Review

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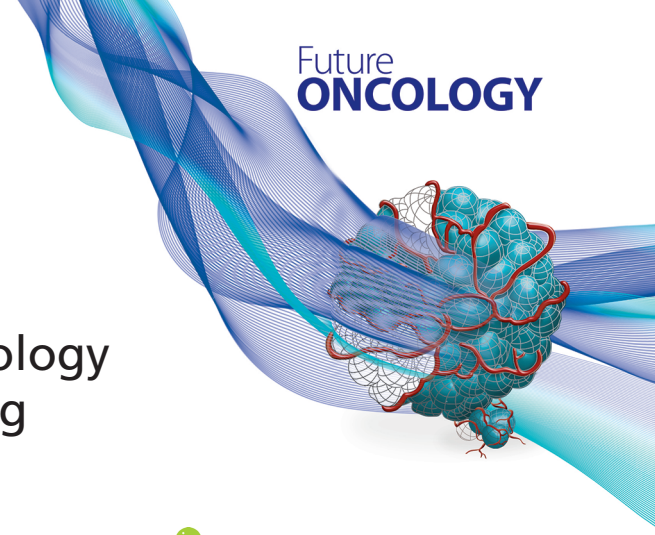

Use of real-world evidence for oncology clinical decision making in emerging economies

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Real-world evidence (RWE) can provide insights into patient profiles, disease detection, treatment choice, dosing strategies, treatment sequencing, adverse event management and financial toxicity associated with oncology treatment. However, the full potential of RWE is untapped in emerging economies due to structural and behavioral factors. Structural barriers include lack of regulatory engagement, real-world data availability, quality and integrity. Behavioral barriers include entrenched healthcare professional behaviors that impede rapid RWE understanding and adoption. These barriers can be addressed with close collaboration of healthcare stakeholders; of whom, regulators need to be at the forefront given their ability to facilitate use of RWE in healthcare policy and legislation.

Lay abstract: Traditionally, randomized clinical trials have been used to provide insights on new medical therapies and continue to remain the gold standard for approval. The-increasing availability of patient level data in the real-world, it is now possible to generate evidence regarding the usage and potential benefits or risks of a medical therapy derived from analysis of real-world data. This evidence is collectively referred to real-world evidence (RWE). randomized clinical trials and RWE are complementary and the area of Oncology especially benefits from RWE to guide clinical decision making across the patient journey. Key benefits include cancer screening and diagnosis, optimal treatment choices (including personalized medicine) and disease management such as dosing and treatment of side effects. In recent times, RWE generation in oncology has been prolific in the USA and western Europe. With expansive biopharmaceutical investments into infrastructure harnessing patient-level data and greater local regulatory guidance, oncology patients in emerging economies may now also have the opportunity to benefit from clinical decision making informed by RWE.

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Randomized control trials (RCTs) are traditionally recognized as the gold standard for generating clinical evidence on treatment efficacy and safety. RCTs offer high internal validity through highly structured trial designs [1]. However, RCTs are resource-intensive, time-consuming, and have stringent inclusion and exclusion criteria that limit the generalizability of study results to the real-world [1,2,3]. Real-world evidence (RWE) can be used to complement RCTs as it can support the generation of insights on usage, benefits, and risks of treatment that have been collected from patient populations in clinical practice (e.g., electronic medical records [EMR], claim databases, registries and patient surveys) [4,5]. This use of RWE provides insights with fewer resources, lower costs, and a shorter amount of

