Getting Published in High-Profile Journals

Edward H. Livingston, MD, FACS, AGAF

Deputy Editor, JAMA
Professor of Surgery and Biomedical Engineering
University of Texas Southwestern School of Medicine

Where Do You Want to Publish?

- NEJM
- JAMA
- Lancet

Issues

- Very few surgeons routinely publish in the very high impact literature
- Why?
  - Types of research done by surgeons
  - Surgeons are not well funded
  - Surgeons have little presence at the major journals
  - Credibility
  - Quality of Science

What Do the Big Journals Want?

- RCTs
- Meta-analyses (rigorous)
- Practice Changing Findings
- Important Discoveries

- Citations/Impact Factor

Types of research done by surgeons

- Observational
- Case Series
- Quality/Outcomes

RCTs

- Routinely done in Medical Subspecialties (Cardiology, Oncology, GI)
- Need more in Surgery
- More difficult to design than drug trials but not impossible

- JAMA Evidence: Users Guide to the Medical Literature. Guyatt et al.
- Ludwig DS, Ebbeling CB, Livingston EH. Surgical vs

Meta analyses

- Must use rigorous methods
- Follow Guidelines (PISMA, MOOSE etc)

What Does Not Work

- Logistic Regression of Administrative Data
- Volume Outcome
- Single Center Studies
- Case Series
- Retrospective Analyses
- Obvious COI

To Promote the Science and Art of Medicine and the Betterment of the Public Health

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JAMA

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Business is About Relationships

- So is Publishing
- Get to know editors
- Review papers (in depth)
- Write editorials, reviews
- The big journals are always looking for reviewers and authors
- We tend to publish who we know

Stability

- Editors and staff-15 years with JAMA
- Purposeful-prospective authors should learn who their contacts are
- Work with societies to publish presented papers
- It may not seem like it-but we are in the business of publishing your papers!

How Do Papers Move Through JAMA?

- 6,000 MS's received each year
- Approximately 4 major papers/week
- Assigned to a specialty contributing editor
- Editor decides to reject/send for peer review
- 2 Content/1 Statistical Reviewer

Editorial Process

- Discuss reviewed papers at bi-weekly editors

- ERBR (editorial review before revision)/Reject/Refer
- ERBR-Repeat re-present at editors meeting
- Accept-Contributing editor edits paper for publication along with copy editors

Paper Structure

- Brevity and Clear Writing
- Abstract-
  - Context: What is the clinical question?
  - Conclusion: Ensure it follows the data
- Introduction
  - 3 Paragraphs
    - Introduction to topic-avoid a summary of what everyone already knows
    - What specific aspect of the clinical problem you will address
    - Explicit statement of a study hypothesis

Paper Structure

- Methods
  - Sufficient detail so others can duplicate study
- Results
  - Include confidence intervals or IQRs for data-never only show point estimates
- Discussion
  - Focused
  - How your findings change clinical thought
- Figure/Tables
  - Visually appealing and simple
- References
  - Complete-make sure you find all pertinent papers-the one you miss is always written by (a now pissed off) reviewer

Common Pitfalls

- Trial registration
  - Intervention trials must be registered BEFORE patients are enrolled
- Study Power
  - Reference prior studies providing assumptions about expected mean, SD etc.

    Rationale for expected differences between groups (MCID)

Common Pitfalls

- Study Design
  - Equivalence
  - Superiority
  - Noninferior

Reporting of Noninferiority and Equivalence Randomized Trials

An Extension of the CONSORT Statement

Gilda Piaggio, PhD
Diana R. Elbourne, PhD
Douglas G. Altman, DSc
Stuart J. Pocock, PhD
Stephen J. W. Evans, MSc
for the CONSORT Group

The CONSORT (Consolidated Standards of Reporting Trials) Statement, including a checklist and a flow diagram, was developed to help authors improve their reporting of randomized controlled trials. Its primary focus was on individually randomized trials with 2 parallel groups that assess the possible superiority of one treatment compared with another but is now being extended to other trial designs. Noninferiority and equivalence trials have methodological features that differ from superiority trials and present particular difficulties in design, conduct, analysis, and interpretation. Although the rationale for such trials occurs frequently, those designed and described specifically as noninferiority or equivalence trials appear less commonly in the medical literature. The quality of reporting of those that are published is often inadequate. In this article, we present an adapted CONSORT checklist for reporting noninferiority and equivalence trials and provide illustrative examples and explanations for those items amended from the original CONSORT checklist. The intent is to improve reporting of noninferiority and equivalence trials, enabling readers to assess the validity of their results and conclusions.

