Get Real

Real-Life Data in Drug Development

GetReal and the RWE Navigator

Heather Stegenga, Senior analyst, NICE

EFSPI/PS meeting, 28th November 2017

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Outline

- Background / context
- IMI GetReal
- RWE Navigator

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Data: focused on the regulators

Real-Life Data in Drug Development

Regulators

E.g.:

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

厚生労働省
Ministry of Health, Labour and Welfare

HTAs/payers

E.g.:

CADTH Evidence Driven.

NICE

HAS
HAUTE AUTORITÉ DE SANTÉ

Zorginstituut Nederland

PBS

AIFA
Agenzia Italiana del Farmaco

Key decision criteria:

Quality, safety & clinical efficacy

Cost & clinical effectiveness

Scope:

Randomised Controlled trials

Data fit for purpose?

Routine clinical practice

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Mind the efficacy-effectiveness gap

Real-Life Data in Drug Development

	Clinical trial	Health system
Population		
Study type/ sources	RCTs	'Real-World Data' Observational studies Pragmatic trials Primary care and hospital records (EHRs) Healthcare databases , etc…
Design features	↑ Internal validity ↓ External validity	↓ Internal validity ↑ External validity
Type of outcome	**Efficacy**	**Effectiveness**

Gap?

No

Yes

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Additional factors prompting the need for change

Environment

- Increasing strength and demands of **HTA/payers**
- Pressures for **earlier access** to new medicines of value
- Possibility of more flexible reimbursement and **access arrangements**
- **Rare disease** populations more prominent, hard to fit into trial paradigm
- Willingness of regulators to **engage**

Data and methods

- Recognition that data arriving at HTA are **sub-optimal**, especially the key data on relative effectiveness
- Growing **availability** (at least in principle) of RWD
- **New methods** to synthesize data and adjust for bias
- **IT infrastructure**: new possibilities for data collection and integration

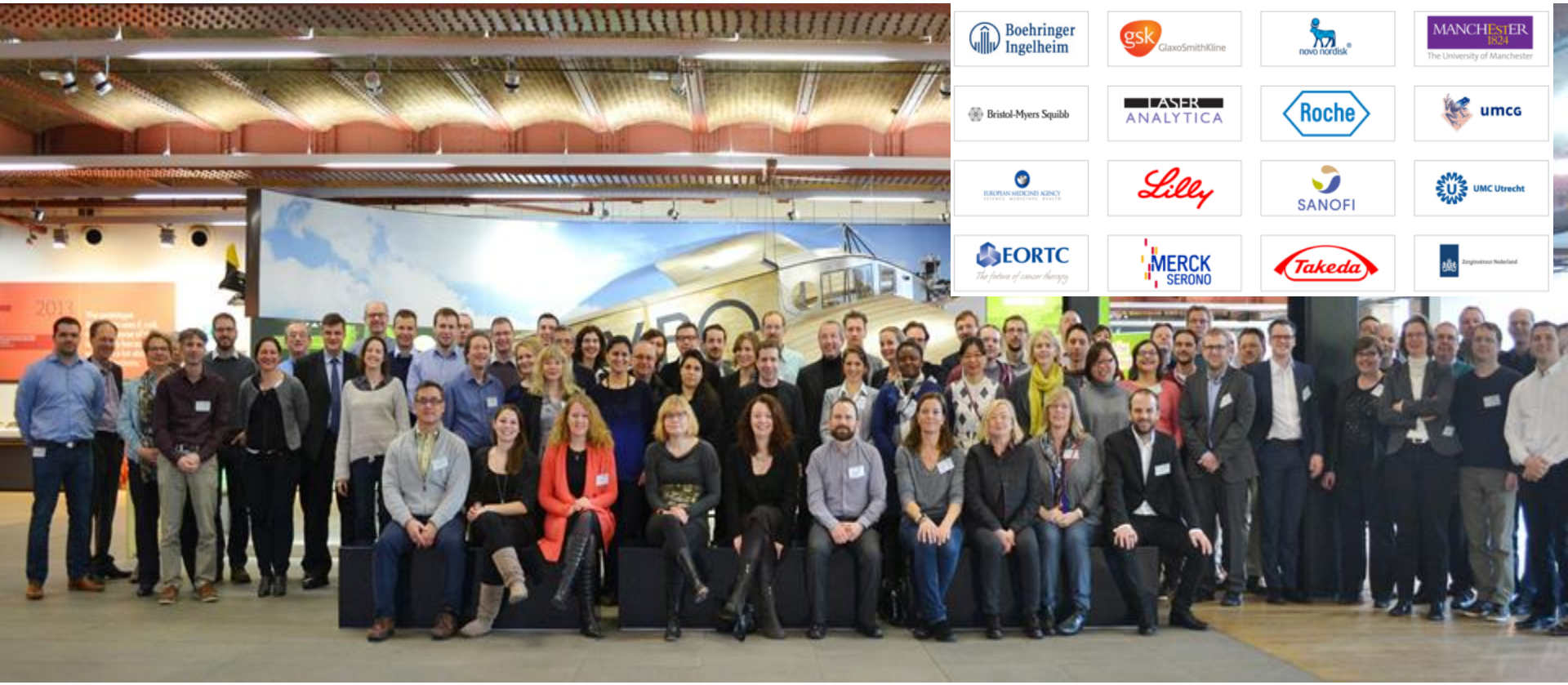
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Get Real

www.imi-getreal.eu
@IMIGetReal

Real-Life Data in Drug Development

Three Years of a *Real* Public Private Partnership

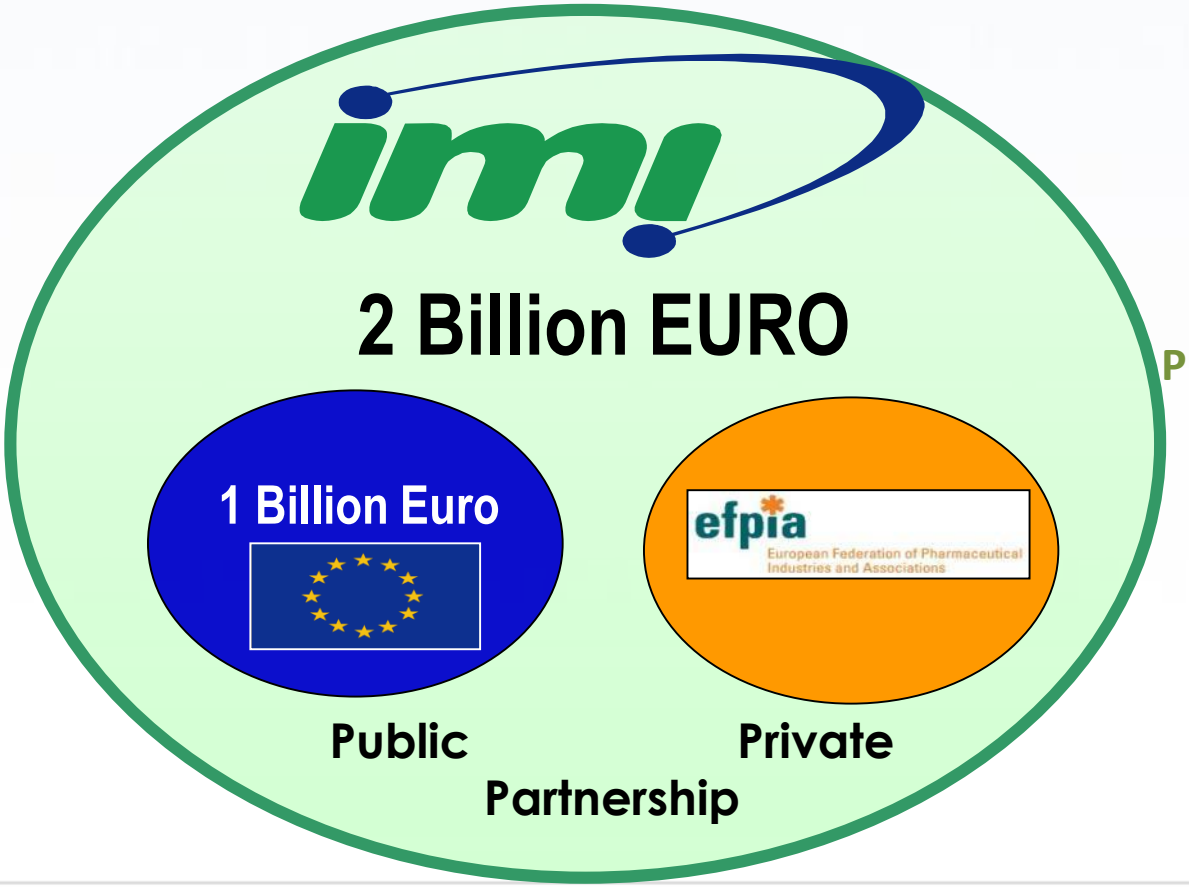


The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Innovative Medicines Initiative (IMI)

