

Additional perspectives on Aprotinin and Diabetes

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Knowledge of results

In a retrospective systematic review, knowledge of the results of existing studies may influence

- the definition of the review question
- the criteria for study selection
- the treatments and patient groups evaluated
- the outcomes to be evaluated (analyzed)

What is a PMA

A prospective meta-analysis (PMA) is a meta-analysis of RCTs identified, evaluated, and determined to be eligible for the meta-analysis before the results of any of those trials become known.

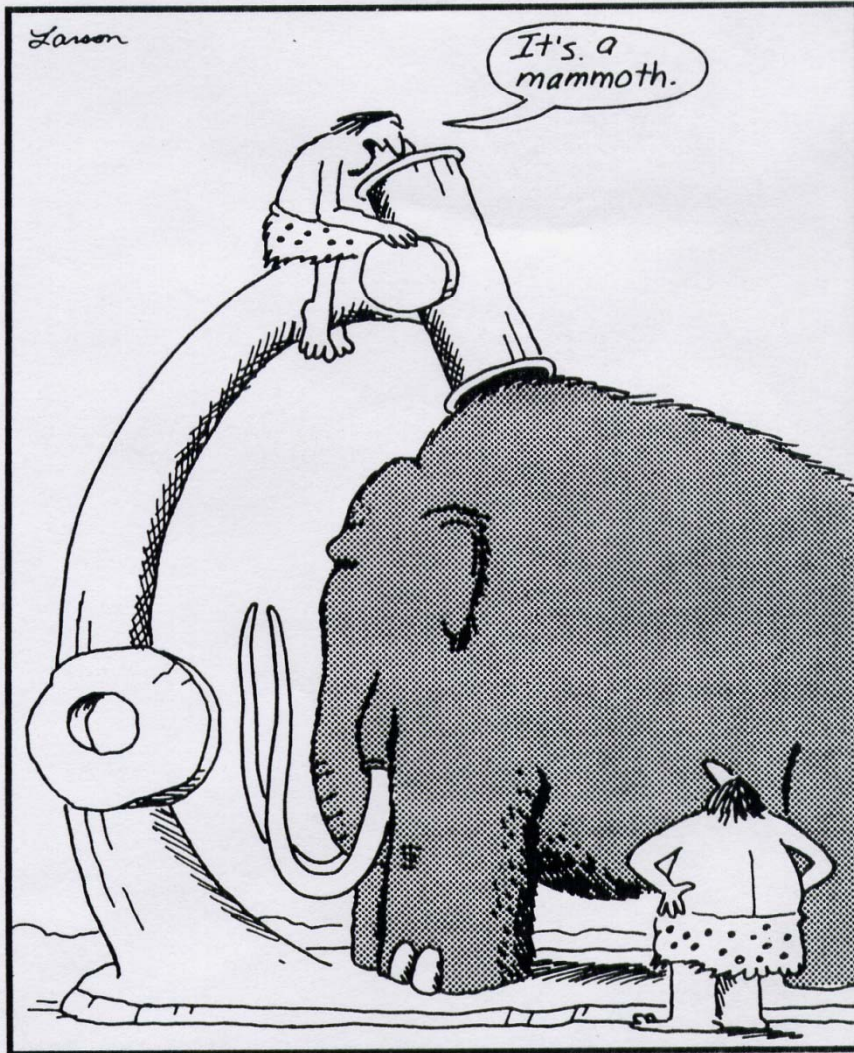
What can PMA do?

- PMA can help to overcome some of the recognized problems of retrospective meta-analyses by enabling PROSPECTIVE:
 - Specification of hypotheses (endpoints, etc.), ignorant of the results of individual trials
 - Application of selection criteria
 - Specification of analysis plans (including subgroup definitions)

Studies with dual purposes

(Focus on diabetes, but similar principles apply to aprotinin)

- In diabetes, efficacy captured by
 - HbA1c
 - Microvascular events
 - Others
- But studies will also capture “macro” CV endpoints (and deaths)
 - Same definitions of the endpoint (or the adverse event) can be specified in all trials!!!!!!!
 - And implemented by the same adjudication committee across all studies



Early microscope

Statistical Issues (among others)

- Sample size considerations
 - **Rule out** RR of 1.8 (at time of approval) or 1.3 (subsequent to marketing), vs. “detect” (per FDA guidance)
 - Upper limit of CI must *exclude* the value
 - Can the sample size be “too big?”
 - What if you meet non-inferiority but RR is statistically significantly above 1.0?
 - Should also specify an upper limit to the point estimate
- An actual “outcomes” study is likely (going) to be needed
 - Can this be large and “streamlined?” or at least broadly inclusive of “real world” patients?

Other issues

- Is some kind of “conditional” or “progressive” approval (Zeger’s “randomized consumer trial”) in our future, more routinely?
- What about observational studies (e.g., Sentinel)?
- Can we use existing EHR systems to improve efficiency (by “building studies into the database”)?
 - Can include randomization
 - Can randomize practices
 - But will clinicians or health systems participate?