# 10-year Follow-up Meets the Real-World: Expectations and Caveats

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Grants / Contracts: American College of Cardiology, American Heart Association, National Institutes of Health (R01 and UG3/UH3), Food and Drug Administration, Edwards Lifesciences, Idorsia

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| Individual Stock(s)/Stock Options | None |
| Royalties/Patent Beneficiary | None |
| Executive Role/Ownership Interest | None |
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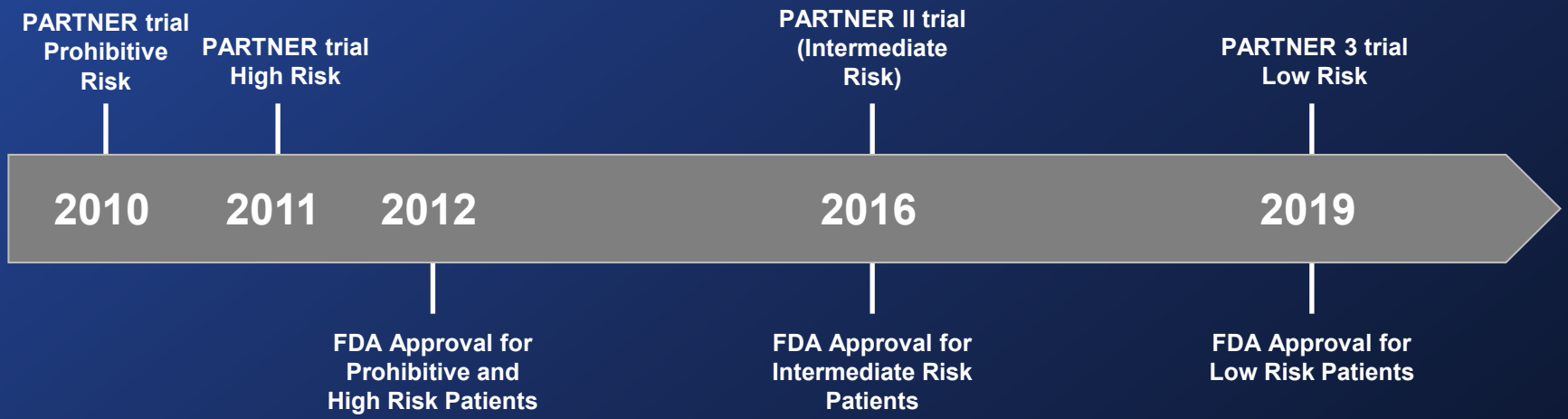
# Outline

- TAVR Evolution, Lifespan, and the Need for 10-year Follow-up
- Practical Difficulties of 10-year follow-up
- Competing Risk of Death
- Missingness at Random and Bias
- Reconsent and Vital Status Sweeps
- A Path Forward: Infrastructure and Consensus Solutions
- Conclusion