FP7 Funding

Cash payment to investigators in Europe: SME/public



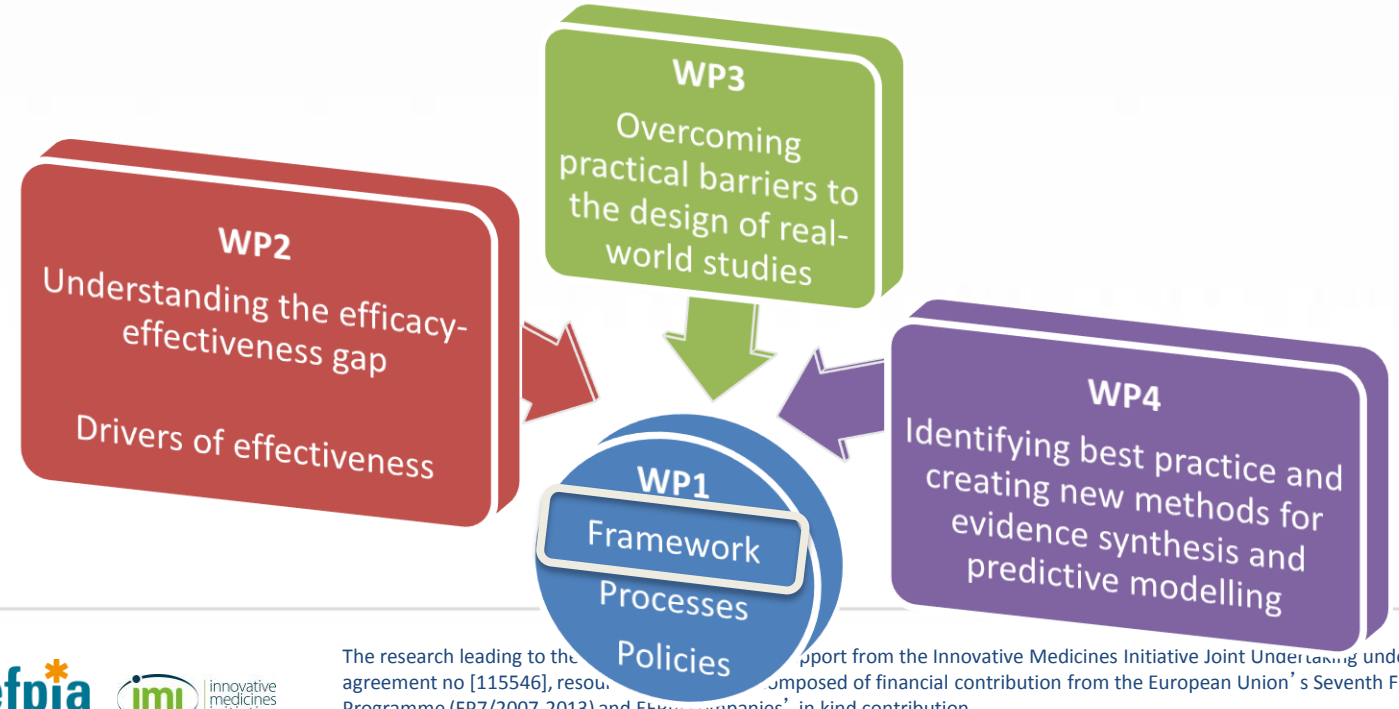
European Federation of Pharma Industries & Assocs.

In kind contribution

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

IMI GetReal aims

- GetReal aimed to consider how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process.



The research leading to the … pport from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resou… omposed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Using RWD is already part of evidence planning within pharma...

Real-Life Data in Drug Development

Development	File and launch	Post-marketing
Analyse RWD to assess effectiveness of existing medicines	Include evidence on use and effectiveness of existing medicines in registration package	Assess relative effectiveness of our new medicine in claims and EMR database analyses
Highlight shortcomings in existing treatments using RWE	Conduct network meta-analysis to estimate relative efficacy (or effectiveness) of new medicine	Synthesize studies on relative effectiveness vs competitor medicines
Incorporate RWD to estimate cost-effectiveness using economic models		

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

...but evidence generation is evolving and GetReal is a key contributor – and resource

Real-Life Data in Drug Development

Development → **File and launch** → **Post-marketing**

- Plan early – consider adaptive pathways
- Use historical cohorts to provide context for single arm clinical studies
- Greater use of analytics to help design clinical trials
- Include trial designs that are more "pragmatic"
- Consider novel techniques to simulate relative effectiveness
- Seek greater dialogue with regulators & HTA agencies

https://www.imi-getreal.eu/

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

GetReal facilitates stakeholder dialogue

Real-Life Data in Drug Development

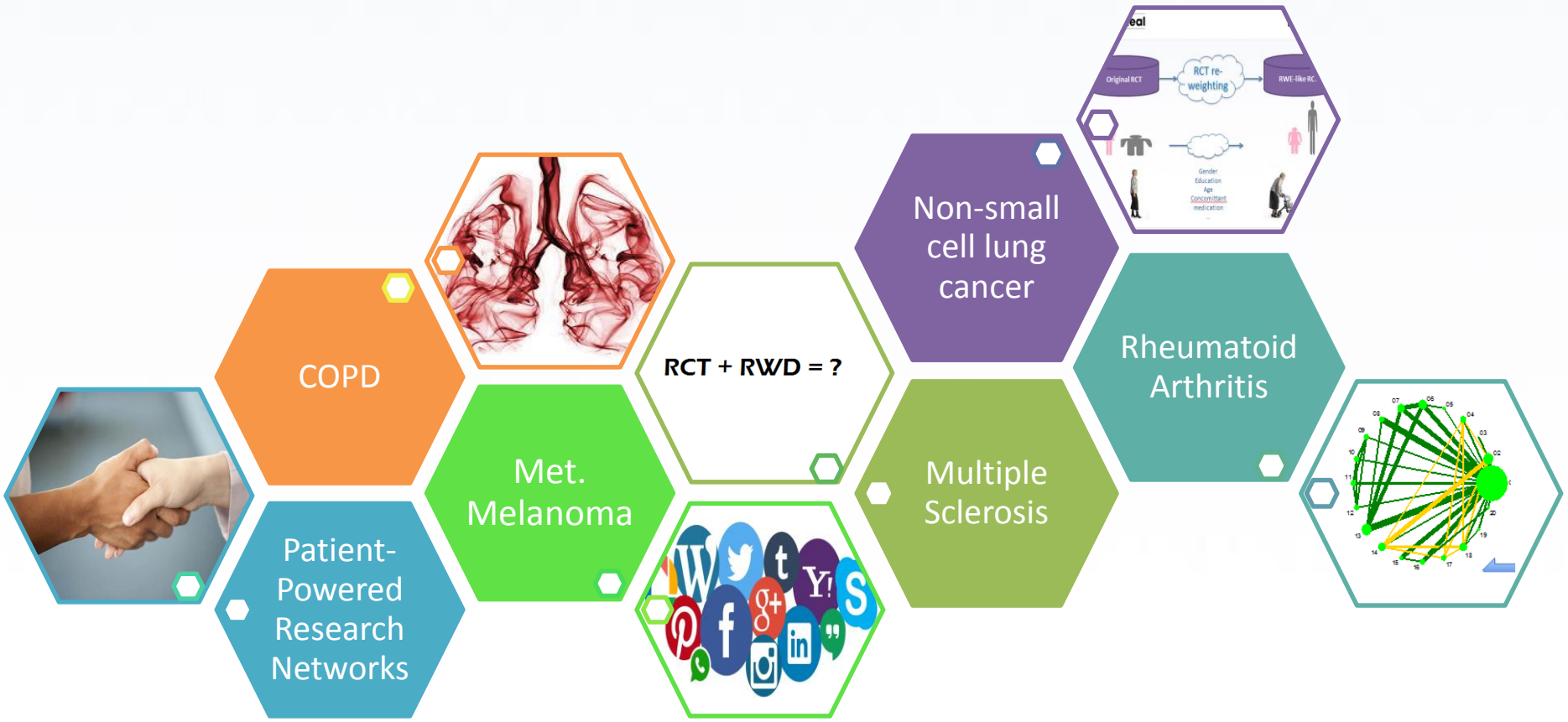
Objectives

- Shared understanding of the technical and process issues from each perspective
- Exploration of novel methodological solutions
- Compilation of best-practice recommendations
- Future research agenda
- Collaboration and trust

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

WP1 Case Studies

Real-Life Data in Drug Development



The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Example GetReal Outputs

Real-Life Data in Drug Development

Original research

- Drivers of effectiveness
- Analytical methods
- Prediction models
- Methodological guidance
- Social media
- Patient-powered research networks (PPRNs)

Methods

- Detection of bias
- Adjustment of bias
- Aggregate RWD in NMAs
- Individual patient data in NMAs

Tools

- Software
- Checklists & templates
- Design options for pragmatic clinical trials

Summaries

- Literature reviews
- Study types
- Sources of data
- Methods

Case studies

- Retrospective analyses of relative effectiveness issues
- Disease area specific issues
- Stakeholder views

**Illustrative examples – not a complete list of GetReal outputs*

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Publications

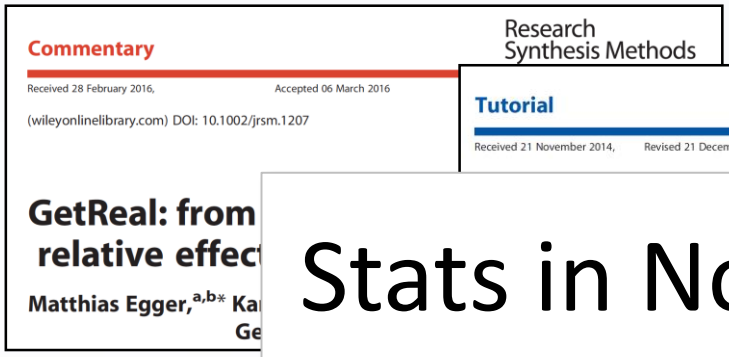
Real-Life Data in Drug Development

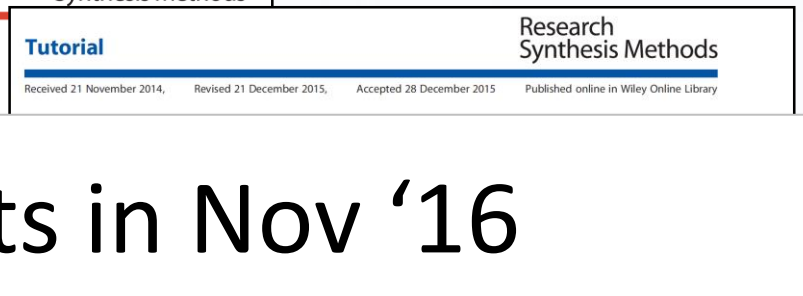
Stats in Nov '16

36 peer-reviewed manuscripts

13 deliverable reports

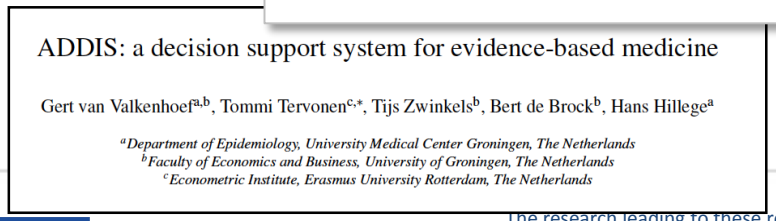
62+ conference presentations


Commentary
Research Synthesis Methods
Received 28 February 2016, Accepted 06 March 2016
(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1207
GetReal: from
relative effect
Matthias Egger,[a,b]*


Tutorial
Research Synthesis Methods
Received 21 November 2014, Revised 21 December 2015, Accepted 28 December 2015 Published online in Wiley Online Library


Kalkman et al. Trials (2016) 17:419
DOI 10.1186/s13063-016-1546-3
RESEARCH
Stakeholders' viev
challenges of prag
pharmaceutical di
Shona Kalkman[1*], Ghislaine J. M. W. van
Mira G. P. Zuidgeest[2], Johannes J. M. van
Consortium


