GetReal and the RWE Navigator

Heather Stegenga, Senior analyst, NICE

EFSP/PS meeting, 28th November 2017
Outline

• Background / context

• IMI GetReal

• RWE Navigator
### Key decision criteria:

**Regulators**
- Quality, safety & clinical efficacy

**HTAs/payers**
- Cost & clinical effectiveness

### Scope:

<table>
<thead>
<tr>
<th>Regulators</th>
<th>HTAs/payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised Controlled trials</td>
<td>Routine clinical practice</td>
</tr>
</tbody>
</table>

**Data fit for purpose?**

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### 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

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Three Years of a Real Public Private Partnership

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

**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

- 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/
GetReal facilitates stakeholder dialogue

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
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Example GetReal Outputs

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*
Stats in Nov ‘16

36 peer-reviewed manuscripts
13 deliverable reports
62+ conference presentations
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*Illustrative examples – not a complete list*
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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.
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’).

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

• A comprehensive **directory of resources** on the use of RWE in medicines, signposting to GetReal outputs and other authoritative sources.
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Example key content categories

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
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 massive structured RWD.

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

## Overview of RWD sources

RWD can be obtained from experimental studies and observational studies. The different study designs can provide RWD. Additional sources of RWD that may provide data for non-structured studies are listed below.

### Table. RWD from existing sources

<table>
<thead>
<tr>
<th>Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient registries</td>
<td>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. <a href="#">Read more</a></td>
</tr>
<tr>
<td>Healthcare databases including electronic health records</td>
<td>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. <a href="#">Read more</a></td>
</tr>
<tr>
<td>Pharmacy and health insurance databases</td>
<td>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. <a href="#">Read more</a></td>
</tr>
<tr>
<td>Social media</td>
<td>Social media are internet-based websites and applications that enable users to create and share content or to participate 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. <a href="#">Read more</a></td>
</tr>
<tr>
<td>Patient-powered research networks</td>
<td>Patient-powered research networks (PPRNAs) are online platforms run by patients to collect and organise health and clinical data. <a href="#">Read more</a></td>
</tr>
</tbody>
</table>

[Related links]

- Generating RWE including different study designs
- Summary of GetReal glossary of terms and definitions
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 predicting effectiveness in the real world using RCT data see here, and for more information about real world data sources see here.

Some experimental and observational study designs that could provide RWE are summarised below. While some study designs may provide evidence on relative effectiveness, some epidemiological observational studies may not be able to provide evidence of relative effectiveness. However, they may be useful to define the disease area and understand the natural disease course and 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 evidence and its interpretation, it is crucial to assess each study individually, whether or not it is an RCT.

For more information about assuring quality and credibility of RWE, see this article.

### Table. Study designs that may provide RWE

<table>
<thead>
<tr>
<th>Experimental study designs</th>
<th>Observational study designs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pragmatic RCT</strong></td>
<td><strong>Cohort</strong></td>
</tr>
<tr>
<td>A pragmatic trial aims to measure the relative effect of two treatments in real-world clinical practice. It combines the data from RCTs with evidence of the added value of a treatment over routine clinical practice. <a href="#">Read more</a></td>
<td>A cohort study follows a group of individuals over a period of time to consider associations between interventions received and outcomes.</td>
</tr>
<tr>
<td><strong>Population enrichment RCT</strong></td>
<td><strong>Case-control</strong></td>
</tr>
<tr>
<td>A population enrichment RCT includes patients typical of those from RCTs combined with predictive modelling techniques to help better predict relative effectiveness in a real-world setting. <a href="#">Read more</a></td>
<td>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 interventional studies.</td>
</tr>
<tr>
<td><strong>Cohort multiple RCT (cmRCT) (also known as or trials within cohorts)</strong></td>
<td><strong>Cross-sectional</strong></td>
</tr>
<tr>
<td>cmRCTs are a type of pragmatic RCT that use a large number of patients as a source of participants for multiple RCTs, thus creating a more generalisable study sample. <a href="#">Read more</a></td>
<td>In a cross-sectional study, data are collected from a population or a representative subset of a population at one specific point in time or over a short period to examine associations between the outcomes and exposure to interventions.</td>
</tr>
<tr>
<td><strong>Controlled before-and-after</strong></td>
<td><strong>Controlled before-and-after</strong></td>
</tr>
<tr>
<td>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. <a href="#">Read more</a></td>
<td>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.</td>
</tr>
</tbody>
</table>

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

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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 (NR55s), 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.
Assure quality and credibility of RWE

The defining feature of a randomised controlled trial (RCT), the random assignment of participants to treatment groups, can ensure that characteristics of participants are similar in the two groups, when the trial is well conducted. This is most important when those characteristics also have a direct impact on the effect of a medicine, such as the severity of the condition or called confounding variables or treatment effect modifiers). While there are non-randomized methods that are sometimes used to ensure equal distribution of these factors between groups (such as matching), random allocation is particularly important as there are no other characteristics that influence a treatment effect that are not known.

