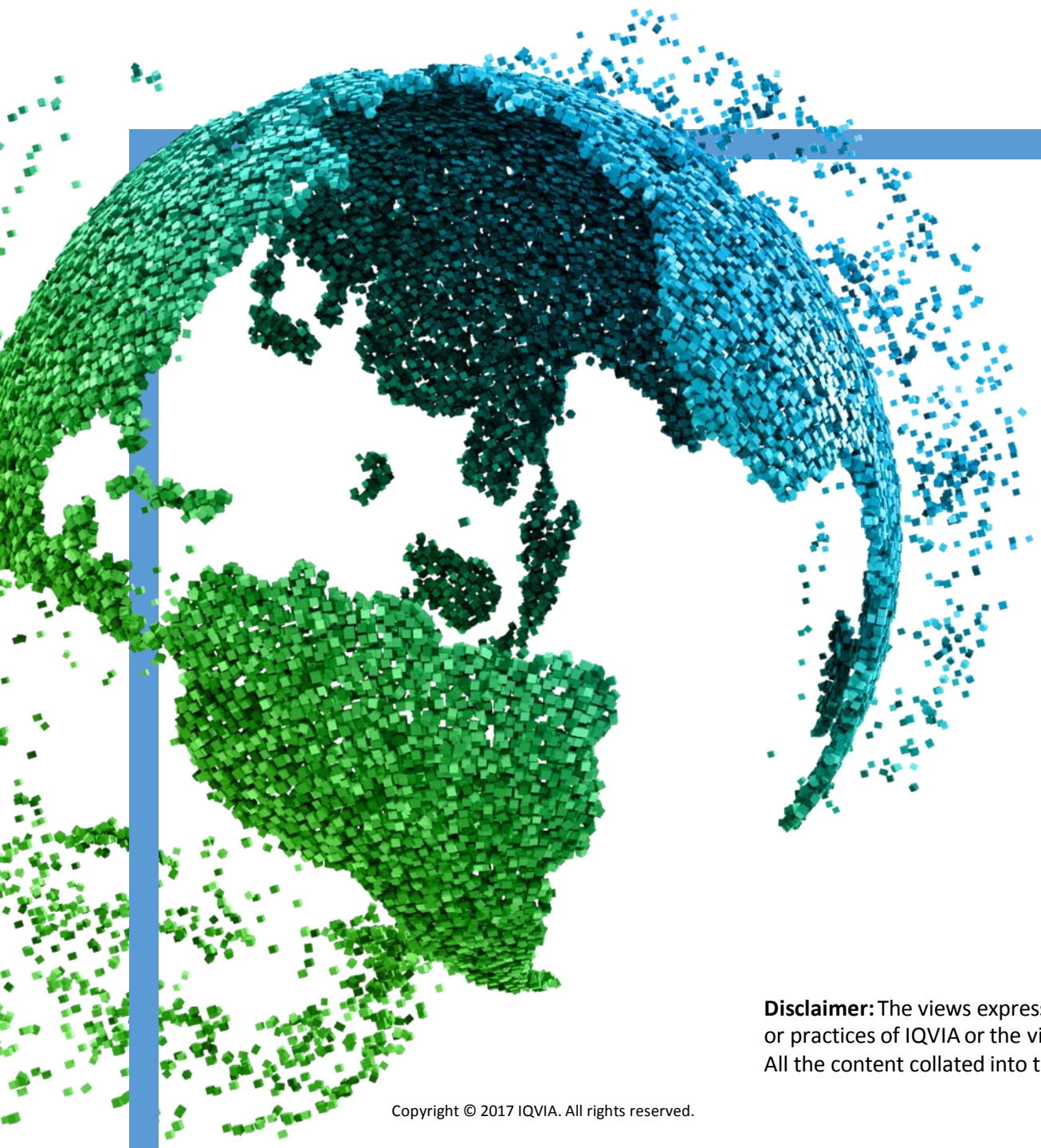

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Real World Evidence Generation and Applications

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Abstract

Applications of Real World Evidence (RWE) are growing, more relevant to patient and provider decision-making, supportive of payment and reimbursement decisions and useful for regulatory purposes.

RWE is transforming innovative product R&D support better and faster clinical development and track the market for commercial success. The 21st Century Cures Act of 2016 calls upon the US FDA to evaluate the use of RWE to support approval of new indications for previously approved drugs and to support or satisfy post approval study requirements.

RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of Real world data (RWD). RWD of primary type, collected specifically for research purpose, are generally obtained from study-specific case report forms, electronic medical and health records, and/or clinical outcomes assessments. These data are collected in interventional phase IV studies and in non-interventional prospective observational studies, pragmatic randomized clinical trials (pRCTs), patient registries and health surveys. RWD of secondary type are often obtained from Clinical setting through electronic medical records (EMRs), Clinical chart reviews where EMRs do not yet exist, claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices.

With the range of data, advanced analytics expertise and technology now available it is vital to leverage real-world insights for all global stakeholders to serve human health. Couple of RWE case studies will be presented with use of statistics analytical and visualization approaches.

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Clinical Research for Drug Development

Randomized Controlled Trials (RCT)

- One of the most powerful tools clinical researchers possess
  - Enables them to evaluate the effectiveness of new (or established) therapies while accounting for the effects of unmeasured confounders and selection bias by indication
- However, RCT reputation has suffered of late, owing to reasonable concern about excess complexity, expense, and time required to recruit study participants, as well as inadequate representativeness
  - E.g., results are not applicable to real-world patients

Problems with Pivotal Phase 3 RCTs

Population - Often restricted, and not (totally) representative of broader target population to be treated

Length of follow-up - often restricted to shorter term surrogate outcomes

Other concomitant medication may be limited (not appropriate for all jurisdictions) or excluded

All these problems mean that decision makers(especially HTA) are faced with considerable uncertainty

Effectiveness vs. Efficacy

- **Efficacy** – The change in a key clinical measure compared to placebo in a cohort of well-defined patients under a standardised care protocol.
- **Relative efficacy** – The change in a key clinical measure compared to a standard alternative in a cohort of well-defined patients under a standardised care protocol.
- **Relative effectiveness** – The change in a variety of endpoints of interest to patients and providers compared to the usual care provided in the population of patients identified as eligible for treatment by clinicians under the normal care provided by the healthcare system, subject to free and variable clinician and patient behaviour.

Effectiveness may be defined as the impact of drug efficacy, when all "interactions" are at play

- The real/actual use of drug
- The patient/disease-related characteristics
- The healthcare system-related characteristics

Decision Making Perspective:

Pharma R&D

Earlier understanding of effectiveness of new products. Better targeting to patients who will gain the greatest benefits.

Regulatory

Increasing interest. Potential for improving public health if **efficacy-effectiveness** gap identified.

HTA

Require evidence of benefit of treatment compared with standard of care in own jurisdiction.

Patients& carers/Clincians/Payers

PICOS Framework – Effectiveness Issues

Population
Study population not consistent with the population for which reimbursement is being sought
Uncertainty of treatment effects in subgroups based on pivotal trial populations

Intervention

Study medication schedule (dose, dose titration/ escalation, frequency, route of admin, monitoring) inconsistent with routine practice
Effectiveness likely impacted by adherence (of intervention and/or comparators) in routine practice

Comparator
Study comparator(s) do not include current standard of care (SOC) for the reimbursement population
Indirect comparison vs SOC is uncertain due to a small number of trials from which to form a valid network

Outcome
Primary Study outcomes of limited interest from reimbursement perspective
Study underpowered to deliver meaningful results for outcomes of interest (e.g. HRQoL)

Study Design/Setting
'Treatment pathway' (refers to the sequence of previous treatments received, based on patient selection criteria and response to previous therapies, often reflected in clinical guidelines) there may be variations across countries or health centres within countries
Trial settings and sites do not reflect usual clinical practice
Time and cost pressures may result in shorter clinical studies measuring outcomes over relatively short time periods, requiring modelling of longer-term effectiveness endpoints to be undertaken

Real World Data

Phase 4 studies also an important phase of drug development. In particular, the real world effectiveness of a drug as evaluated in an observational, non-interventional trial in a naturalistic setting which complements the efficacy data that emanates from a pre-marketing randomized controlled trial (RCT).

Phase 4 trials are conducted for a variety of reasons, which may include

- Post-marketing surveillance (PMS) studies
- To investigate a marketed drug in pediatric patients,
- Compare a drug head-to-head with another drug,
- Investigate the effect of a drug at a lower/higher dose or with different administration schedules,
- Study a drug in combination with other drugs, or testing a drug for other indications.

Real World Data

Patient Registries

Patient registries are organised systems with a 'predetermined scientific, clinical or public health purpose'. They are used to prospectively collect, analyse and disseminate data on a group of patients with specific characteristics in common, for example people with a particular condition, having a certain treatment or using a health-related service. They are cohort studies that are developed with a predetermined health-related aim. Patient registries evolved from paper-based records in a doctor's office to data collected electronically, usually in databases. They often containing large amounts of data, such as clinical information or biological samples stored in biobanks.