JAMA. 2006;295:1152-1160 wwww.jama.com

Trial Design

- Superiority
  - Minimal Detectable Difference
  - Minimal Clinically Important Difference
- Equivalence/Noninferiority
  - Equivalence Margin

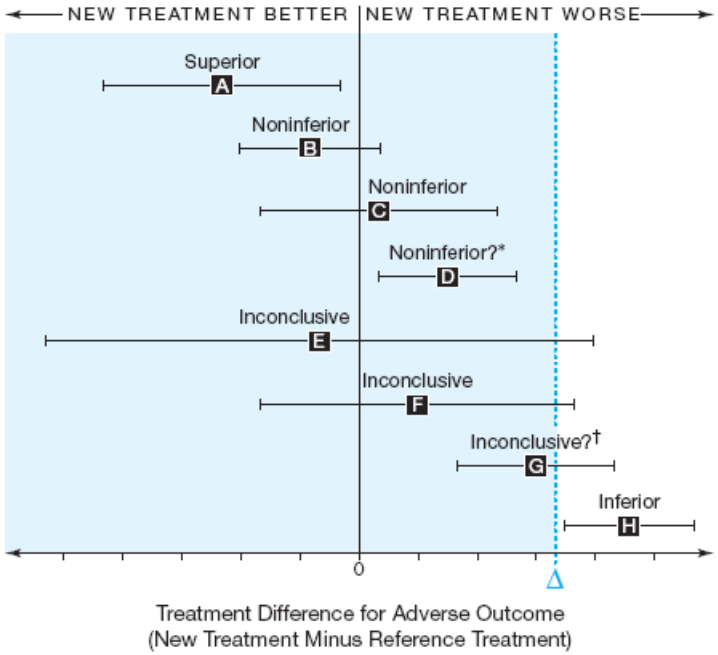
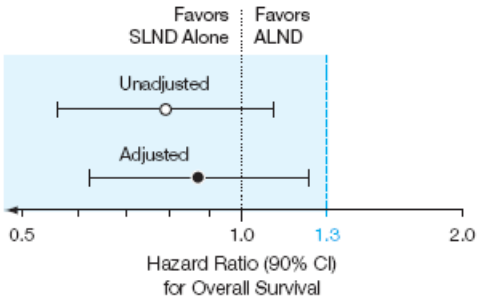


Figure 3. Hazard Ratios Comparing Overall Survival Between the ALND and SLND-Alone Groups



Common Pitfalls

- Clear definition of Primary Outcome Variable
- Secondary Outcomes
  - Rarely adequately powered
  - Best if secondary analysis is included in study protocol as an a priori analysis

Study Protocol

- We will ask for original study protocol and IRB

- These must be consistent with the paper (bad news if it is not-and that has happened-see “ethical problems”)

Statistics

- Differences between groups should be

- Pharma studies: we will ask for independent statistical review with publication of the independent and not industry statistical analysis.

Presentation

- Follow author instructions-we will reject on

- If sent elsewhere first:
  - Not as much of a problem as many authors think
  - Ensure that you address prior reviewers critiques. We may ask for the prior reviews

Statistical Matters

- Missing Data
  - Missing at Random?
  - Dropping observations is suboptimal
  - Random Effects Regression
  - Multiple Imputation
  - Last Observation Carried Forward (LCOF)
    - Can bias towards more favorable results if patients drop out
  - First Observation Carried Forward (FOCF)

- Propensity Matching

Analysis of Observational Studies in the Presence of Treatment Selection Bias

Effects of Invasive Cardiac Management on AMI Survival Using Propensity Score and Instrumental Variable Methods

Thérèse A. Stukel, PhD
Elliott S. Fisher, MD, MPH
David E. Wennberg, MD, MPH
David A. Alter, MD, PhD
Daniel J. Gottlieb, MS
Marian J. Vermeulen, MHSc

Context Comparisons of outcomes between patients treated and untreated in observational studies may be biased due to differences in patient prognosis between groups, often because of unobserved treatment selection biases.

