EVIDENCE SYNTHESIS IN DRUG DEVELOPMENT

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

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AGENDA

- **What do we mean by evidence synthesis?**
- **Evidence synthesis methods**
- **Using evidence synthesis in drug development**
- **Amgen's HTA evidence based methods platform**
- **Strategic role for statisticians**
- **Conclusions**

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WHAT DO WE MEAN BY EVIDENCE SYNTHESIS?

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EVIDENCE SYNTHESIS DEFINITION*

- **Evidence synthesis** involves the development of techniques to combine multiple sources of quantitative **evidence.** In health technology assessment, meta-analysis is a well-established body of techniques for combining **evidence** from high-quality trials.
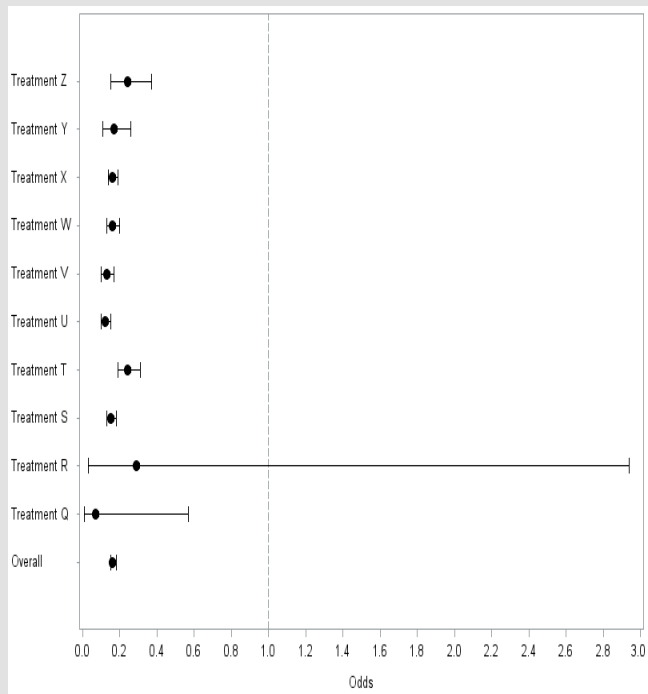
* Source: Wikipedia

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EVIDENCE SYNTHESIS METHODS
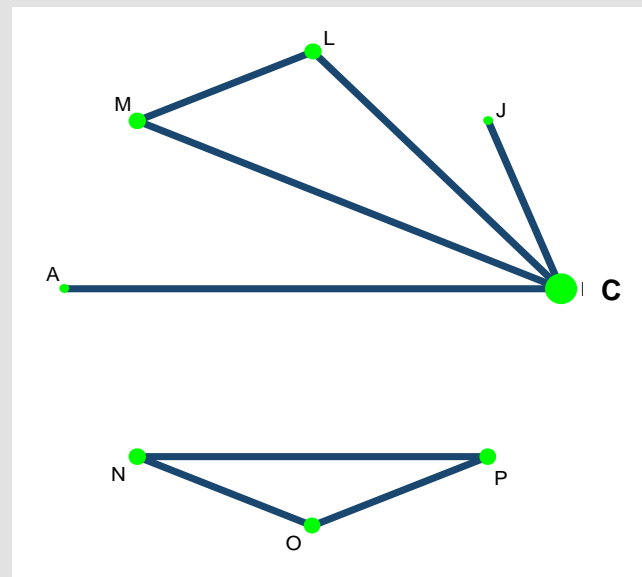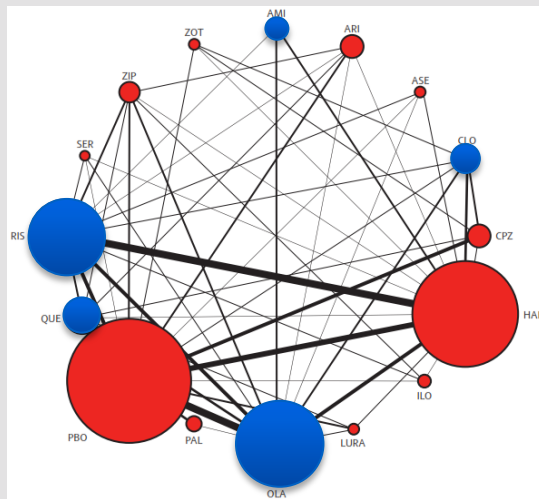
EVIDENCE SYNTHESIS METHODS

