Indirect and Mixed Treatment Comparisons in Arthritis Research

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Biologic Therapies in Inflammatory Joint Diseases: Models for Decision Making
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Outline

- Introduce Indirect and Mixed Treatment Comparisons (IC and MTC)
- Discuss the factors that can introduce ‘bias’ into indirect comparisons ***AND*** pair-wise meta-analysis (equally ?)
- Discuss the role of IC and MTC in decision making in some recent NICE appraisals

Pair-wise Meta-analysis

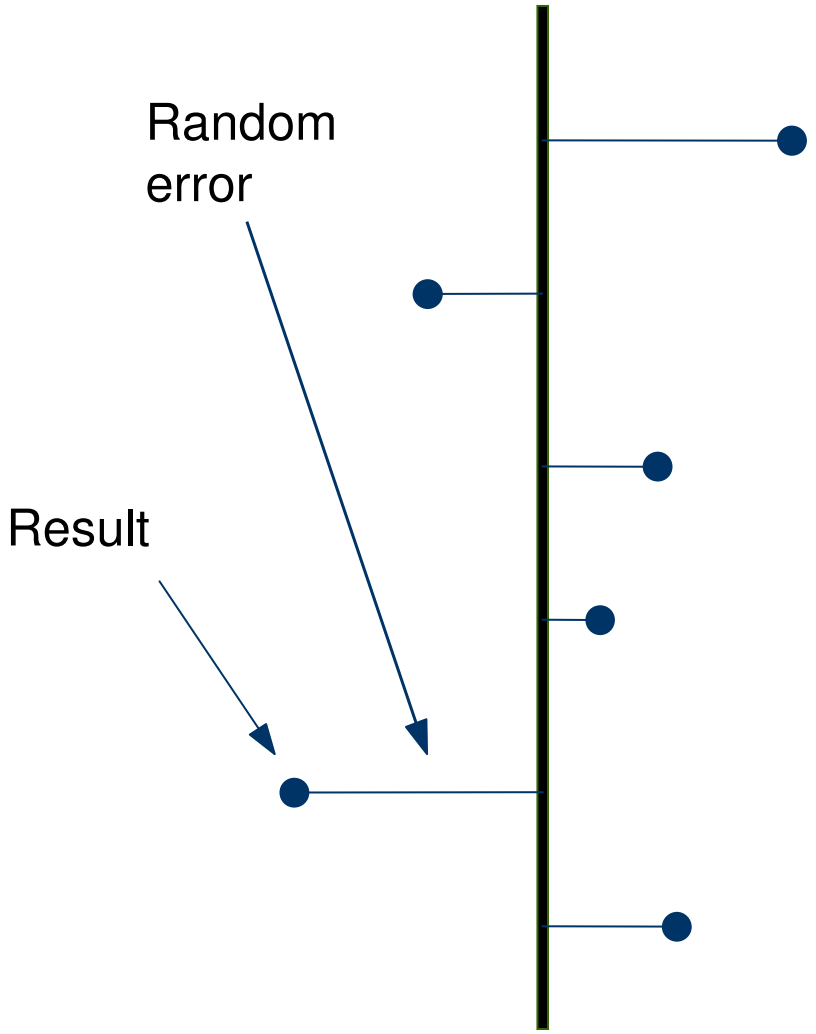
- Combines results from several A vs B trials
- "Fixed Effect": every trial is estimating the same treatment effect of "B vs A", d_{AB}.
- "Random Effect": every trial is estimating a different – but 'similar' treatment effect, from a common distribution.

