

# Treatment Success in Pragmatic RCTs: A review of trials funded by the UK HTA programme

Louise Dent, James Raftery

University of Southampton Clinical  
Trials Unit / NIHR Evaluation Trials  
and Studies Coordinating Centre



# Equipoise and treatment success

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## Review of results of trials

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# The paradox of equipoise: the principle that drives and limits therapeutic discoveries in clinical research

## Acknowledgment of Uncertainty: A Fundamental Means to Ensure Scientific and Ethical Validity in Clinical Research

*Benjamin Djulbegovic, MD, PhD*

### **Address**

Interdisciplinary Oncology Program, Division of Blood and Bone Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, 12902 Magnolia Drive, Tampa, FL 33612, USA.  
E-mail: djulbebm@moffitt.usf.edu

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Recognition of the importance of uncertainty in the design of randomized, controlled trials (RCT) has reached the status of a principle. The "uncertainty principle," or less ambiguously, equipoise, holds that a patient should be enrolled in an RCT only if there is substantial uncertainty about which of the trial treatments would benefit the patient most. In fact, the "uncertainty principle" addresses the most important issue of a clinical trial—the choice of an adequate comparative control. Studies in which intervention and control group are believed to be non-equivalent violate the uncertainty principle. Therefore, one would expect that both editors and authors would be particularly careful to include a statement concerning prior beliefs of the investigator(s) about the uncertainty of the treatments that are reported. However, we found no evidence of such a policy in the randomized, controlled trials we examined. We also show that there is a predictable relationship between the uncertainty principle, that is, the moral principle upon which trials are based, and the ultimate outcomes of clinical trials. We postulate that about 50% of innovations are successful, leading to the conclusion that recognizing the ethics of clinical research

ever-increasing health-care costs [3,4]. Recently, a compelling case was made that "the failure to train learners properly for clinical uncertainty" [5] was "the greatest deficiency of medical education throughout the twentieth century" [4]. However, these ideas have been to a large extent ignored by most physicians and researchers. In part, this lack of attention was due to the fact that uncertainty has not been considered of immediate practical, scientific, or ethical importance in clinical medicine. This article further articulates the fundamental role that uncertainty plays in clinical medicine, particularly in the area of therapeutics. A similar case can be made for diagnostic testing.

### **Tools for Resolution of Uncertainty**

Uncertainty can have many gradations. It can range from simply "not knowing" to complete ignorance about the relative benefits and risks of the treatment alternatives. It always relates to a choice of one treatment over another. What are the tools at our disposal to resolve these uncertainties? In general, we can deal with uncertainty in several ways. Regardless of how we choose to deal with uncertainty, our strategy will always depend fundamentally on our pre-existing knowledge about the therapeutic value of the treatments to be compared. In some cases, the truthfulness of pre-existing knowledge may depend entirely on the experience and inferences of individual practitioners and authorities, and our dilemma may be easily solved by heeding their advice. The history of medicine contains examples of the limited, uncontrolled experiences of individuals occasionally resulting in accurate description of the

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→ **Expect 50% of trials to favour new treatment**

## Treatment Success in Cancer

### *New Cancer Treatment Successes Identified in Phase 3 Randomized Controlled Trials Conducted by the National Cancer Institute–Sponsored Cooperative Oncology Groups, 1955 to 2006*

Benjamin Djulbegovic, MD, PhD; Ambuj Kumar, MD, MPH; Heloisa P. Soares, MD; Iztok Hozo, PhD; Gerold Bepler, MD, PhD; Mike Clarke, DPhil; Charles L. Bennett, MD, PhD, MPP

**Background:** The evaluation of research output, such as estimation of the proportion of treatment successes, is of ethical, scientific, and public importance but has rarely been evaluated systematically. We assessed how often experimental cancer treatments that undergo testing in randomized clinical trials (RCTs) result in discovery of successful new interventions.

**Methods:** We extracted data from all completed (published and unpublished) phase 3 RCTs conducted by the National Cancer Institute cooperative groups since their inception in 1955. Therapeutic successes were determined by (1) assessing the proportion of statistically significant trials favoring new or standard treatments, (2) determining the proportion of the trials in which new treatments were considered superior to standard treatments according to the original researchers, and (3) quantitatively synthesizing data for main clinical outcomes (overall and event-free survival).

