

Real-world evidence (RWE) Navigator launch

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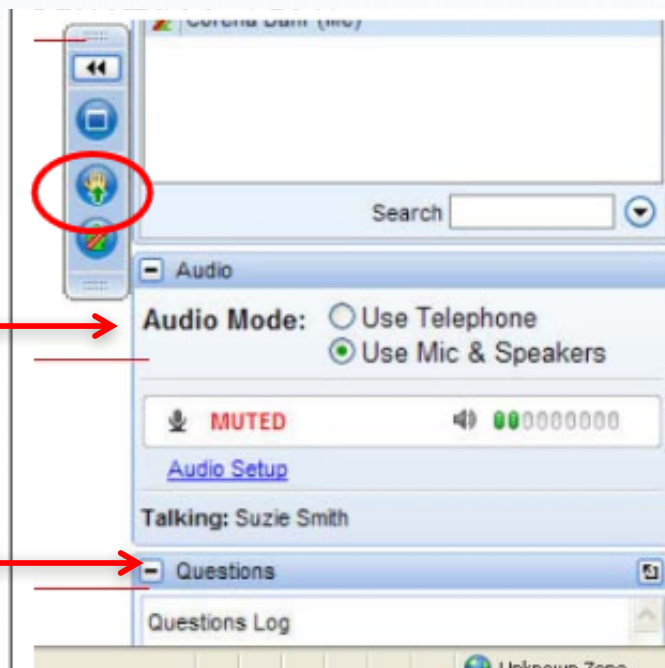
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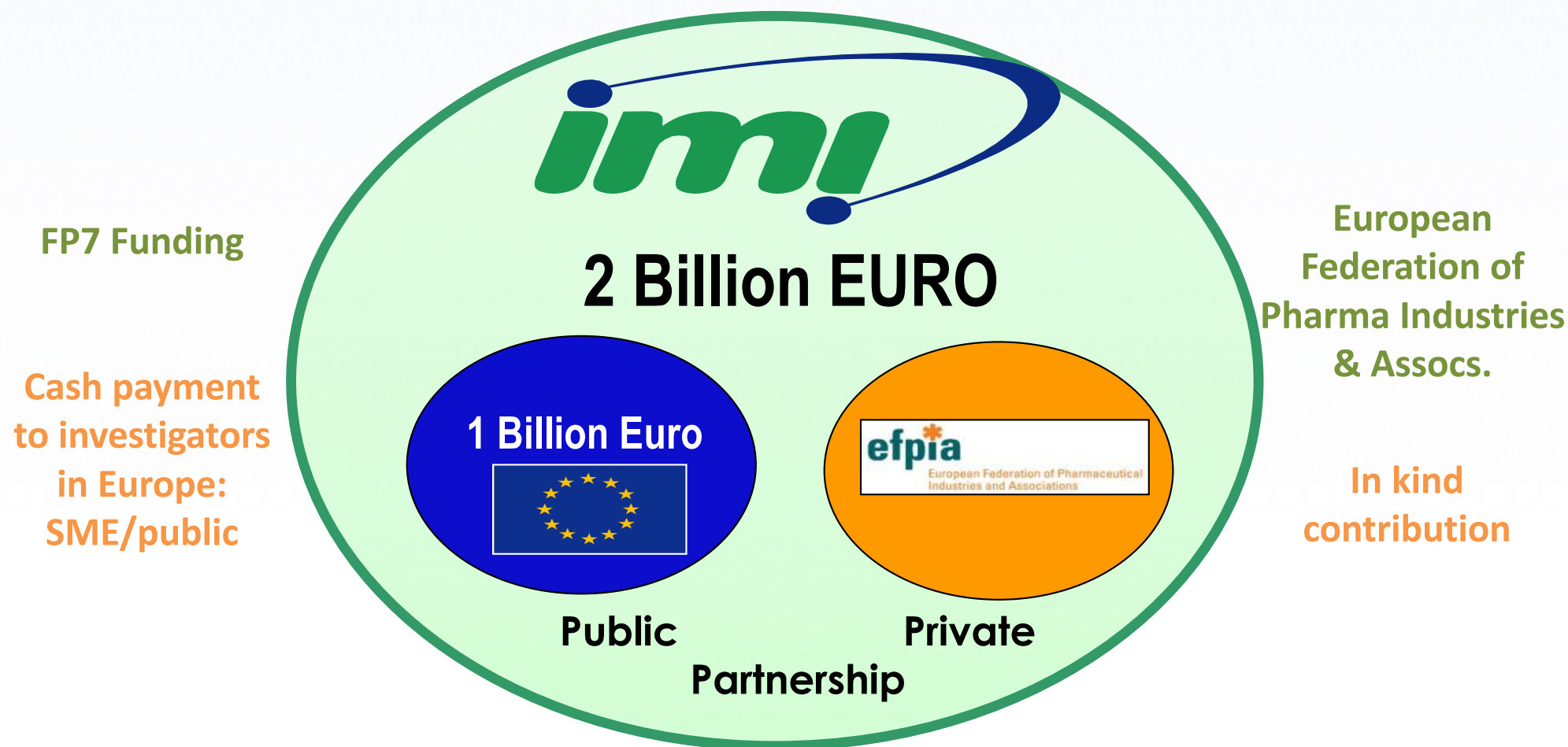
Raise your hand

