OPTUM Labs®

Research and Innovation: Using Real World Evidence to deliver innovation through translation

THE BAZALGETTE SERIES

Investigating the use of data in health care for research, prevention and better care

PREVIEW

The Bazalgette Series is a group of seminars hosted by OptumLabs® that investigate the use of data in health care for prevention, better care and research. The series is named after Sir Joseph Bazalgette, an engineer who redesigned the systems to bring clean water to Londoners by separating sewerage and drinking water in the 19th Century; thereby reducing the burden of communicable disease.

The 3rd seminar, "Research and Innovation: Using Real World Evidence to Drive Medical Innovation", assessed the potential for observational data in health care research. The 4th seminar, "Research and Innovation: Delivering Medical Innovation through Translation", discussed policies and efforts to encourage and deliver innovation in practice.

Each seminar re-imagines different aspects of the health system and proposes alternative methods to support data driven health care delivery and system transformation that is more suited to the epidemiological change to non-communicable disease that has occurred in the 21st Century.

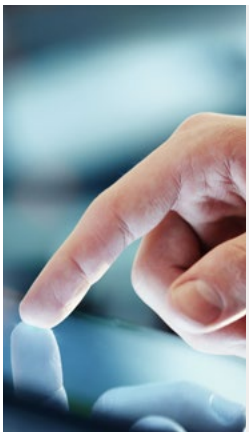
We believe that re-thinking these separate elements of the health system will generate topics of discussion that provide comprehensive proposals for delivering improved health to the population.

THE TOPICS TO BE ADDRESSED BY THE SERIES INCLUDE:

- Data Infrastructure
- Data Governance
- **Research and Innovation: Using Real World Evidence to drive medical innovation**
- **Research and Innovation: Delivering medical innovation through translation**
- Patient Empowerment
- Enabling Clinicians
- New Analytical Methods
- Learning Health Systems

The series aims to re-imagine the use of health data as the new engineering to tackle the burden of non-communicable disease.

KEY TAKEAWAYS



- Real World Evidence should be viewed as complementary to Randomised Control Trials and not as a threat or replacement
- The health system needs to urgently increase its capacity in data curation capabilities
- Evidence needs to be relevant, reusable and communicated clearly to the public
- Collaboration between the NHS and organisations from other sectors should be encouraged
- Complementary skills and opportunities across sectors leads to innovation

Introduction

Throughout the Bazalgette Series a consensus has emerged that medical research should be considered a primary function of the health system. Rapid changes in demography and the development of new technologies are leading to changes in society in general, and to the way health care is delivered in particular. Driven by the need to better understand non communicable disease (NCD) progression and accommodate changing patient preferences,[1] new sources of data for research are being used to drive medical innovation.

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One of these new data sources is data generated outside of a clinical trial environment, or Real World Evidence (RWE). As access to such data increases, researchers and other analysts are developing advanced capabilities to curate this data and to use it to find new ways to develop, evaluate and approve treatments.

Although they are limited in number, previous studies have indicated that *'there is little difference between the results obtained for RCTs [Randomised Control Trials] and observational studies'*.[2] In a recent survey conducted by the London School of Economics that considered the value and importance placed on RWE by 10 different European countries, policymakers in the United Kingdom made clear their desire to expand use of this type of data in domestic research and innovation.[3] However, in order for RWE's promise to be realised in the UK, collaboration across the NHS and other sectors including the private, charitable, social care and local government must be improved and accelerated – particularly as generation of RWE is likely to accelerate over the coming years.

Real World Evidence

Real World Evidence Definition: For the purpose of this report we define Real World Evidence as the evidence generated from clinically-relevant data collected outside of the context of conventional randomised controlled trials, such as electronic health record data.

◀ RWE presents opportunities to reflect a more comprehensive population health view

RWE can add value to the delivery of direct care provided by clinicians as well as research methodologies by providing a more detailed and well-rounded picture of an individual's health as well as other life circumstances. For example, RWE presents opportunities to learn more about the social determinants of health and reflect a more comprehensive population health view for system leaders as compared to evidence generated from controlled research environments. As health systems transition to models that promote population health management and Integrated Care Systems (ICSs), such data will be essential to achieving the patient-centred approaches that form the models' basis.

1. Crouch H. Patient survey reveals preference for digital communications. https://www.digitalhealth.net/2018/01/patient-survey-digital-communications/. Published Jan. 22, 2018. Accessed May 24, 2018.