BMC Medical Research Methodology
Open Access
ed Controlled
tient but biased?
uate the
nRCT design
Pieter Van Staa[1,2]


ADDIS: a decision support system for evidence-based medicine
Gert van Valkenhoef[a,b], Tommi Tervonen[c,*], Tijs Zwinkels[b], Bert de Brock[b], Hans Hillege[a]
[a]Department of Epidemiology, University Medical Center Groningen, The Netherlands
[b]Faculty of Economics and Business, University of Groningen, The Netherlands
[c]Econometric Institute, Erasmus University Rotterdam, The Netherlands


H 19 (2016) 75–81
www.sciencedirect.com
eDirect
ELSEVIER
journal homepage: www.elsevier.com/locate/jval
Comparative Effectiveness Research/Health Technology Assessment (HTA)
The "Efficacy-Effectiveness Gap": Historical Background and Current Conceptualization
Clementine Nordon, MD PhD[1,*], Helene Karcher, PhD[2], Rolf H.H. Groenwold, PhD[3], Mikkel Zöllner Ankarfeldt, PhD[4], Franz Pichler, PhD[5], Helene Chevrou-Severac, PhD[6], Michel Rossignol, MD, PhD[7], Adeline Abbe, MSc[8], Lucien Abenhaim, MD, PhD[2], on behalf of the GetReal consortium
[1]LASER Research, Paris, France; [2]LASER Analytica, London, UK; [3]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands; [4]Novo Nordisk A/S, Soborg, Denmark; [5]Eli Lilly and Company, Melrose Park, Australia; [6]Takeda Pharmaceuticals International, Glattpark-Opfikon, Switzerland; [7]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada; [8]Sanofi R&D, Chilly Mazarin, France

The research leading to these results has received s
agreement no [115546], resources of which are co
Programme (FP7/2007-2013) and EFPIA companies
www.imi.europa.eu

Tools

Real-Life Data in Drug Development

**Illustrative examples – not a complete list*

The research leadin g under grant
agreement no [115 enth Framework
Programme (FP7/20
www.imi.europa.e

GetReal online course

Real-Life Data in Drug Development

The drug development landscape LU1	Real World Evidence Generation LU2	Real World Evidence Synthesis LU3	Decision making and weighting evidence LU4	Changing drug development timelines & generating /evaluating RWD in your own work place LU5
> describe the drug development (value) chain > describe the perspectives of various stakeholders on this chain > recognize the main terminology used in this research area & explain the difference between efficacy and effectiveness > understand what is meant by RWE > understand the main issues in moving RWE generation to a pre-launch environment	> name which main study designs exist to generate RWE and explain key characteristics > explain the importance of knowing which are the drivers of effectiveness in real life > explain which are the main study design choices influencing whether you answer a relative effectiveness or an efficacy question > recognize the main operational challenges involved in pragmatic trials on drug treatment effectiveness > explain the interplay between design choices in a pragmatic trial, operational feasibility and the methodological soundness of the trial	> explain the concept and the need for evidence synthesis of drug treatment effects > describe different sources of evidence that can be synthesized > describe current methods in evidence synthesis and in predicting relative effectiveness of drugs (both incorporating RWD) and understand their key differences > recognize the main challenges and potential limitations of these current methods in evidence synthesis > retrieve the key information from publications of real world evidence synthesis > discuss and evaluate ways how to integrate real world data into drug development and decision- making	> describe the existing frameworks for regulatory/HTA decision-making within clinical development timelines, with a focus on the influence of different study designs on the various decisions to be made > discuss new decision models to the generation of evidence over time (for example adaptive licensing/managed market entry) > consider how alternative study design options, and their associated pros and cons, fit into these decision models > explain how MCDA can be applied to the benefit-risk assessment of a medicinal product	> describe the role, perspectives and requirements of key decision makers > identify trade-offs between meeting the needs of different decision makers: Pharma R&D, regulatory agencies, reimbursement agencies > explain the potential for different drug development programmes, focusing in particular on those which make more use of real world data (RWD) > describe the different ways in which RWD can be used in development programmes > explain how to evaluate and prioritise development programmes > explain the process of parallel Scientific Advice and making submissions to decision-makers

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

RWE Navigator

rwe-navigator.eu

Get Real

About | Step 1: Clarify the issues | Step 2: Find RWE options | Use RWD | Case studies | Background | Glossary | Directory of resources

Real-world evidence (RWE) Navigator

The Real-world evidence (RWE) Navigator:

- **Is an educational resource**: helping users to find out more about the potential issues in demonstrating relative effectiveness of new medicines (referred to as 'effectiveness issues').
- **Provides guidance**: guiding users to specific types of analyses or study designs using RWE to support the development of medicines.
- **Is a directory of resources**: a comprehensive resource on the use of RWE in medicines, signposting to outputs from the GetReal projects and other authoritative sources of information on RWE.

The RWE Navigator has been designed for a wide variety of users. For example, pharmaceutical companies may find it useful to increase awareness about the use of RWE among their staff members, or patients may use it to understand concepts related to RWE and better understand challenges of using or generating RWE.

Understanding GetReal and the RWE Navigator

Step 1: Clarify the issues

Step 2: Find RWE options

Directory of resources

Main purposes of the RWE Navigator

- An **educational resource** to find out more about the potential issues in demonstrating relative effectiveness of new medicines ('effectiveness challenges').

Step 1
Clarify the Issues

- A **guide** to specific types of analyses or study designs using RWE to support development of medicines.

Step 2
Find the RWE Options

- A comprehensive **directory of resources** on the use of RWE in medicines, signposting to GetReal outputs and other authoritative sources.

Directory of Resources

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Get Real

Real-Life Data in Drug Development

Who is it for ?

Clinicians

Patients

HTA agencies and payers

Shared platform for understanding and collaboration

Regulators

Researchers

Pharmaceutical companies

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Sources of existing RWD

Generate RWE (study designs)

Summarise and synthesise evidence

Assure quality and credibility of RWD/RWE

Model effectiveness in real world setting

Adjust for bias in non-randomised /obs studies

Governance of RWD

Example key content categories

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Sources of existing RWD

Sources of real-world data

Real-world data (RWD) is an overarching term for data on the effects of health interventions (such as benefits, risks or resource use) that are not collected in the context of conventional randomised controlled trials (RCTs).

While definitions vary, RWD tends to be structured, in that it has 'data models' with data residing in a fixed field, for example in databases and spreadsheets. RWD has more in common with epidemiological data than big data, which involves large or complex unstructured data sets, such as data from social media. However, the term big data is sometimes used more broadly, also referring to more structured RWD.

RWD can be collected both prospectively and r
Data collected may include, but are not limited
outcomes and health-related quality of life.

Related links

- Generating RWE including different study designs
- Summary of GetReal glossary of terms and definitions

Overview of RWD sourc

RWD can be obtained from experimental studie
The different study designs that can provide RW

Additional sources of RWD that may provide da
structured studies are listed below.

Table. RWD from existing sources

Patient registries	Patient registrie collect, analyse, patients with sp
Healthcare databases including electronic health records	Healthcare data systems into wh laboratory data in 'real-world' (o well as the relat more
Pharmacy and health insurance databases	Pharmacy and h database syster billing and othe monitoring of h also be used in

Table. RWD from existing sources

Patient registries	Patient registries are organised systems that are used to prospectively collect, analyse, and disseminate observational data on a group of patients with specific characteristics in common. Read more
Healthcare databases including electronic health records	Healthcare databases, such as electronic health records (EHRs), are systems into which healthcare providers enter routine clinical and laboratory data during usual practice. Healthcare databases can be used in 'real-world' (observational) studies to assess the benefits and risks, as well as the relative effectiveness, of different medical treatments. Read more
Pharmacy and health insurance databases	Pharmacy and health insurance databases are types of healthcare database systems that are set up by pharmacists or health insurers for billing and other healthcare administration and management, such as monitoring of healthcare service use. Data collected in these systems can also be used in medical research to assess the effectiveness of healthcare interventions in 'real world' observational studies. Read more
Social media	Social media are internet-based websites and applications that enable users to create and share content or to participant in social networking. They can provide patient perspectives on health topics such as adverse events, reasons for changing treatments and non-adherence, and quality of life. Read more
Patient-powered research networks	Patient-powered research networks (PPRNs) are online platforms run by patients to collect and organise health and clinical data. Read more

efpia

Generate RWE (study designs)

RWE Navigator / U ence

Generate real-world evidence

Conventional randomised controlled trials (RCTs) alone may not provide sufficient evidence of relative effectiveness to support reimbursement decision-making. An estimation of how well a medicine may work in the real world can be estimated from analyses of the existing RCTs. However, it may be possible to generate 'earlier' estimates of the relative effectiveness of the new medicine of interest in time to inform reimbursement decision-making by analysing existing real-world data sources or by conducting new studies to generate real-world evidence (RWE). For more information about the limitations of RCTs to estimate relative effectiveness see here and here, for an overview of methods for predicti effectiveness in the real world using RCT data see here, and for more information about e data sources see here.

Some experimental and observational study designs that could provide RWE are summar below. While some study designs may provide evidence on relative effectiveness, some 'r epidemiological' observational studies may not be able to provide evidence of relative eff However, they may be useful to define the disease area and understand the natural disea provide information about a relevant comparator if there is no comparative data.

Since the quality and credibility of a study may have a significant impact on the reported medicine and its interpretation, it is crucial to assess each study individually, whether or n element of randomisation. For more information about assuring quality and credibility of

Table. Study designs that may provide RWE

Experimental study designs	
Pragmatic RCT	A pragmatic trial aims to measure the relative effec treatments in real-world clinical practice. It combin of RCTs with evidence of the added value of a treat routine clinical practice. Read more
Population enrichment RCT	A population enrichment RCT includes patients typ from RCTs combined with predictive modelling tec better predict relative effectiveness in a real-world Read more
Cohort multiple RCT (cmRCT) (also known as or trials within cohorts)	cmRCTs are a type of pragmatic RCT that use a larg patients as a source of participants for multiple RC more generalisable study sample. Read more

Related links

- RWD sources
- Pragmatic trials
- Overview of methods for predicting outcomes to bridge the efficacy-effectiveness gap
- Assuring quality and credibility of

Comprehensive cohort study (CCS)	CCS is a type of pragmatic RCT that includes participants who do not consent to be randomised to the treatment group. This reduces selection bias and improves generalisability. Read more
Cluster RCT	Cluster RCTs randomise groups or clusters rather than individual participants as in traditional RCTs. Read more
Non-randomised controlled trial	Any experimental study allocating participants to different treatments using a method other than randomisation, such as clinician or patient preference.
Observational study designs	
Cohort	A cohort study follows a group of individuals over a period of time to consider associations between interventions received and outcomes.
Case-control	A study that examines associations between outcomes and prior exposures by comparing people with an outcome of interest to those without the outcome. These are not often used for interventions.
Cross-sectional	In a cross-sectional study, data are collected from a population or a representative subset of a population at one specific point of time or over a short period to examine associations between the outcomes and exposure to interventions.
Controlled before-and-after	Similar to a case series, in which observations are recorded on a series of individuals before and after receiving an intervention, but this study design includes a control group.