# The evolution of TAVR



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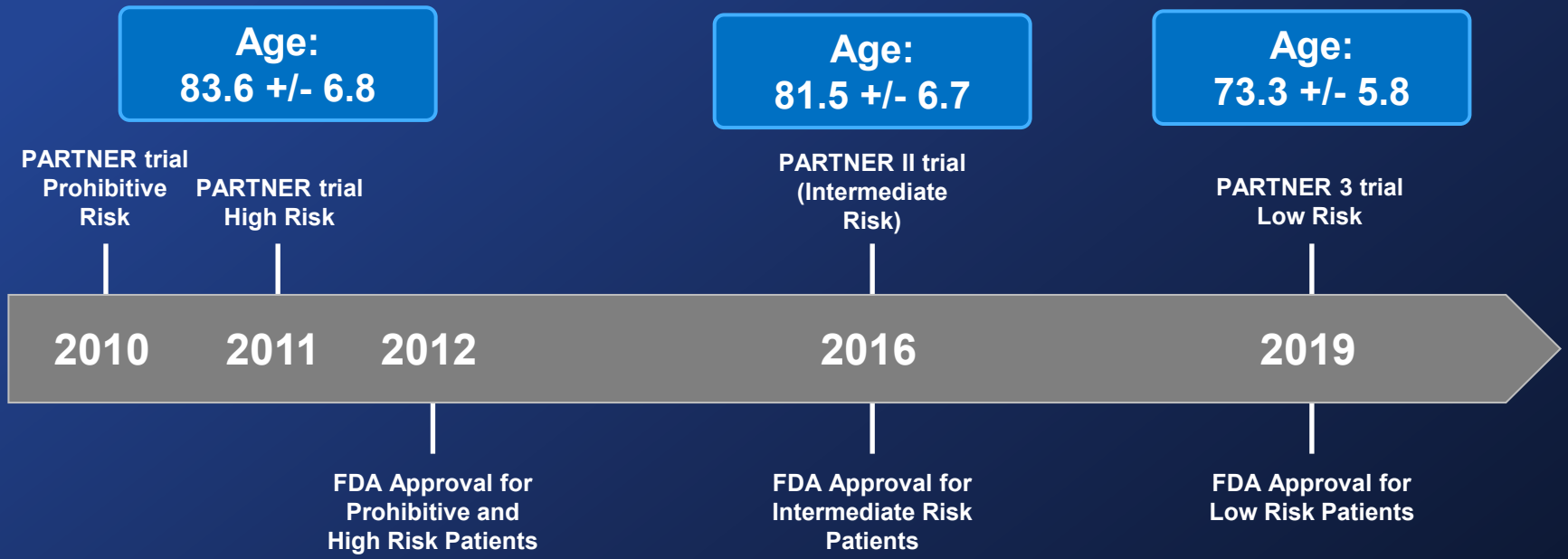