**Results:** Data from 624 trials (781 randomized comparisons) involving 216 451 patients were analyzed. In

all, 30% of trials had statistically significant results, of which new interventions were superior to established treatments in 80% of trials. The original researchers judged that the risk-benefit profile favored new treatments in 41% of comparisons (316 of 766). Hazard ratios for overall and event-free survival, available for 614 comparisons, were 0.95 (99% confidence interval [CI], 0.93-0.98) and 0.90 (99% CI, 0.87-0.93), respectively, slightly favoring new treatments. Breakthrough interventions were discovered in 15% of trials.

**Conclusions:** Approximately 25% to 50% of new cancer treatments that reach the stage of assessment in RCTs will prove successful. The pattern of successes has become more stable over time. The results are consistent with the hypothesis that the ethical principle of equipoise defines limits of discoverability in clinical research and ultimately drives therapeutic advances in clinical medicine.

*Arch Intern Med.* 2008;168(6):632-642

**A**LTHOUGH CANCER REMAINS the second leading cause of deaths in the United States,<sup>1</sup> there have been continuous improvements in survival and other outcomes in patients with cancer over time.<sup>1</sup> To a large

There are ethical, public policy, and scientific reasons for evaluating the success of new treatments in RCTs. New discoveries cannot be made without the willingness of patients to enroll in clinical trials.<sup>7</sup> Because they are being asked to volunteer for these trials, it has been suggested that pa-

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ORIGINAL INVESTIGATION

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- Classified primary results from 624 trials into 1 of 6 categories....

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# Methods



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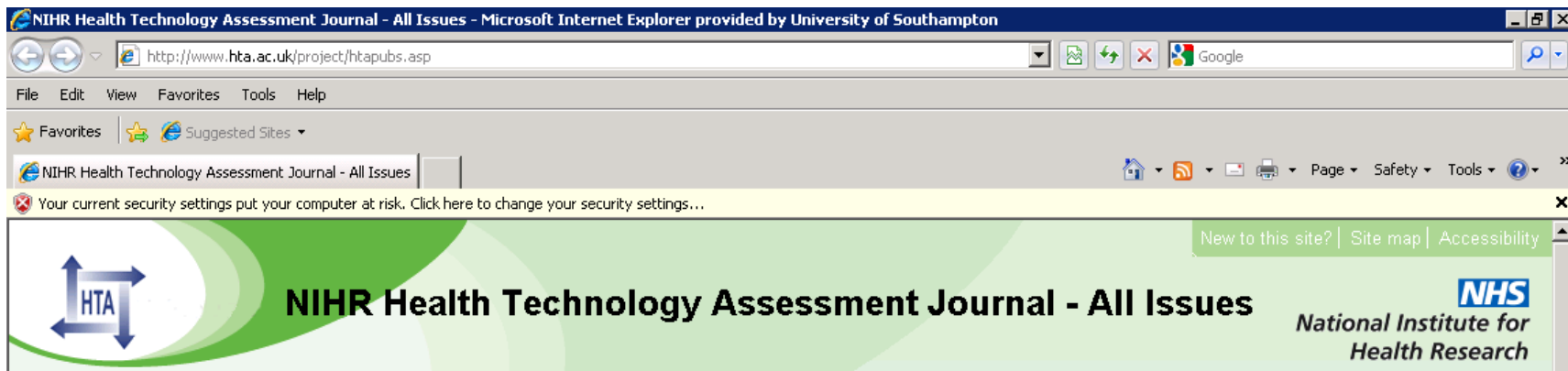
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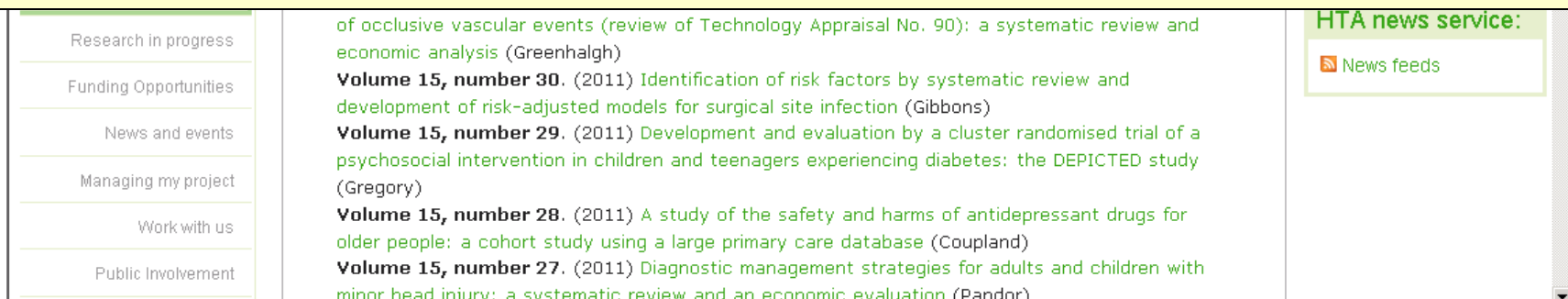
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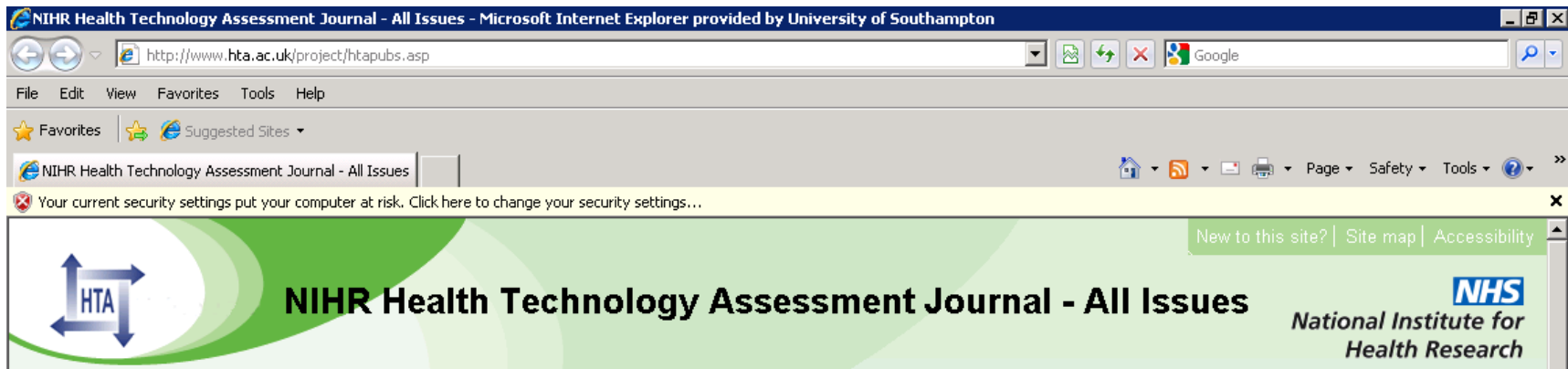
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- Included HTA superiority RCTs 1993 to 2008