Objective To compare 4 analytic methods for removing the effects of selection bias in observational studies: multivariable model risk adjustment, propensity score risk adjustment, propensity-based matching, and instrumental variable analysis.

Design, Setting, and Patients A national cohort of 122 124 patients who were elderly (aged 65-84 years), receiving Medicare, and hospitalized with acute myocardial infarction (AMI) in 1994-1995, and who were eligible for cardiac catheterization. Baseline chart reviews were taken from the Cooperative Cardiovascular Project and linked to Medicare health administrative data to provide a rich set of prognostic variables. Patients were followed up for 7 years through December 31, 2001, to assess the association between long-term survival and cardiac catheterization within 30 days of hospital admission.

Main Outcome Measure Risk-adjusted relative mortality rate using each of the analytic methods.

Results Patients who received cardiac catheterization (n=73 238) were younger and had lower AMI severity than those who did not. After adjustment for prognostic factors by using standard statistical risk-adjustment methods, cardiac catheterization was associated with a 50% relative decrease in mortality (for multivariable model risk adjustment: adjusted relative risk [RR], 0.51; 95% confidence interval [CI], 0.50-0.52; for propensity score risk adjustment: adjusted RR, 0.54; 95% CI, 0.53-0.55; and for propensity-based matching: adjusted RR, 0.54; 95% CI, 0.52-0.56). Using regional catheterization rate as an instrument, instrumental variable analysis showed a 16% relative decrease in mortality (adjusted RR, 0.84; 95% CI, 0.79-0.90). The survival benefits of routine invasive care from randomized clinical trials are between 8% and 21%.

Conclusions Estimates of the observational association of cardiac catheterization with long-term AMI mortality are highly sensitive to analytic method. All standard risk-adjustment methods have the same limitations regarding removal of unmeasured treatment selection biases. Compared with standard modeling, instrumental variable analysis may produce less biased estimates of treatment effects, but is more suited to answering policy questions than specific clinical questions.

JAMA. 2007;297:278-285 www.jama.com

Propensity Match

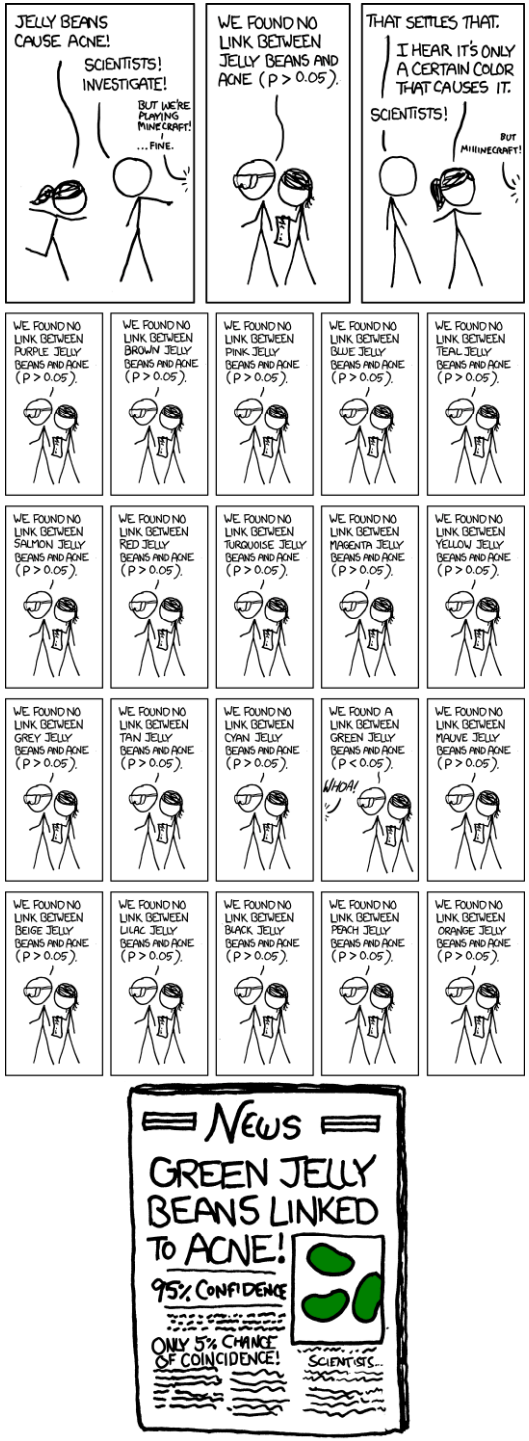
Table 1. Select Baseline Characteristics According to Receipt of Cardiac Catheterization*