Dial in or headphones

Ask a question



Innovative Medicines Initiative (IMI)



Why 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

Mind the gap

Efficacy

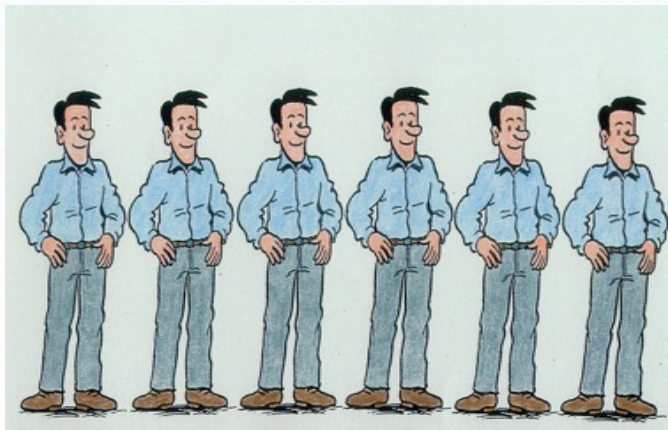
Can it work?



Effectiveness

*Does it work?
(for my
population)*

Efficacy vs effectiveness



- Benefit and harm in experimental and closely monitored research studies, normally RCTs
- RCTs minimise bias (high internal validity)
- Generalisable?



- Benefit and harm in everyday practice. (Pragmatic clinical trials, Observational studies, synthesis)
- 'Dirty' - variability and biases



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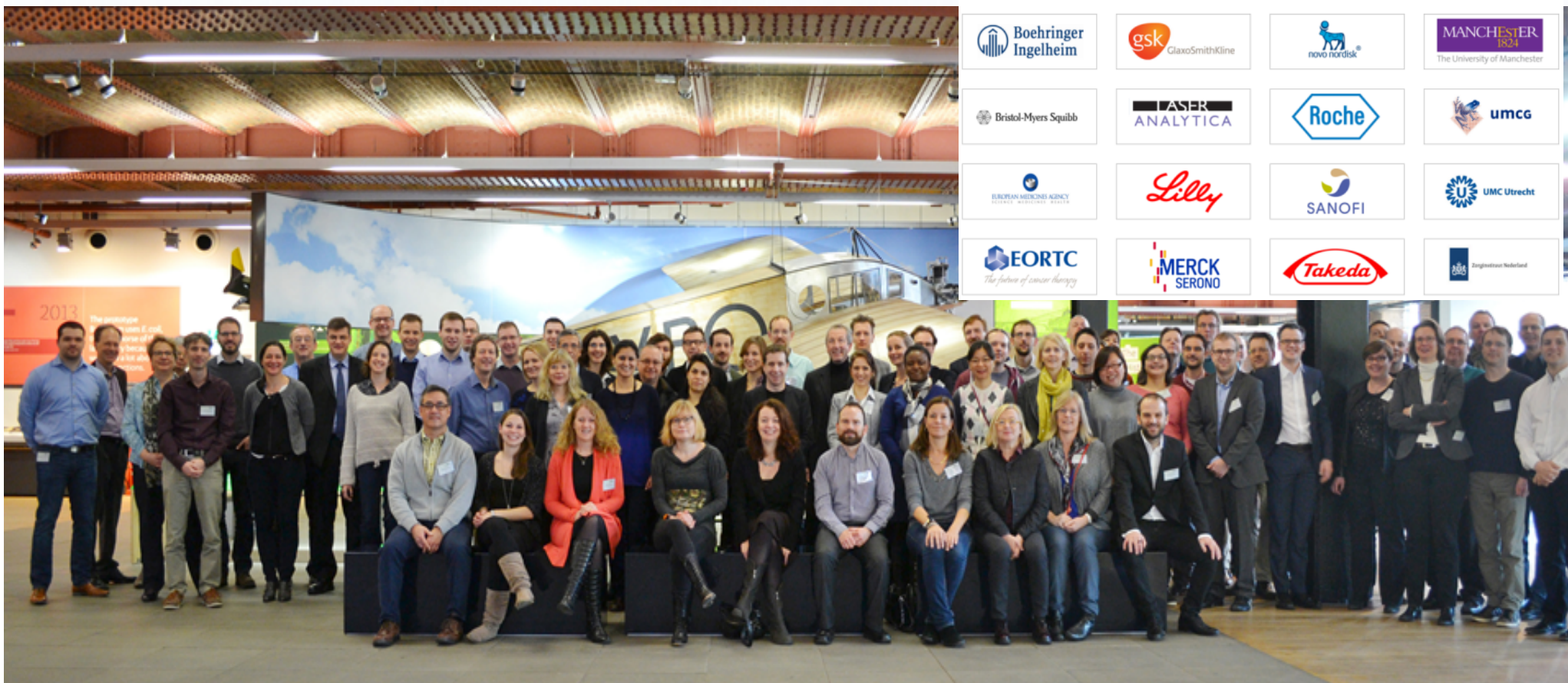
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Three Years of a *Real* Public Private Partnership





