GetReal - Project No. 115546

WP1: Deliverable D1.3

Glossary of Definitions of Common Terms

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The work leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [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.
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1. Executive Summary

The IMI GetReal consortium has drawn up definitions of key terms, both for the purpose of GetReal, and also with the aim of providing clarity to external stakeholders around these terms. In order to explore the origin and context of some of these terms, the glossary is preceded by an overview of real world data and the origin of the key concepts associated with the term. In addition, this document explores the definitions of both 'efficacy' and 'effectiveness' and attempts to define how efficacy studies can be distinguished from effectiveness (pragmatic) studies.

2. Defining Real World Data, and its origins

Healthcare funding decisions increasingly rely on evidence beyond that which is collected in randomised controlled trials (RCTs), which are required by regulatory authorities for marketing authorisation. There are many reasons for this, including the need to understand health outcomes in routine clinical practice, which it is recognised may differ from those observed under the idealised conditions of a RCTs (for more on this, refer to the section '3. Effectiveness versus Efficacy'). This has long been referred to as the collection of real world data, without consensus on the definition of real world data, or what constitutes a real world study. The evolution of this terminology is probably due to the continual and rapid development of IT infrastructures and capabilities; increasing availability of databases and linked datasets; and methodological refinements in data collection. Fifty years ago researchers used paper patient records to establish a link between smoking and lung cancer. The 1980s brought access to real world data on medicine use at the patient level when administrative information about medicine use was first stored at a significant level.[1] In addition, there is no single legal instrument or guidance specific to real world data collection (in the UK at least; recognised by the ABPI), and levels of support for and practical use of real world evidence varies across markets.[2,3]

[1] van Staa and Klungel 2013. Real-life data and learning from practice to advance innovation. Background paper commissioned by the WHO (http://www.who.int/medicines/areas/priority_medicines/BP8_4Data.pdf)
[2] Quintiles report 2013: Real World Evidence and Implications for Emerging Technologies (http://www.namcp.org/journals/spring13/Faulkner%20Emerging%20Technologies.pdf)
[3] IMS Consulting report 2013: International comparisons of the impact of Real World Evidence on creating value from medicines (http://www.imsconsultinggroup.com/deployedfiles/consulting/Global/Content/Our%20Latest%20Thinking/Static%20Files/rwe_market_impact_on_medicines.pdf)

Since the evolution of an ISPOR task force dedicated to assisting healthcare decision-makers in dealing with real world data, there appears to be greater consensus and consistency in the terminology used by authoritative bodies about real world data.

The ISPOR task force offers the broad definition of "everything that is not collected in conventional randomised controlled trials".[4] However some comments received during consultation of the report suggested the definition be restricted to primary data collected at patient level by methods that minimise the imposition of artificial constraints (i.e. excludes secondary analyses like systematic reviews and decision analytic models). The ABPI guidance on real world data specify the lack of an intervention: "data obtained by any non-interventional methodology that describes what is happening in normal clinical practice". Or more simply put: "data which describes what is really happening in everyday normal clinical health care practice".[5] The European Forum "Relative Effectiveness" Working group (part of the European Commission) offer a similar explanation of real world data as "a measure in understanding health care data collected under real life practice circumstances".[6] To differentiate between real world 'data' and 'evidence', the ISPOR task force explain that "data conjures the idea of simple factual information, whereas evidence connotes the organization of the information to inform a conclusion or judgment. Evidence is generated according to a research plan and interpreted accordingly, whereas data is but one component of the research plan. Evidence is shaped, while data simply are raw materials and alone are non-informative."

The commonly discussed outcomes investigated in real world evidence are clinical, economic, and HRQoL/PRO. The ABPI guidance additionally refers explicitly to treatment pathways, service models and patient preference/experience/compliance.

As the definitions of real world data are broad, and may be open to interpretation, it might be more relevant to investigate thoughts on how to collect these data, i.e. understand definitions of real world studies. The ISPOR task force defined 6 sources of real world data:

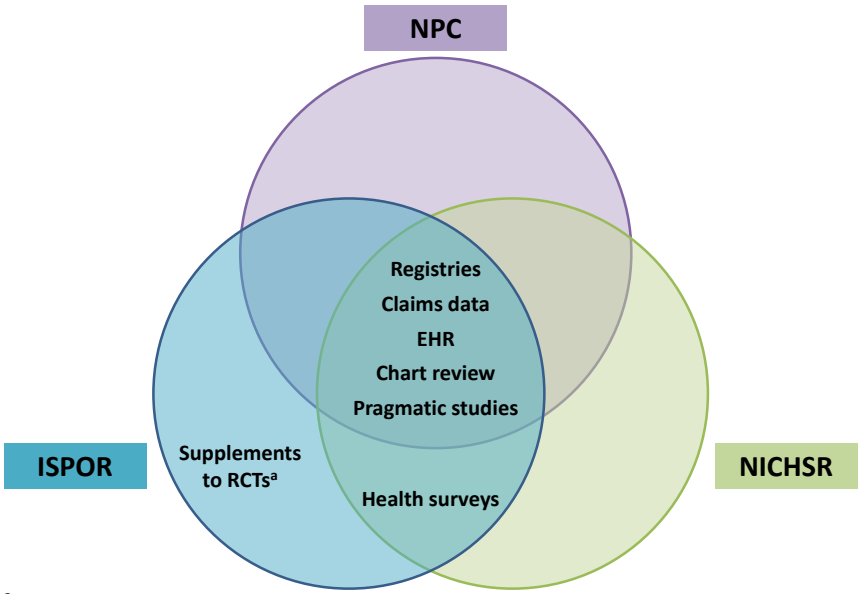
1. **Supplements to traditional registration RCTs:** to collect PRO, HRQoL, resource use and cost data.
2. **Pragmatic clinical trials (also known as large simple trials or practical clinical trials):** involve prospective, randomised assignment but are aimed at larger more diverse real world population. These trials are by design larger than conventional RCTs.

[4] Garrison et al. ISPOR task force report (http://www.ispor.org/workpaper/RWD_TF/RWTFManuscript.pdf)
[5] ABPI Guidance 2011: Demonstrating Value with Real World Data (http://www.abpi.org.uk/our-work/library/guidelines/Documents/2011-06-13%20ABPI%20guidance%20-%20Demonstrating%20value%20with%20real%20world%20data.pdf)
[6] http://www.ispor.org/news/articles/oct07/rld.asp

3. **Registry studies:** prospective, observational cohort studies of patients who have a particular disease and/or are receiving a particular treatment or intervention. By definition registries are assembled prospectively, but data on exposure, treatments and events occurring before enrolment may be assembled retrospectively at baseline.
4. **Claims databases/administrative data:** Typically retrospective or real time, if possible. Lend themselves to retrospective longitudinal and cross-sectional analyses of outcomes at patient, group, or population levels.
5. **Health surveys:** to collect descriptions of health status and wellbeing, health care utilisation, treatment patterns, and health care expenditures from patients, providers, or individuals in the general population. Health surveys typically collect information on representative individuals in the target population (patients, physicians or general population).
6. **Electronic health records (EHR) and medical chart reviews:** such as the UK General Practice Research Database (GPRD). These contain more detailed, longitudinal information including disease-specific symptoms at the patient level.

These 6 data sources are echoed in publications from Quintiles and IMS Consulting. Very similar lists are suggested by the National Pharmaceutical Council (NPC) and National Information Center on Health Services Research and Health Care Technology (NICHSR) in the USA (Figure 1).

Figure 1 Venn diagram to illustrate the areas of agreement in the definition of real world studies across national and international organisations (ISPOR, NPC and NICHSR)

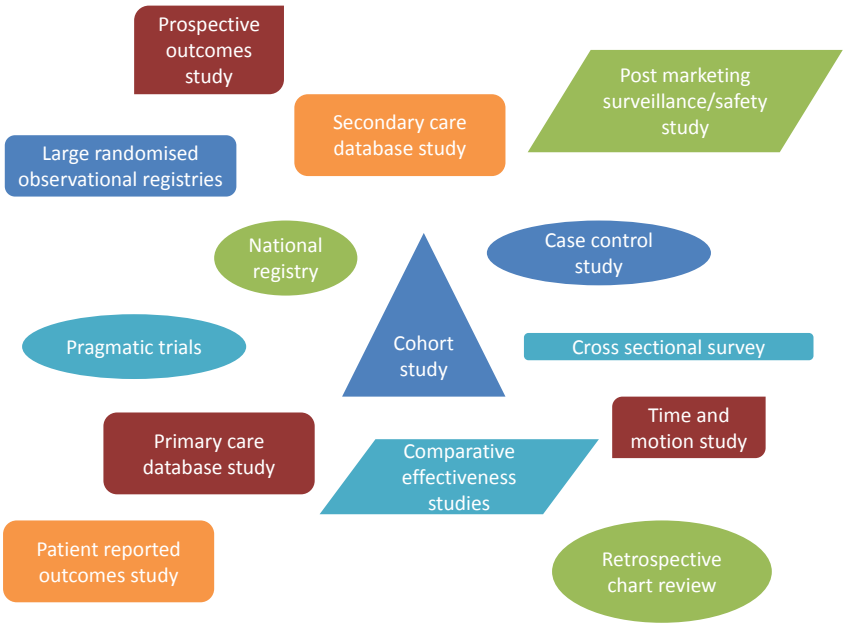


[a]Collection of patient reported outcomes (PRO), resource use and cost data

EHR, Electronic Heath Records; ISPOR, International Society For Pharmacoeconomics and Outcomes Research; NICHSR, National Information Center on Health Services Research and Health Care Technology (USA); NPC, National Pharmaceutical Council (USA); RCTs, Randomised Controlled Trials

The ABPI guidance on real world data provides a much longer list of observational data sources, but these can essentially all be grouped into 1 of the 6 study types provided by the ISPOR task force. A contradiction in terms exists in the ABPI guidance, in the suggestion of "large randomised observational registries". By definition (according to ISPOR), a registry does not involve randomisation. This goes to show that some confusion still exists in the industry.