$$\delta_{AB,j} \sim \text{Normal}\ (d_{AB}, s^2)$$

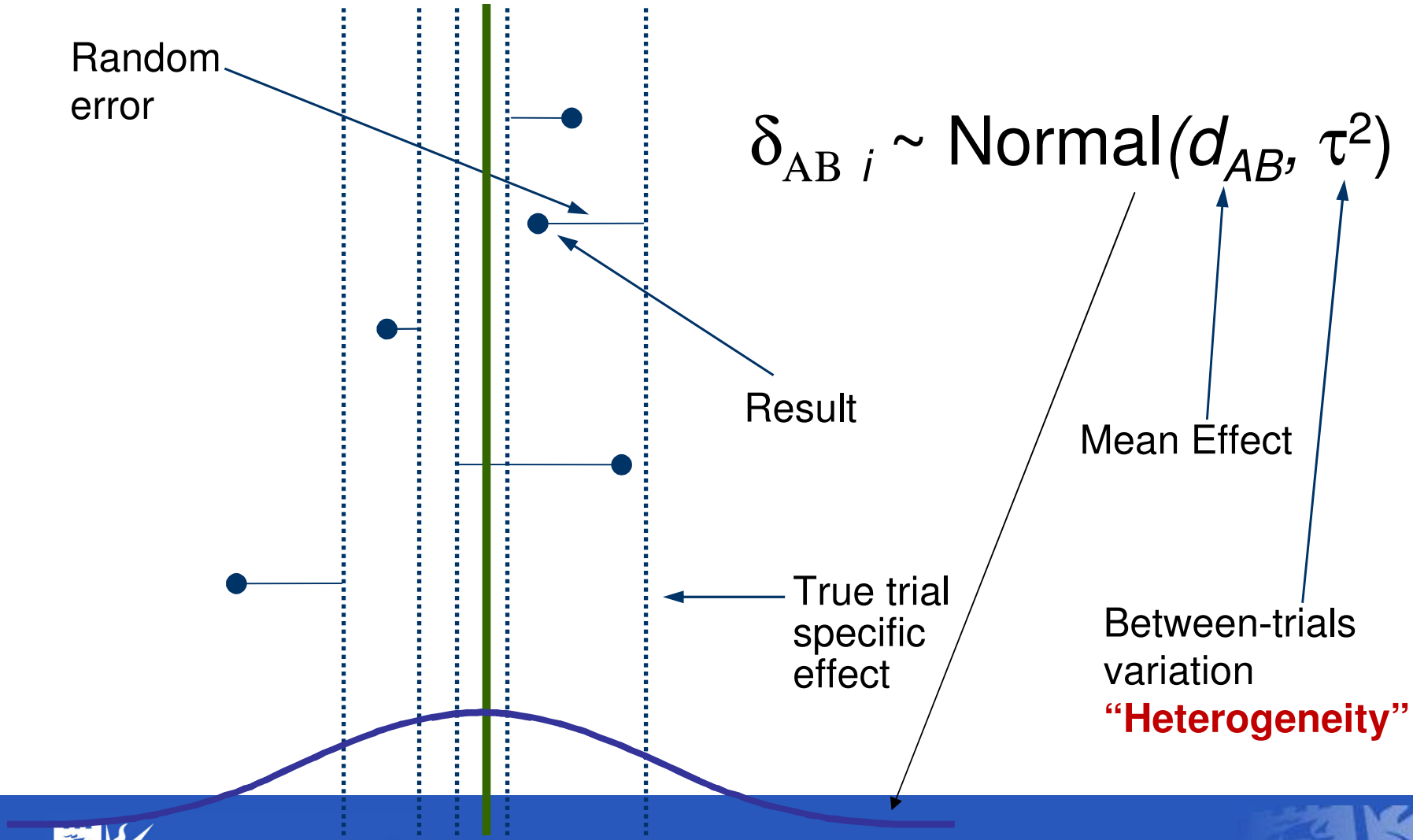
FIXED EFFECT MODEL

- Statistical homogeneity

- We estimate the common true effect, d_{AB}



RANDOM EFFECTS MODEL



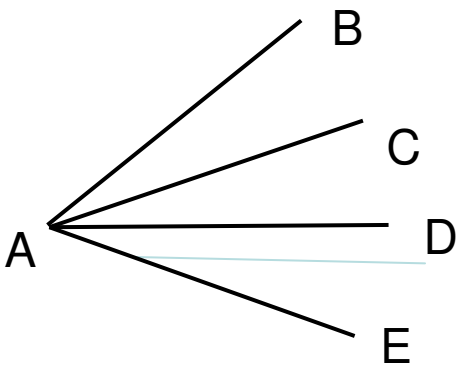
$$\delta_{AB\ i} \sim \text{Normal}(d_{AB}, \tau^2)$$