- **Pooling data across studies**
- **Meta-analysis (MA)**
- **Network meta-analysis (NMA)**
  - **Indirect comparisons**
  - **Mixed treatment comparisons**
- **Matched adjusted indirect comparisons (MAIC)**
- **Simulated Treatment Comparisons (STC)**

Variety of methods available to synthesis a variety of data sources

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EVIDENCE SYNTHESIS EXAMPLES

Meta-Analysis

Network Meta-Analysis

AVAILABLE EVIDENCE (NETWORK) DETERMINES EVIDENCE SYNTHESIS APPROACH - EXAMPLES

Comparator evidence

Range of Evidence Synthesis Methods

Direct H2H RCT(s)

- Meta-analysis (MA)
- Network-Meta Analysis (NMA) with Mixed Treatment Comparison

No direct H2H RCTs, *but*
Connected network of evidence to comparator RCTs

- Network-Meta Analysis (NMA)
- Indirect Treatment Comparison (ITC)

No direct H2H RCTs
No connected network of evidence to comparator RCTs

- Matched Adjusted Indirect Comparison (MAIC)
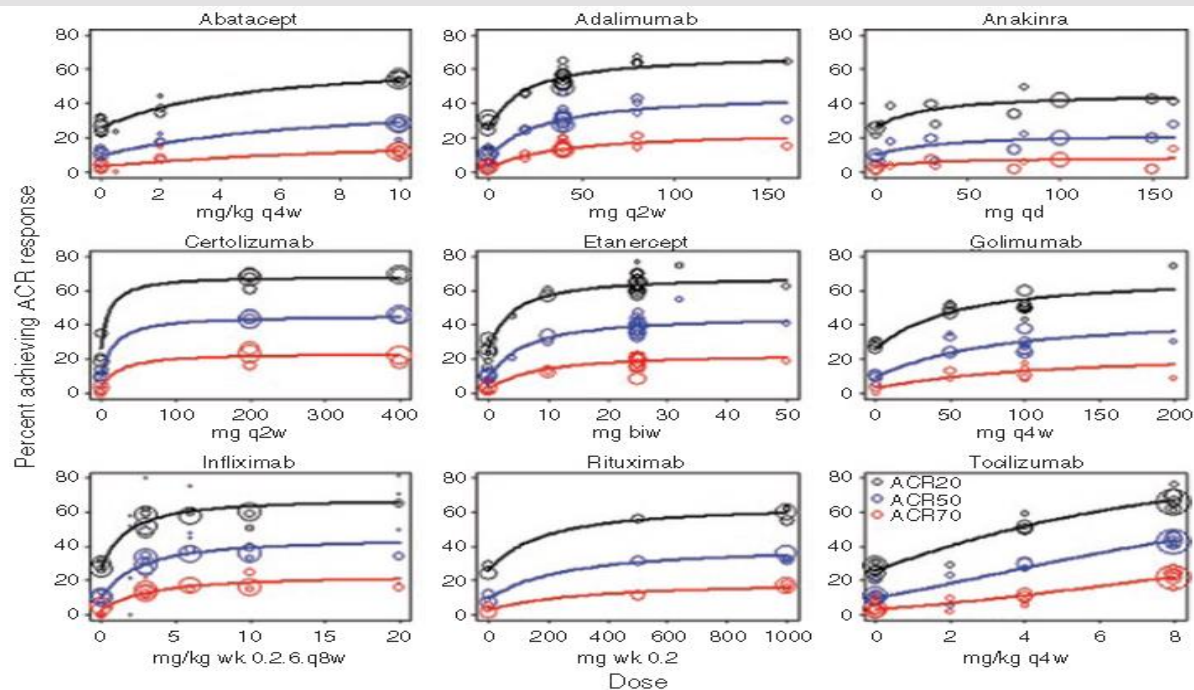- Model-based meta-analysis (MBMA)