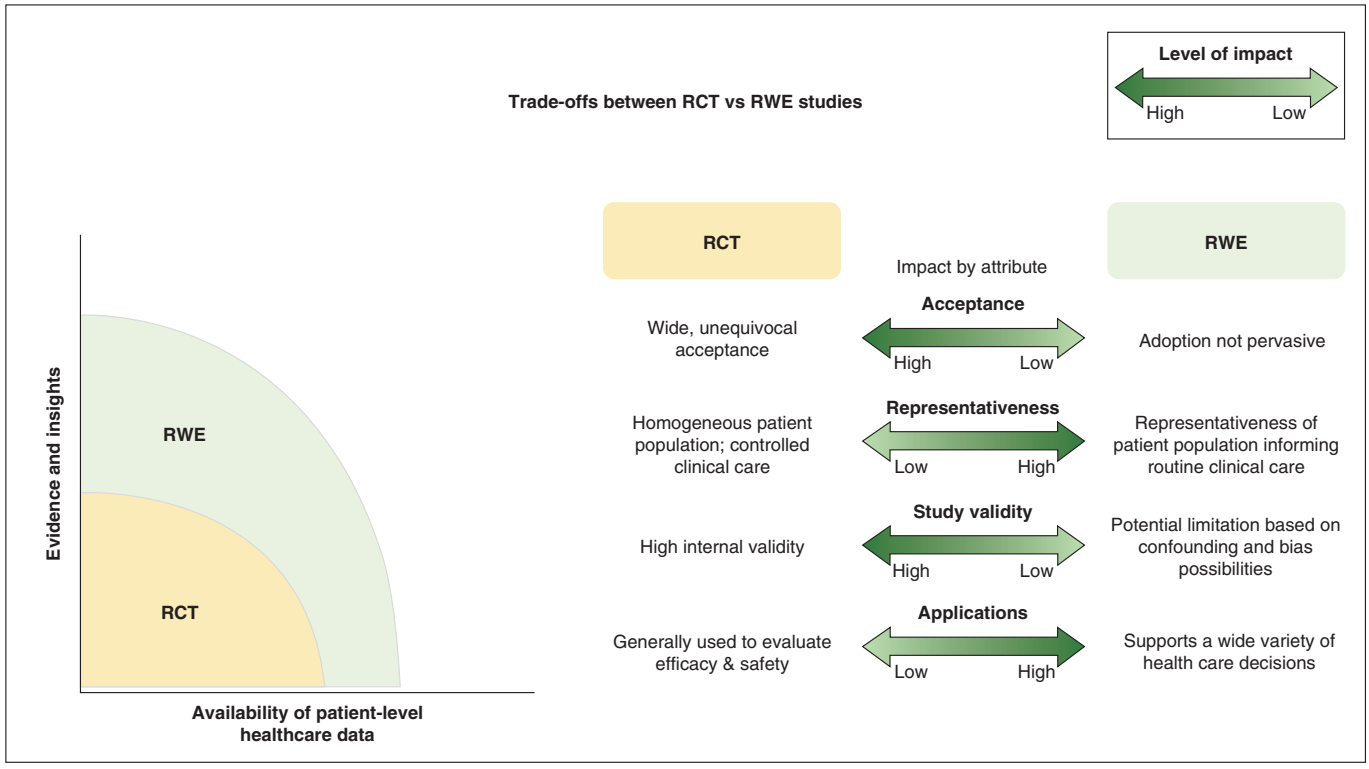

Figure 1. Tradeoffs between real-world evidence and randomized control trial studies.

time than traditional RCTs [6]. As detailed in Figure 1, tradeoffs exist between RWE and evidence from RCTs. These include limited stakeholder acceptance, questions around reliability and limitation of bias and confounders when generating RWE. Despite these tradeoffs, RWE complement RCTs by providing insights that have a high degree of external validity and can improve clinical decision-making for various therapeutic areas including oncology. For example, real-world overall survival is a measure accepted by oncologists due to it objectivity and comparability to overall survival (OS) data observed in RCTs [7,8]. Furthermore, the American Society of Clinical Oncology (ASCO) has provided guidance on classification around level of evidence, with RWE classified as level III or IV evidence, in other words, moderate to low strength. However, the ASCO guidance framework considers RWE as a valuable tool for clinical oncology research when it comes to answering questions not explored or considered feasible in RCTs [9].

