Clinical Research and Adjudication

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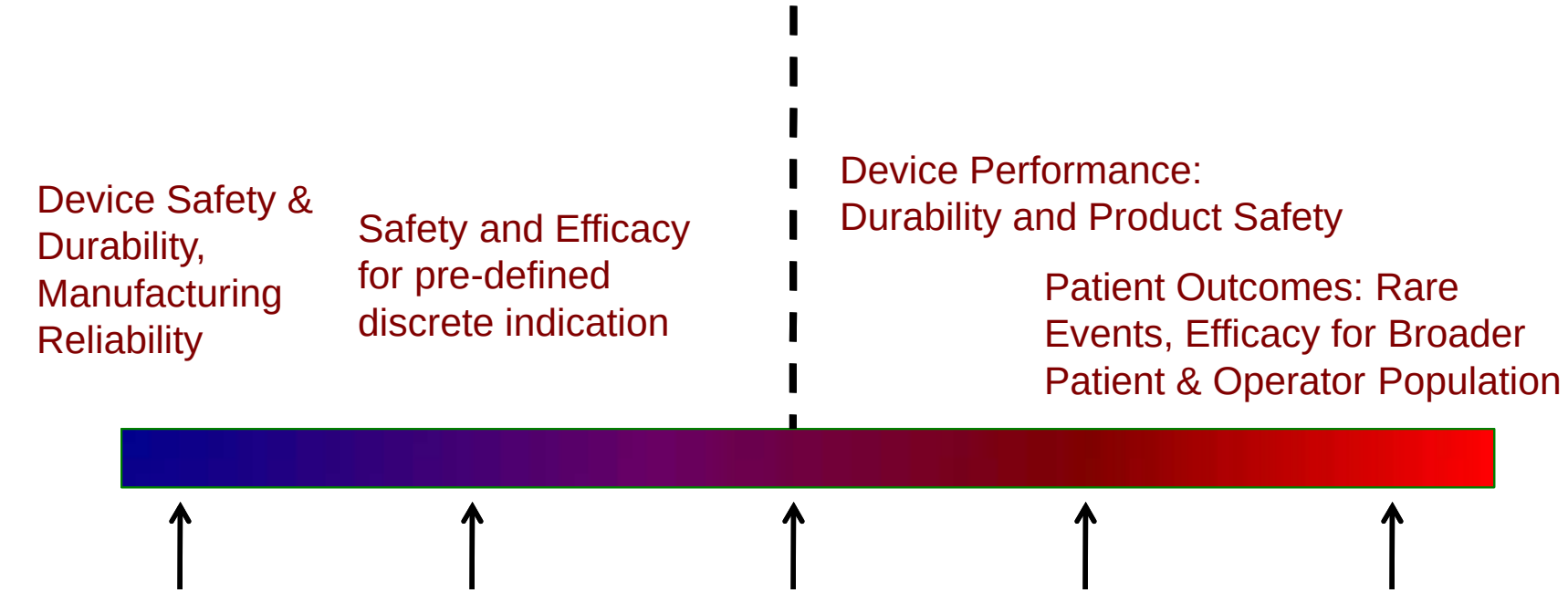
Medical Device Unanswered Questions
Need for Surveillance