Patient registries may be classified as:

- disease or condition registries, based on populations with a particular disease or group of diseases
- product-specific registries, based on populations using specific products (often developed by manufacturers to assess long-term safety and adverse effects).

Examples of patient registries

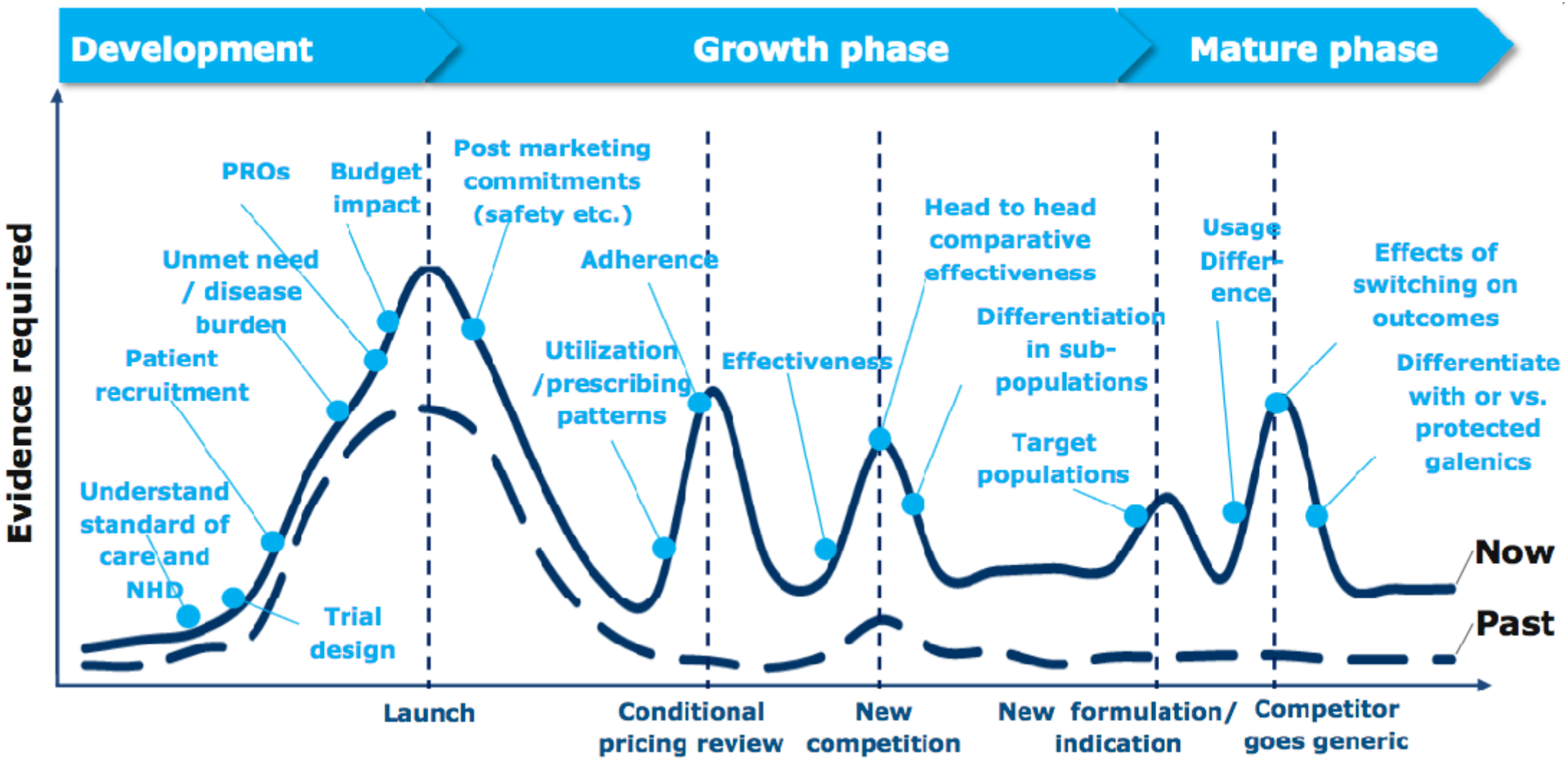
- The European Cystic Fibrosis Society registry is used to collect data on cystic fibrosis and its treatment, both to improve treatment and provide data for epidemiological research.
- The Cross-border Patient Registries Initiative (PARENT) has developed a 'registry of registries' that lists over 200 patient registries across Europe.

