Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

L. Jay Katz MD, FACS
Wills Eye Hospital
Philadelphia
Financial disclosure

- **Consultant**: Alcon, Allergan, Glaukos, Amorphex, Merck, Sucampo, Bausch and Lomb, Sensimed, Inotek, Aerie
- **Research**: Aerie, Alcon, Allergan, Glaukos, Lumenis, Pfizer, Mati, Merck, Bausch and Lomb
- **Speaker**: Alcon, Allergan, Lumenis, Merck, Sucampo
Issues

- Does this benefit patient, industry, clinicians, scientists, FDA process?
- Is this a legitimate score?
- Does glaucoma lend itself to the process?
- Could there be drawbacks to the system?
- Should MIGS be exposed to this novel grading?
Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

- Composite Endpoints (CEP): consists of a # of endpoints (outcomes: efficacy or safety)
- Occurs as soon as one of its end points occurs
- Result = increase event rate -> decrease sample size -> more rapid, less costly trial
Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

CEP dependent on:
- Clinical question
- Outcomes chosen
- Analysis
Sample size

- Control efficacy event rate = 10%
- Device efficacy event rate = 5%
- RRR = 10 - 5/10 = 50%

Sample size 1170

Add control safety event rate = 20%  20%
Add device safety event rate = 10%  17.5%

Sample size 330  1450
Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

CEP advantages
- Decrease sample size
- Estimates the net clinical benefit
- Avoids choosing a single primary endpoint

CEP disadvantages
- Interpretation difficult when endpoints not equal importance
- Efficacy and safety = importance?
- Sponsors, patients, investigators, IRB, FDA may not agree
- Individual claims for product labeling difficult
Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

- Efficacy outcomes only
- Safety parameters only
- Mixture of efficacy and safety parameters

CEP “Surgical success score”??
Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

CEP: where is the benefit?
- Industry: to allow for economical trials?
- Patients: access to score?
- Physicians: to rapidly interpret device role?
- FDA: to streamline evaluation and approval process?
Should efficacy and safety remain separate inquiries?

Balancing risk vs benefit has been traditional process

Merging may mask important aspects of either efficacy or safety
Composite endpoint of efficacy may be low with an outstanding single parameter but low in other outcome measures.

May lower IOP 25% but may require continuation of meds and unable to reach target IOP of 15 mm Hg.
Comparison of Devices:

- CEP “Surgical success rates” are placed in device labeling
- Different populations and designs make it difficult to use score to compare devices
- Still need RCT to compare device A vs device B
Device highly effective but serious side effects would have low CEP (Device A 95% efficacy – 30% safety = CEP 65% vs Device B 72% -2%= CEP 70%)

Should that device be available for the right population and specific labeling?
Composite Safety and Effectiveness Endpoints: Are They Necessary to Measure Device Trial Success?

CONCERN 5

- CEP scores are public information
- Patient given device A with CEP 65 and does poorly....finds that device B has CEP 70
- Device B not ideal choice for that particular patient
- Legal ramifications?
Glaucoma: too complex to utilize a CEP score to have a truly beneficial meaning?

The disease is a group of disorders: POAG, SOAG, PACG, SACG, ....

The disease severity staging, rapidity of progression, ability to take glaucoma medications, life expectancy, quality of life issues......ALL factor in decision making and minimize the impact of CEP scores???

Simpler may not always be better
References

- Kowalski CJ Composite Endpoints: Sometimes More Than a Solely Economic Consideration
- Ferreira-Gonzalez I Methodologic Discussions for Using and Interpreting Composite Endpoints are Limited But Still Identify Major Concerns
  J Clin Epid 2007; 60: 651-657
- Cannon CP Clinical Perspectives in the Use of Composite Endpoints
  Controlled Clin Trials 197; 18:517-529