Commentary

Making Clinical Practice Guidelines Pragmatic: How Big Data and Real World Evidence Can Close the Gap

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Abstract

Clinical practice guidelines (CPGs) have become ubiquitous in every field of medicine today but there has been limited success in implementation and improvement in health outcomes. Guidelines are largely based on the results of traditional randomised controlled trials (RCTs) which adopt a highly selective process to maximise the intervention's chance of demonstrating efficacy thus having high internal validity but lacking external validity. Therefore, guidelines based on these RCTs often suffer from a gap between trial efficacy and real world effectiveness and is one of the common reasons contributing to poor guideline adherence by physicians. "Real World Evidence" (RWE) can complement RCTs in CPG development. RWE—in the form of data from integrated electronic health records—represents the vast and varied collective experience of frontline doctors and patients. RWE has the potential to fill the gap in current guidelines by balancing information about whether a test or treatment works (efficacy) with data on how it works in real world practice (effectiveness). RWE can also advance the agenda of precision medicine in everyday practice by engaging frontline stakeholders in pragmatic biomarker studies. This will enable guideline developers to more precisely determine not only whether a clinical test or treatment is recommended, but for whom and when. Singapore is well positioned to ride the big data and RWE wave as we have the advantages of high digital interconnectivity, an integrated National Electronic Health Record (NEHR), and governmental support in the form of the Smart Nation initiative.

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The Role of Clinical Practice Guidelines and Their Limitations

Clinical practice guidelines (CPGs) have become ubiquitous in every field of medicine over the past few decades with thousands being published annually. Guidelines attempt to improve healthcare by: 1) guiding practitioners in the implementation of the latest research findings into practice, 2) promoting cost-effective treatments that are shown to reduce mortality and morbidity whilst discouraging ineffective, dangerous or wasteful practices; and 3) establishing standards so that patients receive consistent care regardless of where and by whom they are treated. Despite significant investment of resources in the development of guidelines yearly, there has been limited

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success in impacting health outcomes and low physician adherence to guidelines has been cited as an important factor.[1] It has been said that changing the behaviour of physicians is as difficult as that of patients, and simply informing physicians of the expected standards of care with guidelines alone is unlikely to achieve sustained adherence.[1]

Many barriers to adherence have been cited, such as the lack of awareness of the guidelines, lack of motivation to change, organisational constraints, and lack of time or resources.[2] However, it has been increasingly recognised that the lack of external generalisability is an important barrier towards the implementation of CPGs in routine clinical practice.[3] Guideline recommendations are preferentially based on data from well designed randomised controlled trials (RCTs) which are traditionally ranked at the apex of the evidence hierarchy.[4] While traditional RCTs are designed to demonstrate efficacy of an intervention, these "efficacy trials" are usually performed under ideal and controlled settings for drug registration purposes and adopt a highly selective process by which patients with any other pre-existing conditions or comorbidities are excluded. Often, less emphasis is placed on whether the treatment effect is achievable under real world conditions. For instance, RCTs in asthma typically exclude patients on the basis of age, smoking status, inadequate adherence, poor inhaler technique and other comorbidities. As a result, RCTs evaluating the efficacy of interventions in asthma and chronic obstructive pulmonary disease (COPD) have traditionally excluded up to 95% and 90% of routine care populations respectively.[5] Therefore, guideline recommendations based on these RCTs often suffer from a gap between trial efficacy and real world effectiveness. This has contributed partly to poor adherence by physicians to CPGs in many fields of medicine.[6]

How Real World Evidence Can Help CPGs Fulfil Their Intended Roles

Today, we are standing at the brink of a new era thanks to the proliferation and integration of electronic health records (EHRs) in both primary and tertiary care in Singapore. EHR contains a wealth of as-yet untapped real world data (RWD) that can be used to generate real world evidence (RWE), which is defined as the evidence derived from the synthesis and analysis of healthcare data outside of traditional clinical research settings.[7] Apart from EHR, RWD can be found in administrative claims and billing data, product and disease registries, health monitoring devices/wearables and even social media.[8]

The incorporation of RWE into guideline development and implementation has the potential to enable guideline developers to close the gap between mere knowledge of guidelines and translation to clinical practice in 4 methods.