Figure 2 ABPI examples of real world studies



ABPI Guidance 2011: Demonstrating Value with Real World Data (http://www.abpi.org.uk/our-work/library/guidelines/Documents/2011-06-13%20ABPI%20guidance%20-%20Demonstrating%20value%20with%20real%20world%20data.pdf)

Very few bodies appear to employ a narrower definition of real world studies than that from the ISPOR task force. The European Commission include the concept of no randomisation in their definition; although this is in reference to observational research, as opposed to real world data specifically (these terms are often used interchangeably). By deduction, this would exclude pragmatic studies from their definition. ISPOR's definition of observational research is more vague on this point, stating that care is not *typically* a result of randomisation (or other forms of patient assignment), presumably to allow the inclusion of pragmatic studies. The classification of pragmatic studies as a method of real world data collection could potentially be a point of contention. The ISPOR task force acknowledge that whether they are strictly real world studies is open to debate.

However, many national and international bodies group include them in their definition of real world studies:

- National Pharmaceutical Council (NPC), USA
- National Information Center on Health Services Research and Health Care Technology (NICHSR[7]), USA
    - The NICHSR appear to differentiate between large simple trials and pragmatic clinical trials, unlike other organisations which used the terms interchangeably. But they explain that some large simple trials are also pragmatic trials.
    - Large simple trials: retain the methodological strengths of prospective, randomised design, but use large numbers of patients, more flexible patient entry criteria and multiple study sites to generate effectiveness data and improve external validity. Fewer types of data may be collected for each patient, easing participation by patients and clinicians. Prominent examples of include the GISSI trials of thrombolytic treatment of acute myocardial infarction (AMI) (Maggioni 1990), the ISIS trials of alternative therapies for suspected AMI (Fourth International Study of Infarct Survival 1991), and the CATIE trial of therapies for schizophrenia (Stroup 2003).
    - Pragmatic trials are a related group of trial designs whose main attributes include: comparison of clinically relevant alternative interventions, a diverse population of study participants, participants recruited from heterogeneous practice settings, and data collection on a broad range of health outcomes.
- Patient-centred outcomes research institute (PCORI), USA
    - PCORI implies that pragmatic studies are categorised as real world studies through its announcement of a new research funding initiative for pragmatic trials ("More Support for Bigger, Longer Real-World Trials").[8]
- Medicines and Healthcare products Regulatory Agency (MHRA), UK
    - It could be inferred from the MHRA business strategies that pragmatic studies (utilising EHR) are considered to produce real world data.[9]
- Farr Institute[10], UK

[7] The NICHSR are part of the US National Institutes of Health (NIH) and were set up at the National Library of Medicine to improve "..the collection, storage, analysis, retrieval, and dissemination of information on health services research, clinical practice guidelines, and on health care technology, including the assessment of such technology."
[8] http://www.pcori.org/blog/introducing-new-pcori-research-funding-initiative-large-pragmatic-clinical-trials
[9] http://www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con261796.pdf

- It could be inferred from the programme for their industry forum meeting (in collaboration with the ABPI) that pragmatic trials are included in their consideration of real world data collection.[11]

To revisit the concept of observational research - it seems the main defining feature of observational research, common across publications, is that care is not dictated or mandated. That is, the investigator does not interfere with choice of the prescribed health intervention such that interventions are prescribed in the usual manner in accordance with the terms of the marketing authorisation.[12,13,14,15] But it is not that simple, as there are inconsistencies internally regarding the definition of an intervention. Depending on local regulations, for example, blood tests and patient questionnaires may be considered interventional in some countries (particularly in Europe) but not in others.

3. Effectiveness versus Efficacy

Distinguishing efficacy from effectiveness and emphasising its importance to decision making dates back to at least 1978 (Office of Technology Assessment 1978), but confusion still exists.

It is widely thought that efficacy is the extent to which a healthcare intervention produces a therapeutic effect *as compared to a placebo* under ideal conditions (i.e. the highly-controlled conditions of *RCTs*).[16,17,18,19,20,21] Because RCTs use randomisation and other features to minimise bias, they can prove a causal relationship between an intervention and an outcome. On the other hand, the effectiveness of an intervention refers to its health benefits in *routine clinical practice* (that is, in *real world studies*; according to the ISPOR task force, and online glossaries published by

[10] The Farr Institute was set up by a 10-founder consortium as well as funds from the Medical Research Council (MRC).
[11] http://www.farrinstitute.org/events/49/2014-12-16/farr-institute-abpi-industry-forum-2014.html
[12] ISPOR Taxonomy of Patient Registries 2013 (ISBN: 978-0-9743289-4-2).
[13] HTA glossary (http://htaglossary.net/HomePage)
[14] Cochrane collaboration glossary (http://www.cochrane.org/glossary/)
[15] European Commission (2001). DIRECTIVE 2001/20/EC of the European Parliament and of the Council. Official Journal of the European Communities. Cited in ABPI Guidance.
[16] ISPOR Taxonomy of Patient Registries 2013 (ISBN: 978-0-9743289-4-2).
[17] Cochrane collaboration glossary (http://www.cochrane.org/glossary/)
[18] HTA glossary (http://htaglossary.net/HomePage)
[19] Holve, E. and P. Pittman, A First Look at the Volume and Cost of Comparative Effectiveness Research in the United States. AcademyHealth. June 2009
[20] European Monitoring Centre for Drugs and Drug Addiction (http://www.emcdda.europa.eu/publications/glossary#cochraneCollaboration)
[21] The International Working Group for HTA Advancement: Milbank Q. Jun 2010; 88(2): 256–276 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2980346/)

the INAHTA and Cochrane Collaboration) where multiple variables that might influence patient outcomes (such as concomitant medication and comorbidities) are introduced. Effectiveness research generally involves at least two active comparators (i.e. compares an intervention to standard practice, rather than placebo).

Disagreement about the terminology across Europe was highlighted at the High Level Pharmaceutical Forum.[22] It was concluded that there is no clear consensus as to whether clinical trials yield efficacy or effectiveness information. While some EU Member States use effectiveness to describe what is actually happening in real life, others use it exclusively to "describe clinical trials that are as far as possible to the effectiveness side of the spectrum".

It has been suggested that any confusion that exists might be attributed to the interchangeable use of the terms efficacy and effectiveness in the FDA's legislation and regulations; effectiveness is used when efficacy is intended. This misapplication of terms been used by other organisations as well. For example, the Drug Effectiveness Review Project (DERP)'s stated mission is to "obtain the best available evidence on effectiveness and safety comparisons between drugs in the same class, and to apply the information to public policy and related activities", yet DERP relies exclusively on evaluations based on RCTs. Similarly, the Cochrane Collaboration describes its reviews as exploring "the evidence for and against the effectiveness and appropriateness of treatments … in specific circumstances", however they also demonstrate an almost complete reliance on RCT literature.[23]

RCTs that assess effectiveness are sometimes called pragmatic or management trials, which denotes a grey area (as discussed earlier, in the discussion of the classification of pragmatic trials). To allow for more fluid definitions in the face of the evolving methodology of clinical trials, some publications refer to a spectrum of trial designs and conduct.[24] Some groups have attempted to develop a tool to distinguish efficacy trials from effectiveness (pragmatic) trials (

[22] High Level Pharma Forum: http://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Final%20version%20of%20Backgroun%20Review%20on%20Relative%20Effectiveness%20Assessment%2Bappendix.pdf
[23] The International Working Group for HTA Advancement: Milbank Q. Jun 2010; 88(2): 256–276 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2980346/)
[24] The International Working Group for HTA Advancement: Milbank Q. Jun 2010; 88(2): 256–276 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2980346/)

Figure 3 and

Figure 4).

Figure 3 Tool to distinguish efficacy from effectiveness studies (Gartlenarner et al., prepared for the Agency for Healthcare Research and Quality [AHRQ][25])

1) Populations in primary care 2) Less stringent eligibility criteria 3) Health Outcomes as principal outcomes (e.g., functional capacity, quality of life, mortality; as opposed to objective or subjective outcomes) 4) Long study duration 5) Assessment of AEs 6) Adequate sample size to assess a minimally important difference from a patient perspective 7) Intention to treat analysis * The tool uses yes/no answers; where yes denotes effectiveness studies (despite acknowledgment from the authors that the 2 study types exist on a continuum).

Figure 4 The 'PRECIS' tool to distinguish efficacy from effectiveness studies (Thorpe et al.[26])

A pragmatic trial across the 10 domains of the PRECIS tool would fulfil the following criteria:

- There are no inclusion or exclusion criteria
- Practitioners are not constricted by guidelines on how apply the experimental intervention
- The experimental intervention is applied by all practitioners, thus covering the full spectrum of clinical settings
- The best alternative treatments are used for comparison with no restrictions on their application
- The comparative treatment is applied by all practitioners, covering the full spectrum of clinical settings
- No formal follow-up sections
- The primary outcome is a clinical meaningful one that does not require extensive training to assess
- There are no plans to improve or alter compliance for the experimental or the comparative treatment
- No special strategy to motivate practitioner's adherence to the trial's protocol
- The analysis includes all participants in an intention-to-treat fashion

[25] Gartleharner G. and Hansen RA. A Simple and Valid Tool for Distinguishing Efficacy from Effectiveness Studies. Journal of Clinical Epidemiology 2006. 59(10):1040-8.
[26] Thorpe KE., Zwarenstein M., Oxman AD., et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol. 2009;62:464–475

4. IMI-GetReal Glossary of Key Terms

The table below contains definitions of key terms relevant to the GetReal consortium. The GetReal glossary working group acknowledges there is a debate around many of these terms, and in some cases no clear consensus has been reached in the international community. However, for the purpose of GetReal these are the definitions proposed for the project.

Please note: the definitions presented here are the result of several rounds of consultation. More specifically, definitions in previous versions of the glossary have been subjected to: an internal GetReal consultation round for consortium members in 2015, a public consultation round for external stakeholders in 2015, as well as second internal GetReal consultation round in 2016. For readers interested in the comments received during these rounds as well as authors' replies, please see the alternative version of the glossary on: https://www.imi-getreal.eu/Publications/Deliverables.

Table 1 Terms of key relevance to GetReal.

Term	Definition	References
Adaptive clinical trial	A clinical trial that evaluates patients' response and reaction to an intervention at pre-determined intervals, beginning with evaluation at an early stage in the clinical trials and subsequently modifying the trial according to findings generated by interim analyses. By means of an adaptive design, researchers thus have the opportunity to modify the trial procedures at different stages on the basis of analysing interim data from study subjects. Such modifications may include, but are not limited to: selected drug dosages, sample size, and patient selection criteria. (see also: "clinical trial") (Adapted from CHMP 2007 and FDA, 2010).	Committee for Medicinal Products for Human Use. (2007). Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. London: EMEA; FDA (2010) *Guidance for industry. Adaptive design clinical trials for drugs and biologics.* Obtained on 5 March 2014. URL: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf
Administrative claims data	Data arising from a person's use of the healthcare system and reimbursement of healthcare providers for that care. (Strom 2005)	Strom, 2005; FDA GUIDANCE ON PHARMACOEPIDEMIOLOGIC SAFETY STUDIES (MAY 2013)
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a health intervention, and which does not necessarily have a causal relationship with this treatment. (ICH, 1994)	ICH (1994). Clinical Safety Data Management: defnitions and standards for expedited reporting. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf
Aggregate (Study) Data	Summary data of the results of a study (e.g. on subjects in a trial), as opposed to Individual Patient Data which represents the raw data of each study subject. Summary data is derived from individual patient data using a (statistical) method of aggregation. (Adapted from Lyman, 2005)	Lyman, G. H., & Kuderer, N. M. (2005). The strengths and limitations of meta-analyses based on aggregate data. *BMC medical research methodology*, *5*(1), 14.
Aggregate Data Drug Information System (ADDIS)	Software designed to aid evidence-based decision-making in the healthcare setting. This software does so by offering on-demand features such as: pair-wise-network analysis, meta-analysis, and multiple-criteria decision analysis. (van Valkenhoef, 2013)	Gert van Valkenhoef, Tommi Tervonen, Tijs Zwinkels, Bert de Brock, Hans Hillege, ADDIS: A decision support system for evidence-based medicine, Decision Support Systems, Volume 55, Issue 2, May 2013, Pages 459-475, ISSN 0167-9236, http://dx.doi.org/10.1016/j.dss.2012.10.005.
Alternative study design	This refers to all scientific studies investigating health interventions whose design does not follow the design of a randomised controlled clinical trial (see also:"randomised controlled clinical trial (RCT)") (Freemantle, 2010)	Nick Freemantle, Thomas Strack, Real-world effectiveness of new medicines should be evaluated by appropriately designed clinical trials, Journal of Clinical Epidemiology, Volume 63, Issue 10, October 2010, Pages 1053-1058, ISSN 0895-4356, http://dx.doi.org/10.1016/j.jclinepi.2009.07.013.
Bayesian methods	Statistical methods based upon Bayes' Theorem, which shows how to update prior knowledge in the light of new data (i.e. posterior probability $\propto$ likelihood x prior probability). Prior knowledge is defined in terms of probability distributions and can be based on subjective opinion, or on objective evidence, such as the results of previous research, or both, and is explicitly included in consequent calculations. Statistical inference is then based on suitable summaries from the posterior probability	Rothman, K.J., Greenland S., Lash T.L. (2008) Modern Epidemiology. Lippincott Williams & Wilkins. ISBN: 978-0-7817-5564-1; HTA Glossary - Bayesian Methods URL: http://htaglossary.net/Bayesian+analysis&highlight=real-world%20evidence

	distribution. (Adapted from Rothman, 2008 and HTA glossary)	
Bias	Systematic (non-random) errors in values of parameters that are the object of study. Errors in estimations can result from, for example, improper study design or analysis, and implicitly affect the internal validity and generalisaibility of study results. There are three main categories of bias: selection bias, information bias and confounding bias. (Adapted from Rothman, 2008 and Delgado-Rodriguez, 2004)	Rothman, K.J., Greenland S., Lash T.L. (2008) Modern Epidemiology. Lippincott Williams & Wilkins. ISBN: 978-0-7817-5564-1; Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. Journal of epidemiology and community health, 58(8), 635-641.
Bridging study	A study, supplemental to a randomised controlled clinical trial, designed to provide additional clinical data on the safety, efficacy, dose and regimen, thus allowing for the extrapolation of external trial data to a new subjects population with (possibly) different population characteristics. An ethnicity briding study is one example of such a supplemental study.(Adapted from ICH, 1998)	ICH (1998) ICH Topic E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf
Case-control study	A study in which the exposure of a group that have experienced a certain outcome (cases) is compared to the exposure of a group who have not (yet) experienced the outcome (controls). Case-control studies can be retrospective or prospective. (Adapted from Rothman, 2008 and Grobbee & Hoes, 2015)	Rothman, K.J. Greenland, S. Lash, T.L. (2008). Modern Epidemiology. Lippincott Williams & Wilkins. 88.; Grobbee, D. E., & Hoes, A. W. (2014). Clinical epidemiology. Jones & Bartlett Publishers.
Clinical endpoint/ outcome	An aspect of a subject's clinical or health status that is measured to assess the benefit or harm of an intervention. A clinical endpoint describes a valid measure of clinical benefit due to intervention: the impact of the intervention on how a subject feels, functions and survives. It is clinically relevant, sensitive (responsive to change) and is both accepted and used by physicians and patients. Clinical endpoints may be a clinical event (e.g. mortality,) a composite of several events, a measure of clinical status (e.g. blood pressure), or health related quality of life (HRQoL). (Adapted from EunetHTA, 2013)	EUnetHTA (2013) Methodology Guidelines. Endpoints used for relative effectiveness assessment of pharmaceuticals: Clinical Endpoints. http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf
Clinical Guideline/ Medical Guideline	A document produced with the intention to guide decisions and inform criteria with regards to disease prevention, disease diagnosis, disease management, and treatment in the routine clinical setting. (Adapted from Council of Europe, 2001)	Council of Europe (2001). Developing a methodology for drawing up guidelines on best medical practices. http://www.leitlinien.de/mdb/edocs/pdf/literatur/coe-rec-2001-13.pdf
Clinical significance	The practical importance of and benefit from a treatment. It describes whether and to which extent the intervention has a real genuine, palpable, noticeable effect on daily life. Clinical significance is usually informed by effect size and statistical significance. (See also "statistical significance") (Adapted from Kazdin, 1999 and Redmond, 2001).	Kazdin, A.E., *The Meanings and Measurement of Clinical Significance*. Journal of Consulting and Clinical Consulting **67** (3): 332–9. doi:10.1037/0022-006x.67.3.332, 1999.

Clinical Trial	Any investigation in human subjects intended to discover or verify the effects of an intervention, such as clinical, pharmacological and/or other pharmacodynamic effects, and/or to identify any adverse reactions to an intervention. (Adapted from ICH, 2001)	Guideline, I. H. T. (2001). Guideline for good clinical practice. *J Postgrad Med*, *47*(1), 45-50.
Cohort study	A study in which a group of subjects, sampled from a certain source population, are classified according to their exposure or determinant status and followed over time to ascertain the occurrence of a certain outcome. (Adapted from Rothman, 2008)	Rothman, K.J. Greenland, S. Lash, T.L. (2008). Modern Epidemiology. Lippincott Williams & Wilkins. 88.
Comparative effectiveness research	The conduct and/or synthesis of research comparing different benefits and harms of alternative interventions and strategies to prevent, diagnose, treat, and monitor health conditions in routine clinical practice (i.e. the real world setting). Comparative effectiveness research includes both primary data collection and secondary analyses (such as systematic literature reviews, meta-analyses and economic evaluations). (IOM, 2009 & Sox, 2009)	The Institute of Medicine (2009) - Initial National Priorities for Comparative Effectiveness Research; http://www.iom.edu/reports/2009/comparativeeffectivenessresearchpriorities.aspx; Sox, H.C. and S. Greenfield, Comparative effectiveness research: a report from the Institute of Medicine. Ann Intern Med, 2009. 151(3): p. 203-5.
Comparator	Reference intervention to which safety, efficacy and/or effectiveness of a health intervention (e.g. pharmaceutical product) are compared. In the case of clinical trials for pharmaceutical products, comparators can comprise a placebo treatment (placebo-control trials), available standard of care, and/or a licensed medication (active-control trial). (Adapted from ICH, 2001)	Guideline, I. H. T. (2001). Guideline for good clinical practice. *J Postgrad Med*, *47*(1), 45-50.
Conditional marketing authorisation	A one-year marketing authorization within the European Union with annual review by the European Medicines Agency (EMA), and which applies in specific cases: (a) Seriously debilitating or life-threatening diseases; (b) Emergency threats determined by the WHO, or the EU Commission; (c) Orphan medicinal products. Accelerated drug approval is the near equivalent of conditional marketing authorisation in the USA. (Boon, 2011)	Boon, H., Conditional Marketing Authorisations in the European Union, in FDA ODAC meeting. 2011: Silver Spring, MD; Goozner, M., Accelerated drug approval: FDA may get tougher; companies cite hurdles. J Natl Cancer Inst, 2011. 103(6): p. 455-7
Confounder	An extraneous variable in a statistical model that correlates with both the dependent variable (e.g. outcome) and the independent variable (e.g. intervention). Lack of consideration of confounders in statistical analyses can lead to spurious statistical relationships between the dependent and independent variables. (Adapted from Greenland, 2001)	Greenland, S., & Morgenstern, H. (2001). Confounding in health research. Annual review of public health, 22(1), 189-212.
Confounding bias	Systematic error that occurs when the estimate of a measure of association between exposure (e.g. healthcare intervention) and outcome (e.g. health status) is distorted by the effect of one or several extraneous variables (confounding factor(s)) that are independently related to the exposure and outcome. (Adapted from Strom, 2006)	Strom B.L., Kimmel S.E. (2006). Textbook of pharmacoepidemiology. John Wiley & Sons, Ltd.

Covariate	A variable that may be predictive of the outcome under study. Alternative terms are *explanatory variable*, *independent variable*, or *predictor*. Depending on its causal impact on the outcome under study, a covariate may be of direct interest, or act as a confounder or effect modifier (Adapted from J. M. Last, 2001).	Last, J.M., (ed.). A Dictionary of Epidemiology [4th ed.]. Oxford UP. ISBN 0-19-514168-7, 2001.
Coverage decisions	Decisions taken by healthcare payers/ insurers to determine allocation of resources with regards to which health interventions to reimburse, and the extent of reimbursement associated with the interventions covered by the payment package. (Steiner, 1996)	Steiner C.A., Powe N.R., Anderson G.F., Das A (1996). The review process used by U.S. health care plans to evaluate new medical technology for coverage. Journal of General Internal Medicine; 11(5); pp 294-302.
Cross-design evidence synthesis	Evidence synthesis comprising the pooling and analysis of data from different studies. The studies from which data is combined can differ in relation to their design types, clinical setting, outcome measures, study interventions, study parameters, or patient population. (See also: "meta-analysis") (Athanasiou, 2011)	Athanasiou T., Darzi A. (2011). Evidence Synthesis in Healthcare: A practical Handbook for Clinicians. Springer, ISBN 978-0-85729-175-8, doi: 10,1007/978-0-85729-206-3
Cross-sectional study	A study in which one ascertains exposure status and outcome status for the observed population at one specific point in time. (Adapted from Rothman, 2008)	Rothman, K.J. Greenland, S. Lash, T.L. (2008). Modern Epidemiology. Lippincott Williams & Wilkins. 88.
Direct treatment comparisons	The comparison of the relative effect(s) of several interventions for a particular therapeutic indication in a trial setting. The basis for comparison can vary (e.g. clinical endpoints, adverse effect rates, or drug adherence rates) and the trial type may vary (e.g. randomised controlled clinical trial, pragmatic clinical trial or observational study). (Adapted from Hetland et al, 2009)	Hetland, M. L., Christensen, I. J., Tarp, U., Dreyer, L., Hansen, A., Hansen, I. T., ... & Østergaard, M. (2010). Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis & Rheumatism*, *62*(1), 22-32.
Discrete-event simulation model	The key components of a discrete-event simulation (DES) model are the units that are simulated, the type of events that can occur, and the rules that govern the progress from one to the next event. Units are typically individual patients, the events could for example be stroke or increase or decrease of blood pressure in cardiovascular disease. Individual level RCT data are used to specify the functional form of the attributes that characterize each unit. Such data also serve to set up the rules that govern the changes in the attributes. DES provides a framework for individual level stochastic simulation: first, a virtual patient is generated, then the time of occurrence and type of the first event are simulated, the event rates and probabilities are updated in the light of the event, the second event is simulated using the new rates and probabilities, and so on. This scheme is repeated until a pre-defined stopping rule is met (for example the virtual patient reaches the end of the follow-up period). Events thus affect the variables that characterize the patient and his or	Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. Value Health. 2012 Sep-Oct;15(6):821-7. doi: 10.1016/j.jval.2012.04.013. J. J. Caro, “Pharmacoeconomic analyses using discrete event simulation,” PharmacoEconomics, vol. 23, no. 4, pp. 323–332, 2005. J. Banks, J. S. Carson, and B. L. Nelson, Discrete-event system simulation. Prentice Hall, 1996.

	her disease state. These variables, in turn, influence the rates of future events. Through this process, the patient's full trajectory over the time span of the simulation is generated. This is repeated for a large number of patients. At the end, the outcome variables are summarized.	
Drivers of effectiveness	Non-drug variables (i.e. related to the healthcare system, the disease, the patient, or the actual use of drug) for which a variation in distribution between real-world settings, as opposed to the setting in RCTs, would impact the outcome of a treatment. In turn, the effectiveness of the drug can be understood as the result of the modification of the pharmacological efficacy by the distributions of these drivers of effectiveness. (See also "effectiveness" and "efficacy") (GetReal, 2016)	IMI-GetReal Glossary Workgroup, 2016
Drug utilisation	Defined by the World Health Organisation as the the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences. This definition contains 2 aspects: the process of drug utilisation, that is the movement of drugs along the drug chain in society, and how drug utilisation relates to the effects of drug use (Baksaas, 1981; Lee & Bergman 1989) (See also "drug utilisation studies") (Sacristén, 1994)	Sacristén, J. A., & Soto, J. (1994). Drug utilisation studies as tools in health economics. *Pharmacoeconomics*, *5*(4), 299-312.
Drug utilisation studies	Research designed to investigate drug utilisation. (See also: "drug utilisation") (Adapted from Sacristén, 1994)	Sacristén, J. A., & Soto, J. (1994). Drug utilisation studies as tools in health economics. *Pharmacoeconomics*, *5*(4), 299-312.
Effect modification	Occurs when the magnitude of the effect of the primary exposure on an outcome (i.e., the association) differs depending on the level of a third variable. (Adapted from VanderWeele, 2009)	VanderWeele, T. J. (2009). On the distinction between interaction and effect modification. *Epidemiology*, *20*(6), 863-871.
Effectiveness	The extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice. (See also "ideal vs.usual conditions") (High Level Pharmaceutical Forum, 2008)	High Level Pharmaceutical Forum 2005-2008. Final Conclusions and Recommendations of the High Level Pharmaceutical Forum. URL: http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf
Effectiveness studies	Clinical studies investigating health interventions whose design does not follow the design of a randomised controlled clinical trial and aims to reflect health intervention effectiveness in routine clinical practice. Effectiveness studies do not typically include randomisation of trial subjects, but there are exceptions (e.g. pragmatic clinical trials). For the purposes of GetReal, effectiveness studies include, but are not limited to, the following: pragmatic clinical trials, non-interventional/ observational studies, drug utilisation studies, post-authorisation efficacy/safety studies. (See also: "real-world studies", "drug utilisation study",	IMI-GetReal Glossary Workgroup, 2016

	"pragmatic clinical trial" and "non-interventional/ observational study") (IMI-GetReal, 2014)	
Efficacy	The extent to which a healthcare intervention does more good than harm as compared to another healthcare intervention under ideal conditions. (See also "ideal vs.usual conditions") (High Level Pharmaceutical Forum, 2008)	High Level Pharmaceutical Forum 2005-2008. Final Conclusions and Recommendations of the High Level Pharmaceutical Forum. URL: http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf Accessed 7 March 2014
Efficacy study	A study aiming to measure the effect of a drug under highly controlled conditions (i.e. in the setting of randomised controlled clinical trials). The study serves to prove the causal relationship between an intervention and an outcome, thus answering the question "can it work?" in an ideal world.	Luce, B.R., et al., *EBM, HTA, and CER: clearing the confusion.* Milbank Q, 2010. **88**(2): p. 256-76.
Efficacy-effectiveness gap	The observed discrepancy between effects of a health intervention in routine clinical practice as compared with the effects demonstrated in randomised controlled clinical trials. (Adapted from Eichler et al., 2011)	Eichler, H. G., Abadie, E., Breckenridge, A., Flamion, B., Gustafsson, L. L., Leufkens, H., ... & Bloechl-Daum, B. (2011). Bridging the efficacyâ€“effectiveness gap: a regulator's perspective on addressing variability of drug response. Nature Reviews Drug Discovery, 10(7), 495-506.
Electronic health/medical record (EHR/EMR)	An electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one healthcare organization. Patient health-related information may include all of the key administrative clinical data relevant to that person's care under a particular provider, including demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data and radiology reports. (Adapted from FDA 2013 and IOM, 2013)	Centers for Medicare en Medicaid Services http://www.cms.gov/Medicare/E-Health/EHealthRecords/index.html?redirect=/ehealthrecords/; FDA (2013). Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.
Electronic healthcare data	An organized set of healthcare data or collection of files available by computer through electronic format. It is derived from a raw electronic healthcare database. Electronic healthcare data include administrative claims data and electronic medical record (EMR) data. (Adapted from Hartzema, 2008 and FDA, 2013)	Hartzema, Tilson, and Chan. Pharmacoepidemiology and Therapeutic Risk Management. Cincinnati: Harvey Whitney Books, 2008.; FDA (2013). Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.
(Clinical) Equipoise	An ethical criterion for recommending subject participation in clinical trials that states that a subject can only be referred to study participation if there is genuine collective professional uncertainty from the medical community regarding the best health intervention for that subject. (Adapted from Miller, 2003)	Miller, F. G., & Brody, H. (2003). A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*, *33*(3), 19-28.
External validity/	Whether the results of a study can be reasonably applied to a definable group of patients in a particular clinical setting in routine practice.	Rothwell, P. M. (2005). External validity of randomised controlled trials:"to whom do the results of this trial apply?". *The Lancet*, *365*(9453), 82-93.

Generalisability / Applicability	(Adapted from Rothwell, 2005)	
Health economic model	A logical mathematical framework demonstrating the quantitative relationship between a defined set of variables (e.g. cost, effectiveness, net benefit) based upon an explicit set of parameters and assumptions. The purpose of modeling is to structure evidence on clinical and economic outcomes in a form that can help to inform decisions about clinical practices and health-care resource allocations. (Adapted from Weinstein, 2003).	Weinstein, M. C., O'Brien, B., Hornberger, J., Jackson, J., Johannesson, M., McCabe, C., & Luce, B. R. (2003). Principles of Good Practice for Decision Analytic Modeling in Health - Care Evaluation: Report of the ISPOR Task Force on Good Research Practices—Modeling Studies. *Value in health*, *6*(1), 9-17.
Health survey	Questionnaires designed to collect descriptions of health status and well-being, healthcare utilization, treatment patterns, and health-care expenditures from patients, providers, or individuals in the general population. (Garrisson, 2007)	Garrison et al. (2007). Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health 10:5, 2007.
Health Technology Assessment	The systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision-making regarding health technologies. (HTAi, 2014)	HTAi - HTA glossary (http://htaglossary.net/health+technology+assessment+%28HTA%29)
Heterogeneity (meta-analysis)	The variability between studies included in an evidence synthesis, due to differences in population, outcomes, interventions, or study design. Such variability may lead to differences in the observed treatment effects that exceed what is expected by chance. In that case, there is statistically detectable heterogeneity. (See also "meta-analysis" and "cross-design evidence synthesis") (Adapted from Higgings, 2008 and Dias, 2013)	Higgins, J.P.T, Green,S. (eds.), Cochrane handbook for systematic reviews of interventions [Part 2, Chapter 9.5]. Vol. 5. Chichester: Wiley-Blackwell, 2008. Dias, S., Sutton, A.J., Welton, N.J., Ades, A.E., *Evidence synthesis for decision making 3 heterogeneity—subgroups, meta-regression, bias, and bias-adjustment*, Medical Decision Making 33.5: 618-640, 2013.
Heterogeneity (network meta-analysis)	An assumption sometimes made in network meta-analysis that the heterogeneity parameters are equal across all possible treatment comparisons , i.e. the variance of the random effects is the same for all treatment comparisons in the network. Such an assumption can be useful when the data are sparse (e.g. few studies per comparison), and simplifies the estimation in the presence of multi-arm studies. (Adapted from Higgins,1996, Salanti, 2008 and Dias, 2013)	Higgins, J.P.T., Whitehead, A., 1996. Borrowing Strength from External Trials in a Meta-Analysis. Stat. Med. 15, 2733–2749. doi:10.1002/(SICI)1097-0258(19961230)15:24<2733::AID-SIM562>3.0.CO;2-0. ; Salanti, G., Higgins, J.P., Ades, A.E., Ioannidis, J.P., 2008a. Evaluation of networks of randomized trials. StatMethods MedRes 17, 279–301. doi:10.1177/0962280207080643; Dias, S., Sutton, A.J., Welton, N.J., Ades, A.E., Evidence synthesis for decision making 3 heterogeneity—subgroups, meta-regression, bias, and bias-adjustment, Medical Decision Making 33.5: 618-640, 2013.
Hierarchical model	A generalization of linear and generalized linear modeling in which regression coefficients are themselves given a model, whose parameters are also estimated from an underlying distribution. For example, in a random-effects meta-analysis, the relative treatment effect parameters in the individual studies are drawn from a random effects distribution, which allows for statistical heterogeneity between studies. (See also "meta-	Gelman, A., Carlin, J. B., Stern, H. S., & Rubin, D. B. (2014). Bayesian data analysis [3rd ed., Part 1, Chapter 5]. Boca Raton, FL, USA: Chapman & Hall/CRC.

	analysis" and "heterogeneity (meta-analysis)") (Adapted from Gelman, 2014)	
Homogeneity (meta-analysis):	The absence of heterogeneity between studies included in an evidence synthesis. (See also "heterogeneity (meta-analysis)") (IMI-GetReal, 2016)	IMI-GetReal Glosssary Workgroup, 2016
Ideal vs. Usual conditions	The context in which a treatment is being studied consists of the mode of administration, side-effects and their treatment, diet, auxiliary care, associated treatments, etc. All the characteristics of this context can be called contextual factors or extraneous factors, i.e. characteristics of the population (e.g. genetics, behaviour towards the drug, co-morbidities), the healthcare delivery system (e.g. physician behaviour of prescription, guidelines etc.), the actual use of the drug (compliance, health beliefs, co-medication, etc.). The ideal condition refers to the situation where the setting is experimental and controlled, and where the contextual factors are fixed and equalized in the two (or more) therapeutic groups through randomization, blinding and/or standardisation. For instance, the intervention status will be set at the beginning of the trial, and emphasis is put on not to change intervention status overtime, etc. Often, the design is optimised to show the most benefit of the investigated interventions. The usual condition (or routine clinical practice) refers to what really happens when an intervention is prescribed by a physician, to a patient. In routine clinical practice, the contextual factors are not fixed: they vary according to the physician's usual habits, the disease severity, patients' preferences, etc.	Schwartz, D. and J. Lellouch, Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis, 1967. 20(8): p. 637-48.
Indirect treatment comparisons	The comparison of several (i.e. 2 or more) interventions (e.g. A and B) for a particular therapeutic indication in the absence of a trial that directly compares the interventions in question. This implies that comparison is done based upon a third intervention (e.g. C) against which A and B have been directly compared in a trial setting. (Adapted from ISPOR, 2011)	Hoaglin, D. C., Hawkins, N., Jansen, J. P., Scott, D. A., Itzler, R., Cappelleri, J. C., ... & Barrett, A. (2011). Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value in Health*, *14*(4), 429-437.
Individual patient data (IPD) / Patient-Level Data	The raw data for subjects included in a study, as opposed to aggregate data (summary data for the comparison groups in a study). (Adapted from Bandolier, 2014)	Bandolier Glossary - IPD; http://www.medicine.ox.ac.uk/bandolier/booth/glossary/individual.html

Information bias	A flaw in measuring exposure, covariate, or outcome variables that results in different quality (accuracy) of information between comparison groups. The occurrence of information biases may not be independent of the occurrence of selection biases. (See also: "bias", "selection bias") (Porta, 2008)	Porta, M., ed. (2008). *A Dictionary of Epidemiology* (Fifth ed.). New York: Oxford University Press. p. 128. ISBN 978-0-19-531449-6.
Informative prior	A prior distribution used to incorporate prior knowledge into a Bayesian analysis. This is useful when some parameters might otherwise not be identifiable, such as the random effects variance when only a small number of studies is available. Informative priors can be based on external sources of evidence or expert judgment. A strongly informative prior may have a noticeable influence on analysis results, and therefore could invalidate results if it is biased. (Adapted from Gelman, 2014)	Gelman, A., Carlin, J. B., Stern, H. S., & Rubin, D. B. (2014). Bayesian data analysis [3rd ed., Part 1, Chapter 2.4]. Boca Raton, FL, USA: Chapman & Hall/CRC.
Internal validity	The extent to which study attributes (e.g. study design) keep the possibility of systematic errors (i.e. biases) to a minimum. (See also "Bias") (Adapted from Rothwell, 2005)	Rothwell, P. M. (2005). External validity of randomised controlled trials:"to whom do the results of this trial apply?". *The Lancet*, *365*(9453), 82-93.
Large simple trials	Large simple trials are pragmatic, randomised clinical trials with minimal data collection protocols that are narrowly focused on clearly defined outcomes that are important to patients as well as clinicians. Their large sample size provides the adequate statistical power to detect a small difference in effects between treatments in a situation where a moderate difference in an important outcome may be important. Additionally, LST's include follow-up that mimics normal clinical practice. LST's are by definition pragmatic clinical trials. (See also "pragmatic clinical trials") (Adapted from Stroup 2011, Peto 1995)	Stroup, T.S., What can large simple trials do for psychiatry? Am J Psychiatry, 2011. 168(2): p. 117-9.; Peto, R., R. Collins, and R. Gray, Large-scale randomized evidence: large, simple trials and overviews of trials. J Clin Epidemiol, 1995. 48(1): p. 23-40; Clinical Trials Transformation Initiative. Large Simple Trials: Facilitating the Use of Large
Longitudinal study	A study in which subjects are followed over time with continuous or repeated monitoring of risk factors or health outcomes, or both. (Adapted from BMJ, 2014)	BMJ, Longitudinal studies http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/7-longitudinal-studies
Marketing authorisation	A licence given by a regulatory authority to a pharmaceutical manufacturer allowing for the marketing of a specific product within the jurisdiction of the regulatory agency. The decision for granting a marketing authorisation is based primarily on the quality, safety and efficacy of the new medicinal product. (Adapted from MHRA, 2014)	MHRA - Marketing Authorisations (http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/index.htm#l3)
Markov model	Stochastic multi-state transition models. Transition between different states in the model are based upon pre-defined conditional probabilities that depend only on the current states (i.e. future evolution depends only on the current state, not the past states). (See also: "multi-state transition model") (Adapted from Briggs, 1993)	A. Briggs and M. Sculpher, "An introduction to Markov modelling for economic evaluation," *PharmacoEconomics*, vol. 13, no. 4, pp. 397–409, Apr. 1998. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993 Oct-Dec;13(4):322-38.

Medicine Adaptive Pathways to Patients (MAPP's)	A prospectively planned, flexible approach to regulation of drugs and biologics. It starts with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence-gathering and the adaptation of the marketing authorisation to allow broader patient populations to access the medicine. Adaptive pathways are sometimes known as 'staggered approval' or 'progressive licensing'. (Adapted from Eichler, 2012 and EMA, 2014).	Eichler, H. G., Oye, K., Baird, L. G., Abadie, E., Brown, J., Drum, C. L., ... & Hirsch, G. (2012). Adaptive licensing: taking the next step in the evolution of drug approval. *Clinical Pharmacology & Therapeutics*, *91*(3), 426-437.; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce
Meta-analysis	Statistical methods allowing for the combination of study outcomes from several studies, while also accounting for uncertainties resulting from the combination of data from varying sources. (See also "evidence synthesis") (Adapted from Greenland S., 2008)	Greenland S, O' Rourke K: Meta-Analysis. Page 652 in Modern Epidemiology, 3rd ed. Edited by Rothman KJ, Greenland S, Lash T. Lippincott Williams and Wilkins; 2008.
Meta-regression	Assessment of the extent of the effect of moderator variables on outcomes presented by a model in the context of meta-analysis. This is achieved through the use of regression techniques, and can be based on both aggregate and individual patient level data. Data for the regression analysis may originate, and be synthesised, from several studies. (See also: "meta-analysis") (Adapted from Stanley, 1989)	T.D. Stanley and Stephen B. Jarrell, (1989). Meta-regression analysis: A quantitative method of literature surveys. *Journal of Economic Surveys*, 19(3) 299-308.
Misclassification bias	Possibility of error associated with the classification of study participants with regards to their exposure status, outcome status, or disease status. Random occurrence of information bias is known as 'non-differential misclassification' while non-random occurence is known as 'differential misclassification'. Missclasification bias falls within the category of information bias. (See also: "Bias" and "Information bias".) (Adapted from Strom, 2006 and Delgado-Rodriguez, 2004)	Strom B.L., Kimmel S.E. (2006). Textbook of pharmacoepidemiology. John Wiley & Sons, Ltd.; Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. Journal of epidemiology and community health, 58(8), 635-641.
Multi-state transition model	Multi-state transition models are used to model prognosis for clinical problems with ongoing risks. The model assumes that the patient is always in one of a finite number of clinical conditions, referred to as states. All events of interest are modelled as transitions from one state to another. Multi-state transition models can be either discrete or continuous time models. For the former the transitions are only possible at certain time points. The time interval from one time point to the next one is referred to as a cycle. The net probability of making a transition from one state to another during a single cycle is called transition probability. This transition probability can be constant over time or not. Multi-state transition models can model a cohort of patients or individuals. In the latter case they are called microsimulation models. A prominent example is the illness-death model with three states representing health, illness and death. (Adapted from Sieber et al, 2012)	Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. Value Health. 2012 Sep-Oct;15(6):812-20. doi:10.1016/j.jval.2012.06.014.

Network meta-analysis (NMA)	An extension of meta-analysis, allowing for the comparison of the relative effects of multiple treatments, either with or without the presence of a common comparator against which all interventions are studied. NMA methods take into account Direct and Indirect Treatment Comparisons and pairwise meta-analysis. (see also: "transitivity assumption", "direct treatment comparisons" and "indirect treatment comparison") (Adapted from Athanasiou, 2011 & Hawkins, 2011)	Athanasiou T., Darzi A. (2011). Evidence Synthesis in Healthcare: A practical Handbook for Clinicians. Springer, ISBN 978-0-85729-175-8, doi: 10,1007/978-0-85729-206-3; Hoaglin, D. C., Hawkins, N., Jansen, J. P., Scott, D. A., Itzler, R., Cappelleri, J. C., ... & Barrett, A. (2011). Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value in Health, 14(4), 429-437.
Non-informative prior	A prior distribution that does not contribute at all to the posterior estimation of a Bayesian analysis. Such priors are often "improper", in that they are not true probability distributions. Although they let the data "speak for themselves", they have the disadvantage that models using non-informative priors may not be identifiable or difficult to estimate. It is, however, increasingly acknowledged that non-informative may not exist, since all priors contain some information. (Adapted from Gelman, 2014 and Lambert, 2005)	Gelman, A., Carlin, J. B., Stern, H. S., & Rubin, D. B., Bayesian data analysis [3rd ed., Part 1, Chapter 2.8]. Boca Raton, FL, USA: Chapman & Hall/CRC, 2014; Lambert, P.C., Sutton, A.J., Burton, P.R., Abrams, K.R., Jones, D.R., 2005. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Stat Med 24, 2401–2428. doi:10.1002/sim.2112
Non-interventional study / Observational study	A study where the investigator does not interfere with choice of the prescribed health intervention i.e. interventions are prescribed in the usual manner in accordance with clinical practice. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the administration of the intervention is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data. (See also "real world study") (Adapted from EC, 2001) Footnote: Depending on local regulations, something considered to be interventional in one country (blood tests and patient questionnaires) may not be in others.	European Commission (2001). DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL. *Official Journal of the European Cmmunities.*
Observational data	Data collected from populations as present in the routine setting of healthcare (i.e. outside the setting of a randomised controlled trial). Sources of observational may data include: routine clinical practice, patient registeries, hospital claims databases/administrative data, health surveys, electronic health records, medical chart reviews and post-marketing safety studies. (Adapted from Machin, 2007)	Machin D., Campbell M.J., Walters S.J. (2007). Medical Statistics: A Textbook for the Health Sciences (4th ed.). Wiley, Chapter 12.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's	FDA (2009) - Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

	response. (FDA, 2009)	
Phase 2 trials	Trials in which the primary objective is to explore therapeutic efficacy and safety in patients. (NIH, 2001)	National Institute of health (2001) - Glossary of terms for human subjects protection and inclusion issues. http://grants.nih.gov/grants/peer/tree_glossary.pdf
Phase 3 trials	Trials implemented to study the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely. (NIH, 2001)	National Institute of health (2001) - Glossary of terms for human subjects protection and inclusion issues. http://grants.nih.gov/grants/peer/tree_glossary.pdf
Phase 4 trials	Studies implemented in a post-marketing setting that are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. (NIH, 2001)	National Institute of health (2001) - Glossary of terms for human subjects protection and inclusion issues. http://grants.nih.gov/grants/peer/tree_glossary.pdf
PICOT(S)	PICOT is an acronym for a method used in evidence based medicine to frame and answer a clinical quesion. "P" stands for patient, problem or population, "I" for intervention, "C" for comparison, control or comparator, "O" for outcomes and "T" for time. Alternative versions also include "S" for study design. (Riva, 2012)	Riva, J. J., Malik, K. M. P., Burnie, S. J., Endicott, A. R., & Busse, J. W. (2012). What is your research question? An introduction to the PICOT format for clinicians. The Journal of the Canadian Chiropractic Association, 56(3), 167–171.
Post-authorisation	The period after market authorization of a specific pharmaceutical/ medical device product. (Adapted from Rang, 2006)	Rang H.P. (2006). Drug Discovery and Development: technology in transition. Elsevier press (2006).
Post-authorisation efficacy studies	Studies conducted within the authorised therapeutic indication to complement available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation(EU Pharmacovigilance Directive). Footnote: Although the term refers to "efficacy", PAES studies collect data in a setting that reflects general clinical practice rather than a randomised controlled trial. Therefore it may be more appropriate to think of these studies as providing "effectiveness" data rather than "efficacy" data.	EMA (2015) - Scientific guidance on post-authorisation efficacy studies: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196379.pdf.
Post-authorisation safety studies	Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. Such studies may be aimed at collecting data to enable the assessment of safety of medicinal products in everyday medical practice. (EU, 2010)	EU Pharmacovigilance Directive 2010/84/EU
Post-marketing	The period after launch of a specific pharmaceutical/ medical device	Wyeth et al. (2013). Postmarket Safety Surveillance of Drugs and

	product in the market. This follows the post-authorisation phase. (Wyeth et al., 2013)	Therapeutic Biologics. http://www.fda.gov/downloads/forpatients/about/ucm410175.pdf
Pragmatic clinical trial	A study comparing health interventions among a randomised, diverse population representing clinical practice, and measuring a broad range of health outcomes. To ensure generalizability, pragmatic trials should represent the intended patients to whom the treatment will be applied as best as possible. For instance, inclusion criteria would be broad (e.g. allowing co-morbidity, co-medication, wider age range, etc.), the follow-up would not be (or not much) interventional and allowing for treatment switching etc. (See also "large simple trials" and "real-world studies") (Adapted from Schwartz, 1967, Tunis, 2003 & Roland, 1998)	Schwartz, D., & Lellouch, J. (1967). Explanatory and pragmatic attitudes in therapeutical trials. *Journal of chronic diseases*, *20*(8), 637-648.; Tunis, S. R., Stryer, D. B., & Clancy, C. M. (2003). Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. Jama, 290(12), 1624-1632.; Roland, M. and D.J. Torgerson, What are pragmatic trials? BMJ, 1998. 316(7127): p. 285.
Pre-authorisation	The period prior to the granting of the marketing authorisation ("approval") / license for a specific pharmaceutical/ medical device product. (see also: "pre-authorisation drug development") (Rang H.P., 2006)	Rang H.P. (2006). Drug Discovery and Development: technology in transition. Elsevier press (2006).
Pre-authorisation drug development	Research and development performed in order to discover new active substances and subsequently demonstrate safety and efficacy of a new drug in order to gain marketing authorisation. This includes the discovery phase, pre-clinical studies (Phase I) and clinical studies (Phase II-III). (Rang H.P., 2006)	Rang H.P. (2006). Drug Discovery and Development: technology in transition. Elsevier press (2006).
Predictive modelling	The activity of developing, validating or adapting models which relate a dependent variable with a set of independent variables in a manner similar to multiple regression analysis. For the purposes of the IMI-GetReal project, this predictive modelling is desinged to predict the (relative) effectiveness of a medical intervention from available clinical and trial-based efficacy/effectiveness data. (Wilson, 2004)	Wilson, A. M., Thabane, L., & Holbrook, A. (2004). Application of data mining techniques in pharmacovigilance. British journal of clinical pharmacology, 57(2), 127-134.
Propensity score	The conditional probability of assignment to a particular intervention given a vector of observed covariates. As such, the propensity score summarizes information of multiple confounders and can be used to adjust for confounding by means of matching, weighting or regression adjustment. (Adapted from Rosenbaum, 1981)	Rosenbaum, P. R., & Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, *70*(1), 41-55.
Protopathic bias	Protopathic bias arises when the initiation of an intervention (exposure) occurs in response to a symptom of the (at this point, undiagnosed) disease under study (outcome). This sort of bias falls within the category of information bias. (Adapted from Strom, 2006 and Delgado-Rodriguez, 2004)	Strom B.L., Kimmel S.E. (2006). Textbook of pharmacoepidemiology. John Wiley & Sons, Ltd.; Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. Journal of epidemiology and community health, 58(8), 635-641.

Randomisation	The process of assigning trials participants to treatment or control groups, using an element of chance to determine the assignments. Randomization is a tool for providing comparable participant groups regarding all measurable and unmeasurable characteristics, apart from the intervention ("active" or control). It ensures the initial comparability of patients between the intervention groups. By randomization, one hopes to equalize the distributions of confounding factors, whether they are known or unknown. (Adapted from Strom, 2006)	Strom, B. and S.E. Kimmel, Textbook of Pharmacoepidemiology. 2006: John Wiley & Sons, Ltd.
Randomised Controlled clinical Trial (RCT)	Clinical trial designed to test the efficacy of a medical intervention within a population of selected subjects. Subjects are subjected to rigorous inclusion and exclusion criteria, and upon inclusion, are randomised into separate treatment and control groups. Considered the gold standard for clinical trials. (See also "clinical trial") (Adapted from Solomon, 2009)	Solomon P., Cavanaugh M.M., Draine J. (2009). Randomoized Controlled Trials: design and implementation for community-based psychosocial interventions. Oxford Press.
Real World Data (RWD)	An umbrella term for data regarding the effects of health interventions (e.g. safety, effectiveness, resource use, etc) that are not collected in the context of highly-controlled RCT's. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes (PRO) and health-related quality of life (HRQoL). RWD can be obtained from many sources including patient registries, electronic medical records, and claims databases. (See also "randomised controlled clinical trial", "real-world evidence" and "real-world study")(Adapted from Garrisson, 2007 and GetReal, 2016)	Garrison et al. (2007). Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health 10:5, 2007.; IMI-GetReal Glossary Workgroup 2016.
Real World Evidence (RWE)	Real World Evidence (RWE) is the evidence derived from the analysis and/or synthesis of real-world data (RWD). (See also "real-world data", "real-world study")(GetReal, 2016)	IMI-GetReal Glossary Workgroup, 2016
Real World Study (RWS)	Studies investigating health interventions whose design does not follow the design of a highly-controlled RCT and aims to reflect health intervention effectiveness in routine clinical practice. Real world studies do not typically include randomisation of trial subjects, but there are exceptions (e.g. pragmatic clinical trials). For the purposes of GetReal, real-world studies include, but are not limited to, the following: pragmatic clinical trials, non-interventional/ observational studies, drug utilisation studies, post-authorisation efficacy/safety studies. RWS, by definition, generate RWD, which can subsequently be analysed and/or synthesised to produce RWE. (See also: "real-world data", "real-world evidence",	IMI-GetReal Glossary Workgroup, 2016