	Overall Cohort			Propensity-Based Matched Cohort			
	Received Cardiac Catheterization Within 30 Days			Received Cardiac Catheterization Within 30 Days			
	No (n = 48 886)	Yes (n = 73 238)	Standardized Difference	No (n = 31 193)	Yes (n = 31 193)	Standardized Difference	Unmatched Patients Receiving Cardiac Catheterization (n = 42 045)
Predicted 1-year mortality (AMI severity), mean (SD)†	32.3 (18.3)	20.9 (13.3)	73.7	26.8 (15.5)	27.8 (12.5)	6.3	15.8 (7.5)
Demographics							
Age range, y							
65-74	40.2	64.4	49.9	45.2	45.3	0.1	78.6
75-84	59.8	35.6	49.9	54.8	54.7	0.1	21.4
Men	49.7	58.4	17.6	53.2	49.6	7.2	65.0
Black	7.5	4.8	11.3	5.7	6.6	3.7	3.5
Social Security income ≥$2600	30.0	29.7	0.9	30.2	30.2	0.1	29.2
Comorbidities							
History of angina	44.1	49.9	11.8	46.0	45.6	0.9	53.2
Previous myocardial infarction	32.9	26.4	14.3	28.7	31.9	6.8	22.3
Previous revascularization	17.8	20.9	7.7	18.0	20.2	5.7	21.3
Congestive heart failure	27.2	10.4	45.7	16.6	18.3	4.4	4.6
Diabetes mellitus	36.6	28.6	17.1	31.8	34.1	4.9	24.5
Peripheral vascular disease	12.8	9.1	12.0	10.6	11.5	2.8	7.3
Chronic obstructive pulmonary disease	24.9	17.6	18.3	20.9	23.3	5.9	13.3
Smoker‡	16.1	18.0	5.0	16.5	17.0	1.2	18.8
AMI clinical presentation characteristics							
Non–ST-segment elevation AMI	41.8	38.9	5.9	39.8	40.1	0.8	38.0
Shock	1.9	1.5	3.0	1.8	2.3	3.4	0.9
Hypotension	3.5	2.3	7.4	3.1	3.6	2.6	1.2
Received CPR	1.8	1.6	1.6	2.3	3.5	7.3	0.2
Peak creatinine kinase >1000 U/L	29.1	32.4	7.2	31.7	31.8	0.2	32.9
Hospital characteristics							
Annual AMI volume >200 patients	20.1	30.4	23.6	22.9	20.5	5.6	37.8
Mortality§							
Died within 1 y	38.6	14.2		34.6	19.0		10.6
Died within 4 y	62.0	27.8		55.4	36.3		21.4

Abbreviations: AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation.
*All data are presented as percentages. Standardized difference is the mean difference divided by the pooled SD, expressed as a percentage.
†Predicted 1-year mortality was computed using the Cox proportional hazards regression model, including all baseline patient characteristics of age, sex, race, socioeconomic status, comorbidities, and clinical presentation.
‡Defined as current smoker.
§Derived by Kaplan-Meier method.

Common Pitfalls

- Multiple comparisons
  - Alpha penalties
- Regression-Elimination Procedures
  - Order and strategy of variable entry/elimination


JELLY BEANS CAUSE ACNE!
SCIENTISTS! INVESTIGATE!
BUT WE'RE PLAYING MINECRAFT!
... FINE.
WE FOUND NO LINK BETWEEN JELLY BEANS AND ACNE (P > 0.05).
THAT SETTLES THAT.
I HEAR IT'S ONLY A CERTAIN COLOR THAT CAUSES IT.
SCIENTISTS!
BUT MINECRAFT!
WE FOUND NO LINK BETWEEN PURPLE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BROWN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN PINK JELLY BEANS AND ACNE (P > 0.05).
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WE FOUND NO LINK BETWEEN RED JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TURQUOISE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN MAGENTA JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN YELLOW JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN GREY JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TAN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN CYAN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND A LINK BETWEEN GREEN JELLY BEANS AND ACNE (P < 0.05).
WHOA!
WE FOUND NO LINK BETWEEN MAUVE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BEIGE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN LILAC JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BLACK JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN PEACH JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN ORANGE JELLY BEANS AND ACNE (P > 0.05).
NEWS
GREEN JELLY BEANS LINKED TO ACNE!
95% CONFIDENCE
ONLY 5% CHANCE OF COINCIDENCE!
SCIENTISTS...

Common Pitfalls

- Interim Stopping Rules
  - Multiple looks and type I error

Randomized Trials Stopped Early for Benefit

A Systematic Review

Victor M. Montori, MD, MSc
Christina Laccheui, MHSc
Teresa W. Leung, BHSc
Elizabeth Darling, RM, BHSc
Dianne M. Bryant, PhD
Heiner C. Bucher, MD, MPH
Holger J. Schünemann, MD, PhD
Maureen O. Meade, MD, MSc
Deborah J. Cook, MD, MSc
Patricia J. Erwin, MLS
Amit Sood, MD
Richa Sood, MD
Benjamin Lo, MD
Carly A. Thompson, BHSc
Qi Zhou, PhD
Edward Mills, PhD
Gordon H. Guyatt, MD, MSc

for benefit.

Study Selection Randomized clinical trials of any intervention reported as having stopped early because of results favoring the intervention. There were no exclusion criteria.

Data Extraction Twelve reviewers working independently and in duplicate abstracted data on content area and type of intervention tested, reporting of funding, type of end point driving study termination, treatment effect, length of follow-up, estimated sample size and total sample studied, role of a data and safety monitoring board in stopping the study, number of interim analyses planned and conducted, and existence and type of monitoring methods, statistical boundaries, and adjustment procedures for interim analyses and early stopping.

Data Synthesis Of 143 RCTs stopped early for benefit, the majority (92) were published in 5 high-impact medical journals. Typically, these were industry-funded drug trials in cardiology, cancer, and human immunodeficiency virus/AIDS. The proportion of all RCTs published in high-impact journals that were stopped early for benefit increased from 0.5% in 1990-1994 to 1.2% in 2000-2004 ($P<.001$ for trend). On average, RCTs recruited 63% (SD, 25%) of the planned sample and stopped after a median of 13 (interquartile range [IQR], 3-25) months of follow-up, 1 interim analysis, and when a median of 66 (IQR, 23-195) patients had experienced the end point driving study termination (event). The median risk ratio among truncated RCTs was 0.53 (IQR, 0.28-0.66). One hundred thirty-five (94%) of the 143 RCTs did not report at least 1 of the following: the planned sample size (n=28), the interim analysis after which the trial was stopped (n=45), whether a stopping rule informed the decision (n=48), or an adjusted analysis accounting for interim monitoring and truncation (n=129). Trials with fewer events yielded greater treatment effects (odds ratio, 28; 95% confidence interval, 11-73).

Conclusions RCTs stopped early for benefit are becoming more common, often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small. These findings suggest clinicians should view the results of such trials with skepticism.

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Frequent JAMA Authors

- 10:1 Reject:Accept Ratio
- Keep Trying
  - But: Take the editors advice when rejected
  - i.e. don’t keep resubmitting the same type of paper that was rejected previously
  - “I need a JAMA publication to get promoted”

Write and Submit

- Write well-it takes practice
- 2nd draft = 1st draft – 10%
- Writing should be interesting to read
- Get others to review MS-especially those not intimately familiar with the topic-take their advice
- Resubmission –Address EVERY point raised by the editors and reviewers

Write and Submit

- Do not argue with peer reviewers
- You can disagree-explain why
- REALLY BAD idea to argue with the editor
- Don’t be afraid to contact editors directly

VA HSRD

- Thanks for having me!
- Edward H. Livingston, MD, FACS, AGAF

- Deputy Editor for Clinical Content
- Journal of the American Medical Association
- 515 N. State Street
- Chicago, Illinois, 60654
- Tel: 312-464-2459
- Fax: 312-464-5824
- edward.livingston@jamanetwork.org