Comparing Treatments By Combining Data From Various Randomized And Observational Studies:
Introduction To Concept, Methods, And Application

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Challenges of heterogenous data

- Numerous challenges remain in synthesizing data across non-randomized studies
- Assessing the quality of evidence and study design
- Modelling systematic and non-systematic bias

**Randomized Controlled Trials (RCTs)**
- Low Bias
- Expensive
- Limited Scope
- Rare

**Non-Randomized Studies (NRSs)**
- High Bias
- Inexpensive
- Broad Scope
- Common

How do we connect them?
- Meta-Analysis
- Naive Pooling
- Design Adjusted Synthesis
- Hierarchical Modeling
- Individual Patient Data
- Sensitivity Analysis

Benefits of integrating non-randomized data

- Combining data yields larger sample sizes and populations that are more representative of target populations
- In situations where treatment has a direct impact on survival and clinical equipoise is lost
- Adherence rates
- Exposure to lines of previous therapy
- Extension studies
NICE guidance on the use of non-randomized data

NICE DSU TECHNICAL SUPPORT DOCUMENT 17:
The use of observational data to inform estimates of
treatment effectiveness in technology appraisal:
Methods for comparative individual patient data

The use of real world data for the estimation of
treatment effects in NICE decision making

NICE priority research requirements

• Manual for the design, analysis and interpretation of results from observational studies into decision making for use in managed entry agreements.

• Research into the extent to which observational designs can complement or substitute those of RCTs in resolving the biases and uncertainties typically encountered.
Data integration concept

Synergies From Integrating Randomized Controlled Trials and Real-World Data Analyses
Mehdi Najafzadeh, Joshua J. Gagne and Sebastian Schneeweiss

- Goal was to bridge three pivotal RCTs of pregabalin (398 North American patients) and large observational study (3159 German patients) in a single platform to predict the potential level of response to pregabalin
- Matched patients from observational study to data from RCT patients, creating six matched datasets
- Validated predictive regression models in each of the six matched datasets against observational data patients that did not match
Hierarchical cluster analysis to identify patient clusters which RCT patients could be matched

- Only 38% of the Observational Study patients matched with these RCT patients.
- However, the other 62% of Observational Study patients’ responses could be correctly predicted with the cluster-based longitudinal models.
- Improved performance of the models based on blending of randomized and observational data to reduce the covariate biases in observational studies.


Framework for expedited evidence generation I

A: One-off analysis with full risk adjustment*  
B: Repeat analysis in rapid cycles each time data refresh*

Framework for expedited evidence generation II

Part 1: An introduction to methods of combining evidence from studies of different design

Part 2: A healthcare payer perspective

Susanne Schmitz, PhD
In this presentation

- We refer to those parameters, which are classically informed by RCT evidence exclusively; most importantly treatment effects.

Objective:
HOW CAN WE Appropriately combine DATA OF DIFFERENT DESIGN?

Comparative Aggregate Data

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Part 1: Introduction to methods

Comparative Aggregate Data

• Naïve Pooling
  Pools across all available studies, not differentiating between designs.
  
  - Simple implementation using standard methods.
  - Cannot account for or measure any differences between designs.
  - Same weightings apply to all designs.

• As prior information
  Observational data is analysed separately and the resulting posterior distribution is then used as prior information for the RCT model.
  
  - Natural implementation in the Bayesian framework.
  - Possible to incorporate bias adjustments and to down weight observational evidence.
  - Can only distinguish between 2 designs.
  - Cannot measure between design heterogeneity.
Part 1: Introduction to methods

Comparative Aggregate Data

- 3-level hierarchical model
  Introduces a study type level between the study level and the overall level allowing for heterogeneity between different designs.
  - Natural implementation in the Bayesian framework.
  - Possible to incorporate bias adjustments and to down weight observational evidence.
  - Multiple designs possible.
  - Measures between design heterogeneity.

BIAS ADJUSTMENT: We can shift or inflate the variance of the prior distribution. If bias is unknown, sensitivity analyses are useful to evaluate the impact.
Comparative Aggregate Data

- 3-level hierarchical model
  Introduces a study type level between the study level and the overall level allowing for heterogeneity between different designs.

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- Multiple designs possible.
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\[
Y_i \sim \text{Norm} (\mu_i, \eta) \\
\mu_i \sim \text{N}(\mu, \tau) \\
\]
i = 1, ..., N designs

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Naïve Pooling
- Combine designs
- Bias adjustment
- Measure heterogeneity
- Multiple designs
- Adjust for individual covariate effects

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Meta regression based on study level co-variates investigates between study heterogeneity.

However, aggregate level analysis has low power compared to IPD analyses. There is also the risk of ecological fallacy.
Part 1: Introduction to methods

Individual Patient Level Data (IPD)

All the above analyses can be generalised to include IPD, where available. (see for example Sutton et al 2008, Riley et al 2008, Saramago et al 2012.)

Such analyses can reduce bias, as heterogeneity can be reduced and regression based on subject level covariate data provides more precise estimates and does not suffer from the same issues as aggregate data meta regression.

- Analyse data homogeneously
- Explore the influence of covariates on individual patient level

Single armed studies

In the assessment of efficacy of treatments, we are **ALWAYS** interested in **RELATIVE EFFECTS**.

E.g. We are not interested in the cure rate of treatment A, but how this rate relates to the cure rate of treatment B.

A single armed trial does **not** answer this question.
Part 1: Introduction to methods

Single armed studies

In order to answer the question of relative effects, we need to create a comparator arm. Several approaches have been proposed:

- Historical controls
- Match based on covariates
- Propensity score
- Matched Adjusted Indirect Comparison
- Simulation studies

Requires IPD for at least one trial.

IPD methods can adjust for the effect of KNOWN covariates; not for unknown covariates.

