Enhancing the way we quantify and communicate benefit to risk in the pre and post approval arena

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Today's Discussion

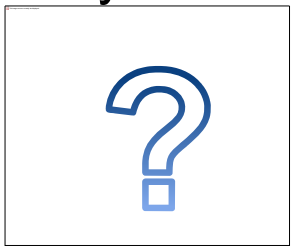
- Benefit to Risk is a Science and a Tool
  - Population level BR
  - Patient level BR
- The BR context matters
  - No Treatment v. Active Comparator BR
  - Intervention v. Prevention BR
  - Pre Market v. Post Market BR
- Communication: It isn't a useful BR analysis if no one understands it
  - NNT
  - Relative Risk
  - Risk Difference
- Governance

What do we mean by Benefit and Risk?

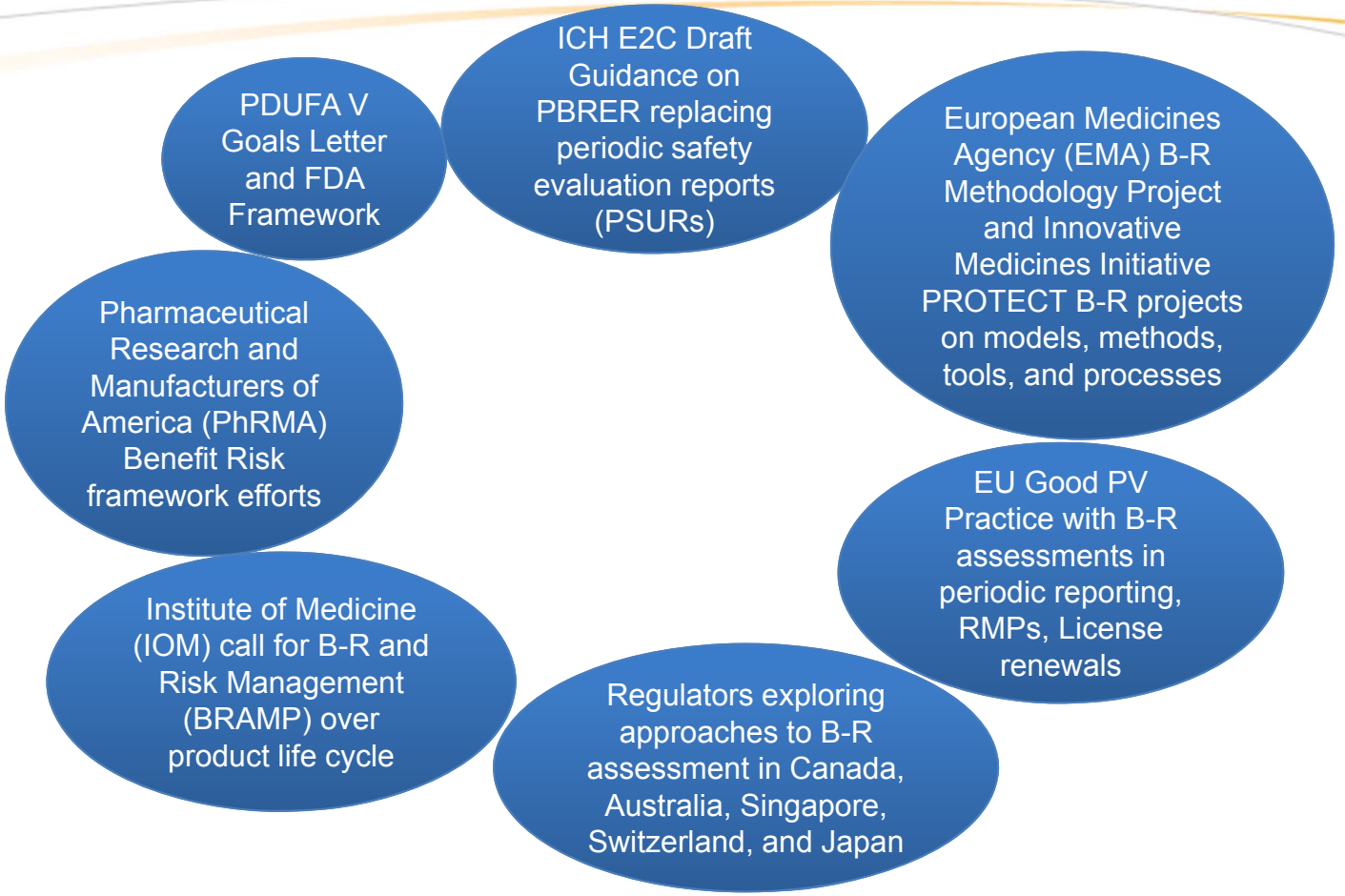
- **Benefit:** what we want a treatment to do for patients and what is important about the outcomes
  - Clinically relevant outcomes or biomarkers / surrogates that are considered favorable effects and rationale for choosing them
  - Intensity, duration, and uncertainty of effects

- **Risk:** the potential consequence to the patient and how to manage the events when they occur
  - Clinically relevant outcomes or biomarkers / surrogates that are considered unfavorable effects
  - Severity, duration, predictability, "monitorability," and reversibility of effects

- **Benefit-Risk Balance:** how the favorable effects compare to the unfavorable effects