Although other factors may influence the internal validity of a study, including the adherence to treatment protocols and the measurement of outcomes, the internal validity of an RCT conducted RCTs is likely to be high, providing more reliable estimates of a medicine’s effect. However, traditional RCTs are less likely to reflect the real world in the way that interventions are administered or in other factors (i.e. they may have low external validity).

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

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**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 (Farie 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 Farie et al 2015.

**Table: Commonly used quality checklists by study design**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Quality checklists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trials (RCTs)</td>
<td>Cochrane risk of bias tool, GASP randomised controlled trial checklist</td>
</tr>
<tr>
<td>Non-randomised study designs, controlled cohort, controlled before-after</td>
<td>In the context of cost-effectiveness analyses: ISPOR checklist for prospective observational studies, ISPOR checklist for retrospective database studies, Checklist for statistical methods to address selection bias in estimating incremental costs, effectiveness and cost-effectiveness (Kreif et al 2015), NICE DSU QUeENS checklist (for use on its own or to complement other checklists)</td>
</tr>
</tbody>
</table>
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.
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 obtained from such studies are less reliable and considered to be biased (this is called selection bias). Well-conducted randomised studies with an adequate study size should eliminate differences between treatment arms which may influence the outcome due to the randomised nature of treatment selection.

To control for some known factors where randomisation has not occurred or biased results, for example stratification or matching, but this is not always possible. Where they do not use randomisation to control for confounding, statistical methods can be used to provide a more accurate estimate of treatment effects. It is ongoing on different methods to control for confounding. Also, statistical methods are used to estimate for unmeasured confounders. The methods can normally be categorised into the following factors and those that adjust for unknown confounding factors below provides some of the more commonly known methods.

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

<table>
<thead>
<tr>
<th>Methods that adjust for known confounding</th>
<th>Methods that adjust for unknown confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regression adjustment</strong> using regression models (such as logistic regression models) by prognostic</td>
<td><strong>Instrumental variable methods</strong></td>
</tr>
<tr>
<td>factors)</td>
<td>This is the most commonly used method to deal with unknown confounding. This approach aims to find a</td>
</tr>
<tr>
<td><strong>Inverse probability weighting (IPW)</strong></td>
<td>variable (or instrument) that is correlated with the treatment, but not directly correlated to the outcome</td>
</tr>
<tr>
<td></td>
<td>(except through the treatment). A causal treatment effect is identified by varying the instrument. For</td>
</tr>
<tr>
<td></td>
<td>a brief description and more resources, see <a href="#">here</a></td>
</tr>
<tr>
<td><strong>Doubly robust methods</strong></td>
<td><strong>Panel data models</strong></td>
</tr>
<tr>
<td></td>
<td>This approach uses an individual as their own control at different time-</td>
</tr>
</tbody>
</table>

Note: [here](#) for more details.
Governance of real-world data

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

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

OECD have identified eight key data governance mechanisms to support privacy and the protective use of 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.
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
Real-world evidence (RWE) Navigator

The Real-world evidence (RWE) Navigator:

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

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

Patient-powered research networks

What is it?

Patient-powered research networks (PPRN) 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:

- Enhance patients’ involvement in research and allow them to contribute to or oversee the research activities of their network.
- 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 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.
Scenario 2: pharmaceutical company preparing an evidence development plan for a new medicine

- 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

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

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

LATE
submission: regulatory approval and reimbursement

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Scenario 2: pharmaceutical company looking for options using RWE

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).
Issues and RWE options for early + population

Select a development stage:
- Early (strategy)
- Mid (operational)
- Late (submissions)

Select a category:
- Population
- Intervention/Comparison
- Outcome
- Study design

All potential effectiveness issues

Possible RWE ‘options’ to address 1st challenge

Click box to reach structured summaries

Darker box for whom this issue is most likely to be relevant at this stage

Click to read more information about the issue

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Structured summary

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

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
Summarise and synthesise real-world evidence

Evidence synthesis

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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.

Links through to pages describing evidence synthesis methods and network meta-analysis (NMA).
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                                                                 | RCT only           | See references here. | See GetReal work and references here. | Real-world data (with or without RCT) | See references here. | See GetReal work and references here. |

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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 practice do not include some of the pairwise comparisons, which can be carried out by undertaking an NMA.

‘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

RCTs may not cover all of the different treatments (A–F) and a set of direct and indirect comparisons may be needed to synthesise all of the evidence.
Scenario 4:
Anyone looking to understand more about GetReal case studies

Detecting channeling bias

- 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 characterised by abnormal social behaviour and may lead to difficulties in distinguishing what is real from what is imaginary. Schizophrenia has been ranked among the top causes of disability worldwide (World Health Organization 1996, Tandon et al 2008).

There is a wide range of competing antipsychotic drugs available in the market. However, there have been many randomised controlled trials (RCTs) that assess most of the available treatments. These 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?

Related links

- Network meta-analysis incorporating RWE

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

Link to publications and deliverables
Thank you!

rwe-navigator.eu

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