Method 1: Incorporating Information on Both Treatment Efficacy and Real World Effectiveness Into Our CPGs

Demonstration of treatment efficacy does not necessarily equate to real world effectiveness and it is here that RWE can bridge the gap in our CPGs by helping guideline developers better understand treatment responses in the heterogenous patient populations of the real world with pragmatic trials. Interventional RWE studies like the Salford Lung Study[9] used a pragmatic RCT trial design where heterogenous patient cohorts were recruited under minimal selection criteria to test the real world effectiveness of an open label once-daily long-acting β agonist/inhaled corticosteroid dry powder inhaler in asthma and COPD. They were monitored under the routine care of physicians with no additional visits or attempts to change adherence in order to mimic true clinical practice by using EHR to capture real time data, track outcomes and minimise participant burden associated with trial visits. While such pragmatic studies sacrifice some internal validity, their results allow better approximation of real world practice than the traditional RCTs which are conducted under ideal conditions with high intensity of follow-up care that is often not economical or practical in real life. Trial pragmatism—which refers to the degree of matching between the care delivered in the trial setting and real world conditions—exists on a continuum and different study designs can make a trial more or less pragmatic.[10]

While pragmatic RCTs like the Salford Lung Study have improved the generalisability of research data, their findings are still nonetheless contextualised to the geographical setting where the trial was conducted and therefore may not be generalisable to other countries or healthcare settings due to various geographical, psychosocial and healthcare system differences (such as effect of climate and environment on the disease, health literacy and health-seeking behaviour of patients or quality or accessibility to health services). It is therefore imperative that there be international collaboration in the conduct of RWE studies to better understand how differences in geographic, psychosocial and healthcare system influence disease patterns and outcomes.

Method 2: Development and Incorporation of Precision Medicine (PM) into CPGs

Real world patient cohorts are heterogenous. However, most of our diagnostics and treatments have been developed for the "average patient" which may be effective for some but not all patients. In addition, international guidelines may not be contextualised for individual local practice settings in terms of local needs and resource availability. This has resulted in the proliferation of local CPGs with their varying interpretations of the available evidence. It is therefore difficult for frontline healthcare practitioners to apply CPGs to their real world patients who don't meet

the description of the "ideal" patient[11] but the emergence of PM may be a game changer.

Advances in genomic analysis have spurred the development of PM, which is defined as diagnostics and treatments that are targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish an individual patient from other patients with similar clinical presentations.[12] Generating RWE from EHR would enable the creation of algorithms for the everyday patient that could assist the frontline healthcare provider in: 1) identifying patients with risk factors for aggressive disease prevention (e.g. prediabetes) and screening, 2) phenotyping and endotyping patients,[13] as well as 3) guiding individualised management in terms of medication selection and administration (Table 1).

Method 3: Enabling Continuous Performance Assessment of Guideline Quality and Conformance

Despite the proliferation in the number of CPGs over the years, the adherence to guidelines has remained low to moderate over the last 2 decades.[14] Poor quality guidelines may cause harm by promoting misuse or overuse of medical services and few, if any, guidelines are evaluated rigorously for efficacy and safety before implementation. RWE can meet this need for quality assurance by enabling post-implementation efficacy and safety analyses in the same way that pharmaceutical companies are required to conduct post-marketing surveillance.[15] This way, guideline developers are kept in a continuous feedback loop which keeps them informed about the impact of individual guideline recommendations on real world practice.

RWE can also facilitate guideline implementation by measuring guideline conformance. This may be performed by deconstructing the guidelines, identification of data elements required to assess each guideline recommendation and establishment of acceptable benchmarks for performance. Multidisciplinary interventions targeted at the patient, healthcare provider and local system are often needed to support guideline conformance and RWE can provide guideline implementation programmes with feedback on the efficacy of individual interventions.

Method 4: Increasing Healthcare System Efficiency and Cost Control by Identifying Gaps in Care and Areas of Low-Value Healthcare in Healthcare Systems for Quality Improvement (QI) and Health Technology Reassessment (HTR) Activities, Respectively

The increasing burden of chronic diseases and their ever-growing availability of diagnostic investigations and treatments has made healthcare today increasingly costly,[16] complex and often fragmented because patients have needs that exceed the temporal and informational capacity of any single healthcare provider.[17] By continuous collection and analysis of data on the health-seeking patterns of patients and prescribing patterns of physicians across primary, tertiary and acute care settings, RWE can support HTR and QI activities with real time data and evidence that: 1) identifies low-value healthcare practices for elimination and disinvestment by policymakers,[18] 2) promotes clinician adherence to high-value interventions, and 3) reduces costs and complexity of care by reducing service duplication and process variation across various healthcare providers.

The Challenges and Limitations of Real World Evidence and Big Data

RWE and big data, however, comes with its own set of strengths and challenges in the form of the 4 "V's," namely, Volume, Velocity, Variety and Veracity[19] (Table 2). The sheer volume and speed (velocity) in the generation of data can increase the potential for noise accumulation which may generate incorrect or unreliable (veracity) conclusions. In

Table 1. Examples of How Real World Data and Evidence Can Be Potentially Applied to Day-to-Day Routine Clinical Practice

Clinical decision support (CDS) tools: Integration of CDS tools with EHR can assist the physician in making prescriptive decisions for every patient encounter at multiple points from initial consultation to diagnosis to follow-up.* Recommendations by the Watson for Oncology CDS tool have been shown to be concordant with conventional tumour board treatment decisions in 93% of breast cancers.†
Telemedicine: The popularity of smart devices that track step count, heart rate, lifestyle habits (diet, physical activity and sleep) can be leveraged to enable the development of telemedicine where trackable health data is relayed to doctors for monitoring. This will also enhance patient engagement and facilitate self-management of chronic diseases such as hypertension and asthma.
Artificial intelligence (AI) and machine learning: Machine learning is an application of AI which allows a programme to learn and improve from reviewing a large amount of data without being explicitly programmed.‡ While the technology and application of machine learning in medicine is still nascent, it has been applied to mammography interpretation in radiology with a performance that was roughly equivalent to the bottom 10% of radiologists.¶

EHR: Electronic health record

*Castaneda C, Nalley K, Mannion C, Bhattacharyya P, Blake P, Pecora A, et al. Clinical decision support systems for improving diagnostic accuracy and achieving precision medicine. J Clin Bioinforma 2015;5:4.

†Somashekhar SP, Sepúlveda MJ, Puglielli S, Norden AD, Shortliffe EH, Rohit Kumar C, et al. Watson for Oncology and breast cancer treatment recommendations: agreement with an expert multidisciplinary tumor board. Ann Oncol 2018;29:418-23.

‡Mayo RC, Leung J. Artificial intelligence and deep learning – radiology's next frontier? Clin Imaging 2018;49:87-8.

¶The Digital Mammography DREAM challenge. Available at: https://www.synapse.org/#!Synapse:syn4224222/wiki/401744. Accessed on 23 July 2018.

Table 2. The 4 "V's" of Big Data – Volume, Velocity, Veracity and Variety[*†]

The enormous volume of data being created daily is what gives big data its name. A total of 153 exabytes (1 exabyte = 1 billion gigabytes) of data were produced in 2013 and it has been estimated that 2314 exabytes of data will be produced in 2020.[‡]
Data velocity refers to the speed at which the data is generated, stored, analysed or refreshed. Data is being continuously produced by both human and machines in various networked systems such as emails, social media and electronic financial transactions. It has been estimated that rate of global internet traffic in 2018 is 50,000 GB per second of data.
Veracity refers to whether the data is accurate, reliable, representative and can be trusted. Datasets often come with inherent biases and lack of precision due to the limitations of data collection in the real world.
Variety refers to the different formats of data being generated daily. This can take the form of structured data formats such as financial statements which conform to a well defined set of norms on how the data is documented. However, the majority of all generated data is "unstructured" in contrast and come in the form of digital images, audio visual files, internet webpages and Twitter feeds and this poses challenges in data aggregation and interpretation.

[*]IBM Big Data & Analytics Hub. Available at: https://www.ibmbigdatahub.com/infographic/extracting-business-value-4-vs-big-data. Accessed on 23 July 2018.
[†]Williamson J. The 4 V's of Big Data. Available at: https://www.dummies.com/careers/find-a-job/the-4-vs-of-big-data/. Accessed on 7 November 2018.
[‡]MC Digital Universe with Research and Analysis by IDC. Vertical Industry Brief: The Digital Universe, Driving Data Growth in Healthcare. Available at: https://www.emc.com/analyst-report/digital-universe-healthcare-vertical-report-ar.pdf. Accessed on 25 November 2018.

addition, the large sample sizes that also give big data its strength may necessitate heavy computational resources and complex analytics to accurately aggregate and interpret the varied unstructured datasets acquired across various time points and sources into a collective dataset (Table 3). If big data is to be translated meaningfully into high quality RWE, it is important to have the necessary expertise in data analytics with trained data scientists and the application of standardised criteria[20] for data collection, analysis and reporting to minimise data "noise" and establish the quality of a RWE result. This is often resource and manpower-intensive. Finally, in light of high profile international occurrences of data breaches at the national level,[21] it is important to adequately address privacy concerns from the use of big data for research such as the distribution of sensitive data to third parties without consent and data security if we are to have the support and trust of the public.[22]

In addition, the quality and amount of data collected might be constrained when busy frontline healthcare workers are enlisted for data entry due to competing needs of patient care. While it is advantageous to collect as much data as possible now to answer research questions of the future, overburdening healthcare workers with the collection of data in a busy setting beyond what is collected for routine healthcare may result in fatigue, diminished participation in data entry and ultimately deterioration in data quality over time. Like any large projects, the balancing act between cost, quality and time is crucial and requires a multidisciplinary approach and innovations to overcome these constraints. In addition, key stakeholders (i.e. healthcare providers) should be engaged early to foster a sense of ownership of the RWE, to participate in the guideline development, implementation, evaluation and review processes generated from their daily practice.

Singapore's healthcare ecosystem is among the first in the world to have a seamless National Electronic Health Record (NEHR) that has connected primary and tertiary healthcare in the public sector since 2011.[23,24] Participation by private sector healthcare providers is currently voluntary and limited but this is soon to change should the government enact new legislation to mandate compulsory participation. In line with this, the government has established legislation such as the Human Biomedical Research Act[25] and Personal Data Protection Act[26] to further strengthen data governance in the era of big data. The time is therefore ripe for RWE studies to be performed in Singapore as we have the advantages of high digital interconnectivity, a truly integrated NEHR, and governmental support in the form of

Table 3. Big Data and Real World Evidence – Potential Benefits and Challenges

Potential Benefits
• Closing the gap between clinical trial efficacy and real world effectiveness in CPG recommendations
• Advancing the development of precision medicine in areas such as disease prevention, screening and treatment selection in the real world
• Facilitating guideline implementation by allowing continuous assessment of CPG conformance and performance
• Supporting quality improvement and health technology reassessment activities thereby increasing healthcare system efficiency and cost control
Challenges
• The reliable collection, aggregation, analysis, reporting and interpretation of big data is resource-intensive and requires specialised technical expertise
• Addressing data privacy and cybersecurity concerns
• Constraints on the amount and quality of big data that can be collected when busy frontline healthcare providers are enlisted for data collection

CPG: Clinical practice guidelines

the Smart Nation initiative.[27]

Conclusion

In conclusion, digital technologies, combined with RWE studies, complements the evidence generated by RCTs and have the potential to fill the gap in current CPGs which are predominantly based on efficacy studies from RCTs with limited generalisability. RWE can enhance the real world applicability of CPGs, incorporate PM into everyday practice, monitor guideline conformance and support clinical decision-making via artificial intelligence. Importantly, RWE allows doctors to take ownership of the data generated from their daily practice and provides them with the confidence to choose the right treatment options for the right patients.

REFERENCES

1. Pearson MG. How can the implementation of guidelines be improved? Chest 2000;117:38S-41S.
2. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458-65.
3. Wong GW, Miravitlles M, Chisholm A, Krishnan JA. Respiratory guidelines – which real world? Ann Am Thorac Soc 2014;11 Suppl 2:S85-91.
4. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
5. Herland K, Akselsen JP, Skjønsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? Respir Med 2005;99:11-9.
6. RS Hayward. Clinical practice guidelines on trial. CMAJ 1997;156:1725-7.
7. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real- world evidence – what is it and what can it tell us? N Engl J Med 2016;375:2293-7.
8. Kalf RR, Makady A, Ten Ham RM, Meijboom K, Goettsch WG, IMI-GetReal Workpackage 1. Use of social media in the assessment of relative effectiveness: explorative review with examples from oncology. JMIR Cancer 2018;4:e11.
9. New JP, Bakerly ND, Leather D, Woodcock A. Obtaining real-world evidence: the Salford Lung Study. Thorax 2014;69:1152-4.
10. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015;350:h2147.
11. Upshur RE. Do clinical guidelines still make sense? No. Ann Fam Med 2014;12:202-3.
12. Jameson JL, Longo DL. Precision medicine – personalized, problematic, and promising. N Engl J Med 2015;372:2229-34.
13. Koh MS, Yii AC, Ong YY. Asthma in Singapore: past, present and future. Ann Acad Med Singapore 2017;46:81-3.
14. Alonso-Coello P, Irfan A, Solà I, Gich I, Delgado-Noguera M, Rigau D, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Qual Saf Health Care 2010;19:e58.
15. Shaughnessy AF, Cosgrove L, Lexchin JR. The need to systematically evaluate clinical practice guidelines. J Am Board Fam Med 2016;29:644-8.
16. Dieleman JL, Squires E, Bui AL, Campbell M, Chapin A, Hamavid H, et al. Factors associated with increases in US health care spending, 1996-2013. JAMA 2017;318:1668-78.
17. Upshur RE. Understanding clinical complexity the hard way: a primary care journey.Healthc Q 2016;19:24-8.
18. Lim BP, Heng BH, Tai HY, Tham L, Chua HC. Health technology disinvestment in Singapore. Ann Acad Med Singapore 2018;47:338-44.
19. IBM Big Data & Analytics Hub. Available at: http://www.ibmbigdatahub.com/sites/default/files/infographic_file/4-Vs-of-big-data.jpg. Accessed on 23 July 2018.
20. Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. Clin Pharmacol Ther 2018;103:202-5.
21. Tham I. Personal info of 1.5m SingHealth patients, including PM Lee, stolen in Singapore's worst cyber attack. The Straits Times. Available at: https://www.straitstimes.com/singapore/personal-info-of-15m-singhealth-patients-including-pm-lee-stolen-in-singapores-most. Accessed on 23 July 2018.
22. College of Family Physicians Singapore, Academy of Medicine, Singapore and Singapore Medical Association. Public Sentiments towards the National Electronic Health Record. Singapore Medical Association News Aug 2018;50:8. Available at: https://www.sma.org.sg/UploadedImg/files/Publications%20-%20SMA%20News/5008/Survey.pdf. Accessed on 23 July 2018.
23. Mossialos E, Djordjevic A, Osborn R, Sarnak D. International Profiles of Health Care Systems, The Commonwealth Fund (May 2017). Available at: https://www.commonwealthfund.org/sites/default/files/documents/media_files_public ations_fund_report_2017_may_mossialos_intl_profiles_v5.pdf. Accessed on 25 November 2018.
24. Accenture, Singapore's Journey to Build a National Electronic Health Record System (2012). Available at: https://www.accenture.com/t20170518T051457w/sg-en/_acnmedia/PDF-51/Accenture-Health-Electronic-Health-Records-Case-Study.pdf. Accessed on 25 November 2018.
25. Ministry of Health. Human Biomedical Research Act. Available at: https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act. Accessed on 28 October 2018.
26. Personal Data Protection Commission Singapore. Legislation and Guidelines. Available at: https://www.pdpc.gov.sg/Legislation-and-Guidelines/Personal-Data-Protection-Act-Overview. Accessed on 7 August 2018.
27. Lim J. Put 'Smart Nation' to work on diabetes care. The Straits Times. Available at: https://www.straitstimes.com/opinion/put-smart-nation-to-work-on-diabetes-care. Accessed on 25 November 2018.