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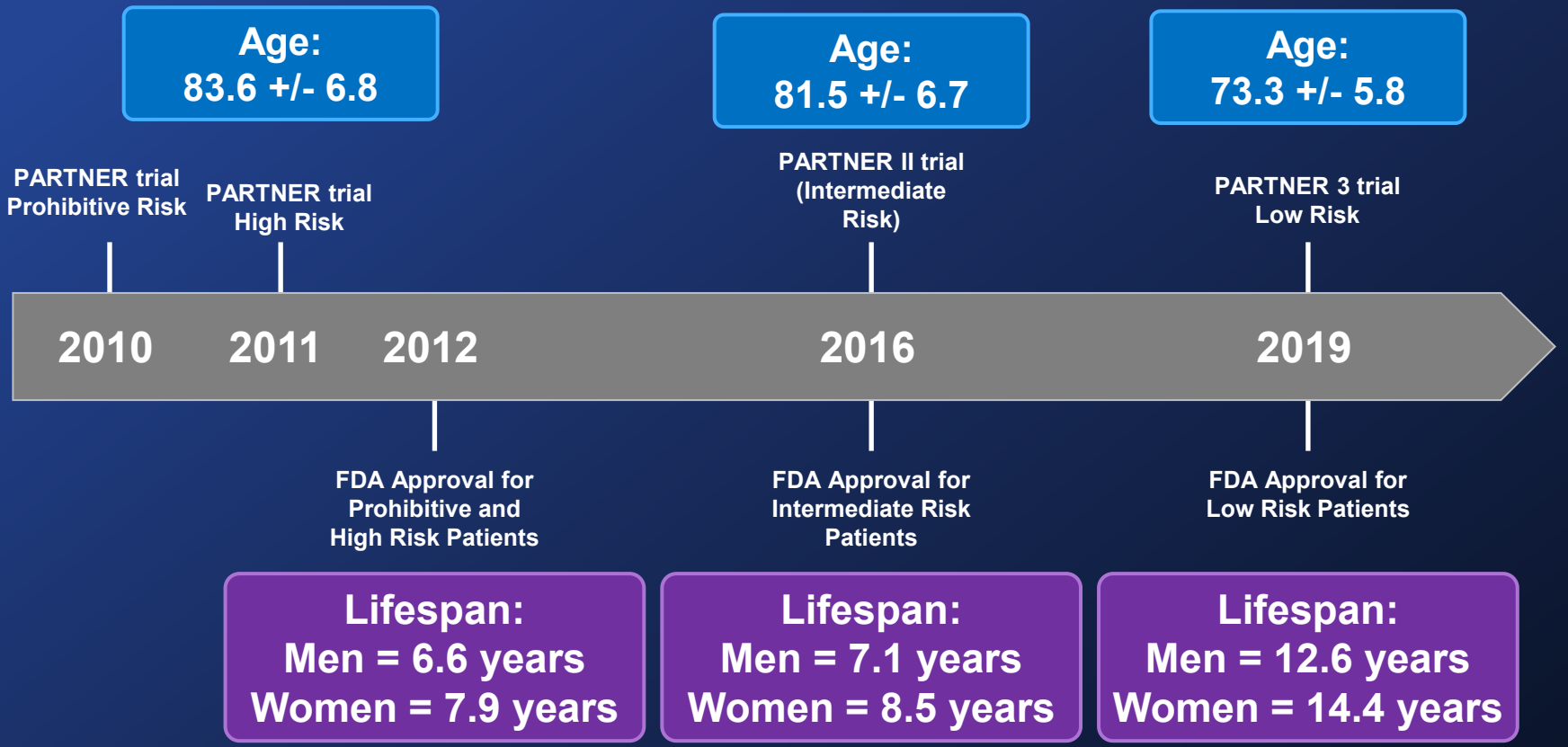
