Is the Juice Worth the Squeeze?

Sharing Clinical Trial Data Workshop
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David L DeMets, PhD
Department of Biostatistics & Medical Informatics
University of Wisconsin-Madison
Outline of Commentary

• Three examples where data sharing uncovered issues
• An example of data sharing that resulted in additional publications
• Observations on challenges
Scenario I: Anturane Reinfarction Trial (ART)

- ART: a RCT of anturane vs placebo in post MI patients
- Not all primary events (mortality) reported in the 1980 NEJM publication: non eligible patients and non analyzable events
- Independent analysis revealed additional events, trends remained the same but statistical significance was lost
- ART probably contributed to the concept of Intention to Treat (ITT) as the primary analysis method
Scenario II: APPROVE Trial

- A RCT of Vioxx (Rofecoxib) vs placebo for colon cancer prevention
- 2005 Paper suggested an increase in CV events, trial terminated early
- Debate over 18 month honeymoon
- No follow up after 14 days off drug by design
- Informative Censoring: Off drug ≠ off study
- 2008 Analyses (DLD) with additional follow up
- References
  - NEJM 2005 Primary Paper
  - NEJM 2006 Editorials
  - Lancet 2008 Approve+1
Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Thrombotic Cardiovascular Events in the Rofecoxib and Placebo Groups, According to the Intention-to-Treat Principle. I bars represent 95 percent confidence intervals.
Figure 1. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed APTC Events in the Rofecoxib and Placebo Groups, According to the Intention-to-Treat Principle.
I bars represent 95 percent confidence intervals.
Scenario III: Genomic Predictors – Nevins & Potti

• Duke investigators, Potti & Nevins, publish a series of papers with genomic predictors for cancer risk and response to treatments
  • 2006 *Nature Medicine* (Potti et al.) 306 times
  • 2006 *New England Journal of Medicine* (Potti et al.) Cited 350 times

• Genomic predictors used in Duke clinical trials

• Statisticians at MD Anderson fail to be able to reproduce the same genomic predictors
Data Sharing Revealed Fraud

  – Data were shared
  – Authors document extensively issues with the data and the analysis
• Ultimately, data & analyses shown to be fraudulent & many published papers withdrawn
• References
  – IOM Report (2012) provides extensive documentation and recommendations
IOM Report Overview
Scenario IV: COMPANION Trial

- COMPANION: A RCT of pacemaker vs pacemaker + defibrillator vs best care in HF patients
- Demonstrated the benefit of pacemaker and defibrillators over best medical care
  - Utilized clinical outcomes of mortality and HF hospitalization
COMPANION Trial (1)

• After initial primary papers published and abstracts presented, investigators and statistical team got busy with new trials
• Data archived at the UW-Madison statistical center
• A decade elapses
• New opportunity arose to conduct further analyses and turn previously presented abstracts into full publications
COMPANION Trial (2)

• First task was to reproduce the 2004 NEJM paper
• Effort took 3 months, even with the COMPANION lead statistician (DLD)
• Lots of documentation but not complete
• Had to retrieve initial analysis program
• One problem: final data file had been slightly updated after NEJM publication with trial close out and new events discovered
• Once successful, new analyses and publications
COMPANION (3) Subsequent Publications

• Bristow MR, Saxon LA, Feldman AM, Mei C, Anderson SA, DeMets DL: Lessons learned and insights gained in the design, analysis and outcomes of the COMPANION trial, J Am College Cardiology, 2016


• Several additional papers have been published or are in progress
COMPANION (4): Collaborations

• Following Lo & DeMets (2016) NEJM, we reached out to COMPANION Steering Committee members as coauthors
  – Obtained their assistance and insights
• Also involved new CV researchers: fellows, younger faculty
• Gained new insights into the use of pacemakers and defibrillators in HF patients
Is the Juice Worth the Squeeze? Final Thoughts

- Takes a lot of effort and cost to archive a complete RCT data file sufficiently for future analyses
- Likely not everything is documented sufficiently
- Catching errors and fraud: not common but important
- Can investigate alternative analyses
- Data sharing can produce further research & maximize the benefit of the trial
Data Sharing: Final Thoughts

• Need to minimize amount of data stored & documented for each trial
  – Phase III RCTS collect more data than is typically ever used

• Should focus our energy & resources on pivotal Phase III trials
  – Would not put much into earlier phase trials

• Some squeeze in the right places can be useful