Comparing Treatments By Combining Data From Various Randomized And Observational Studies:

Introduction To Concept, Methods, And Application

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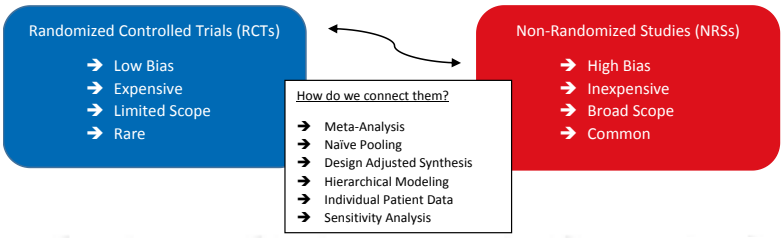
Challenges of heterogenous data

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



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

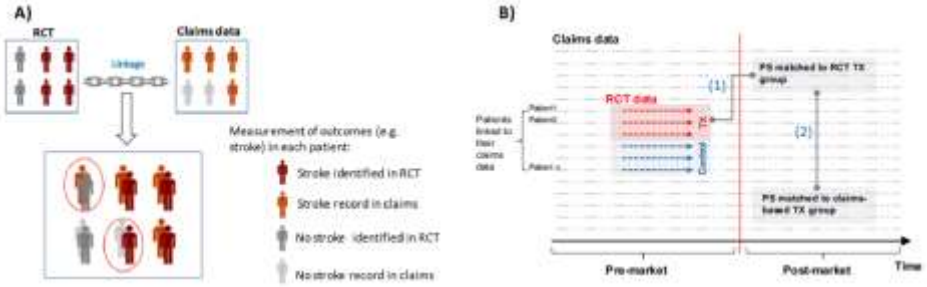
- Manual for the design, analysis and interpretation of results from observational studies into decision making for use in **managed entry agreements.**

- 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[1], Joshua J. Gagne[1] and Sebastian Schneeweiss[1]



Najafzadeh M, Gagne JJ, Schneeweiss S. Synergies From Integrating Randomized Controlled Trials and Real-World Data Analyses. Clin Pharmacol Ther. 2017 Oct 16.

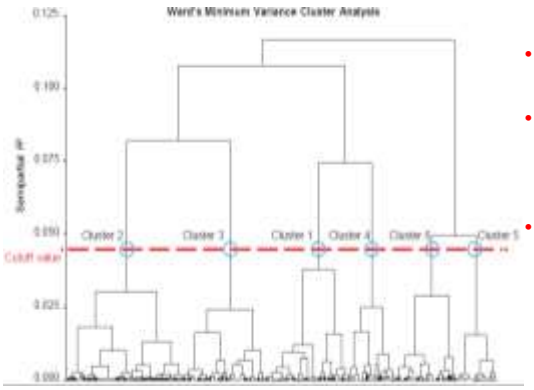
Integrating data from randomized controlled trials and observational studies to predict the response to pregabalin in patients with painful diabetic peripheral neuropathy

Joe Alexander[1*], Roger A. Edwards[2*], Alberto Savoldelli[3], Luigi Manca[3], Roberto Grugni[3], Birol Emir[3], Ed Whalen[4], Stephen Watt[3], Marina Brodsky[3] and Bruce Parsons[3]

- 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

Alexander J, Edwards RA, Savoldelli A, Manca L, Grugni R, Emir B, Whalen E, Watt S, Brodsky M, Parsons B. Integrating data from randomized controlled trials and observational studies to predict the response to pregabalin in patients with painful diabetic peripheral neuropathy. BMC Med Res Methodol. 2017 Jul 20;17(1):113.

Hierarchical cluster analysis to identify patient clusters which RCT patients could be matched

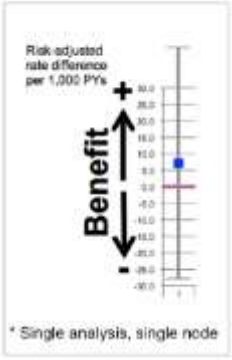


- Only 38% of the Observational Study patients matched with these RCT patients.
- However, the other 62% of Observational Study patients' responses could be correctly predicted with the cluster-based longitudinal models.
- **Improved performance of the models based on blending of randomized and observational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

Alexander J, Edwards RA, Savoldelli A, Manca L, Grugni R, Emir B, Whalen E, Watt S, Brodsky M, Parsons B. Integrating data from randomized controlled trials and observational studies to predict the response to pregabalin in patients with painful diabetic peripheral neuropathy. BMC Med Res Methodol. 2017 Jul 20;17(1):113.