Benefit-Risk is a shared standard

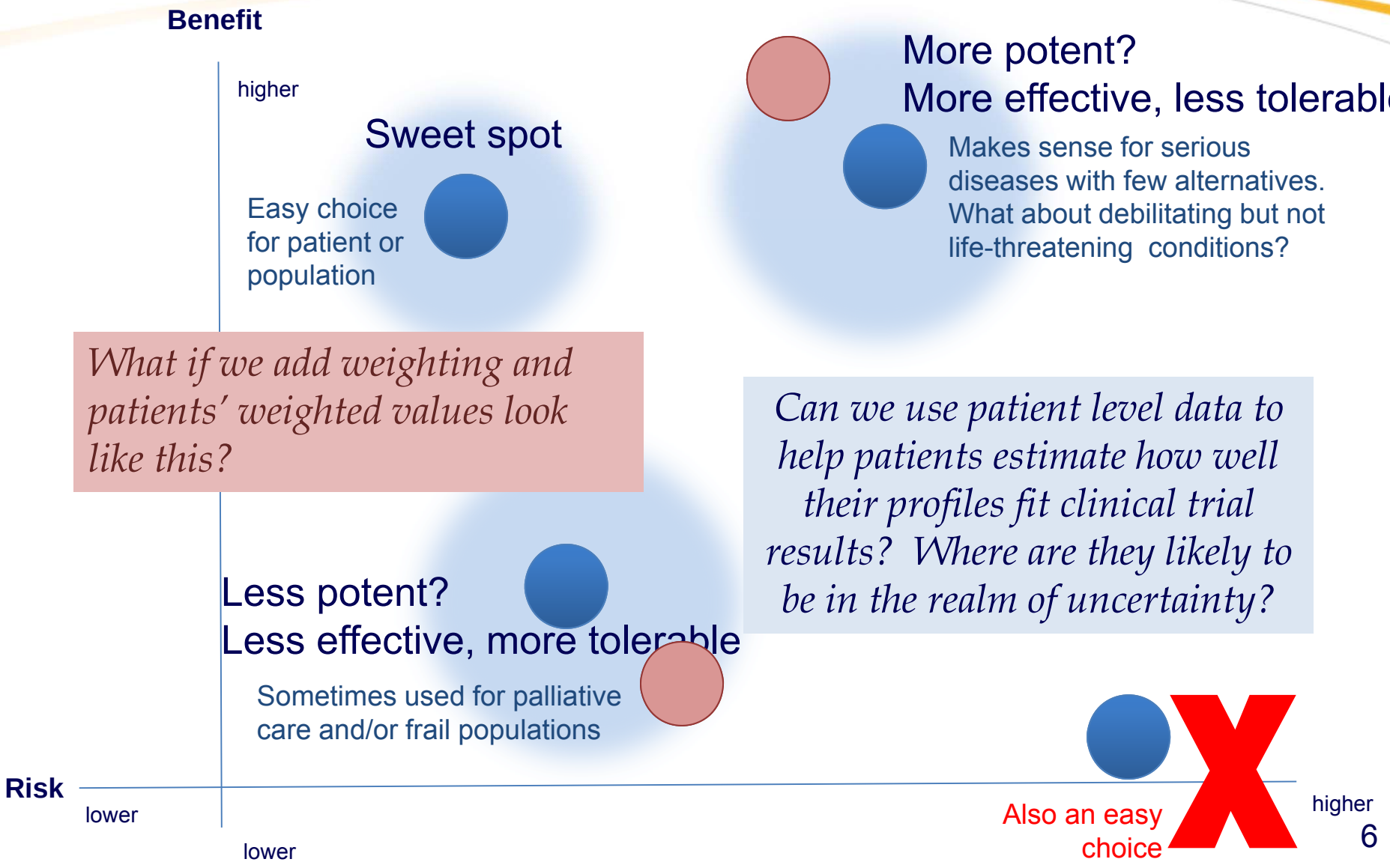


PV and B-R are pre-competitive (and post-competitive), especially with the advent of regulatory changes and global interest

The BR context matters

- Patients need Comparative BR
  - Is any treatment better than no treatment? No, not in all cases
- Treatment for a serious condition v. one that is not life-threatening or debilitating
- Prophylaxis - intervention v. prevention
- Pre-market v. post-market
- Weighting

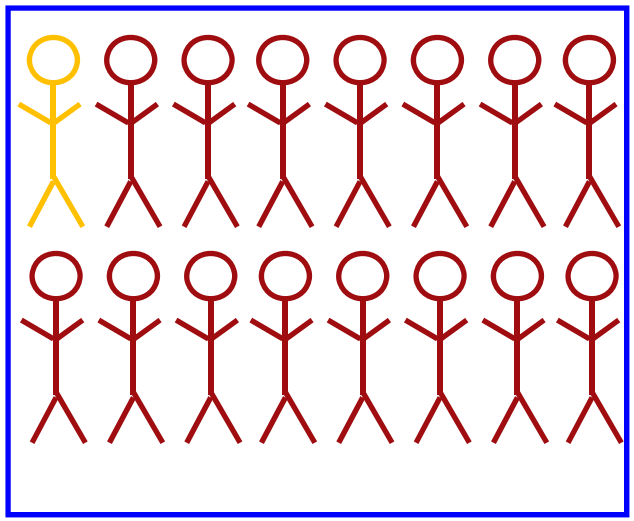
Compare BR of Drugs



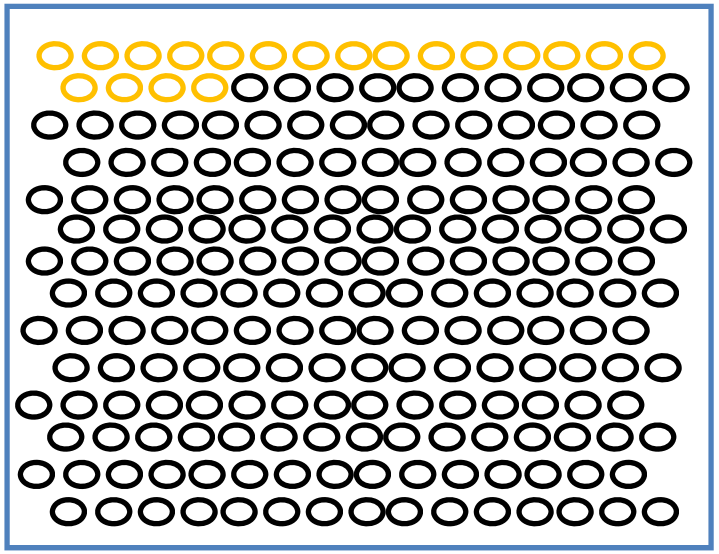
Moving from the population level to the patient level is not straightforward

We usually measure benefit and risk with population level frames…

We need data on a lot of people to see the outcomes of interest

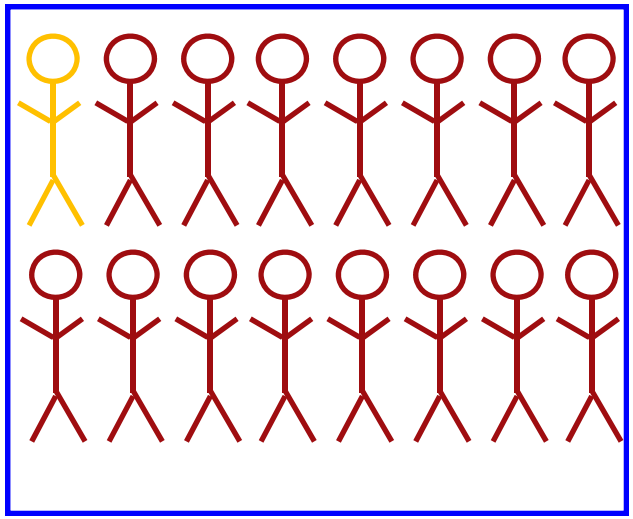


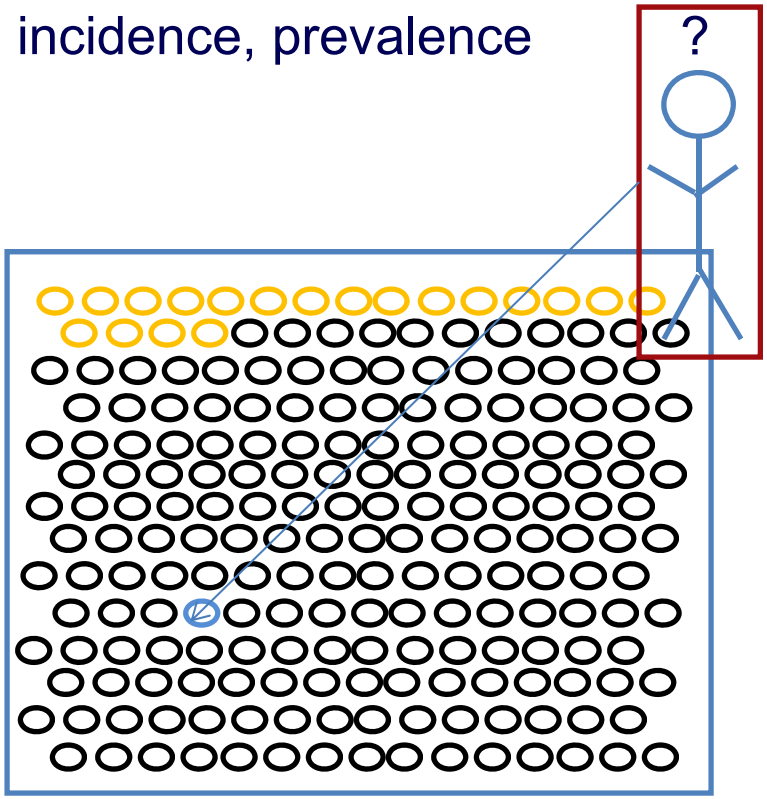
Results are geared toward regulators, policy makers, and payers trying to use the findings on behalf of a larger population