2. Anglemyer A, Horvath H, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review). The Cochrane Library. 2014; 4.

3. Gill J, Avouac B, Duncombe R. The use of Real World Evidence in the European context. http://eprints.lse.ac.uk/68442/1/RWE_in_Europe_Paper1.pdf. Published 2016. Accessed May 5, 2018.

RWE can also provide valuable insight into the incidence, prevalence and treatment of NCD. Although much attention and research focuses on the four main NCDs (cardiovascular and chronic respiratory diseases, common cancers and diabetes), it is estimated that 55 per cent of the global burden of NCD comes from outside of these main four.[4] Use of RWE in analysis of co and multimorbidity can provide a blueprint for patient segmentation and treatment protocols to reduce the burden of disease for both patients and health systems.

Real World Evidence Opportunities

While RCTs remain the standard method for approving efficacy of drug development, RWE offers new opportunities to complement the evaluation of treatments approved through standard RCT processes. For example, RWE can:

◀ RWE offers new opportunities to complement the evaluation of treatments approved through standard RCT

- Enable analysis of a wider range of populations as RCT restrictions, such as inclusion/exclusion criteria that limit the diversity of the patients studied, are not applicable;
- Provide data and information that is more specifically relevant to the way that patients actually receive clinical care;
- Reveal gaps in evidence where further RCTs might be required to improve a drug's efficacy or expand its use, and identify rarer incidence of NCDs;
- Provide evidence for regulators to approve existing therapies for use with additional conditions and populations, for example through adaptive licensing;
- Provide insight into patient safety and outcomes as RWE enables near real-time monitoring of clinical interventions;
- Transition research from efficacy to effectiveness by allowing direct comparison between competing therapies – a key advantage for decision makers when allocating NHS resources within tight constraints; and
- Allow for greater inclusion of patients with co and multimorbidities in research studies.

Previous government initiatives have encouraged the curation of data to support collaboration for improving health outcomes. RWE could be a considerable factor in ensuring that these strategies come to fruition,[5,6,7,8] as well as become a key component for delivering the new 10 year plan for sustaining the future of the NHS.

Real World Evidence Challenges

There are, however, challenges to address so that the potential from RWE can be fully realised. The health workforce has significant gaps in the analytical skills and capabilities required to effectively curate and analyse data across the system. In addition, market research has demonstrated a shortage of UK-based technologists specialising in artificial intelligence (AI) and related data science disciplines across all industries, adding to the challenge of attracting talent to the health sector in such a competitive employment environment.[9]

Given the variances in quality and robustness of RWE, health systems need to invest in coding and standardisation so that research can be conducted outside of a controlled study environment – a time-consuming and costly endeavour.

4. Lopez A, Williams T, Levin A. Remembering the forgotten non-communicable diseases. BMC Medicine. 2014; 12: 200

5. Bell J. Life Sciences Industrial Strategy. https://assets.publishing.service.gov.uk/.../LifeSciencesIndustrialStrategy_acc2.pdf. Published Aug.30, 2017. Accessed May 16, 2018.

6. NHS England. Next Steps on the NHS Five Year Forward View. https://www.england.nhs.uk/wp-content/uploads/2017/03/NEXT-STEPS-ON-THE-NHS-FIVE-YEAR-FORWARD-VIEW.pdf. Published March 2017. Accessed May 23, 2018.

7. GOV.uk. Accelerated Access Review: Final Report. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/565072/AAR_final.pdf. Published Oct. 24, 2016. Accessed May 16, 2018.

8. Wachter R. Making IT work: Harnessing the power of health information technology to improve care in England. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/550866/Wachter_Review_Accessible.pdf. Published Sep. 7, 2016. Accessed May 16, 2018.

9. Odgers Berndston. Employers scramble for top AI specialists. https://www.odgersberndtson.com/en-us/insights/employers-scramble-for-top-ai-specialists. Published April 17, 2018. Accessed May 24, 2018.

RWE needs to be collected consistently and routinely at all clinical encounters to maximise the volume and variety of data available for research. The clinical community must engage with patients and researchers to explore the best way to communicate the value that this data offers and to explain why it is being collected and how it is being used. This engagement could produce greater public and clinician support for sharing and using patient data for alternative models of care and research methods. Health systems should create a framework to clarify the goals and proper protocols for use of RWE, to provide clarity to the public as well as potential data users.

