

Adjudicating Cardiovascular Events in Immuno-oncology Trials

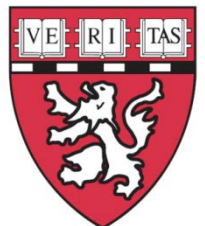
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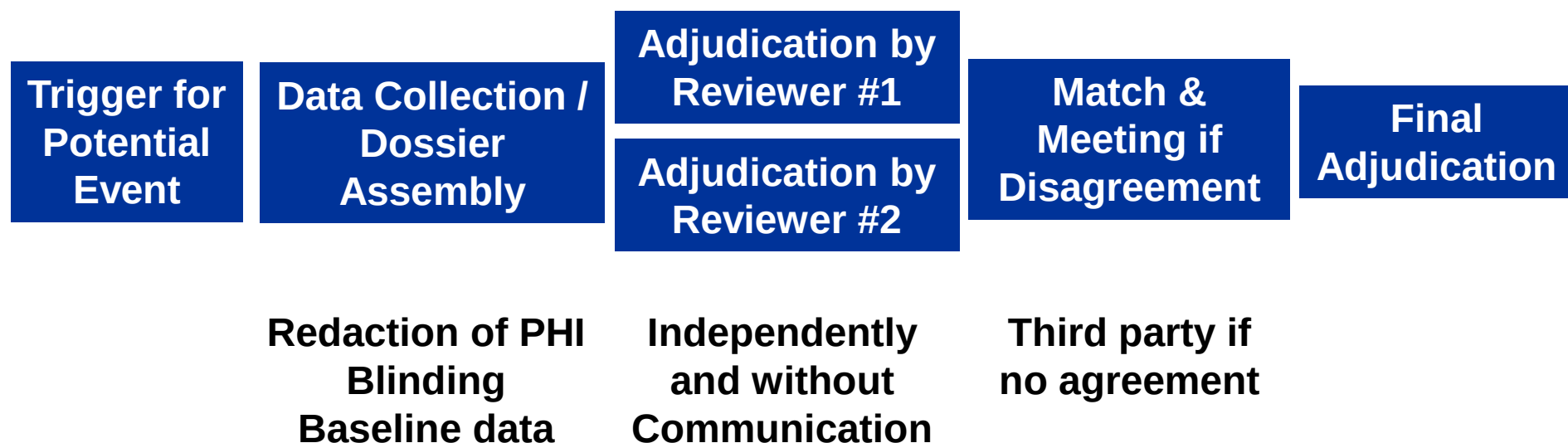
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| Heart & Vascular Center |





General Process of Adjudication



Uniform definitions increase specificity and may allow for comparisons across trials



General Considerations

What is the primary goal of adjudication?

Efficacy

- Trials well powered
- Site initiated reporting
- Events generally familiar to investigators
- Often dedicated event pages
- Prospective collection

Safety

- Often underpowered / rare events
- May be triggered from safety data
- Off target effects may be unfamiliar to investigators
- May be initiated mid trial with mix of retrospective and prospective collection



Scope of Adjudication

Narrow – only event of interest?

Broad – other related events?

Potential Drug Effect

**Myocardial injury /
Myocarditis**

Potential indicators:

- Elevation of Cardiac Biomarkers
- Cardiac dysfunction
- Dyspnea / Chest pain

Side effects of Background Therapies & Procedures

**Hypertension &
Hypertensive Crisis**

Potential Indicators

- Elevation of Cardiac Biomarkers
- Cardiac dysfunction
- Dyspnea / Chest pain

Common Events Related to Disease State

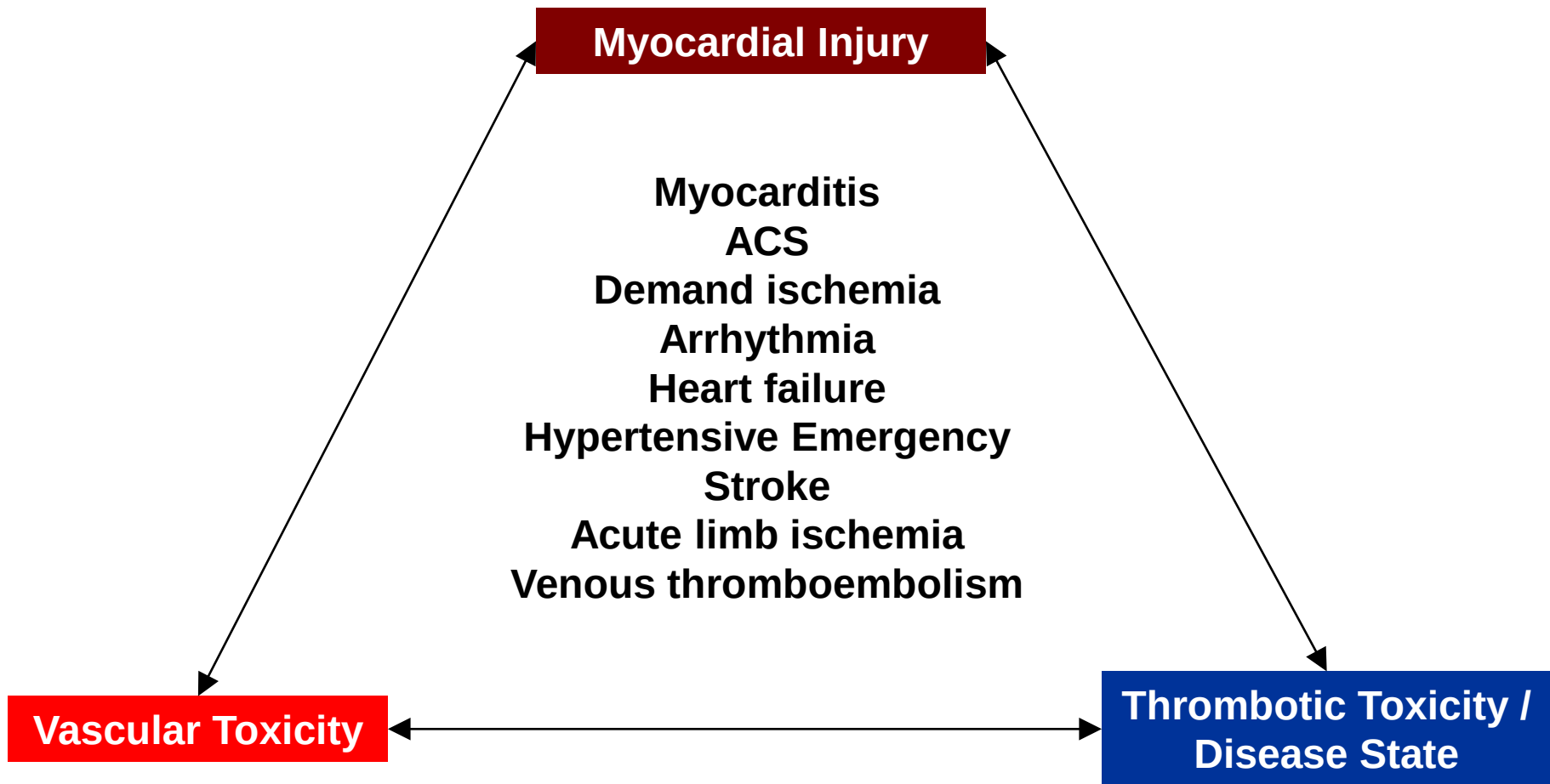
**Venous
Thromboembolism**

Potential Indicators

- Elevation of Cardiac Biomarkers
- Cardiac dysfunction
- Dyspnea / Chest pain

Scope

Primary Concern Cardiac Toxicity (Narrow)



Comprehensive Cardiac and Vascular Scope



Triggering of Events

Site Triggered

- Sites need to be trained on which events to report
- Everything entered is adjudicated
- Dedicated forms allow for structured data collection
- Usually done for efficacy and sometimes known safety events

Centrally Triggered

- Reviewer triggered – what sensitivity /specificity?
- Only events meeting specific criteria adjudicated
- No dedicated forms, based on event terms and narratives
- Usually safety especially if identified after trial initiation



Triggering of Events

Site / Investigator Triggering

- Cast a broad net (example periprocedural MI)
- Don't have to agree with diagnosis
- Unbiased
- Create traps to capture missed events (biomarkers, SAE review, etc.)

