Challenges in assessing journal authors' awareness of emerging standards for handling missing data, with illustrations from a focused review of Hepatitis C trials

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Outline

Extent of Missing Data in Trials

- **Historical Awareness, Early Standards**
- **Recent Emerging Standards**

Authors' awareness in publication of trials

- **Preliminary assessment: citing of standards**
- **Focused review of Hepatitis C trials**

Discussion

- **potential metrics for quantifying awareness**
- **Future directions: quantify key-phrase use**
- **Recommendations: standard use of terms**

➢ **Questions? *welcome throughout***

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Missing data in studies: problem long recognized

Over 4 decades ago, comment by researchers:

"Obviously the best way to treat missing data is not to have them"

Orchard & Woodbury, 1972

➢ *Recent commentary by researcher focused on providing practical toolkits for data analysts:*

"prevailing scientific practice is to downplay the missing data"

Stef van Buuren, 2012

Rare to explicitly quantify missing data

- 2001/2010 standards of CONSORT flow diagram: a start

CONSORT
TRANSPARENT REPORTING of TRIALS

CONsolidated Standards Of Reporting Trials

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Historical Awareness: early standards

Clinical Trials, decade since CONSORT TRANSPARENT REPORTING of TRIALS

Wood *et al* published 2004 review in SCT SOCIETY FOR CLINICAL TRIALS journal of the same name

Publications of 4 journals: *BMJ, JAMA, Lancet, NEJM* ; 71 trials

Review findings:

incomplete data prevalent (89%),

yet scope of methods limited

Horton & Switzer published review in New England Journal (NEJM), 2005

26 (8%) articles mention missing data methods

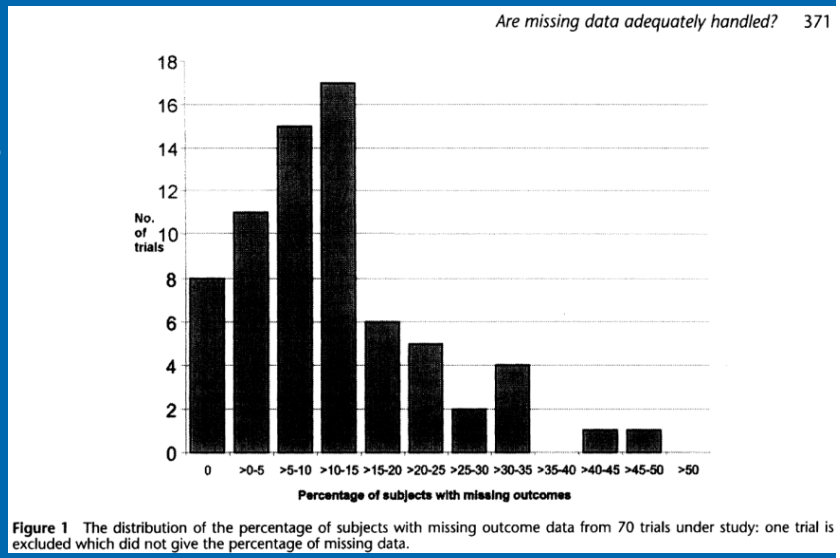

Figure 1 The distribution of the percentage of subjects with missing outcome data from 70 trials under study: one trial is excluded which did not give the percentage of missing data.

1996...

2001 — 2002 — 2003 — 2004 — 2005 — 2006 — 2007

[review targeted July - December 2001]

[review targeted Jan2004 - Jun2005]

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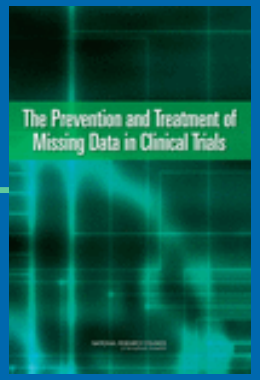
most acutely aware: Regulatory Trialists

→ emerging standards

- FDA commissioned a study and report
  - National Research Council (NRC) panel: deliberated > 1 year
  - The Prevention and Treatment of Missing Data in Clinical Trials
    available free online



report

FDA view published

article (NEJM)

2008 2009 2010 2011 2012 2013

workshop `blog

- 18 recommendations
  - Design/conduct
  - Analysis (Sensitivity analysis)
  - Reporting standards

