WICKENSTONES
PARTNERS IN BUILDING VALUE

Evidence generation

A real approach to real-world evidence

The use of real-world evidence is now commonplace but not all real-world evidence is equal and, in the race to deliver an evidence plan, sometimes sight is lost of the ultimate utility of the data

There is no denying that real-world evidence is a topic of huge importance and interest to pharmaceutical and device manufacturers, payers, regulators and healthcare providers alike. For example, the use of real-world claims data in US costing studies is well-established, post-authorisation observational studies/outcomes-based agreements have become normal, and even their potential suitability for regulatory use has been considered, as recently outlined in a systematic review of current and ongoing real-world evidence studies published by the European Medicines Agency (EMA).1 Both European and US strategies are in place encouraging development and use of real-world data; the EU Network Strategy to 2020 identifies real-world evidence as a key enabler to bring innovative products to patients and support safe, effective use, and the US 21st Century Cures Act (2016) places additional focus on real-world evidence in regulatory decision making.2,3

Evidence or data?

It is worth mentioning the distinction between data and evidence, although the two terms are often used interchangeably. Real-world data is the data from whatever source (e.g. electronic healthcare records, registries, hospital records and health insurance claims databases – and broadening with digital technologies outside a controlled environment such as wearables or implantables) and gathering real-world data can be seen as fishing for information using a very wide net. On the other hand, real-world evidence is the analysed data demonstrating the key conclusions that can be

drawn (for pharmaceutical/device manufacturers, of course, the real interest lies in real-world evidence – the meaningful information that can be generated regarding usage and benefits/risks in a real-world setting). Real-world evidence requires a carefully planned and well executed programme of research and an associated analysis plan.

In this article, we ask: does healthcare technology assessment now require a large, expensive real-world evidence study and dedicated team, and examine some of the key considerations in designing and executing real-world evidence generation activities.

How is a real-world study designed?

For optimal study design and execution:

- Decide the objectives, keeping your overall strategy in mind.
- Decide on the data needed and have a robust analysis plan. At this early stage, thinking carefully and realistically about how the evidence from your study will fill an information gap and how the filling of this gap will be useful to each of the stakeholders (e.g. product manufacturer, patient advocacy group, clinician) can help cut out gathering non-essential information that might increase time and cost.
- Decide on the level of detail required (given the trade-off with time and cost).
- Find the most efficient way to gather data. For example, for rare diseases, seeking specialist centres and patient registries in multiple countries can use up time and money. In contrast, close collaboration with patient groups and easily accessible online survey platforms can yield ample patient-reported data, sufficiently representative of the patient population (not only on utility and healthcare resource use, but also diagnostic data, which – although not as high in quality as physician-reported diagnosis – can nevertheless be sufficient to generate meaningful information depending on the study objective).
- Execute and communicate the findings brilliantly, reaching those who need to hear.

The key factor in study design is that it is underpinned by clear, strategic objectives – which are carried through to the outputs – rather than driven by methodology or data sources. A recent EMA review found just ~70% of completed studies clearly matched their stated objectives, which is a worryingly low rate for scientific studies.1 Clinical trial design wouldn't begin with the type of clinical tests and diagnostics used; similarly, there is no reason for the data already available to drive real-world evidence generation.

Is an established network of real-world study collaborators needed?

Engagement with various stakeholders, such as healthcare professionals and patient groups, is an integral element of a carefully designed and strategically valuable study – from the earliest steps of study design, all the way through to analysing and interpreting results. This is true not only of a prospective survey, but also in retrospective studies.

As well as vital real-world insight, we have found that close collaboration on real-world evidence generation studies gives great opportunity for manufacturers, healthcare professionals and patient groups to develop long-standing and mutually beneficial relationships. An established network of collaborators could help set this up, but isn't required to make these relationships effective – a research question that is relevant to all stakeholders and the promise of a meaningful research outcome are the two important elements for a successful collaboration.

Do we need to purchase access to a proprietary database?

Real-world databases (proprietary or public) have their place – they are a hugely valuable source of data for large numbers of patients provided you ask the right questions and know what to do with the answers; otherwise they can be large, expensive data dumps – or worse, you can end up with misleading results if you do not have an appropriate plan to deal with missing and mistaken data inputs.

Large data sources can seem like a pre-packaged solution to almost any question. However, they are frequently severely limited by:

- Patient selection bias (even within claims datasets)
- Loss of patients in follow-up, patient duplication and missing data
- Inaccurate and misleading recording of information
- Lack of granularity within the data

> In my experience, the biggest issue with electronic healthcare records is incorrectly recorded information (e.g. typographical errors) or blocks of missing information. If you don't deal with those issues correctly you can get skewed results that don't really represent the target population.
>
> *Shahina Begum*
> *Statistician, Wickenstones*

It can also be difficult to determine whether an existing database will give what is needed, and hidden disparities in data entry can lead to bias. Usually you can run a small feasibility assessment using a weighted random sampling at minimal cost allowing you to check data fields against a gold standard (if feasible) and the number of patients with the disease of interest. We recommend careful, detailed discussion of the data available in the context of the study objectives, with personnel knowledgeable of the database and data collection, before proceeding.

Sometimes, the questions to be answered won't be recorded in an existing database – such as exploring in depth the real-world patient and family burden of disease (especially rare diseases).

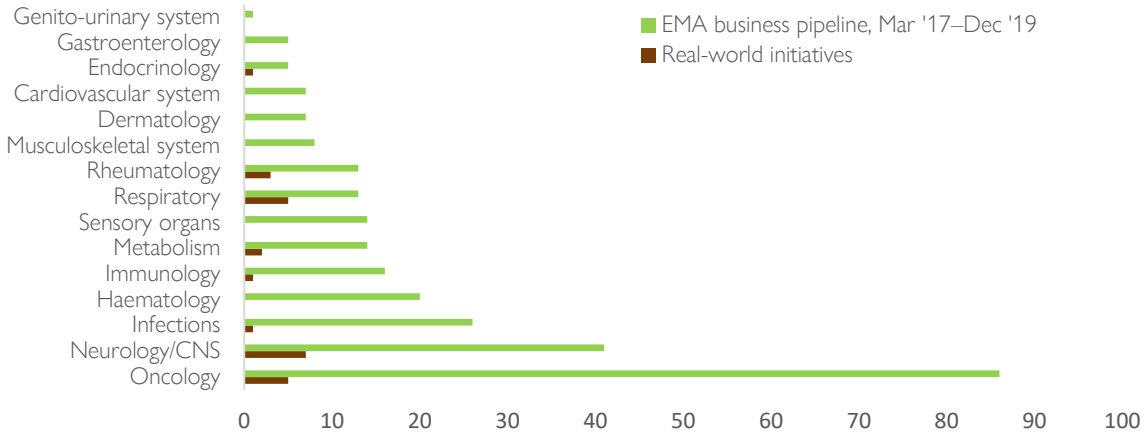
Should we invest in specialist digital technology?

Real-world evidence is commonly bundled together with the "big data" or "digitisation of healthcare" discussion. It's true, the topics are related – digital technology and increased availability of routine electronic data can both facilitate real-world studies, but a real-world study does not necessarily imply the use of routinely collected data or even electronic data at all. For example, one of our recent real-world evidence generation studies was even delivered on paper, as it was felt by the investigator to be more useable.

When designing a real-world study, there are a few factors at play as to the role of digital technology in data collection – in the "for" camp are efficiency and accuracy versus paper; however, conversely, accessibility/usability needs to be considered – will an electronic data collection tool bias the population to more "tech savvy" respondents? Is it appropriate at all in the patient population? What will be the impact if a digital tool will result in a proxy administering the survey versus respondent completing paper themselves? Or vice versa?

In some cases, a digital platform is a huge opportunity to directly reach patient groups who would not be reached via traditional paper surveys – for example, responses could be elicited directly from a very young child aged, say 2 years, using a tablet-based tool, whereas paper surveys would need to be administered by an adult.[4] Similarly, an online survey could reach geographically sparsely distributed or

remote populations – important, for example, with rare diseases or to ensure a good spread of both rural and urban patients. Provided careful characterisation/testing is carried out before going ahead, there are now a range of good online survey platforms which may be used to construct real-world data collection surveys in a cost-effective manner.



Therapeutic areas covered by initiatives identified, compared with EMA business pipeline (from Plueschke et al. 2018[1])

Conclusion

There is clear need for high quality, co-ordinated and sustainable efforts across the field of real-world evidence generation. The EMA review of publicly funded real-world evidence studies highlighted disparity between initiatives to collect data and the pipeline for product development – proprietary databases and manufacturer studies may go some way to plug these gaps, but there is certainly room for improvement across the board.

So, does healthcare technology support require a large, expensive real-world evidence study and dedicated team? Our answer is – maybe, but for optimal outcomes, one size can never fit all.

References

1 Plueschke, K., McGettigan, P., Pacurariu, A., Kurz, X. & Cave, A. EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making. *BMJ open* **8**, e021864, doi:10.1136/bmjopen-2018-021864 (2018).

2 EMA. *EU Medicines Agencies Network Strategy to 2020*, <https://www.ema.europa.eu/en/about-us/how-we-work/european-medicines-regulatory-network/eu-medicines-agencies-network-strategy-2020> (2015).

3 FDA. *FDA 21st Century Cures Act 2016*, <https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act> (2018).

4 Pitchford, N. J. & Outhwaite, L. A. Can Touch Screen Tablets be Used to Assess Cognitive and Motor Skills in Early Years Primary School Children? A Cross-Cultural Study. *Frontiers in psychology* **7**, 1666, doi:10.3389/fpsyg.2016.01666 (2016).

Written by
Tammy Wynne
Tammy@wickenstones.com
www.wickenstones.com

WICKENSTONES
PARTNERS IN BUILDING VALUE

Wickenstones is a global strategy consultancy with expertise in evidence, value and access