Size Matters:
Non-Inferiority Margin Reporting In Clinical Trials

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Background

- Non-Inferiority (NI) trials suggest the intervention is no worse than standard therapy based on a specified NI margin
- Improper NI justification can lead to incorrectly declaring a new drug to be as good as standard therapy
- Previous research suggests that roughly 35% of trials from 1990 to 2014 reported NI margin justification
  - Assessment of trials >2012 has been done in registered trials
- Knowledge gap: assessment of NI margin in registered and non-registered trial published between 2010-2015

Objectives

Primary

The number of studies that reported all of the following:

- Preserved fraction of effect versus placebo
- Evidence supporting preserved fraction
- Both Per Protocol (PP) and Intention to Treat (ITT) analyses
- Use of correct end of the confidence interval
- Appropriate sample size calculation

Secondary

- Reporting of the individual components of primary outcome
- Proportion of pre-specified NI design in protocol
- Impact of funding source on components of primary outcome

Methods

- **Systematic search for NI trials:** MEDLINE from January 2010 to August 2015
- **Inclusion:** Pharmaceutical trials, English, RCTs, Full Trials
- **Exclusion:** Bioequivalent & equivalence studies, reviews, design papers, non-human trials
- **Sample size:** 225 trials to meet 95% CI with assumption 30% of trials will justify the NI margin
- **Systematic random sampling:** 930 citations found, screened 314 citations, excluded 91 abstracts and 3 full text, leaving 222 trials
- **Data extraction:** Independent & duplicate
- **Analysis plan:** Descriptive and inferential analyses with Chi-squared tests for comparisons

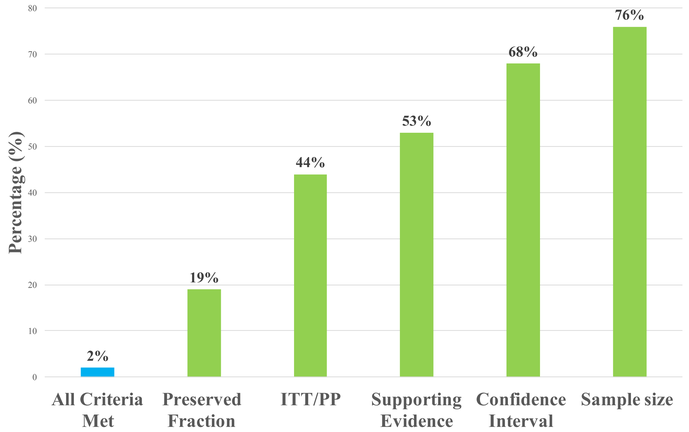

Figure 1: Primary Outcome (N=222)

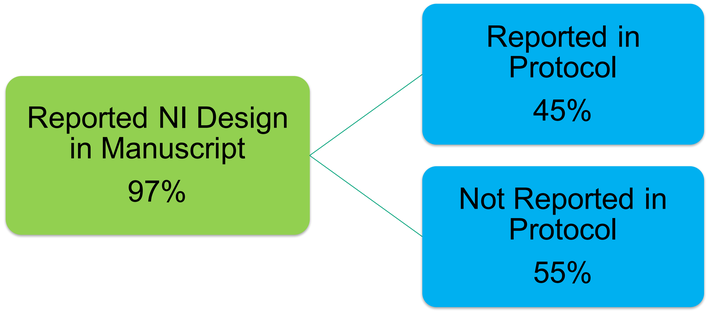

Figure 2: Pre-specified Non-Inferiority Design in Protocol (N=186)

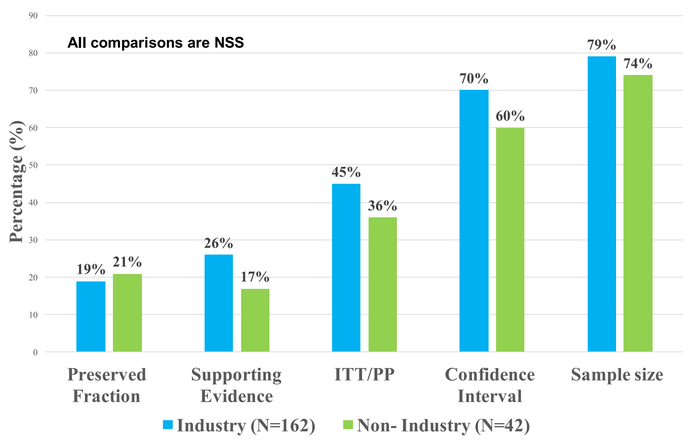

Figure 3: Impact of Funding on Primary Outcome

Results

- Very few studies reported:
  - On all components of the primary outcome
  - Pre-specified NI design in their protocol
- 39/222 (18%) only reported a PP analysis
  - PP is the preferred and most conservative analysis
- No identified association between funding source and quality of reporting
- Common justifications for NI margins were based on NI margins from previous studies
- Single studies were the most common form of supporting evidence for NI margins

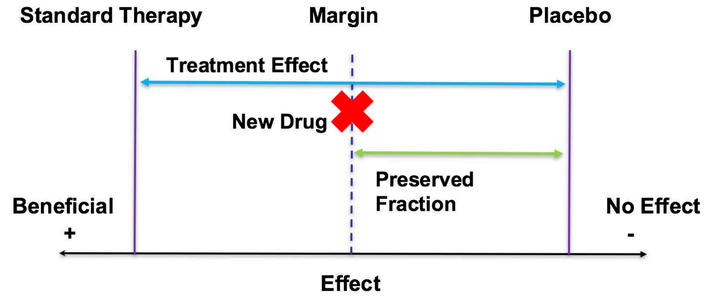

Figure 4: Preserved Fraction

Limitations

- Assessed reporting, not appropriateness of NI margins
- Did not contact authors regarding missing information
- This study was not designed to find associations between funding and reporting quality

Conclusion

- Few NI trials reported sufficient information for thorough appraisal and assessment of NI margins
- Less than half the studies pre-specified NI design in their protocol which may indicate a design change after results were known

Our Recommendations:

- Journal editors should insist that all details of NI design be reported
- Protocol registries should require reporting of NI design details

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