Are All Comparators Identical?

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Are all comparators identical?

- Indirect comparisons are computationally simple to conduct.
- However, interpretation of the results can be less straight forward.

Recap

- Two trials conducted with the following randomised treatments
  - Trial 1: Placebo and Treatment A
  - Trial 2: Placebo and Treatment B
- Both treatments were studied in a placebo controlled trial, which allows the indirect comparison of A and B.
- This assumes that the common treatment, placebo, exhibits a similar effect in both trials.

Are all comparators identical?

- We will investigate two scenarios that query when a common comparator is truly common.

1. Advances in standard of care may lead to differences in the severity of patients at baseline.

1. 'Placebo Creep' due to the use of more effective concomitant medications or medical procedures may lead to differences in placebo response rates.

Advances in standard of care

- Standards of care generally improve over time, as more effective concomitant therapies become available and more is known about the disease or condition in question.

- In general, most patients enter a clinical trial if they feel they have something to gain from the experience.

Advances in standard of care

- In the chronic setting, one could envisage that patients enter a clinical trial since they are no longer happy with their existing medication.
- With the passage of time one would expect a greater number of more effective medications to be available for a chronic condition.

Advances in standard of care

- Patients entering a ‘new clinical trial’ may be more severe / refractory than patients who entered the older clinical trial as they have tried and failed a greater number of medications.

Epilepsy Example

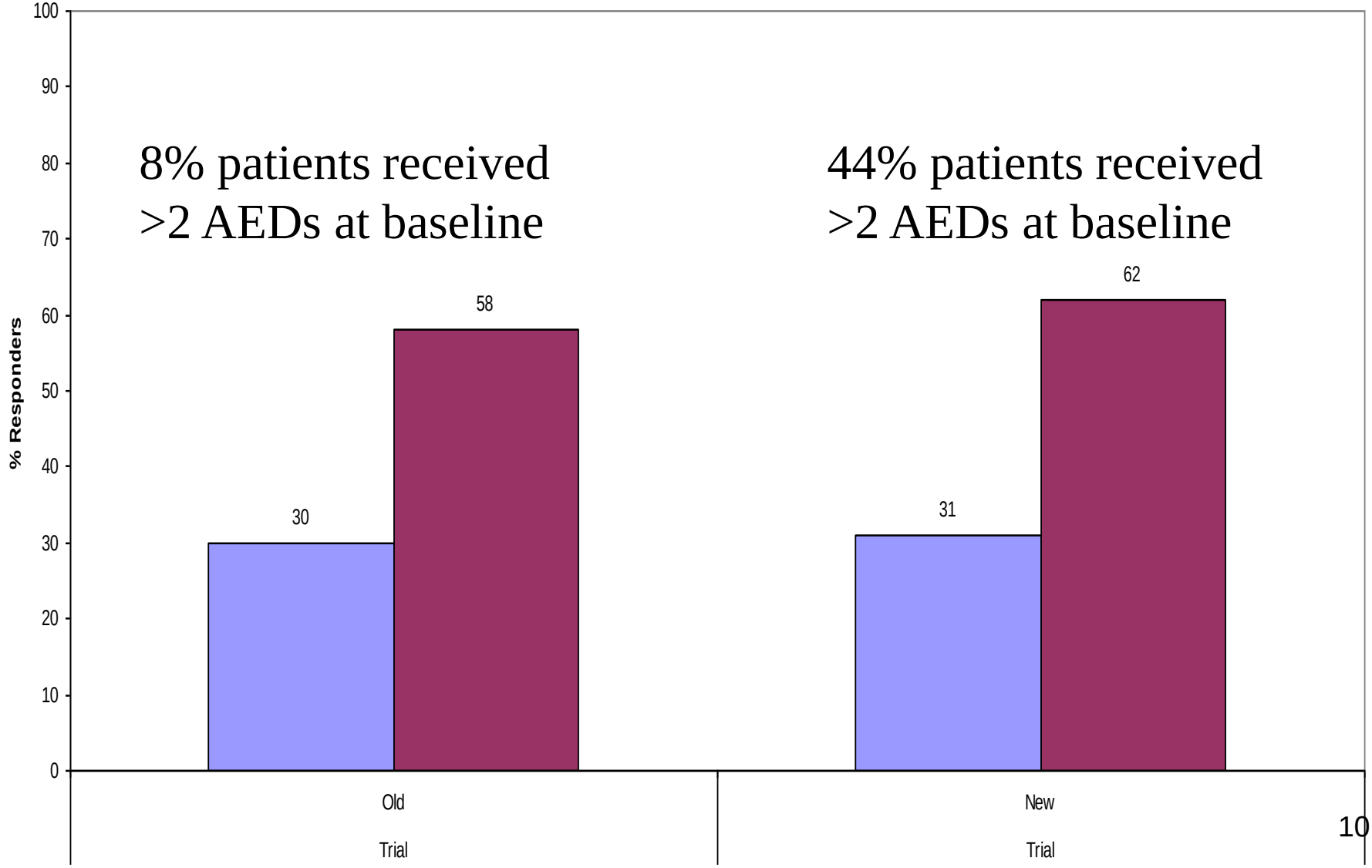
- KOLs believed a new treatment for epilepsy was an improvement on existing treatments. However, results appeared surprisingly similar:

- Old trial
  - % Responders for Old Trt = 58%
  - % Responders for Placebo = 30%
- New trial
  - % Responders for New Trt = 62%
  - % Responders for Placebo = 31%

Epilepsy Example

- Patients entering the new trial had similar demographics and no. baseline seizures compared to older trials
- However, in new trial patients took a greater no. anti-epileptic meds vs. patients entering older epilepsy trials, despite similar entry criteria.
  - Mean no. anti-epileptic medications were similar, but distribution skewed towards greater proportion of patients taking >2 meds in new trial.

Response Rates for Old Trial and New Trial



Epilepsy Example

- Need to adjust for the number of anti-epileptic medications taken at baseline.
  - Old Trial: 8% patients taking more than 2 medications at baseline
  - New Trial: 44% patients taking more than 2 medications at baseline
- Patients in new trial were more refractory than patients in old trial.

Epilepsy Example

- Newer treatments that are more effective than older treatments may not appear to be, since with the passage of time they are treating more severe or refractory patients.

- Similarly, clinical trials performed with different inclusion / exclusion criteria may fail to differentiate a more effective treatment.

Possible Solutions
Advances in standard of care

- Investigate whether there are important covariates that could confound the treatment effects.
  - Compare demographic and baseline characteristics of patients between trials or sets of trials
  - Adjust for any discrepancies in the analysis.

- Two possible adjustment methods:
  - i) use individual patient data (IPD) and perform ANCOVA
  - ii) use meta-regression.

Possible Solutions
Advances in standard of care

- Using published information.
  - May be difficult to obtain IPD if trials of the comparator drug are sponsored by another company.
  - Meta-regression adjusting for baseline covariates can only be used when there are a large number of trials.
- Minimum - highlight issue and comment on any bias due to the lack of adjustment.

Problems with Interpretation
'Placebo Creep'

- As background concomitant therapies improve, the placebo response rate improves making it more difficult to detect differences between an old treatment and a new treatment.