To evaluate awareness by trialists broadly:
we winnow down to

⇒ "Top 10" in 2013 update (PCORI)

pcori | Patient-Centered Outcomes Research Institute

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Evolving standards: streamlined

pcori | Patient-Centered Outcomes Research Institute

TOP 10

- sponsored systematic review*, multidisciplinary panel

39 guidances → 10 mandatory standards, 3 "DOMAINS"

1. Define research question, in particular, the outcome(s)
2. Take steps in design & conduct to minimize missing data
3. Prespecify statistical methods for handling missing data
4. Continue collecting information on key outcomes
5. Monitor missing data
6. Account for uncertainty in handling missing data in the analysis
7. Discourage single-imputation methods
8. Conduct sensitivity analysis
9. Account for all participants entered in the study in reporting the results
10. Report on data completeness and strategies applied to handle missing data

CONDUCT

ANALYSIS

REPORTING

FDA guidance used in developing above, more forthcoming

Reporting standards now emerging in EU legislation

02 April 2014: European members of parliament voted 547 to 17 to adopt the Clinical Trials Regulation. This new law (effective mid-2016) requires any ***new*** drug clinical trial in Europe to be publicly registered and the results reported, whether its outcome was positive or negative. Impacts Missing Data on BROADER SCOPE: trial data sought by AllTrials initiiative

+AllTrials

* Li, Hutfless, Scharfstein, Daniels, Hogan, Little, Roy, Law and Dickersin (2014): Standards should be applied in the prevention and handling of missing data for patient-centered outcomes research: a systematic review and expert consensus. *Journal of Clinical Epidemiology* 67(1):15-32. PubMed PMID: 24262770

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Preliminary assessment: citing of initial NRC panel standards

PubMed & GoogleScholar search conducted on 26Nov2013: entries that cite panel's 2012 article

The NEW ENGLAND JOURNAL of MEDICINE

	PubMed search results	PubMed Central articles (open-access / pending)	Google Scholar search results
Count of results	10	17	71
Percent search results that present clinical findings instead of methods	70%	71%	56%

Do trial publications implicitly apply standards, instead?

To find useful metrics beyond explicit citing of standards, we focus on one disease...

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Focused Review of actual trials: Hepatitis C Antiviral Treatment

(many new ones, e.g., sofosbuvir)

Implicitly applying standards

- How? Carefully defined 1º Outcome:
  - Sustained Virologic Response (SVR)
    - serologic HCV RNA < LLOQ 12/24 wks post-treatment completion
    - presumed **SVR negative** if missing post-randomization serologies

- Review: set of trials registered on clinicaltrials.gov
  - Identified by search of clinicaltrials.gov and PubMed
  - Phase 2-4 randomized controlled trials
  - Limit to trials ongoing after 2007, with published results
  - Yielded total of 66 publications

HCV RNA=Hepatitis C Virus RNA; LLOQ=Lower Limit Of Quantification

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Focused Review of actual trials: Hepatitis C Antiviral Treatment

Quantifying awareness of standards

Dichotomous Criteria: screening by two rough measures

(a) explicitly address "missing" outcomes or "sensitivity analysis"

(b) implicitly define outcomes to be ascertained in all randomized, treated participants, minimizing "analysis dropouts"

- HepC trials frequently use SVR as 1º outcome
  - Thus, most meet criterion (b): 52 of 66 (79%)
  - However, minority met criteria (a): 22 of 66 (33%)
  - Meeting either (a) or (b): 57 of 66 (86%); naïve 95%CI:77-94%

Other trials: may not follow conventions such as those in (b)

For example, intervention trials for obesity often fail to address

[comparisons in Future Directions]

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Focused Review of actual trials: Hepatitis C Antiviral Treatment

Quantifying awareness: using ~6 search "terms"

"missing", "sensitivity analysis", "last observation/value carried forward", "baseline observation/value carried forward", "lost to followup", "dropout"

Standards met: apparent from subset of 57 pubs

- Define research question, in particular, the outcome(s) for handling missing data: 91%
- Conduct sensitivity analysis, i.e., presumed to do so by using the actual phrase: 5%
- Report on...strategies applied to handle missing data, by using terms: 95% (majority due to SVR outcome)
- Not associated with: industry sponsorship, having site(s) in US

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Focused Review of actual trials: Hepatitis C Antiviral Treatment

