Summer program on multiplicity and reproducibility in scientific studies

Working group on Subgroup Analysis

Panel Discussants

- Juliet Shaffer, Moderator
- Alok Krishen – GlaxoSmith Kline
- Gary Rosner – M.D. Anderson Cancer Center
- S. Sivaganesan – University of Cincinnati

- Alok Krishen is a Senior Director of Biostatistics at Glaxo Smith Kline
- Inc.(GSK), he supports the Neuroscience Medicines Development center at
- GSK. His main area of expertise is development of late phase medicines
- to treat psychiatric and neurologic conditions. He has been at GSK for
- the past 18 years. Most recently he serves as his company's
- representative on the Multiple Endpoints Expert Team sponsored by the
- Pharmaceutical Research and Manufacturers of America. This group was
- formed to look into multiple co-primary endpoints for drug approval and
- it has published its findings in a report to appear in the Drug
- Information Journal. Alok's early training was in abstract Mathematics,
- he subsequently received a degree in Statistics from the Florida State
- University in 1976.

- Gary Rosner: I received my doctorate in
- biostatistics from the Harvard School of Public Health. I am Professor
- of Biostatistics in the Department of Biostatistics and Applied
- Mathematics at the University of Texas M.D. Anderson Cancer Center,
- where I've been since 2000. I am also Adjunct Professor of Statistics
- at Rice University. My areas of research interest are Bayesian methods
- for complex data, clinical trial design, population modeling for
- pharmacokinetics and pharmacodynamics, and pharmacogenetics.

- I am Siva Sivaganesan. I am professor in the Department of
- > Mathematical Sciences, University of Cincinnati.

An interesting quote

- Antoine Augustin Cournot (1801-1877)-
- French Philosopher, Mathematician, and Economist – wrote in 1843:

- "…it is clear that nothing limits…the number of features according to which one can distribute categories."

- As an example he mentions investigating the chance of a male birth.
- “One could distinguish first of all legitimate births from those occurring out of wedlock, … one can also classify births according to birth order, according to the age, profession, wealth, or religion of the parents…”

- He goes on to point out that as one increases the number of such “cuts” (of the material into two or more categories) it becomes more and more likely that by pure chance for at least one pair of opposing categories the observed difference will be significant.

- :As a result…the probability that an observed deviation can not be attributed to the vagaries of chance takes on very different values depending on whether one has tried a more or less large number of cuts before having hit on the observed deviation. …

- Usually these attempts through which the experimenter passed don’t leave any traces; the public will only know the result that has been found worth pointing out; and as a consequence, someone unfamiliar with the attempts which have led to this result completely lacks a clear rule for deciding whether the result can or can not be attributed to chance.”

Some subgroup issues

Overall analysis insignficant, many subgroups tested separately: Many Possible outcomes:

One or more subgroups significant

(a) Not significantly different from other groups

(b) Significantly different from other groups

(c) Two subgroups significant in opposite directions

- Overall analysis significant: Many subgroups tested separately:
  Also many possible outcomes:
- not significant in any subgroup
- significant in some but not others, but no significant subgroup differences
- significant in opposite directions in different subgroups

- BiDilStory
- The FDA recently approved BilDil for treatment of congestive heart failure in African-Americans, making it the first therapy approved for a specific racial group. Although this decision is controversial, it is quite a detective story, being a case where subgroup analysis led to a new, life-saving treatment approved by the FDA.