H2H   **head to head**

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USING EVIDENCE SYNTHESIS IN DRUG DEVELOPMENT

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EVIDENCE GENERATION AND TRIGGERS FOR EVIDENCE SYNTHESIS
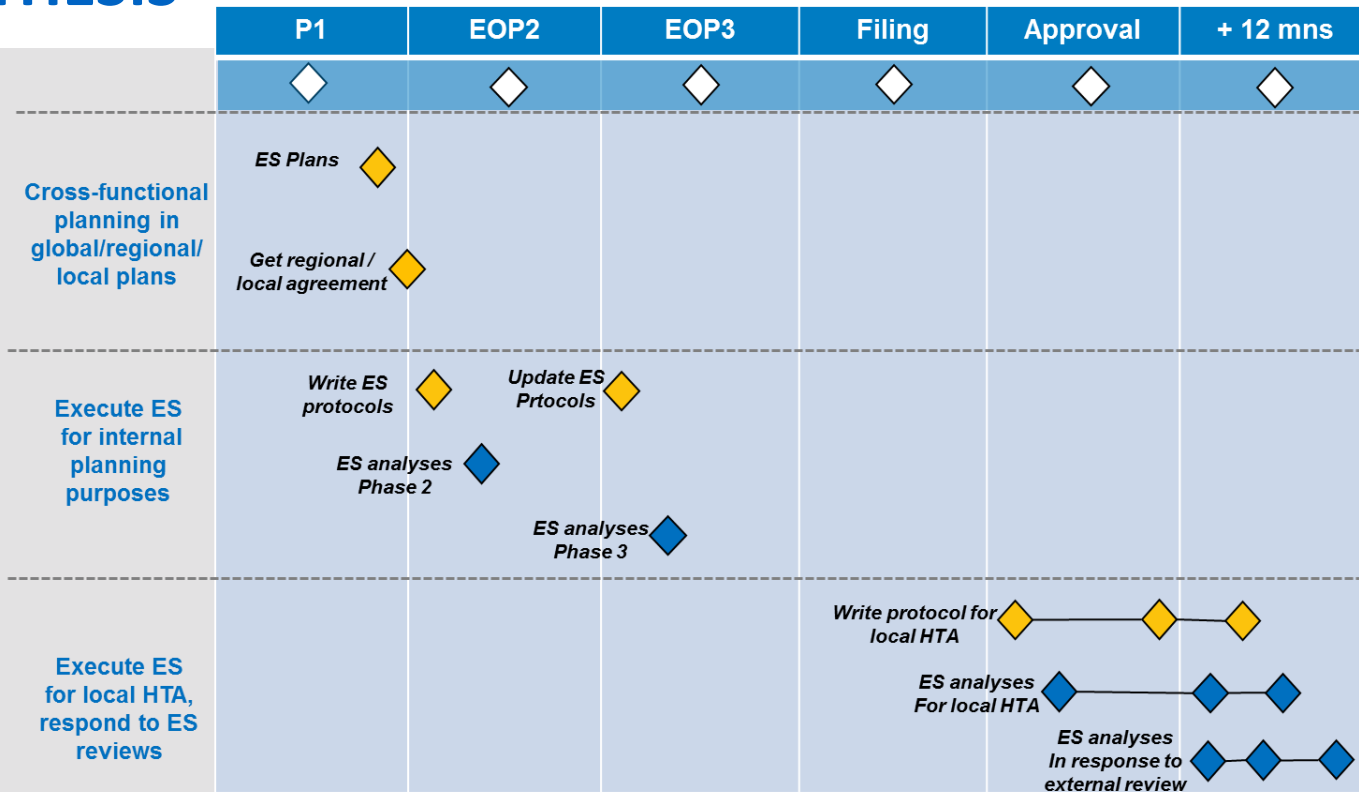
EXAMPLE: PHASE 2A DOSE-RESPONSE RELATIONSHIPS

A dose-response meta-analysis for quantifying relative efficacy of biologics in rheumatoid arthritis. Mandema et a.

