaluation, then react to random market and safety variances
    - Methods: One-off marketing and COA (conditions of approval) studies combined with a passive system of complaint handling, return product analyses, *ad hoc* market research and expert advisory panels

Product Characterization *progressing from a Pre-Market/Post Approval Mindset to Total Product Life Cycle Mindset*



Product Characterization *progressing from a Pre-Market/Post Approval Mindset to Total Product Life Cycle Mindset*

Product Engineering
Technology Development,
Design Verification,
Design Validation

Preclinical
Bench Testing,
Modelling,
Simulation,
Animal Testing

Clinical
Pilot,
Feasibility,
Pivotal
Studies and Trials

Paradigm	Philosophy	Tools
Present		
Static product characterization Fully characterized in pre-market, Short- and long-term efficacy and safety estimated and predicted, +/- Condition of Approval Studies **Assumption:** Post Approval and Premarket conditions are largely equivalent	Accept pre-market characterization (estimates and predictions) as gold standard Passively monitor known and novel adverse events through voluntary feedback **Consequences:** Inefficient and unreliable method to rapidly detect or predict problems, moderate likelihood of real or perceived catastrophe	Voluntary complaints, Returned Product Analyses, Complaint trends (not incidence rates), Expert opinions, Literature, Applied Quality Processes and SPC mindset
Future		
Dynamic product characterization Assume unknown Post-Approval dynamics affect prod. characterization + Real world variance + Lack of long-term data + Unknown use conditions in variable health care systems. **Mandate detailed product pre-market characterization for future comparison**	Update pre-market product characterization *via* **active re-characterization** against the pre-market product profile, **Results pro-actively reviewed quarterly** Consequences: 1. More controlled discovery of benefits and harms, more controlled actions 2. Platform for other value measurements 3. More robust product design feedback	*All of the above inputs, selectively applied, **plus**:* **Proactive** Observational studies, Device Registries, Electronic Health Records, **Focused Medical Safety** oversight with Clinical Research mindset

Medtronic Post-Market Product Evaluation Infrastructure v2.0

Post-Market Dynamics

- The post-market conditions that affect target population, product performance, use characteristics, health economics and safety are dynamic and underappreciated
  - Critical components:
    - Target population and use characteristics:
      - Real world use is not tested in pre-market controlled study sample, agnostic to dynamic and variable health care systems that change the patient mix
      - Long-term natural history of the disease and device interaction unknown
    - Product characteristics affected by:
      - Performance: Changes in efficacy, effectiveness, comparative effectiveness
      - Economic: Variable health care systems impact on costs, economic value, and cost-effectiveness
      - Safety: Assurance of pre-market safety claims and responsible discovery of new hazards in the near- and long-term

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Stakeholder Demands

- The critical stakeholders expect robust and quantified post-market data
  - Regulatory agencies:
    - Strong demand for product safety characterization using quantitative metrics and a clinical research mindset (medically classified adverse events, rates, comparisons)
    - More of an epidemiological mindset versus quality process mindset
    - Assurance that Field Corrective Actions are not driven by commercial interests
    - Demand for durability and Total Product Lifecycle (TPLC) data
  - Payers:
    - Increasing demand for economic value evidence for initial reimbursement
    - Data for proposed bundle payments