Central triggering

- Potential for under ascertainment – unlikely to bias but may lower event rates (and power to determine difference)
- Difficult due to “noise” and lack of specificity in safety data

Blinding Important!



Charter Definitions

Death

- CV (cause specific) vs. non-CV

Cardiac Events

- ACS
- Non-ischemic injury
 - Myocarditis
 - Non-specific (biomarker)

Pulmonary Edema / Heart Failure

Heart Rhythm Events

Hypertensive Complications

Cerebrovascular Events

Peripheral Artery Events

- Thrombotic/ischemic
- Vasospasm
- Dissection

Venous thromboembolism

Established
Definitions

Emerging
Definitions

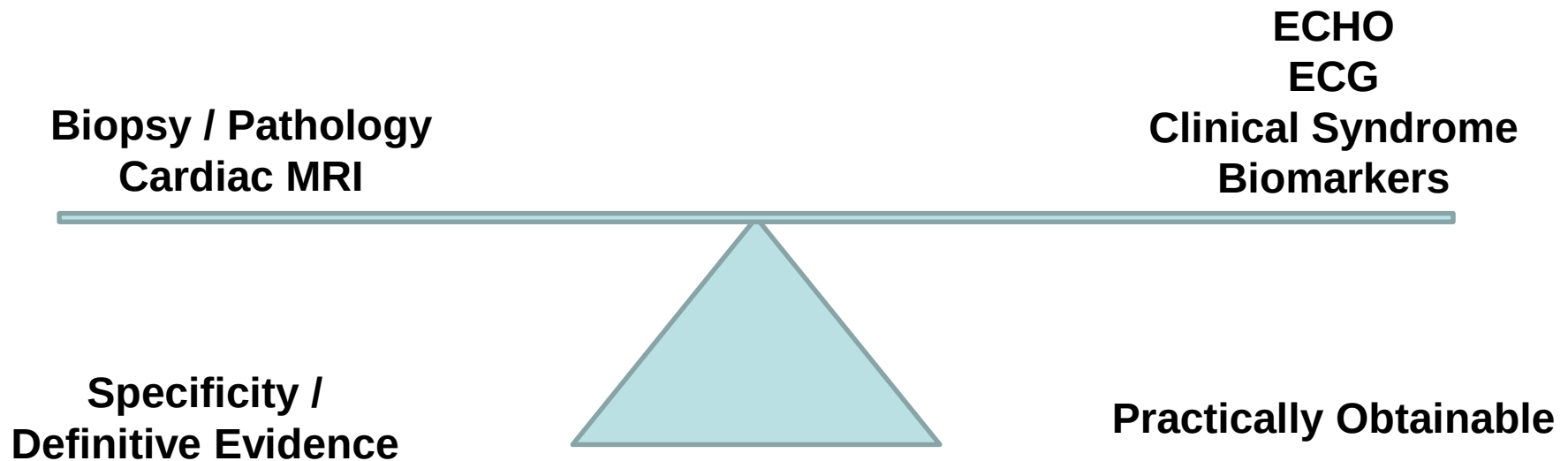
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Adjudication Definitions

*Balance need for definitive diagnostic
information against what may be practically
obtainable in multinational trials*

*What can sites be reasonably asked to provide
as part of standard of care?*



Myocarditis – A Proposed Definition

Hierarchical definition (similar to stent thrombosis) accounting for different levels of evidence

Pathology

Imaging

ECG

Syndrome

Biomarkers

For all – other diagnosis / explanations (e.g. ACS) must be excluded

Definite Myocarditis:

- Pathology
- Diagnostic CMR + syndrome + (biomarker or ECG)
- ECHO WMA + syndrome + biomarker + ECG + negative angiography