RWE is anticipated to benefit stakeholders involved throughout the oncology care continuum, including healthcare professionals (HCPs), regulators, patient advocates and payers [10]. In particular, RWE has been used by oncologists to improve different aspects of clinical decision-making, such as patient profiling [11], disease detection [12], optimal dosing [13], understanding of treatment patterns [14,15,16] and management of adverse events (AEs) with greater confidence [17,18,19,20]. Additionally, RWE can inform treatment choices in light of financial toxicity; an important consideration for both patients and caregivers in emerging economies [21,22].

Regulators in the USA and the EU have supported the utilization of RWE by releasing guidance for RWE submissions and have shown a willingness to accept RWE for submissions related to drug approval and label expansion [4,23,24]. While USA and EU are viewed at the forefront of leveraging RWE, emerging economies are also witnessing a surge of interest in RWE. Among emerging economies, countries in the Asia-Pacific (APAC) region are leading the way in terms of RWE generation and adoption in comparison to the Africa and Middle East (AFME) region and Latin America (LATAM) region. This is evident from the trend in the number of real-world oncology studies published in these economies over the past 5 years (Figure 2) and acknowledgment of RWE by regulators in the emerging economies (Table 1).

Despite the upward trend of RWE studies (Figure 2), the full potential of RWE in clinical decision-making remains untapped due to barriers such as limited availability of quality real-world data (RWD), data integrity, entrenched stakeholder behaviors and lack of RWE expertise in interpreting and conducting RWE studies [25,26].

