How statisticians deal with the difference between efficacy and safety reporting

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Some history

- When statisticians started to work on clinical trials they did:
  - Sample size calculations
  - Special clinical trial design features to make studies more efficient and to fulfill regulatory requirements
  - Nearly all was efficacy related and originally even restricted to the planning phase. Reporting and interpretation was left over to others
- Biostatistics departments developed and are today involved not only in the planning phase but also in efficacy reporting, safety reporting and interpretation of results. But activities and thinking still centers around efficacy:
  - Exceptions: CRM designs in phase 1 or thoughts on reporting adverse events

The real need

- Drugs can fail because of safety as of efficacy
- Trial size can depend on efficacy as on safety
- Regulatory decisions are generally based on benefit risk balancing efficacy gains versus side effect risk
- Additionally:
  Some drugs have their benefits primarily in improved safety or convenience

- Efficacy and safety appear the same level but statisticians still perceive efficacy as much more interesting and safety rather boring. Why?

Why is there a preference of statistics for efficacy?

- Efficacy and safety analyses are different. Regulatorywise
  - We need ro demonstrate an efficacy claim
  - We do not need to demonstrate a safety risk
- Safety *appears* more boring as long as we deal with frequency tables. It is more standardized than efficacy
- Safety *is* more complex
  - The causal relationship of safety events is less clear
  - Often little information is available as we talk about signals
  - There is high level of multiplicity

- All in all, this speaks for rather more biostatistics involvement than less!

Reporting of safety data, especially AEs

- Typically based on simple proportions. This requires a lot of unrealistic assumptions, nevertheless
  - Easy to understand by all
  - Easy for signal screening
  - Track record that it seems to work (we did not miss signals in the past)
- There are a lot of initiatives and publications out to propose alternative methods
  - Annualized event rates
  - Time to event
  - SAVVY working group
  - …
- Better methods often used for AEs of special interest but not generaly for screening. Why?

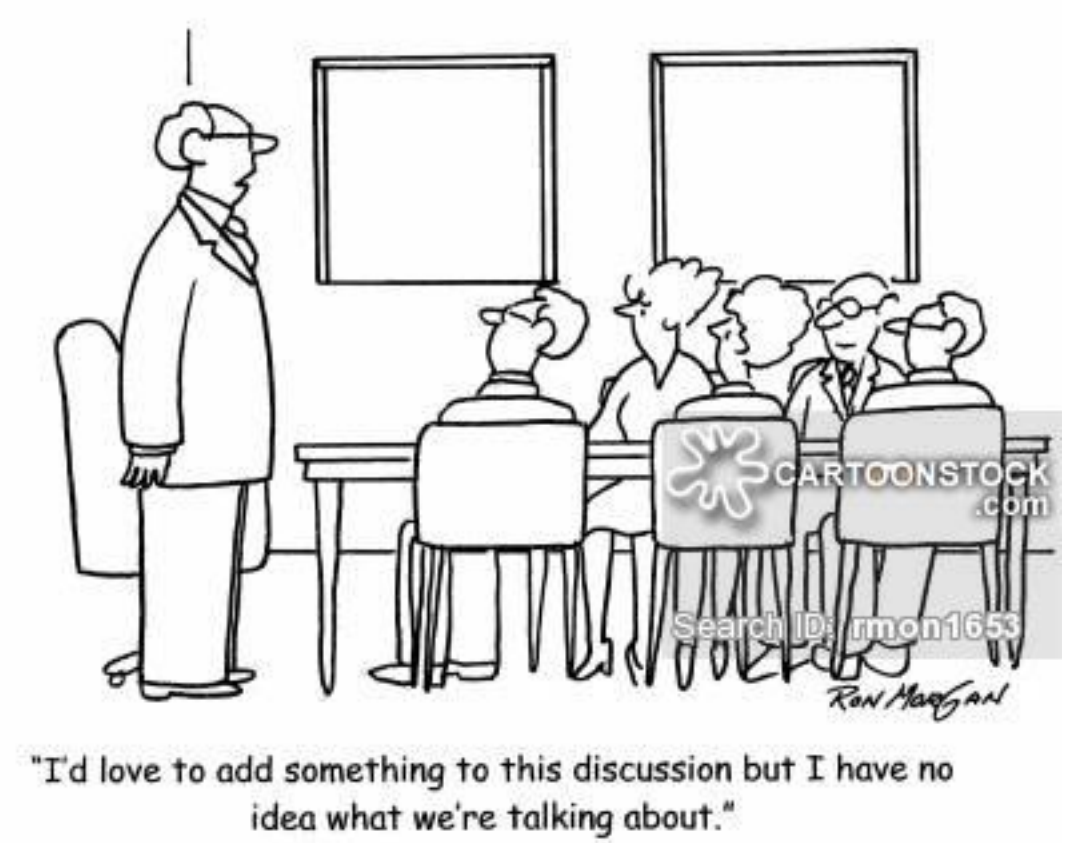
Why is there a preference of statistics for efficacy?

- We are often still facing the *perception*:
  - Safety easy (a lot of boring work...)
  - Safety not statistical enough to attract interest as we do not need inference
  - Safety reviews from HAs often not statistical, HA statisticians not looking into it...
  - Efficacy still top priority. We get excited about benefits not about draw backs and risks
  - Safety reporting often very standardized (for the right reason) – again not that attractive
  - For study planning the assumption is often that safety will be «ok»

What do we need to do?

- Our biggest value we provide are in areas which are important and challenging, safety is one of them!
- Causality assessments more difficult in safety, even in RCTs
  => Where things are more difficult we should get involved
- Regulatory assessments and questions are often on safety as they are on efficacy. But safety question often tend to be more tricky
- To make it more interesting: We should apply better methods than frequency tables, even for screening. Multiplicity is again and again a big issue

Discussion



"I'd love to add something to this discussion but I have no idea what we're talking about."