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Using Indirect Comparisons to Support a Health Technology Assessment (HTA)

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- The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen.

Outline

- Introduction to indirect comparisons
- Integrating indirect comparisons into drug development
- Case study
- Some hot topics in indirect comparison methodology
- Conclusions

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Introduction to Indirect Comparisons

Also referred to as “Network Meta-Analyses”

Indirect Comparison Definition

Indirect comparisons enable us to combine trials that compare different sets of treatments, and form a network of evidence, within a single analysis. This allows us to use all available direct and indirect evidence to inform a given comparison between treatments.

- 4 key assumptions:
  - Exchangeability
  - Homogeneity
  - Similarity
  - Consistency
- NMAs are observational, can lack internal validity and have lower precision

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Example of network diagram

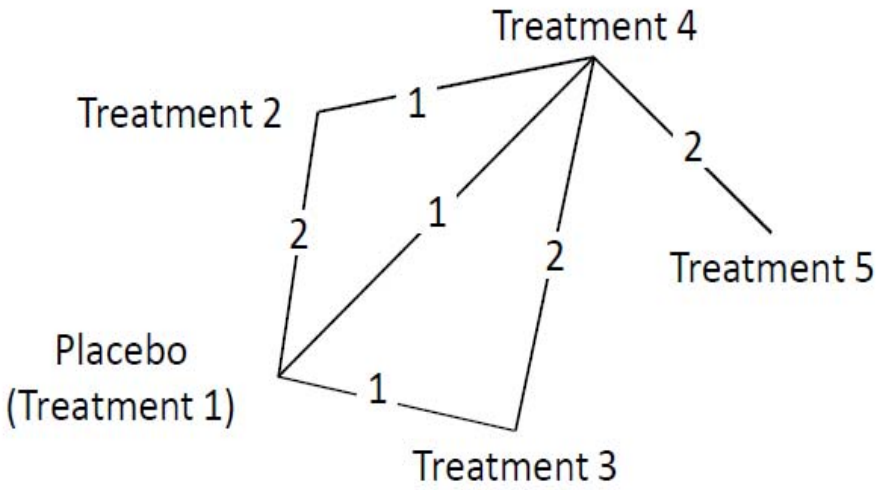

Figure 3 Parkinson network: each edge represents a treatment, connecting lines indicate pairs of treatments which have been directly compared in randomised trials. The numbers on the lines indicate the numbers of trials making that comparison.

Bucher's Method (example)

- Simple method used with a single common comparator (usually placebo)
- Method

  δ_{ac} is the meta-analysis estimate of the difference between treatments A and C

  δ_{bc} is the meta-analysis estimate of the difference between treatments B and C

  The indirect estimate of the difference between A and B is

$$\delta^{i}_{ab} = \left(\delta_{ac} - \delta_{bc}\right) \quad SE\left(\delta^{i}_{ab}\right) = \sqrt{Var\left(\delta_{ac}\right) + Var\left(\delta_{bc}\right)}$$

$$95\%CI : \delta^{i}_{ab} \pm 1.96 \times SE\left(\delta^{i}_{ab}\right)$$

Bucher et al (1997)

Bayesian approach (example)

In study i, the response in each group could be modelled as follows:

control	logit[$p_{c(i)}$] =	$\mu_{(i)}$
trt1	logit[$p_{1(i)}$] =	$\mu_{(i)} + \delta_{1c}$
trt2	logit[$p_{2(i)}$] =	$\mu_{(i)} + \delta_{2c}$
trt3	logit[$p_{3(i)}$] =	$\mu_{(i)} + \delta_{3c}$
trt4	logit[$p_{4(i)}$] =	$\mu_{(i)} + \delta_{4c}$

Study effects $\mu_{(i)} \sim$ prior N(0,1E06)

Study differences

$\delta_{1c} \sim$ normal ($[d_1 - d_c]$, σ^2)

$\delta_{2c} \sim$ normal ($[d_2 - d_c]$, σ^2)

$\delta_{3c} \sim$ normal ($[d_3 - d_c]$, σ^2)

$\delta_{4c} \sim$ normal ($[d_4 - d_c]$, σ^2)

Treatment effects $d_c, d_1, d_2, d_3, d_4 \sim$ prior N(0,1E06)