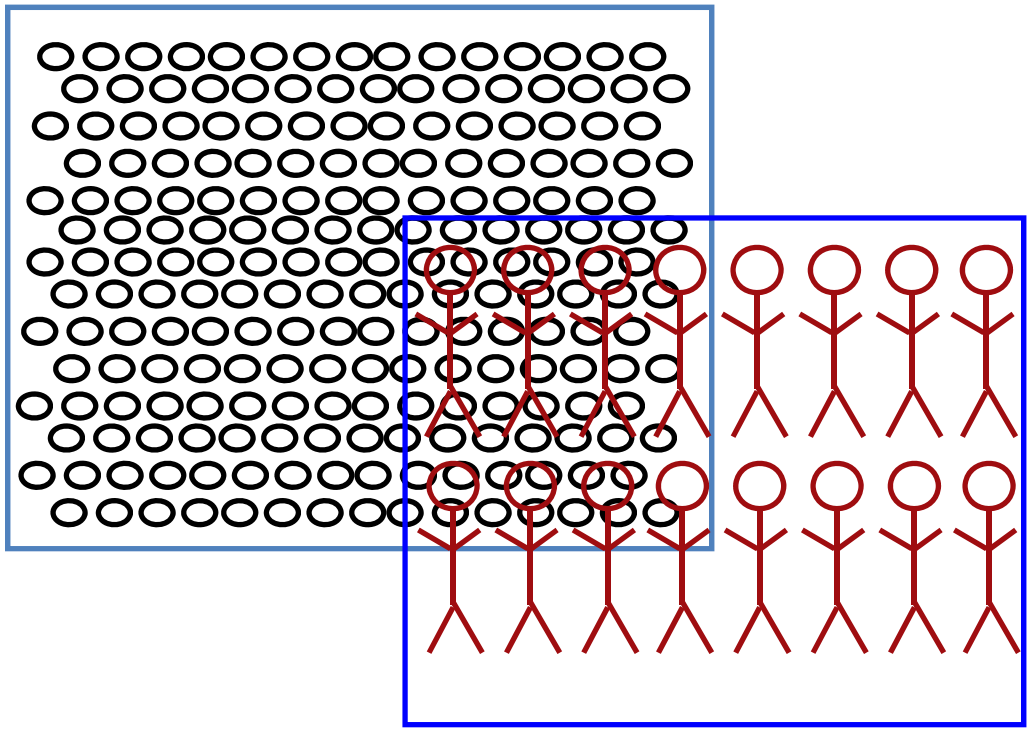
…and population level outcomes of interest

e.g., morbidity, mortality, incidence, prevalence

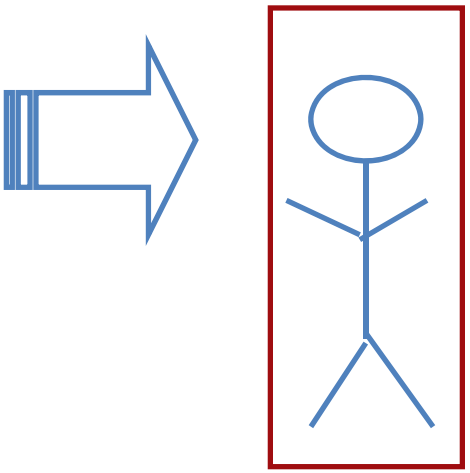




If we think of a patient weighing benefits and risks, we often think it's a matter of communication



Speak clearly and in simple terms, and the person will understand the implications to herself/himself



Well of course it's not just about saying it simply,

…it's about having *more to say*.

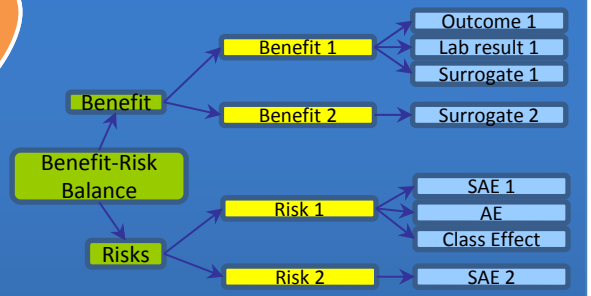
So where do we start?

At the beginning!

Benefit Risk Evaluation Overview

A facilitated process and appropriate tools help drug development teams measure and articulate key benefits and risks

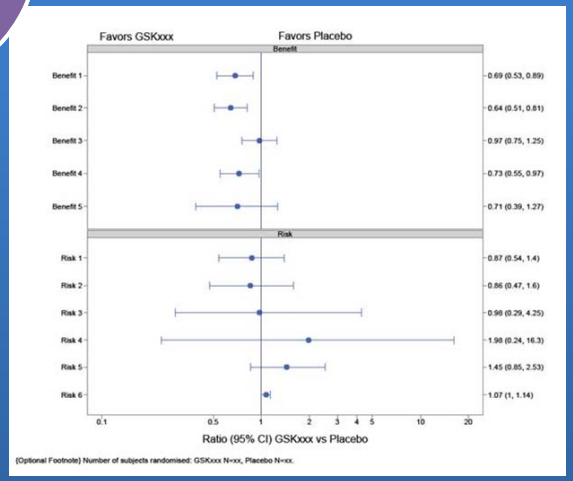
Brief



Framing

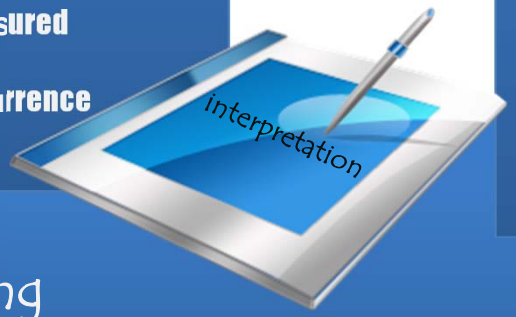
- disease context
- unmet need
- how benefit and risk are measured
- reversibility, monitorability
- long-term vs. short-term occurrence
- subgroup differences

Visualize



Graphing

displaying benefit and risk side by side on a scale appropriate for the data



Summarize

Writing

- team's understanding of their findings and what they mean for patients
- discussion of needs for label, risk management plan, additional studies

Key Elements

1. Brief
   - Describe the context for evaluating benefit and risk
   - Name and measure benefits and risks

2. Visualize
   - Construct graphic(s) that illustrate the key benefit/risk trade-offs
   - Identify a visualization that suits your data

3. Summarize
   - Explain your conclusions about the balance of benefit to risk for your product
   - Describe any further exploration needed based on your findings, if applicable

