Adjudicating Cardiovascular Events in Immuno-oncology Trials

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General Process of Adjudication

Trigger for Potential Event

Data Collection / Dossier Assembly

Redaction of PHI
Blinding
Baseline data

Adjudication by Reviewer #1

Adjudication by Reviewer #2

Independently and without Communication

Match & Meeting if Disagreement

Third party if no agreement

Final 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

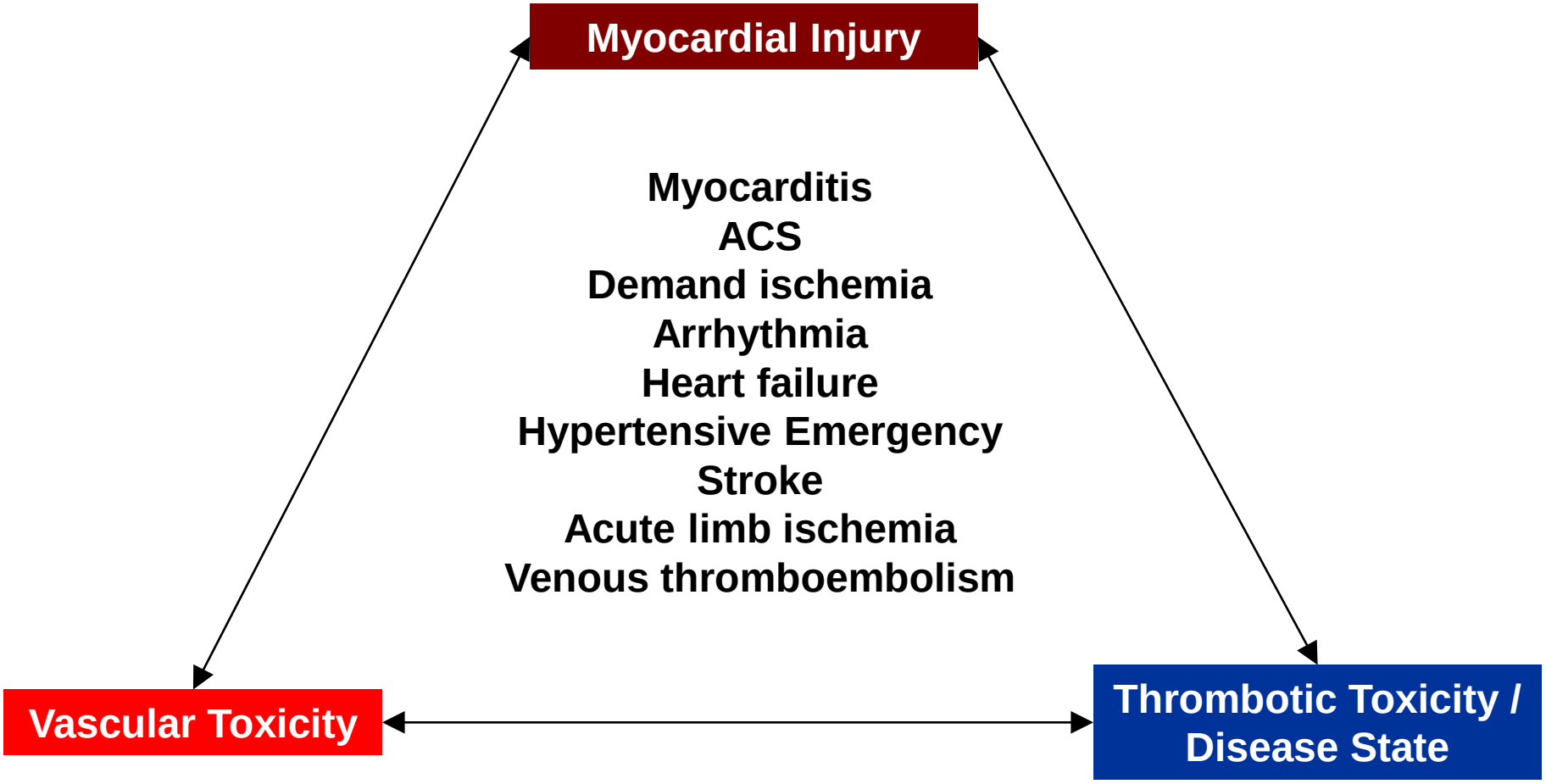
Common Events Related to Disease State

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

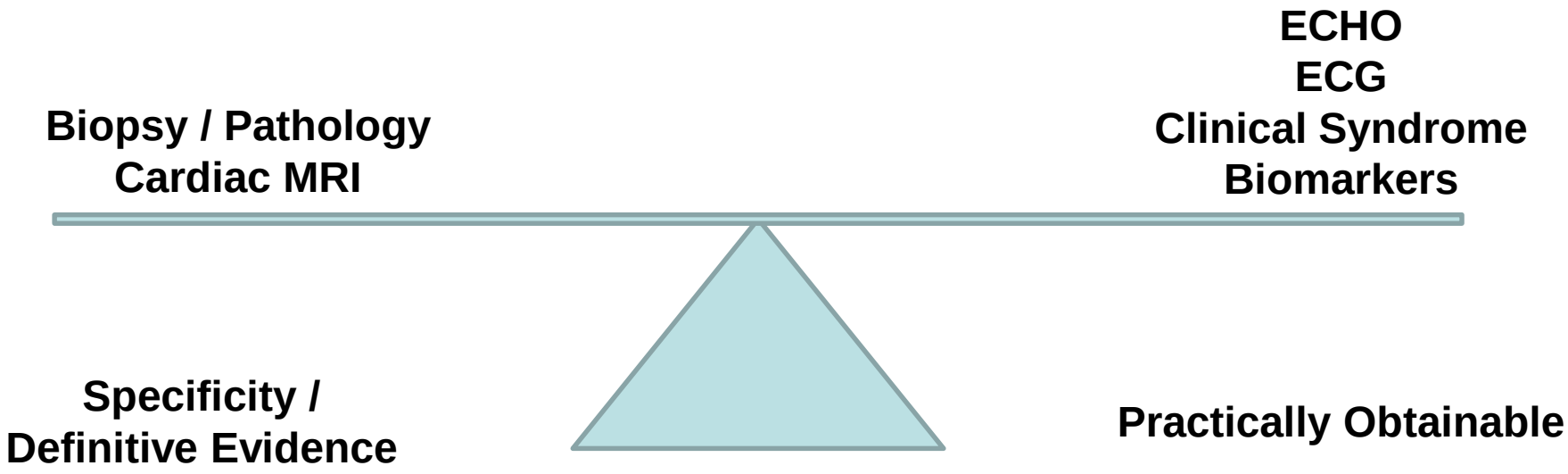
Emerging Definitions

?????

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

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

Definite Myocarditis:

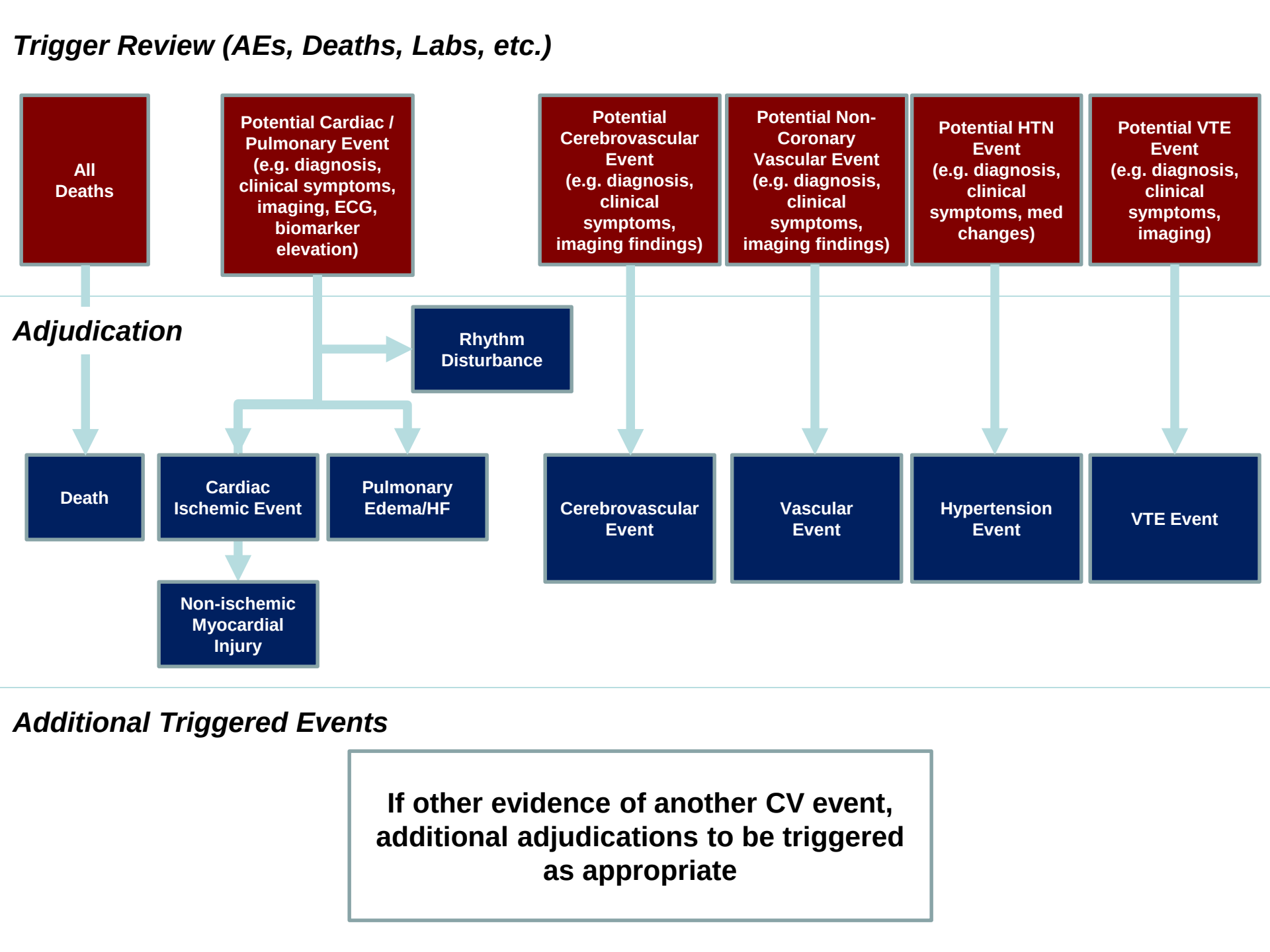
- **Pathology**
- **Diagnostic CMR + syndrome + (biomarker or ECG)**
- **ECHO WMA + syndrome + biomarker + ECG + negative angiography**

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.)
All Deaths
Potential Cardiac / Pulmonary Event (e.g. diagnosis, clinical symptoms, imaging, ECG, biomarker elevation)
Potential Cerebrovascular Event (e.g. diagnosis, clinical symptoms, imaging findings)
Potential Non-Coronary Vascular Event (e.g. diagnosis, clinical symptoms, imaging findings)
Potential HTN Event (e.g. diagnosis, clinical symptoms, med changes)
Potential VTE Event (e.g. diagnosis, clinical symptoms, imaging)
Adjudication
Rhythm Disturbance
Death
Cardiac Ischemic Event
Pulmonary Edema/HF
Cerebrovascular Event
Vascular Event
Hypertension Event
VTE Event
Non-ischemic Myocardial Injury
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**