High proportion of high quality randomized clinical trials conducted by the NCI are negative or inconclusive

Ambuj Kumar, Heloisa Soares
and
Benjamin Djulbegovic
Moffitt Cancer Center & Research Institute
at the
University of South Florida

Background

- Phase III Randomized clinical trials (RCT) remain the primary mean for development of new treatments for the prevention and cure of cancer.

- However, sometimes a RCT fails to show a **significant** difference between the experimental and the control treatments

Objective

True negative vs. false-negative results?

- Is the new intervention truly not effective, i.e.

  evidence of absence of treatment effect

  or

- The trial's results were inconclusive, i.e.

  absence of evidence of treatment effect

Altman, DG et.al. in *BMJ* 1995;311:485 (19 August)

Defining true negative or inconclusive

- **True negative**

  -if the effect size and the 95%CIs were entirely outside the pre-determined limit of equivalence

- **Inconclusive**

  - if the 95%CIs crossed the line of no effect and one or both limits of pre-determined equivalence

Interpretation

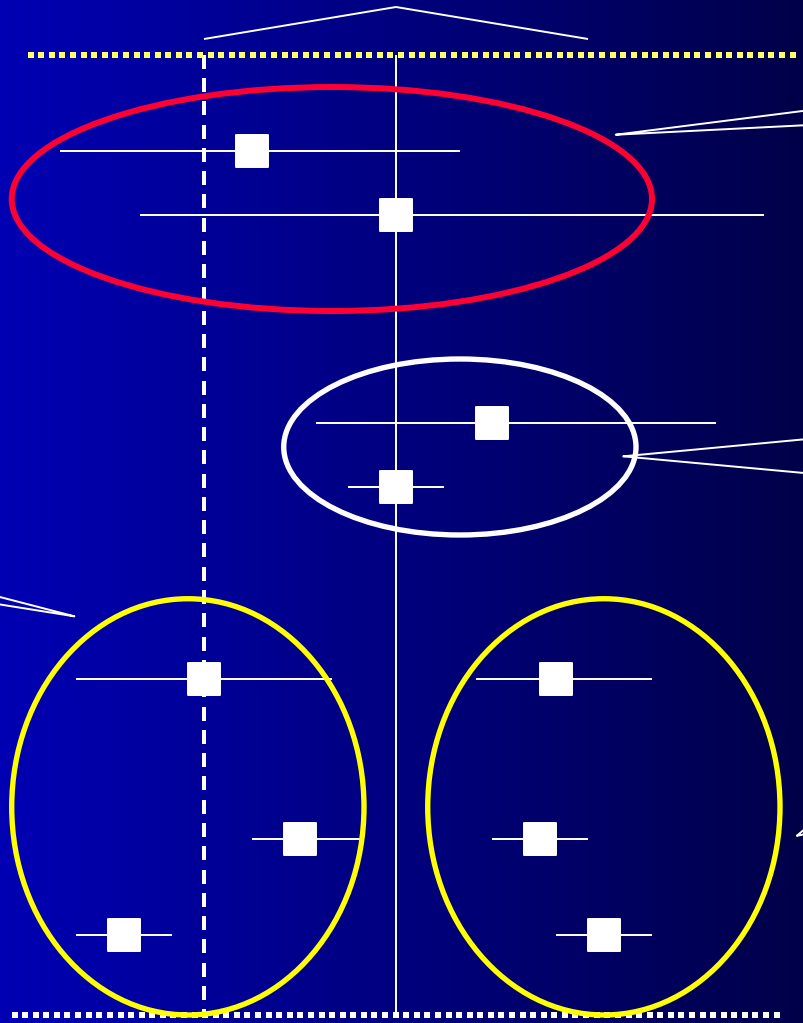
Insufficient evidence to confirm or exclude If experimental treatment is better than the standard or vice-versa

Statistically significant difference, unclear if it's important to patients

Statistically significant difference, not important to patients

Important difference

Pre-defined limits of equivalence



Line of no effect
(relative risk, odds ratio=1, risk difference=0)

Characteristics of Confidence interval

Inconclusive

Outcomes statistically significant favoring innovation

True Negative (excluding benefit from experimental treatment)

Outcomes statistically significant favoring standard

Adapted from Alderson, P. BMJ 2004;328:476-477

Methods

All consecutive phase III RCTs conducted by three NCI sponsored Cooperative Groups were reviewed (protocols and final publications)

Cooperative group	No. of Studies	
Radiation Therapy Oncology Group (RTOG)	38	All consecutive trials from 1955-2000
Children's Oncology Group (ChOG)	91	
Gynecologic Oncology Group (GOG)	25	

Why NCI-sponsored cooperative group RCTs?