Naming and Measuring Benefits and Risks

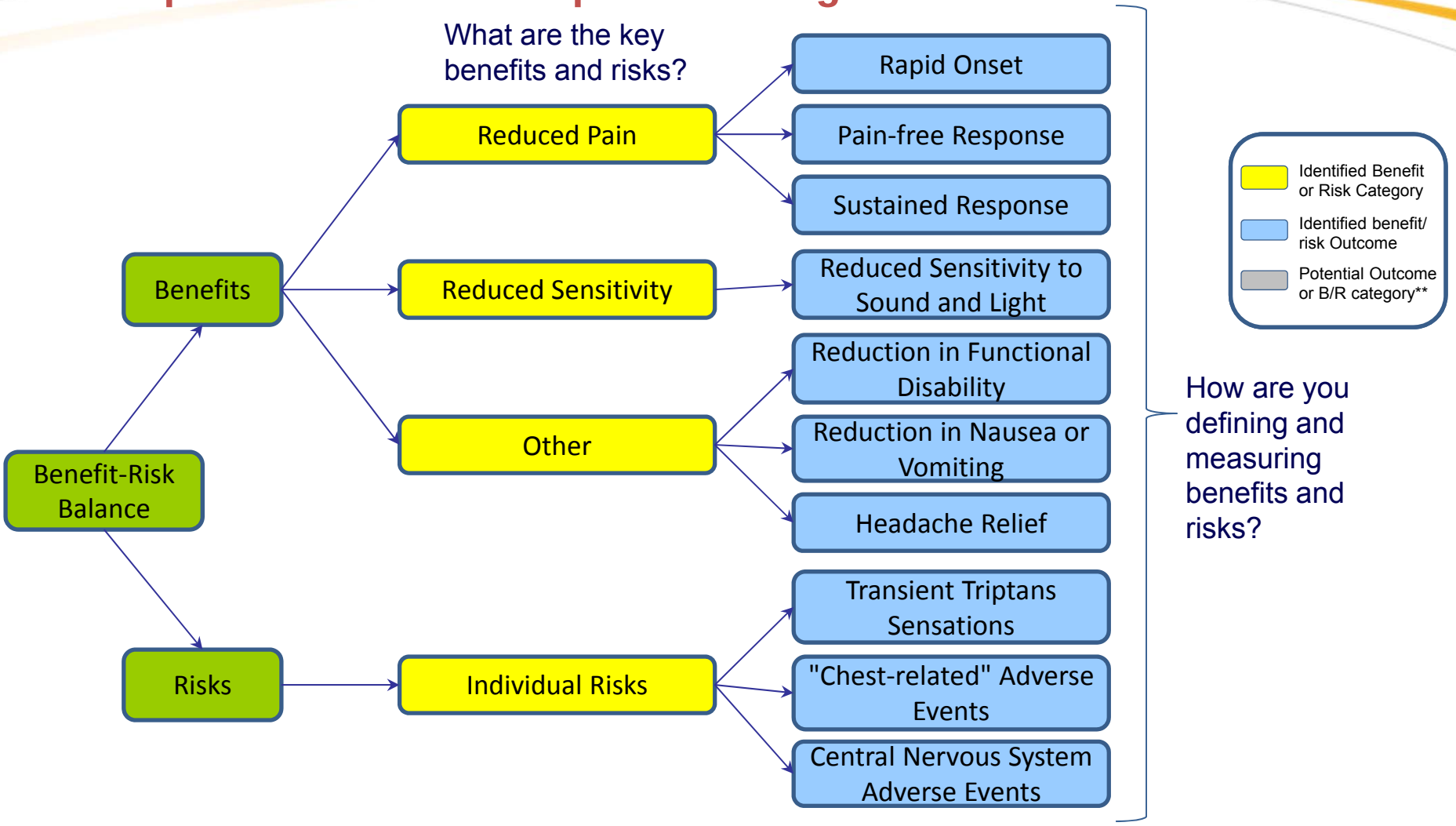
- Clinically relevant outcomes or biomarkers / surrogates that are considered benefits (favorable effects) and risks (unfavorable effects)
- Uncertainty around favorable and unfavorable effects
- Rationale for how they were identified and selected
- How well surrogates predict the benefit/risk outcome
- Intensity or severity and duration of benefit and risk
- “Monitorability” and reversibility of risks
- Any ranking or weighting that was applied

Describing context for evaluating benefit and risk

- What is currently known about the disease or condition and characteristics of the patient population
- Target product profile (TPP) (characteristics for label)
  - how it leads to the asset profile (value, competitiveness)
  - how it meets the needs of patients, healthcare providers, regulators, and payers
- Plans for addressing divergence from the TPP
- Go/no go criteria
- Comparisons to standard of care, placebo, or other alternative treatment as appropriate

A value tree can help frame your thinking

Example Value Tree for Triptans* as Migraine Treatment



*from PhRMA BRAT Framework; EMA has successfully field tested a similar "effects tree"

** uncertain relationship to treatment

Measures of comparison

- Relative Risk (RR):

$$RR = P_C / P_T$$

- Odds Ratio (OR):

$$OR = P_C (1 - P_T) / P_T (1 - P_C)$$

- Absolute Risk Reduction (ARR):

$$ARR = P_C - P_T$$

- Number needed to treat (NNT): 1/ARR*

*implicitly based on assumption that $1/(P_C-P_T) = 1/P_C-1/P_T$ (uh, oh!)