Between study variance $\sigma^2 \sim$ prior uniform(0,0.6) [sparse data]

Estimate d_c, d_1, d_2, d_3, d_4 using constraint of $d_1 = 0$, then all treatment effects can be interpreted as log-odds difference to trt1

Example of fitting indirect comparisons using *SAS*®

MAIN PAPER

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.533

Published online in Wiley Online Library

Statistical approaches for conducting network meta-analysis in drug development†

Byron Jones,[a]* James Roger,[b] Peter W. Lane,[c] Andy Lawton,[d] Chrissie Fletcher,[e] Joseph C. Cappelleri,[f] Helen Tate,[g] Patrick Moneuse,[h] and on behalf of PSI Health Technology Special Interest Group, Evidence Synthesis sub-team

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Key Steps for an Indirect Comparison

1. Research Project Plan
   - Objectives
   - Endpoints
   - Systematic Review
   - Analysis methodology
   - Deliverables (outputs)
2. Systematic Literature Review
   - Protocol
   - Searches
   - Review
   - Extraction
   - Analysis
   - Reporting
3. Indirect Comparison Analysis
   - Check assumptions
   - Perform modelling
   - Model checking
   - Sensitivity analyses
   - Subgroups
   - Reporting

Sources of Heterogeneity

- Differences in inclusion/exclusion criteria or baseline characteristics
- Variability in control and treatment
  - Dose, timing, brand
- Broader variability in management
  - Care setting, co-medication, intermediate outcomes/crossovers, wash in/out, compliance
- Differences in outcome measures
  - Follow-up times, outcome definitions
- Variation in analysis
  - Withdrawals, drop-outs, stopping rules, handling crossovers
- Quality in design and execution, with bias or imprecision

Reporting Indirect Comparisons (ISPOR)

Introduction	State the rationale and objective of the analysis clearly
Methods	Description of the eligibility criteria Information sources Search strategy Study selection process Data extraction Validity assessment of individual studies
	Are the outcomes measures described
	Description of analytical methods/models Handling of potential bias/inconsistency Analysis framework
	Sensitivity analyses
Results	Include a summary of the studies included in the network of evidence Assessment of model fit, comparing different models Present the results of the evidence clearly; differentiating direct, indirect and NMA comparisons Present the results of sensitivity analyses
Discussion	Describe the main findings and the internal validity of the analysis Discuss external validity Describe limitations Give implications of results for target audience

Summary of HTA Agency* Guidelines on NMA

- NMAs should only be conducted when H2H RCTs don't exist
- Less weight is given to an NMA compared to direct evidence from RCTs
- Observational data should not be used in an NMA
- Most note that an NMA has relatively low power to detect important differences
- All HTA bodies comment on the underlying assumption that an NMA is only valid if the contributing RCTs are similar

* UK National Health Service (NHS) Health Technology Assessment (HTA) Programme
US Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Australian Pharmaceutical Benefits Advisory Committee (PBAC) and PBAC Working Group
German Institute of Medical Documentation and Information (DIMDI)

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Recommendations by EUnetHTA on direct and indirect comparisons

1. Systematic review is a pre-requisite
2. Only combine comparable studies
3. Choice of model (fixed vs random) based on characteristics of studies
4. Investigate potential sources of bias
5. Apply range of sensitivity analyses, e.g. outliers
6. Direct evidence preferred
7. Evaluate direct and indirect evidence separately
8. Use methods that maintain randomisation
9. Choice of method relies on network of evidence
10. Only conduct analyses if data are homogeneous and consistent
11. Explicitly state the assumptions made
12. Justify choice of priors for Bayesian methods
13. Aim for most parsimonious model