Quantifying awareness: beyond terms to phrases

"last observation/value carried forward" ≡ "SVR per prior HCV RNA used if [12 wk < LLOQ &] 24 wk value is missing"

Standards-ready methods*:* apparent from our review

Few "commonly used" methods for missing data explicitly used

- Multiple imputation (e.g., NCCAM's SyNCH, Roche/Lundbeck depression)
- Inverse probability weighting
- Likelihood-based methods
- Bayesian approaches

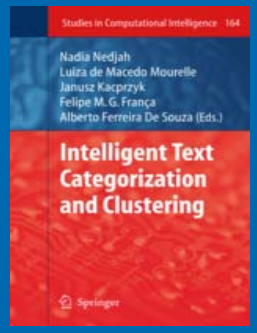
May become apparent when automating review:

[Future Directions]

Natural Language Processing

Symbolic Data Cluster Analysis

informed by panel consensus



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Focused Review of actual trials, if time: Discussion of Challenges, opportunities in future

Quantification issue:

inconsistent use of terms

For example, observations

"carried forward" appears only

in **caption text** of 1 article on approved drug boceprevir, yet

not used in companion trial report

in same journal issue!

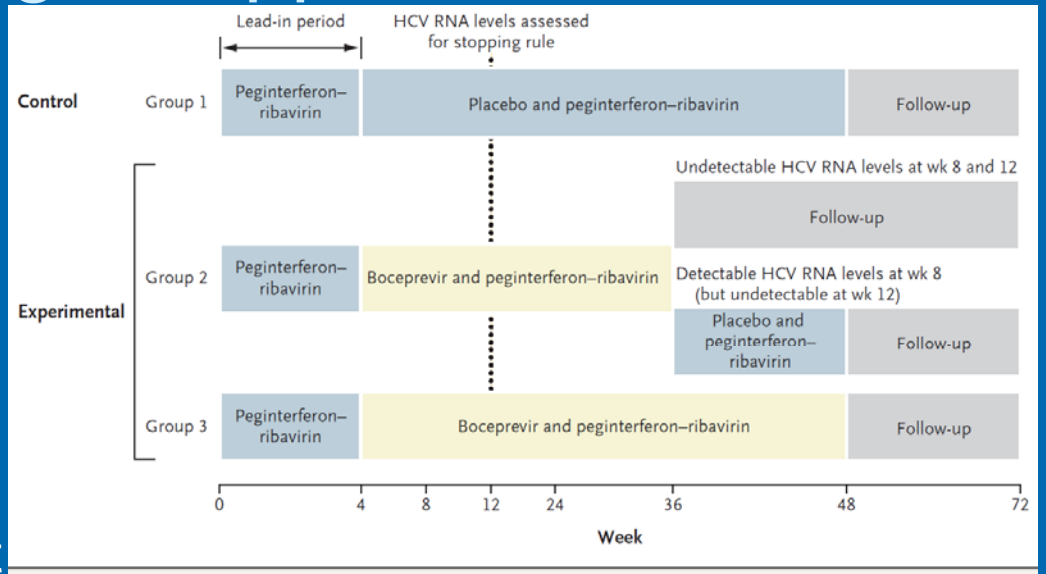

Figure 1. Study Design.

For 13 patients for whom the HCV RNA measurement at the end of the follow-up period was missing, the measurement obtained at 12 weeks of follow-up was carried forward; of these patients, a sustained virologic response was achieved in 2 (1 in group 2 and 1 in group 3). Patients with a detectable HCV RNA level at week 12 were considered

N ENGL J MED 364;13 NEJM.ORG MARCH 31, 2011

...SVR negative

Challenges: per review

- majority of those qualifying as "aware" due to disease-specific convention
- Implicit: (b) SVR ascertained in **all** randomized, treated participants
- Scientific rationale for using single imputation not explicitly cited or given
  - Hypothesis tests / confidence intervals do not perform as expected
- More general: relegation of details to online supplements

Focused Review of actual trials, if time: Discussion of Challenges, opportunities in future

Challenge: to translate best practices into standards

- Nonstandard use of jargon: only 8 of 52 explain explicitly how (b) SVR ascertained in all participants

Can encourage use of strict terminology in articles, per

Short of this: use text mining/classification methods, informed by expert panel input

Easier still: checklist supplement to CONSORT's

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Questions?

Thank you for your attention.