EXAMPLE: SIMULATE COMPETITOR KEY TRIAL RESULTS DURING PHASE 2B

Treatment	Control
Drug 1	PBO
Drug 1	PBO
Drug 2	PBO
Drug 2	PBO
Drug 3	PBO
Drug 4	PBO
Drug 4	PBO
Drug 5	PBO
Competitor 1	PBO
Competitor 2	PBO
Competitor 2	PBO

0.25 0.50 0.75 1.00 1.20

Relative risk (< 1 favors treatment)

EXAMPLE: HTA SUBMISSION

Strontium

Denosumab

Alendronate

Raloxifene

Risedronate

1 Trial

2 Trials

4 Trials

Teriparatide

Etidronate

3 Trials

2 Trials

1 Trial

2 Trials

Zoledronate

1 Trial

Placebo

1 Trial

Ibandronate

········· Indirect analysis ——— Head-to-head study

Freemantle et al. Osteoporosis, International Osteoporosis Foundation and National Osteoporosis Foundation. 2012
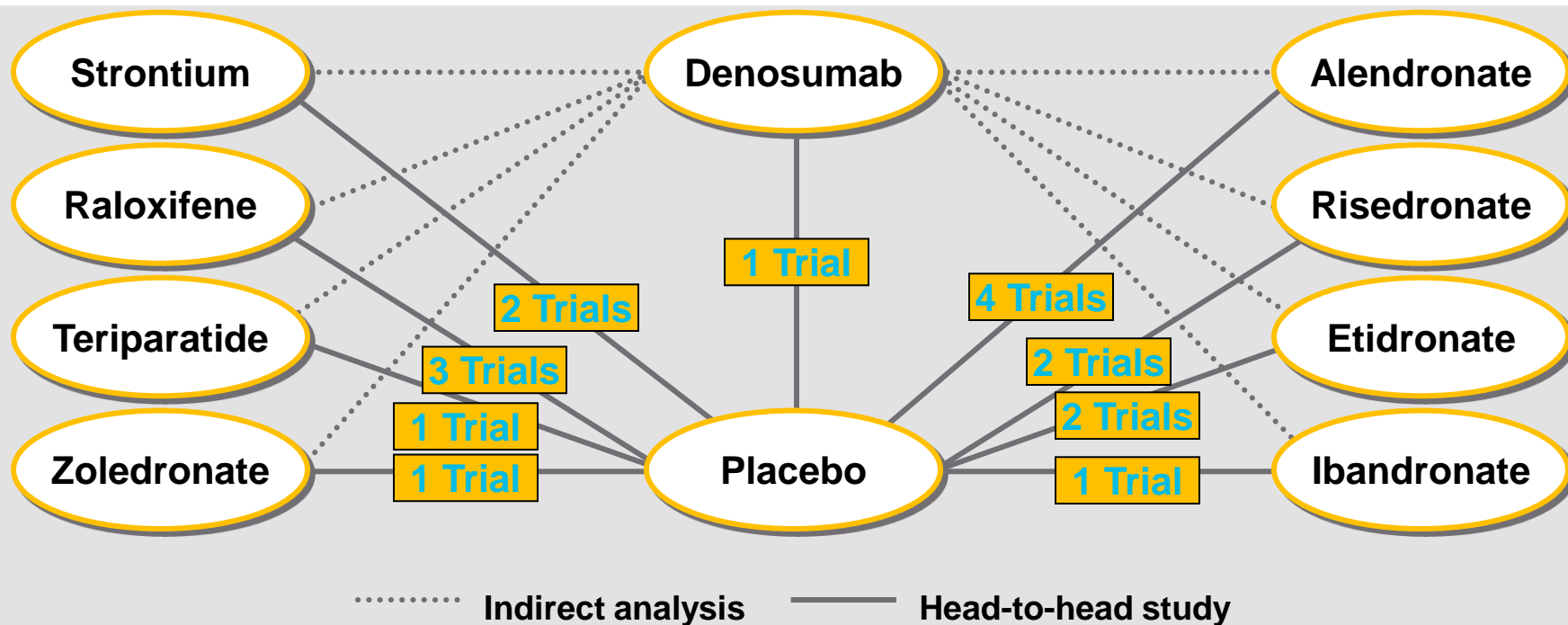
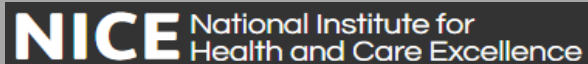**AMGEN**