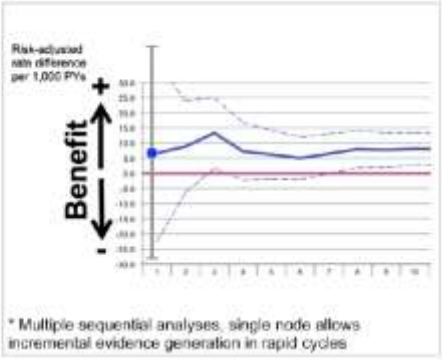
Framework for expedited evidence generation I

A: One-off analysis with full risk adjustment*



* Single analysis, single node

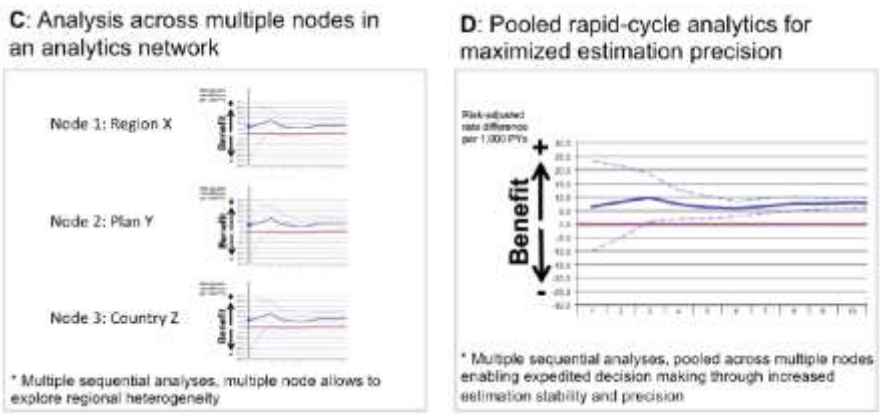
B: Repeat analysis in rapid cycles each time data refresh*



* Multiple sequential analyses, single node allows incremental evidence generation in rapid cycles

Schneeweiss S, Eichler HG, Garcia-Altes A, Chinn C, Eggimann AV, Garner S, Goettsch W, Lim R, Löbker W, Martin D, Müller T, Park BJ, Platt R, Priddy S, Ruhl M, Spooner A, Vannieuwenhuyse B, Willke RJ. Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making. Clin Pharmacol Ther. 2016 Dec;100(6):633-646.

Framework for expedited evidence generation II



Schneeweiss S, Eichler HG, Garcia-Altes A, Chinn C, Eggimann AV, Garner S, Goettsch W, Lim R, Löbker W, Martin D, Müller T, Park BJ, Platt R, Priddy S, Ruhl M, Spooner A, Vannieuwenhuyse B, Willke RJ. Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making. Clin Pharmacol Ther. 2016 Dec;100(6):633-646.

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

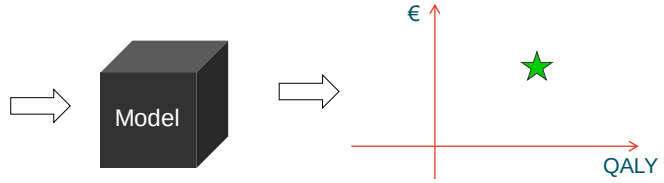
Part 2: A healthcare payer perspective

Susanne Schmitz, PhD

Part 1: Introduction to methods

Economic modelling requires a large variety of input parameters:

e.g.
Natural history,
Effectiveness,
Safety, Adherence,
Cost, Utilities etc.



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?

Part 1: Introduction to methods

Comparative Aggregate Data

	Naïve Pooling	As prior	3 level
Combine designs	★	★	★
Bias adjustment		★	★
Measure heterogeneity			★
Multiple designs			★

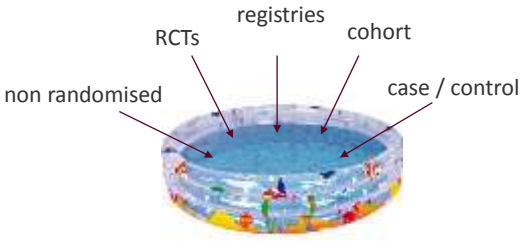
Schmitz, Adams, Walsh. Incorporating data from various designs into a mixed treatment comparison model. Statistics in Medicine (2013). DOI: 10.1002/sim.5764

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.

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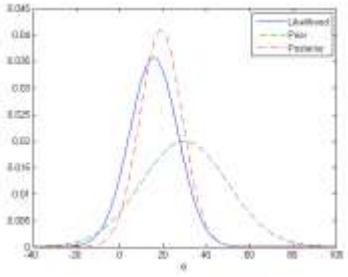
Part 1: Introduction to methods

Comparative Aggregate Data

- As prior information

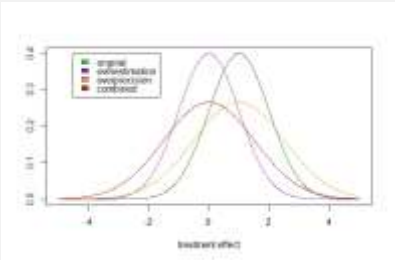
Observational data is analysed separately and the resulting posterior distribution is then used as prior information for the RCT model.

