Outcome Reporting Bias in Trials (II)

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MRC Hubs for Trials Methodology Research

North West Hub

Outcome reporting bias

- Selection of subset of original recorded outcomes, on the basis of the results, for inclusion in publication
- Fully reported: OR 2.2 to 4.7 if statistically significant
  (Dwan et al, *PLoS ONE* 2008)
- Reports vs protocols: 40–62% at least one primary outcome changed, newly introduced or omitted

Outcome Reporting Bias in Trials (ORBIT)

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The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews

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- 42 significant meta-analyses
  - 8 (19%) would not have remained significant
  - 11 (26%) would have overestimated the treatment effect by >20%

- <u>BUT</u> the majority of outcomes were efficacy outcomes

- Focus of high risk of bias was centred around non-significant results (p>0.05)

What about ORB for harms?

- Empirical evidence
  - Reporting of harms data is worse than efficacy (Chan 2004)
  - Interviews with trialists (Smyth 2011)

"When we looked at that data, it actually showed an increase in harm amongst those who got the active treatment, and we ditched it because we weren't expecting it and we were concerned that the presentation of these data would have an impact on people's understanding of the study findings"

"We didn't bother to report it, because it wasn't really relevant to the question we were asking. That's a safety issue thing; there was nothing in it so we didn't bother to report it. It was to keep ethics committee happy. It is not as if we are using a new drug here, it is actually an established one, just an unusual combination, so if we are using new things we report all that sort of stuff, so it's not that experimental"

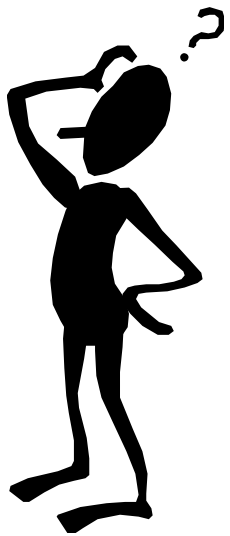
- Is the mechanism for assessing ORB in harms the same as for efficacy outcomes?

What do we think.....

- Assessment could be the same as for efficacy outcomes
  - Bias could be associated with non-significant results ($p>0.05$)

- BUT assessment could also be more complex
  - Harms are measured very differently
    - Specific testing/questioning for a particular harm
    - Open questions (e.g. have you experienced an AE?)
    - Combination of both

- Risk of bias will be influenced by what is known about the harms that are reported
  - Bias could also result from significant harm results ($p<0.05$)
  - Or an undesirable outcome



MRC ORBIT II

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- To examine the prevalence, nature and impact of selective outcome reporting for harms

- All reviews of harms have been identified by members of the Cochrane Adverse Effects Methods Group
  - Collaboration with Yoon Loke

- ORBIT II Study cohort: unselected cohort of 234 reviews
  - RCTs within both Cochrane and Non-Cochrane Reviews
  - 99/234 reviews (post-2007) contained a mix of RCTs/NRS
  - Other work on selective reporting in NRS

Benefit-Harm Ratios

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- In healthcare decisions are made all the time
  - **Patient** – decides whether to receive a treatment
  - **Health care provider** – decides whether to offer treatment
  - **UK NICE –** decides whether it should be prescribed (cost-effectiveness)
  - **Regularity authorities (MHRA/FDA)** – decide whether to give it a licence (safety/quality/benefit harm balance)
  - **Pharmaceutical company** – decides whether to develop and apply for a licence

Benefit-Harm trade-off is often key to decision making

An example - Gastro-intestinal bleeds

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- Two systematic reviews comparing aspirin vs. placebo:
  - **Gastro-intestinal (GI) bleeding (harm)**
    - McQuaid & Laine, 2006 (22 studies)

RR 2.07 (95% CI 1.61, 2.66) [placebo]

  - **Prevention vascular events (efficacy)**
    - Herbert & Hennekens 2000 (4 studies)

RR 0.87 (95% CI 0.81, 0.95) [aspirin]

Benefit-Harm ratio (NNT/NNH)

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- Using methods of Loke, 2002 (risk adjusted):
  - **Per 10,000 patients aspirin therapy for 1-year**
    - Prevent **65** cardiovascular events (95% CI 25,95)
    - Cause **32** GI bleeds (95% CI 18,50)

- Taking aspirin suggests twice as many vascular events prevented compared to harms observed (GI bleeds)

BUT

- Only 14/22 studies contributed data to the meta-analysis of GI bleeds

Outcome reporting bias?

- Eight studies not reporting on GI bleeds
  - Clear that complications and bleeding were measured
  - No data on GI bleeds presented

- Were data suppressed because they suggested a disadvantage for aspirin?
  - If YES, this would have introduced bias
  - True results being even more favourable towards placebo.

- How does this affect the Benefit-Harm ratio?

Sensitivity analysis

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- Applying the sensitivity analysis (Williamson & Gamble,2007)
  - Adjusted RR for GI bleeds:

RR 2.55 (95% CI 1.98, 3.28) [placebo]

- Revised risk adjusted Benefit-Harm ratio
  - Prevent **65** cardiovascular events (95% CI 25,95)
  - Cause **47** GI bleeds (95% CI 29,68) [+ 15 events per 10,000]

- Does this difference tip the balance on whether to treat?

Conclusions

- Trade-off between benefits and harms is very important
- Making informed decisions that consider both benefits and harms of an intervention in an unbiased way is essential
- Important to identify ORB in harms as well as efficacy measures
- Notably this study looks at RCTs only
  - Common to investigate harms using NRS
  - 99/234 reviews contained a mix RCTs/NRS
  - Selective reporting in NRS is being investigated as part of another collaboration