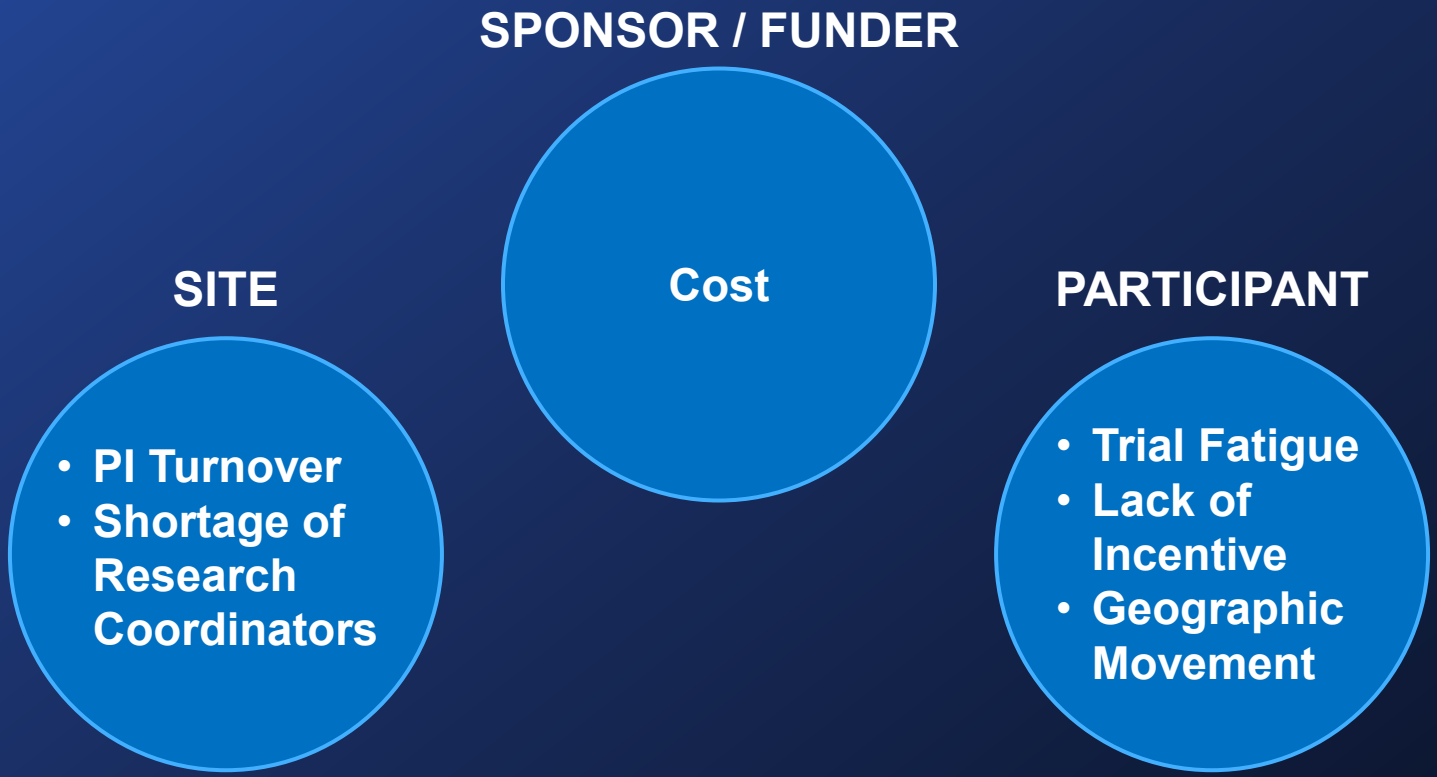
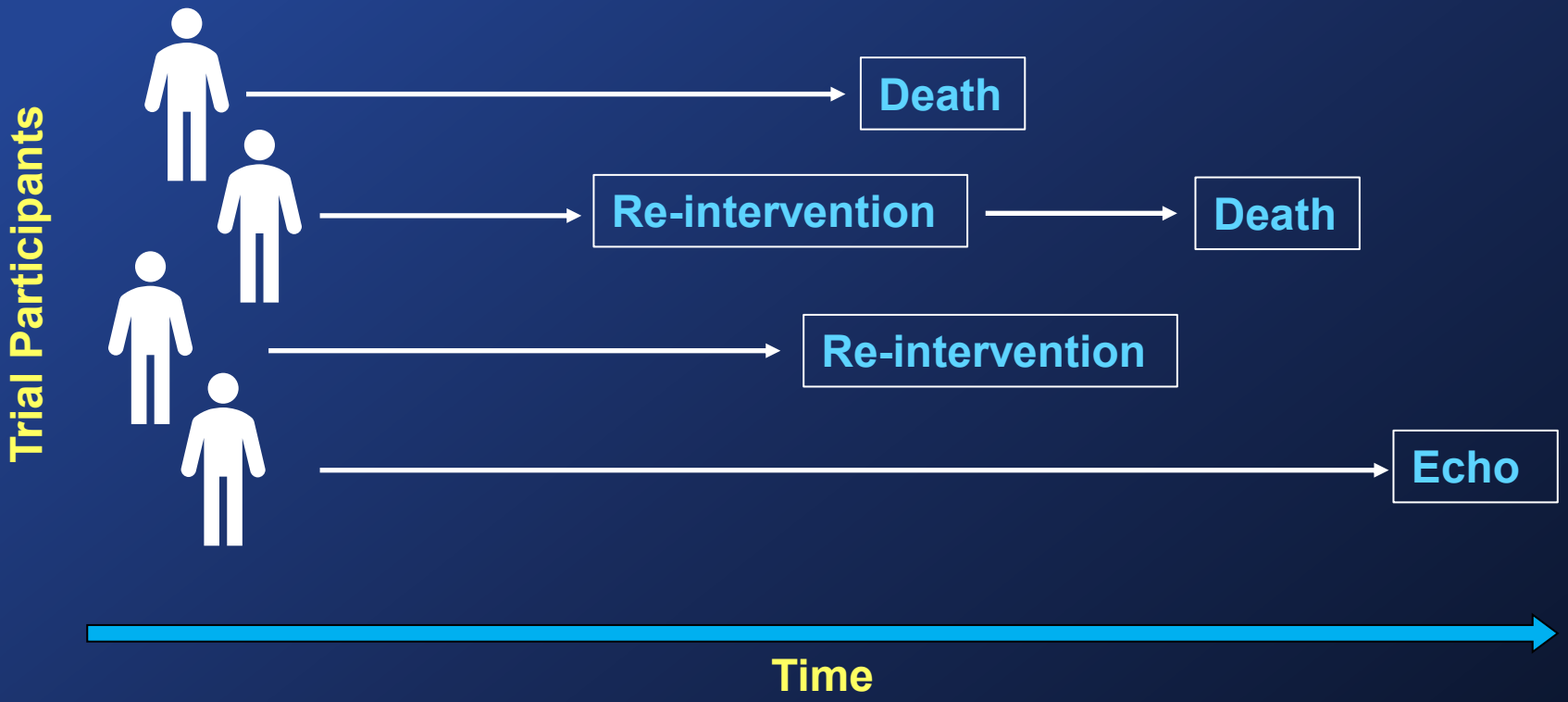