Summarise and synthesise evidence

RWE Navigator / Use real-world data /

Summarise and synthesise real-world evidence

Evidence synthesis

Evidence synthesis is the process of retrieving, evaluating and summarising the findings of all relevant studies on a certain subject area. Ideally, a systematic review is conducted to identify all the relevant available studies to support the evidence synthesis. For more information about systematic reviewing, see the Cochrane handbook for systematic reviews of interventions. (a description of a systematic literature review in the context of exploring and identifying drivers of effectiveness is found here).

Meta-analyses may then be used to combine the estimates from the individual studies identified.

Network meta-analysis (NMA) is an extension of the standard, pairwise meta-analysis, and can be used to synthesise results from studies that compare multiple competing interventions for the same condition.

For more information about evidence synthesis and network meta-analysis see here.

Including RWD in evidence synthesis

Meta-analysis and NMA are usually limited to the synthesis of evidence from randomised controlled trials (RCTs) because they are considered to be the most reliable source of information on relative treatment effects. However, there is a growing interest in the medical community in incorporating evidence from non-randomised studies (NRSs), patient registries and other real-world data (RWD).

This strategy is particularly appealing when there are few RCTs to answer a specific research question. It may also be useful when the available RCTs do not align with the target population, prescription strategies and/or primary outcomes of the research question (i.e. when there is an efficacy-effectiveness gap, see a definition here).

Including RWD may be also be helpful to connect disconnected networks of interventions (i.e. if trials comparing interventions are not available) or to supplement existing RCT evidence when the results are conflicting or evidence is limited.

For more information about incorporating RWD into an NMA see here.

Related links

- Overview of evidence synthesis and NMA
- Cochrane handbook for systematic reviews of interventions
- Conducting a literature review to explore and identify drivers of effectiveness

Assure quality and credibility of RWD/RWE

Assure quality and credibility of RWE

The defining feature of a randomised controlled trial (RCT), the random assignm
treatment groups, can ensure that characteristics of participants are similar in th
compared, when the trial is well conducted. This is most important when those
also have a direct impact on the effect of a medicine, such as the severity of the
called confounding variables or treatment effect modifiers). While there are non
methods that are sometimes used to ensure equal distribution of these factors b
groups (such as matching), random allocation is particularly important as there n
characteristics that influence a treatment effect that are not known.

Although other factors may influence the **internal validity** of a study, including th
to treatment protocols and the measurement of outcomes, the internal validity
conducted RCTs is likely to be high, providing more reliable estimates of a medic
However, traditional RCTs are less likely to reflect the real world in the populatio
the way that interventions are administered or in other factors (i.e. they may hav
external validity).

The use of data collected outside RCTs (real-world data [RWD]) may have better
validity. However, the potential lack of internal validity and the potential for bias
uncertainty regarding the robustness of the data when used as a source of evide
effectiveness.

Checklists for quality assessment

One of the key concerns about the use of evidence collected outside RCTs is the quality of studies used.

In the field of evidence-based medicine, checklists are often used to assess the quality of different study designs, aiming to ensure consistency across quality assessors. A number of existing checklists focus on methodological quality, but some also incorporate broader elements such as those relevant to cost-effectiveness analyses considered by payers or health technology assessment agencies.

A NICE Decision Support Unit technical support document (Faria et al 2015) has been produced 'to help improve the quality of analysis, reporting, critical appraisal and interpretation of estimates of treatment effect from non-RCT studies'. This document includes a review and assessment of a number of existing checklists for quality assessment of the analysis of non-randomised studies.

The table below includes a list of commonly used checklists, organised by study design, some of which were reviewed by Faria et al 2015.

Table: Commonly used quality checklists by study design

Study design[a]	Quality checklists
Randomised controlled trials (RCTs)	Cochrane risk of bias tool CASP randomised controlled trial checklist
Non-randomised study designs, controlled cohort, controlled before-	**In the context of cost-effectiveness analyses:** ISPOR checklist for prospective observational studies[b] ISPOR checklist for retrospective database studies[b] Checklist for statistical methods to address selection bias in estimating incremental costs, effectiveness and cost-effectiveness (Kreif et al 2013)[b] NICE DSU QuEENS checklist (for use on its own or to complement other checklists)

The research leading to these r
agreement no [115546], resour
Programme (FP7/2007-2013) a
www.imi.europa.eu

Model effectiveness in real world setting

RWE Navigator / Use real-world data / Model effectiveness in the real world

Model effectiveness in the real world

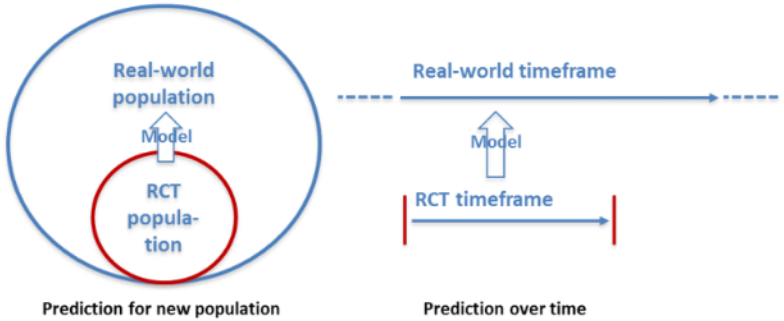
Modelling is commonly used to support decision-making by health technology assessment (HTA) agencies, particularly to predict treatment effects beyond the timeframe in the existing RCTs.

GetReal has examined two uses of modelling to address the potential gap between the efficacy of a treatment observed in RCTs and effectiveness in the real world:

- Extrapolating treatment effects to the long-term, using real-world data (RWD).
- Predicting effectiveness of treatments in a real-world population.

The figure below summarises how modelling can be used to extend RCT data over time or across populations.

Figure. Use of modelling to extend RCT data.



For more information on methods for predicting outcomes to bridge the efficacy-effectiveness gap, including a review of the existing literature and a summary of the approaches examined by GetReal see here.

Related links

- Overview of methods for predicting outcomes to bridge the efficacy-effectiveness gap
- Software for evidence synthesis or predictive modelling

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Adjust for bias in non-randomised /obs studies

RWE Navigator / Use real-world data / Adjust for bias in non-randomised and observational studies

Adjust for bias in non-randomised and observational studies

Studies that use non-randomised methods to determine who will receive different treatments (for example, by clinician preference and patient suitability) may, as a result, have systematic differences between participants in different treatment arms. When these differences, whether known or unknown, are also related to the outcome they are considered to be confounding factors. For example, if participants in one arm have more severe disease, they may respond differently to the treatment. Results

g are less reliable and considered to be biased (this is called **selection bias**)

well-conducted randomised studies with an adequate study size should eli
vn differences between treatment arms which may influence the outcome
ias) due to the randomised nature of treatment selection.

e to control for some known factors where randomisation has not occurred
s biased results, for example by stratification or matching, but this is not a

hat do not use randomisation to control for confounding, statistical metho
esults and provide a less biased and more accurate estimate of treatment
still ongoing on different methods to control for confounding; also, statisti
nsate for unmeasured confounders. The methods can normally be categor
nown confounding factors and those that adjust for **unknown confounding**
below provides some of the more commonly known methods.

Related links

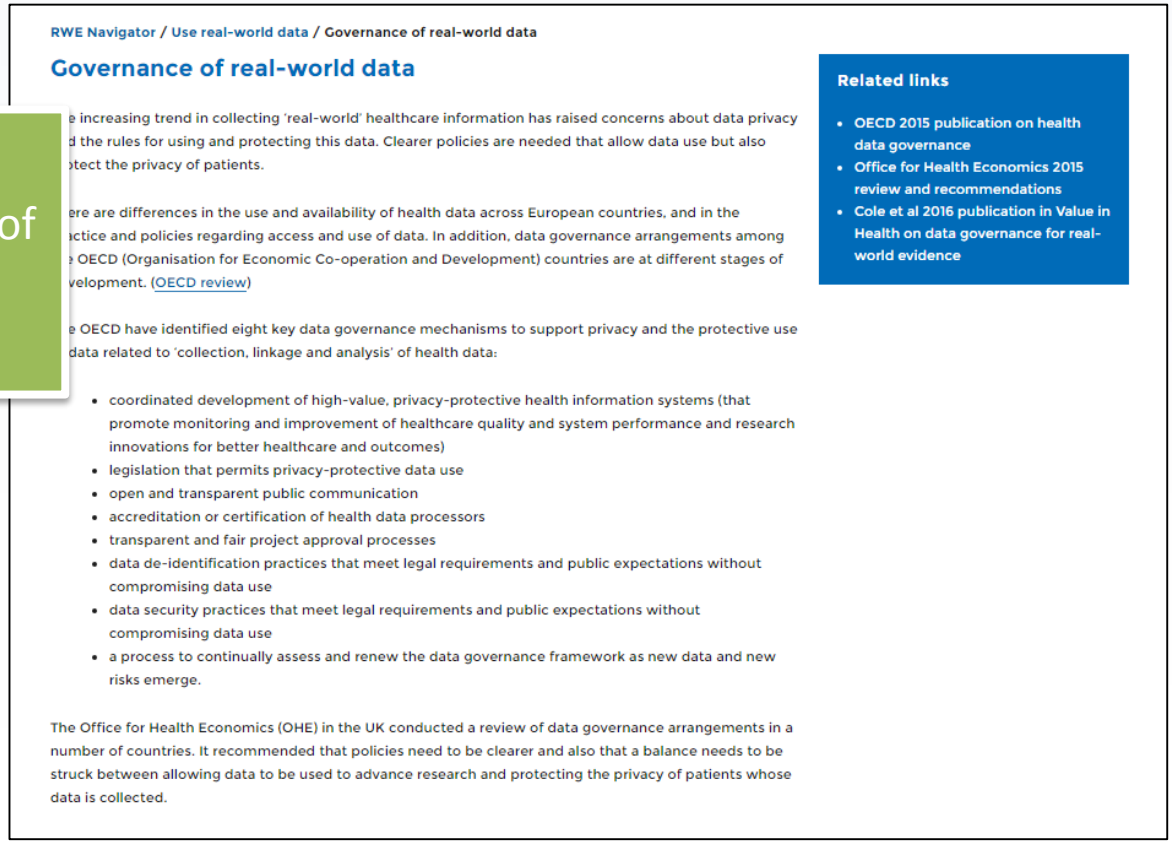
- Schmidt et al 2016 publication in Epidemiology on methods for adjusting for confounding in early post-launch settings