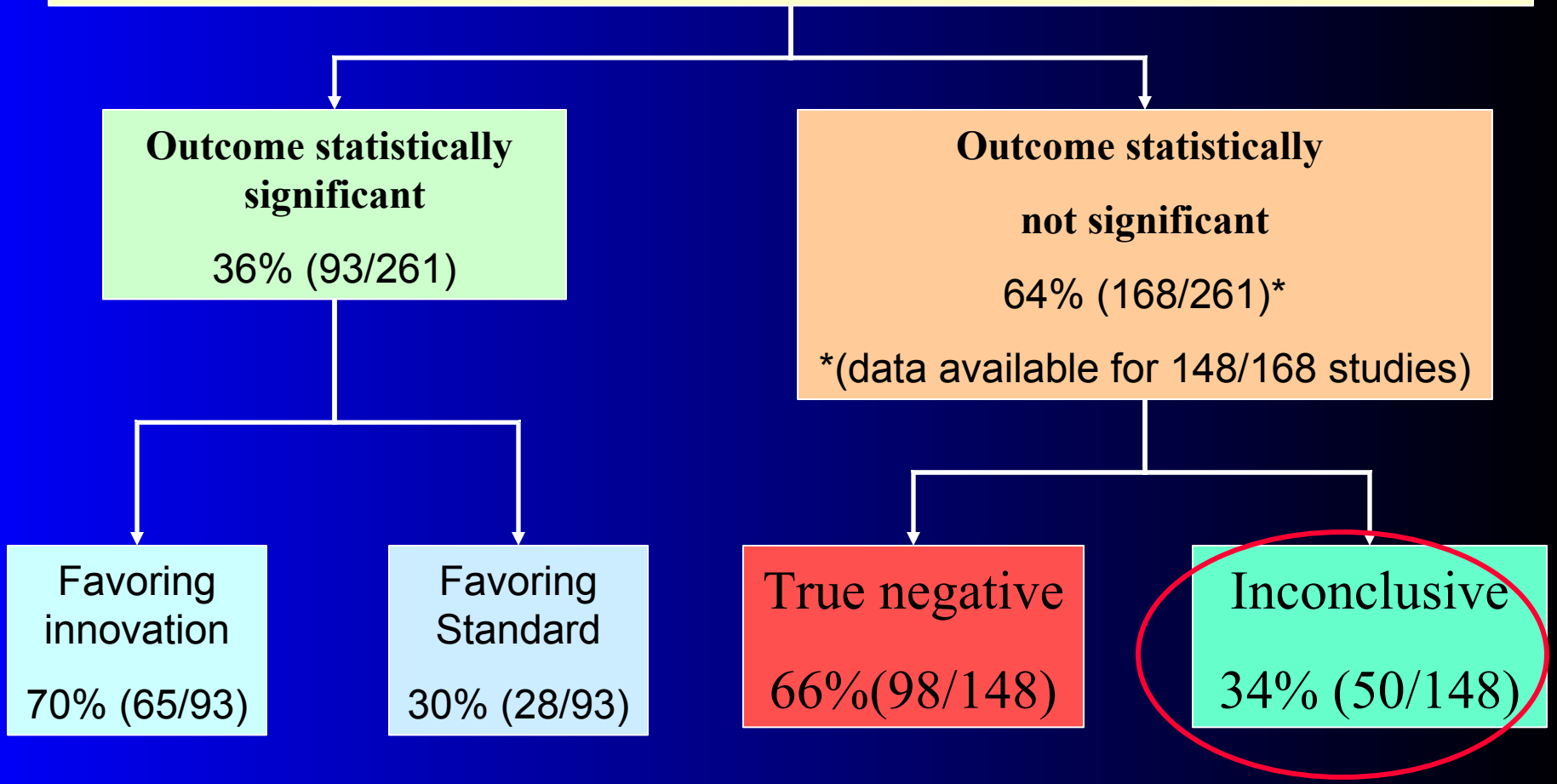
- NCI- sponsored COGs conduct all the publicly funded RCTs in the USA
- All COG research protocols pass a rigorous peer-review process.