Real World Evidence Generation: Pragmatic Trials

Pragmatic trials aim to measure the relative effectiveness of treatment strategies in real-world clinical practice, as first described by Schwartz and Lellouch in 1967. They provide evidence of the added value of a treatment strategy in routine clinical practice, while maintaining the strength of a randomised controlled trial.

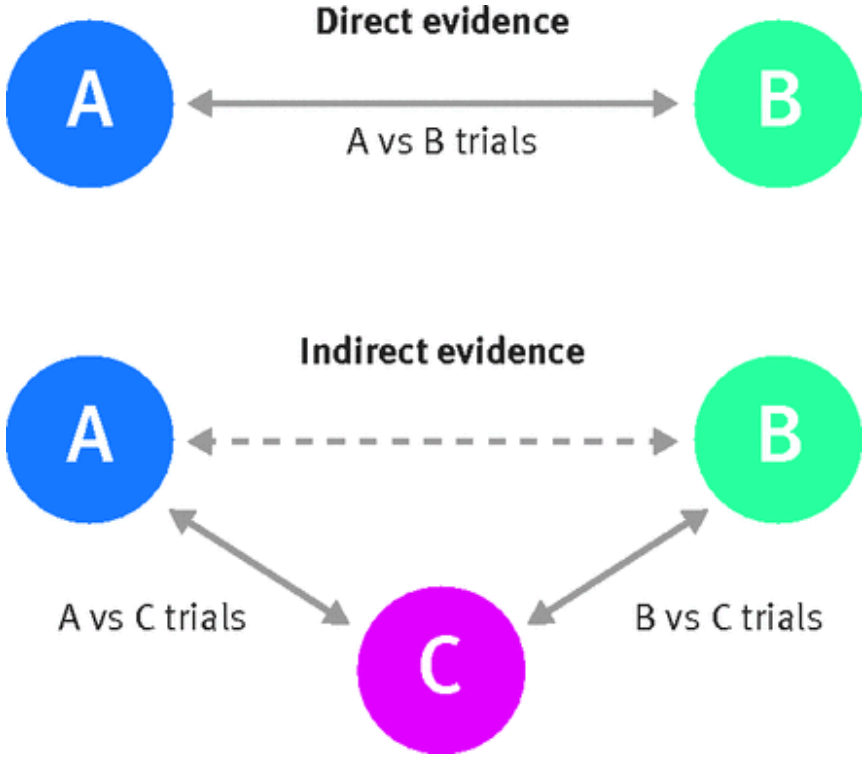
Can treatment work? ➔ EFFICACY - Hypothesis testing - Ideal circumstances	WHAT?	Does treatment work? ➔ EFFECTIVENESS - Comparing treatment strategies - Usual care
Assess cause – effect of drug	WHY?	Inform decision makers
Minimize variation: - Rigid protocol	HOW?	Maximise generalisability: - Protocol reflecting usual care
Selective inclusion	WHO?	Broad inclusion
- Data collection > usual care - Outcomes research relevant	METHOD?	- Data collection = usual care - Outcomes clinically relevant

RWE through out Product Life Cycle



Source: IMI GetReal

Network Meta Analysis (NMA)