- Extracted data from each RCT on:
  - Trial design & interventions
  - Sample size calculation
  - Primary outcome result(s) with 95% CI for treatment diff

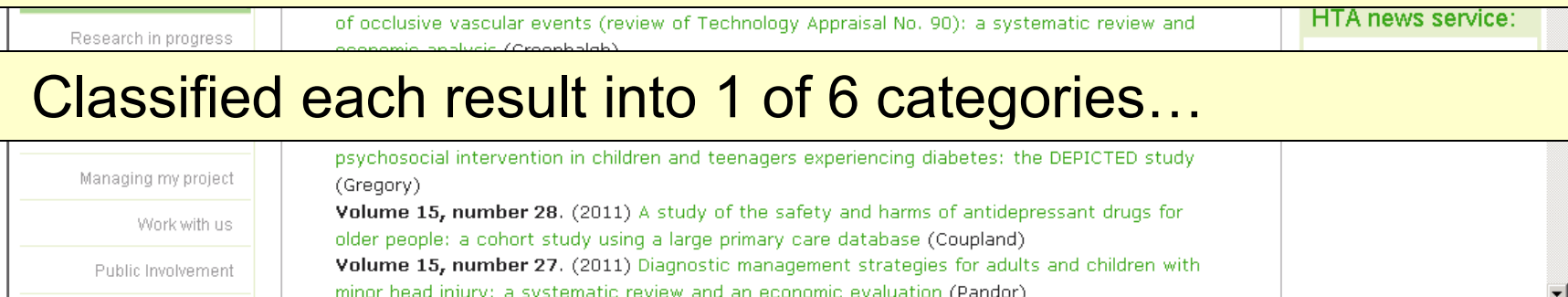




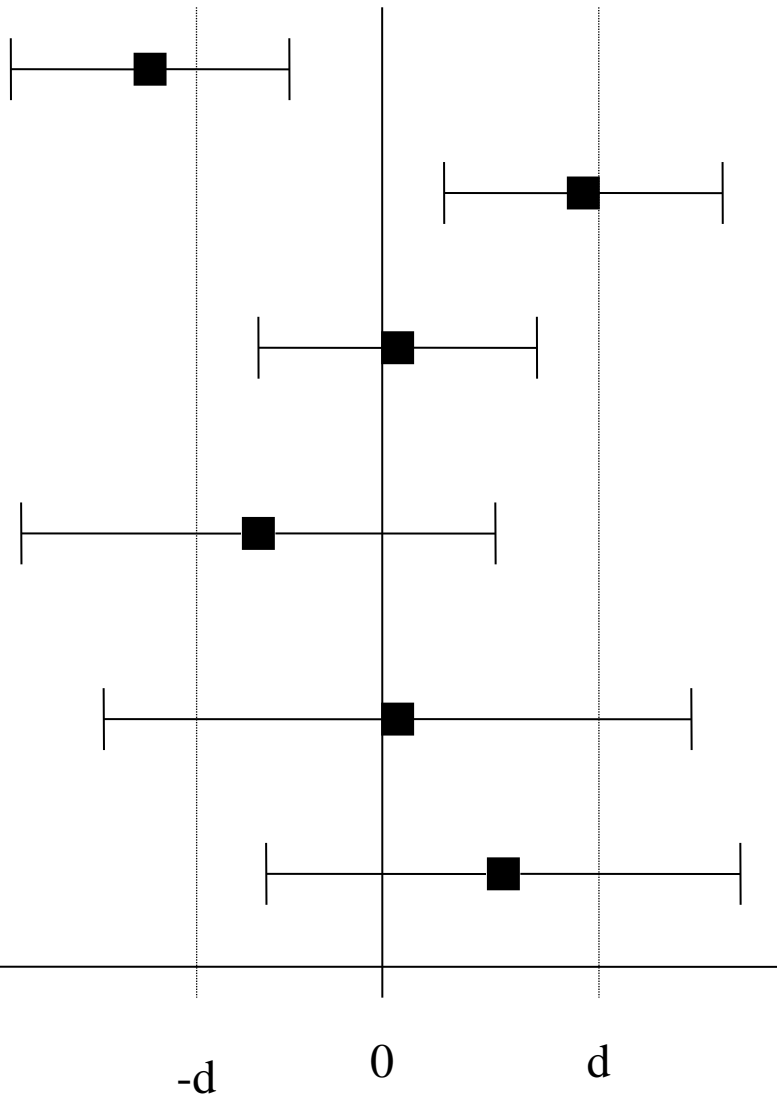
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- Classified each result into 1 of 6 categories...