Table. Summary of methods to adjust for either known or unknown confounding

Methods that adjust for known confounding	
Regression adjustment using regression models (such as logistic regression models by prognostic factors[a])	Regression models depend on covariates (such as progn predict the outcome. Models are fit for both the treated samples, and the treatment effects are then based on th between the predictions of the two models. Read more
Inverse probability weighting (IPW)[a]	This method aims is to make the groups more comparab propensity score function to 'weight' the mean dependir covariates or prognostic factors (a propensity score is a p based on different patient characteristics). The inverse o score is used to calculate a weighted mean. Read more
Doubly robust methods	This method combines regression adjustment and IPW. adjustment is made for the outcome, but not the treatm resulting in a model being estimated for the probability treatment but not for an outcome. Read more
Doubly robust methods	This method combines regression adjustment and IPW. Regression adjustment is made for the outcome, but not the treatment selection, resulting in a model being estimated for the probability of receiving treatment but not for an outcome. Read more
Regression based on propensity score*	This method uses the propensity score to control for correlation between treatment and covariates; the method most often uses parametric regression for the outcome variable. Read more This method may only be sufficient when there are relatively few outcomes (see here).
Regression based on disease risk score[a]	This method uses the disease risk score to control for correlation between treatment and covariates. This method may only be sufficient (and less biased) when there are relatively few outcomes (Schmidt et al 2016).
Matching	While matching can be done in a study design, it can also be an analytical method, aiming to 'match' control individuals who are similar to treated patients in one or more characteristic. This may be done based on a propensity score. For a brief description and more resources, see here.
Parametric regression on a matched sample	This approach combines regression adjustment with matching, using the regression to control for any factors not adjusted for with matching. Read more
Methods that adjust for unknown confounding	
Instrumental variable methods	This is the most commonly used method to deal with unknown confounding. This approach aims to find a variable (or instrument) that is correlated with the treatment, but not directly correlated to the outcome (except through the treatment). A causal treatment effect is identified by varying the instrument. For a brief description and more resources, see here.
Panel data models	This approach uses an individual as their own control at different time-

The research leading to these res
agreement no [115546], resource
Programme (FP7/2007-2013) and
www.imi.europa.eu

Governance of RWD



RWE Navigator / Use real-world data / Governance of real-world data

Governance of real-world data

e increasing trend in collecting 'real-world' healthcare information has raised concerns about data privacy d the rules for using and protecting this data. Clearer policies are needed that allow data use but also otect the privacy of patients.

ere are differences in the use and availability of health data across European countries, and in the ctice and policies regarding access and use of data. In addition, data governance arrangements among e OECD (Organisation for Economic Co-operation and Development) countries are at different stages of velopment. (OECD review)

e OECD have identified eight key data governance mechanisms to support privacy and the protective use data related to 'collection, linkage and analysis' of health data:

- coordinated development of high-value, privacy-protective health information systems (that promote monitoring and improvement of healthcare quality and system performance and research innovations for better healthcare and outcomes)
- legislation that permits privacy-protective data use
- open and transparent public communication
- accreditation or certification of health data processors
- transparent and fair project approval processes
- data de-identification practices that meet legal requirements and public expectations without compromising data use
- data security practices that meet legal requirements and public expectations without compromising data use
- a process to continually assess and renew the data governance framework as new data and new risks emerge.

The Office for Health Economics (OHE) in the UK conducted a review of data governance arrangements in a number of countries. It recommended that policies need to be clearer and also that a balance needs to be struck between allowing data to be used to advance research and protecting the privacy of patients whose data is collected.

Related links

- OECD 2015 publication on health data governance
- Office for Health Economics 2015 review and recommendations
- Cole et al 2016 publication in Value in Health on data governance for real-world evidence

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

RWE Navigator is...

an educational resource

a source of guidance

a directory of resources

a shared platform

NOT a decision-making/support tool

Does **NOT** replace formal scientific advice

Does **NOT** guarantee approval, access or funding

Methods tested still experimental

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

RWE Navigator

rwe-navigator.eu

Get Real

About | Step 1: Clarify the issues | Step 2: Find RWE options | Use RWD | Case studies | Background | Glossary | Directory of resources

Real-world evidence (RWE) Navigator

The Real-world evidence (RWE) Navigator:

- **Is an educational resource**: helping users to find out more about the potential issues in demonstrating relative effectiveness of new medicines (referred to as 'effectiveness issues').
- **Provides guidance**: guiding users to specific types of analyses or study designs using RWE to support the development of medicines.
- **Is a directory of resources**: a comprehensive resource on the use of RWE in medicines, signposting to outputs from the GetReal projects and other authoritative sources of information on RWE.

The RWE Navigator has been designed for a wide variety of users. For example, pharmaceutical companies may find it useful to increase awareness about the use of RWE among their staff members, or patients may use it to understand concepts related to RWE and better understand challenges of using or generating RWE.

Understanding GetReal and the RWE Navigator

Step 1: Clarify the issues

Step 2: Find RWE options

Directory of resources

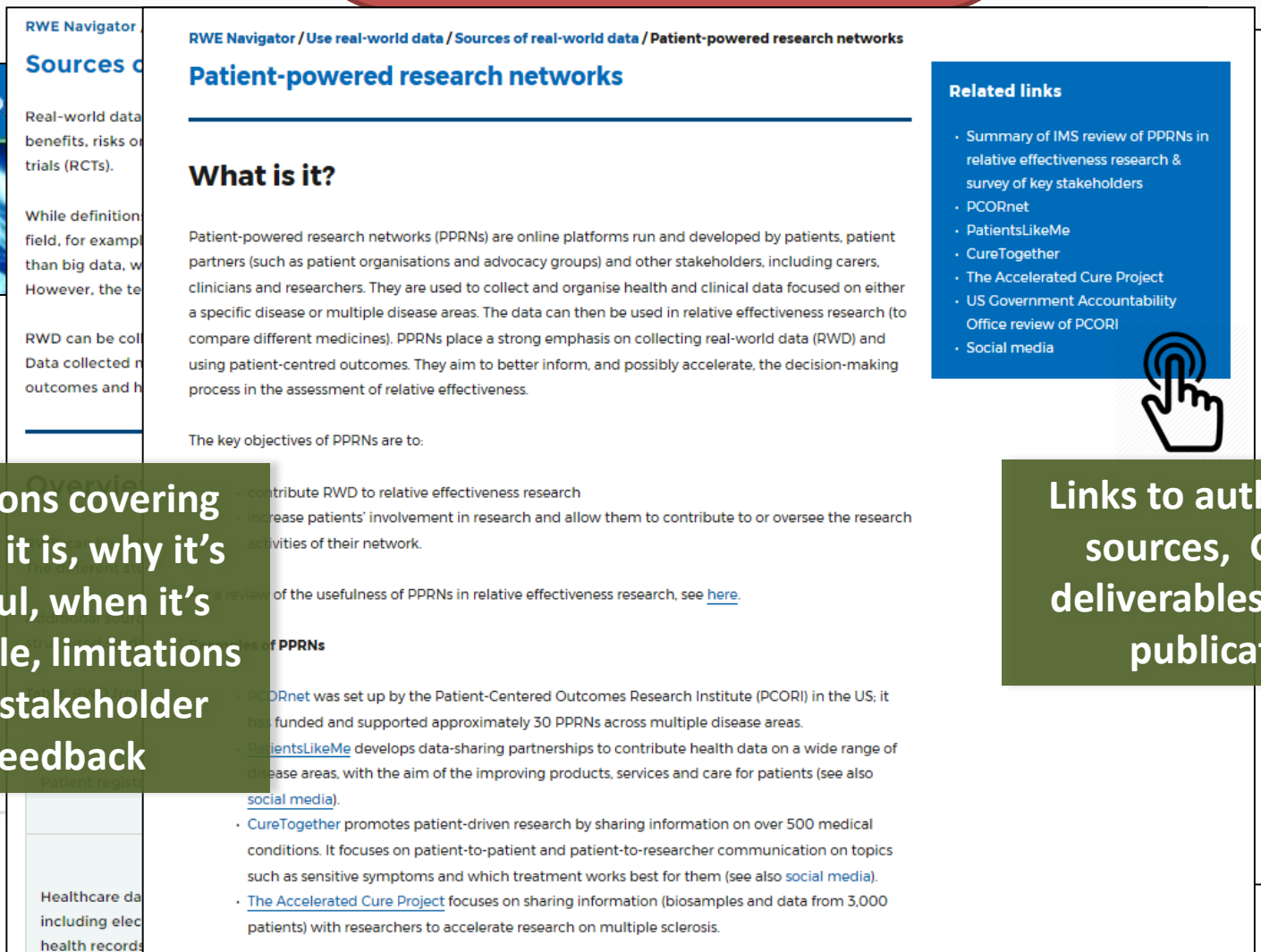
rwe-navigator.eu

Scenario 1: Clinician interested in learning about patient powered research networks

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

rwe-navigator.eu

Scenario 1: Clinician interested in learning about patient powered research networks



RWE Navigator / Use real-world data / Sources of real-world data / Patient-powered research networks

Patient-powered research networks

What is it?

Patient-powered research networks (PPRNs) are online platforms run and developed by patients, patient partners (such as patient organisations and advocacy groups) and other stakeholders, including carers, clinicians and researchers. They are used to collect and organise health and clinical data focused on either a specific disease or multiple disease areas. The data can then be used in relative effectiveness research (to compare different medicines). PPRNs place a strong emphasis on collecting real-world data (RWD) and using patient-centred outcomes. They aim to better inform, and possibly accelerate, the decision-making process in the assessment of relative effectiveness.