Original research

- Drivers of effectiveness
- Analytical methods
- Prediction models
- Methodological guidance



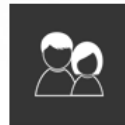
Methods

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



Summaries

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



Case studies

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



Tools

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

Illustrative examples – not a complete list of GetReal outputs

Putting real-world healthcare data to work

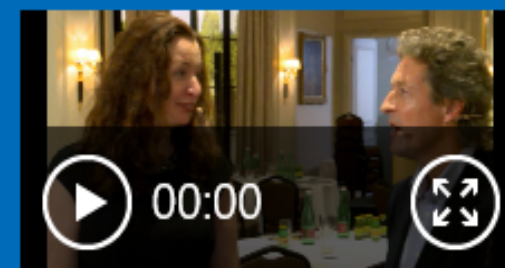
Real-world evidence (RWE) Navigator

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

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

+ Real-Life Data in
Drug Development

Development

Analyse RWD to assess effectiveness of existing medicines

Highlight shortcomings in existing treatments using RWE

Incorporate RWD to estimate cost-effectiveness using economic models

File and launch

Include evidence on use and effectiveness of existing medicines in registration package

Conduct network meta-analysis to estimate relative efficacy (or effectiveness) of new medicine

Post-marketing

Assess relative effectiveness of our new medicine in claims and EMR database analyses

Synthesize studies on relative effectiveness vs competitor medicines

...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/>

Putting real-world healthcare data to work

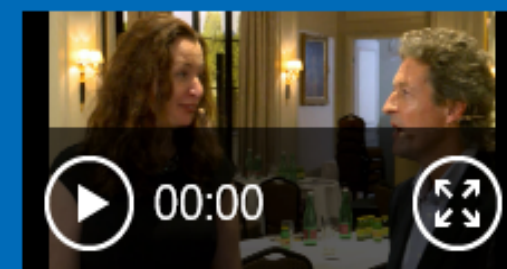
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Understanding GetReal and the RWE Navigator



Step 1: Clarify the issues

Step 2: Find RWE options

Directory of resources

- 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

Who is it for ?



What will I find?

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

Organising principles

Effectiveness issues (challenges)