Observational studies and disconnected networks

- Thom et al (2015) propose the use of a random effects on baseline model to incorporate single armed observational studies.

- Leahy et al (2016) conduct a simulation study to explore under which circumstances single arms matched to the remaining network are beneficial. Benefit depends among others on the SD of the study effect and covariate effect.

- Schmitz et al (2017) explore the space of possible matches to capture associated uncertainty.
Part 2: A healthcare payer perspective

Ideally a decision maker would base a decision on a meta analysis of several large, well conducted RCTs of suitable follow up in populations representative of his jurisdiction.

- minimise bias
- minimise uncertainty

Early access to medication and lack of comparative evidence reduces the quality and quantity of information available for evidence based decision making.

- increased bias
- increased uncertainty

BUT: A decision needs to be taken, regardless of the uncertainty.

- Observational evidence can provide additional information, especially when other evidence is sparse.

- However, the use of observational data comes with a greater risk of bias and uncertainty and does not limit the need for high quality randomised controlled trials.

- In many jurisdictions, the risk associated with additional uncertainty is carried by the decision maker alone.

- Risk sharing schemes may provide options of reducing the impact of a wrong decision in such situations.
Part 2: A healthcare payer perspective

- Patients in clinical trials do not necessarily represent the general patient population, observational studies may provide useful insights into the generalisability of effects.
- Observational studies may provide useful insights into the differences of individual behaviour and subsequent effectiveness of treatments in real life settings.

A Manufacturer’s perspective

- Farhan Mughal, MRPharmS, MSc
- Associate Director, HEOR and Pricing, Celgene Ltd
Disclaimer

- All views expressed here are from a personal perspective and not to be taken as representing those of Celgene Ltd, any industry group, or NICE

Objective to make innovative technologies available to patients as soon as possible

- Various data sources often exist to inform clinical effect estimates
- Objective is to present unbiased estimates of relative effectiveness and safety
  - RCT data remains the Gold standard however not always available and has its limitations
- Greater focus in recent times on how non-RCT data could be used in decision-making
- However, there is still a general reluctance to move away from RCT data
- Disconnect between regulatory and payer evidence requirements
Early access to medicines: Challenges from a Manufacturers perspective

• Medicines are becoming more and more specialised over time
• Regulatory approval processes (FDA and EMA) are adapting with the changing landscape in drug development
  • Fast track routes for Regulatory approval such as EAMS, PRIME, Adaptive pathways
• Availability of well conducted Phase 3 RCT against relevant comparator
  • Ethics where no standard of care exists
• Evidence requirements for Regulatory approval versus HTA
  • Phase 1 or Phase 2 data
  • Single arm trials, “Immature” data...
  • Are Payers comfortable with making decisions on immature/limited evidence bases
• Are there any solutions...

NICE are seeking to make decisions earlier in the drug development path

• Current proposals on increasing capacity and maximising efficiencies in the TA program including earlier submissions for oncology/non-oncology products
• Recent Government proposals on the Accelerated Access Pathway in the UK proposing faster access for the most promising therapies
• With earlier assessment may come greater uncertainty
• Increasing use of RWD as part of managed access agreements will require adequate assessment of uncertainty surrounding treatment effects
• Recent NICE DSU paper but further methodological guidance is welcome on combining RCT and non-RCT evidence in reimbursement decision-making
• EXAMPLE - Single arm clinical trials are increasingly being used to support licensing of drug therapies
HTA Decisions Based On Phase 2 Data for Selected Drugs


CONCLUSION

This review found that using Phase 2 alone is not an absolute barrier to reimbursement, but the uncertainty stemming from a less comprehensive evidence base may influence payers’ decisions.

Outcomes-based contracting has been increasing

Overview of the Cancer Drugs Fund process

1. All new cancer drugs expecting to be licensed are referred to NICE prior to Marketing Authorisation
2. NICE makes an initial recommendation based on clinical and cost effectiveness
3. Interim funding is provided via the CDF whilst NICE make their final recommendation
4. NICE makes final recommendation. Drugs entering the CDF must meet commercial requirements
5. CDF drugs are evaluated against specific RWE criteria and for a duration necessary to resolve uncertainty
6. After this period, drugs through the CDF are then given a ‘yes’ or ‘no’

Further considerations

- Greater collaboration between Regulators, Payers and Manufacturers on the design of clinical studies should be included in formal scientific advice discussions to ensure the design of such studies are likely to meet Payer needs prior to them being performed
  - NICE Joint Scientific Advice with Regulatory

- Introduction of flexible pricing models, such as outcomes based pricing, may allow for creative solutions to ensure that the risk is shared between the manufacturer and the Payer
Conclusion

• Steps have been made forward in the acceptance of non-RCT data for purposes of estimating treatment effect
  • Recent NICE DSU guidance is one example
• However, there is still some way to go...
• Appropriate use of non-RCT data could be used to reduce uncertainty (rather than increase uncertainty)
• The future drug development landscape requires that routes exist to include non-RCT data in reimbursement decision-making to prevent delays in access to innovative new medicines for patients
• Solutions such as conditional reimbursement, managed access agreements, flexible pricing models, underpinned by RWE collection, may help to reduce uncertainty and share some risk with the Payer

Live Polling Questions
Poll: Combining RCT and non-randomized data will be useful in my work/organization?

Poll: “As a payer, I am inclined to use results from research efforts combining RCT and non-randomized data at this time”
Poll: “As a manufacturer, I am inclined to use results from research efforts combining RCT and non-randomized data at this time”

Poll: “I would be more inclined to use evidence from combining RCT and non-randomized data, only after the issuance of more methodological guidance”
Poll: Quantifying and clearly communicating the uncertainty associated with the use of non-randomized data can advance the implementation of risk-sharing agreements

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