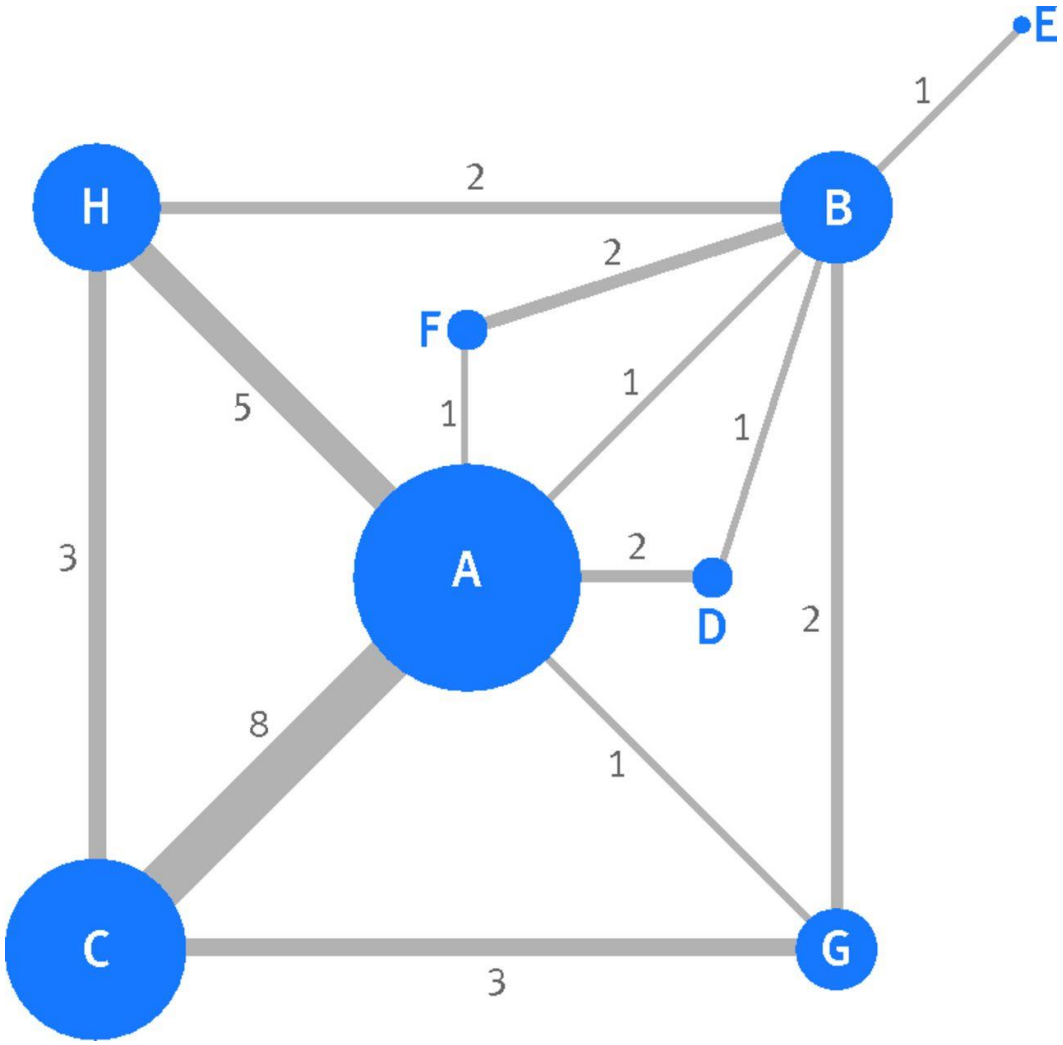
Visual representation of direct and indirect evidence toward the comparison of A versus B

The benefit of treatment A versus B can be inferred from the indirect evidence by comparing trials of just treatment A versus C with trials of just treatment B versus C, in addition to the direct evidence coming from trials of treatment A versus B

"Consistency" assumption

Richard D Riley et al. BMJ 2017;358:bmj.j3932

Example: Comparison of Eight Thrombolytic Treatments after acute Myocardial Infarction



Aim to estimate the relative efficacy of eight competing treatments in reducing the odds of mortality by 30-35 days

- Network map of the direct comparisons available in the 28 trials examining the effect of eight thrombolytics (labelled A to H) on 30-35 day mortality in patients with acute myocardial infarction.
- Each node (circle) represents a different treatment, and its size is proportional to the number of trials in which it is directly examined.
- The width of the line joining two nodes is proportional to the number of trials that directly compare the two respective treatments (the number is also shown next to the line).
- Where no line directly joins two nodes (eg, treatments C and D), this indicates that no trial directly compared the two respective treatments.

With 8 treatments there are 28 pairwise comparisons of potential interest; Only 13 of comparisons were directly reported in at least one trial