Examples

Population: Trial population mix differs from routine practice

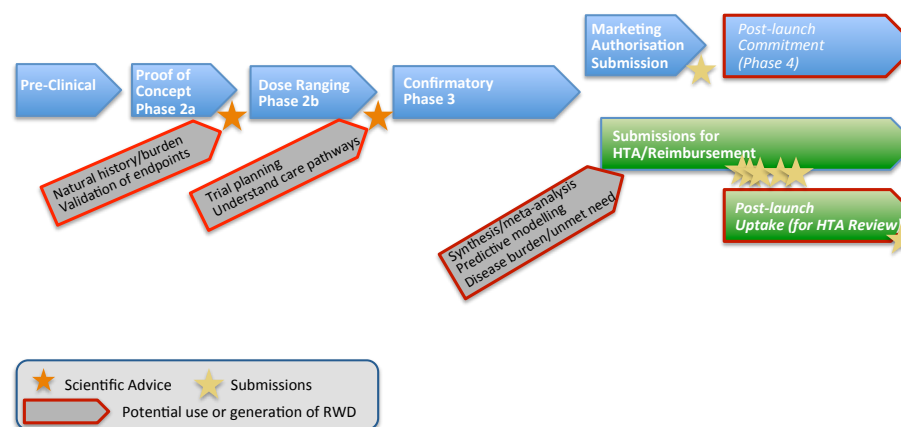
Intervention: Adherence in study differs from usual practice

Comparators: Trial comparators do not include current usual care or standard of care

Organised by: PICO-S &
Development Phase

Evidence development pathways

Standard 'Evidence Development pathway'



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



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Putting real-world healthcare data to work

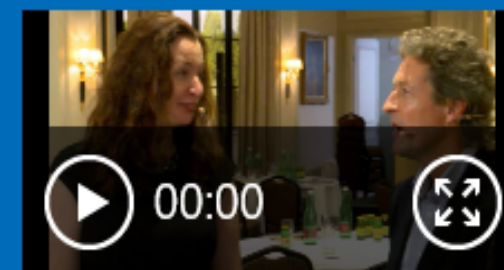
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Understanding GetReal and the RWE Navigator

[Step 1: Clarify the issues](#)[Step 2: Find RWE options](#)[Directory of resources](#)

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

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

Data sources



Generate evidence

Summarise and synthesise evidence

Model effectiveness

Assure quality and credibility

Adjust for bias


Data governance

Software for evidence synthesis and modelling



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

About Step



RWE Navigator

Sources of real-world data

Real-world data (RWD) can be collected from a variety of sources, including electronic health records (EHRs), patient registries, and surveys. RWD can provide valuable insights into patient health and disease, but it also has limitations, such as data quality and privacy concerns.

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.


For a review of the usefulness of PPRNs in relative effectiveness research, see [here](#).

Examples 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




Resources



er grant
framework

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



Healthcare data
including elec
health records

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

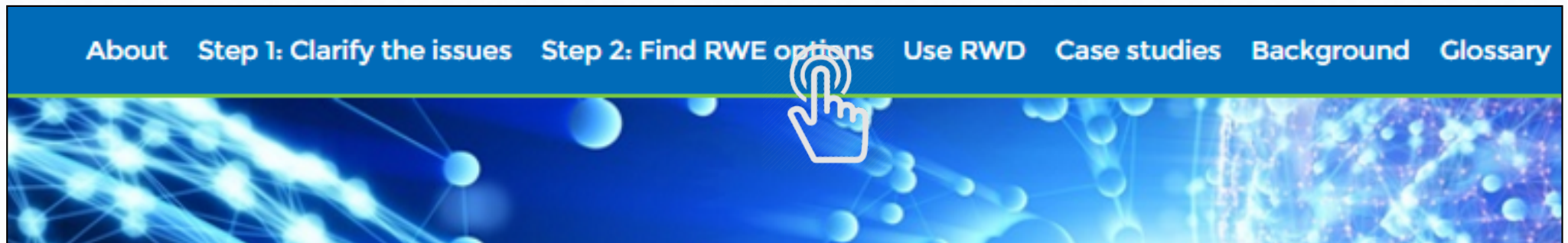
About Step 1: Clarify the issues Step 2: Find RWE options Use RWD Case studies Background Glossary



- 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



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



Find potential options using
RWE to address the
identified issues

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)
 - Choose a development stage (Early, Mid or Late)
- You will find different options for using RWE based on the stage of development of your medicine. For each issue you can find this issue relevant to this stage of medicine development.
- Click 'Read More' to find out more about the corresponding RWE option.