Results

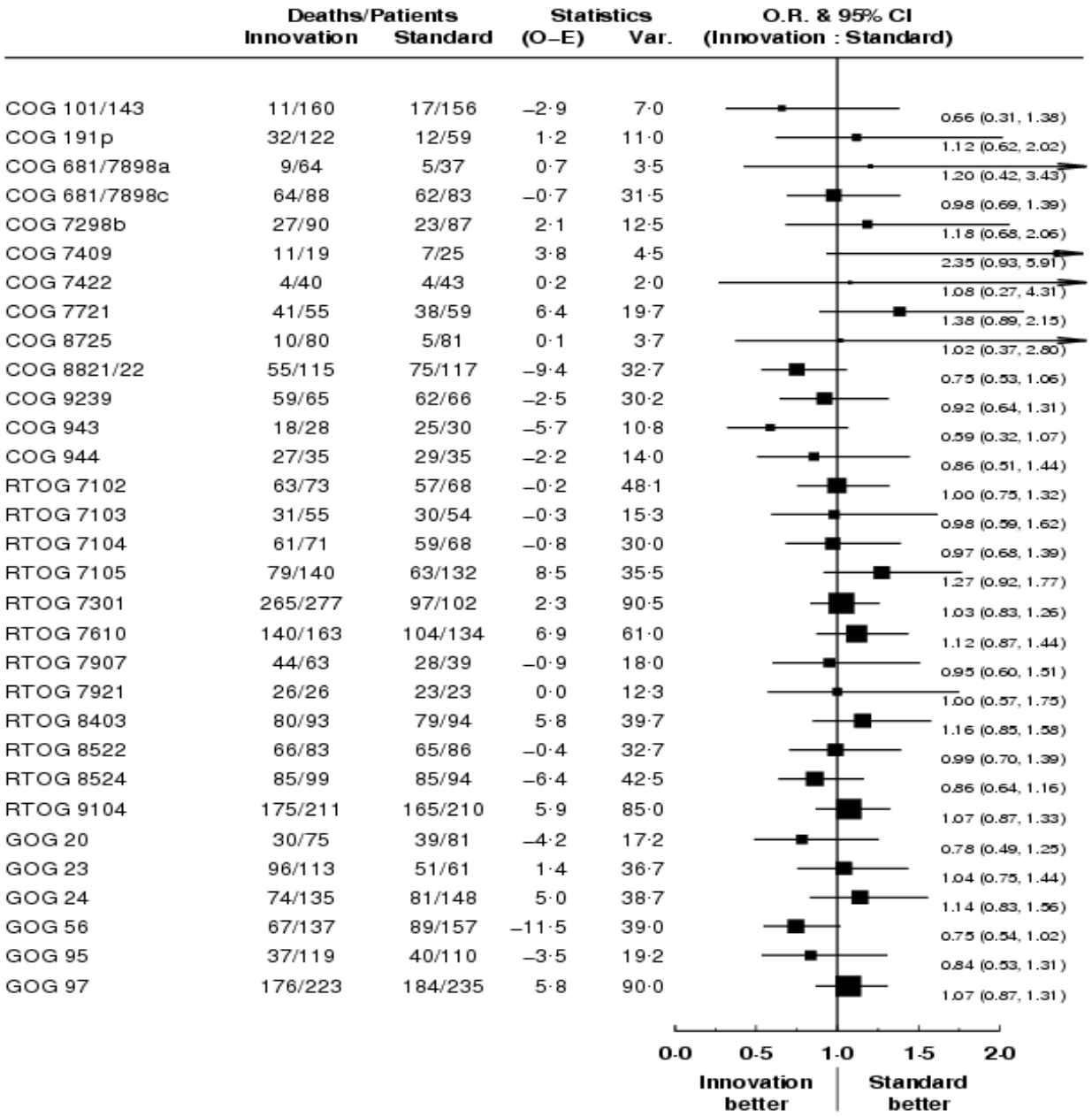
3 NCI sponsored cooperative group trials included in the review

(Radiation Therapy Oncology Group, Children's Oncology Group and Gynecologic Oncology Group)

N=261 (~50,000 patients)



Meta Analysis – inconclusive trials
Primary end point: Survival



Why there were so many inconclusive studies?