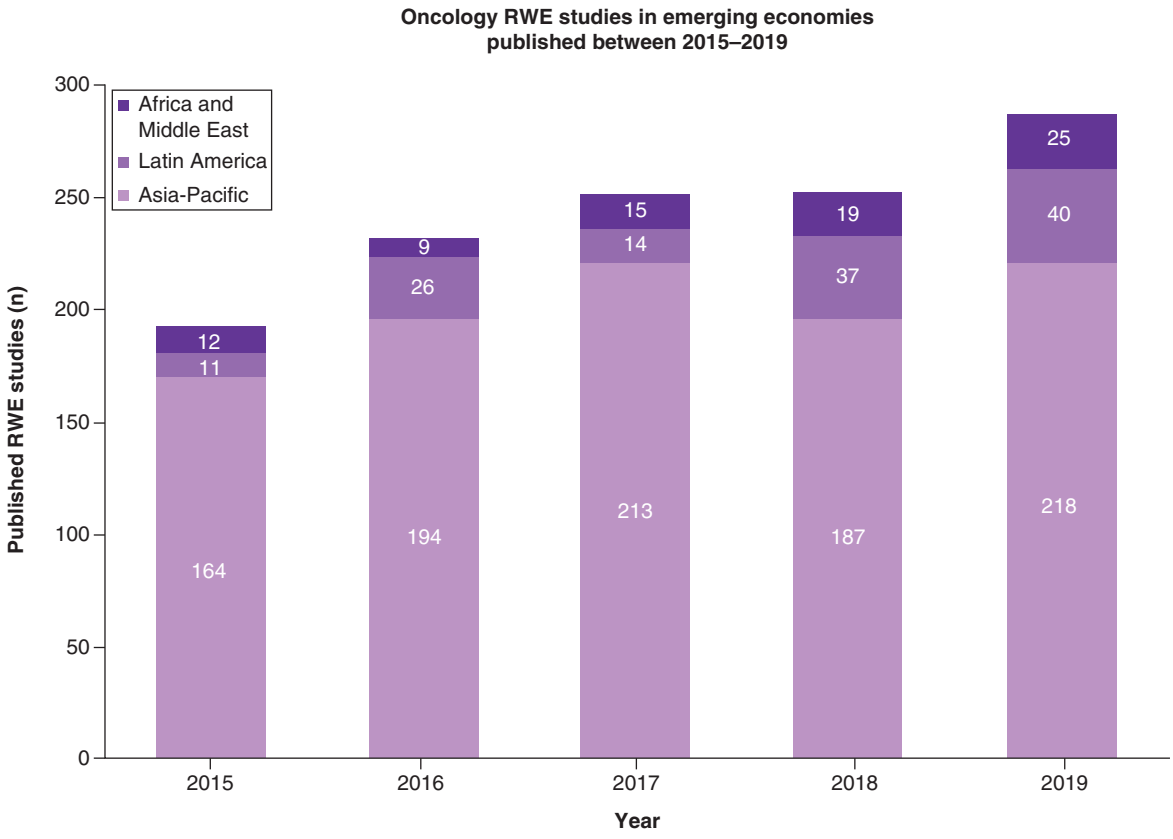

Figure 2. Oncology real-world evidence studies in emerging economies published between 2015 and 2019†.
†The regions considered for the search were APAC (China, Taiwan, Malaysia, Thailand, Philippines, Indonesia, India), LATAM (Argentina, Brazil, Colombia, Mexico, Chile, Peru), AFME (Algeria, Egypt, Jordan, Kuwait, Lebanon, Morocco, Nigeria, Qatar, Saudi Arabia, South Africa, Tunisia, UAE). Compound annual growth rate defined as the average year-on-year growth rate of RWE studies published over the past 5 years.
AFME: Africa and Middle East; APAC: Asia-pacific; LATAM: Latin Americ; RWE: Real-world evidence.
Source: PubMed.

Table 1. Definition of real-world data and real-world evidence by various regulatory agencies.

Regulatory Agency	Definition	Ref.
US FDA	RWD: any data on health interventions in routine clinical practice, and can be reported by providers, payers or patients	[4]
	RWE: the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD	
EMA	RWD: routinely collected data relating to a patient's health status or the delivery of healthcare from a variety of sources other than traditional clinical trials	[25]
	RWE: defined as the information derived from analysis of RWD	
China NMPA	RWD: all kinds of data related to patients' health status and/or diagnosis and treatment and healthcare collected on a routine basis	[26]
	RWE: clinical evidence about the use and potential benefits or risks of medical products, obtained through the analysis of RWD, including evidence obtained through interventional studies including retrospective or prospective observational studies or pragmatic clinical trials	
Taiwan FDA	RWD: data that is routinely collected and details the health status of patients or healthcare processes healthcare	[27]
	RWE: clinical evidence generated by appropriate analysis methods using real-world data as the source of information. This evidence can be used to help explain the use of drugs and their benefits and risks	
Saudi FDA	RWD: data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources	[28]
	RWE: clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD	

NMPA: National Medical Products Administration; RWD: Real-world data; RWE: Real-world evidence; SFDA: Saudi Food and Drug Authority; TFDA: Taiwan Food and Drug Administration.

Pragmatic solutions, including the development of regulatory RWE guidance, are needed to address each barrier to further increase the adoption and use of RWE in the emerging economies. This can be achieved through close collaboration between regulatory agencies, pharmaceutical companies and academic institutions [25,26].

This paper's objective is to identify benefits and major barriers associated with use of RWE for oncology clinical decision-making in emerging economies and propose pragmatic ways to address these underlying barriers. Recommendations are based on oncology expert opinions and desk research that include examples from RWE studies conducted in emerging economies.

Materials & methods

For the purposes of this paper, 'emerging economies' were defined as economies with low-to-middle per-capita income that are rapidly transforming into developed nations [27,28]. The emerging economies targeted in this review include countries from APAC (China, Taiwan, Malaysia, Thailand, Philippines, Indonesia, India), Latin America (LATAM; Argentina, Brazil, Colombia, Mexico, Chile, Peru) and Africa and the Middle East (AFME; Algeria, Egypt, Kuwait, Jordan, Lebanon, Morocco, Nigeria, Saudi Arabia, South Africa, Tunisia, UAE, Qatar).

A targeted literature review was conducted using PubMed to collect RWE oncology studies published between January 2015 to June 2020. In total, 1184 publications were identified which is presented in Figure 2. The search terms used include: 'RWE', 'RWD', 'real-world', 'routine clinical care', 'observational studies', 'case-controlled studies', 'cohort studies', 'cross sectional studies', 'external comparators', 'pragmatic trials', 'chart abstraction', 'EMR', 'health records', 'claims', 'registry', 'oncology', 'cancer', 'hematology' and 'tumor' (search string examples available in Supplementary Material 1). Targeted gray literature and government and relevant public agency websites were also reviewed. The literature review was used to better understand current applications and challenges associated with RWE use in emerging economies. The results of the literature review are presented in the subsequent sections of this review.