# Practical difficulties of 10-year follow-up



# Practical difficulties of 10-year follow-up

# Competing risk of death

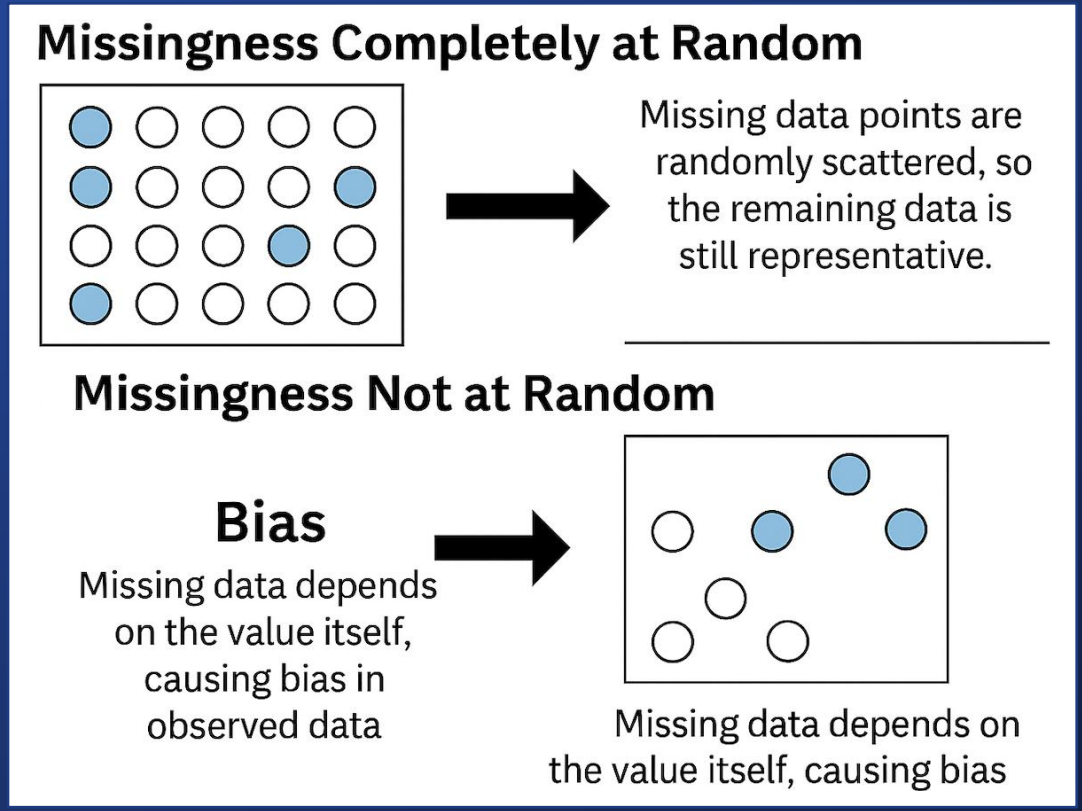


# Competing risk of death

Trial Participants

1. Death prevents the observation of non-fatal events / data
2. “Missingness” of non-fatal endpoints due to death is unavoidable and likely in TAVR trials due age and comorbidity
3. Sensitivity analyses to account for competing risk of death

# Missingness at random and bias



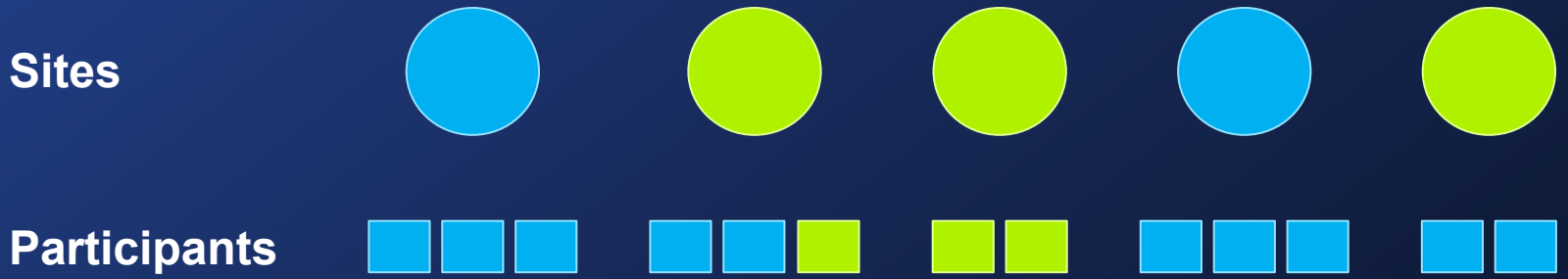

**Previous analyses suggest Missingness is non-random**

**Greater Missingness in:**

- **Lower QOL**
- **Surgical Patients**
- **Older age / frailty**
- **Distance to site**