The key objectives of PPRNs are to:

- contribute RWD to relative effectiveness research
- increase patients' involvement in research and allow them to contribute to or oversee the research activities of their network.

of the usefulness of PPRNs in relative effectiveness research, see here.

of PPRNs

- PCORnet was set up by the Patient-Centered Outcomes Research Institute (PCORI) in the US; it has funded and supported approximately 30 PPRNs across multiple disease areas.
- PatientsLikeMe develops data-sharing partnerships to contribute health data on a wide range of disease areas, with the aim of the improving products, services and care for patients (see also social media).
- CureTogether promotes patient-driven research by sharing information on over 500 medical conditions. It focuses on patient-to-patient and patient-to-researcher communication on topics such as sensitive symptoms and which treatment works best for them (see also social media).
- The Accelerated Cure Project focuses on sharing information (biosamples and data from 3,000 patients) with researchers to accelerate research on multiple sclerosis.

Related links

- Summary of IMS review of PPRNs in relative effectiveness research & survey of key stakeholders
- PCORnet
- PatientsLikeMe
- CureTogether
- The Accelerated Cure Project
- US Government Accountability Office review of PCORI
- Social media

Sections covering what it is, why it's useful, when it's suitable, limitations and stakeholder feedback

Links to authoritative sources, GetReal deliverables, full-text publications

Scenario 2: pharmaceutical company preparing an evidence development plan for a new medicine

rwe-navigator.eu

- How & why effectiveness differs from efficacy (the 'gap') and 'drivers of effectiveness'
- Planning questions to consider for each aspect of PICO (population, intervention, etc)
- Methods to explore the gap
- Examples

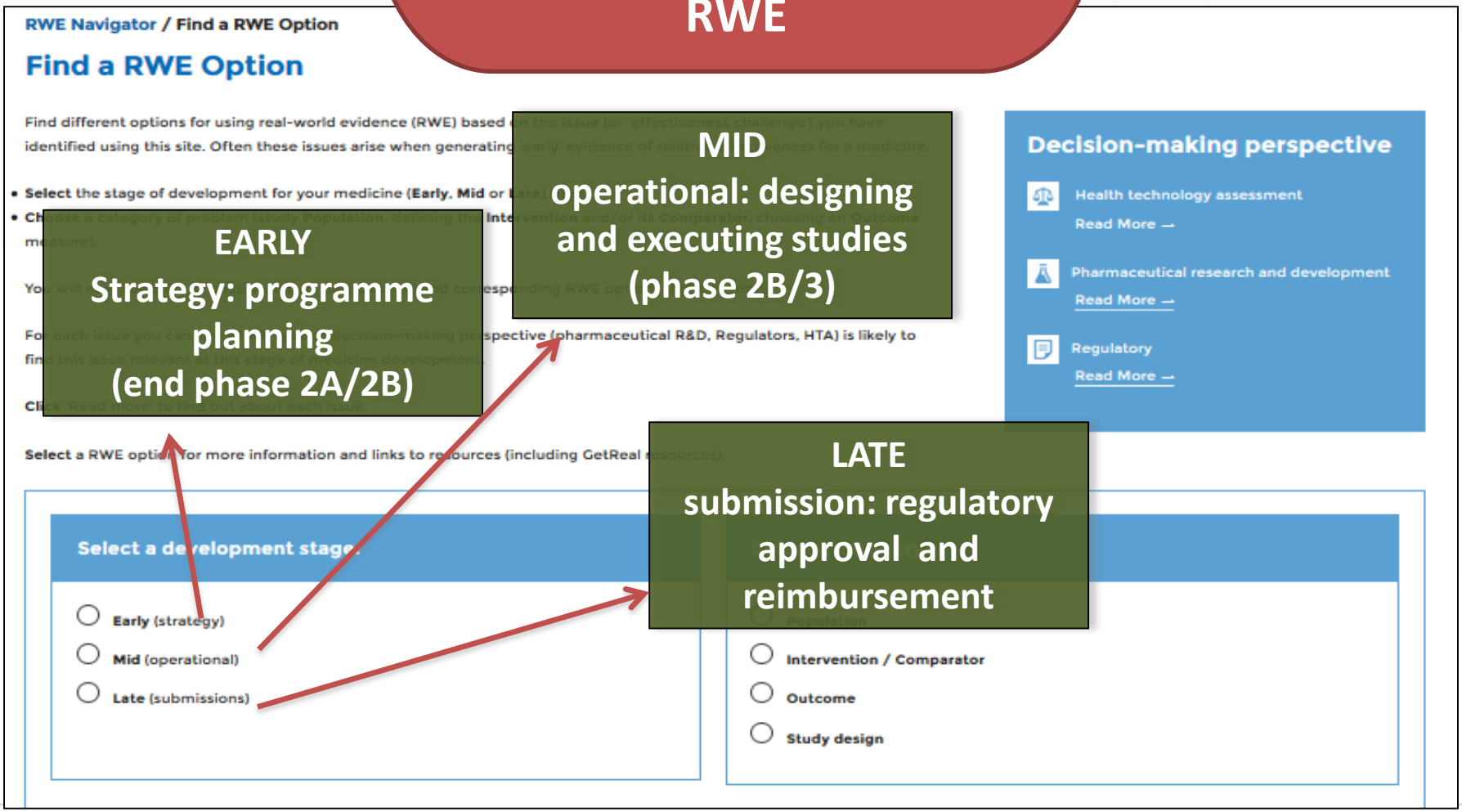
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Scenario 2: pharmaceutical company looking for **options using RWE**

Find potential options using RWE to address the identified issues

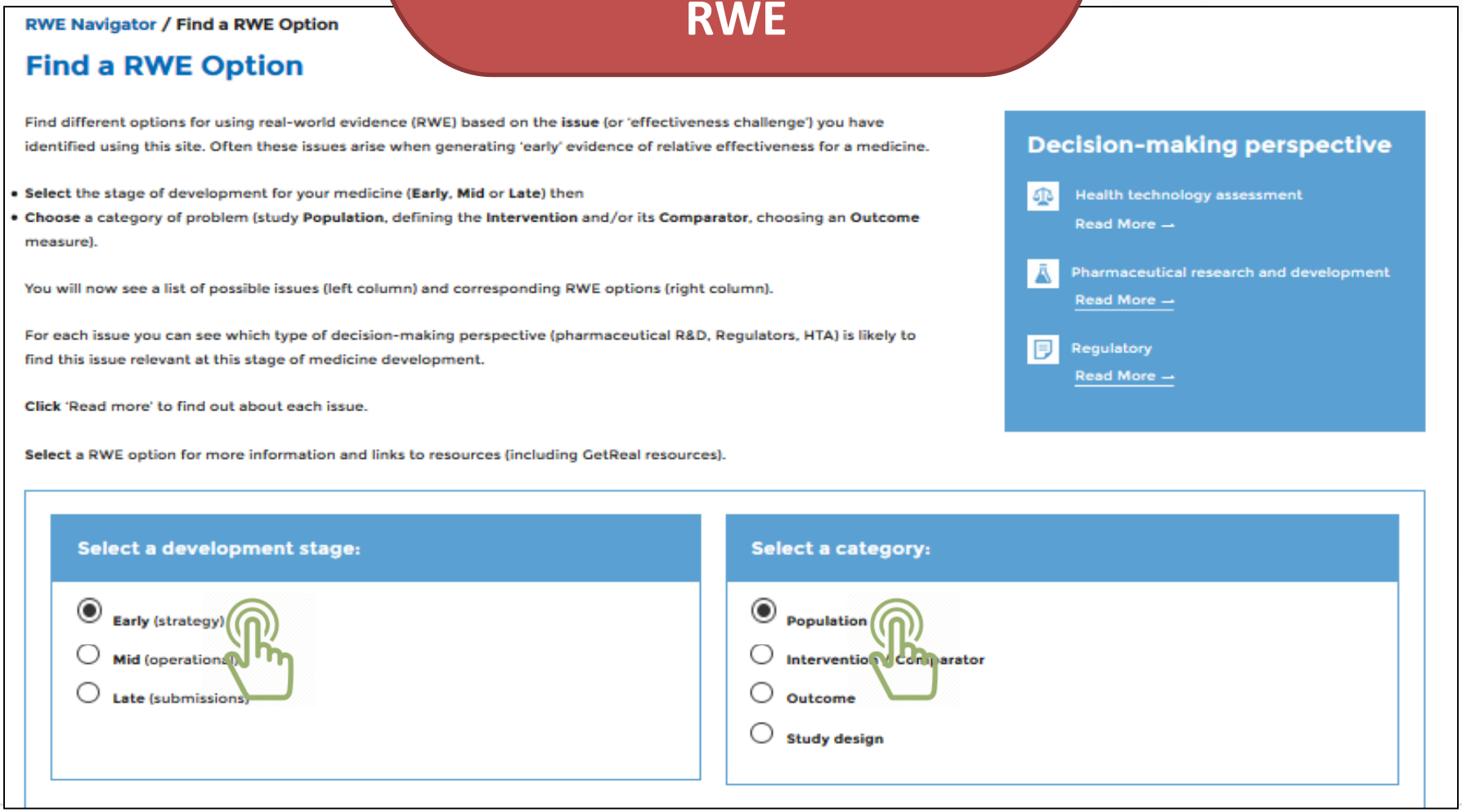
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Scenario 2: pharmaceutical company looking for **options using RWE**



The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Scenario 2: pharmaceutical company looking for **options using RWE**



RWE Navigator / Find a RWE Option

Find a RWE Option

Find different options for using real-world evidence (RWE) based on the **issue** (or 'effectiveness challenge') you have identified using this site. Often these issues arise when generating 'early' evidence of relative effectiveness for a medicine.

- **Select** the stage of development for your medicine (**Early**, **Mid** or **Late**) then
- **Choose** a category of problem (study **Population**, defining the **Intervention** and/or its **Comparator**, choosing an **Outcome** measure).

You will now see a list of possible issues (left column) and corresponding RWE options (right column).

For each issue you can see which type of decision-making perspective (pharmaceutical R&D, Regulators, HTA) is likely to find this issue relevant at this stage of medicine development.

Click 'Read more' to find out about each issue.

Select a RWE option for more information and links to resources (including GetReal resources).