EXAMPLE: RESPOND TO EXTERNAL REVIEWS

Traditional HTA Assessments

New Value Frameworks

AMGEN'S HTA EVIDENCE BASED METHODS PLATFORM

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HTA AGENCIES REQUIRE ROBUST, EVIDENCE-BASED METHODS

Scoping	Evidence Selection	Evidence Evaluation	Evidence Synthesis and Interpretation

Scoping
- Frames evaluation of comparative effectiveness, with defined populations, interventions, comparators, outcomes and study design (PICOS)

Evidence Selection
- Systematic Literature Review (protocol-driven)
- Inclusion/exclusion criteria aligned with PICOS criteria in scope

Evidence Evaluation
- Assessment of quality of evidence
- Assessment of feasibility of evidence synthesis
- Assessment of alternative synthesis methods

Evidence Synthesis and Interpretation
- Qualitative Analyses
- Quantitative Analyses
  eg - Network Meta-Analyses
- Evaluation of external validity
- Generalisability of evidence and results to local clinical practice

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ROLLING EVALUATION OF COMPARATIVE EFFECTIVENESS – P1 THROUGH TO FILING/LAUNCH

Comparative effectiveness evaluation	Timing	Methods for evidence selection/evaluation	Evidence synthesis	Informs
Preliminary evaluation of comparators only -little or no product data	Phase 1+	• Rapid Review - to identify key landmark comparator trials	Preliminary ES e.g. NMA	Phase II/III RCT design / HTA planning
Full evaluation vs new product -Includes Phase II/III RCT data -New comparators	Phase II Updated at Phase III and at Filing	• Full Systematic Literature Review (SLR) • Evidence synthesis Feasibility Assessment	Full robust evidence synthesis	HTA planning / Cost Effectiveness model
Customised evaluation -to meet country-specific requirements -Updated comparators -Revised methods	Regulatory filing/ Launch	• Update Systematic Literature Review (SLR) • Update review of Evidence synthesis Feasibility Assessment	Tailored evidence synthesis to meet country requirements	HTA readiness

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STRATEGIC ROLE FOR STATISTICIANS

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STRATEGIC ROLE FOR STATISTICIANS

- **Identify evidence gaps and ES needs**
- **Contribute to evidence generation strategy – populations, comparators, outcomes**
- **Contribute to systematic literature reviews**
- **Lead the ES feasibility assessment – which methods most appropriate**
- **Lead ES analyses – robust and fit for purpose**

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CONCLUSIONS

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EVIDENCE SYNTHESIS IS ESSENTIAL IN DRUG DEVELOPMENT

Put in place early a strategy for evidence synthesis for comparative effectiveness needs

- A rolling process for evaluation of comparative effectiveness needs P1 through to post launch

- Standardized, robust methods and processes for evidence selection, evaluation and synthesis aligned with HTA requirements

Statisticians have a key role in developing the evidence synthesis strategy

- Maximising evidence generation activities

- Planning and conducting robust evidence synthesis strategies and analyses

Evidence synthesis methodology is evolving and is becoming more complex

- Opportunities to integrate real world data with randomised controlled trials

- Lots of assumptions, potential biases and limitations which need careful assessment

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REFERENCE: EVIDENCE SYNTHESIS TECHNICAL SERIES DOCUMENTS (NICE)

TSD 1   Introduction to evidence synthesis for decision making

TSD 2   A general linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials (last updated Sept 2016)
WinBUGS system(.odc) files (last updated Sept 2016)

TSD 3   Heterogeneity: subgroups, meta-regression, bias and bias-adjustment

WinBUGS system(.odc) files

TSD 4   Inconsistency in networks of evidence based on randomised controlled trials (last updated April 2014)
WinBUGS system(.odc) files (last updated March 2013)

TSD 5   Evidence synthesis in the baseline natural history model
WinBUGS system(.odc) files

TSD 6   Embedding evidence synthesis in probabilistic cost effectiveness analysis: software choices

TSD 7   Evidence synthesis of treatment efficacy in decision making: a reviewer's checklist
This report refers to a checklist table, which can be downloaded in Word version here

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