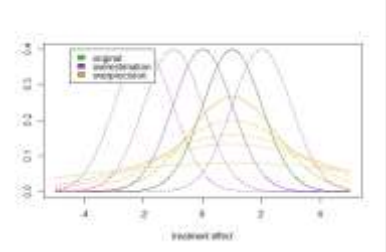


- Natural implementation in the Bayesian framework.
- Possible to incorporate bias adjustments and to down weight observational evidence.
- Can only distinguish between 2 designs.
- Cannot measure between design heterogeneity.

Part 1: Introduction to methods

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.





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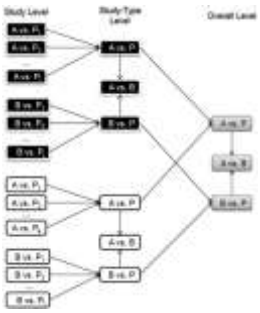
Part 1: Introduction to methods

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.

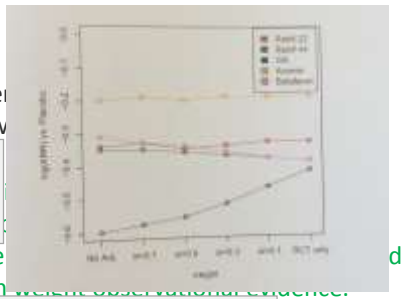


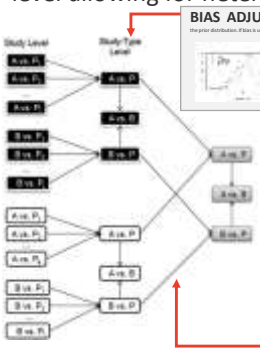
- Natural implementation in the Bayesian framework.
- Possible to incorporate bias adjustments and to down weight observational evidence.
- Multiple designs possible.
- Measures between design heterogeneity.

Comparative Aggregate Data

- 3-level hierarchical model

Introduces a study type level betwee
level allowing for heterogeneity betw





- Possible
to down

d

Between design heterogeneity

$Yi \sim Norm(\mu_i, \eta i)$

$\mu i \sim N(\mu, \tau)$ i = 1,…,N designs

geneity.

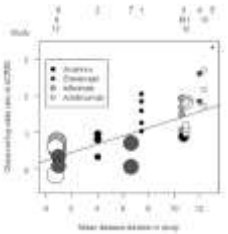
Comparative Aggregate Data

Only the 3-level model allows for the appropriate modelling of heterogeneity between different designs.

	Naïve Pooling	As prior	3 level
Combine designs	★	★	★
Bias adjustment		★	★
Measure heterogeneity			★
Multiple designs			★
Adjust for individual covariate effects			

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.



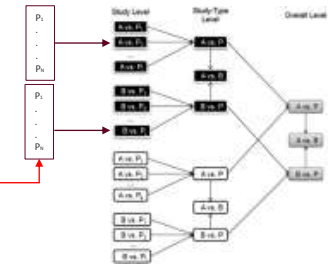
Source: Nixon R et al (2007)

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.

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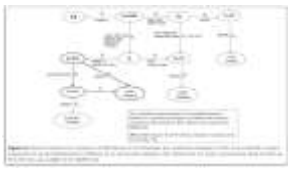
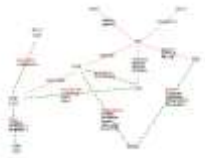
Part 1: Introduction to methods

Observational studies and disconnected networks

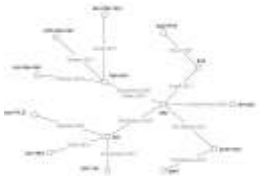
- Thom et al (2015) propose the use of a random effects on baseline model to incorporate single armed observational studies.

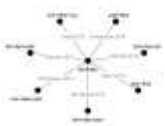


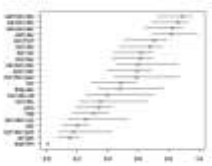
- Leahy et al (2016) conduct a simulation study to explore under which circumstances single arms matched to the remaining network are beneficial. Benefit depends among others on the SD of the study effect and covariate effect.



- Schmitz et al (2017) explore the space of possible matches to capture associated uncertainty.