EARLY
Strategy: programme
planning
(end phase 2A/2B)

MID
operational: designing
and executing studies
(phase 2B/3)

LATE
submission: regulatory
approval and
reimbursement

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)

- ☐ 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

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** (operations)
- ☐ **Late** (submissions)

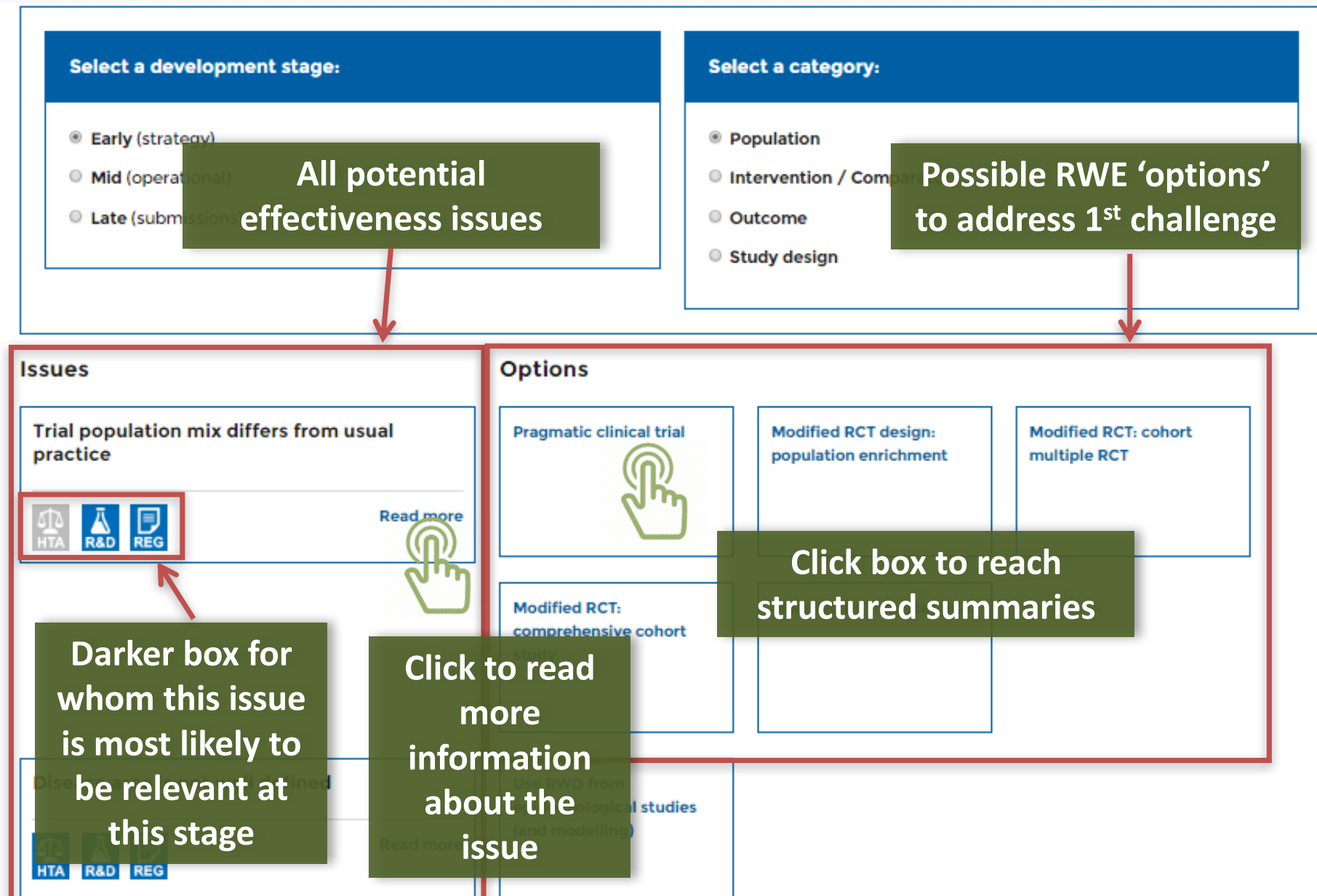


Select a category:

- ☒ **Population**
- ☐ **Intervention / Comparator**
- ☐ **Outcome**
- ☐ **Study design**



Issues and RWE options for early + population



Structured summary

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

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 assess the difference between two treatment strategies, including extraneous factors (for example, the effect of the treatment on quality of life) to maximise generalisability to a broader setting or patient population.

For most new market-approved treatments, the clinical trial evidence is often 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.

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

Related links

- Learn more about study design considerations in pragmatic trials
- Pragmatic 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 pragmatic trials

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

- Cohort multiple randomised controlled trials (cmRCTs) / trials within cohorts (TriCoh)

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



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



What technique for evidence synthesis are available to use?