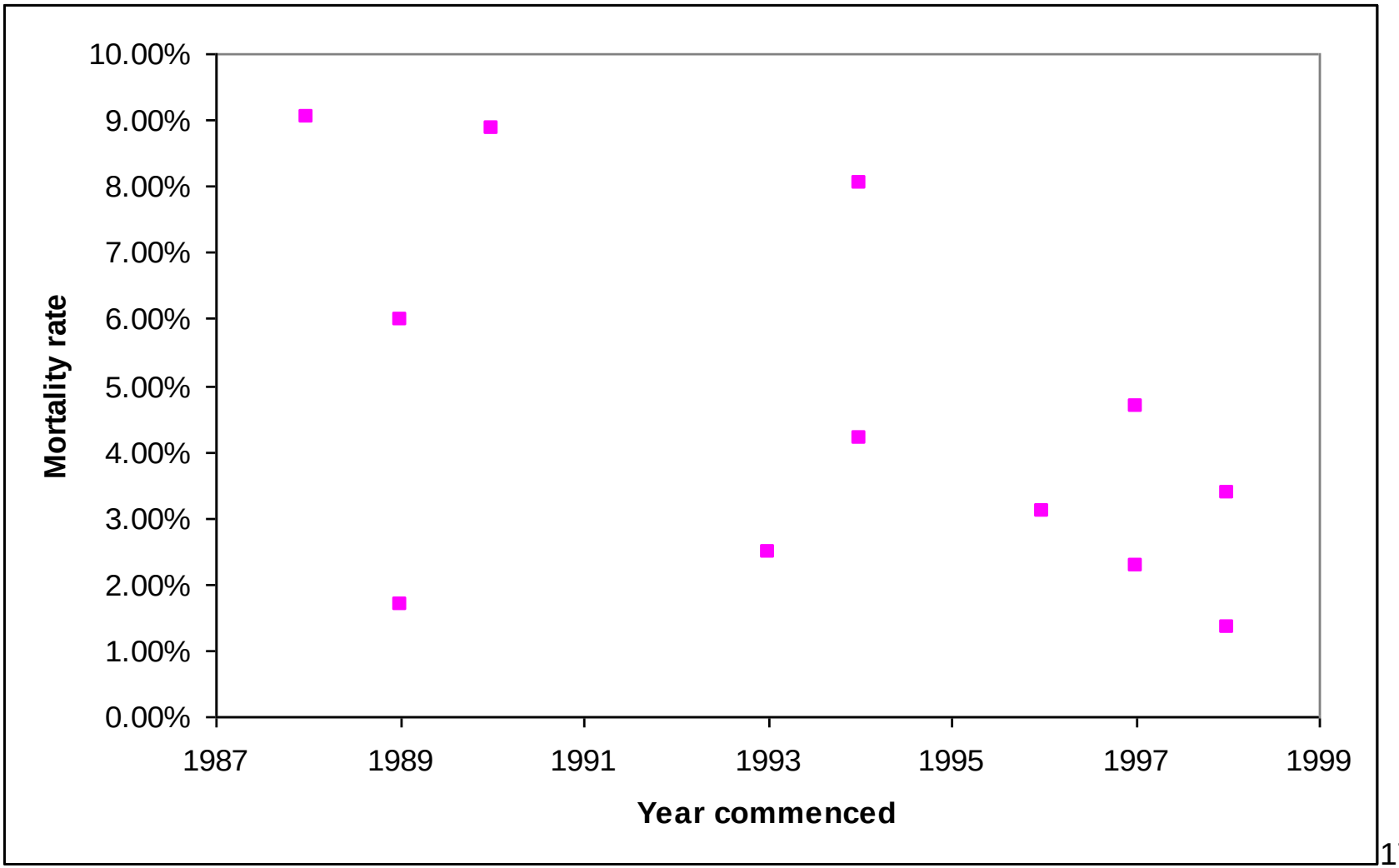
Placebo Response in Published Literature

- Placebo response improves (i.e. fewer events) over time for both endpoints.