	"effectiveness study", "drug utilisation study", "pragmatic clinical trial" and "non-interventional/ observational study") (GetReal, 2016)	
Referral bias	Occurs if reasons for referring a patient to a health intervention/ health care institute are related to the drug exposure status e.g. when the use of the drug contributes to the diagnostic process. This sort of bias falls within the category of selection bias. (See also "Selection bias") (Adapted from Strom, 2006 and Delgrado-Rodriguez, 2004)	Strom B.L., Kimmel S.E. (2006). Textbook of pharmacoepidemiology. John Wiley & Sons, Ltd.; Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. Journal of epidemiology and community health, 58(8), 635-641.
Registry	Database resulting from prospective, observational cohort studies of patients who have a particular disease and/or are receiving a particular treatment or intervention. (Garrisson, 2007)	Garrison et al. (2007). Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health 10:5, 2007.
Relative effectiveness	The extent to which an intervention does more good than harm, when compared to one or more alternative interventions for achieving the desired results and when provided under the routine setting of health care practice. (See also "ideal vs.usual conditions") (High Level Pharmaceutical Forum, 2008)	High Level Pharmaceutical Forum. High Level Pharmaceutical Forum 2005-2008. Final Conclusions and Recommendations of the High Level Pharmaceutical Forum. URL: http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf Accessed 7 March 2014
Relative efficacy	The extent to which an intervention does more good than harm when compared to one or more alternative interventions under ideal conditions. (See also "ideal vs.usual conditions") (High Level Pharmaceutical Forum, 2008)	High Level Pharmaceutical Forum. High Level Pharmaceutical Forum 2005-2008. Final Conclusions and Recommendations of the High Level Pharmaceutical Forum. URL: http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf Accessed 7 March 2014
Risk-sharing agreements	Agreements concluded by payers and pharmaceutical companies to diminish the impact on the payer's budget of new and existing medicines brought about by either the uncertainty of the value of the medicine and/or the need to work within finite budgets. (Adamski, 2010)	Adamski, J., Godman, B., Ofierska-Sujkowska, G., Osińska, B., Herholz, H., Wendykowska, K., ... & Gustafsson, L. (2010). Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC health services research, 10(1), 153.
Safety	The presence or absence of an adverse effect as a direct or indirect result of treatment intervention. (See also "adverse event") (ICH, 1994)	ICH (1994). Clinical Safety Data Management: defnitions and standards for expedited reporting. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf
Scientific advice	Advice given by a regulatory/ reimbursement authority to a manufacturer on appropriate tests and studies to be performed during product development/ application for product reimbursement, in order to avoid major objections being raised during evaluation of the marketing authorisation application/ reimbursement application. (Adapted from EMA, 2009)	EMA - Scientific advice and protocol advice. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

Selection bias	A systematic error introduced due to the selective inclusion of subjects who differ in characteristics from the target population, or selective drop-out of subjects in a study. (Adapted from Strom, 2006 and Delgrado-Rodriguez, 2004)	Strom B.L., Kimmel S.E. (2006). Textbook of pharmacoepidemiology. John Wiley & Sons, Ltd.; Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. Journal of epidemiology and community health, 58(8), 635-641.
Self-selection bias	An error occuring when study participants decide themselves to particpate in or to leave a study based on both drug exposure and change in health status. This sort of bias falls within the category of selection bias. (See also "Selection bias") (Adapted from Strom, 2006 and Delgrado-Rodriguez, 2004)	Strom B.L., Kimmel S.E. (2006). Textbook of pharmacoepidemiology. John Wiley & Sons, Ltd.; Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. Journal of epidemiology and community health, 58(8), 635-641.
Stakeholder	For the purposes of the IMI-GetReal project, a stakeholder is an individual, organisation or initiative that participates in, is involved with, influences the outcomes of, or is influenced by the outcomes of, or the implications of, the IMI-GetReal project. (Adapted from Varvasovszky, 2000 and Freeman, 2010)	Varvasovszky, Z., & Brugha, R. (2000). A stakeholder analysis. Health policy and planning, 15(3), 338-345.; Freeman, R. E. (2010). Strategic management: A stakeholder approach. Cambridge University Press.
Standard of care	Care delivered by a healthcare provider for a specific patient which should correspond to the care that an averagely competent physician in the same field would provide under similar circumstances. (Adapted from Strauss, 2009)	Strauss D.C., Thomas J.M. (2009). What Does the Medical Profession Mean By “Standard of Care?” JCO Nov 10, 2009: e192-193; published online on September 21, 2009.
Statistical significance	A measure that describes the extent to which conclusions from a statistical analysis are supported by the data. Alternatively, it can be defined as the conclusion that findings from statistical analysis are true (i.e. not true due to random chance) for the sample studied, thus expected to be highly reliable. Footnote: High statistical significance does not necessarily mean that the finding is of great importance or decision-making utility. (See also "clinical significance") (Adapted from Redmond, 2001)	Redmond, C., Colton, T., *Clinical significance versus statistical significance, Biostatistics in Clinical Trials*. Wiley Reference Series in Biostatistics [3rd ed.]. West Sussex, United Kingdom: John Wiley & Sons Ltd. pp. 35–36. ISBN 0-471-82211-6, 2001.
Sub-group analysis	Anlaysis conducted to assess whether, and how, observed endpoints in a study are sensitive to/ affected by characteristics attributable to a specific sub-group of the study population. Such characteristics can relate to, for example, age, gender, genotype, or patient history. (Adapted from ICH, 1998)	ICH (1998) - E9 Guideline: Statistical Princinples for Clinical Trials. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. Biomarkers Definitions Working Group.Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001 Mar;69 (3):89-95.
Surrogate endpoint/ outcome	A variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible or practical. It is intended to replace a clinical endpoint of interest that cannot be observed in a trial. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. (Adapted from ICH, 1998 and Biomarkers Definitions Working Group, 2001)	ICH (1998) - E9 Guideline: Statistical Princinples for Clinical Trials. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf; Biomarkers Definitions Working Group.Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001 Mar;69 (3):89-95.

Time horizon	Period of time within a pharmacoeconomic model over which costs and health outcomes are gathered during a pharmacoeconoimc evaluation. (Ademi, 2013)	Ademi, Z., Kim, H., Zomer, E., Reid, C. M., Hollingsworth, B., & Liew, D. (2013). Overview of pharmacoeconomic modelling methods. *British journal of clinical pharmacology*, *75*(4), 944-950.
Transitivity assumption	If the safety, efficacy, effectiveness or HRQoL of health intervention A is quantitatively related to that of B, and that of B to C, then A is related to C for all A, B and C in the domain of the relation. This is a fundamental assumption of indirect treatment comparisons and network meta-analysis. (see also:"mixed treatment comparisons") (Athanasiou, 2011 and Efthimiou, 2016)	Athanasiou T., Darzi A. (2011). Evidence Synthesis in Healthcare: A practical Handbook for Clinicians. Springer, ISBN 978-0-85729-175-8, doi: 10,1007/978-0-85729-206-3; Efthimiou O., Debray, T.P.A., van Valkenhoef G., et al. (2016). GetReal in network meta-analysis: a review of methodology. Wiley, Research Synthesis Methods 1759-2887, http://dx.doi.org/10.1002/jrsm.1195
Vague (weakly informative) prior	A prior distribution that provides a very small amount of information that allows a model to be estimated, while not having a large influence on the posterior estimation of a Beysian analysis. For example, a vague prior might specify that heterogeneity will not cause more than five orders of magnitude differences in the odds ratio, or that a change in blood pressure lies in the -500 to +500 mmHg range with 95% probability. In practice, vague priors may offer a better compromise between objectivity and practicability. (Adapted from Gelman, 2014)	Gelman, A., Carlin, J.B., Stern, H.S., & Rubin, D.B., Bayesian data analysis [3rd ed., Part 1, Chapter 2.9]. Boca Raton, FL, USA: Chapman & Hall/CRC, 2014.
Work package	A specific subset of a project assigned to the execution of a specific aim. Work packages are defined by brief statements of: Activity Description, Activity Resources of Skill and Expertise, Activity Estimates of Effort and Duration, Activity Schedule, Activity Risks, and Activity Budget. (Weiss, 1992)	Weiss J.W. (1992). 5-Phase Project Management: a practical planning & implication guide. Addison-Wesley, 1992. ISBN 0201563169, 9780201563160