Richard D Riley et al. BMJ 2017;358:bmj.j3932

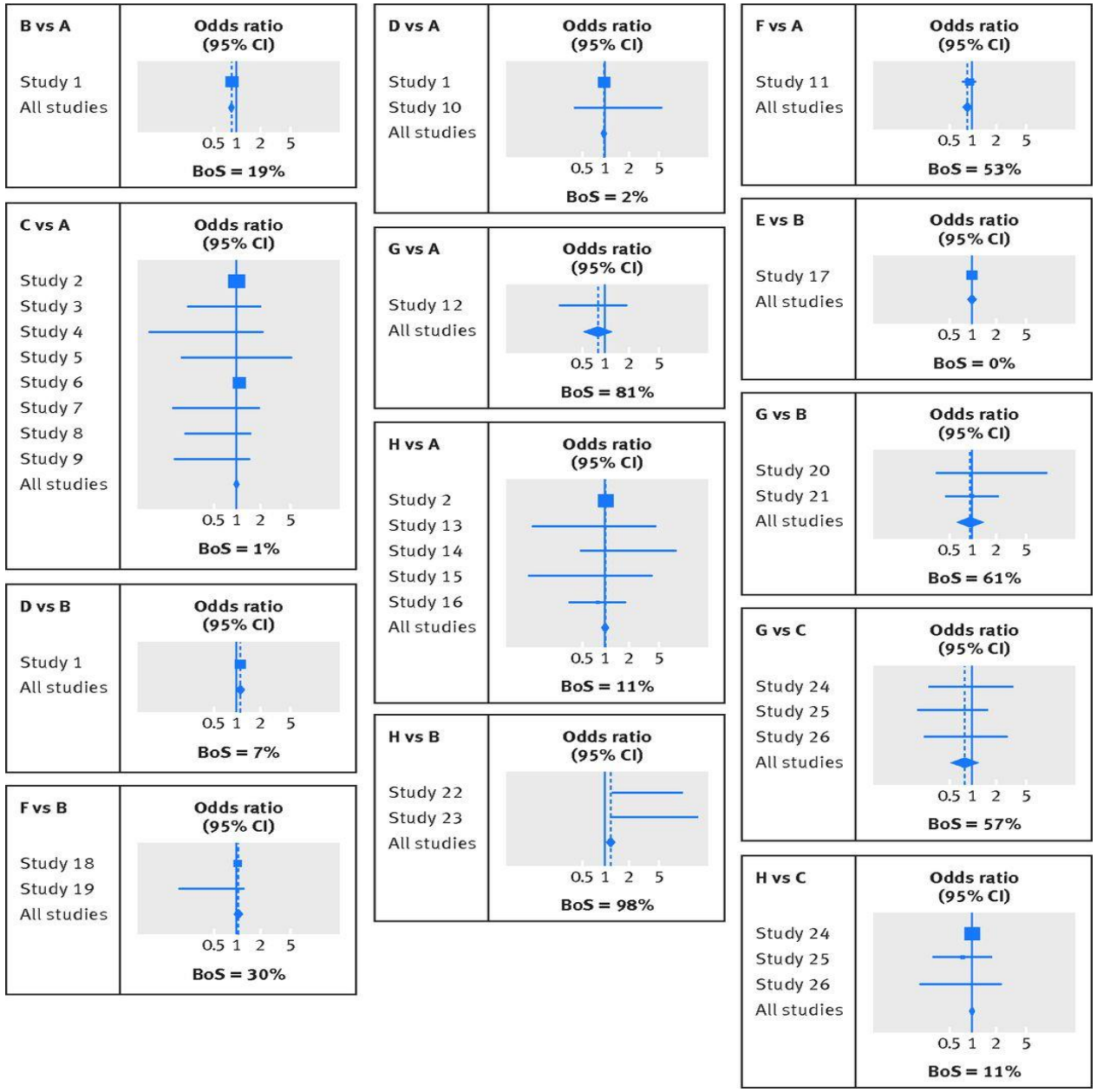
Network Meta Analysis Results
Extended Forest Plot

- Network meta-analysis through a multivariate random effects meta-regression model applied
- Extended forest plot showing the network meta-analysis results for all comparisons where direct evidence was available in at least one trial.
- Each square denotes the odds ratio estimate for that study, with the size of the square proportional to the number of patients in that study, and the corresponding horizontal line denotes the confidence interval.
- The centre of each diamond denotes the summary odds ratio from the network meta-analysis, and the width of the diamond provides its 95% confidence interval.
- BoS denotes the borrowing of strength statistic, which can range from 0% to 100%

Example: Treatment effect of H versus B in the NMA of all 28 trails, Odds ratio 1.19, 95% CI 1.06 to 1.35