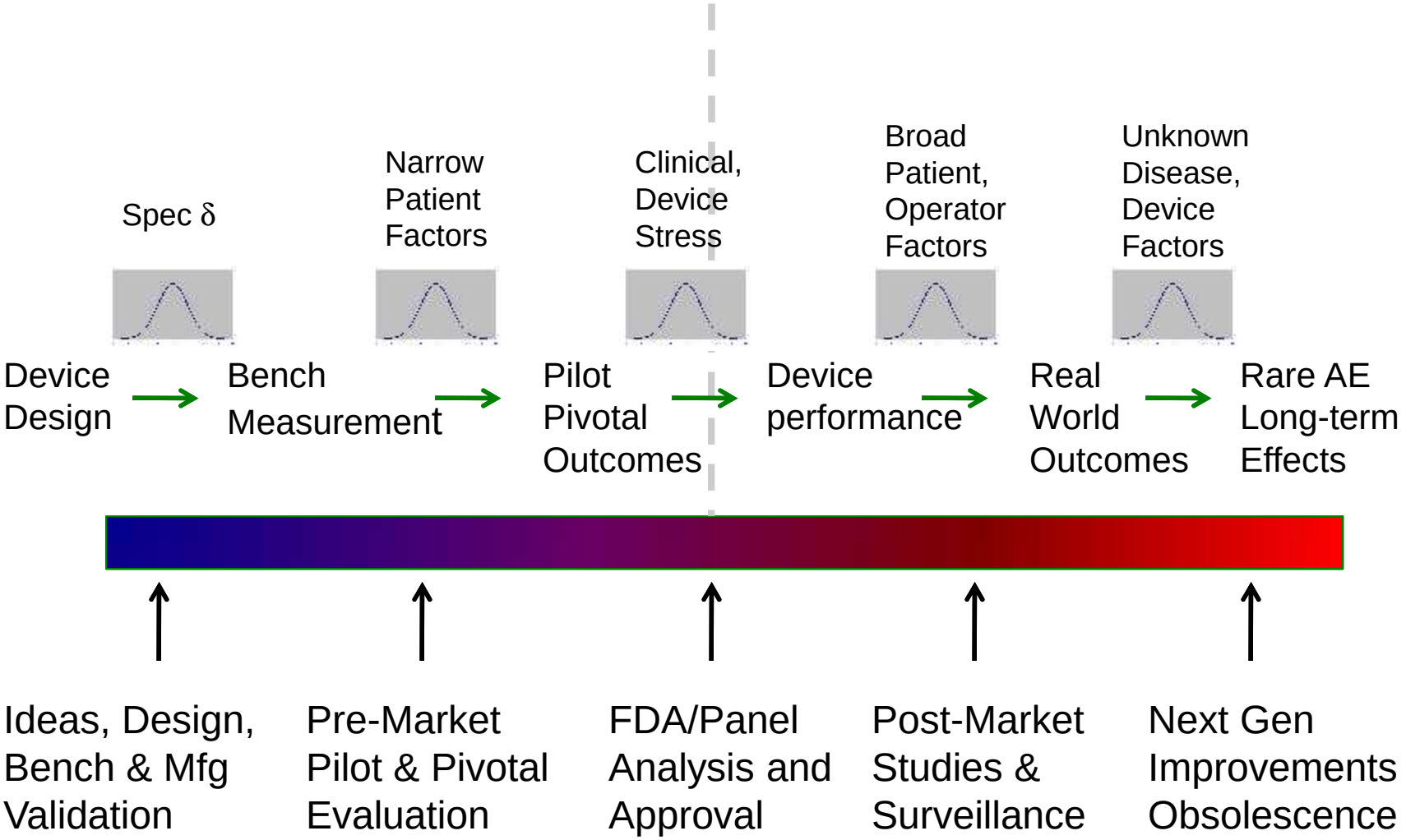
- **Device performance: Efficacy confirmation**
  - Does the device work as intended, confirming pre-market study expectations?
- **Long-term device efficacy**
  - Does the device have a sustainable effect, change the natural history of the disease, or improve the Standard-of-Care?
- **Device Effectiveness: 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



Medical Device Lifecycle (TPLC)
Pathophysiology-Treatment Variables



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

Design Element	Comments
Patient Capture at Entry	How is the patient captured for research: partial or complete?
Follow-up Method	Is the follow-up passive or active. Are "pertinent negatives" documented?
Endpoint Specificity	How specific are the endpoints to the device? Is the data from electronic health records, general research fields, or special "add-on" elements?
Follow-up Ascertainment	What is the completeness of follow-up and the minimization of missing data? Many studies show that >95-98% follow-up is needed for reliability
Source for Inference	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)?

Medical Device Surveillance

Variations in Methodology and Reliability

Level	Patient Entry Capture	Follow-Up	Data Specificity	Follow-up Ascertain-ment	Inference Source	Example	Comment
I	None	Passive Volun-tary	High	Very Low	Reference population	FDA MAUDE	-Low Cost -Qualitative -Low biased rates
II	None	Active	Low	High	Reference population	US/UK National Death Index	-Low Cost -Reliable rates -Poor specificity
III	Low	Active	High	Low	Random patient sample	Most device registers	-Biased rates -Poor inference

Medical Device Surveillance

Variations in Methodology and Reliability (2)

Level	Patient Entry Capture	Follow-Up	Data Specificity	Follow-up Ascertain--ment	Inference Source	Example	Comment
IV	High	Active	High	High	Sample Clinical Sites	Post-approval network (PAN)	-Low Cost -Qualitative -Low biased rates
V	High	Active	Moderate	High	Reference Population	-UK NHS CPRD	-Reliable rates -Good inference on subsets
VI	High	Active	High	High	Reference Population	NHS National Joint Registry	-Reliable rates -Good inference on subsets -High specificity

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.

Spertus J.
Circ Cardiovasc Qual Outcomes. 2014 Jan;7(1):2-4.

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
Cutts E, Paulsen J, Jones P, et al. *Heart Rhythm*, May 2014

Kuntz RE, Keaney KM, Senerchia C, Baim DS. Estimating the late results of coronary intervention from incomplete angiographic follow-up. *Circulation* 1993;87:815-30.

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