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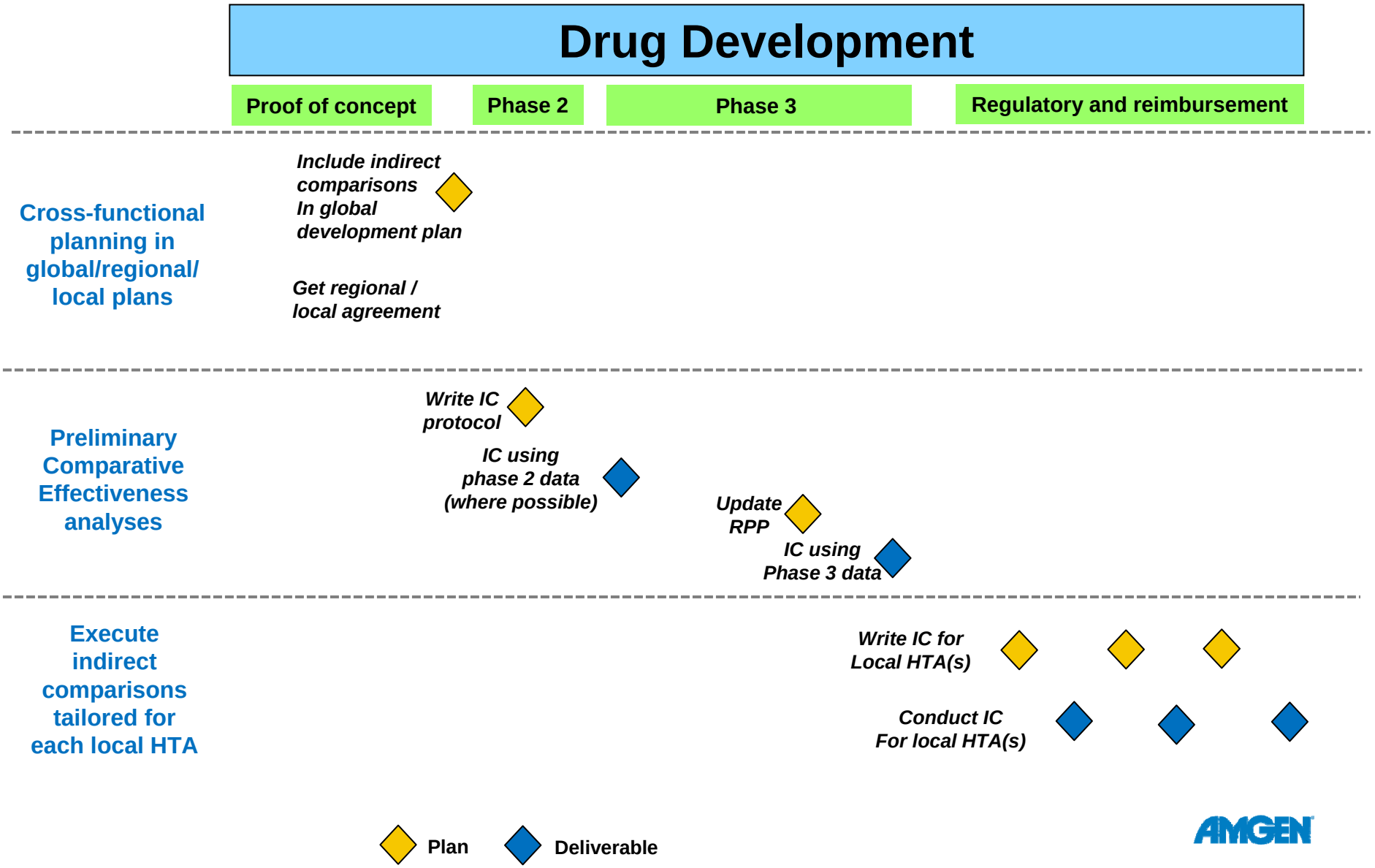
Integrating Indirect Comparisons in Drug Development

Build in comparative effectiveness analyses early in drug development



Recommended Team Composition

- Health economics
- Statistics
- Clinical
- Epidemiology
- Payer/Access
- Country (local) experts