The specific technique or analytical method used for the synthesis of evidence will depend on the nature of the data available, please see the table below.

Source of data	Links to relevant references on issues not covered by GetReal		Link to page describing method covered by GetReal work	
	Aggregate		IPD, Aggregate + IPD	
RCT only	See references here .		See GetReal work and references here .	See references here .
Real-world data (with or without RCT)	See references here .		See references here .	See GetReal work and references here .

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

'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 not associated either directly or indirectly with the relative effectiveness of the interventions and

do not include some of the pairwise comparisons that could be obtained by undertaking an NMA.

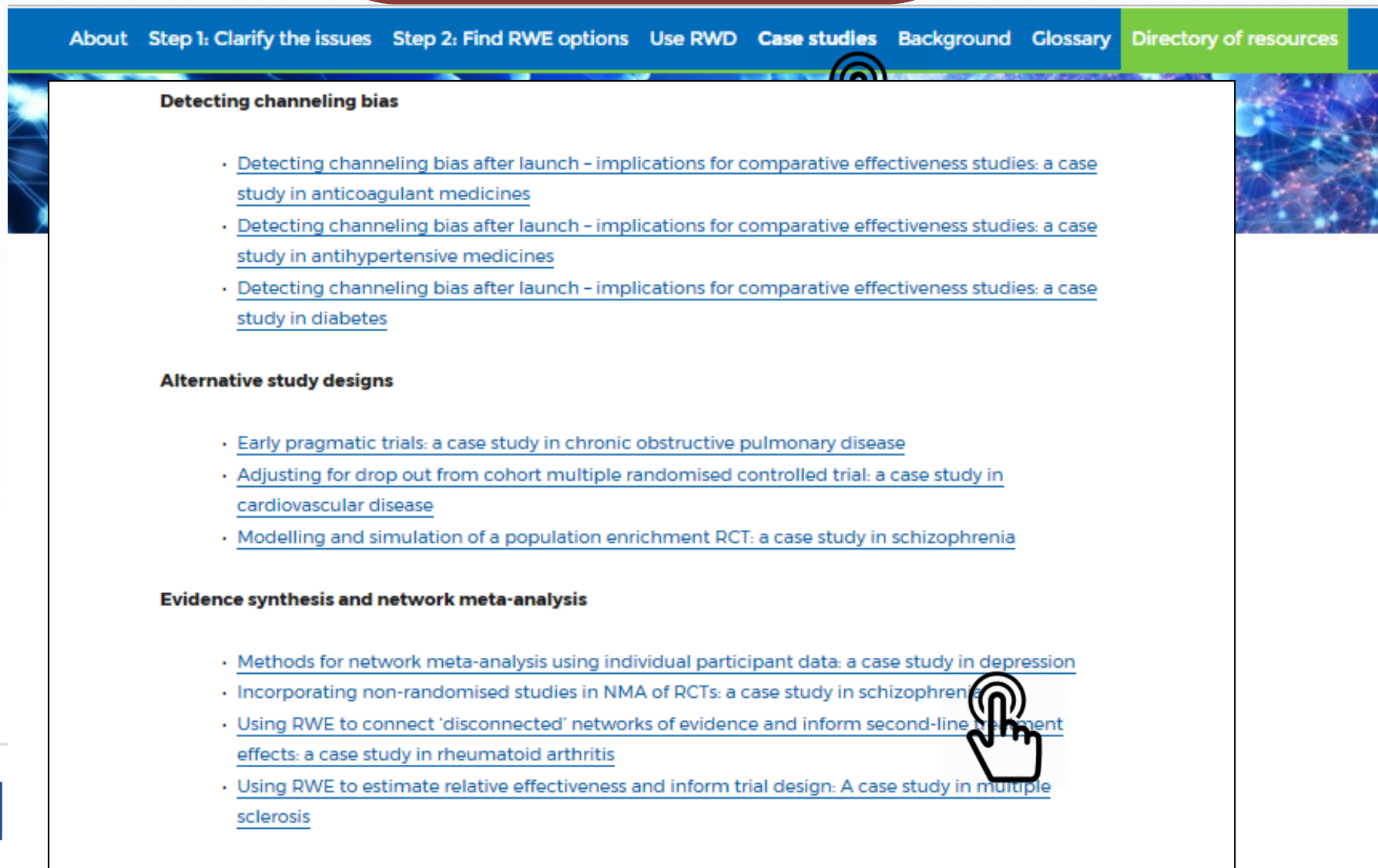
For example, a comparison between treatments B vs. C, may be carried out directly, or it may be carried out indirectly, by comparing B vs. A and A vs. C. In the diagram below, for B vs. C there is no direct evidence, so no sources of evidence can be

comparisons

comparisons

RCTs may not cover all of the treatments (A-F) and a set of comparisons may be available, but not all of the pairwise comparisons. For example, for comparison A vs. F there may be direct and indirect evidence. To synthesise all of the evidence