To supplement the literature review, we conducted interviews with five oncologists from APAC, LATAM and AFME, of which three oncologists are key opinion leaders (KOLs) in their field. The oncologists were approached via email and invited to participate in the interviews. Prior to obtaining consent for their participation, the oncologists were provided with context of the interview, including the rationale for conducting the interview.

The open-ended discussion questions that were used during the interviews are presented in the (supplementary Material 2). Topical areas included the impact of RWE on day-to-day treatment decision, regulatory landscape of RWE, applications and perception of RWE. The interviewers had no previous relationship with the KOLs/oncologists. In addition to providing the regional specific insights, two of the experts were also involved in the detailed conceptualization, development and oversight of this review.

Results & discussion

Traditionally, oncologists in emerging economies have relied on guidelines, such as the ASCO resource stratified guidelines and European Society for Medical Oncology Asia-Pacific, for oncology clinical decision-making [29,30]. However, there is a growing awareness on the benefits of RWE in understanding patient profiles, facilitating earlier disease detection and diagnosis, guiding treatment selection, understanding treatment patterns, aiding in AE management and informing treatment choices in light of financial toxicity. These benefits can enable oncologists to make optimal clinical decisions for their patients.

Patient profile

RWE can contextualize local patient profiles and dispositions to outcomes by factoring in demographic characteristics and patient behaviors. For example, the Haemato-Oncology Latin America (HOLA) study characterized multiple myeloma patients in Latin America and revealed hypertension, diabetes and heart disease as the most common patient comorbidities [16]. Elderly patients (≥65 years) had a greater comorbidity burden and were substantially less likely to receive autologous stem cell transplantation compared with patients aged <65 years. The study revealed age to be one of the key factors associated with treatment decisions in the region. Elderly patients were less likely to receive bortezomib-based therapy and more likely to receive chemotherapy compared with patients with age of <65 years. In addition, the study provided insights on treatment patterns in the region, such as demonstrating that bortezomib-based therapy was more frequently used in patients who were treated in private clinics and in patients who underwent autologous stem cell transplantation [16].

Disease detection

Early detection and diagnosis of cancer is the cornerstone to successful oncology treatment, with RWE having the potential to play a critical role, such as through appropriate screening programs. For example, Ma *et al.* conducted an RWE study in rural China, aiming to understand the effectiveness of cervical cancer screening programs by comparing three available cervical cancer screening methods. This study factored cervical cancer detection performance and real-world clinical considerations, such as training requirements and specimen collection. Based on these considerations, this study concluded that the human papillomavirus test was the preferred diagnostic test in low-resource regions [12].

Treatment choice

As mentioned earlier, patient profiles differ across geographies, including demographics, genetic characteristics and patient behaviors, all of which have an impact on treatment response. HCPs can use RWE as a lever for selection of appropriate treatments based on a better understanding of patients' needs. The OSSMAR study revealed that sunitinib is an effective and safe treatment for metastatic renal cell carcinoma patients in the Middle East [17]. In another example, the RENATA study, which examined the use of palbociclib in Argentinian patients with hormone receptor-positive metastatic breast cancer, determined long-term treatment outcomes and treatment adherence. Specifically, the study results showed real-world progression-free survival (rw-PFS) of 36.7 months with first-line use of palbociclib. For this Argentinean population in the real-world setting, the RENATA study also demonstrated that palbociclib had lower incidences of dose interruption, delay, reductions and discontinuations in real-world settings, when compared with data from pivotal RCTs [18].