# Classification of RCT result(s) using 95% CI and diff (d) from sample size calc



1. Statistically significant in favour of control

2. Statistically significant in favour of new

3. True negative

4. Inconclusive in favour of control

5. Truly inconclusive (equal chance that control better than new and vice-versa)

6. Inconclusive in favour of new

Djubegovic used  $-d=0.8$  and  $d=1.2$  as outcomes OR, RR, HR

Favours control treatment

Favours new treatment

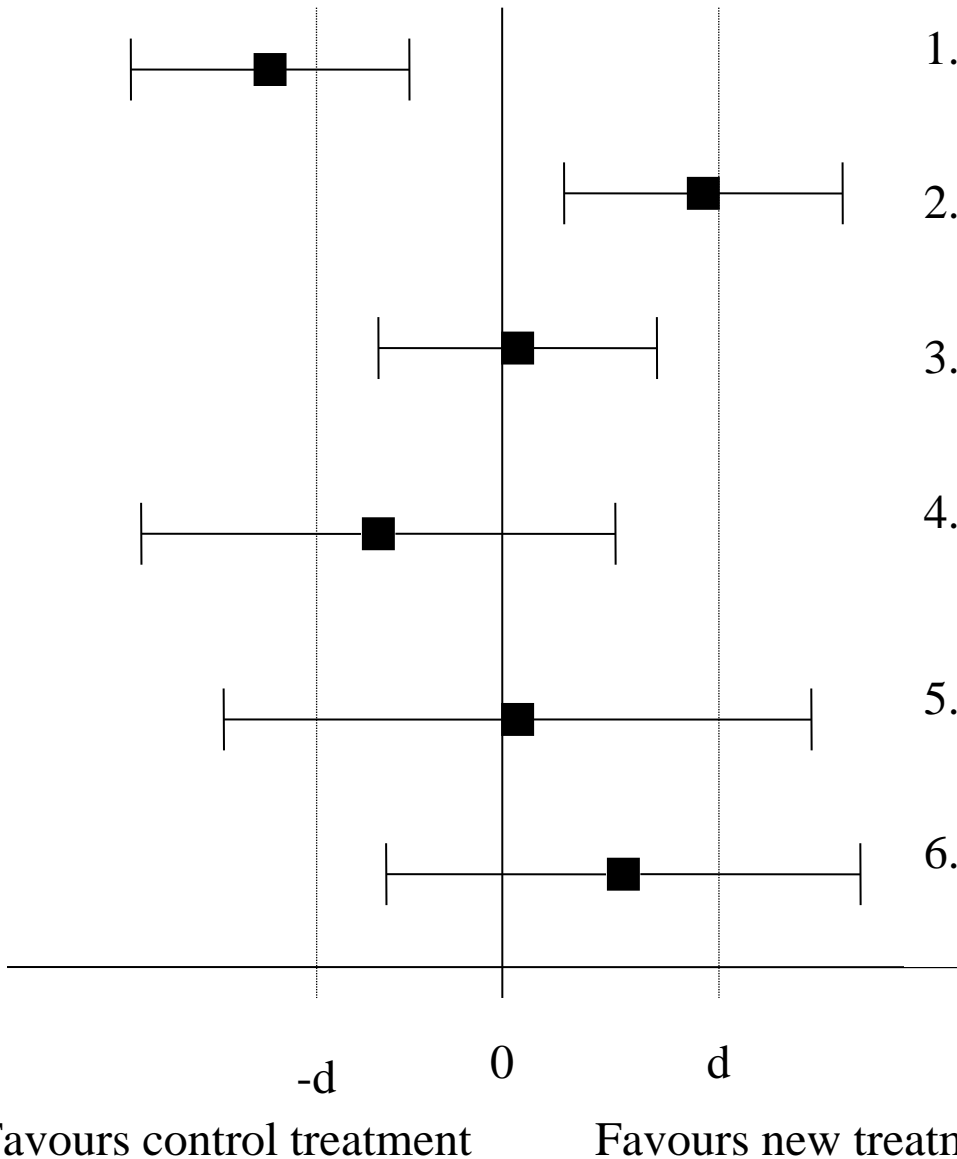
# Assessments

1. Calculated no. of conclusive trial results
2. Assessed if results consistent with equipoise
3. Compared results to cancer trials