Critical components of a RCT

α (usually 0.05)
β (usually 0.2)
} α , β usually fixed

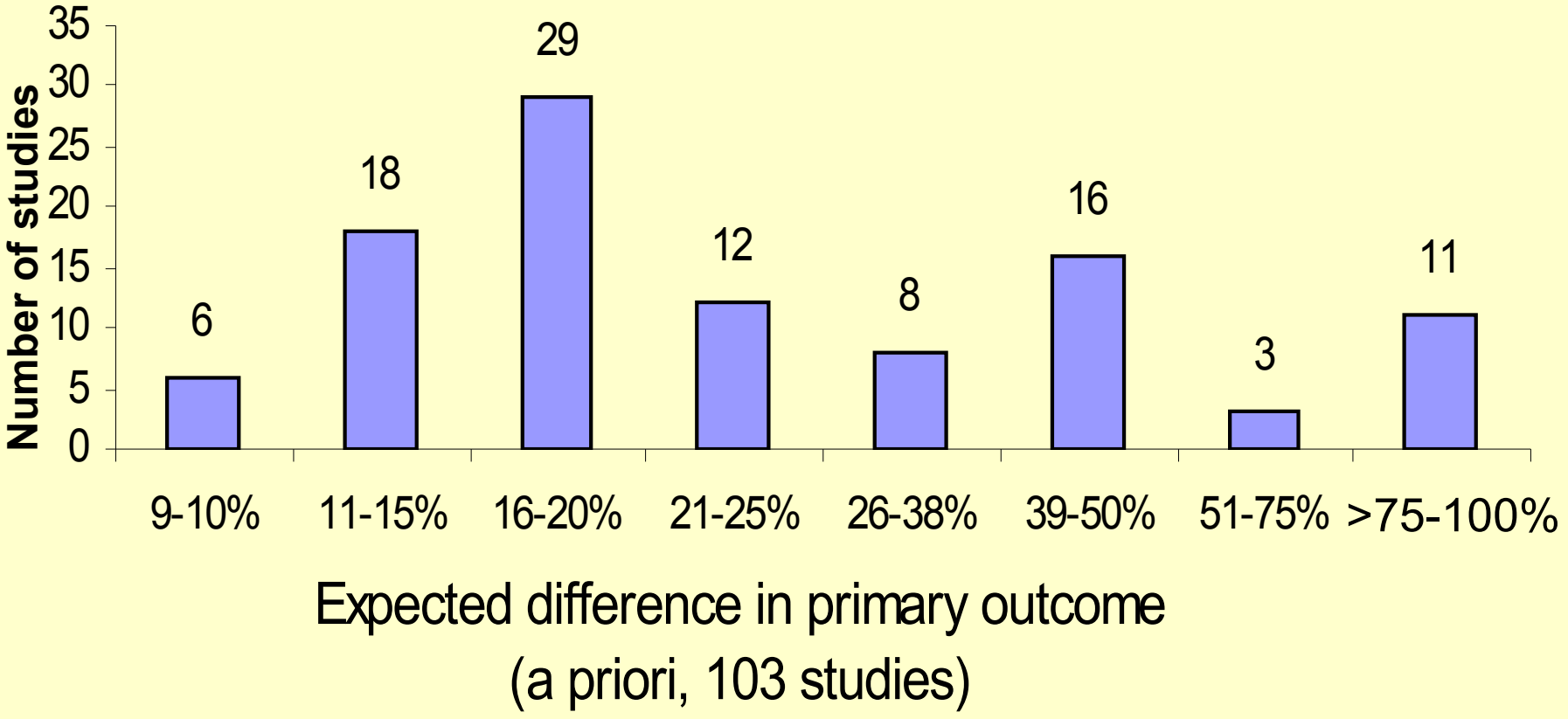
Sample size = $N_{inn} + N_{std} = N_t$ (total)

Δ Effect size (expected difference)

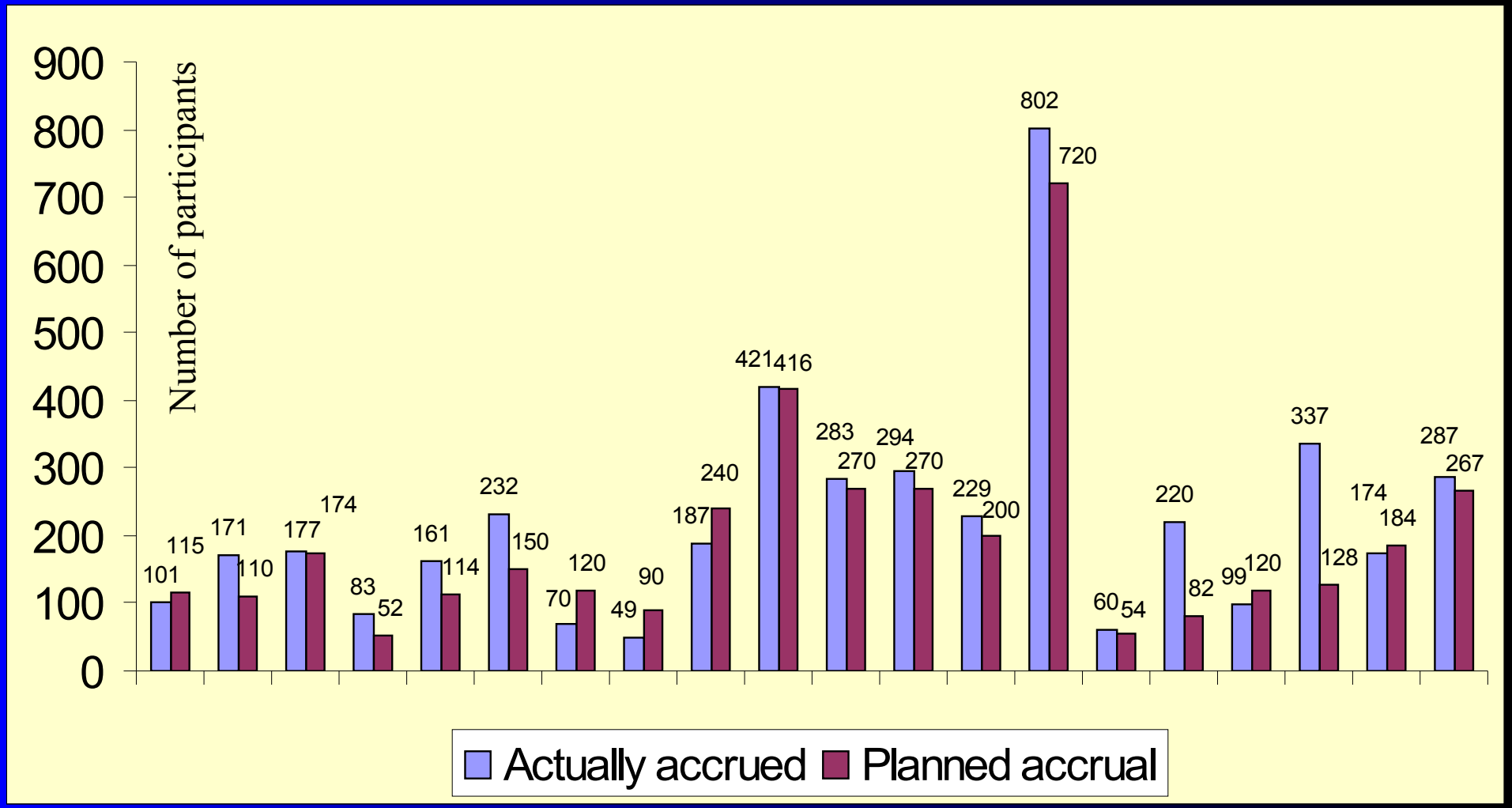
Results

- Quality of trials was high.
- 70% (103/148) of the studies had undertaken a pre-trial power analysis.
- The investigators chose to detect difference in primary outcomes between competing treatments ranging from 9% to > 100% .

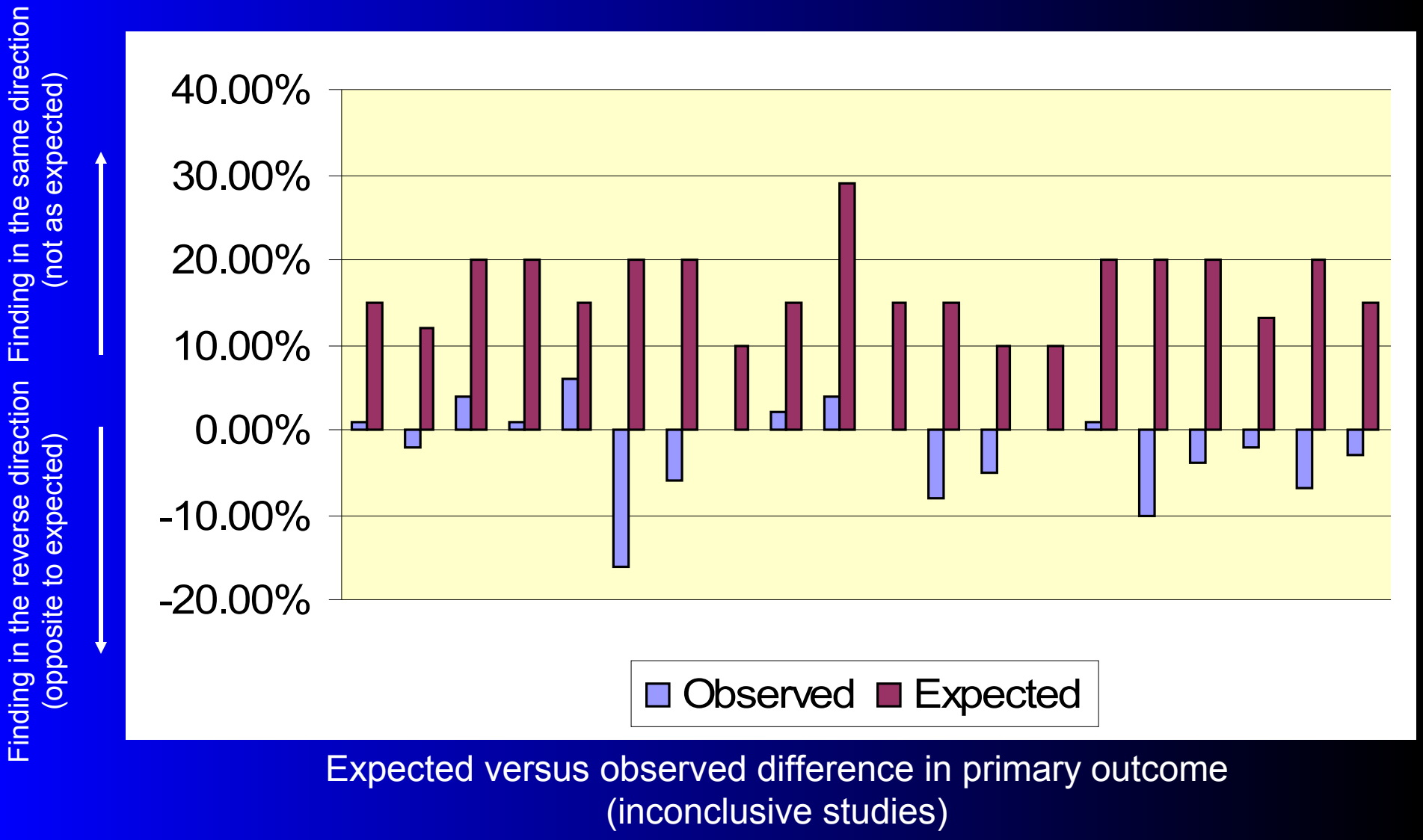
Distribution of expected difference in primary outcome (as stated in research protocols)



Planned accrual versus actually accrued (inconclusive studies only)



Expectation bias – the culprit?



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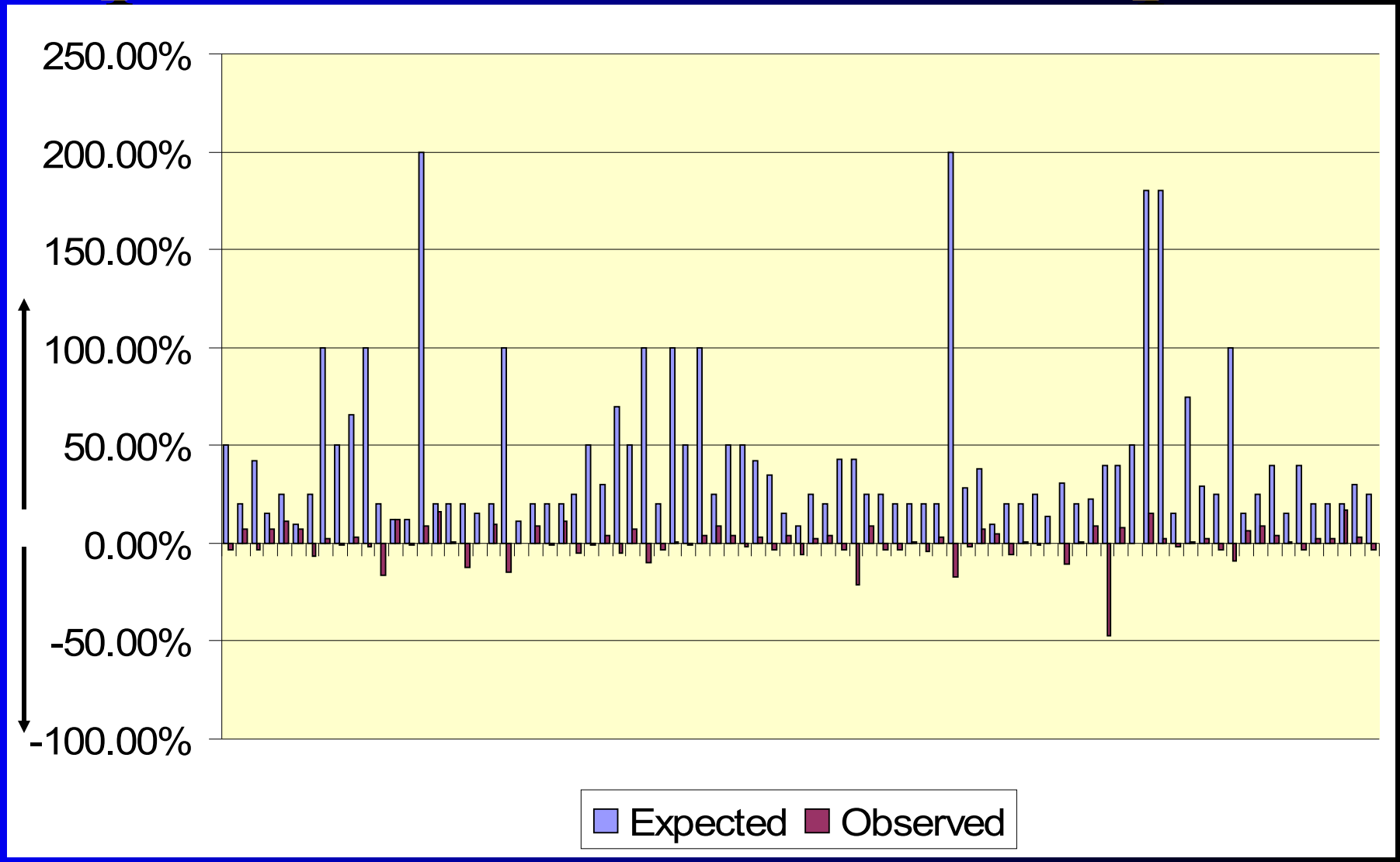


Expected versus observed difference in primary outcome (negative studies)

Conclusion

- Even high-quality RCTs conducted by prestigious institutions and respected research groups often produce inconclusive or negative findings

- That is, results that are statistically consistent with both, absence and presence of a benefit

Unrealistic expectations in treatment effect

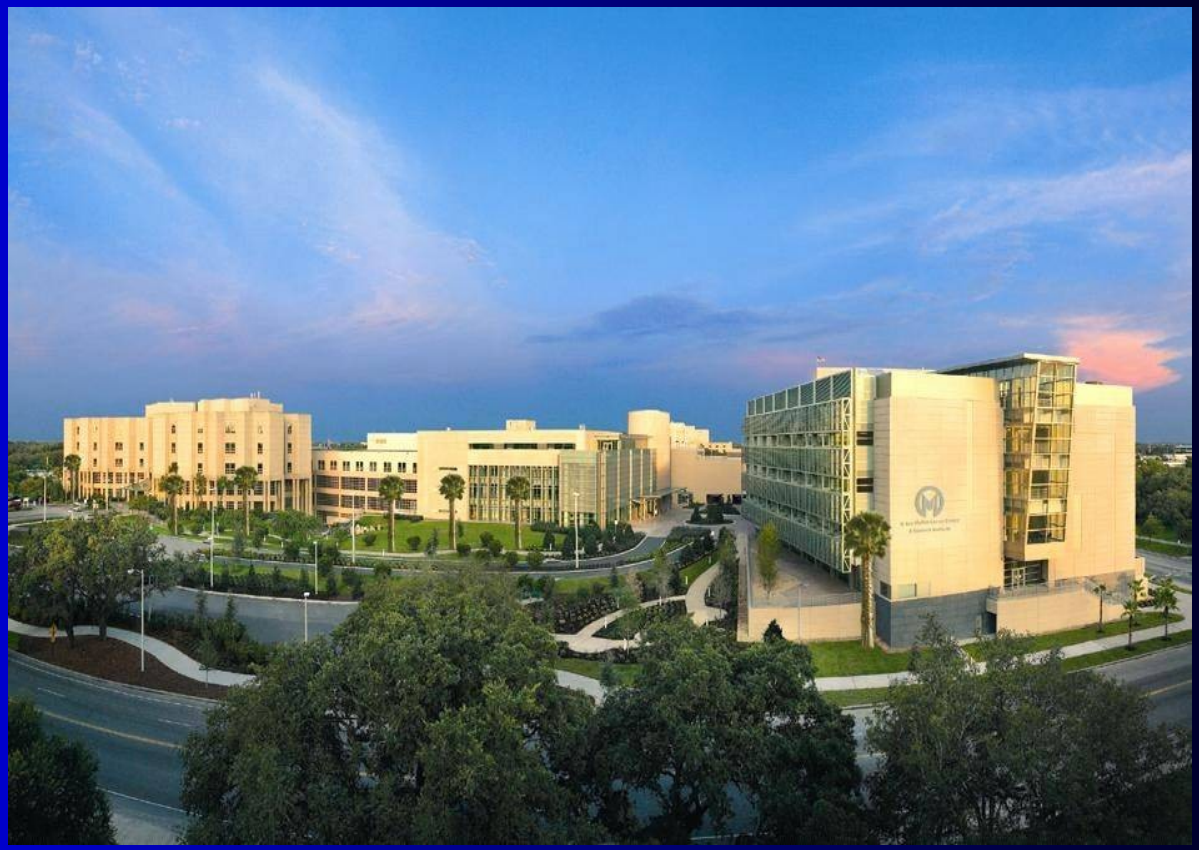
- Investigators rarely, if ever, provided a rationale for determination of the chosen effect size.

Conclusions

- Unrealistic expectations in treatment effect may hamper advancements in medicine
- Making investigators aware of their unrealistic expectations may result in designing more realistic studies
  - Which can optimize the chances of discovery of small but worthwhile treatment effects
- Precious resources were wasted
- Patients participated in unnecessary trials

  -Breach of contract with patients

Thank you



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