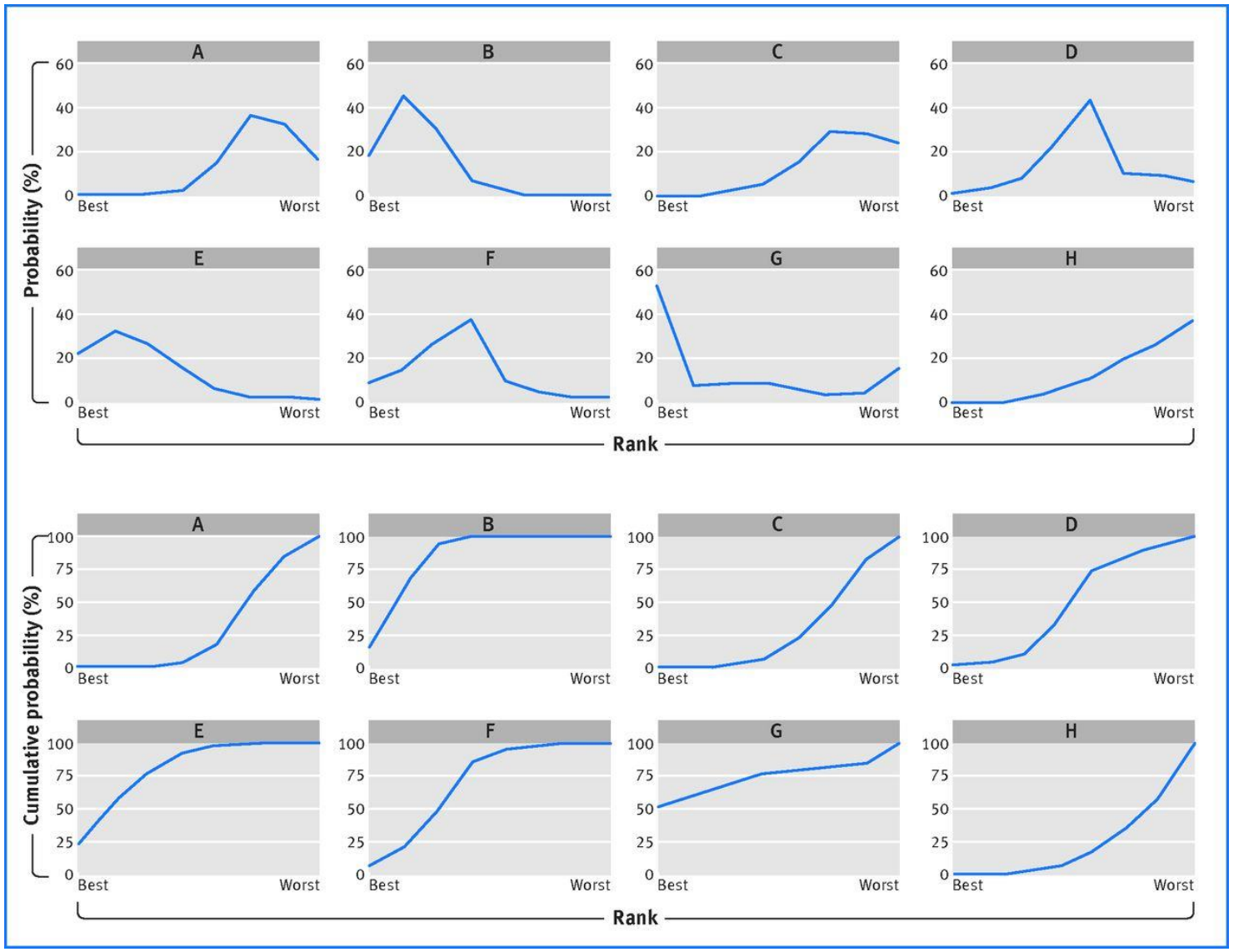
Standard pairwise meta-analysis of two trials, summary

Odds ratio 3.87, 95% CI 1.74 to 8.58



Richard D Riley et al. BMJ 2017;358:bmj.j3932

Ranking Probability for Each Treatment



- Simulation or resampling methods, use of thousands of samples from distribution of summary treatment effects, to identify the percentage of samples(probability) that each treatment has the most (or least) beneficial effect.

- Plots of the ranking probability for each treatment considered in the thrombolytics network meta-analysis.
- (Top panel) the probability scale;
- (Bottom panel) the cumulative probability scale

- Treatment G has the highest probability(51.7%) of being most effective at reducing the odds of mortality, followed by treatments E (21.5%) and B(18.3%)
- Based on the Surface Under the Cumulative Ranking curve(SUCRA), treatments B and E have the best mean ranks, followed by treatment G.

Network Meta Analysis

To predict real-world effectiveness using individual participant and/or aggregate data

- Meta-analysis methods combine quantitative evidence from related studies to produce results based on a whole body of research
- Studies that do not provide direct evidence about a particular treatment comparison of interest are often discarded from a meta-analysis of that treatment comparison
- Network meta-analysis methods simultaneously analyse multiple treatments which allows more studies to contribute towards treatment comparison
- Summary results for each treatment comparison now incorporate indirect evidence from related treatment comparisons, in addition to any direct evidence
- This often leads to a gain in information, which can be quantified by the "borrowing of strength" statistic, BoS (the percentage reduction in the variance of a summary result that is due to indirect evidence)
- Network meta-analyses gain information through a consistency assumption, which should be evaluated in each network where possible. There is usually low power to detect inconsistency, which arises when effect modifiers are systematically different in the subsets of trials providing direct and indirect evidence
- Network meta-analysis allows multiple treatments to be compared and ranked based on their summary results. Focusing on the probability of being ranked first is, however, potentially misleading: a treatment ranked first may also have a high probability of being ranked last, and its benefit over other treatments may be of little clinical value
- Novel network meta-analysis methods are emerging to use **individual participant data**, to evaluate dose, to incorporate **"real world" evidence** from observational studies, and to relax the consistency assumption by allowing summary inferences while accounting for inconsistency effects