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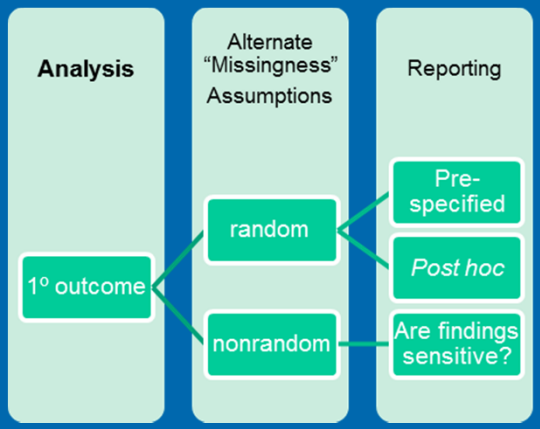
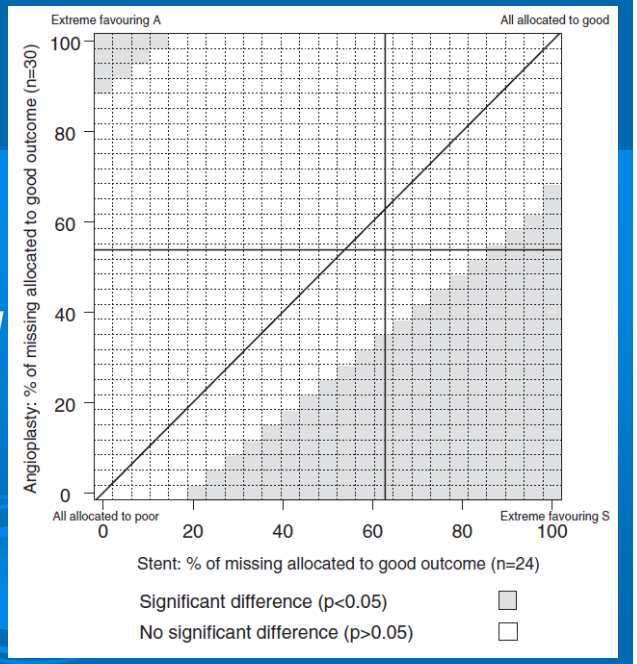
If more time: impact on systematic reviews & meta-analyses

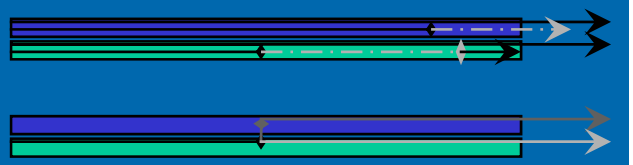
- *Taking it to a higher level of evidence-base…*
  - Binary outcomes more readily check sensitivity
    - Variance *p(1-p)* in terms of expected value
    - Expected value *p* has natural bounds [0,1]
    - NOTE: *p = Pr(outcome [death] occurs)*
  - *Can consider all subjects with missing values* have *OR* do not have *good/poor outcome*
  - *Can consider scenarios for experimental treatment's comparison to control:*
    - *best-case (all* good *outcomes for experimental subjects, all* poor *for controls)*
    - *worst-case (all* poor *outcomes for experimental subjects, all* good *for controls)*
  - Sally Hollis, 2002 proposed graphical framework to assess treatment effect under intermediate values:
    - Coronary bypass graft trial example at right
    - Experimental stent versus angioplasty control





If more time: impact on systematic reviews & meta-analyses

- *CONSORT statement – Box 6: Intention-to-treat analysis*
  - *"Intention-to-treat analysis corresponds to analysing the groups exactly as randomised. Strict intention-to-treat analysis is often hard to achieve for two main reasons—*
    - *missing outcomes for some participants &*
    - *non-adherence to the trial protocol."*



- *Meta-analyses of clinical trials not currently situated to assess adequacy of reporting (let alone* implementation*) of sens. anal.*
- *The Cochrane Collaboration*
  - Gamble & Hollis (2005) uncertainty intervals: way to evaluate missing binary outcomes' impact (beyond best/worst)
  - Higgins, White & Wood (2008) generalize approach to employ such uncertainty, with informative missing odds ratios (IMORs)
  - Recent extension of IMORs (2013) to network meta-analyses
  - However, their freely-available software, Review Manager (RevMan) does not accommodate missing data directly
  - Continuous outcomes lack standard approach (Wiebe, 2006)