# Reconsent

- Reconsent may be required when study follow-up is extended
- There is no clear guidance on how to obtain reconsent
- Reconsent is an “intercurrent event” that can improve data completeness but can also introduce bias



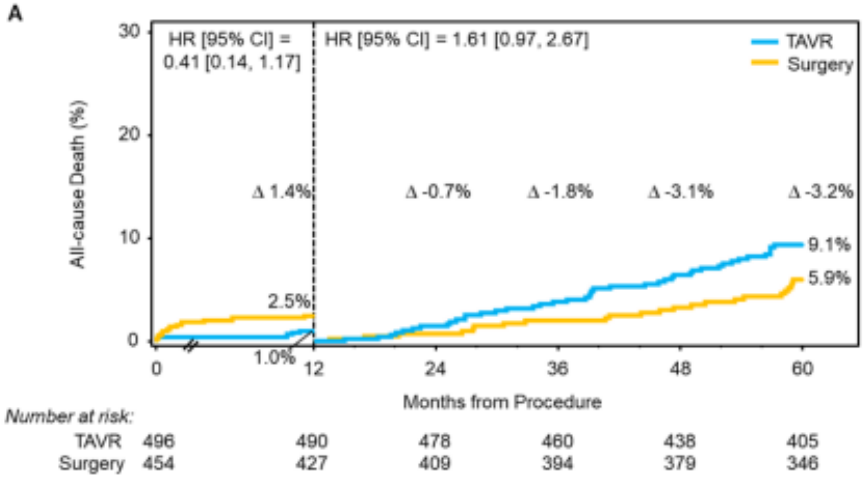
# Vital status sweeps

- Electronic Medical Records Review
- Obituaries
- Next of Kin / PCP / Designated Contact
- Lexis/Nexis
- National Death Index (12–24-month data lag)
- ~~Social Security Death Index~~
- National Health Databases (not available in US)

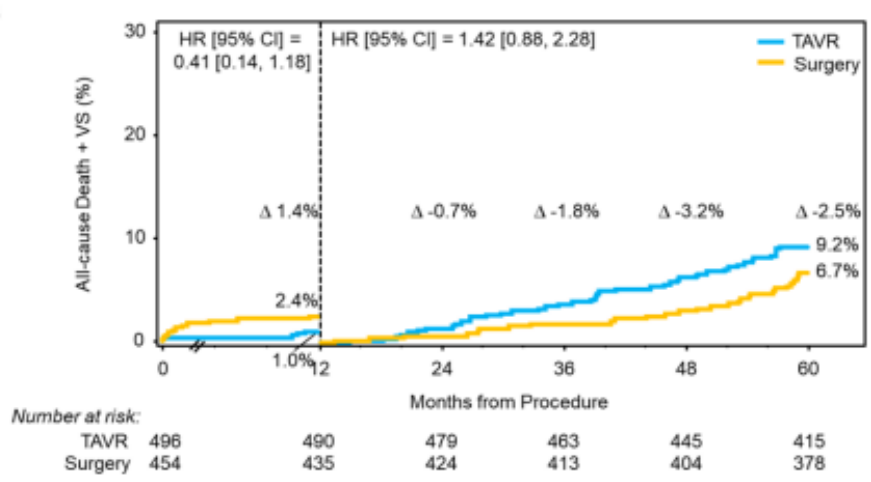
# Landmark Analysis and missingness in long-term follow-up: PARTNER 3 trial 5-year follow-up