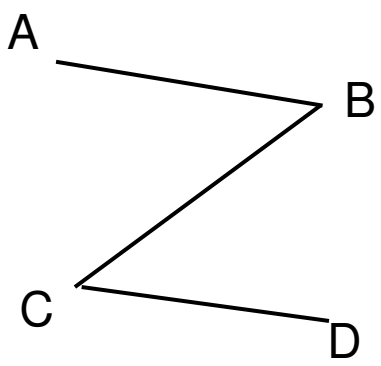
Mean Effect

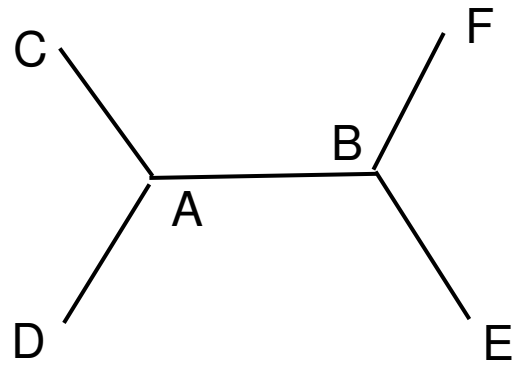
Between-trials variation
"Heterogeneity"

Indirect Comparisons?

- No longer *just* A vs B:
- Now, several treatments have been trialed against (a) common comparator(s): ie A vs B, A vs C, A vs D



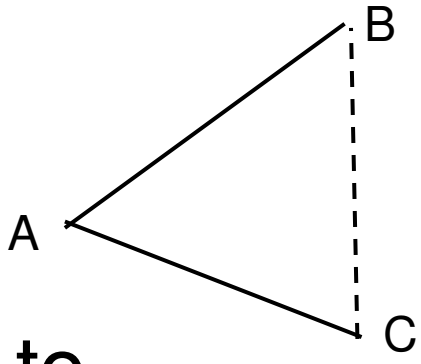




Why Indirect Comparisons ?

- "Direct" evidence A vs B can be combined with "Direct" evidence A vs C, to draw conclusions about the relative treatment effect of C vs B:

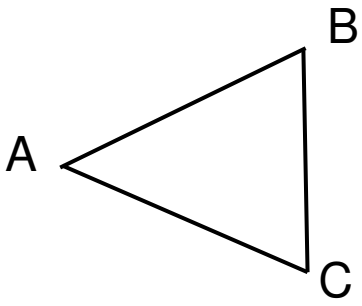
$$\hat{d}_{BC}^{Indirect} = \hat{d}_{AC}^{Direct} - \hat{d}_{AB}^{Direct}$$