Decision-making perspective

Health technology assessment
Read More →

Pharmaceutical research and development
Read More →

Regulatory
Read More →

Select a development stage:

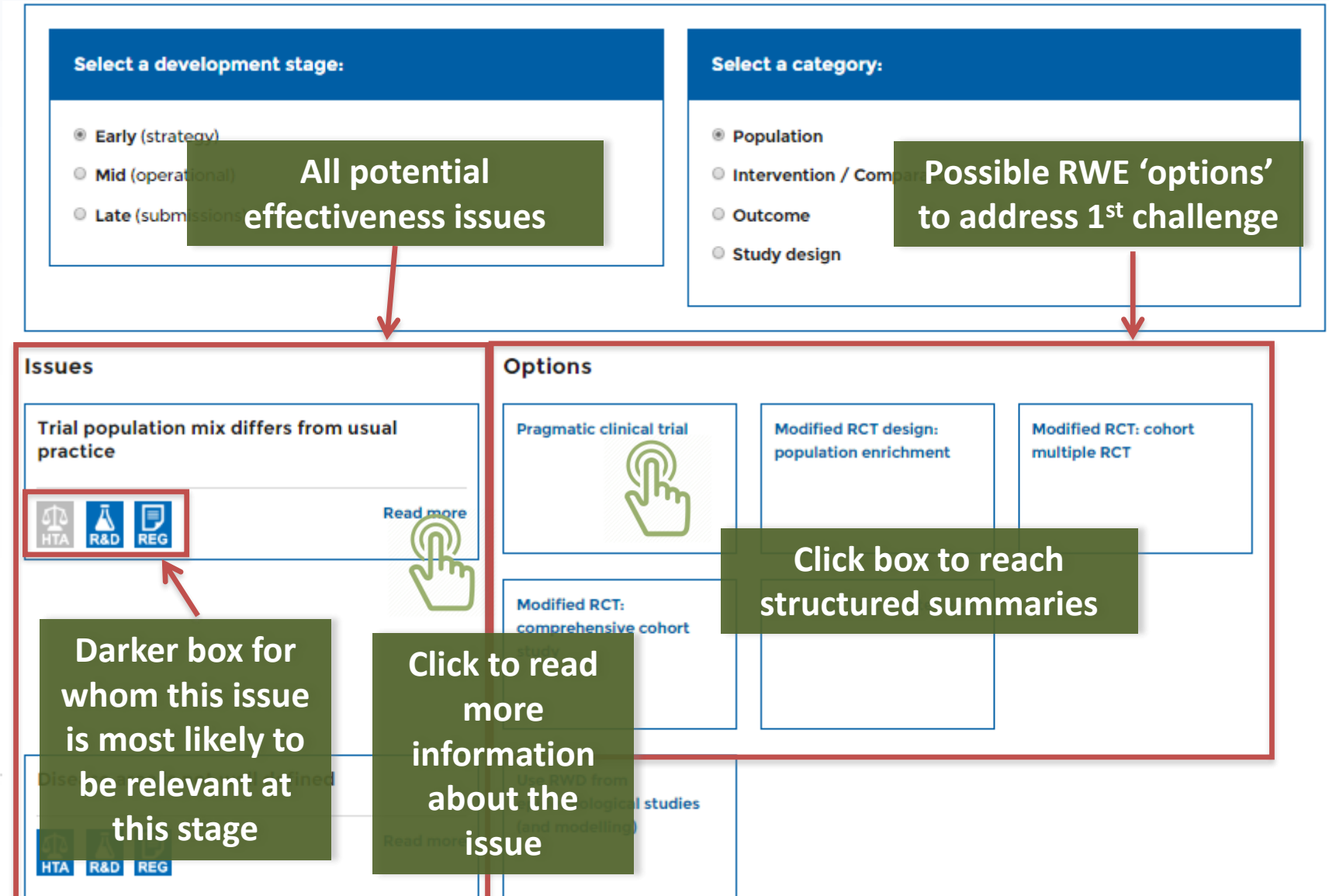
- (●) **Early** (strategy)
- ( ) **Mid** (operational)
- ( ) **Late** (submissions)

Select a category:

- (●) **Population**
- ( ) **Intervention / Comparator**
- ( ) **Outcome**
- ( ) **Study design**

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Issues and RWE options for early + population



rwe-navigator.eu

Structured summary

RWE Navigator / Use real-world data / Generate real-world evidence / Study design: Pragmatic trial

Study design: Pragmatic trial

What is it?

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.

This entails the comparison of randomised groups of patients that are similar to the target group in the characteristics that modify drug response, in the setting where they would be treated in real life. The treatment strategies for comparison and outcome measures should be relevant for routine clinical practice. The term 'pragmatic trial' is commonly used for trials that asses the difference between treatment strategies, including extraneous factors (for example, the effe to maximise generalisability to a broader setting or patient population.

For most new market-approved treatments, the c still insufficient to fully guide clinicians and policy makers in choosing the optimal treatment for their patients. Pragmatic trials can help supplement this data with real-world evidence.

Related links

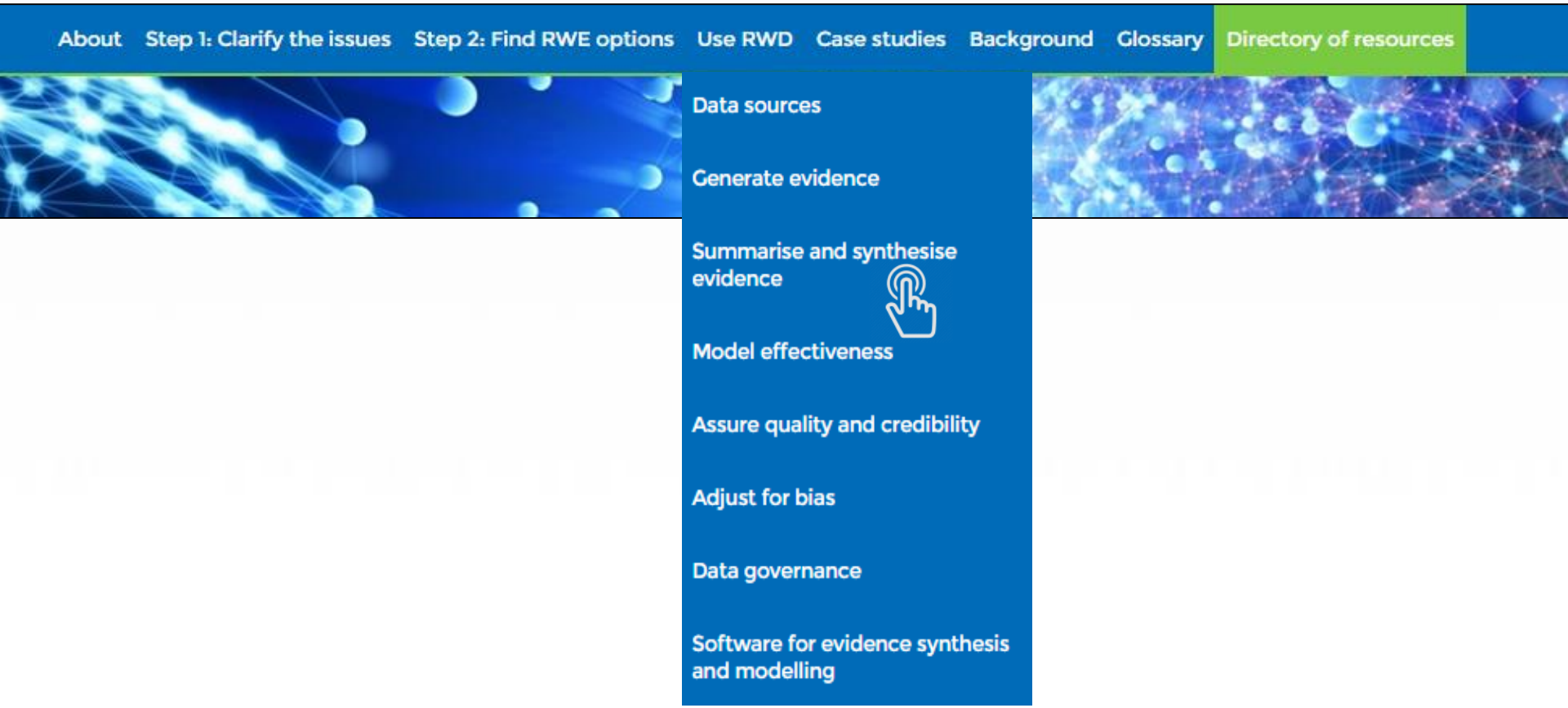
- Learn more about study design considerations in pragmatic trials
- Pragmagic tool
- Nieuwenhuis et al 2016 publication in J Clin Epidemiol on the affect of pragmatic trial design features on features affect validity, generalizability, precision, or feasibility
- Sackett 2013 Clinical Trials publication on pragmatic trials
- van Staa et al 2014 HTA publication on
- Cohort multiple randomised controlled trials (cmRCTs) / trials

Sections covering what it is, why it's useful, when it's suitable, limitations and stakeholder feedback

Links to authoritative sources, GetReal deliverables, full-text publications

Scenario 3:
HTA analyst wishing to understand how RWE/RWD can be incorporated in evidence synthesis

rwe-navigator.eu



The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Summarise and synthesise real-world evidence

Evidence synthesis

Evidence synthesis is the process of retrieving, evaluating and summarising the findings of all relevant studies on a certain subject area. Ideally, a systematic review is conducted to identify all the relevant available studies to support the evidence synthesis. For more information about systematic reviewing, see the Cochrane handbook for systematic reviews of interventions.

Meta-analyses may then be used to combine the estimates from the individual studies identified.

Network meta-analysis (NMA) is an extension of the standard, pairwise meta-analysis, and can be used to synthesise results from studies that compare multiple competing interventions for the same condition.

For more information about evidence synthesis and network meta-analysis see here.

