Is the Juice Worth the Squeeze?

Sharing Clinical Trial Data Workshop
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Outline of Commentary

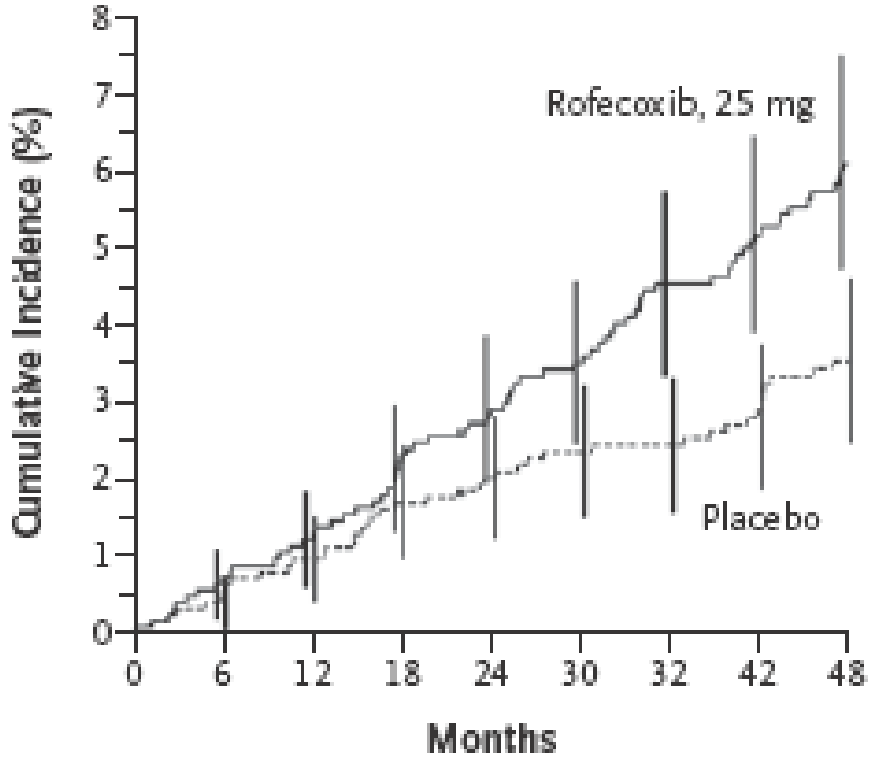
- Three examples where data sharing uncovered issues
- An example of data sharing that resulted in additional publications
- Observations on challenges

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 Teat (ITT) as the primary analysis method
- The Anturane Reinfarction Trial Research Group. Sulfinpyrazone in the prevention of sudden death after myocardial infarction. N Engl J Med 1980;302:250-256.
- Temple R, Pledger GW. The FDA's critique of the Anturane Reinfarction Trial. N Engl J Med 1980;303:1488-1492