Also, makes it possible to compare A,B and C in a CEA, *incrementally*

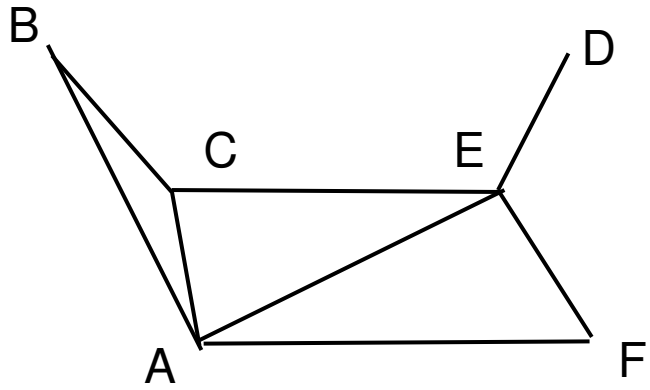
Mixed Treatment Comparisons

- Loops of evidence: eg AB, AC, BC



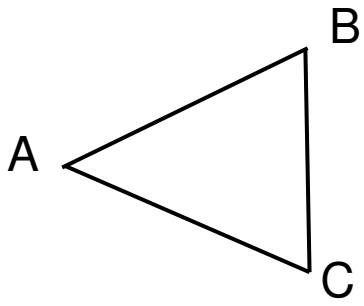
… now combine the "Indirect" AND "direct" evidence on d_{BC}

… or any ***CONNECTED*** network



Significance of MTC / Network Meta-analysis : inference

- Loops of evidence: eg AB, AC, BC



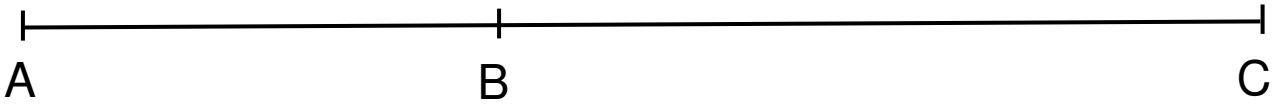
(1) combines the "Indirect" AND "direct" evidence on d_{BC}

(2) also, we can assess "inconsistency" between direct and indirect evidence.

Not possible in Indirect Comparisons

MTC in cost-effectiveness analysis

- An MTC analysis produces estimates which are internally consistent:

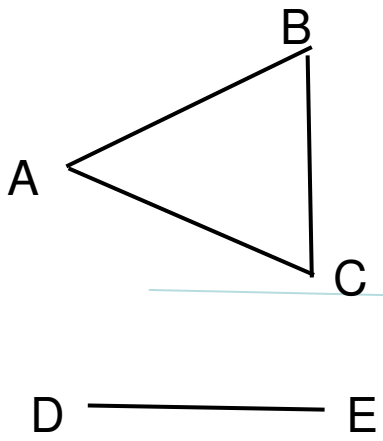


$$d_{AC} = d_{AB} + d_{BC}$$

- NICE Methods Guide specifies “Incremental CEA”, not separate CEAs for B vs A, C vs A, C vs B. Only possible with consistent estimates…. **MTC / IC the only option.**

What about Disconnected Networks ?

Like pair-wise MA, IC and MTC pool information on *Relative* Treatment Effects, ie the kind of data obtained from RCTs.



Drawing conclusions about A vs E, or D vs C, would in effect be using non-randomised studies.

What about Disconnected Networks ?

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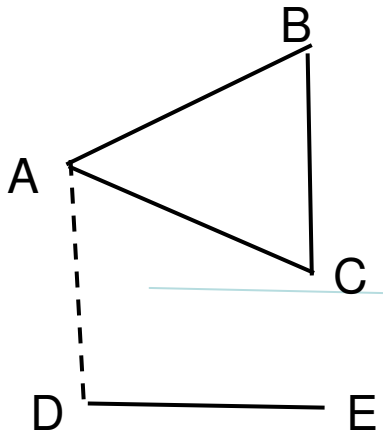

… or connect the pieces by making explicit assumptions about any one of the links …(ie A vs D)

Are Indirect Comparisons reliable (1) ?

- Is pair-wise meta-analysis reliable ?
- Are TRIALS reliable ?

$$\hat{d}_{BC}^{Indirect} = \hat{d}_{AC}^{Direct} - \hat{d}_{AB}^{Direct}$$

- The indirect estimate can only be biased (*inaccurate*) if the direct evidence is biased
- But indirect evidence tends to be less ***precise***

Are ICs reliable (2) ?