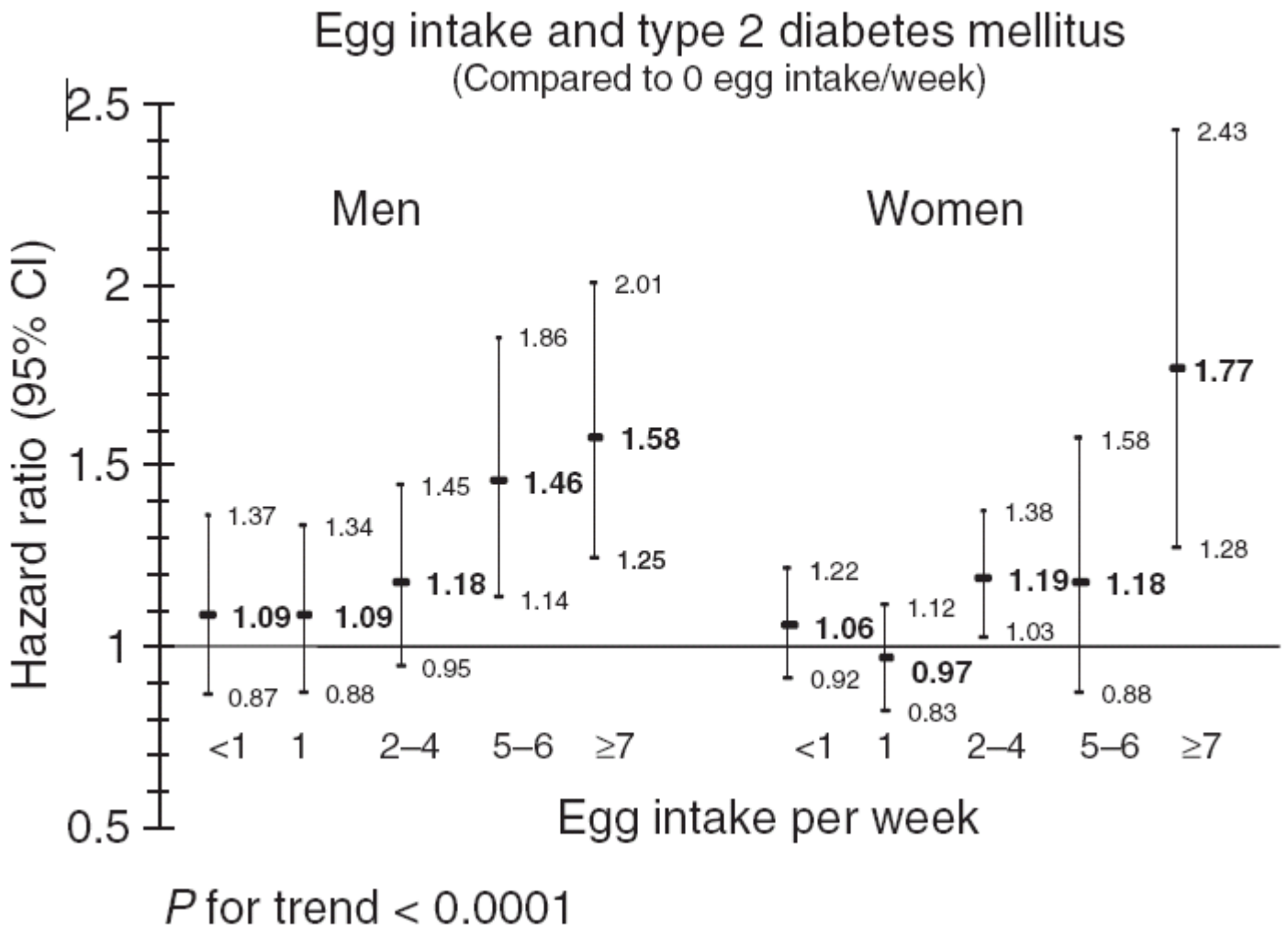
P_T = Probability of an event (benefit or harm) on treatment, P_C the same for control

Interpretation of Number Needed to Treat or Number Needed to Harm (from a psychiatrist to fellow docs)

- NNT or NNH represents how many patients one would need to treat with one intervention v. another in order to encounter one additional beneficial (NNT) or harmful (NNH) outcome.
- If the NNT or NNH were three, it would mean with every three patients, a difference in outcome would be expected, and possibly commonly encountered in day-to-day clinical practice.
- First step in appraising evidence is to check statistical significance and confidence interval.
- Ask how often will this difference in risk be encountered in day-to-day clinical practice.

from Citrome L. Relative vs. absolute measures of benefit and risk: what's the difference? Acta Psychiatr Scand 2010: 121: 94–102

Published application of NNH and Evidence Based Medicine



from Citrome L. Relative vs. absolute measures of benefit and risk: what's the difference? Acta Psychiatr Scand 2010: 121: 94–102

How to determine advice to the patient

- Use the crude annualized incidence rates to calculate NNH (=137) comparing egg consumption vs. no egg consumption in a 1-year period.
- For a woman with similar characteristics to those in the studied cohort, risk of developing diabetes is 77% higher if she consumes at least 7 eggs per week, but the development of diabetes will be encountered in only one extra woman in every 137 women who eat at least 7 eggs per week v. those abstaining from eggs completely.
- Over time, this risk may be unacceptable, but probably remains overshadowed by overall poor diet (including what else is being consumed along with the eggs), physical inactivity and advancing age.
- Also unanswered is whether or not there are appreciable relative or absolute risk differences when comparing persons among the different categories and along the continuum of egg consumption.

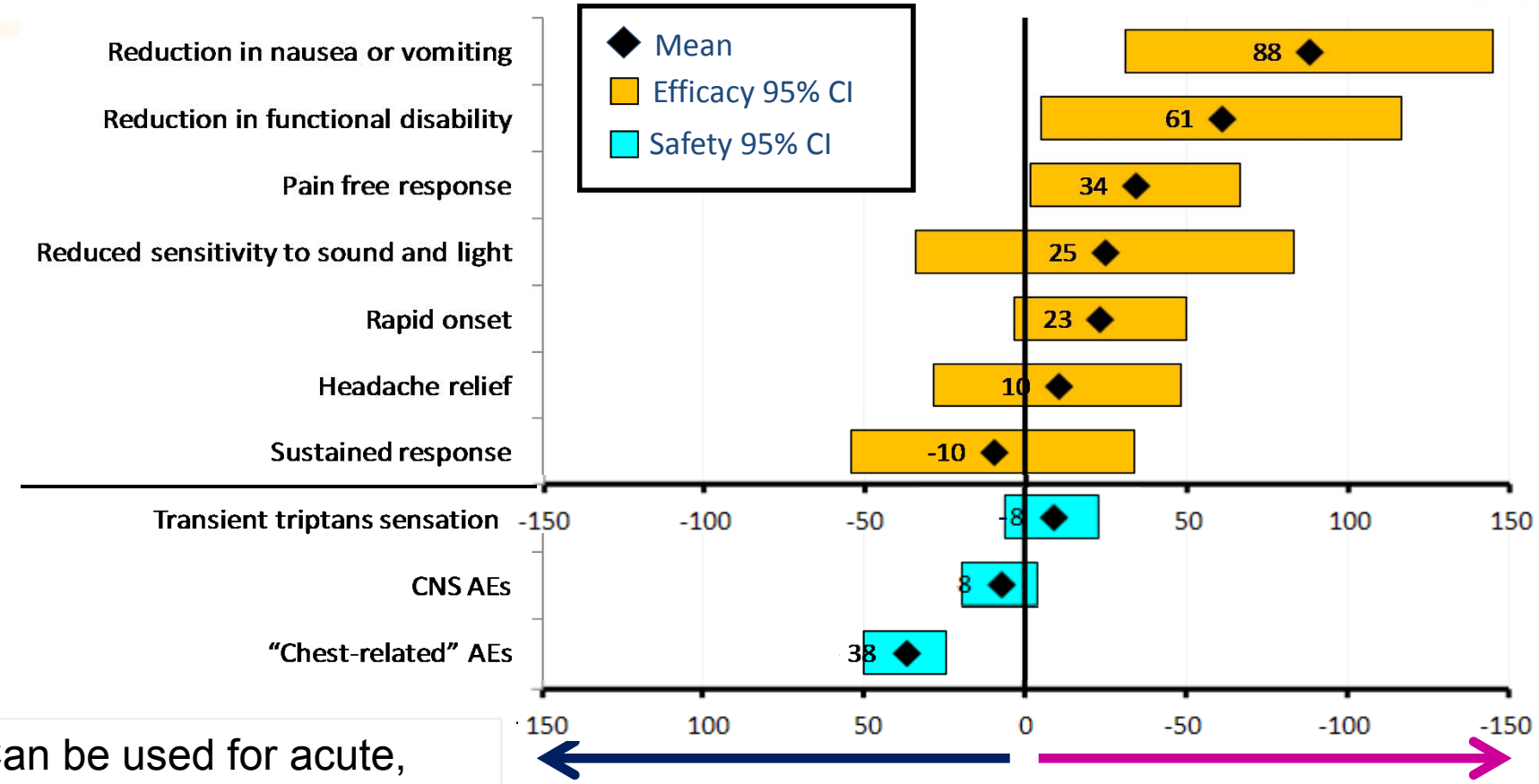
from Citrome L. Relative vs. absolute measures of benefit and risk: what's the difference? Acta Psychiatr Scand 2010: 121: 94–102