Propensity Weighting Method for Relative Effectiveness

- The propensity weighting method uses an external real-world data (RWD) source to derive propensity scores. These are used to reweight data available from an RCT to provide estimates of relative effectiveness that may be more relevant for decision makers.
- In this context the 'propensity score' denotes the approximate probability of a patient being enrolled in the trial of interest.

Case Study:

- In a GetReal case study the use of this method was explored using RCT data (JMDB trial) and RWD data (FRAME study) for pemetrexed in stage IIIB/IV non-small-cell lung cancer (NSCLC). Data were made available to GetReal by GetReal partner. Estimates of the relative effectiveness of pemetrexed + cisplatin vs. gemcitabine + cisplatin in stage IIIB/IV NSCLC were generated for the population described by the FRAME study, assuming this to represent a target population for reimbursement.
- The analysis was carried out as follows:
- Patient data from the JMDB and FRAME studies were combined, using a membership indicator to denote each study.
- A logistic regression model was constructed using the membership indicator as the dependent variable and the other covariates as the independent variables.
- Standardised differences were used to examine the propensity-adjusted balance between the source studies and between the weighted treatment cohorts in the RCT (JMDB study).
- Each patient's propensity score was calculated by applying the logistic model to the given covariates for that patient.

Propensity Weighting Method for Relative Effectiveness (Case Study)

- Efficacy in the RCT was re-calibrated relative to the FRAME population using the general approach proposed by (Cole & Stuart 2010). Each patient in the JMDB trial was assigned a weight based on the inverse of their propensity score, resulting in a weighted trial population appearing to represent a random sample from the FRAME study.
- The quality of the calibration was assessed by comparing demographic characteristics, and the balance in baseline covariates after weighting, between the RCT study groups.
- Overall and progression-free survival was computed for each patient in the trial, and calibrated efficacy was estimated as the hazard ratio (HR) from a weighted Cox proportional hazards model comparing the study arms.
- Adjusted outcomes for treatments in the reweighted RCT were also compared with outcomes in FRAME for the same treatments, using Cox proportional hazards and Kaplan-Meier methods.
- The variability and confidence interval of the calibrated efficacy was assessed using a non-parametric bootstrap procedure.
- As a sensitivity analysis, a more refined weighting algorithm was also applied, using entropy weights (Hainmueller 2012).

Propensity Weighting Method for Relative Effectiveness (Case Study)

Results with propensity weighting compared to the original analysis

Category	Treatment	N	Median OS (months)	Hazard ratio	95% LCL	95% UCL
No weighting	Gemcitabine	608	10.15	0.851	0.746	0.972
	Pemetrexed	614	11.14			
					Bootstrap 2.5 percentile	Bootstrap 97.5 percentile
Weighted	Gemcitabine	593	10.15	0.915	0.599	1.333
	Pemetrexed	616	15.57			

Abbreviations: HR – hazard ratio, OS – overall survival, LCL – lower confidence level, UCL – upper confidence level.

The reweighted analysis of the clinical trial yielded a HR closer to 1, with greater uncertainty (HR: 0.91, 95% CI: 0.60 to 1.33) compared with the original (HR: 0.85, 95% CI: 0.75 to 0.97) in a similar population in the clinical trial.

Overall survival differences appeared to be more pronounced. Sensitivity analyses to both the methods of reweighting and the inclusion of baseline covariates gave broadly similar results.

Effectiveness challenge addressed by the method

This analytical method allows a real-world treatment effect to be predicted based on trial efficacy data, while accounting for a possible efficacy-effectiveness gap. The gap here is due to the trial population having different characteristics to the target population for (local) reimbursement.

Summary

- Real-world evidence (RWE) is the evidence derived from the analysis and/or synthesis of real-world data (RWD)
- Robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process
- Summarise and synthesis real-world evidence using network meta-analysis
- Explore and Model effectiveness in the real world and predict the outcomes which bridge the efficacy-effectiveness gap, using propensity weighting method and model-averaging approach to predict long-term effectiveness
- Adjust for bias in non-randomized and observational studies, using various methods that adjust for known and unknown confounding
- Assure quality and credibility of RWE

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THANK YOU