Perspectives on implications when adjudication is post-hoc and how wide a net should be cast

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- **Disclaimer – There are limited data in the public domain on these topics**

Pros and Cons for Post-Hoc Assessments

- **PROS – if performed blinded to treatment assignment and without knowledge of overall study results, the integrity of the adjudication process remains relatively intact and results still could improve precision of diagnosis**
- **CONS – in completed trials, retrieval of additional source or clinical information from site investigators/coordinators is typically impossible making the proportion of events insufficient to adjudicate higher than when a prospective study is performed**

Treatment-Emergent MACE Investigator-Reported vs Adjudicated Post Hoc

Randomized Controlled Trials

n [rate per patient-yr]
95% CI

MACE	Investigator reported		Adjudicated Post Hoc	
	Gout drug A	Gout Drug B	Gout drug A	Gout drug B
	N = 2690	N = 1277	N = 2690	N = 1277
Overall	10 [0.37] 0.18-0.68	4 [0.31] 0.09-0.8	10 [0.37] 0.18-0.68	4 [0.31] 0.09-0.8
CV death	3 [0.11] 0.02 - 0.33	2 [0.16] 0.02-0.57	3 [0.11] 0.02-0.33	2 [0.16] 0.02-0.57
Nonfatal MI	6 [0.22] 0.08-0.49	2 [0.16] 0.02-0.57	5 [0.19] 0.06-0.43	2 [0.16] 0.02-0.57
Nonfatal stroke	1 [0.04] 0.001-0.21	0 0-0.29	2 [0.07] 0.009-0.27	0 0-0.29
Nonfatal cardiac arrest	1 [0.04] 0.001 - 0.21	0 0 – 0.29		

Capturing CV Events by Casting a Wide Net

Is this a productive activity?

Examples of difficult-to-ascertain terms from MedDRA 15.1 (total n = 988)

- Conduction disorder
- Palpitations
- Chest pain
- Edema
- Elevated CPK
- Tachycardia
- Dizziness
- Paresthesia

Examples of other wide-net terms from MedDRA 15.1 (total n = 988)

- Apparent life-threatening event
- Brain operation
- Electrocardiogram change
- Fumbling
- Man in the barrel syndrome
- Psychogenic movement
- Somnolence

CONTRAST - Criteria for MACE and Corresponding MedDRA Preferred Terms in Database for Investigator-Reported Analyses

MACE Criterion	MedDRA Preferred Term
Cardiovascular death	The following MedDRA were associated with CV death: Acute Myocardial Infarction Cardiac Arrest Cardiac Failure Congestive Hypertensive Heart Disease Myocardial Infarction Retroperitoneal Hemorrhage Sudden Death
Non-fatal myocardial infarction	Acute Myocardial Infarction Myocardial Infarction Silent Myocardial Infarction
Non-fatal stroke	Brain Stem Infarction Cerebral Hemorrhage Cerebrovascular Accident Lacunar Infarction
Non-fatal cardiac arrest	Cardiac arrest

Contrasting ‘Serious’ versus ‘Non-Serious’ Potential Cardiovascular Events in Trials

Serious	Non-Serious
Information quality is typically good and includes narratives (CIOMS), source documents from the hospital, actual lab reports, ECGs, cath reports, and imaging studies	**Information quality is typically not good and does not include narratives (in most cases), has poor source documentation, may even just be the reporter term**
Likelihood of Committee voting insufficient information is low	**Likelihood of Committee voting insufficient information to adjudicate could be high**
Retrieval of additional or followup information is often possible	**Retrieval of additional or follow-up information is often not possible**

Evaluation from an ongoing prospective CV outcomes trial in a non-CV disorder

- Cardiovascular outcome study in population with non-CV disorder and enriched cardiovascular disease
- Double-blind randomized with similar requirements to the type 2 diabetes guidance
- Primary endpoint is cardiovascular death, nonfatal MI, nonfatal stroke, unstable angina requiring urgent revascularization

Cardiovascular end point results from an ongoing prospective CV outcomes trial when a sample of 10% of non-serious adverse events (non-SAE) and all serious events are reviewed

SAE Review (n = 946)	Non-SAE Review (n = 97)
N (%) found to be a primary end point: 258 (27%)	N (%) found to be a primary end point: 0 (0%)
N (%) found to be either non-CV event or not a separate event: 257 (27.1%)	N (%) found to be either non-CV event or not a separate event: 59 (60.8%)
N (%) found to be insufficient information to adjudicate: 9 (0.95%)	N (%) found to be insufficient information to adjudicate: 7 (7.2%)
N (%) found to be some type of CV event excluding the primary end point: 422 (45%)	N (%) found to be some type of CV event excluding the primary end point: 31 (32%)

The CV events adjudicated from the non-SAE pool have the same diagnosis as the site reporter term

Non-SAE CV events (adjudicated)
Arrhythmia not associated with ischemia (e.g. atrial fibrillation) n = 11
Heart failure n = 2
Other CV event (e.g. syncope, treatment emergent hypertension) n = 14
Transient ischemic attack n = 1
Venous thromboembolic events (DVT) n = 3

Conclusions

- Prospective evaluation of potential cardiovascular end points is superior to post hoc analysis – reduction of bias and improvement in data collection
- Evaluation of a wide net of CV terms of a serious nature has a high yield of confirmed primary and secondary CV end points
- Evaluation of a wide net of CV terms of a non-serious nature has a much lower yield of confirmed primary and secondary CV end points and the terms do not differ from the reporter
- Other than arrhythmias, there is typically no source information for non-serious CV Aes in most clinical trials.