Cautions with NNT

- Should not be used for statistical analysis and inference given its properties. All statistical procedures (estimation, hypotheses testing, trial design) are more natural and transparent for Absolute Risk Reduction.
- The name NNT/NNH may encourage the idea that it is a precise number, but it has probabilistic content. If presenting NNT, setting, time period, outcome, and baseline risk of patients for whom the NNT is thought to be applicable should be considered.
- It is incorrect to draw conclusions at the level of individual patients based on NNT calculations.
- A clear distinction should be made between data analysis and subsequent risk communication. NNT may be considered as a way of presenting results, not as a tool for statistical computations.

from Quartey G et al. internal technical review document based on Rockhold F. and Fedorov V. Pitfalls of Number Needed to Treat (NNT) as a Measure of Comparative Benefit or Risk. Internal GSK presentation. Citing Bender R., Calculating confidence intervals for the NNT, 2001, Controlled Clinical Trials **22**, pp.102-110 and Lesaffre E. and Pledger G., A note on the NNT.,1999, CCT, **20**, pp. 439 - 447

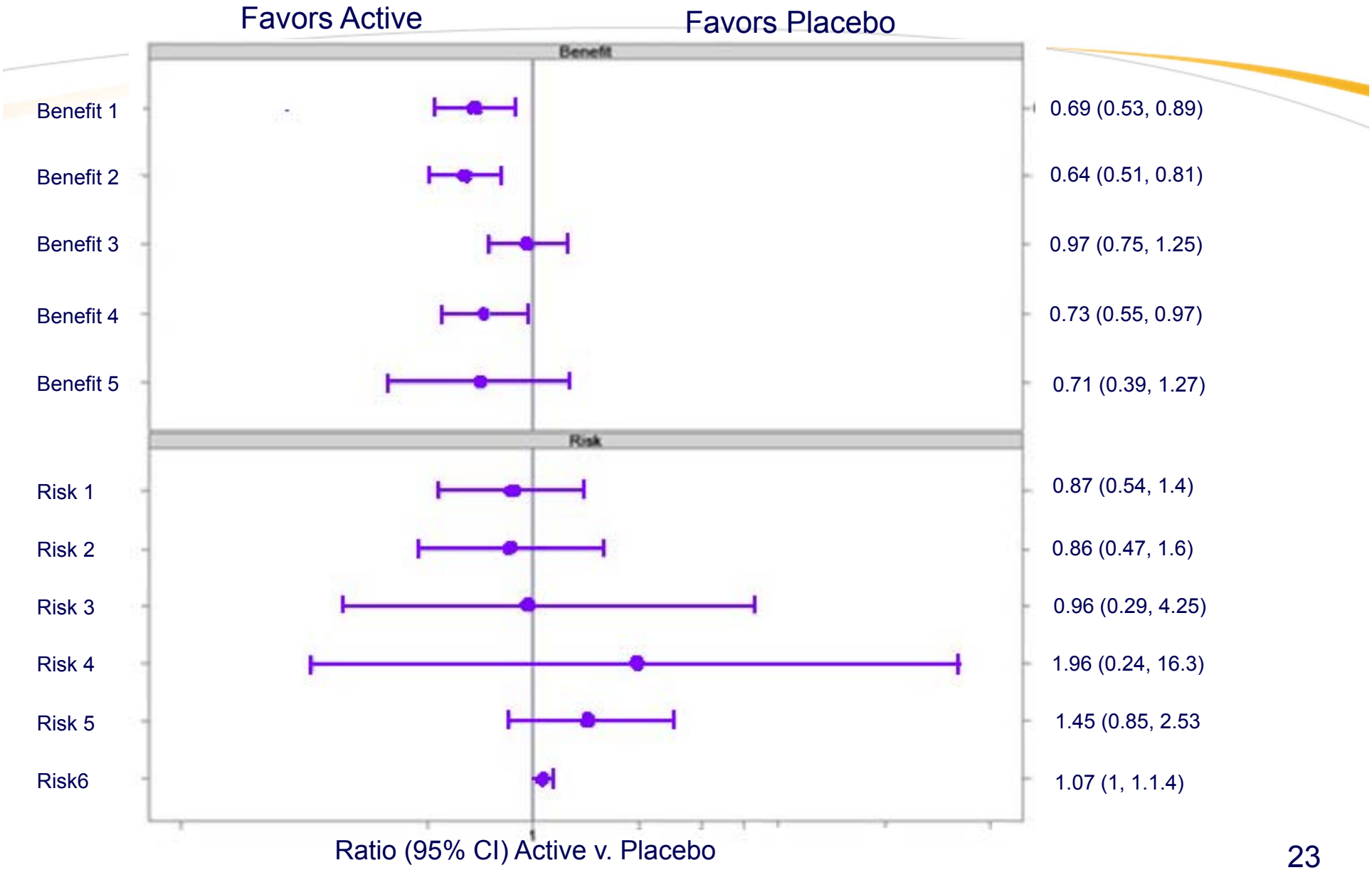
Example of Interval Plot to Display Risk Differences*



Can be used for acute, dichotomous endpoints and ranked in order of importance

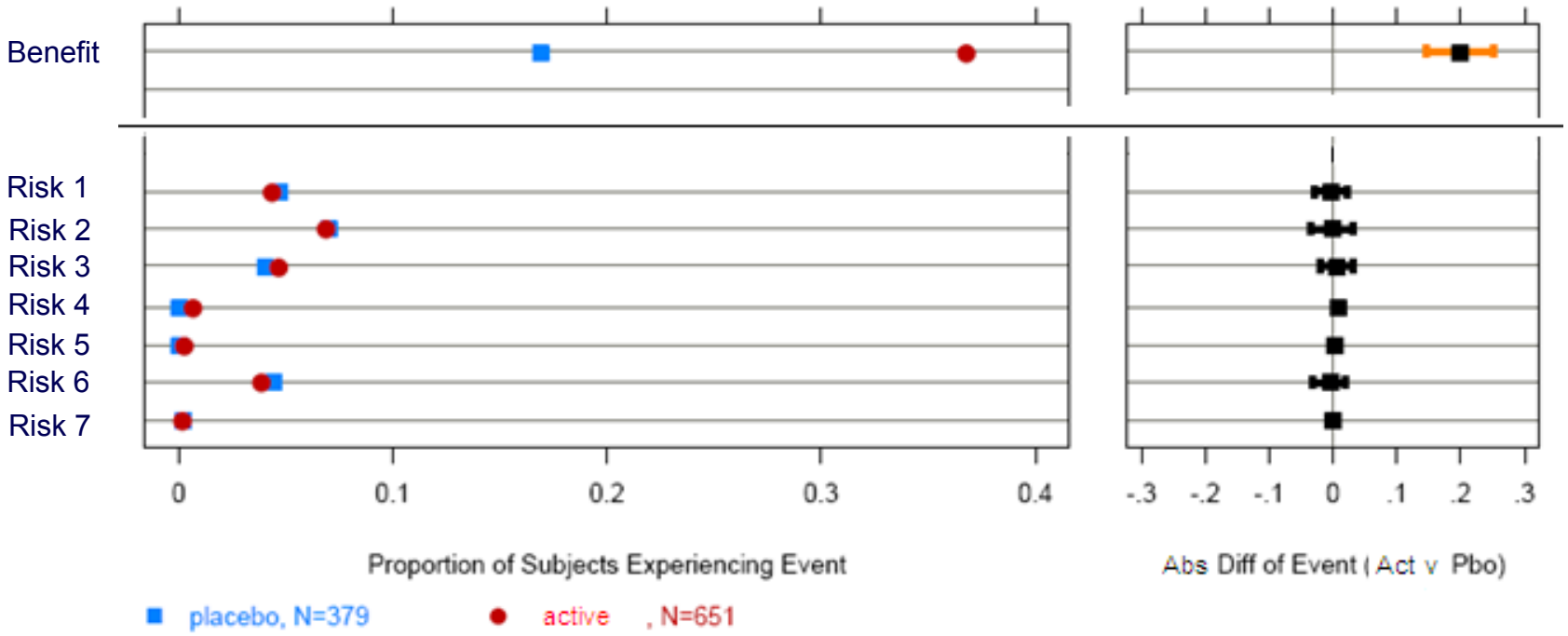
*Created by Bennett Levitan et al., PhRMA Benefit Risk Action Team (BRAT)