# Results



# Results - 51 HTA trials



1. Statistically significant in favour of control  
**5% (4/85)**

2. Statistically significant in favour of new  
**19% (16/85)**

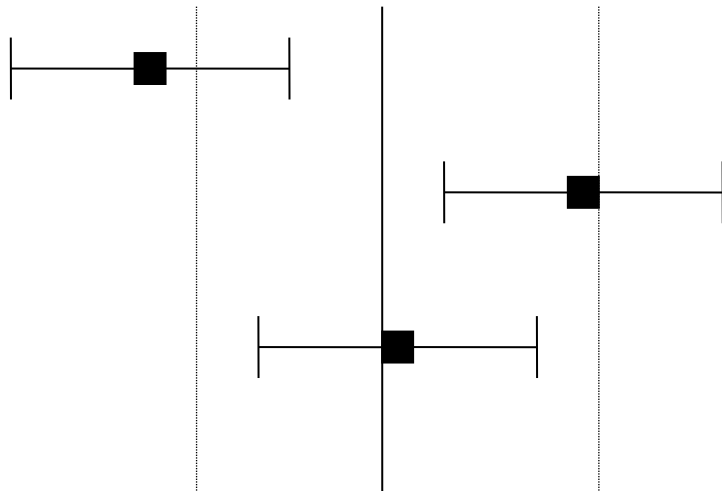
3. True negative  
**22% (19/85)**

4. Inconclusive in favour of control  
**18% (15/85)**

5. Truly inconclusive  
**24% (20/85)**

6. Inconclusive in favour of new  
**13% (11/85)**

# Results – Conclusive?



1. Statistically significant in favour of control  
**5% (4/85)**

2. Statistically significant in favour of new  
**19% (16/85)**

3. True negative  
**22% (19/85)**

**46% of results were conclusive  
(5% + 19% + 22%)**

-d

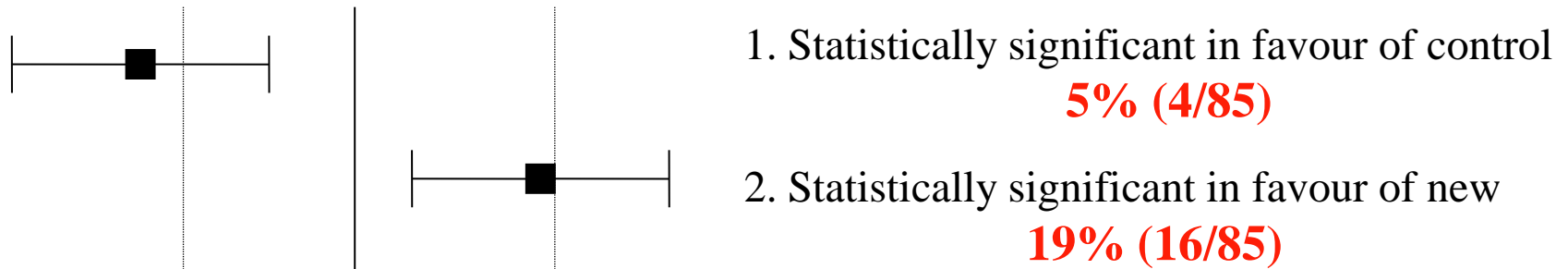
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Favours control treatment