***Of 95 patients identified, the alive or death status was obtained for 66 patients (N=21 TAVR, N=45 Surgery).***

## Without Vital Status Sweep

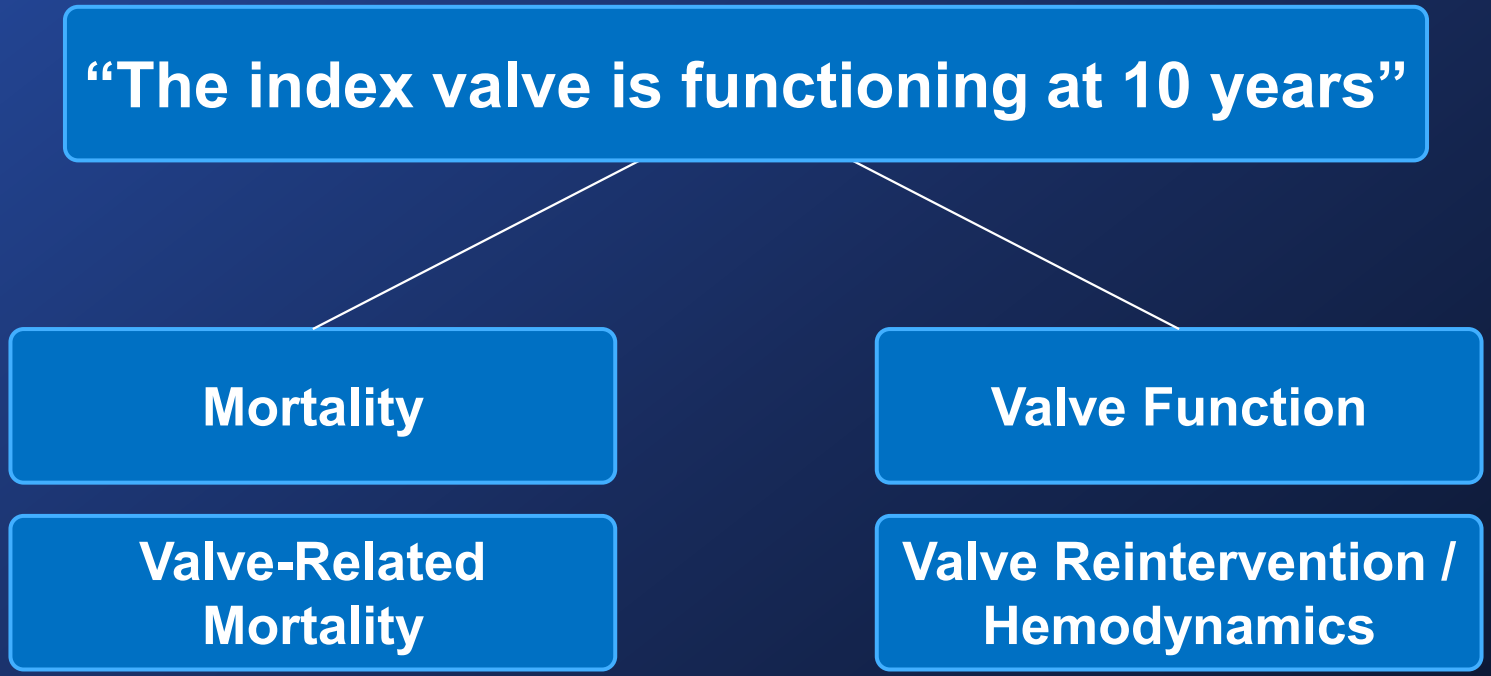



## With Vital Status Sweep



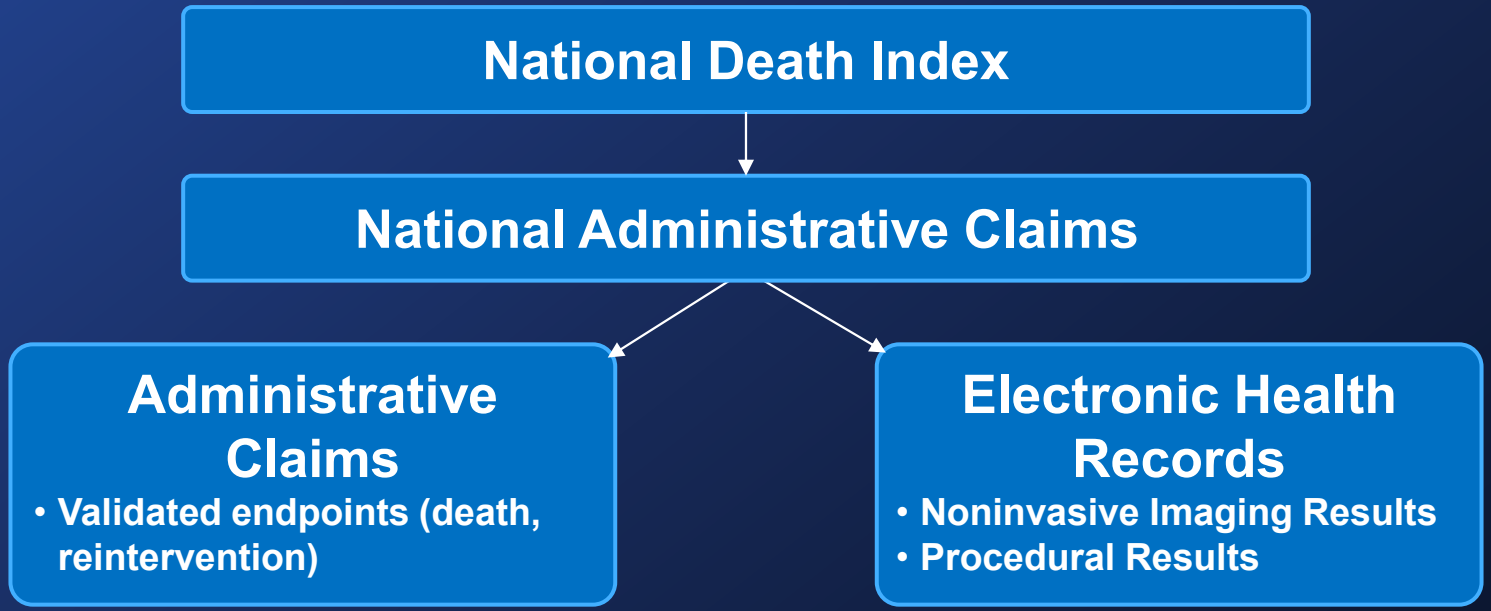

Mack MJ, et al. N Engl J Med 2019;380(18):1695-1705.

# A path forward: endpoint of interest



# A (reusable) path forward

- Consent to linkage at study enrollment
- Data Sources




# Are we there yet?


| Data Source | Pros | Cons | Validation State |
|---|---|---|---|
| Administrative Claims | Easy availability | Lacks granularity<br>Doesn't procedural and non-invasive imaging results | Well validated against adjudicated data for Death, Heart Failure Hospitalization, Re-intervention |
| National Death Index Lexis/Nexis | Definitive national resource on vital status | Lag in Data (12 – 24 months) | Well validated |
| Electronic Health Records | Granular | Unstructured, difficult data access | Little validation against gold standard (adjudicated data, audited registries) |
| National Registries | Intermediate granularity | Data Ownership, Data Lag, Decreasing Data Completeness over time | Data is audited, National Coverage Decisions, Previous Adjudication of selected endpoints |
| Chargemasters | Granular device data with serial numbers | Difficult data access | Little validation against gold standard |
| Direct to Patient Apps / Patient Reported Data | Mobile, Asynchronous, "Low touch" | Requires upfront consent for contact and alternative contact. Patient burden | Prior Research (Adaptable Trial) suggests Direct to Patient Doesn't Correspond Well to EHR for Hard Outcomes |

# Conclusions

- **The application of TAVR to lower risk and younger patient populations drives the need for 10-year follow-up**
- **10-year follow-up is currently burdensome for sponsors, health systems, and patients and is created de novo for each trial**
- **Burden → non-random missing data → bias**
- **Completeness of data**
  - Reconsent → bias
  - Endpoint of interest: “The index valve is functioning at 10 years”
  - Path forward:  Supplement trial data with fit for purpose passive follow-up data
- **We still need validation of many data sources**

# What to watch for in long-term studies

- **Endpoints of Interest:  Mortality, Re-intervention, Hemodynamics**
- **Is Competing Risk of Death Appropriately Addressed for Non-Fatal Endpoints?**
  - Echos not done due to death do not represent poor trial conduct!
- **For True Missing Data is There Any Attempt to Assess for Non-Random Missingness?**
- **Combating Missingness: Reconsent and Vital Status Sweeps?**
- **Are There Attempts Made to Account for Missingness?**

# *Thank you*

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