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SOME EXISTING REAL WORLD EVIDENCE STUDIES

Intensive treatment and Severe Hypoglycaemia

Research conducted on data in OptumLabs Data Warehouse (OLDW) (a curated data set of administrative claims, medical records and self-reported health information) showed more than 20 per cent of patients with type 2 diabetes received intensive treatment that may be unnecessary. The results showed that excessive intensive treatment for patients with high clinical complexity nearly doubles the risk of severe hypoglycemia.[10]

OPERAND (Observational Patient Evidence for Regulatory Science And uNderstanding Disease)

OptumLabs is conducting the OPERAND project designed to better inform the use of RWE for retrospective observational studies in medicine and regulatory decision making. Some of the objectives include using retrospective observational data to determine if its use can confirm previously published RCT results so as to assess such data's validity. While previous RCTs have been replicated using observational data, they have not been replicated simultaneously across multiple therapeutic areas.

To conduct these simulations, OptumLabs has partnered with the Multi-regional Clinical Trials Centre at Brigham and Women's Hospital in Boston, USA to raise confidence in the appropriate use of RWE in medicine and regulatory decision-making.

Further, as regulators develop and evolve their approval methods, drug development will need to evolve as well. Over the coming years drug developers are likely to target more refined cohorts, because of developments such as precision medicine, leading to narrower clinical trials that are more easily identified from RWE.

10. McCoy R, Lipska K, Yao X et al. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. Jama Internal Medicine. 2016; 176(7): 969-78.

Understanding the policy context

In 2017, The Academy of Medical Sciences' report 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines' called for three areas of improvement regarding RWE:

1. The generation of scientific evidence to ensure it is robust, reliable and relevant to patients;
2. The trustworthiness of scientific evidence so that information is disclosed in an accessible, assessable, and usable manner; and
3. The communication of evidence to ensure it is presented in a clear, accurate and actionable way.[11]

How to ensure robustness

RWE must be relevant and reusable so that a wide variety of research can take place using the same data set(s). Data that is considered robust should also provide information about the issues that are most relevant to direct patient care and improving patient outcomes. For example, understanding the causes of inconsistencies in low adherence rates to chronic medicines could result in a decrease in multimorbidities and other adverse health events, and improve life quality.[12]

How to ensure trustworthiness

There is widespread agreement that increased transparency about data collection, sharing and use with researchers, the clinical community and the public is key to the success of increased health data linkage. System leaders should forge more robust relationships amongst academia and industry that recognise the expertise of each sector, and how they complement one another. Demonstrating and communicating a sense of public benefit from such collaborations provide a key approach to improving public trust.

◀ Demonstrating and communicating a sense of public benefit provide a key approach to improving public trust

How to ensure clear communication

Evidence should be communicated to the public in a clear, accessible and meaningful way to secure public understanding of why and how their data may be used by third parties. Health information should be easier to understand so that patients can more effectively evaluate the risks and benefits for specific treatments, according to their preferences. In one example of how to advance such a communications strategy, the Academy of Medical Royal Colleges recently launched a campaign in England to encourage doctors to speak in "plain English" when communicating with patients. In the guidance titled 'Please write to me', the Academy advises doctors to make specific changes to common phrases used in letters they send to patients following a consultation.[13]

The UK Life Sciences Strategy

The UK Government's industrial strategy set out a path to increase economic productivity in the UK, in particular in light of increasing technological change. As part of this overall strategy, the UK Life Sciences Strategy sets out recommendations to position the UK to take advantage of emerging health technology trends. As RWE increasingly becomes an evidence base for health decision making, the strategy sets out how the data eco-system should account for emerging data sources. The strategy suggests that RWE should be considered a priority for the health system as its use is essential to advancing both personalised and precision medicine.

◀ RWE should be considered a priority for the health system as its use is essential to advancing both personalised and precision medicine

11. The Academy of Medical Sciences. Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines. https://acmedsci.ac.uk/file-download/44970096. Published 2017. Accessed Apr. 5, 2018.
12. Tonarelli L. Tackling the challenge of non-adherence. http://www.pmlive.com/pharma_thought_leadership/tackling_the_challenge_of_non-adherence_1196464. Published July 17, 2018. Accessed May 24, 2018.
13. Campbell D. New drive to encourage doctors to wrote to patients in plain English. https://www.theguardian.com/society/2018/sep/04/new-drive-doctors-urged-write-patients-plain-english. Published Sep. 3, 2018. Accessed Sep. 27, 2018.

The UK Life Sciences Strategy strongly supports collaboration across sectors, removing barriers between public and private organisations to enable and encourage cooperation, and accelerating research in order for innovation to occur. The strategy relies on three core fundamental platforms:

1. Government support for and dedication to developing a research environment in the top quartile of Research and Development spend across developed nations;
2. The single payer NHS system that connects to 65 million people; and
3. A more coherent approach to curating data across the health system.

Of these three foundational elements of the government's strategy, the demands of data curation will likely prove the most challenging. Systems will need to be capable of incorporating a variety of data including clinical, socioeconomic, demographic, genomic and proteomic data to provide a comprehensive understanding of an individual's health. Further, the emergence of AI across health care delivery and research which many experts think will become more prevalent over the coming years relies on access to large datasets.

In the UK, AI in health care is currently most advanced with regard to medical imaging, and some system leaders have suggested that the NHS build a nationwide digital pathology network to enable further use of AI in diagnosis and treatment decisions. As a similar example, in The Netherlands, the PALGA, a structured nationwide histopathology and cytopathology network and archive encompasses every pathology laboratory in the country. The data generated forms the basis of the national cancer registry, which is essential for population screening programmes while supporting patient care and scientific research.

Currently, the health system in the UK is structured as a reactive rehabilitation service and largely lacks a mechanism for testing new interventions. To achieve the goals of the UK Life Sciences Strategy, such a mechanism will need to be developed so that new research methodologies and clinical interventions can be tested, using the health system's vast data assets to position the UK as a global leader in research and innovation. In such a system, emerging technologies could be developed and tested more quickly, and information regarding rarer diseases and interventions could be captured in greater detail.

One such model that exists for building prospective patient cohort registries is the Thrombosis Research Institute's AF Garfield and VTE Garfield registries that have amalgamated information for patients of Atrial Fibrillation and Venous Thromboembolism. These data sets contain clinical data from tens of thousands of patients across more than 35 countries, providing researchers with key insights into strategies to prevent stroke and improve patient outcomes.

Lessons from existing linked data models

Experience from the world leading UK Clinical Record Interactive Search (UK-CRIS) data programme outlined four points that should be considered when developing linked health data programmes. These include:

1. Linked data sets should be scalable in a way that does not create overly bureaucratic decision-making. UK-CRIS has adopted a federated model so that assets and control are localised but collaboration is supported across different centres.
2. Linking data from primary, secondary and tertiary care is essential to create a comprehensive holistic and longitudinal patient record. UK-CRIS is now linking data across organisations and has plans to link with other sources such as UK Biobank. Connecting varied data sources will bring additional pathological insights that increase the quality of health and care services.

14. https://www.palga.nl/en/about-stichting-palga/stichting-palga.html

15. http://www.tri-london.ac.uk/our-research/

3. Following the collation of data, stakeholders must interrogate the data to derive insights that are actionable. Programmes will need to have sufficient data science expertise to turn data into intelligence to enact effective and meaningful interventions.
4. Consistent governance approaches must be established across the health system. Currently, the system is saturated with multiple organisations issuing uncoordinated guidance as demonstrated in a map published by OptumLabs.

Some Ideas for New Health Sector Collaborators

The UK Life Sciences Strategy sets out a bold vision for collaboration between the health sector and other organisations. New entrants to – and existing stakeholders in – the health sector have the opportunity to make use of various schemes to navigate national and regional complexities.

Organisations in England have the opportunity to engage with the Academic Health Science Networks (AHSNs). Designed to accelerate innovation and collaboration, AHSNs offer a platform for innovators to convene; and for new interventions to be developed, tested and evaluated.

Organisations can also access NHS Digital and its prolific data asset that offers wide opportunities for research and discovery. However, organisations should not underestimate the information governance requirements that come with data access privileges. High profile examples have demonstrated how even well-resourced companies have fallen short in this respect and that this can have damaging consequences that delay and impede innovation.

Lastly, organisations should consider forming an ethics committee when choosing to operate in the life sciences sector. For example, for entities that must ensure that information they access remains anonymised, demonstrating a transparent accountability process can provide a powerful statement to the public that ethics are a priority.

Conclusion

Health and health care are increasingly influenced by factors outside of the health system. Whether these factors are societal, environmental or due to the design of the system itself, the researchers and innovators need access to wider sources of data so that the health care interventions developed address as many of the factors that determine health as possible. Inclusion of RWE provides a complementary data source that can add value to RCTs in addition to providing unique insights on its own.

The health system and its stakeholders can gain great value from the data that they hold to enable high performing scientific research, improve system efficiency and delivery higher quality care. The UK Life Sciences Strategy has set out an ambitious agenda to support stakeholder collaboration, enhance the use of data in research and build a high performing destination for scientific research. By supporting collaboration and access to RWE, the health system can enable organisations from across the public, private and third sectors to offer complementary skills and opportunities that lead to discovery, innovation and medical breakthroughs that benefit both individual patients as well as society as a whole.

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