Related links

- Overview of evidence synthesis and NMA
- Cochrane handbook for systematic reviews of interventions

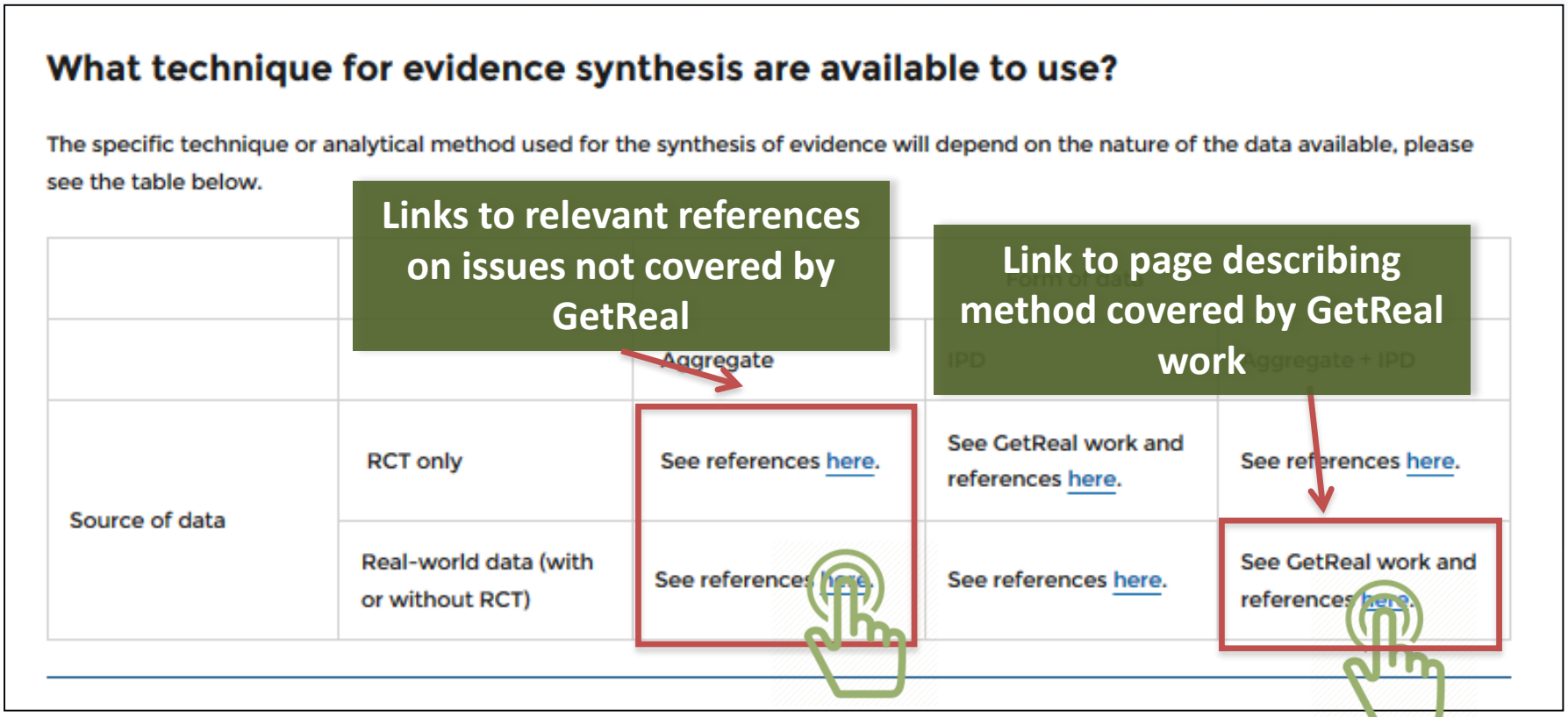
Links through to pages describing evidence synthesis methods and network meta-analysis (NMA)

Including RWD in evidence synthesis

Meta-analysis and NMA are usually limited to the synthesis of evidence from randomised controlled trials (RCTs) because they are considered to be the most reliable source of information on relative treatment effects. However, there is a growing interest in the medical community in incorporating evidence from non-randomised studies (NRSs), patient registries and other real-world data (RWD).

This strategy is particularly appealing when there are few RCTs to answer a specific research question. It may also be useful when the available RCTs do not align with the target population, prescription strategies and/or primary outcomes of the research question (i.e. when there is an efficacy-effectiveness gap, see a definition here).

Explains why you might consider RWD in evidence synthesis and links to pages explaining how this can be done



The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

More information on evidence synthesis & NMA

Indirect treatment comparison and network meta-analysis

Meta-analysis is a widely accepted statistical tool, used for synthesising evidence on the relative effects of interventions obtained from multiple individual RCTs. However, the value of pairwise meta-analysis may be limited in real-world clinical

do not include some of the pairwise

by undertaking an NMA.

son, B vs. C, may be carried out

e carried out indirectly, by

diagram below, for B vs. C there is

o sources of evidence can be

arisons

parisons

CTs may not cover all of the

reatments (A-F) and a set of

but not all of the pairwise

comparison there may be direct and

to synthesise all of the evidence

'Best practice' for conventional indirect comparisons/network meta-analysis using aggregate RCT data

Network meta-analysis (NMA)

Information on best practice for conventional indirect comparisons and network meta-analysis (NMA) is summarised on this page, with links to useful resources.

For more information describing NMA see here. The GetReal review on NMA methods can be found here and the articles identified in this review can be found here.

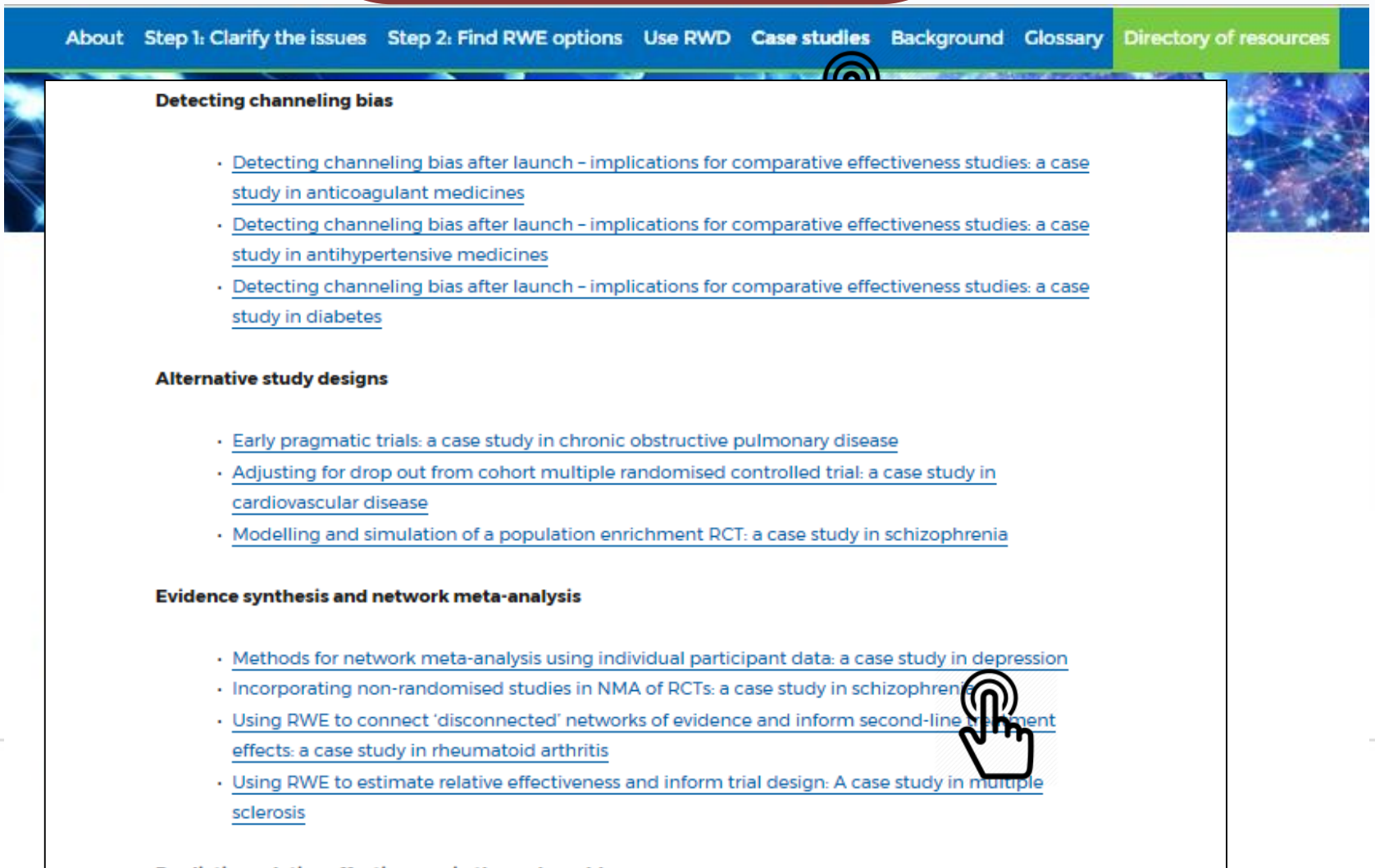
Assessing the assumptions of NMA

NMA adopts the same set of assumptions as a usual (pairwise) meta-analysis, but also uses an additional assumption that may be hard to assess, called transitivity (also called similarity or exchangeability) (Ades 2011, Salanti 2012, Efthimiou et al 2016).

- Transitivity assumes that information for the comparison between treatments B and C can be obtained via another treatment, A, using the comparisons A vs. B and A vs. C.
- Researchers can assess this assumption by checking the distribution of effect modifiers across comparisons (Jansen et al 2011).
- They can also use conceptual considerations, for example, checking whether the missing treatments in each trial are 'missing at random' or whether the choice of treatment comparisons in the trials is

rwe-navigator.eu

Scenario 4: Anyone looking to understand more about GetReal case studies



Incorporating non-randomised studies in NMA of RCTs: a case study in schizophrenia

Context

Schizophrenia is a mental disorder which affects the way a person thinks, feels and behaves. It is characterised by abnormal social behaviour and may lead to difficulties in distinguishing between what is real and what is imaginary. Schizophrenia has been ranked among the top causes of disability in the world (Murray et al 1996, Tandon et al 2008).

There are a wide range of competing antipsychotic drugs available in the market and there have been many randomised controlled trials (RCTs) that assess most of the available treatment options. These trials cover a wide range of treatment comparisons, forming a network of evidence (see here for a description of network meta-analysis). In addition, there have been non-randomised studies (NRSs) measuring the effectiveness of drugs in real-world clinical settings. However, the two different types of evidence have not been jointly synthesised. The benefits of adding NRS, a type of real-world data (RWD), to the synthesis is explained here.

What was examined in this case study?

The aim of this case study was to assess existing methodology and develop new methods for combining evidence from RCTs and NRSs in a network meta-analysis (NMA). Specific issues examined were:

- How can inconsistencies between the different types of evidence (randomised and non-randomised) be assessed?
- What analytic methods can be used to incorporate RWE from NRSs into an NMA?

Related links

- Network meta-analysis incorporating RWE
- Efthimiou et al 2016 publication in StatMed on combining randomised and non-randomised evidence in an NMA [TO BE ADDED]

Headings give context, explain brief methods, findings/conclusions, limitations of case study, (any) stakeholder feedback

Link to publications and deliverables

Get Real

Thank you!

Real-Life Data in Drug Development

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115546], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu