Guidance

Demonstrating Value with Real World Data: A practical guide

May 2011

Foreword

In late 2008, the ABPI's Innovation campaign kicked off with a series of projects which were aimed at looking at the innovative potential of the UK, as a place for investment in life sciences. As part of this initiative, the Real World Data campaign team were tasked with appraising the UK's strengths in demonstrating the value of medicines using Real World data i.e. data obtained by any non-interventional methodology that describes what is happening in normal clinical practice.

At that time, the team recognised that data about patients' use of medicines in normal clinical practice, or in settings which reflect the reality of health care delivery, was becoming increasingly important in decisions affecting patients' access to medicines in the UK. Indeed, this forward thinking has come to fruition through recent healthcare system reforms with the intention to maximise patients' health gains.

At the time of my joining the ABPI, the campaign was already well underway, working to influence thinking on the value of Real World data and how the clinical development model could be enhanced further by the demonstration of value of a medicine in actual clinical practice. The campaign team were already working on an ABPI Discussion Paper: 'Demonstrating Value with Real World Data' to argue the case for the potential competitive edge the UK could develop. It was then, following discussion with our members, that it became apparent that industry would benefit from more detailed guidance on definitions, use and practical issues surrounding the conduct of Real World data studies.

The team has endeavoured to cover all these topics in this Guidance, drawing on the expertise of companies and individuals to produce a practical guide for research and development, marketing, commercial and health outcomes colleagues; which can also be used as a reference guide for other allied colleagues within industry.

We hope you find this useful. We look forward to seeing the UK grow from strength to strength in the expertise required to deliver Real World data to demonstrate the value of medicines to patients.

Dr Allison Jeynes-Ellis
Medical & Innovation Director, ABPI

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Glossary

AHRQ	The Agency for Healthcare Research and Quality - mission to improve the quality, safety, efficiency, and effectiveness of health care in the U.S.A. AHRQ supports research that helps people make more informed decisions and improves the quality of health care services. AHRQ was formerly known as the Agency for Health Care Policy and Research
AWMSG	All Wales Medicines Strategy Group
CTIMP	Clinical Trial Investigational Medicinal Product
EMA	European Medicines Agency
EUCTD	EU Clinical Trials Directive
FDA	Food and Drug Administration (USA)
GPRD	General Practice Research Database - the world's largest computerised database of anonymised longitudinal medical records from UK primary care that is linked with other healthcare data.
HES	Hospital Episode Statistics - the national statistical data warehouse for England of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere. HES is the data source for a wide range of healthcare analysis for the NHS, Government and many other organisations and individuals.
HTA	Health Technology Assessment
ICH GCP	International Conference of Harmonisation (ICH) Good Clinical Practice (GCP)
REC	Research Ethics Committee
IRB	Institutional Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRES	National Research Ethics Service
PROs/PROMs	Patient Reported Outcome Measures
RCT	Randomised Clinical Trial
RW	Real World
SMC	Scottish Medicines Consortium
SmPC/SPC	Summary of Product Characteristics
THIN	The Health Improvement Network - a medical research database of anonymised patient records from information entered by UK general practices in their ViSion patient clinical record systems.

Section 1: Purpose of the guidance

- Real world (RW) data are likely to become increasingly important in decisions that affect patients' access to medicines in the UK and worldwide.

- In the past, decisions as to whether grant market authorization and access to new medicines in national markets were mainly informed by data generated from clinical trials, particularly RCTs. Increasingly, there is a recognition of the role played by data about patients' use in normal clinical practice or in settings better reflecting the reality of health care delivery.

- Recent reforms of the English health system, including the publication of the White Paper and the Department of Health consultation document on Value Based Pricing, highlight the government's intention to improve healthcare outcomes and the importance for the life sciences industry to demonstrate that their medicines can contribute to that. The collection and use of RW data can enable all parties to achieve their objectives and, ultimately, to maximise patients' health gains given the limited NHS resources.

- RW data is a broad term which has been used to describe a variety of data types including data gathered in large randomised observational registries, comparative effectiveness studies and pragmatic trials through to local single centre audits or service evaluations.

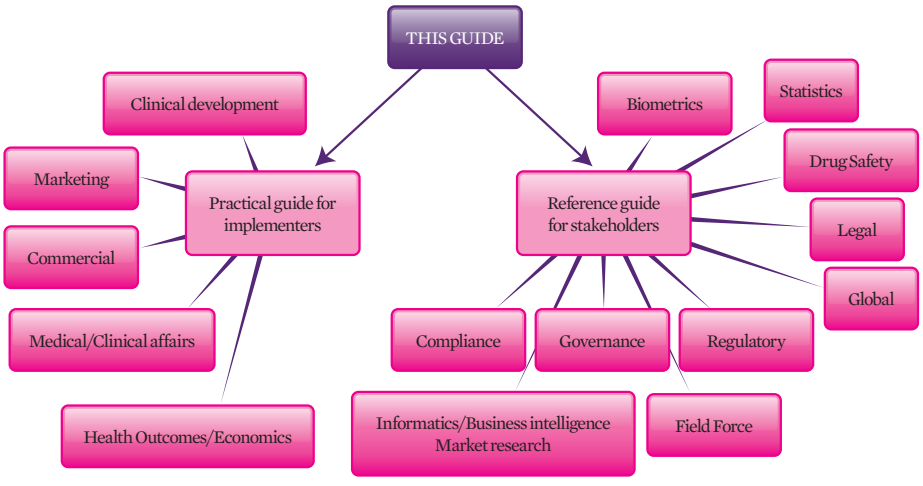
- For the purposes of this guidance, RW data will refer to data obtained by any non-interventional methodology that describes what is happening in normal clinical practice.

- This ABPI guidance seeks to provide further clarity around the definitions, use and practical issues which arise when undertaking RW data projects.

- It is aimed at a variety of personnel working within the pharmaceutical industry including those who may need a reference guide and those seeking support with the practical aspects of undertaking RW data projects (Figure 1).

- This guidance should be read alongside the ABPI Code of Practice and the most recent relevant regulatory, legal, ethical and national government policy documents, the majority of which are referred to throughout this guide, to ensure that up to date guidance and regulations are followed.

Figure 1: Audience for this guide



Section 2: Background

2.1 The UK context

Cooksey's review, commissioned by the UK Government in 2006, highlighted that there is *"a gap in the translation of new medical interventions into everyday practice ... from research observation to routine clinical practice"*[1].

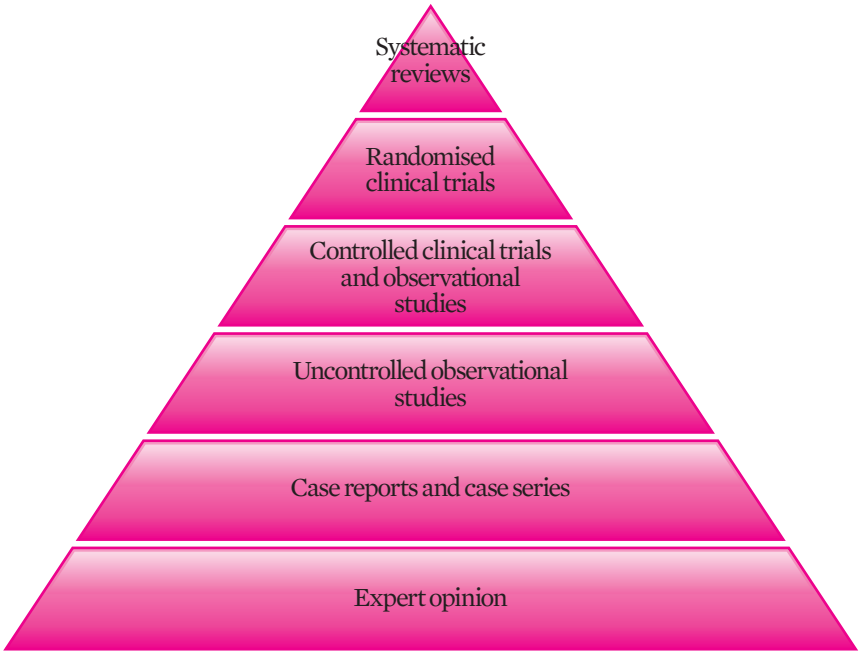
The report identified two key gaps in the translation of health research:

Firstly, translating ideas from basic and clinical research into the development of new products and approaches to treatment of disease and illness (known as the first translational gap);

Secondly, implementing those new products and approaches into clinical practice (known as the second translational gap).

Generating RW data helps demonstrate the value of medicines and closes the second translational gap.

Figure 2: Hierarchy of evidence



Traditionally, Randomised Clinical Trial (RCT) data has been regarded as being at the top of the hierarchy of evidence quality (Figure 2). However, more recently there has been recognition among key opinion leaders that RW data have a place alongside RCT data providing valuable evidence of use in clinical practice that cannot be gained from RCTs.

In 2008, Professor Sir Michael Rawlins, Chairman of the National Institute for Health and Clinical Excellence (NICE), argued that we need a new approach to analysing clinical evidence[2].

"RCTs, long regarded as the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of 'hierarchies' of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base."

"Observational studies are also useful and, with care in the interpretation of the results, can provide an important source of evidence about both the benefits and harms of therapeutic interventions"

2.2 The International context

Professor Rawlins' view is echoed by other commentators outside the UK.

Professor Vandenbroucke, of Leiden University identified a place for observational research in discovery and explanation of diseases. He advocates the use of two separate evidence hierarchies, recognising that both observational and interventional studies are needed for complete evidence generation[3]. Similarly Concato et al. concluded that there is no justification for an evidence hierarchy which places RCTs above observational studies. Observational studies produced similar effect sizes to the RCTs when they examined published meta-analysis of RCTs and observational studies that addressed the same clinical topic in 5 different areas[4].

These views have translated into policy statements and guidelines across European and US agencies (EMA and FDA) responsible for the review of evidence for licensing decisions; and have resulted in an increase in demand for Real World data globally.

2.3 The UK NHS Environment

The UK NHS is changing rapidly and is under constant financial pressures. Decision makers at national and local levels increasingly require broader and more sophisticated evidence on which to base informed treatment choices.

The Government set out its vision for the NHS in the White paper, *"Equity and Excellence: liberating the NHS"* published in July 2010[5]. The paper states that in order for the Government to achieve their ambition for world-class healthcare outcomes, the NHS must move away from meeting targets and be focused on quality and outcomes. In order to demonstrate quality and value, it will be important to evaluate normal clinical practice embracing a variety of RW data methodologies. The White paper makes extensive reference to the importance of the conduct of research, and the use of research evidence, as key elements of the NHS. It recognizes that *"Research is vital in providing the new knowledge needed to improve health outcomes and reduce inequalities"*.

In this NHS environment, it is therefore likely that RW data will become increasingly important in decisions that affect patients' access to medicines. Data collected about new medicines pre-launch are constrained by the limited ability of RCTs to reflect routine practice, or the reality of practice in a particular health care system. The introduction of Value-Based Pricing for medicines used in the NHS from 2014 will need to be underpinned by robust RW evidence of value, incorporating broader considerations than the narrow efficacy demonstrated in RCTs.

'Our industry must demonstrate the full value of its medicines, it is for government to put in place processes which assess that full value, and then secure access to that value for NHS patients,' Richard Barker, Director General, ABPI (December 2010)

2.4 The Patient perspective

Over recent years, the importance of the patient perspective has risen to the top of the agenda. Patients' views are key to two aspects of RW data. First, systematically recording and evaluating patients' experiences of their health care, including their satisfaction with the delivery of services, is increasingly recognised as relevant to assessments of the quality of health care. Capturing patient feedback has been recognised as a significant driver for improved services, essential for service design and delivery, monitoring improvements and key to ensuring high quality care for all.

Second, there is increasing recognition that patients' views of their own health, measured using validated and reliable survey instruments (Patient Reported Outcome measures – 'PROs', or 'PROMs') provide an important and highly relevant way of assessing the effects of treatment, which are complementary to conventional clinical endpoints. The usefulness of patients' self-reported health is reflected in the NHS PROMs programme. Introduced in 2009, this is a unique initiative initially involving the routine measurement of patient reported outcomes in four areas of elective surgery[6]. More recently, building on the emphasis on patient outcomes in the NHS reforms, the collection of both patient experience and patient reported outcomes will become more common across a wide range of NHS services[7].

"If quality is to be at the heart of everything we do, it must be understood from the perspective of the patient."

"Just as important [as clinical measures] is the effectiveness of care from the patients' own perspective which will be measured through patient reported outcome measures (PROMs)".

Next Stage Review June 2008

Section 3: What is RW data?

RW data is a broad term and it is possibly easier to define RW data by what it is not, rather than what it is:

RW data has been defined by an International Task Force as data used for clinical, coverage, and payment decision-making that are not collected in conventional randomised controlled trials (RCTs)[8].

However, a more positive and pragmatic definition is data which describes what is really happening in everyday normal clinical health care practice. This can include RW data from existing secondary sources (e.g. NHS databases) and the collection of new data, both retrospectively and prospectively.

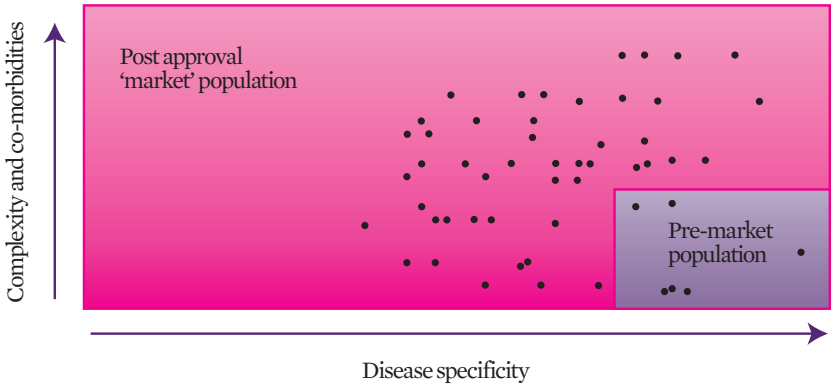
RW data includes data on:
- Outcomes (clinical and patient-reported)
- Resource use (NHS, patient and societal)
- Treatment pathways
- Service models
- Patient preference/experience/compliance

RW data projects are often also referred to as non-interventional or observational studies which are used inter-changeably. Certain projects are also termed audits or service evaluations. Most importantly, no treatment or test would be changed for a RW data project. RW projects can be comparative, considering 'which is best?' or descriptive, looking at 'what is happening?' and they can be undertaken either retrospectively or prospectively in a primary, secondary or tertiary care setting.

3.1 What are the advantages of RW data vs. RCT data?

- **Generalisable**
  While RCTs provide data with high internal validity, necessary to accurately illustrate the efficacy, safety and quality of an intervention, their comprehensive exclusion criteria may produce studies in a narrow segment of the population only, leading to results with limited external validity. Groups which are often under-represented in RCTs include women[9], children[10], the very elderly[11] ethnic minorities[12] and those with multiple co-morbidities. In contrast, by including an unselected sample of the whole, diverse RW population, a RW study produces results which are more likely to be generalisable to the patient population who may present for treatment.

Figure 3 - Scope of RW studies vs. RCTs in the population



- **Contextualised**
  RCTs of medicines focus on efficacy, safety and quality as endpoints. Randomisation, strict inclusion and exclusion criteria and rigorously protocolised treatment and monitoring procedures are designed to eliminate all other factors which may affect these endpoints, except the pharmacological effect of the investigational medicinal product.

  RW studies consider a more contextualised endpoint, which may be described as 'effectiveness'. This takes account of the constraints on outcomes imposed in normal clinical care by such factors as unavailability of diagnostic or monitoring tests, poor adherence to treatment and non-standard dosing or administration. This provides a more realistic picture of what can be achieved with a new medicine in normal clinical practice as opposed to the highly standardised context of the randomised clinical trial.

- **Cost-effective and quick to set-up**
  Large RCTs can cost many millions and take years to even reach recruitment of the first patient (average time from funding to recruitment of first patient 621 days[13]). RW data collection requires a much lower level of funding and due to the different regulatory requirements, can be rolled out and completed much more quickly than a randomised clinical trial.

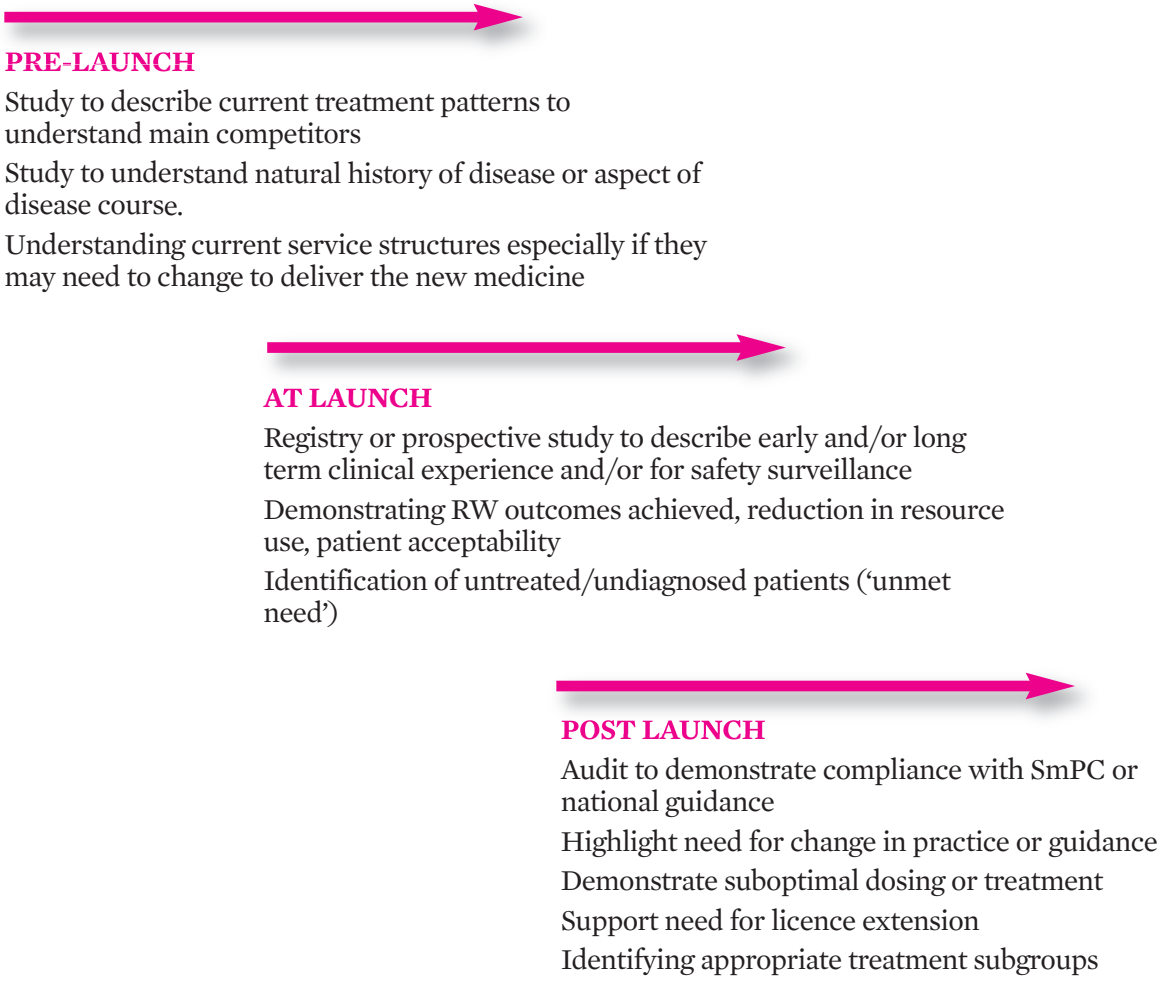
Table 1. Summary of differences between RCTs and RW studies

	RCTs	Real World Studies
Type of Trial	Experimental / interventional	Observational / non-interventional
Primary focus	Efficacy, safety and quality	Effectiveness
Patient population	Narrow and restricted	Wide and unrestricted
Monitoring	Intense (ICH-GCP compliant)	Not required
Comparators	Gold standard / placebo	None / standard clinical practice
Randomisation & Blinding	Yes	No
Cost	££££	£

3.2 When in the product lifecycle?

Although a medicine can only be studied in normal clinical practice once it is licensed and being used, RW data collection projects can be valuable at all stages in the product life cycle:

Figure 4: Examples of RW data projects throughout the product lifecycle



Section 4: Why is RW data important?

There are many different ways in which RW data can support the marketing of a medicine. With its increasing acceptability, it can be considered as an alternative methodology to a randomised clinical trial to generate new evidence or to increase the robustness and credibility of existing claims.

4.1 Demonstrating value

It is vital to demonstrate the additional value provided by a medicine. This can be in terms of:

Resource use
- Resource use associated with individual episodes of care (using time and motion study methodology)
- Total NHS resources

Outcomes
- Demonstrating clinical outcomes
- Patient reported outcomes

Service delivery
- Patient or clinician satisfaction
- Capacity
- Patient journey (e.g. chair time, throughput etc.)

When randomised clinical trial data has been gathered outside of the UK, RW data projects can provide the opportunity to demonstrate the value of any medicine to a relevant UK population and in the context of UK clinical practice.

4.2 Getting HTA ready

A RW data project can ensure that you are armed with the breadth of evidence required to demonstrate a robust economic and budget impact argument to HTA bodies. This includes an understanding of the current base case against which HTA bodies will assess any new medicine including
- Burden of illness
- Current outcomes
- Current treatment pathways and NHS resource use
- Current models of service
- Patient Utilities and other PROs
- Patient and NHS satisfaction

The robust collection of RW data will ensure that the economic and budget impact models developed are based on relevant data to demonstrate the case rather than basing the model on RCT data or expert opinion. This data can be collected on a country specific basis if required by SMC or AWMSG or UK wide.

Current NICE guidance is issued with audit criteria and this can also be an opportunity to collect RW data to demonstrate compliance or support further re-appraisals or reviews.

4.3 Capturing early clinical experience

Clinicians are often keen to evaluate new medicines when they become available and this may be a local requirement of their Trust or local commissioners in order to formally assess the benefits of any new medicine. A RW data project may be a suitable alternative to a phase IV study. This is considered of particular relevance in high cost disease areas or in orphan or rare conditions where randomised clinical trial data can be limited.

4.4 Evaluating partnership working and best practice

It is recognised that the outcome of every joint working project between the NHS and the Pharmaceutical Industry should be measured[14]. The ABPI guidance recommends that a set of baseline measurements should be established at the outset of any project to track and measure the success of the project aims, particularly patient outcomes.

Sometimes it may not be the data gap that is the issue but the understanding of the local practice and potential need for change by the NHS. In these circumstances the actual process of collecting RW data on current practice can support the decision maker to re-evaluate current practice and adopt new practices.

4.5 Informing internal decision making

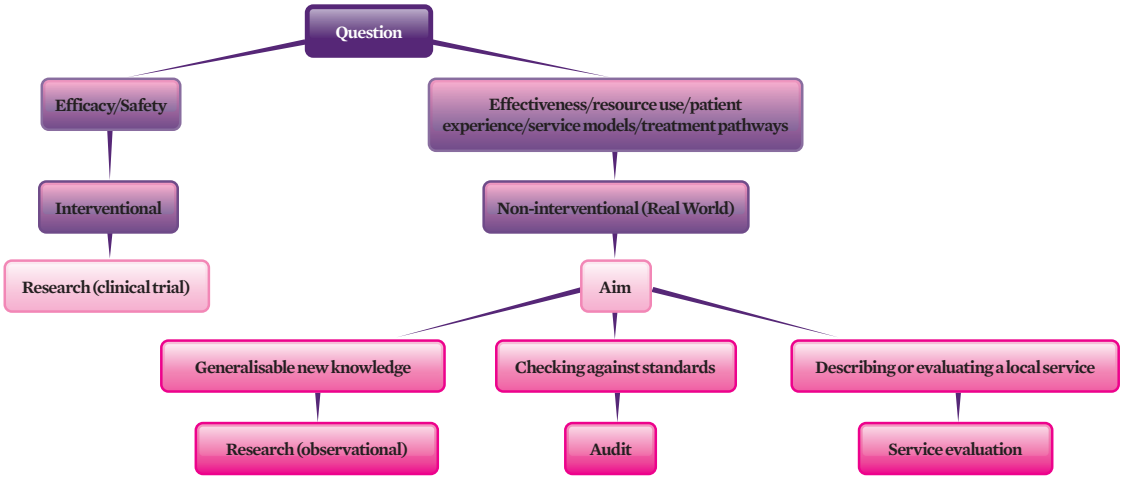
RW data can be used to increase the breadth of information upon which key internal company decisions are based. For example, there may be uncertainty about the potential market segments which can be addressed, the size of the market or the competitor products in practice as opposed to theory.

Section 5: What types of RW projects are there?

- Most RW data is obtained via research, which may be international, national or local in scope or context.
- Every country has its own regulatory framework for research and according to the UK regulatory classification of data collection projects, RW data may also be obtained from Local Service Evaluations and Clinical Audits, which are by definition or in practice, local in scope.
- In the UK it is important to distinguish between research, audit and service evaluation projects because:

1. the regulatory framework which applies to research is more extensive than that applying to audit and service evaluation.
2. the uses to which data collected in an audit or service evaluation can be put are more restricted than the uses of research data.

Figure 5. How do I decide what type of project I need to do?



5.1 Research vs. Audit vs. Service evaluation

The main criterion for considering whether a project constitutes audit, research or service evaluation is not what data are collected (as is often supposed), but the **purpose or aim** of the data collection:

Audit
Clinical audit is a **quality improvement process** that seeks to improve patient care and outcomes through systematic review of care **against explicit criteria** and the implementation of change[15]

Research
"Research can be defined as the attempt to derive **generalisable** new knowledge by addressing clearly defined questions with systematic and rigorous methods."[16]

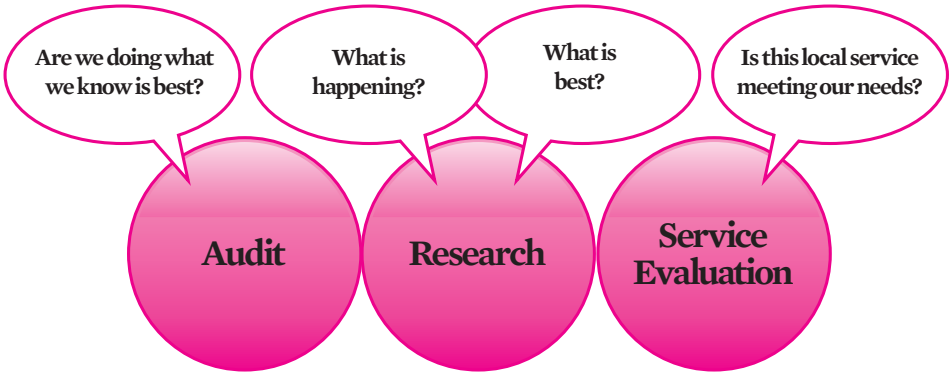
Service Evaluation
"Evaluation provides **practical information** to help decide whether a development or service should be continued or not. Evaluation also involves making judgements about the value of what is being evaluated"
"Evaluation is concerned with producing internal recommendations for improvements that are not intended to be generalised beyond the setting in which the evaluation took place"[17]

In summary,

- The AIM of audit is quality assurance and subsequent improvement to meet a pre-set standard
- The AIM of research is to describe practice, define best practice, or to compare practices/interventions to see which is best.
- The AIM of service evaluation is to inform local service planning decisions.
- Considering which type of project you are planning to conduct is paramount for smooth implementation

Figure 6: Audit, Research Service Evaluation

For further guidance on distinguishing research, audit and service evaluation see the National Research Ethics Services (NRES) website:
http://www.nres.npsa.nhs.uk/applications/guidance/research-guidance/?entryid62=66984



5.2 Prospective and retrospective designs

Once the aim of the RW project has been agreed, the second consideration is the most appropriate methodology by which to collect the data. Audit, service evaluation or non-interventional research projects can all be carried out by retrospective or prospective data collection. Some factors to consider in choosing the appropriate methodology are shown in Table 2.

Table 2: Uses, relative merits, limitations of prospective and retrospective designs

	Prospective	Retrospective
Data quality	Can ensure complete dataset	Relies on quality of clinical records
Scope of dataset	Can include data not routinely recorded e.g. Reasons for decisions, formal disease rating scales, PROs, patient experience. Data reflects current treatment	Can only include routinely recorded data Need to balance need for current data vs. eligibility period needed to obtain enough patients vs. number of sites
Timelines	Depend on rate of presentation of suitable patients	Predictable, short data collection period
Involvement of clinical staff	Usually involved to collect data as patients present	Do not have to be involved – data collected in planned sessions by research staff
Patient consent	Easy to seek as patients present to clinic	Can be more difficult to obtain – by post from ex-patients – poor response rate

Example project types: (not a comprehensive list)

- **Designs – retrospective**
  - Retrospective chart review
  - Primary care database study
  - Secondary care database study
  - Case control study

- **Designs – prospective**
  - Cohort study
  - Prospective outcomes study
  - Time and motion study
  - National registry
  - Cross sectional survey
  - Patient reported outcomes study
  - Post marketing surveillance/safety study

5.3 What existing databases can provide RW data?

- In the UK, there are a number of commercially-available pre-collected datasets of patient data, which can be analysed to answer a variety of RW questions.
- The largest and most well-established datasets contain primary care data only e.g. The Health Improvement Network (THIN), General Practice Research Database (GPRD).
- Secondary care databases do exist but these are currently less accessible for commercial research (Dr Foster) or are only local in scope (Tayside Master Patient Index).
- Linkage between datasets (e.g. GPRD and HES) is provided by some databases for additional fees, but databases linking primary and secondary care data at the patient level are limited in scope (Tayside).
- RW data can be obtained quickly and cost-effectively from pre-collected datasets
- However, the data are not collected for research but for reimbursement or pre-specified audit purposes, and so the coding may be undertaken to meet the peculiar requirements of these uses for the data.

5.4 International and country-specific studies

It is possible to conduct international RW data projects using a similar model to large, powerful RCTs, pooling data from several countries with disparate health care systems, particularly where the endpoints of interest are outcomes of treatment. However, like RCTs, this approach to RW data collection requires large numbers of patients, can be difficult and expensive to organise; and may mask valuable intelligence about crucial factors affecting the successful implementation of a new medicine, which are related to a specific health care system.

Where the endpoints relate to resource use and service delivery, it is essential to conduct studies in each different healthcare system with study design tailored to address questions which are relevant to users and payers in that system, but possibly not in others, and to obtain relevant results. Separate studies are more achievable within commercial timelines and budgets. These can be conducted with valuable ownership from the smaller number of investigators, if they are appropriately involved in study design and review of results, to ensure that the study answers questions that are relevant to clinicians and/or payers and that appropriate comment is provided on the results to stimulate a change in practice.

Alternatively it may be appropriate to conduct a RW study using an international protocol, but powered so that the data from each country can be analysed separately in case of differences between countries in how patients are defined, as well as who is treated and how – whether

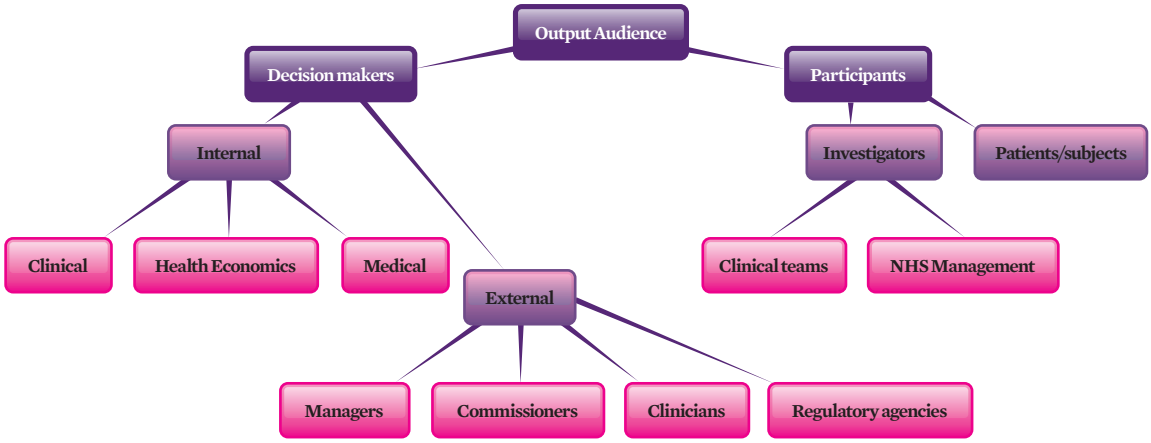
this is appropriate will depend on the therapy area or the type of question to be answered by the research:

- Safety registries may need to be international and pool all the data
- Resource use and patient pathway descriptions need to be local

5.5: Outputs

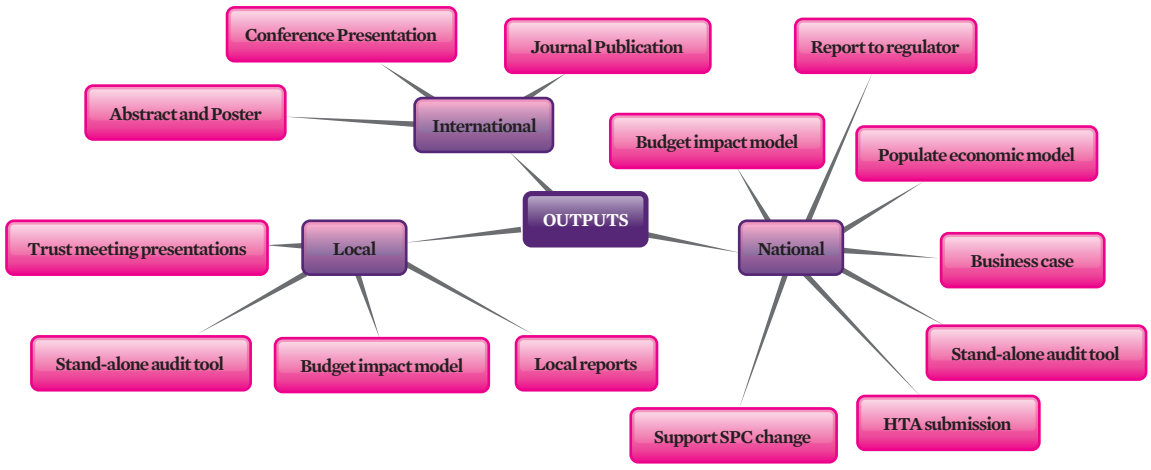
RW data projects can provide a valuable source of information and consideration of the audience(s) should be given when designing any project so that the project is able to deliver its intended purpose. Figure 6 provides some examples of RW project audiences.

Figure 6: Examples of Target Output audiences



As illustrated, RW data projects can have a variety of audiences and each may have different requirements from the output of the project. Figure 7 provides examples of the different forms the output from RW data projects can take.

Figure 7: Examples of Real World Data Outputs



Section 6: What is the external framework for undertaking RW studies?

There is no single legal instrument or guidance specific to RW data collection in the UK, but an assortment of laws and binding codes of practice which have principles or clauses which must be applied to RW projects in England and Wales, Scotland and NI. These are less challenging than for an RCT however the rights, dignity and well-being of patients must be protected just as in clinical trials. It is critical to be familiar with the necessary regulatory obligations for the specific design of RW data projects being undertaken.

6.1 Medicines and Healthcare products Regulatory Authority (MHRA) Approval

The MHRA is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe. The MHRA is an executive agency of the Department of Health. The MHRA applies the 'Medicines for Human Use (clinical trials) Regulations 2004', (amended 2006) (which is derived from the EU Clinical Trials Directive (EUCTD) 2001). This legislation applies only to interventional clinical trials of medicinal products (determining safety and/or efficacy) and does not apply to observational research ('non-interventional'). This is defined in the Directive as a study where:

- Medicines are prescribed in the usual manner and in accordance with the marketing authorisation
- The decision to prescribe a medicine is clearly separated from the decision to include the patient into the study
- No randomisation into groups
- No additional diagnostic or monitoring procedures are applied
- Epidemiological methods are to be used to analyse the data

RW studies should meet all the above requirements to be classified as 'non-interventional' and if they do, they are exempt from compliance with the Directive and the study can be conducted without applying to the MHRA for a Clinical Trials Authorisation (CTA).

Where patient reported outcome measure (PROM) questionnaires, or clinician rating scales that are not in routine use in normal clinical practice, are to be used to obtain data in study, careful consideration should be given as to whether their use would constitute an 'additional diagnostic or monitoring procedure' within the terms of the Directive and if necessary advice can be obtained from the MHRA.

6.2 NHS Trust Research & Development Approval

NHS Trust Research and Development (R&D) departments are responsible for research governance within hospital and primary care trusts. The framework they work within to do this is the DoH Research Governance Framework (RGF)[18]. This applies to all research whether non-interventional or clinical trials. It sets standards for conduct of research in England, outlines the responsibilities of all the groups involved, and requires mechanisms to ensure compliance. It also describes how compliance will be monitored and the sanctions to be applied for failure to comply. Similar but separate RGFs apply in Scotland[19], Wales[20], and Northern Ireland[21].

For further information see:
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

R&D approval is needed for all NHS sites involved in a research study (but not for RW projects designed as an audit or service evaluation). Approval to release data from a Trust (including anonymised or coded data) is needed for audit and service evaluation, and this can usually be obtained from the Trust Data Protection Officer (Caldicott Guardian) via the R&D department. Data Protection Officers must satisfy themselves that the data are to be released for a legitimate purpose, and that there is either valid patient consent for the data release, or the data are adequately anonymised so that no patient can be identified by anyone outside the Trust. It is advisable to ensure that approval for data release is obtained in writing.

6.3 Ethics Approval

The National Research Ethics Service is a network of Research Ethics Committees (RECs) which have a remit to protect the safety, rights, dignity and well-being of research participants and to promote good quality research. The Department of Health Research Governance Framework for Health and Social Care 2005 requires that all research conducted in the NHS is submitted to a Research Ethics Committee for independent review via the National Research Ethics Service.

The ABPI Code of Practice for the Pharmaceutical Industry 2011 requires submission to an ethics committee of all PROSPECTIVE non-interventional studies that involve collection of patient data and it encourages compliance with the same standard for all other types of non-interventional studies including epidemiological studies and registries; and other studies that are retrospective in nature.

The Governance Arrangements for Research Ethics Committees (GAfREC) also requires that approval from a REC must be sought for all research, (including non-interventional research) involving NHS patients, recently deceased on NHS premises, relatives and carers[22]. Ethical review is not required for audit or service evaluation[23]. See section 4.1 for definitions of audit and service evaluation.

For further information see: http://www.nres.npsa.nhs.uk/

6.4 Patient consent and data access

The World Medical Association Declaration of Helsinki, which is a code of ethics covering all research involving human subjects requires that voluntary informed consent of subjects is sought before they are involved in any medical research[24].

The requirements of the Data Protection Act 1998, when applied to research mean that patient consent must also be obtained for access of researchers to identifiable medical records for the purposes of research, whether interventional or non-interventional. A specific research exemption allows clinicians to access their own patients' records for research, without obtaining patient consent to use the record for a different purpose than that which it was created (that purpose being clinical care of the patient). Non-clinical researchers do not have the right to access patients' records without specific consent but anonymised data can be supplied by clinicians to researchers without patient consent[25].

The NHS Act 2006 provides for access of researchers to identifiable patient data without patient consent, on the approval of the National Information Governance Board for Health and Adult Social Care (NIGB)(established by The Health & Social Care Act 2008). The NIGB apply stringent tests as to whether the research is sufficiently important to the public interest and whether anonymised data could be obtained instead, or whether consent could be sought. Approval is only given in exceptional cases.

For more details see: http://www.nigb.nhs.uk/ecc

The doctor's duty of confidentiality endures beyond death and the known wishes of deceased patients in respect of their medical information must be respected. The GMC gives detailed guidance on factors affecting a decision to disclose a deceased patient's data for any purpose, including research, where their wishes are unknown[26].

For the full guidance see: http://www.gmc-uk.org/guidance/ethical_guidance/confidentiality.asp

6.5 NHS Costing template

The National Institute for Health Research (NIHR) was created by the DoH with the goal of improving the quality of research, researchers and facilities for research in the NHS. Within the NIHR, the Clinical Research Network (CRN) forms the local infrastructure to deliver this goal by helping researchers to set up clinical studies quickly and effectively, supporting the life-sciences industry to deliver their research programmes, providing health professionals with research training and working with patients to ensure their needs are at the very centre of all research activity[27].

One initiative of the NIHR to address a specific recommendation made in the Cooksey Report around the need for a transparent and consistent national costing system for commercial research, is the Industry Costing Template.

The costing templates under the NIHR CRN Costing Programme have been implemented to speed up the initiation of industry contract trials by reducing the time required for site-by-site negotiations. It is based on the principles articulated in the NHS Finance Manual and is intended to provide transparency, greater consistency and predictability on costing for companies.

NIHR CRN Industry costing templates will be used for all relevant studies intended for adoption by the NIHR Clinical Research Networks (England) Portfolio. Although developed primarily to support these studies, the methodology is freely available to companies interested in running trials outside the Networks Portfolio. NIHR CRN is working with the devolved nations to facilitate development of comparable systems for implementation across the UK.

For further information and the Costing Template tools see:
http://www.ukcrn.org.uk/index/industry/costing.html

6.6 ABPI Code of Practice

The ABPI Code of Practice for the Pharmaceutical Industry 2011 includes four clauses which have a bearing on the conduct on non-interventional studies; clauses 13, 18, 20 and 21:

Clause 13: Non-interventional Studies of Marketed Medicines requires that for all non-interventional studies of marketed medicines summary details and results must be published in line with the obligation for clinical trials (clause 13.2). Prospective non-interventional studies are to be conducted for scientific purpose (clause 13.3) and criteria are given by which this requirement may be judged; such studies must not constitute an inducement to prescribe. Although only applying in strict terms to prospective studies, companies are encouraged to comply with clause 13.3 for all other types of studies, including epidemiological studies and registries; and other studies that are retrospective in nature. Clause 13 also limits the scope of sales representative activity in prospective non-interventional studies (clause 13.3).
Clause 18 sets out guidance for appropriate provision of grants or other funding and contracts for provision of services by institutions, companies or associations, which includes supporting research. Such provision must not constitute an inducement to prescribe.
Clause 20 gives guidance for appropriate use of paid Consultants.
Clause 21 requires that non-interventional studies are approved and supervised by the company's scientific service (also clause 13.3).

For the full guidance see: http://www.pmcpa.org.uk/files/sitecontent/ABPI_Code_2011.pdf 28

Section 7: What are the internal considerations for undertaking real world projects?

The following points should be considered internally when developing a RW project.

- Consider conducting RW projects at all stages of a product's lifecycle in order to maximise pre-launch opportunities and ensure HTA-ready data is obtained, as well as generating post-launch evidence.
- Set clear objectives and questions
  - It is important to ensure RW projects are designed for their intended purpose and audience from the outset.
  - Consider the scope of use and limitations of the RW data output generated for the intended purpose and audience.
  - Careful consideration needs to be applied to ensure the methodology, evidence data collection and research hypothesis, if applicable, are clearly defined.
  - Consider feasibility issues around data collection – is it practically possible, how accurately will the data be collected (e.g. compliance to treatment)
- Involve all relevant stakeholders and expertise
  - Designing RW projects commonly require input from a variety of stakeholders both within Pharma and external. Internally this may include, although not limited to, a multidiscipline approach with Medical Affairs, Clinical Development, health economics, brand teams, pharmacovigilance, statistical and regulatory departments.
  - External expert input during the design process may be valuable in assessing feasibility of the design, data evidence collection and data statistical considerations.
- Adequate timelines and budgets should be made available to cover costs associated for design, conducting the project and output generation.
- Internal review/approval process/ SOP
  - Consideration of peer review of RW projects internally and who/which departments need to review/approve.
  - Existing Standard Operating Procedures (SOPs) are often written for the purpose of conducting clinical trials and may, by default, incorporate RW projects within their scope. However, RW projects are not clinical trials and it may be appropriate to consider generation of SOPs both country/affiliate-specific and international, specific to RW projects, differentiating between research, audit and service evaluation.
- Alignment of the conduction of RW project/s can support publication and brand plan strategy.
- Some RW projects may generate additional safety data relating to medicines and/or procedures and consideration should be given, when designing the study, as to how (Serious) Adverse Drug Reactions and pregnancy information is collected and the responsibilities for reporting.