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



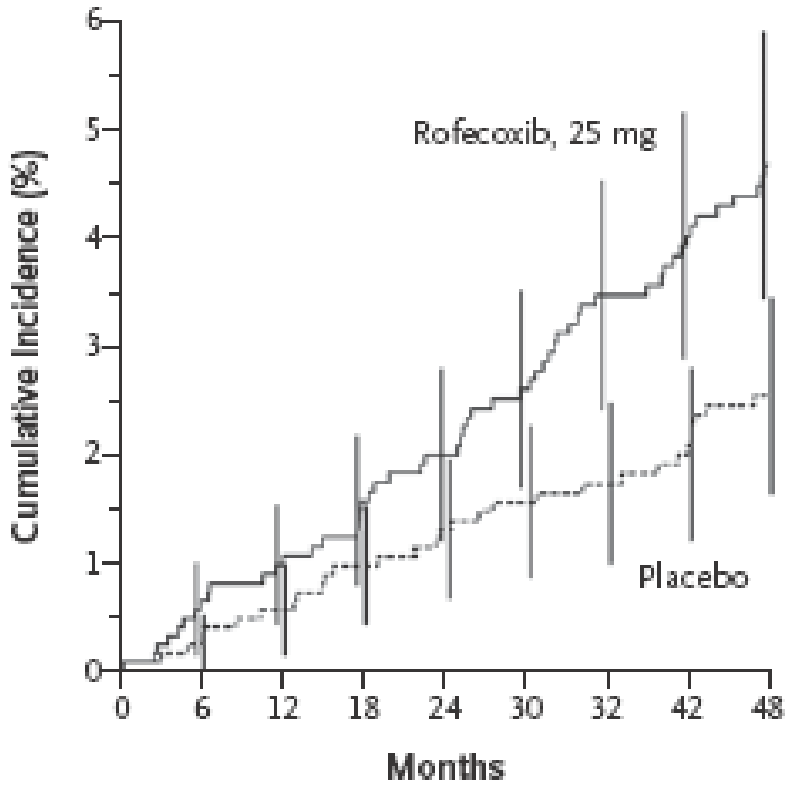
No. at Risk

Rofecoxib	1287	1221	1187	1152	1131	1117	1092	1032	989
Placebo	1300	1247	1224	1189	1173	1157	1133	1071	1027

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.

NEJM 2006; 355:203-05



No. at Risk

Rofecoxib	1287	1220	1188	1158	1140	1125	1102	1042	1002
Placebo	1300	1249	1228	1196	1181	1165	1140	1079	1036

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.

NEJM 2006; 355:203-05

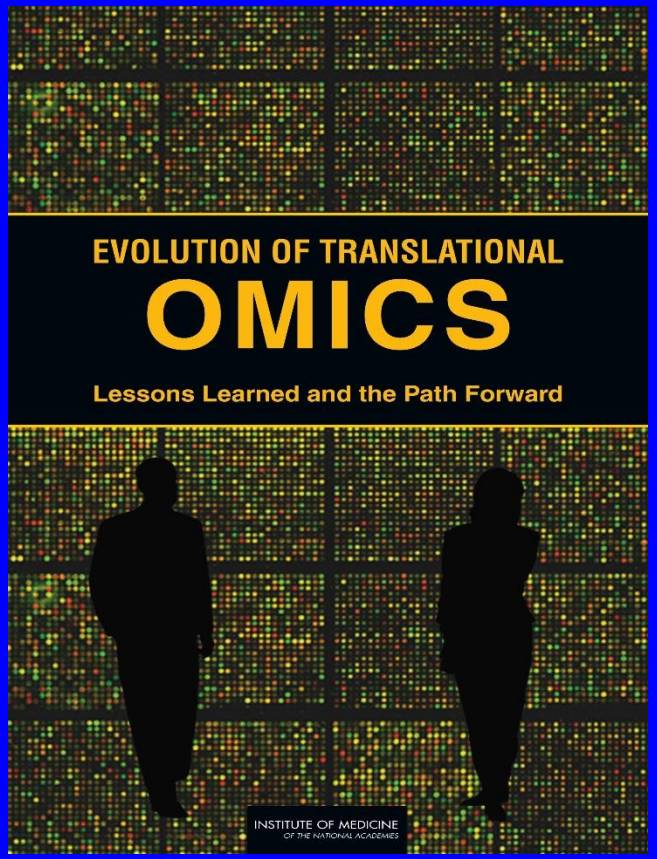
Scenario III: Genomic Predictors – Nevins & Potti

- 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

- Baggerly & Coombes (2009) Annals of Applied Statistics
  - 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
  - DeMets D, Fleming T, Geller G & Ransohoff D, Institutional Responsibility and Flawed Genomic Predictors at Duke University, J of Ethics in Science and Engineering, Nov 24, 2016

IOM Report Overview



Scenario IV: COMPANION Trial

- COMPANION: A RCT of pacemaker vs pacemaker + defibrulator 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
- Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure. New Engl J Med 2004; 350:2140-50.

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

- Shamoun F, De Marco T, DeMets D, Mei CQ, Lindenfeld J, Saxon LA, Boehmer JP, Leigh JYong P, Feldman AM and Bristow MR. Impact of Degree of Left Ventricular Remodeling on Clinical Outcomes From Cardiac Resynchronization Therapy. JACC-Heart Fail. 2019;7:281-290.

- 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
  - Shamoun F, De Marco T, DeMets D, Mei CQ, Lindenfeld J, Saxon LA, Boehmer JP, Leigh JYong P, Feldman AM and Bristow MR. Impact of Degree of Left Ventricular Remodeling on Clinical Outcomes From Cardiac Resynchronization Therapy. JACC-Heart Fail. 2019;7:281-290.

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