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Case Study

Denosumab (Prolia®) NICE HTA

- Initial NICE scoping meeting Jan 2009
- UK HTA core team created May 2009
- Systematic review protocol created Jun 2009
  - Initial search completed
- Research Project Plan created Oct 2009
- Final NICE Scope issued in Nov 2009
  - Final and updated systematic review completed
- HTA submitted Jan 2010
- Preliminary recommendations (ACD) May 2010
- Final guidance (FAD) Oct 2010

http://guidance.nice.org.uk/TA/Wave20/75

Case study - osteoporosis

Osteoporos Int
DOI 10.1007/s00198-012-2068-9

ORIGINAL ARTICLE

Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis

N. Freemantle · C. Cooper · A. Diez-Perez · M. Gitlin · H. Radcliffe · S. Shepherd · C. Roux

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Systematic Review

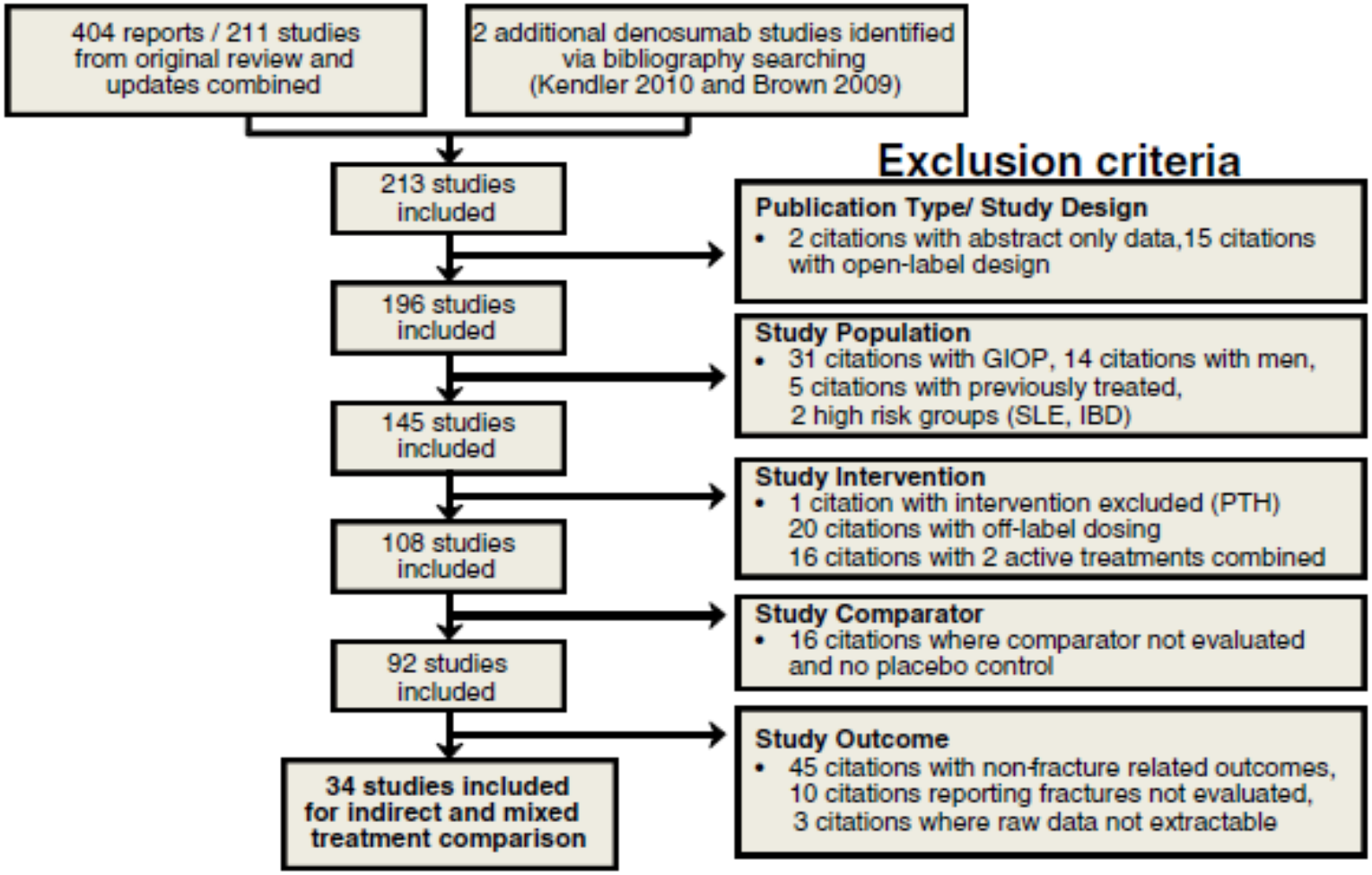

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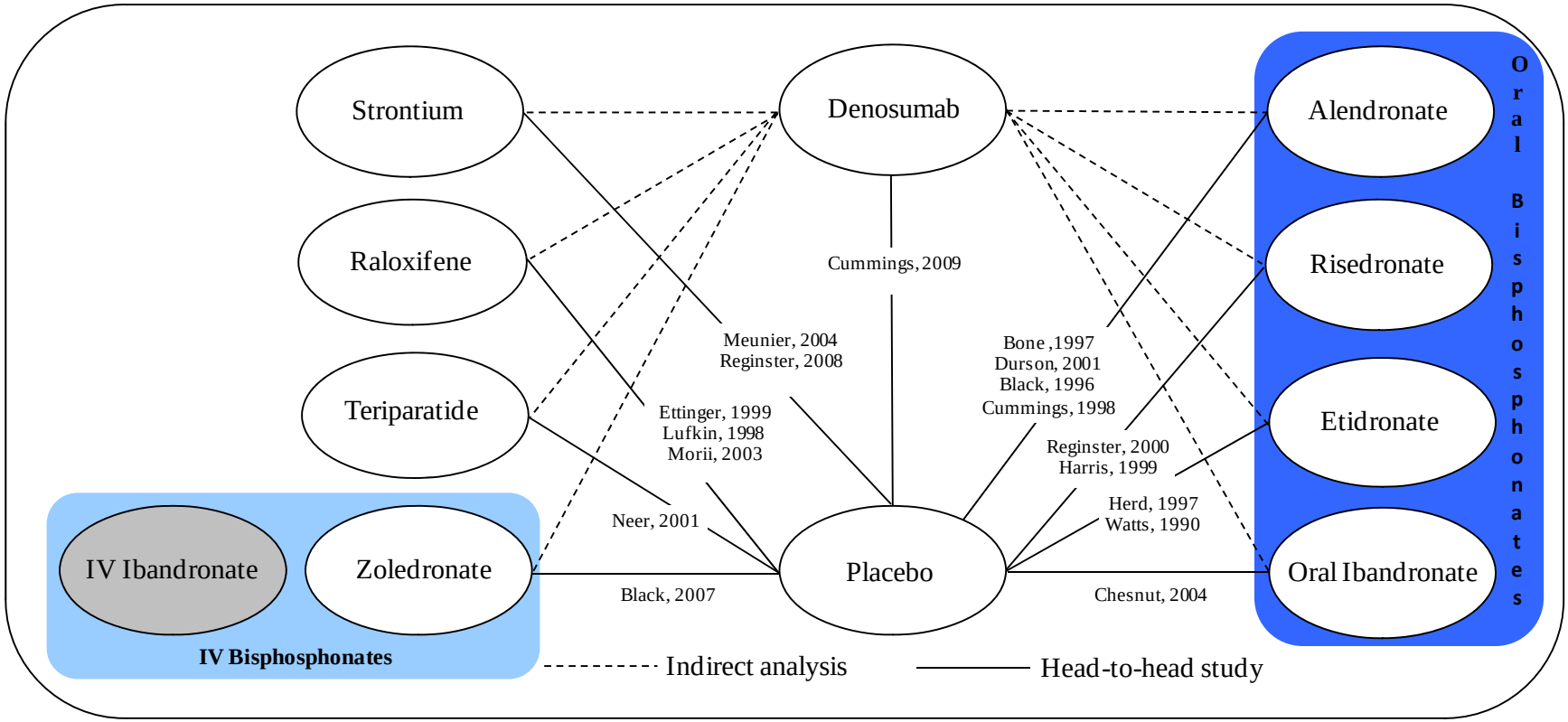
Fig. S1 Network Diagram for Network Meta-analyses: New Vertebral Fractures (Primary Analyses)