Section 8: How to generate robust real world data

Real world projects can differ widely in methodology and purpose as discussed in the previous sections, however, the following can be regarded as common elements of the practical design and conduct of RW projects.

- Development of RW Project proposal for internal purposes detailing the aim of the project and what the project intends to achieve.
- Generation of Hypothesis (for research) or Standards (for audit)
- Protocol – all RW data collection projects should be supported by a scientific protocol detailing the rationale, methodology and analyses being undertaken. For further information on the sections contained within a protocol, please refer to Appendix 1.
- Study sponsorship, funding and support
  - Identity of Sponsor if a research study. Identification of funder for research, audit and service evaluations.
  - Contracts - Contract outlining roles and responsibilities are required between Sponsor/funder and research centre. Consider use of contract fit for use for RW projects, (i.e., the ABPI Model Clinical Trial Agreement is not suitable as refers to clinical trial terminology and governance).
  - Remuneration - Payment to researchers using NHS NIHR CRN costing template (as discussed in Section 6.5)
- Data ownership
  - Clarification of who owns the rights to any data or any potential intellectual property generated.
- Statistical Analysis Plan
  - Consideration should be given as to how the statistical analysis is performed. This may include generation of a database, data cleaning activities and statistical methods.
- Data storage
  - Clarification of how long data should be stored and by whom and under what conditions. Data collected via RW projects are often kept for shorter time periods than clinical trials.
- Use of terminology
  - Consideration should be given to use terminology appropriate for RW projects. Many acronyms and standard terminology exist for clinical trials, however, there is potential for confusion if used in relation to RW projects. With different regulatory and governance environments associated with these types of project it is important to give clarity and distinction to all stakeholders and audiences. Table 3 provides some common differences in appropriate terminology between research and audit/service evaluation.
- Project Management.
  - Delivering RW projects on budget within timelines will require appropriate project management and multi-disciplinary resource and should be allocated and monitored closely.

Table 3: Terminology associated with Real World projects

Research	Audit/Service evaluation
Study	Audit/project
Investigator	Clinician
Researcher	Routine/Clinical Care Team
Sponsor	N/A
Funder	Funder
Participant (Subjects - CTIMPS only)	Patients/service users
Researcher	Auditor
Protocol	Plan

Section 9: Practical checklist

Real world projects can differ widely in methodology and purpose as discussed in the previous sections, how

Step 1: Develop the Real World Project Concept		Supporting Section Number
Define objective/s	☐	Section 4: Why is RW data important?
Generate hypothesis/es (research) / standards (audit)	☐	Section 7: What are the internal considerations for undertaking real world projects?
Ensure project scope is within the definition of Real World	☐	Section 3: What is RW data?
Identify multi-disciplinary project team of internal and external stakeholders	☐	Section 7: What are the internal considerations for undertaking real world projects?
Align project with internal strategy (brand, publications, etc)	☐	Section 4: Why is RW data important?

Step 2: Design the Real World Project		Supporting Section Number
Define methodology, design, dataset	☐	Section 5: What types of RW projects are there?
Seek external stakeholder input (NHS, NICE, KOL, etc)	☐	Section 7: What are the internal considerations for undertaking real world projects?
Seek internal stakeholder input (pharmacovigilance, statistical, etc)	☐	Section 7: What are the internal considerations for undertaking real world projects?
Develop protocol & supporting documents	☐	Section 8: How to generate robust real world data
Undertake feasibility analysis e.g. data, target population available etc	☐	Section 7: What are the internal considerations for undertaking real world projects?
Identification of participating sites	☐	Section 8: How to generate robust real world data
Define target audience of project output	☐	Section 4: Why is RW data important?

Step 3: Real World Project Management		Supporting Section Number
Identify internal SOP and approval processes and secure approval to proceed	☐	Section 7: What are the internal considerations for undertaking real world projects?
Real World Project Management resource allocated	☐	Section 8: How to generate robust real world data
Review legal considerations (Identification of Sponsor, data ownership, contracts)	☐	Section 8: How to generate robust real world data
Agree timelines	☐	Section 7: What are the internal considerations for undertaking real world projects?
Agree and secure budget	☐	Section 7: What are the internal considerations for undertaking real world projects?
Confirm requirement for IEC/IRB review and secure necessary approval	☐	Section 6: What is the external framework for undertaking RW studies?
Generation of data collection tool and reporting facilities (e.g. data capture form, database)	☐	Section 8: How to generate robust real world data

Step 4: Output		Supporting Section Number
Data analysis and report generation resource available and allocated	☐	Section 7: What are the internal considerations for undertaking real world projects?
Generation of output to agreed audience (report, publication, HTA application, etc)	☐	Section 5: What types of RW projects are there?

Appendices

Appendix 1: Real world project protocol

A protocol for a Real World Study could include the following; however, consideration is required in reference to any pharmaceutical Company Standard Operating Procedures:

a. Title
b. Protocol synopsis – an executive summary of the main sections of the protocol
c. Background – set the scene for the study and explain why this study is needed
d. Aim & Objectives – aim is a general statement of what the study is aiming to find out; objectives are specific questions the study aims to answer, with a measurable endpoint associated with each one. The most important one should be listed as the primary objective and used in the power calculations to determine an appropriate sample size for the study. This may be expressed as a study hypothesis to be tested – a statement of what you expect the result to be (though for statistical reasons usually expressed as a null hypothesis – a statement of what you hope to disprove e.g 'There is no difference between X and Y')
e. Centre selection – list criteria by which centres will be selected to take part in the study or state if centres will be selected randomly
f. Patient selection – explain:
    i. how eligible patients will be identified/selected
    ii. how/whether these patients will be informed of/approached to take part in the study
    iii. How they will be recruited – will consent be sought? If so, how, when and by whom?
    iv. Inclusion and exclusion criteria
g. Study design –
    i. retrospective/prospective
    ii. single/multicentre
    iii. primary/secondary care
h. Methodology
    How and by whom will data be collected, checked, cleaned, analysed and reported.
i. Study dataset
    What data points will be collected.
j. Statistical considerations
    i. Sample size with justification – provide enough detail to allow another statistician to replicate your calculation.
    ii. Description of statistical methods of analysis
    iii. Study design limitations
k. Regulatory and ethical considerations
    i. Ethical review
    ii. Ethical issues in the study
        1. Patient consent
        2. Confidentiality
    iii. Relevant legislation and guidance that will be complied with
l. Pharmacovigilance requirements
m. Data ownership, custody, access & storage arrangements

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