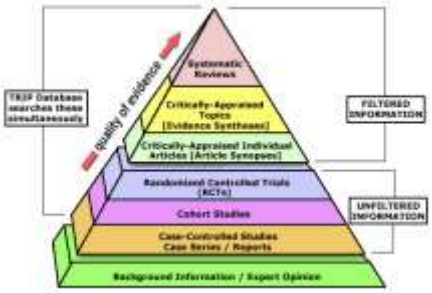




Part 2: A healthcare payer perspective

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

Part 2: A healthcare payer perspective

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 insides into the generalisability of effects.
- Observational studies may provide useful insides 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

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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

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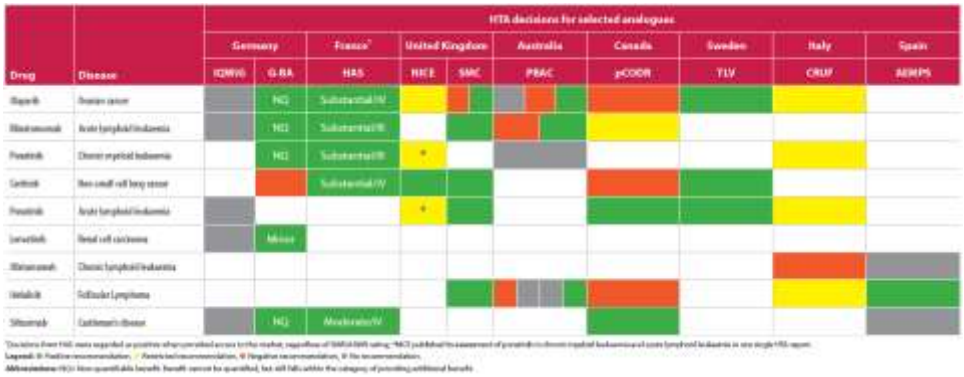
Early access to medicines: Challenges from a Manufacturers perspective

- 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



A. Duran, R. Morlock, X. Lie, R. Dekkers, R. Gani, A. van Engen S. Holmstrom. Assessment of Health Technology Appraisals To Identify Key Drivers for Reimbursement of Oncology Drugs With Only Phase 2 Clinical Data. Presented at the 20th Annual Congress of the International Society For Pharmacoeconomic and Outcomes Research November 4–8, 2017, Glasgow, Scotland

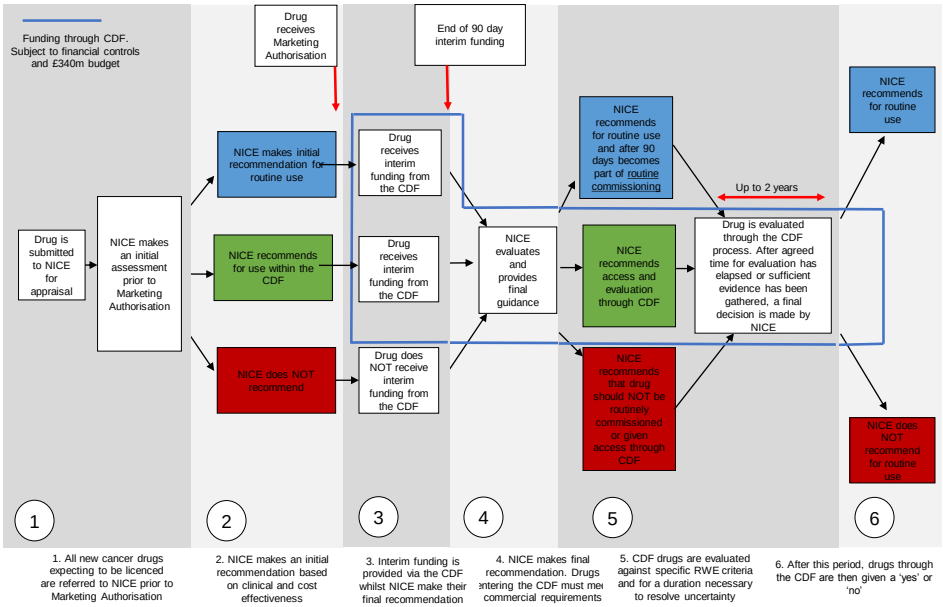
CONCLUSION

- 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

Nazareth, Tara, et al. "Outcomes-Based Contracting Experience: Research Findings from US and European Stakeholders." *Journal of Managed Care & Specialty Pharmacy* 23.10 (2017): 1018-1026.

Overview of the Cancer Drugs Fund process



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

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Live Content Slide

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

Live Content Slide

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

Live Content Slide

When playing as a slideshow, this slide will display live content

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

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: “I would be more inclined to use evidence from combining RCT and non-randomized data, only after the issuance of more methodological guidance”

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Quantifying and clearly communicating the uncertainty associated with the use of non-randomized data can advance the implementation of risk-sharing agreements

Contacts for further discussion

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