Results

Table 1 Random effects meta-analysis and MTC results for fracture endpoints

Meta-analysis: active comparator vs. placebo	New vertebral, RR (95 % CI)	Clinical vertebral, RR (95 % CI)	Nonvertebral, RR (95 % CI)	Hip, RR (95 % CI)	Wrist, RR (95 % CI)
Denosumab	*0.33 (0.26 to 0.41)*	*0.32 (0.21 to 0.48)*	*0.81 (0.69 to 0.96)*	*0.61 (0.37 to 0.98)*	0.84 (0.64 to 1.11)
Strontium ranelate	*0.72 (0.57 to 0.90)*	*0.65 (0.50 to 0.84)*	*0.88 (0.78 to 0.99)*	0.89 (0.67 to 1.18)	0.98 (0.73 to 1.31)
Raloxifene	*0.65 (0.54 to 0.78)*	0.45 (0.05 to 3.82)	0.66 (0.16 to 2.65)		
Teriparatide	*0.35 (0.22 to 0.55)*		*0.47 (0.25 to 0.88)*	0.25 (0.03 to 2.24)	0.29 (0.06 to 1.38)
Zoledronic acid	*0.30 (0.24 to 0.38)*	*0.23 (0.14 to 0.37)*	*0.75 (0.65 to 0.87)*	*0.59 (0.42 to 0.83)*	
Alendronate	*0.56 (0.46 to 0.69)*	*0.45 (0.28 to 0.74)*	*0.85 (0.75 to 0.97)*	0.65 (0.41 to 1.03)	0.81 (0.37 to 1.80)
Risedronate	*0.62 (0.50 to 0.77)*		*0.81 (0.71 to 0.92)*	*0.74 (0.59 to 0.94)*	0.68 (0.42 to 1.07)
Etidronate	0.46 (0.17 to 1.31)		3.96 (0.45 to 34.86)	2.97 (0.12 to 72.11)	4.95 (0.24 to 101.92)
Ibandronate oral (2.5 mg)	*0.51 (0.34 to 0.74)*	*0.54 (0.32 to 0.89)*	1.1		
Bisphosphonates (IV—includes ibandronate oral)[a]	*0.38 (0.23 to 0.63)*	*0.35 (0.15 to 0.81)*	0.8		
Bisphosphonates (oral—includes ibandronate oral)	*0.58 (0.50 to 0.66)*	*0.49 (0.35 to 0.70)*	*0.8*		
Bisphosphonates (oral and IV)	*0.52 (0.42 to 0.66)*	*0.38 (0.23 to 0.64)*	*0.8*		
Adjusted indirect comparison: denosumab vs. comparator	New vertebral, RR (95 % CI)	Clinical vertebral, RR (95 % CI)	No		
Denosumab vs. strontium ranelate	*0.45 (0.32 to 0.63)*	*0.49 (0.30 to 0.80)*	0.9		
Denosumab vs. raloxifene	*0.50 (0.37 to 0.68)*	0.70 (0.08 to 6.17)	1.2		
Denosumab vs. teriparatide	0.94 (0.55 to 1.58)		1.7		
Denosumab vs. zoledronic acid	1.08 (0.78 to 1.51)	1.40 (0.73 to 2.67)	1.0		
Denosumab vs. alendronate	*0.58 (0.42 to 0.79)*	0.70 (0.37 to 1.32)	0.9		
Denosumab vs. risedronate	*0.53 (0.38 to 0.73)*		1.0		
Denosumab vs. etidronate	0.70 (0.24 to 2.02)		0.2		
Denosumab vs. ibandronate oral (2.5 mg)	0.64 (0.41 to 1.01)	0.59 (0.31 to 1.14)	0.7		
Denosumab vs. bisphosphonates (IV, includes ibandronate oral)[a]	0.85 (0.49 to 1.50)	0.91 (0.35 to 2.34)	0.9		
Denosumab vs. bisphosphonates (oral, includes ibandronate oral)	*0.57 (0.43 to 0.74)*	0.64 (0.37 to 1.11)	0.9		
Denosumab vs. bisphosphonates (oral and IV)	*0.62 (0.44 to 0.87)*	0.83 (0.43 to 1.62)	0.9		
Mixed treatment comparison: active comparator vs. placebo	New vertebral, RR (95 % CrI) [*P*(RR<1)]	Clinical vertebral, RR (95 % CrI) [*P*(RR<1)]	No C		
Denosumab vs. placebo	*0.32 (0.22 to 0.46) [1.00]*	0.31 (0.04 to 2.77) [0.90]	0.8		
Strontium ranelate vs. placebo	*0.72 (0.57 to 0.90) [0.99]*	0.65 (0.08 to 5.52) [0.75]	0.8		
Raloxifene vs. placebo	*0.63 (0.48 to 0.80) [1.00]*	0.40 (0.04 to 1.89) [0.87]	0.8		
Teriparatide vs. placebo	*0.34 (0.20 to 0.58) [1.00]*		*0.4*		