Year	Occlusion Rate	Event Rate	Comparison to
1984	0.35	0.63	Low Dose
1989	0.23	0.44	High Dose
1990	0.18	0.33	Low Dose
1991	0.11	0.30	High Dose
1993	0.09	0.17	Low Dose

Source bmj.com Rapid Responses for Lim et al.,327 (7427)1309

CVD Mortality for Placebo in Clinical Outcomes Studies from 1988 to 1998



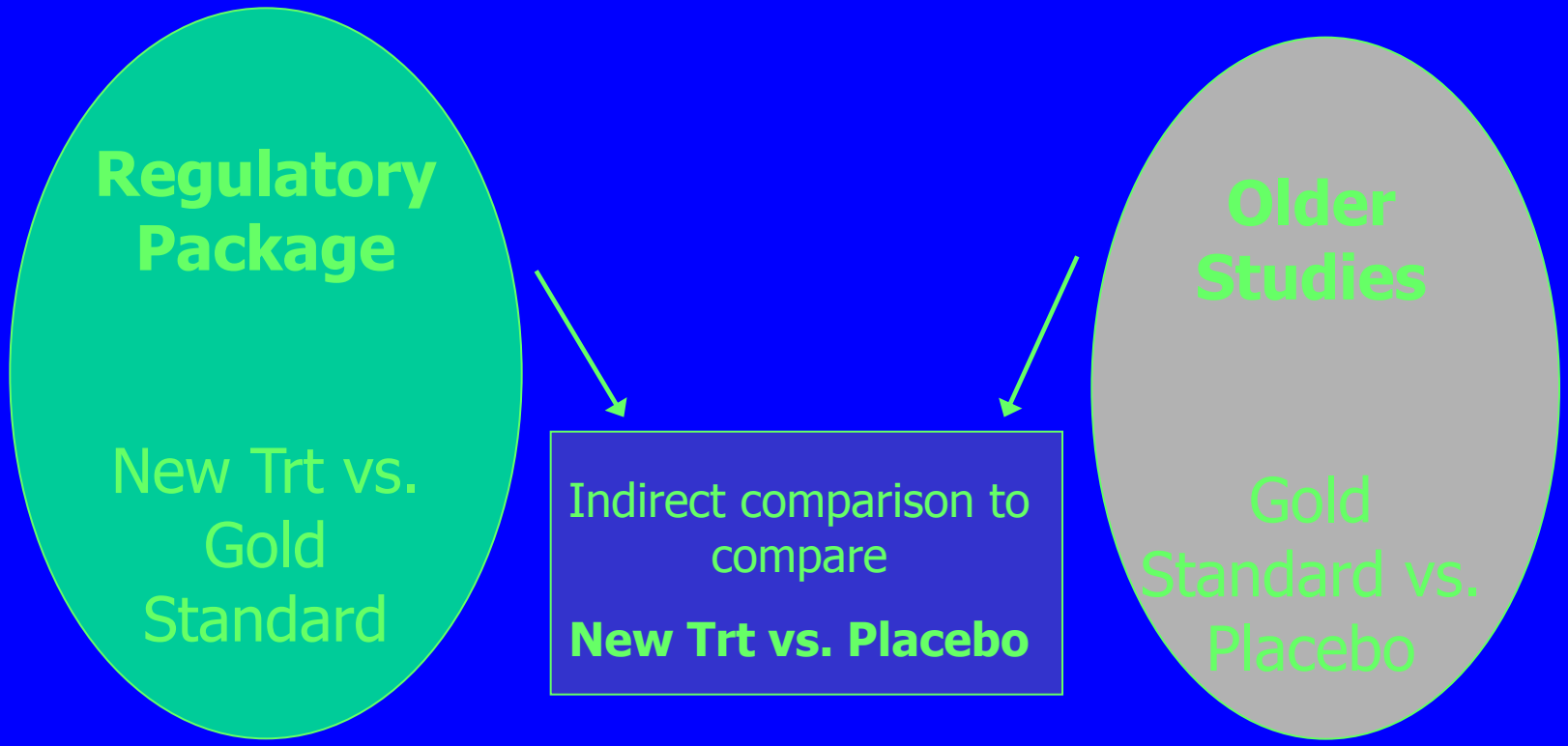
Graphic courtesy of Dane Levison – Pfizer Australia

‘Placebo creep’ in the Regulatory Setting

- For ethical reasons, trials may compare a new treatment to active control.
- However, regulatory agencies may want proof of assay-sensitivity, hence may need to compare new treatment to older placebo controlled studies.
- The decision as to which studies are used can have a huge impact on the results seen.

