Lessons learned from E14

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E14?

• It is an ICH Guidance
  – ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
  – E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
Noisy link of QT to arrhythmia

ECG
↓ *
QT (biomarker) = f_1(HR, [drug])
↓ *
QTc = f_2([drug])
↓ *
Arrhythmia = f_3(QTc)
+ 
{Other mechanisms of arrhythmia (false -)}
- 
{Stabilizing drug effects (false +)}
Result of uncertainties

• E14 asserts a MID for QTc
• QT effects are dichotomized on this MID
• “Regulatory certainty” at the expense of
  – A nuanced appreciation of risk
  – Discouraging development of some benign or acceptably toxic drugs
Is BP a better surrogate?

• We behave as if it were...
  – Established basis for approval of drugs
  – Guidance and labeling reflecting expected benefits
  – No threshold for treatment
Support of BP as surrogate

- Epidemiology
Effects of BP on CV Outcomes

MacMahon et al., 1990 Lancet 335:765-774.

Similar relationship holds for effects of antihypertensive drugs.
Other Risk Factors—Age

Figure 9. Ischemic heart disease mortality rate in each decade of age versus usual blood pressure at the start of that decade.
Support of BP as surrogate

- Epidemiology
- Outcome studies
  - with a wide variety of drugs from many drug classes, bearing in common
    - not site of action
    - not mechanism of action
    - only reduction in BP
  - achieve risk reduction largely equivalent to having an untreated BP at new level
High Quality Data with BP

• Better data on harm associated with BP enables an approach that is more quantitative and less arbitrary
Assessing Benefit (Symptoms)

• Value of benefit
  – High for death, stroke
  – Low for wrinkles
  – Mean, distribution

• Effect size is **absolute change in symptom**
  – Comes from studies
  – Mean, distribution
  – CI is f(nature, power)
Assessing Benefit (Events)

- **Value of benefit**
  - High for death, stroke
  - Low for wrinkles
  - Mean, distribution

- **Effect size is absolute change in likelihood of event**
  - Comes from studies
  - Mean, distribution
  - CI is f(nature, power)
Assessing harms

- Similar process, if you have the data
- Similar dependence of CI on power
- See Dr. Madabushi’s worked example
- Need to get on same scale as benefits (QALY or similar)
Assessing multiple benefits or harms

- Death
- MI
- Stroke

Net
Assessing net benefit or harm

- Benefit
- Harm
- Net
How BP is not like QT

• Because you know something quantitative about the risks, you can…
  – Apply what you know quantitatively about benefits
  – Make rational, defensible R-B decisions
  – Adjust the population to ensure net benefit