Table 1 (continued)

Meta-analysis: active comparator vs. placebo	New vertebral, RR (95% CI)	Clinical vertebral, RR (95% CI)	Nonvertebral, RR (95% CI)	Hip, RR (95% CI)
Zoledronic acid vs. placebo	*0.30 (0.21 to 0.43) [1.00]*	0.22 (0.02 to 1.95) [0.94]	0.75 (0.55 to 1.01) [0.97]	0.58 (0.28 to 1.22) [0.95]
Alendronate vs. placebo	*0.57 (0.44 to 0.75) [1.00]*	0.45 (0.05 to 4.07) [0.84]	0.83 (0.65 to 1.02) [0.97]	0.63 (0.33 to 1.19) [0.93]
Risedronate vs. placebo	*0.62 (0.46 to 0.83) [1.00]*		*0.80 (0.65 to 0.95) [0.99]*	0.75 (0.50 to 1.15) [0.93]
Etidronate vs. placebo	0.43 (0.14 to 1.19) [0.95]		5.31 (0.58 to 172) [0.07]	146 (0.49 to 1771 [0.06]
Ibandronate oral (2.5 mg) vs. placebo	*0.50 (0.31 to 0.80) [1.00]*	0.54 (0.06 to 4.85) [0.80]	1.11 (0.76 to 1.63) [0.28]	
Bisphosphonates (IV—includes ibandronate oral)[a]	0.38 (0.12 to 1.25) [0.96]	0.34 (0.08 to 1.5) [0.95]	0.90 (0.28 to 3.06) [0.65]	0.59 (0.30 to 1.14) [0.96]
Bisphosphonates (oral—includes ibandronate oral)	*0.57 (0.49 to 0.68) [1.00]*	0.49 (0.16 to 1.47) [0.94]	*0.84 (0.73 to 0.96) [0.99]*	0.73 (0.53 to 1.01) [0.97]
Bisphosphonates (oral and IV)	*0.52 (0.41 to 0.66) [1.00]*	*0.37 (0.16 to 0.89) [0.98]*	*0.82 (0.73 to 0.93) [1.00]*	*0.69 (0.54 to 0.89) [0.99]*
Mixed treatment comparison: denosumab vs. comparator	New vertebral, RR (95 % CrI) [*P*(RR<1)]	Clinical vertebral, RR (95 % CrI) [*P*(RR<1)]	Nonvertebral, RR (95 % CrI) [*P*(RR<1)]	Hip, RR (95 % Cr [*P*(RR<1)]
Denosumab vs. strontium ranelate	*0.45 (0.29 to 0.68) [1.00]*	0.48 (0.02 to 9.90) [0.77]	0.92 (0.61 to 1.36) [0.70]	0.68 (0.23 to 2.09) [0.80]
Denosumab vs. raloxifene	*0.51 (0.33 to 0.81) [1.00]*	0.77 (0.06 to 20.91) [0.65]	0.93 (0.58 to 1.61) [0.64]	
Denosumab vs. teriparatide	0.95 (0.50 to 1.80) [0.57]		1.74 (0.83 to 3.93) [0.07]	3.71 (0.33 to 108) [0.17]
Denosumab vs. zoledronic acid	1.08 (0.65 to 1.77) [0.38]	1.42 (0.06 to 31.63) [0.35]	1.08 (0.69 to 1.70) [0.32]	1.03 (0.34 to 3.24) [0.48]
Denosumab vs. alendronate	*0.56 (0.36 to 0.86) [0.99]*	0.70 (0.03 to 15.23) [0.65]	0.98 (0.67 to 1.49) [0.58]	0.96 (0.33 to 2.82) [0.54]
Denosumab vs. risedronate	*0.52 (0.33 to 0.82) [0.99]*		1.02 (0.71 to 1.51) [0.47]	0.81 (0.33 to 2.09) [0.70]
Denosumab vs. etidronate	0.76 (0.25 to 2.37) [0.69]		0.12 (0.00 to 1.24) [0.96]	0.005 (0.00 to 1.8 [0.95]
Denosumab vs. ibandronate oral (2.5 mg)	0.64 (0.36 to 1.16) [0.94]	0.59 (0.03 to 12.45) [0.71]	0.72 (0.43 to 1.21) [0.92]	
Denosumab vs. bisphosphonates (IV—includes ibandronate oral)[a]	0.86 (0.11 to 6.35) [0.61]	0.93 (0.08 to 10.87) [0.54]	0.92 (0.12 to 7.16) [0.57]	1.02 (0.39 to 2.64) [0.48]
Denosumab vs. bisphosphonates (oral—includes ibandronate oral)	*0.56 (0.37 to 0.82) [1.00]*	0.65 (0.11 to 4.15) [0.78]	0.96 (0.68 to 1.39) [0.62]	0.82 (0.37 to 1.81) [0.71]
Denosumab vs. bisphosphonates (oral and IV)	0.62 (0.32 to 1.18) [0.93]	0.84 (0.15 to 4.66) [0.63]	0.98 (0.71 to 1.36) [0.54]	0.88 (0.44 to 1.79) [0.65]

