Cardiac Safety Research Consortium

Cardiac Safety Research Consortium Adjudication Thinktank

A Cardiac Safety Research Consortium Thinktank in collaboration with the FDA

The role of study design and PI expertise on the need for adjudication

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Declaration of Interests

Type of job or financial support	Research Institution / Company
Salary Ordinary funds Position in Public Committees	IRCCS San Raffaele Roma – CV WP European Medicines Agency - Italian Drug Agency (AIFA) The views presented in this talk are personal and should not be understood or quoted as being made on behalf of or reflecting the position of AIFA or EMA
Speaker in C.M.E. Events	European Society of Cardiology Int Soc Cardiovasc Pharm American Heart Association Heart Failure Association Heart Failure Society of America Societa' Italiana di Farmacologia
Conflict for this presentation	No competing interests for this talk No consultancies to Companies related to medicinal products

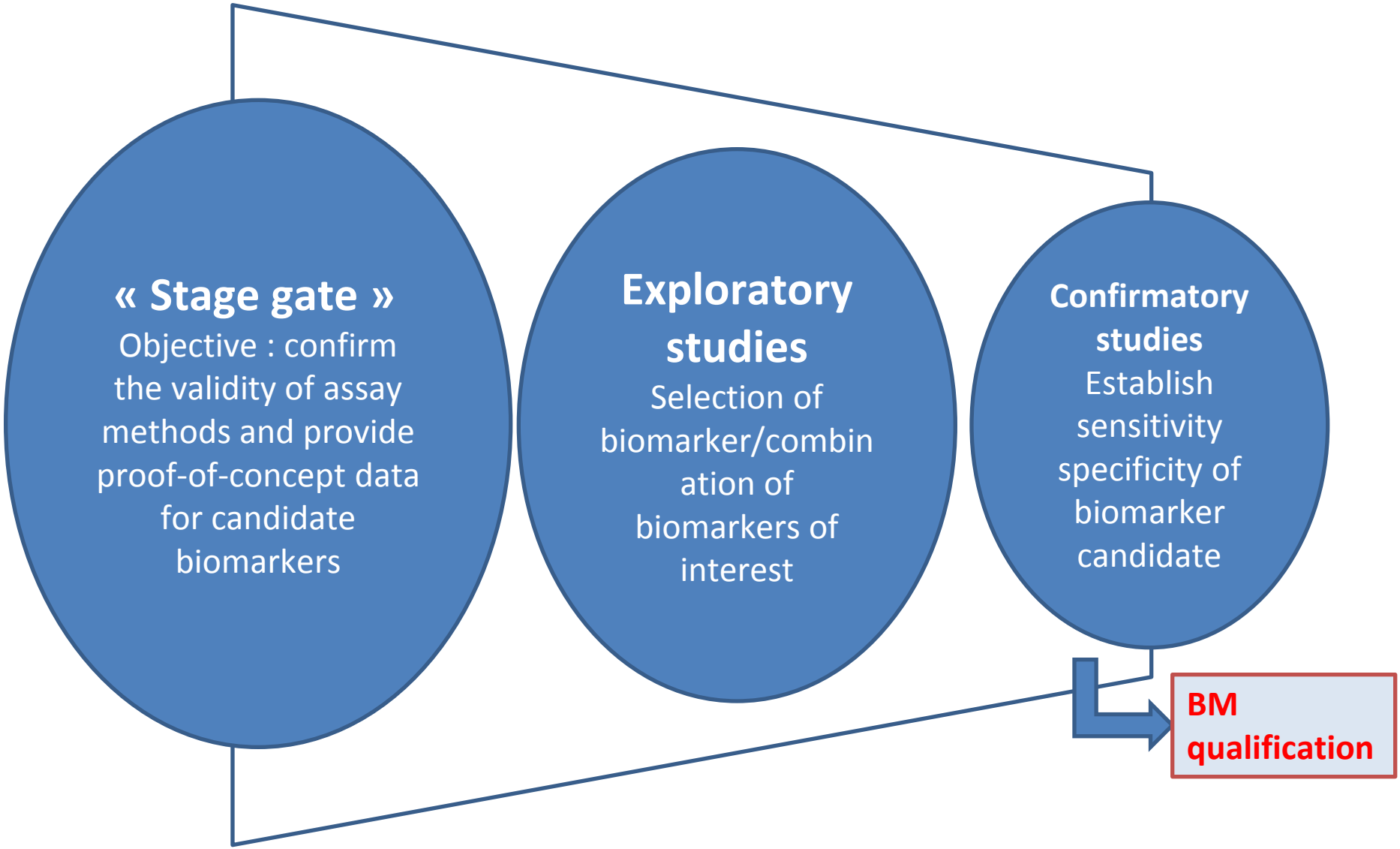
EMA and Adjudication

- EMA does not adjudicate end points because it does not handle raw data
- Therefore, it cannot adjudicate treatment success/treatment failure and it has to rely on the judgments made by the Adjudicating Event Committee and by the DSMB of the studies conducted by the MAH
- It may inspect sites to verify the correspondence between source data and reported end point

EMA and Adjudication

- The only cases in which EMA performs a sort of adjudication is in the process of biomarker qualification
- In this process EMA defines directly the end points together with the company that proposed the biomarkers / surrogate endpoints
- This is, however, an intermediate situation between the definition of validity' and plausibility of an endpoint

Biomarker Qualification Process



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

GUIDELINE ON DATA MONITORING COMMITTEES

- **Endpoint Adjudication Committees**

In clinical studies where end-points are complex to assess and/or include subjective components or the study cannot be blinded, an Endpoint Adjudication Committee, consisting of clinical experts in a specific clinical area, might be set up to harmonise and standardise endpoint assessment.

Reasons for CEC

- Blinding
- Uniformity
- Regional variation
- Sample size

Reasons for favouring a CECs

- Treatments influencing physiological parameters may induce biases that may alter the ability to detect a treatment effect
- Investigators tend to under-report end points
- Under-reporting influences event rates and this may influence the outcome of the

Cardiovascular end-points for which a CEC is needed

- Cardiovascular death (in absence of autopsy)
- Sudden death (equivocal)
- Hospitalisation for cardiac cause
- Hospitalisation for heart failure
- Myocardial infarction
- Unstable angina
- Acute coronary syndromes

CECs on MI classification
The PURSUIT Trial

- Rates of end-point infarction or reinfarction higher than those reported in prior trials of patients with ACS
- CEC identified more events than the site investigators
- Site investigator and the CEC assessments of MI disagreed in 20% of the cases

CECs on causes of death classification

The MOST study

- The CEC and the site investigators disagreed in classifying
- 41 cases (10.7%) at the major level
- 117 cases (30.9%) at the minor level
- In resolving internal disagreements, the full CEC agreed with 1 of 2 CEC reviewers in 85.9% of cases

Conclusion

- *What influences the need for adjudication?*
  The quality of the end point
- *Do we need adjudication of events in a trial with a primary CV endpoint if the investigative site has CV expertise?*
  Yes
- *How does the study design influence the applicability of adjudication strategies?*
  It does not influence the applicability
- *Are there differing concerns in superiority vs. a non-inferiority trial?*
  No