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



The screenshot shows the 'rwe-navigator.eu' website. The top navigation bar includes links for 'About', 'Step 1: Clarify the issues', 'Step 2: Find RWE options', 'Use RWD', 'Case studies' (which is highlighted with a green background), 'Background', 'Glossary', and 'Directory of resources'. The main content area is titled 'Detecting channeling bias' and lists three case studies. Below this is the 'Alternative study designs' section with three case studies. The final section is 'Evidence synthesis and network meta-analysis' with four case studies. A hand cursor icon is pointing at the fourth case study in the last section.

Case studies

- [Detecting channeling bias after launch - implications for comparative effectiveness studies: a case study in anticoagulant medicines](#)
- [Detecting channeling bias after launch - implications for comparative effectiveness studies: a case study in antihypertensive medicines](#)
- [Detecting channeling bias after launch - implications for comparative effectiveness studies: a case study in diabetes](#)

Alternative study designs

- [Early pragmatic trials: a case study in chronic obstructive pulmonary disease](#)
- [Adjusting for drop out from cohort multiple randomised controlled trial: a case study in cardiovascular disease](#)
- [Modelling and simulation of a population enrichment RCT: a case study in schizophrenia](#)

Evidence synthesis and network meta-analysis

- [Methods for network meta-analysis using individual participant data: a case study in depression](#)
- [Incorporating non-randomised studies in NMA of RCTs: a case study in schizophrenia](#)
- [Using RWE to connect 'disconnected' networks of evidence and inform second-line treatment effects: a case study in rheumatoid arthritis](#)
- [Using RWE to estimate relative effectiveness and inform trial design: A case study in multiple sclerosis](#)

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 a chronic condition that may lead to abnormal social behaviour and may lead to difficulties in distinguishing between reality and the imaginary. Schizophrenia has been ranked among the top causes of disability in the world (World Health Organization 1996, Tandon et al 2008).

There are a wide range of competing antipsychotic drugs available in the market. There have been many randomised controlled trials (RCTs) that assess most of the available treatment options. RCTs 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?

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

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]

Link to publications and deliverables

Other useful content...

Generate RWE
(study designs)

Assure quality
and credibility
of RWD/RWE

Key related
initiatives

Adjust for bias
in non-
randomised /
observational
studies

Governance of
RWD

Model
effectiveness
in real world
setting

Policies &
perspectives
on RWD

Glossary





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WE NEED YOUR INPUT!

- You've seen a presentation of the tool, what specific recommendations or improvements would you like to see to use to tool to facilitate patient access?
- Please tell us using the question field on your webinar desktop

You can also ask your own questions too!



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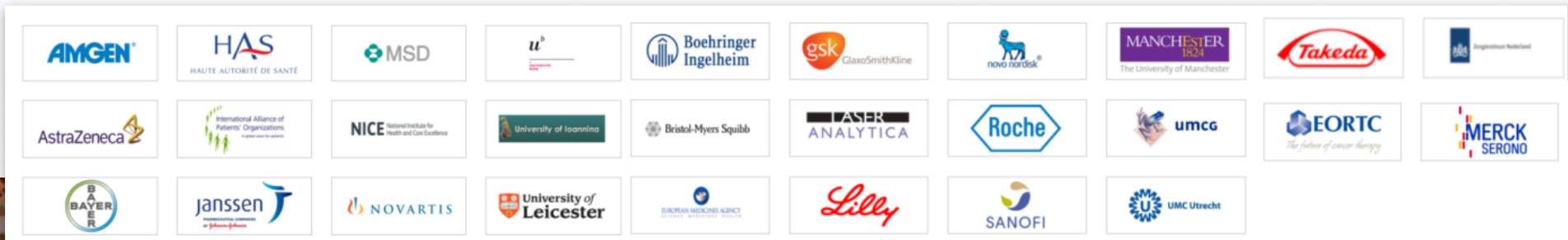
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