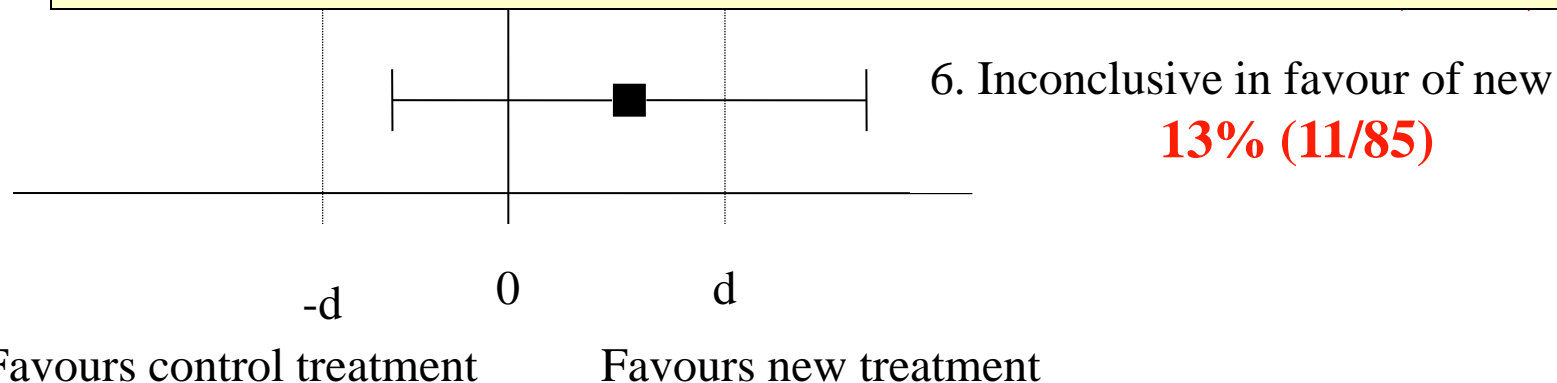
Favours new treatment

# Results – Consistent with equipoise?



**New treatment favoured in 61% of comparisons  
95% CI (49.9% to 71.6%)**

**80% of significant results favoured new treatment**



# Comparison to other studies..

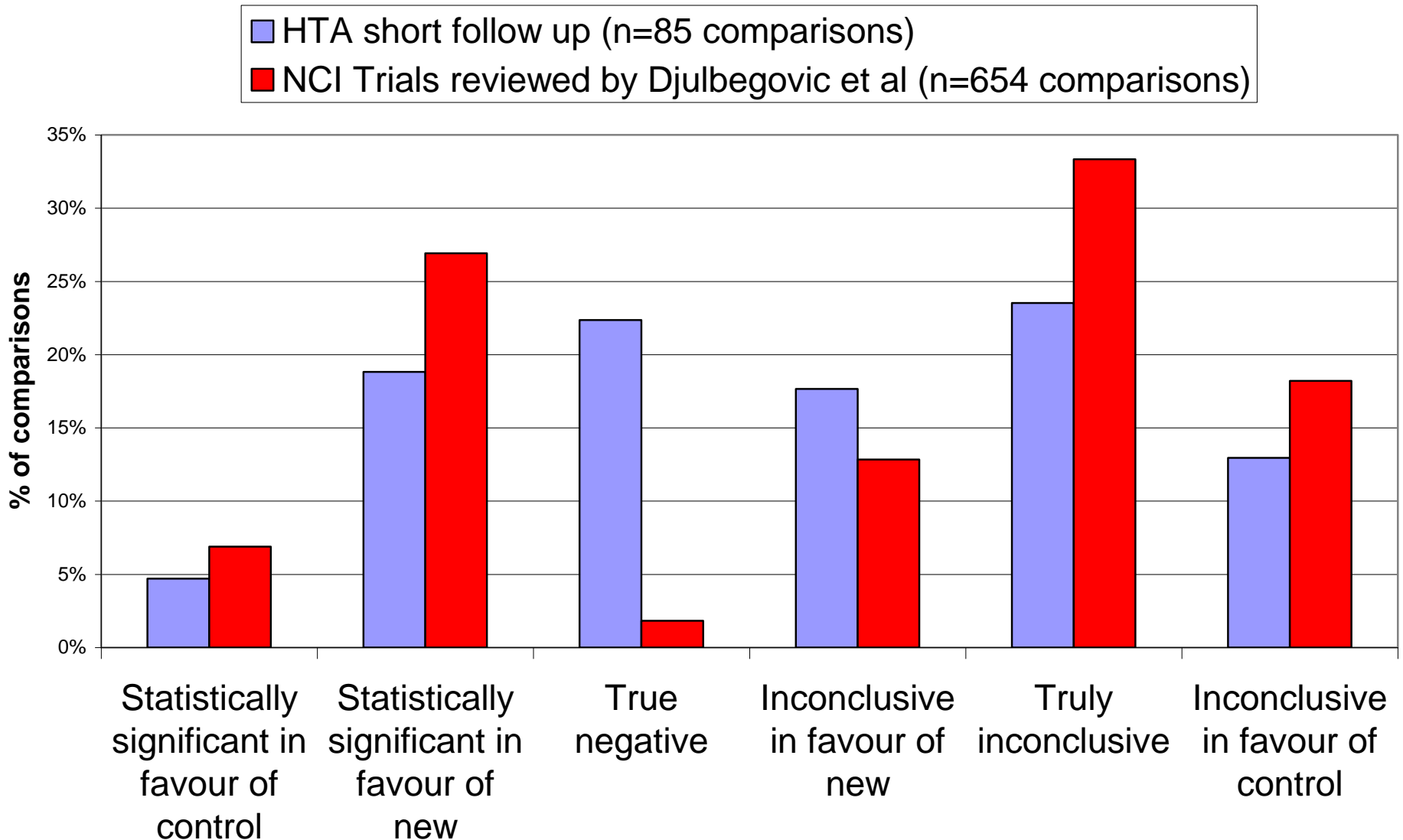
% statistically significant:

- 24% versus 12%, 29%, 32%, 34%

% statistically significant favour new:

- 80% versus 72%, 80%, 86%, 90%

# Comparison to National Cancer Institute trials



# Conclusions

- Trial success not just about statistical significance
- HTA trial results reassuringly consistent with equipoise and other trial results
- Classification useful

# Any questions / comments ?

Dent L, Raftery J: Treatment success in pragmatic randomised controlled trials: a review of trials funded by the UK Health Technology Assessment programme. *Trials* 2011, 12:109.



**[l.dent@soton.ac.uk](mailto:l.dent@soton.ac.uk)**



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**023 80795154**