Comparisons with the CI or CrI excluding 1 are rendered in italics

Summary of indirect comparison and MTC results

Fracture type **Intervention Comparison**	**Random Effects Meta-Analysis and Adjusted Indirect Comparison RR (95% CI)**	**Mixed Treatment Comparison RR (95% CrI)**
New Vertebral		
Denosumab vs. Placebo	**0.33 (0.26, 0.41)**	**0.32 (0.22, 0.46)**
Denosumab vs. Oral BPs	**0.57 (0.43, 0.74)**	**0.56 (0.37, 0.82)**
Non-Vertebral		
Denosumab vs. Placebo	**0.81 (0.69, 0.96)**	0.81 (0.60,1.11)
Denosumab vs. Oral BPs	0.96 (0.79, 1.17)	0.96 (0.68,1.39)
Hip		
Denosumab vs. Placebo	**0.61 (0.37, 0.98)**	0.60 (0.27,1.36)
Denosumab vs. Oral BPs	0.83 (0.49, 1.41)	0.82 (0.37, 1.81)

RR: relative risk; CI: confidence interval; CrI: credible interval; BPs: bisphosphonates

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Hot Topics in Indirect Comparison Methodology

Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research

- Using individual patient data (IPD) from trials in one treatment in indirect comparisons to address limitations when using only aggregate data
- After attempting to match inclusion/exclusion criteria, weight IPD so that the weighted mean baseline characteristics match reported trials without IDP
  - Propensity score weighting
- Examples
  - Vildagliptin versus sitagliptin in Japanese patients with Type II diabetes (resolve differences in key baseline characteristics)
  - Adalimumab versus etanercept in the treatment of psoriasis (reduce sensitivity to effect measure)
  - Guanfacine extended release versus atomoxetine in children and adolescents with attention deficit/hyperactivity disorder (compare clinically relevant dosages)
  - Nilotinib versus dasatinib in newly diagnosed chronic myelogenous leukemia chronic phase (resolve differences in outcome measures)

Signorovitch et al, 2012

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Inconsistency between direct and indirect evidence of competing interventions: a meta-epidemiologic study

- Examined112 independent trial networks that allowed direct and indirect comparison of two treatments
- Compared direct with indirect comparisons and found ‘significant’ inconsistency in 14% of networks.
- Risk of inconsistency is associated with fewer trials, subjective outcomes, and statistically significant outcomes
- Concludes that inconsistency may be more prevalent than previously observed, direct and indirect evidence should be combined only after assessment of consistency.

Song et al. BMJ (2011)

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Conclusions

Conclusions

- Indirect comparisons are a key component of drug development plans and support defining product “value”
- Indirect comparisons enable therapies used in clinical practice and new therapies to be compared indirectly when there is a lack of head to head randomized controlled trials
- Indirect comparisons are observational with strong assumptions and need to be interpreted with caution with key limitations and biases fully described
- Indirect comparisons require cross-functional engagement and alignment
- Recommend statisticians keep abreast of the evolving indirect comparison methodology

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