Regulatory Setting

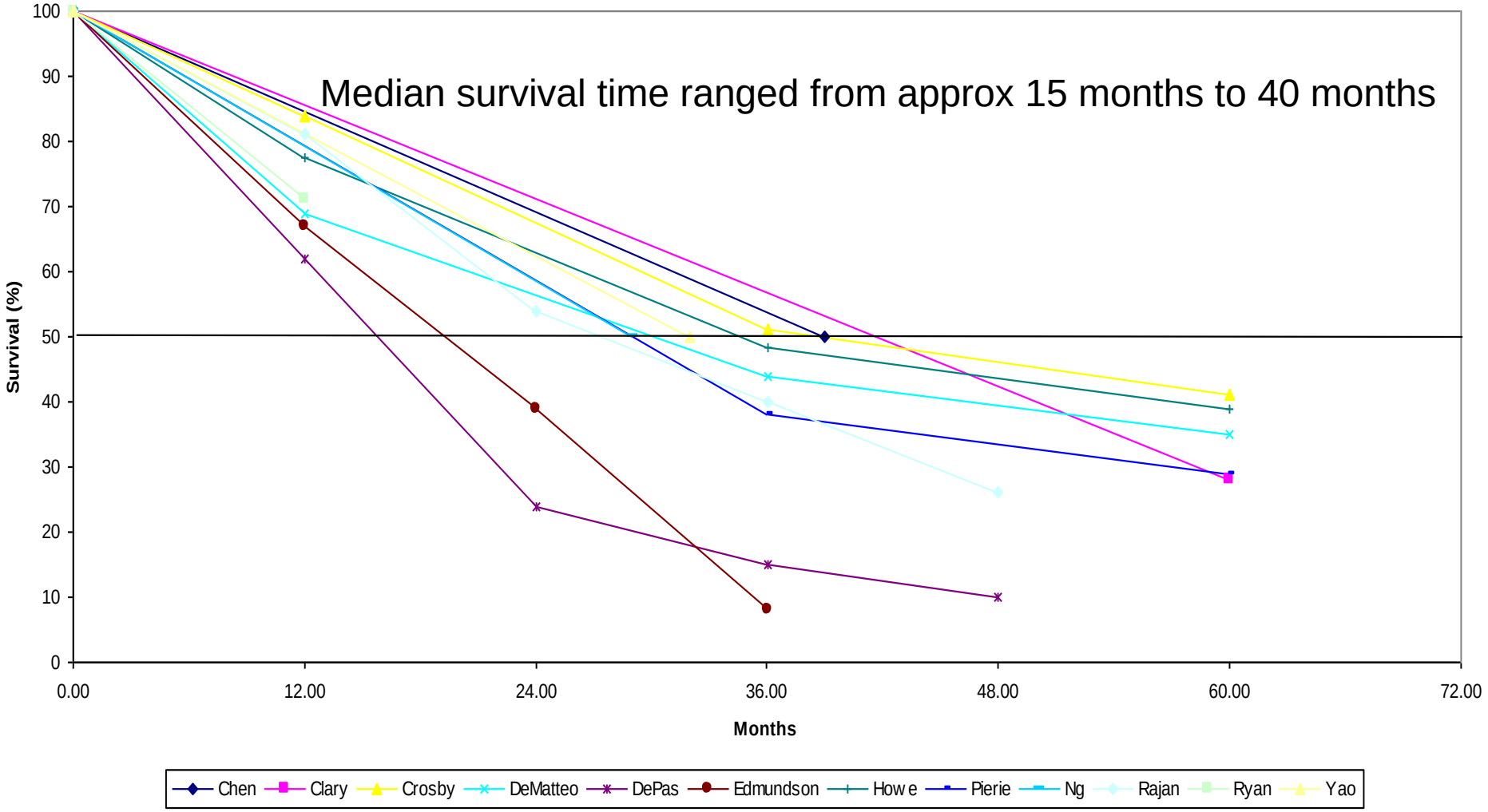
In the presence of 'placebo creep', results of this analysis may depend on which placebo-controlled trials were selected for comparison