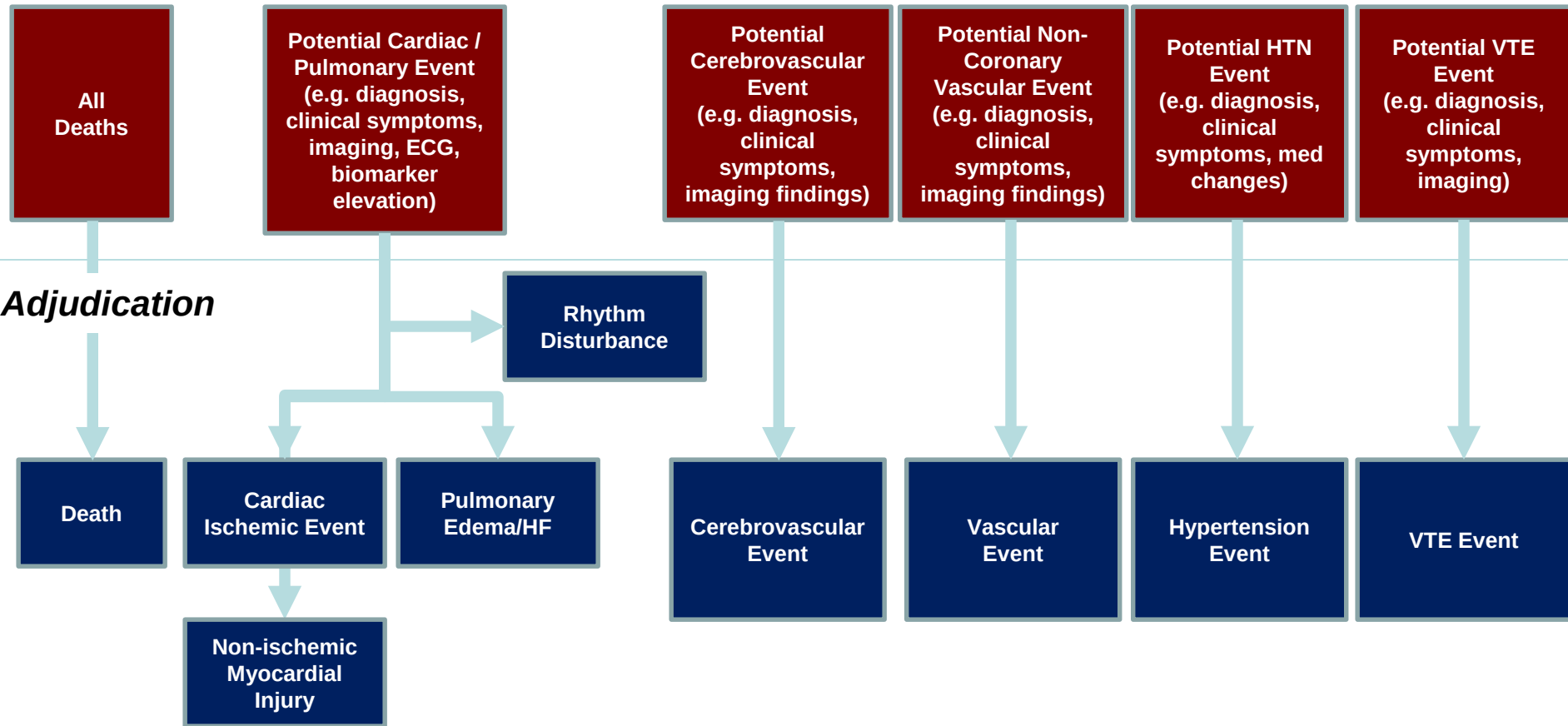
Probable Myocarditis:

- Diagnostic CMR (no syndrome, ECG, biomarker)
- Suggestive CMR with either syndrome, ECG, or biomarker
- ECHO WMA and syndrome with either biomarker or ECG
- Syndrome with PET scan evidence and no alternative diagnosis

Possible Myocarditis:

- Suggestive CMR with no syndrome, ECG or biomarker
- ECHO WMA with syndrome or ECG only
- Elevated biomarker with syndrome or ECG and no alternative diagnosis

Trigger Review (AEs, Deaths, Labs, etc.)



Additional Triggered Events

If other evidence of another CV event,
additional adjudications to be triggered
as appropriate



Summary

- **A broad approach to CV event ascertainment and adjudication allows for comprehensive assessment in setting risks from disease state, background therapies, and randomized therapy**
- **Adjudication allows for event characterization with a high degree of specificity and may be most important for complex uncommon diagnoses (e.g. myocarditis)**
- **Event ascertainment through site training with dedicated reporting pages at beginning of trial is ideal**
- **Routine ascertainment and adjudication of CV events using uniform definitions across trials would enable pooling of data and enable more robust understanding of risks and potential risk factors**