METHODOLOGICAL CHALLENGES & SOLUTIONS

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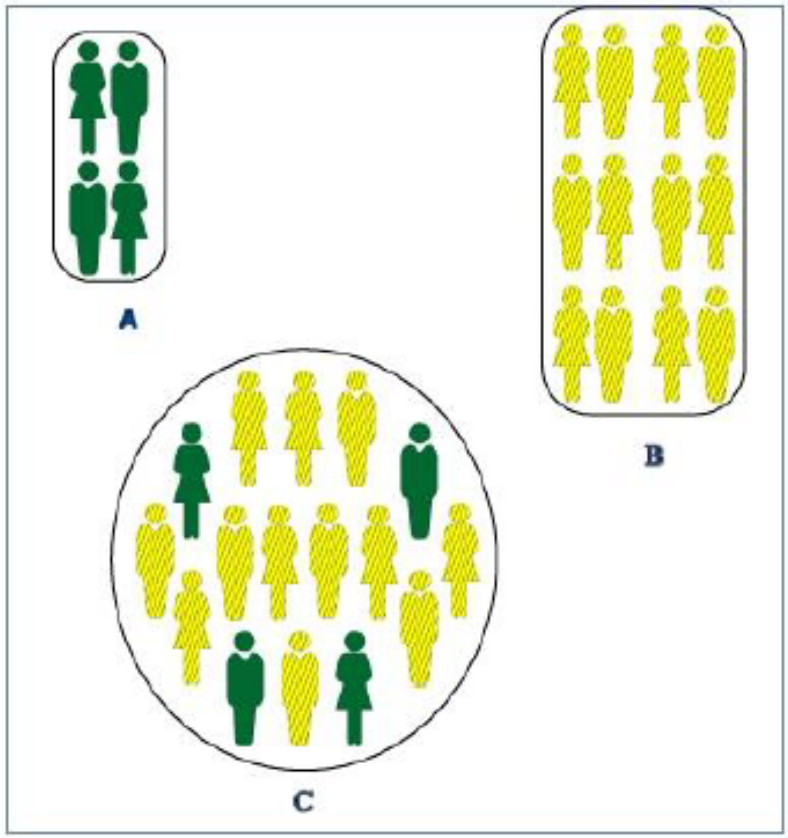
(on behalf of the Medical Device Registry Task Force)

KEY SUMMARY POINTS

- CRNs will involve **heterogeneity** in data collection, patient populations, clinical centers, and operators
- Information **aggregated** to the component registry level may be sufficient for some device assessment activities but insufficient for others

KEY SUMMARY POINTS

- CRN construction should focus on:
  - Minimizing **quality heterogeneity** (data element definitions, measurement error, etc.)
  - Supporting **poolability** to maximize information from enriched
    - Patient populations
    - Device populations
    - Operator populations



KEY SUMMARY POINTS

- Capitalize on **variation** across component registries within the CRN to quantify benefits/risks for particular:
  - Patient subgroups
  - Medical devices
- **Signal detection** via CRN requires consistent, standardized data with sufficiently specified devices and outcomes

KEY SUMMARY POINTS

- CRN data can provide vital information for **premarket** designs
  - **Label extensions**: pool data across heterogeneous patient populations exposed to a particular device to learn about benefits/risks in a **new population**
  - **Clearance** for competitive iterations of similar devices: pool data across multiple devices within a particular patient group to infer benefits/risks for a **new but similar device**

3 PILOT STUDIES

Pilot I

Determining the Sufficiency of Summary Statistics for Use in CRNs Methodology-focused pilot project: theoretical derivations, simulation-based summaries, and illustration of approaches to characterizing conditions in (in the context of a CRN) which: • component registry summary statistics provide unbiased estimates of device performance • summary statistics are biased • missing data	
1. Disease/device focus	Applicable to any condition or device
2. Immediate research question(s)	When do component registry summary statistics provide unbiased estimates of device performance? When are registry summary statistics biased and can approaches reduce the bias?
3. Stakeholders engaged	Statistical and epidemiological researchers from industry, academia, and FDA; for illustrative application, patient representatives from example device area and CRN component registry owner representatives.
4. Existing national resources leveraged	Methodology illustrated using existing national or international registries such as ICOR, TVT Registry, etc.
5. Efficiencies promoted	Study results will indicate when it is statistically valid to use a "distributed" network approach versus combining individual participant data. Consequently, results from this pilot will promote the best (optimal) use of patient data and thereby reduce the number of observations (patients) required to inform regulators, patients, and physicians.

Pilot II

Pooling Data for Making Regulatory Decisions in CRN Methodology-specific pilot: theoretical derivations, simulation-based summaries, and empirical approaches to characterizing the validity of pooling assumptions and the coherence of comparisons, determination of a minimum number of observations required, and approaches to representing uncertainty of the strengths of relationships in the context of label extensions, signal detection,, and clearance of predicate devices.	
1. Disease/device focus	Applicable to any condition or device
2. Immediate research question(s)	What is the validity of pooling assumptions made in the context of CRNs? What types of devices and populations can be compared? What is the minimum number of observations required for label extensions or clearance of predicate devices? How can uncertainty of the strengths of relationships be best represented? How can big data techniques (e.g., data mining, machine learning) be utilized for signal detection?
3. Stakeholders engaged	Statistical and epidemiological researchers from industry, academia, and FDA; for illustrative application, patient representatives from example device area and CRN component registry owner representatives.
4. Existing national resources leveraged	Methodology illustrated using existing national or international registries such as ICOR, TVT Registry etc.
5. Efficiencies promoted	Study results will indicate how to develop more efficient (statistical efficiencies) estimates for regulatory inferences.

Pilot III

Statistical Approaches for Informing the Device Total Product Life Cycle Because the CRN will enable shifting some premarket device data collection requirements to the postmarket setting, this shift requires the use of valid and reliable data elements that reflect the outcomes of interest in well-defined populations. Approaches for using CRN data to provide: (a) important long-term device performance information for mature devices; (b) solid intelligence to help improve the device; and (c) evidence on which patients are the best candidates for a device require assessment and illustration	
1. **Disease/device focus**	Applicable to any condition or device
2. **Immediate research question(s)**	How comparable are data elements and definitions between claims data and pivotal clinical trials? Case Study: percutaneous mitral valve devices will be used to assess validity of outcomes event ascertainment (death, re-hospitalization, heart failure progression, stroke, etc.) using claims data compared to classical clinical trial processes. Can patient reported outcomes be utilized to assess device benefit? How can stakeholder preferences be factored into the benefit/risk assessment?
3. **Stakeholders engaged**	Statistical and epidemiological researchers from industry, academia, and FDA; for illustrative application, patient representatives from example device area and CRN component registry owner representatives.
4. **Existing national resources leveraged**	Methodology illustrated using existing national registries such as the MDEpiNet PASSION programs, the ACC-NCDR TVT registry; ONC/CDISC definition dictionaries; ICD code structures. Stakeholder utility banks could be constructed and leveraged for future device assessments.