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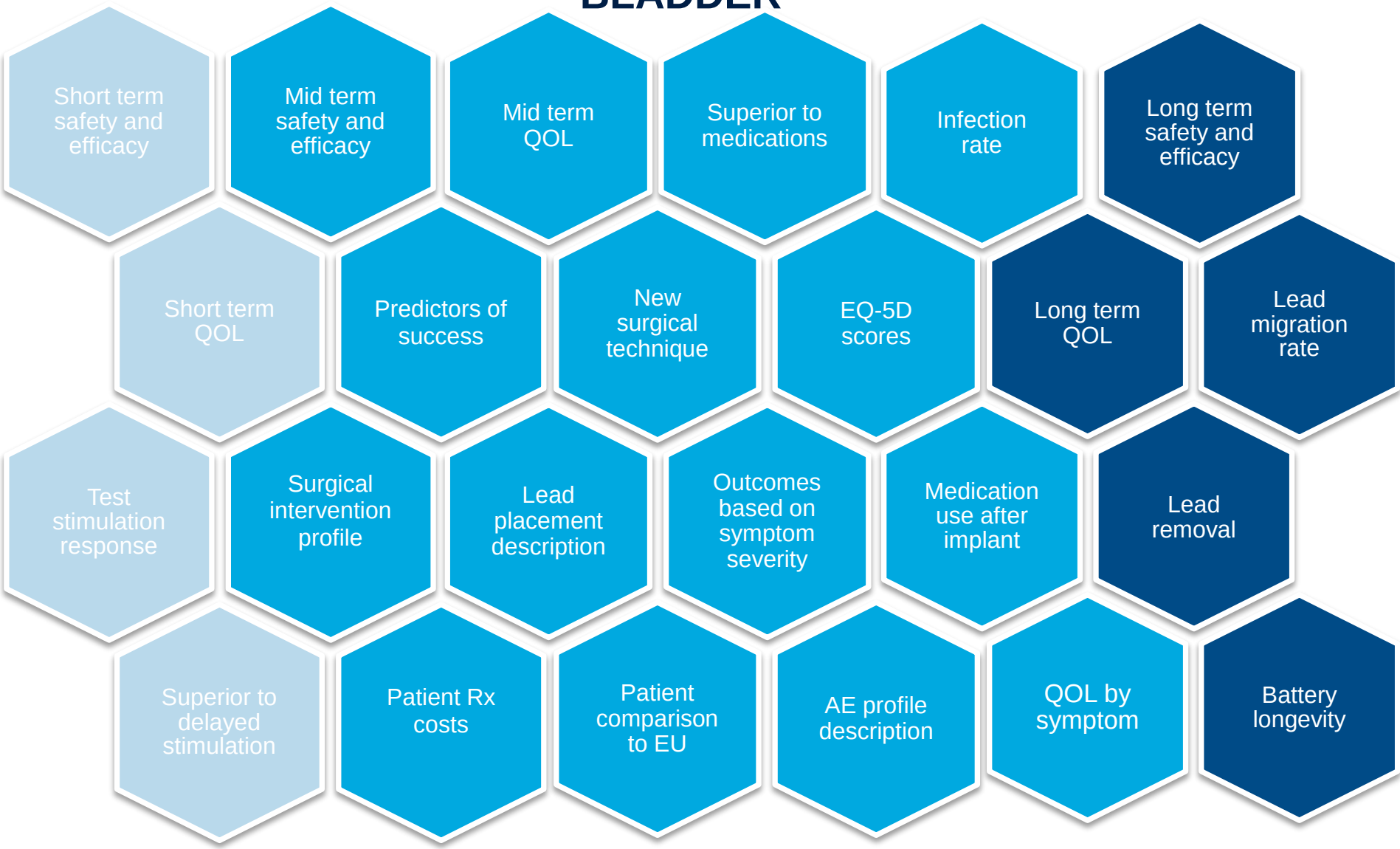
Stakeholder Demands

- The critical stakeholders expect robust and quantified post-market data
  - Providers:
    - Assurance of the performance and safety characteristics of the device that they prescribed is validated
    - Aware that decision-making may affected by subjective beliefs and marketing campaigns rather than solid evidence from rigorous post-market safety and efficacy follow-up and evaluation
  - Patients:
    - Assurance of the performance and safety characteristics that they signed up for in the decision to have the product used on their body
  - Academics:
    - Data transparency to corroborate claims
  - Internal:
    - Need robust quantitative performance data feedback loop to product designers
    - Robust economic data for economic value programs

LEARNINGS ABOUT INTERSTIM THERAPY FOR OVERACTIVE BLADDER



Medtronic

Medtronic Post-Market Product Evaluation Infrastructure v2.0

Present Limitations

Present shortcomings in meeting post-market data demands

- Lack of standard post-market data infrastructure
  - Market, product performance and safety data demands will not be satisfied by one-off use of existing clinical research tools *(traditional clinical trial & study development conduct)*
  - Future: Leveraging lean clinical platforms and repurposing practice data (EHRs)
- Antiquated post-market passive vigilance program based on voluntary complaints and arbitrary classification of safety concerns in terms of severity and frequency:
  - Qualitative measurements reduce certainty of agreement on actions
  - Analyses and reporting (MDRs) are not used in any meaningful way
  - All stakeholders, including the FDA, are eager to develop a better vigilance system
- Unclear Medical Safety Leadership:
  - Not well-defined in the medical technology industry
  - Medical/epidemiological mindset not core to Quality Management system

OBJECTIVES

Modernize Post Market Surveillance System to:

- Improve estimate of real harm post market approval with leading indicators
- Optimize Complaint Handling system:
  - Preserve sensitivity for new harms/new failure modes
  - Reduce burden of low value activities & lagging indicators
  - Allow focus on continuous improvement (collective statistics feed into design/production)
- Develop stronger partnership between industry and FDA by providing better transparency
- Align with Total Product Life Cycle and post-market clinical study commitments

WHY

- Improve reliability of Post Market Surveillance Data
- Complaints are lagging indicators and not indicative of true rates as there is a bias in reporting complaints

- Improve patient/user/HCP/regulator confidence in our products

- Current process of submitting individual MDRs
- Is not aligned with goals of post-market surveillance to improve patient safety and standard of care
- Does not inform product quality decisions (although Medtronic Diabetes is now submitting 7x more individual MDRs, these are known problems, the business unit did not learn anything new)
- Is not sustainable with current volumes (spiralling out of control) – emphasis on minute processes/record quality vs holistic value
- Does not inform patients

WHAT

- **Introduce Registry** to:
- Measure rates of known harms & benefits determined by pre-market studies and published literature
- Scale:
  - Develop core data standards
  - Leverage practice data/EHR wherever possible (improve practice standards)