Template Created Internally for Statisticians



Our thanks to GengQian Cai and Andrew Miskell for this software template

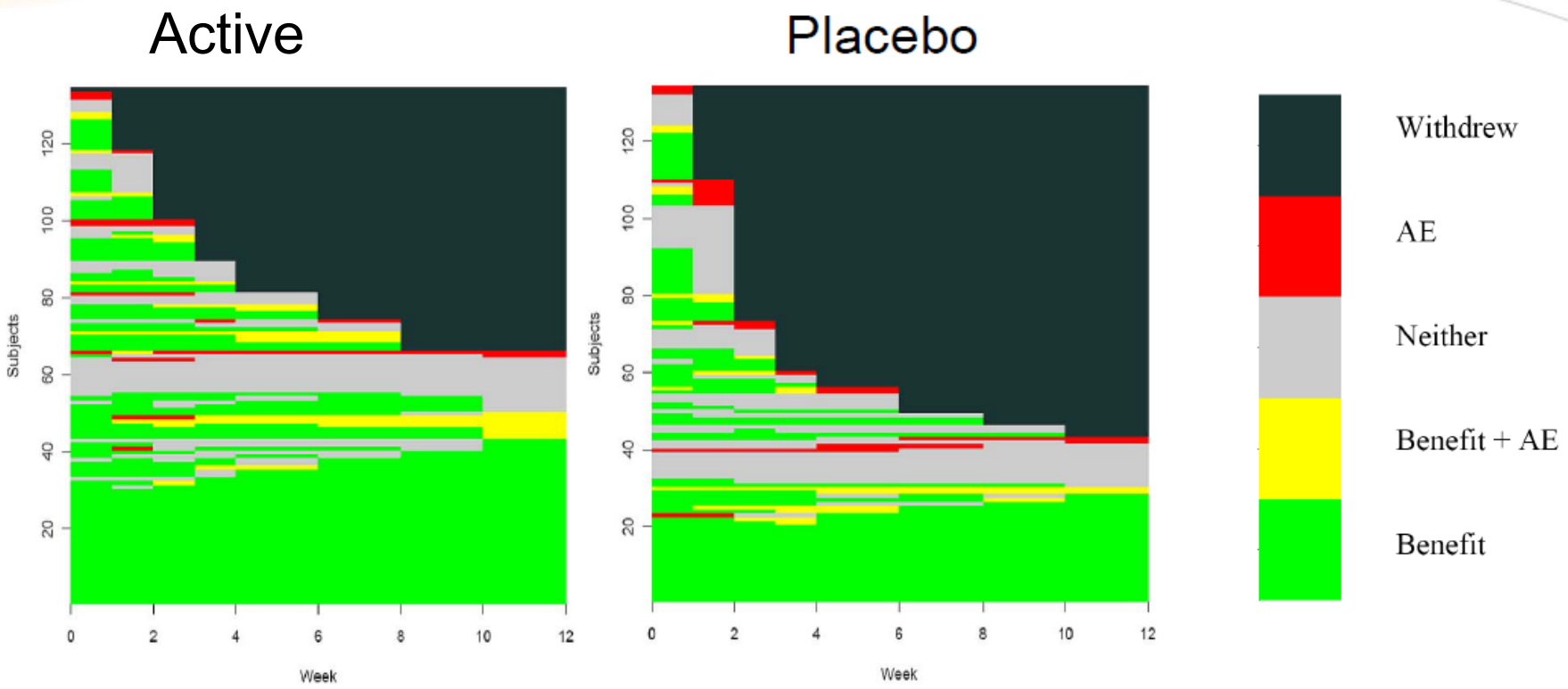
Adding Benefit to a Standard Safety Graph



Can be used for acute, dichotomous endpoints and ranked in order of importance. Could also compare subgroup responses.

Graph by Bob Schriver, Mike Durante, Mike Williams, Marilyn Metcalf

Benefit and Risk Over Time, for Each Patient



Each row is a patient

- Sorted from most withdrawal time to most time on benefit
- Can see whether the same patients experience both benefit and risk

From Jonathon Norton, FDA. A Longitudinal Model and Graphic for Benefit-risk Analysis, with Case Study. DIJ 2011.

Weighting

- Like any analysis, weighting is a structured way to capture thinking, not an answer in and of itself.
- Weighting of Benefits and Risks is difficult and controversial
- Methods for collecting weights exist and can be improved.
- Methods for ***communications*** among groups who offer different weights will be the more important contribution.

Explaining your conclusions from your analysis

Does benefit outweigh risk?

How does your evidence support this conclusion*?

Consider the following:

- How much uncertainty is there around the favorable and unfavorable effects?
- Is the benefit durable?
- Does the risk increase or decrease over time?
- Do some patients experience more benefit and/or more risk than others?
  - Are there subgroup differences? (e.g., age, sex, ethnicity, organ function, disease severity, or genetic polymorphism)
  - Do those patients at higher/lower risk experience higher or lower benefits?
- What are the implications for the patient?

What it all boils down to – Clear Communication

- Complete Disclosure and Clear & Transparent communications = meaningful dialogue about potential impact of treatment to patients and providers
- Disclosure (e.g. label) does not automatically equal transparency.

What it all boils down to - finding meaning

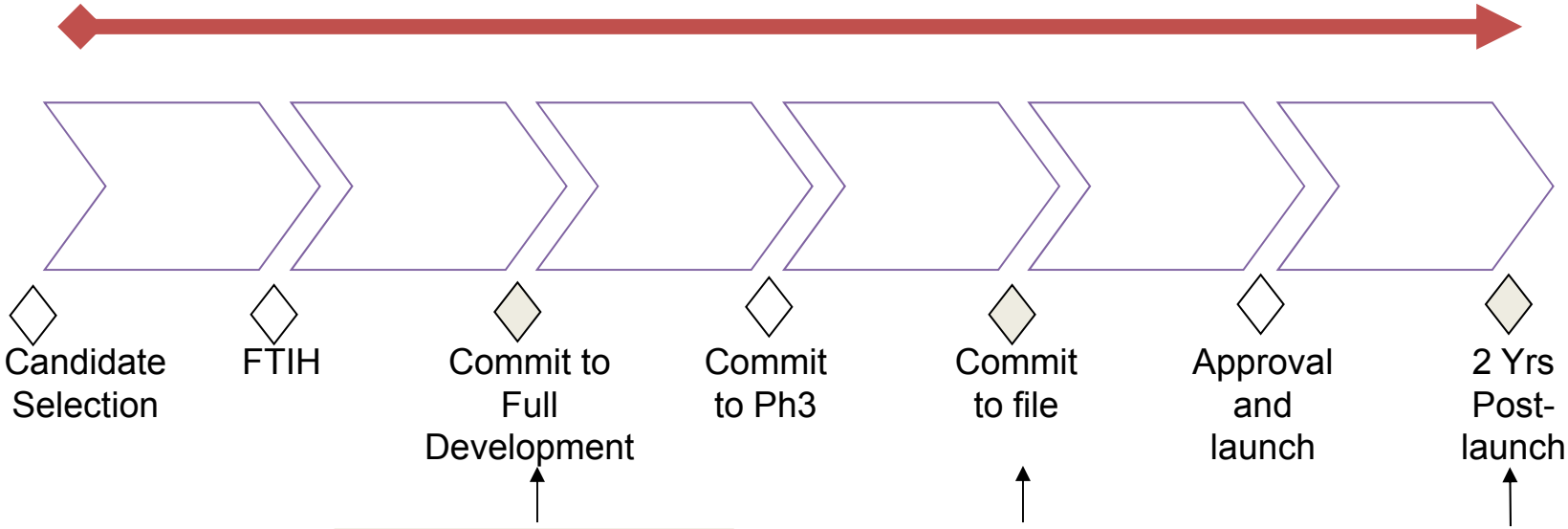
- Disclosure ≠ Transparency
- Transparency ≠ Understanding
- Understanding ≠ Agreement
- Soooo….
  - Not every approved medicine is right for every patient
  - Not every approved medicine is funded by every payer
  - Not every funded medicine is preferred by every patient
  - Etc.

Governance

- Pharmacovigilance lasts throughout the life of a medicine, and is a continual process. Ensuring that benefit to risk remains positive throughout that lifecycle requires consistent assessment within a product and some level of uniformity across products.
- Milestone reviews provide an opportunity for these kinds of consistent BR assessments.

Timing for Benefit / Risk Evaluations

A favorable balance of benefit to risk for patients must be maintained throughout the lifecycle



Level and diversity of human data grows with time

Summary of Today's Discussion

- Benefit to Risk is a Science and a Tool
- The BR context matters:
  - Patients need Comparative BR
  - Intervention v. prevention dictates different patient messages
  - Pre-market v. post-market BR evaluations utilize different information but need to be connected.
- Communication: It isn't a useful BR analysis if no one understands it
  - Regulator
  - Payer
  - Physician
  - Patient
- Governance: Timing and consistency of evaluations are important
- Weighting of benefits and risks remain important philosophical issues with no immediate tactical solutions

Q&A

Backup

Abstract

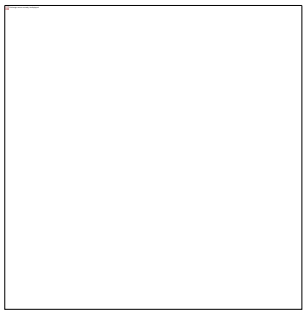
- ABSTRACT: The term Benefit to Risk has long been used in the Pharmaceutical Industry, but not until the last ten years has much work been done in attempting to quantify this concept at either the population or patient level. Numerous activities in the US and Europe have been spawned to look at this and some regulators have been strong proponents of such a quantitative approach. The advantage is that it supplies a balanced and objective framework to weigh benefits and risks of medicines, while the drawbacks may be in the clarity of the presentation of the findings. The level of rigor needed to “quantify” these concepts remains a topic of debate, but what is eminently clear is the need to communicate the methods and findings to a broad audience of diverse backgrounds. The merits and examples of simple ways to communicate the concepts at the population and patient level will be discussed.

From stats to individual

- What is the threshold for the patient's "group"? Maximize the BR for that patient's group
- Venn diagrams of probability – does the patient sit at the right intersections?
- Enough information for the patient to have a reasonable belief that they will receive benefit

TransCelerate Biopharm Inc (Hever) in a nutshell:

TBI is a professional organization of major pharmaceutical companies dedicated to finding new ways to accelerate drug development, identified five collaboration opportunities which are estimated to produce **multi-billion dollar annual cost savings** to the industry, while improving quality and outcomes.



The five near-term collaboration opportunities, which are estimated to produce multi-Billion annual cost savings to the industry over a three-year time period, are focused on high-quality, risk-based monitoring, a common investigator site portal, centralization of qualification and training, common clinical data standards, and a model for comparative drug pricing.

Non-profit entity (TransCelerate BioPharma Inc) funded by 10 member pharmaceutical companies. Based in Philadelphia. 5 initial workstreams. $56M investment. $3+ Billion in projected industry savings. 3 year timeframe. Aligned with Industry Initiatives (CTTI, CDISC, IMI etc) and Regulators FDA, NHS, EMA etc)

Standard Approach for High Quality, Risk-Based Monitoring

Upfront assessment of critical variables or data for risk mitigation in Data Review Plans and Study Management Plans. Elimination of non-value added activities including the high level of Source Data Verification at sites

Common Investigator Site Portal

Single interface for all Pharma companies and CROs to use; platform for cross-industry, delivery of content and services. Near-term goal includes assessing existing portals and designing a common portal solution

Centralization / Shared Site Qualification and Training

Streamlining external training that sites can use for Good Clinical practice / Fair Market Value. Standardize process for requesting information from sites
Developing a framework for site qualification / credentials

Clinical Data Standards – Efficacy

Common Clinical Data Standards and metadata standards, a foundation for end-to-end data flow

Comparator Drugs for Clinical Trials

Creating a “hub and spoke” supply model for sharing and negotiating pricing for Group members to purchase comparator drugs used for clinical trials from each other.

The current approach to BR lends itself to broader application

- Greater expectation for discussion of benefit and risk in dossiers
- EU legislation, including Periodic Benefit Risk Evaluation Reports (PBRERs) to replace Periodic Safety Update Reports (PSURs)

Drug lifecycle

Discovery	Clinical study design	Regulatory submissions	Launch	Post-marketing surveillance

Where BR thinking could be applied

What will the drug do for the patient?	Do we need to design outcomes studies and what should they be?	What should be in the benefit/risk section of the dossier?	What should be emphasized in the risk(-benefit) communications?	When do we need to update information to regulators and the public?

Summary

- Medicine Safety and PV is a complex and fascinating exercise
- Statistics and statisticians play a central and pivotal role in methods development and interpretation
- Sources of data are varied driving the need for a variety of methods
- Inference goes well beyond the p-value -- needs true linkage of data, analysis, medical expertise and thought.
- Data Visualization tools are vital to interpretation
- Safety is a key component of Quantifying benefit to Risk