NICE Example

- Trials of imatinib for gastrointestinal stromal tumour (GIST) were uncontrolled.
- NICE needed to assess the impact of the treatment being available compared to natural disease progression.
- Needed to use historical control data
  - Trials conducted between 1987 and 2003.

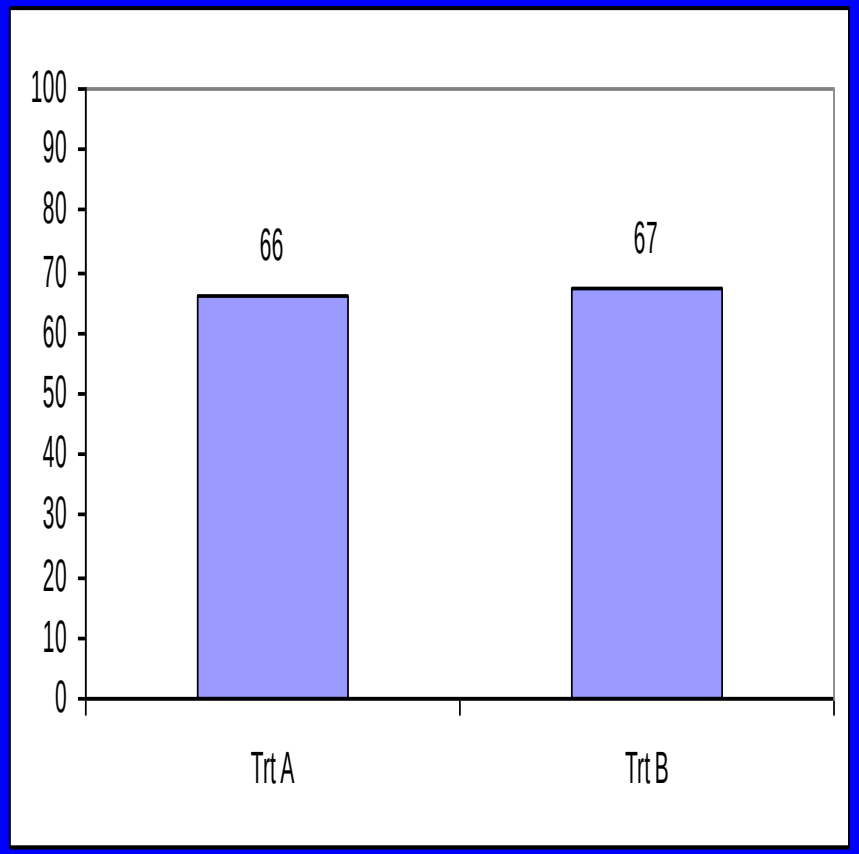
Historical Control Data for GIST



NICE used Clary 2001 (Pink) as historical control, as one of largest studies

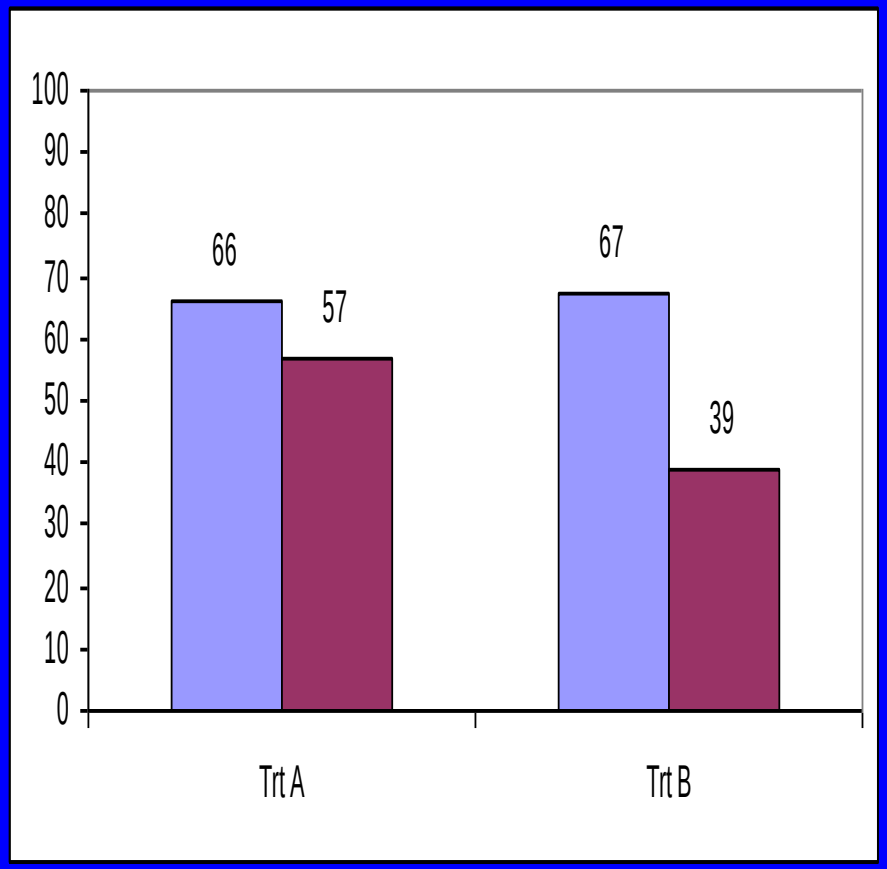
Example of 'Placebo Creep'

- Indirect comparison showed Trt B was significantly different from Trt A.
- Active response rates were similar:
- Trt A = 66%
- Trt B = 67%



Example of 'Placebo Creep'

- Significance due to placebo response rates
- Placebo A = 57%
- Placebo B = 39%



Example of 'Placebo Creep'

- Relative risk Treatment A = 1.16
- Relative risk Treatment B = 1.72
- Absolute risk Treatment A = 9%
- Absolute risk Treatment B = 28%

- Although active response rates were similar, placebo-adjusted treatment effects of Treatment A were significantly smaller than placebo-adjusted treatment effects of Treatment B.

Example of 'Placebo Creep'

- Can be difficult to know why placebo response rates are so different if only have publication of trials.
- Without an plausible explanation, difficult to demonstrate that active treatments provide similar benefit.

Problems of Interpretation
'Placebo Creep'

- Caution should be exercised when making comparisons over time.
- In the presence of 'placebo creep' it is not sufficient to assess whether different studies are homogenous in terms of entry criteria or demographics.
- Trials conducted over time could have similar patient populations and yet observe different treatment effects.

Possible Solution
'Placebo Creep'

- Meta regression could be used to account for year of study, if there are sufficient numbers of studies.

- If only a small number of studies (see previous example), comment on to how not allowing for 'placebo creep' could bias the results.

Conclusions

- Indirect comparisons are computationally simple to perform.

- Issues arise relating to the interpretation of the results and ensuring that trials are homogeneous in terms of patient populations and comparator effects.

Take-Home Messages

- Don't just rely on the fact that two sets of trials used 'placebo' or another common comparator.
- Assess the responses reported for the common comparator for any systematic differences.

Take-Home Messages

- Review differences in patient demographics, inclusion/exclusion criteria, use of concomitant medications etc.
- Review the literature to assess if 'placebo' response has altered over time.
- Assess the impact of adjusting for important covariates.

References

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