- **Preserve CH system** to:
- Register all complaints- counts will be used to drive continuous product improvement
- Improve investigations on new harms/malfunctions/failure mode

- **Reduce CH activities**
- on individual complaint records that do not help to characterize known harms/malfunctions/failure modes

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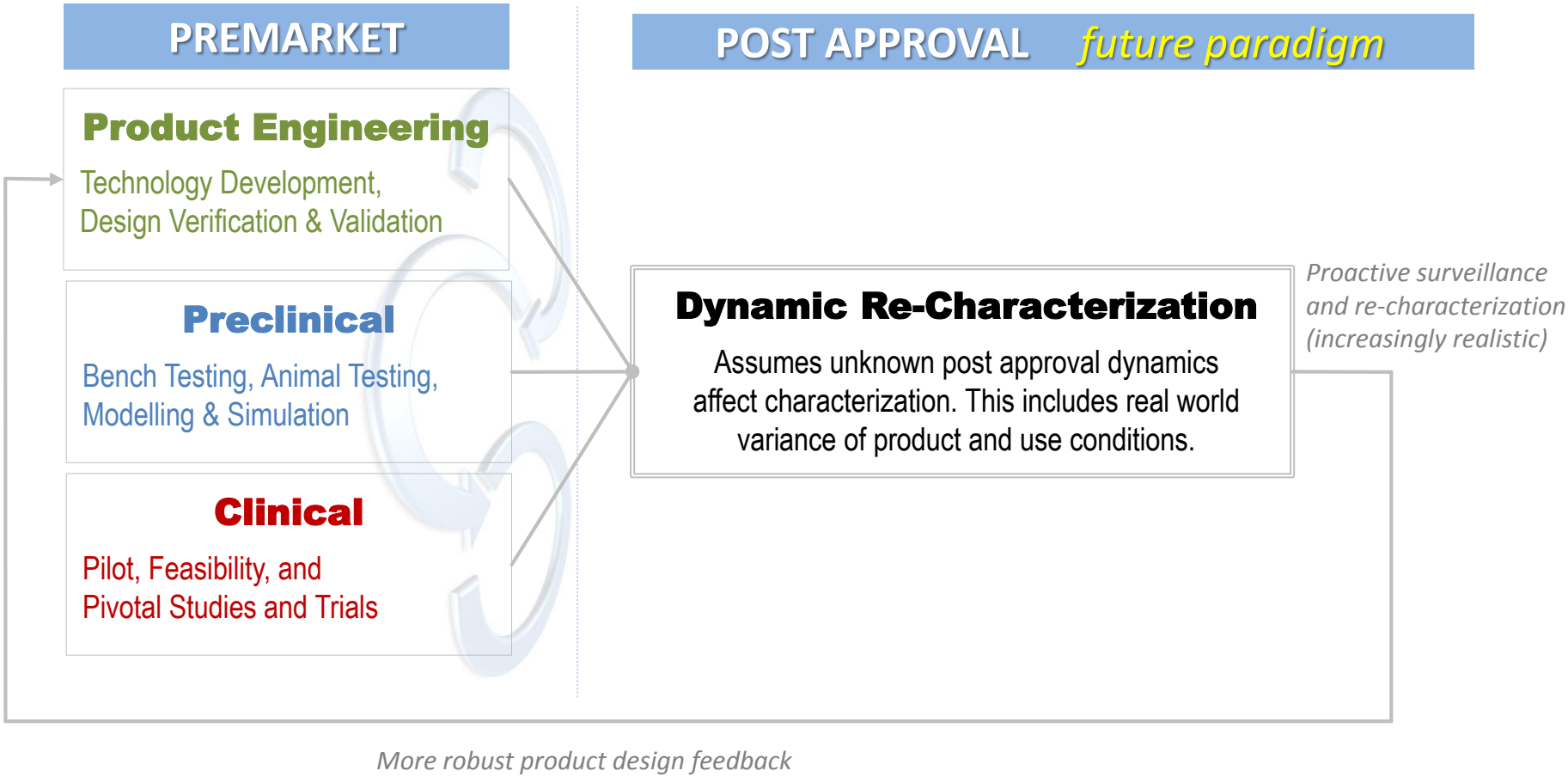

Registries: Lessons Learned

Experience from >15 years post-market surveillance registries

- Finding scale is hard
- Registries are expensive
- Investigators want pet data sets to participate
- Not a solution for Class II devices (surgical stapler, syringe needle, rubella test…)
- TVT is not scalable for Class III devices
- Sample smartly (not everyone needs to be evaluated)
- Leverage the growing standardization of EHRs whenever possible

National Device Registry

Step in the right direction

- Must mesh with post-market vigilance quality system
- Standalone registry for all devices is a stop gap measure
- Developing a single practice dataset that serves both practice and surveillance should be the ultimate goal
  - **For Class II and III device surveillance, an interoperable multi-source program of data (registries, EHRs, claims) will be be the best program.**
- Transparency and data sharing among all stakeholders is the key to success
- Payment for the National Registry will have to come from reduction in the current CH Vigilance system