- To clarify: we have a specific decision problem and target population (eg biologics in patients who have failed on DMARDS)
- We have (eg) trials Infliximab+MTX vs MTX, and Etanercept+MTX vs MTX
- If both give unbiased estimates for the specific target popn, then conclusions about Inf+MTX vs Eta+MTX *must also be unbiased*

..are RCTs and PWMA “reliable”?

- Evidently not! As heterogeneity is so frequent! Seems to arise two ways:
- 1. Trials give different results (ie different RELATIVE effects) because of (unrecognised) differences in the patients, protocols.
- 2. Random biases - usually favouring the “newer” treatment - due to poor execution, unblinded assessment, lack of blinding, etc

… but, even so …

- (Some) ICs may be **more** vulnerable to bias than Pair-Wise meta-analysis.
- Example: suppose we have trials comparing several biologics (B,C,D…) to a DMARD (A)
- The trials may differ in, eg, disease severity, which could be a ***relative effect modifier***.
- Head-to-head comparisons of biologics less vulnerable as ***severity would affect both arms equally***

NICE on IC/MTC, 2008 Methods Guide

- Direct H2H evidence favoured.
- Indirect evidence OK in absence of Direct
- Can include unavailable or not recommended treatments to form a connected network
- Direct H2H is base case, but MTC can be presented also (ie can pool direct and indirect)
- BUT: if Incremental CEA, and >2 treatments, then MTC / IC is only option. (Not explicit, but recognised)

MTC / IC: does this affect NICE decisions in arthritis?

- In Rheumatoid and Psoriatic Arthritis, trials look at initial response to treatment, over 3 to 6 months
- Let's look at some specific NICE appraisals and see what role indirect comparisons, or mixed treatment comparisons, have played in the decision

Psoriatic Arthritis: TA 199

- Etanercept, Infliximab, Adalimumab : all recommended for PSA not responding to 2 DMARDS.
- Evidence: Eta vs Pl, Inf vs Pl, Ada vs Pl, 2 trials each. (Indirect comparison)
- CEA showed Ada and Eta highly effective and cost-effective against placebo (ICER < £20k).
- Inf not CE against Ada or Eta (ICER > £45k).
- Ind Comps provided no reason to believe there was any material difference in efficacy
- DECISION: All OK, but use one with lowest cost

TA 72 : Anakinra for RA

- Anakinra added to drug sequence at different points:
- Evidence: Trials of Anakinra+MTX vs MTX, and Anakinra vs placebo. Indirect comps with Inf and Eta suggested Anakinra was significantly inferior
- CEA (Birmingham model) showed sequences with Anakinra not cost-effective against those without
- DECISION: Not recommended – on the basis that Anakinra was not CE against no Anakinra.

TA 186 : Certolizumab for RA (1)

- Background: TA130 had recommended Inf, Ada, and Eta dual therapy with MTX in patients who had failed on DMARDS, or monotherapy if intolerant to MTX.
- Dual therapy Evidence: Trials of Cert, Ada, Eta, Inf dual therapy (+MTX), vs MTX alone. Trials of Eta+MTX vs Inf+MTX (requested by Appraisal Cttee).
- Monotherapy evidence: IC involving Cert, Ada, Eta all vs Placebo

TA 186 : Certolizumab for RA (2)

- Efficacy: All highly effective, no reason to believe any better than the others. Eta best in dual
- CEA: Cert+MTX cost-effective against MTX, Cert Cost effective against Placebo. In an Incremental CEA, Cert CE against the others, says Mnfacturer
- Certolizumab recommended “as an option” alongside the TA130 options.
- Role of MTC? Committee able to review the role of Cert alongside other options, but decision based on cost effectiveness against standard trt, not biologics

Role of MTC/IC: summary

- AntiTNF drugs have similar efficacy, based on IC and small amount of direct evidence
- Biologics are being recommended, based on being CE against the standard comparators they have been trialed against.
- No biologic has been ruled out on basis on indirect evidence
- The effect of direct H2H trials on biologics would only be to rule one or more out, if (a) clear inferiority and (b) lack of cost-effectiveness.