Get Real

Real-Life Data in Drug Development

GetReal: Three Years On

Sarah Garner, Rob Thwaites, Páll Jónsson

on behalf of WP1

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], 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.
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Why the need for change?

Get Real
Real-Life Data in Drug Development

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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WP1 activities mirrored the set of activities across GetReal, but also brought the programme together

Get Real
Real-Life Data in Drug Development

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

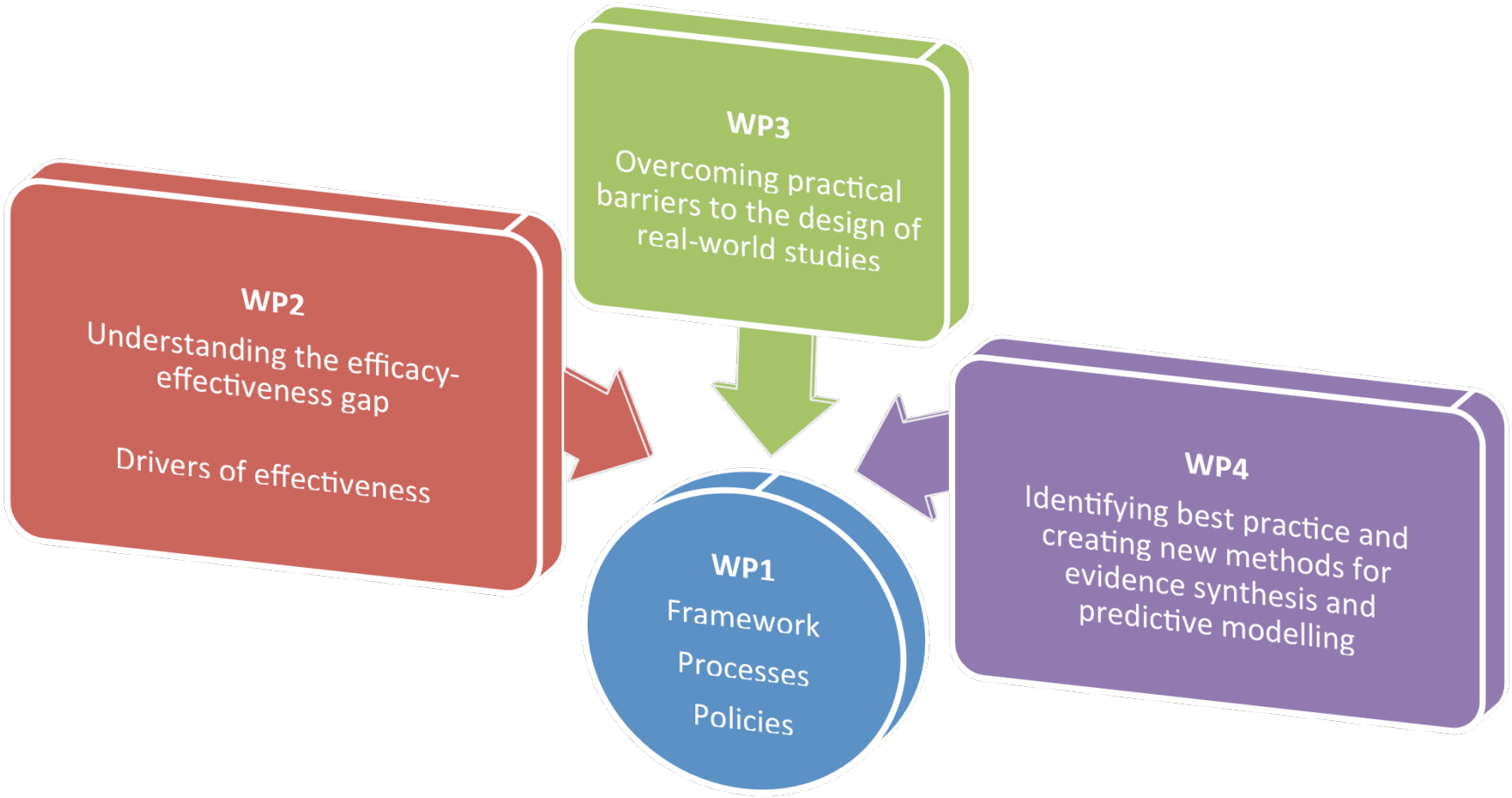
Summaries
- Study types
- Sources of data
- Methods
- Literature reviews

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

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

IMI GetReal: Work Package structure

Get Real
Real-Life Data in Drug Development



Three Years of a *Real* Public Private Partnership

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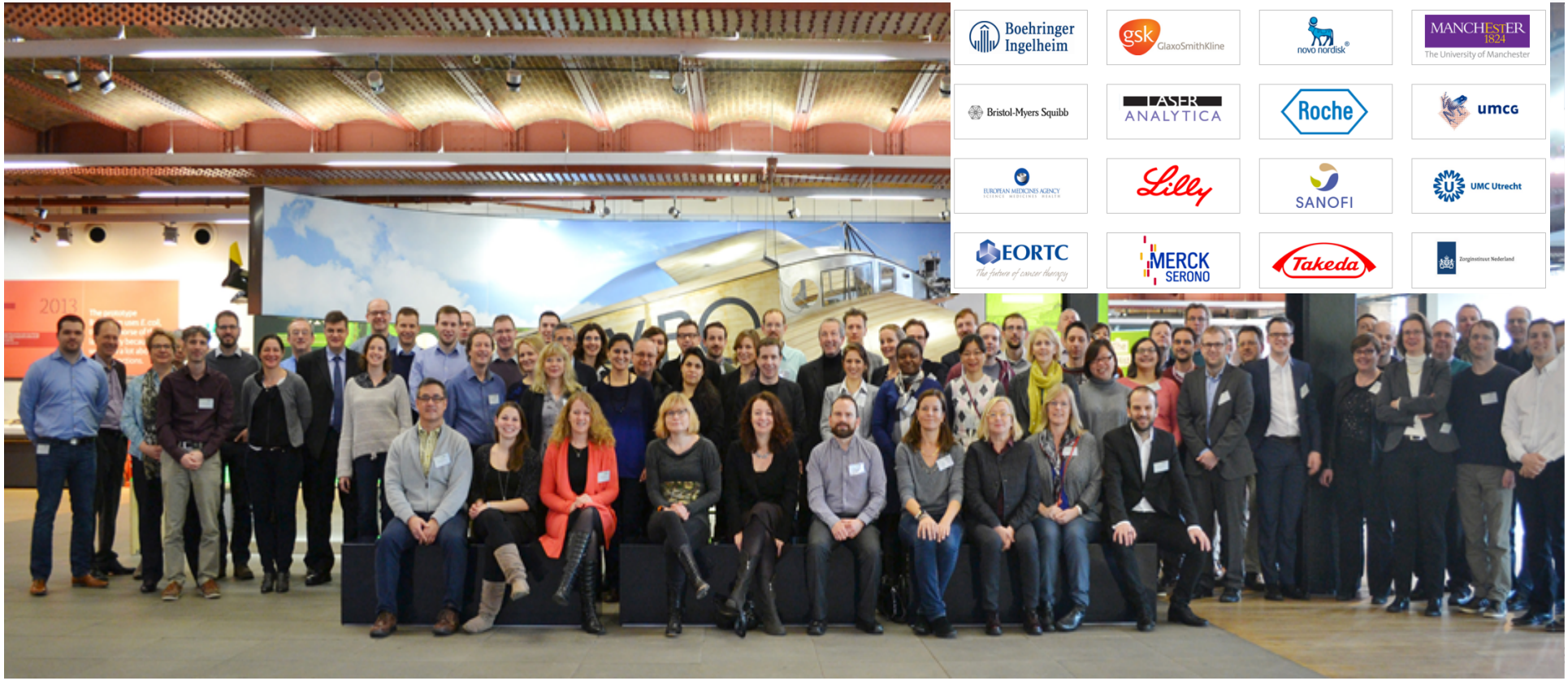

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Through this partnership we were able to address a range of RWE issues together

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- Shared understanding of the technical and process issues from each perspective
- In-depth exploration of 6 challenging disease areas to highlight the issues
- Exploration of novel methodological solutions
- Compilation of best-practice recommendations
- Future research agenda
- Collaboration and trust

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WP1 Case Studies:
Testing Use and Synthesis of Real-World Data

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Real-Life Data in Drug Development

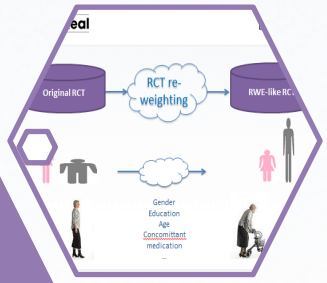
COPD

Patient-Powered Research Networks

Met. Melanoma

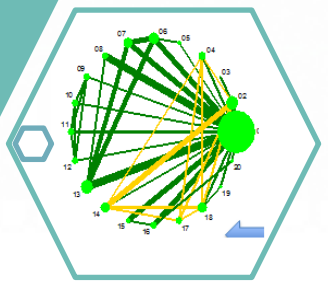
RCT + RWD = ?

Non-small cell lung cancer



Multiple Sclerosis

Rheumatoid Arthritis



Some (practical) lessons learned...

- External stakeholder engagement is important (but takes time)
- It takes time to build up trust and establish ways of working together
- Case studies with actual examples are useful to gather views on usefulness, acceptability and impact of solutions
- Staff turnover can be an issue (esp. private sector)
  - Retaining knowledge /Bringing new people up to speed
- Good communication of issues and solutions is required
- Sustainability and implementation plans beyond the projects are needed

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

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Examples

Development	File and launch	Post-marketing
• Analyse RWD to assess effectiveness of existing medicines • Highlight shortcomings in existing treatments using RWE • Incorporate RWD to estimate cost-effectiveness using economic models	• 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	• Assess relative effectiveness of our new medicine in claims and EMR database analyses • Synthesise studies on relative effectiveness vs competitor medicines

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

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Examples

- 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 and HTA agencies

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

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Example GetReal Outputs

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

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Anything of interest?

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Example GetReal original research

- Modelling effectiveness in the real-world (with case studies)
- Incorporating RWE in NMA (with case studies)
- Software for evidence synthesis (ADDIS)
- Patient powered research networks
- Social media
- Drivers of effectiveness (with case studies)
- RWE to inform RCT design
- Adjusting for confounding in early post launch settings (with case study)
- ⋮

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Real-world evidence framework

The Innovative Medicines Initiative's GetReal project

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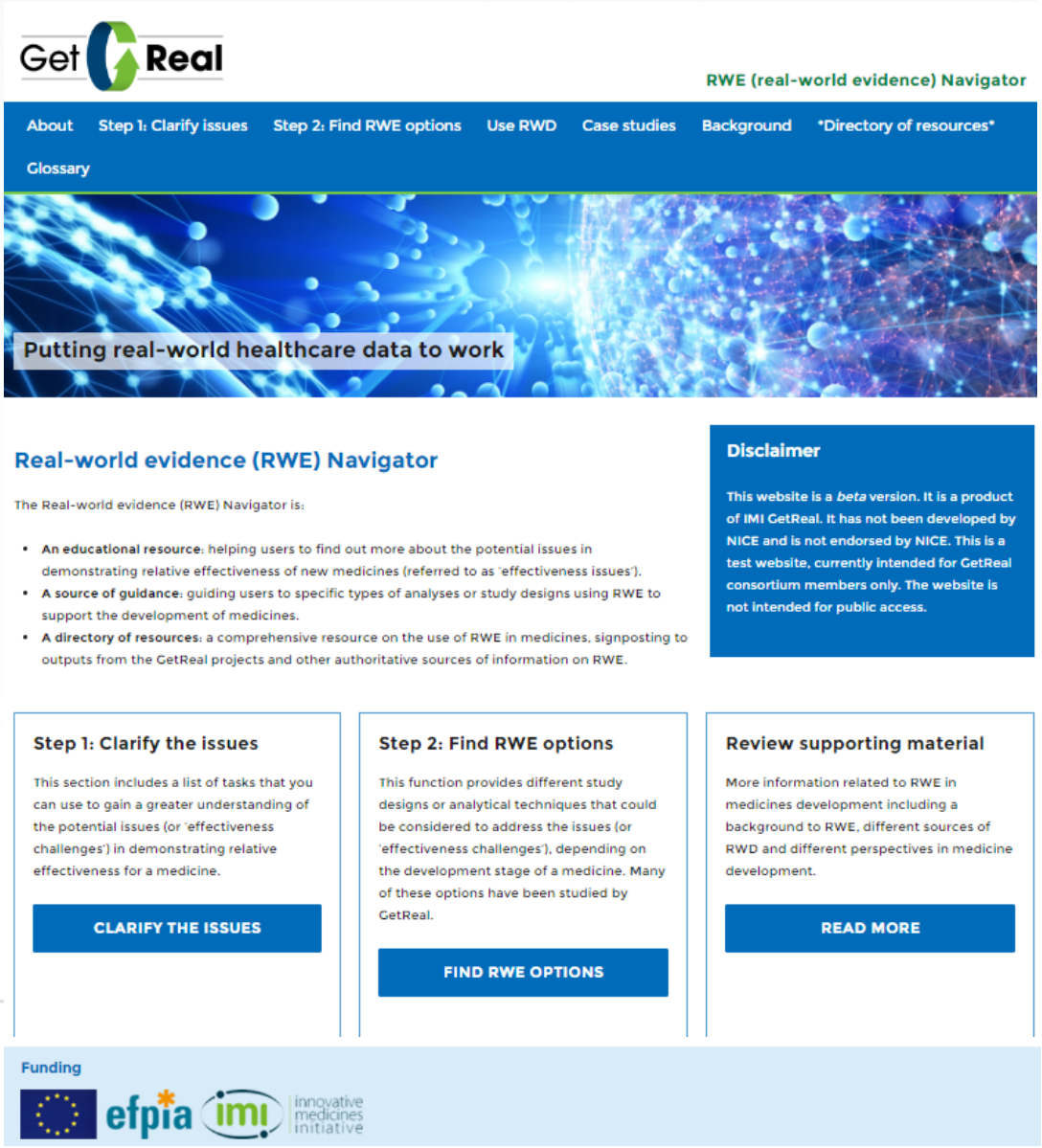
Two main functions:

An **educational resource** to help find out more in general about the potential use of RWD to support the development of new medicines

An expert resource to **guide users to specific types of analyses or study designs** relevant to RWE, many of which have been tested by the GetReal project



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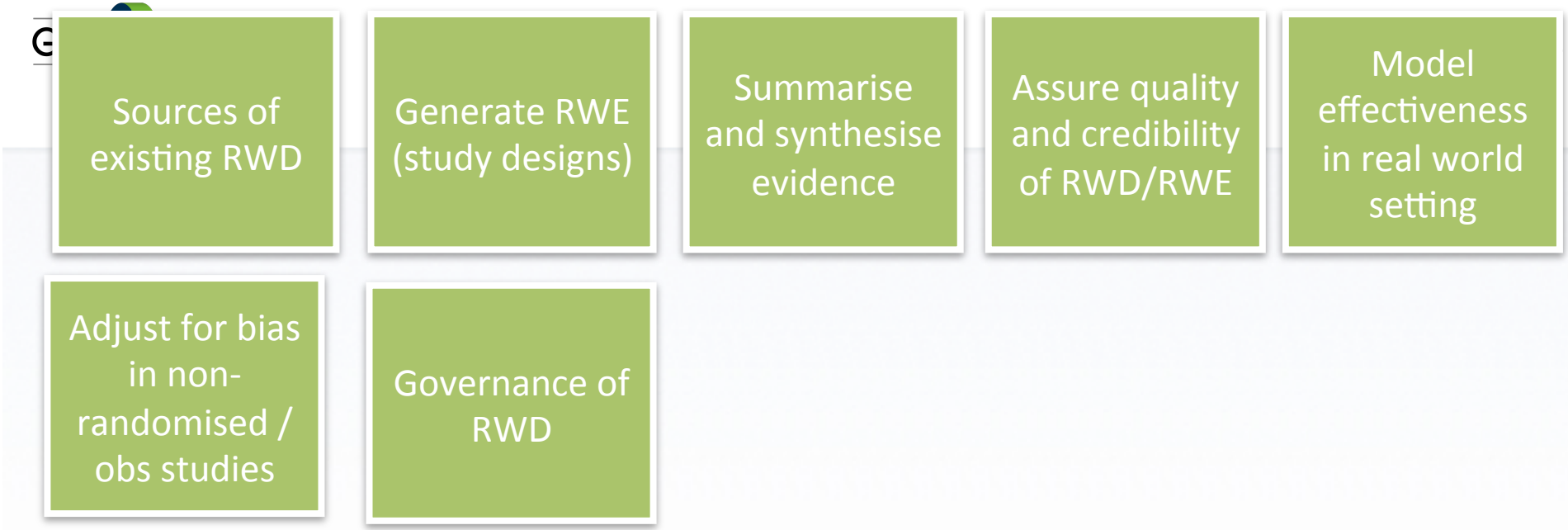

Example key content categories

Sources of existing RWD

-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). 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).

RWD can be collected both prospectively and retrospectively from observations of routine clinical practice. Data collected may include, but are not limited to, clinical and economic outcomes, patient-reported 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 sources

RWD can be obtained from experimental studies, such as pragmatic trials, or from observational studies. The different study designs that can provide RWD are described here.

Additional sources of RWD that may provide data on the effects of medicines but are not necessarily part of structured studies are listed below.

Patient registries	Patient registries are organised systems that are used to prospective 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 are types of healthcare database systems that are set up by pharmacists or health insurers for

	treatments. Read more.
Pharmacy databases and health insurance records	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 networkin They can provide patient perspectives on health topics such as advers 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

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Real-Life Data in Drug Development

Generate RWE (study designs)

RWE Navigator / Use real-world data / Generate real-world evidence

Generate real-world evidence

Conventional randomised controlled trials (RCTs) alone may not provide sufficient evidence of relative effectiveness to support reimbursement decision-making (see here). An estimation of how a medicine may work in the real world can be estimated from analyses of the existing RCTs (see here). 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 (see here) or by conducting new studies to generate real-world evidence (RWE).

Some experimental and observational study designs which could provide RWE are summarised in the table below. While some study designs may provide evidence on relative effectiveness, some more 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 progression, or provide information about a relevant comparator where there is no comparative data.

Since the quality and credibility of a study may have a significant impact on the reported effect of a medicine and its interpretation, it is crucial to assess each study individually whether or not they include an element of randomisation (see here).

Related links

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

Study designs that may provide RWE

Experimental study designs	
Pragmatic RCT	A pragmatic trial aims to measure the relative effectiveness of treatments in real-world clinical practice. It combines the strength of RCTs with evidence of the added value of a treatment strategy in routine clinical practice. Read more.
Population enrichment RCT	A population enrichment RCT includes patients typically excluded from RCTs combined with predictive modelling techniques to better predict relative effectiveness in a real-
Cohort multiple RCT (cmRCT) (also known as or trials within cohorts)	cmRCTs are a type of pragmatic RCT that use a large cohort of patients as a source of participants for multiple RCTs, providing a more generalisable study sample. Read more.
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.
Enriched enrolment withdrawal RCT (EERWT)	EERWTs aim to better reflect real-world settings by pre-selecting study participants for RCTs, usually based on response to the study medicine in a pre-randomisation phase or on non-response to a similar medicine. Read more. [LINK NEEDED]
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

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Summarise and synthesise evidence

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.

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 or 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 of the gap on this page]). 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

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Assure quality and credibility of RWD/RWE

RWE Navigator / Use real-world data / Assure quality and credibility of RWE

Assure quality and credibility of RWE

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

Although other factors may influence the **internal validity** of a study, including the adherenc to treatment protocols and the measurement of outcomes, the internal validity of well-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 populations included, the way that interventions are administered or in other factors (i.e. they may have lower **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 causes most uncertainty regarding the robustness of the data when used as a source of evidence on relati effectiveness.

Checklists

One of the key concerns about the use of evidence collected outside RCTs is the quality of studies used. However, even RCTs need to be assessed for potential bias.

In the field of evidence-based medicine, checklists are often used to assess the quality of different study designs, aiming to ensure consistency across 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
	In the context of cost-effectiveness analyses: ISPOR checklist for prospective observational studies[b] ISPOR checklist for retrospective database studies[b]

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Model effectiveness in real world setting

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

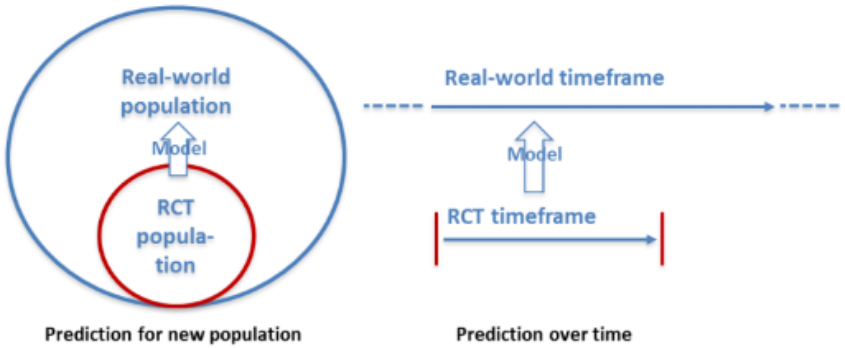
Model effectiveness in the real world

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.



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
- Find software for evidence synthesis or predictive modelling

Adjust for bias in non-randomised / obs studies

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

-randomised and observational studies

methods to determine who will receive different treatments
ence and patient suitability) may result in systematic
s in different treatment arms. When these differences,
also related to the outcome they are considered to be
le, if participants in one arm have more severe disease, they
atment. Results from studies with confounding are less reliable
is is called **selection bias**).

omised studies with an adequate study size should eliminate both known and unknown differences between treatment arms which may influence the outcome (i.e. have low risk of selection bias) due to the randomised nature of treatment selection.

In the absence of randomisation, it is possible to control for some known factors where randomisation has not occurred and attempt to produce less biased results, for example by stratification or matching, but this is not always possible.

It is possible to use statistical to adjust the results from studies that do not use randomisation (i.e. to control for confounding) to provide a less biased and more accurate estimate of treatment effect. However, research is still ongoing on different methods to control for confounding; also, statistical methods cannot fully compensate for unmeasured confounders. The methods can normally be categorised into those that adjust for **known confounding** factors and those that adjust for **unknown confounding** factors. The table below provides some of the more commonly known methods.

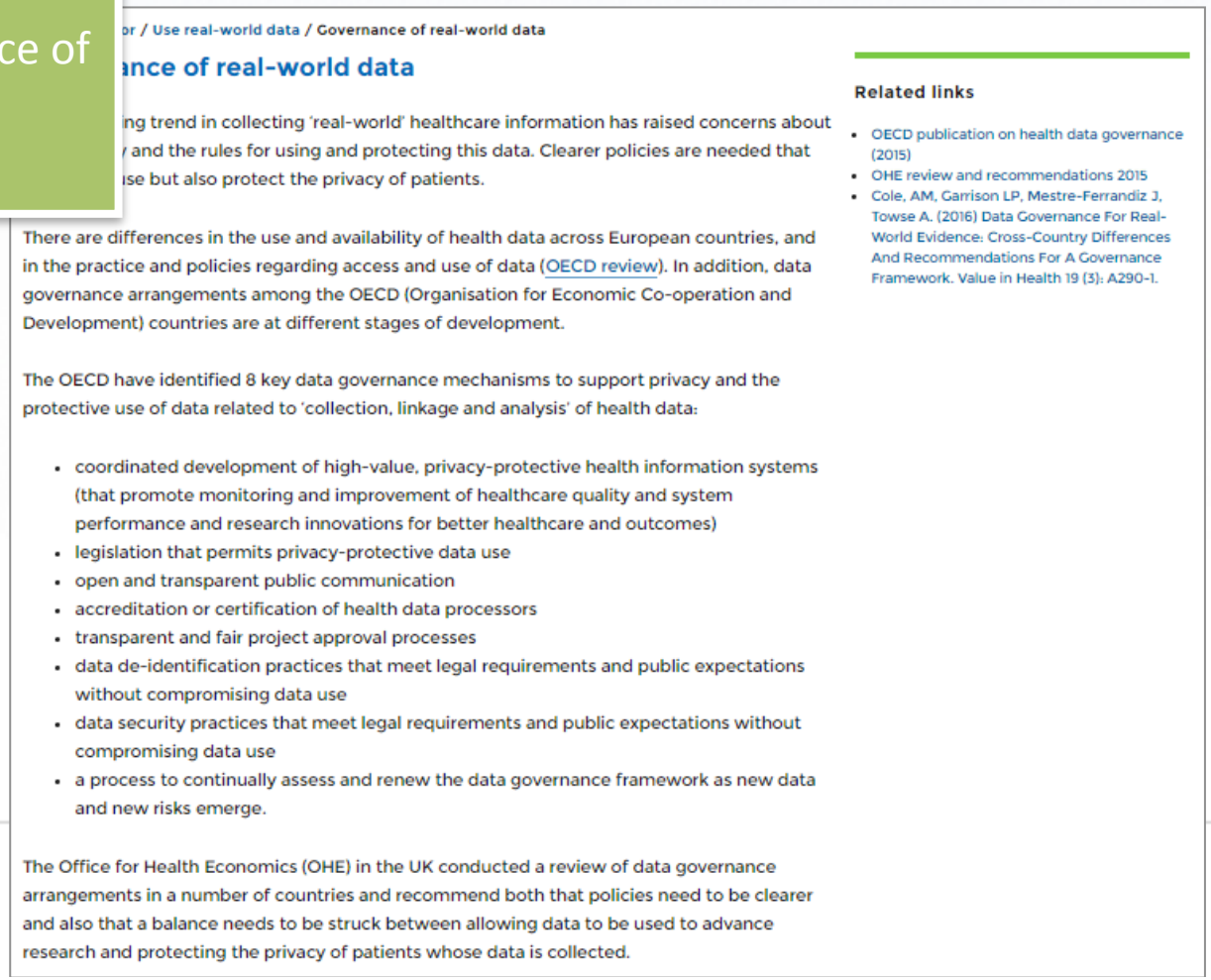
Methods that adjust for known confounding	
Regression adjustment using regression models (such as, logistic regression models by prognostic factors*)	Regression models depend on covariates (such as prognostic factors) to predict the outcome. Models are fit for both the treated and untreated samples and the treatment effects are then based on the differences between the predictions of the two models. Read more here.

Related links

- Schmidt et al publication methods for adjusting fo early post-launch setting
- Schneeweiss 2006 publi Pharmacoepidemiology sensitivity analysis and e for unmeasured confoun
- Faria et al 2015. NICE DS observational to inform treatment effectiveness comparative IPD)
- Assuring quality and cre

	calculate the weighted mean. Read more here.
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 here.
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 here. This method may only be sufficient when there are relatively few outcomes (see here).
Regression based on disease risk score*	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 (see here).
Matching	While matching can be done in a study design, it can also be an analytical method, aiming to 'match' control individuals which are similar to the treated ones in one or more characteristics. 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 here
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.

Governance of RWD



or / Use real-world data / Governance of real-world data

ance of real-world data

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

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

The OECD have identified 8 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 and recommend both 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 publication on health data governance (2015)
- OHE review and recommendations 2015
- Cole, AM, Garrison LP, Mestre-Ferrandiz J, Towse A. (2016) Data Governance For Real-World Evidence: Cross-Country Differences And Recommendations For A Governance Framework. Value in Health 19 (3): A290-1.

Demonstration This Lunchtime

- Soft launch today of the GetReal Navigator
- We are inviting comments and suggestions!