Treatment sequencing

RCTs can provide valuable information on efficacy and safety but are not always ideal for treatment sequencing because of high resource requirements. RWE studies offer a practical alternative in understanding treatment sequencing strategies based on examination of real-world treatment patterns and outcomes, without the expense and time needed for an RCT. A systematic review of global RWE studies conducted between 2015 and 2018 demonstrated that treatment with first-line abiraterone acetate, followed by enzalutamide, improved rw-PFS in patients with metastatic castration-resistant prostate cancer [31]. In the USA, RWE studies have been used to inform clinical decisions beyond first- and second-lines of treatment. A 2019 retrospective study demonstrated that first-, second- and third-line palbociclib treatment followed by subsequent hormonal therapy improved rw-PFS in patients with hormone receptor + and HER2- metastatic breast cancer [31]. In another study, Dhakal *et al.* demonstrated that a treatment sequence of everolimus following palbociclib-progression (first, second, third and fourth line) led to improved rw-PFS [32]. RWE studies have also been conducted in emerging economies to better understand treatment sequencing. In a 2019 Taiwanese retrospective study, investigators proved that treatment with first-line cetuximab followed by chemotherapy in second-line and bevacizumab in third-line lead to improved overall survival and clinical outcomes in patients with wild-type KRAS exon 2 mCRC [15].

Dosing strategy

RWE can help HCPs determine optimal dosing strategies that balance safety and effectiveness for specific patient populations. A patient's ethnicity may influence response to a therapy. In comparison to the USA and Europe, there is limited data around dosing of oncology treatments for patient populations in emerging economies. In a recent Asian RWE study, attenuated sunitinib doses were examined since prior research suggested the conventional dose (50 mg/day, 6-week cycles: 4 weeks on treatment, 2 weeks off treatment) was associated with high toxicities in Asian populations with metastatic renal cell carcinoma [13]. This study showed that the attenuated dose regimen of sunitinib (37.5 mg/d, 4 weeks of treatment, then 2 weeks of no treatment) had comparable real-world overall survival and rw-PFS, while significantly reducing toxicities as compared with the conventional doses [13].

AE management

RWE can guide clinical decision-making in the management of AEs. In a Chinese RWE study conducted in 2019, investigators examined real-world use of olaparib for treatment of advanced ovarian cancer in order to evaluate its safety and effectiveness. Findings identified several AEs during the follow-up stage such as abdominal distension, decreased blood pressure, increased body hair, burning, leg swelling and stomach sensations, which were unreported

Table 2. Identified structural and attitudinal barriers preventing adoption and use of real-world evidence in emerging economies.

Barriers		Contributing factors	Ref.
Structural	RWD availability	• Absence of commercially available secondary datasets outside of registries • Resource-intensive nature of RWD collection, management and analysis • Often times investigators are driving RWD collection	
	RWD quality	• Missing data • Data entry errors • Lack of data standardization	
	RWD integrity	• Data security breaches • Data governance not pervasive	
	Lack of regulator engagement	• RWE policy and applications not proactively addressed • Guidance on data standards and RWD credibility framework not issued • RWE not routinely considered for regulator decision making	[27]
Attitudinal	Entrenched HCP behaviors	• RWE studies unable to evoke similar level of confidence as RCTs • Culture and legacy training continue to govern clinical decision making	

HCP: Healthcare professional; RWD: Real-world data; RWE: Real-world evidence.

in earlier RCTs. The findings suggested that serious AEs can be effectively managed by dose reductions or temporary dose interruptions instead of treatment discontinuation [20].

Financial toxicity

RWE can help HCPs develop strategies that mitigate the effects of 'financial toxicity' associated with cancer treatment. This is especially important in emerging economies where patients may have reduced access to healthcare resources (e.g., healthcare insurance) and may be more vulnerable to high costs (direct and indirect) of medical care [22,33]. In a retrospective RWE study conducted in South Korea, investigators examined if nivolumab dose and scheduling could be modified to reduce financial toxicity among patients with non-small-cell lung cancer. Findings from this study suggested reduced nivolumab dose regimens maintained clinical effectiveness and could serve as an alternative treatment option in settings where financial toxicity may be prevalent [21].

Barriers preventing full use of RWE for clinical decision making

There are several barriers in emerging economies that prevent full use of RWE in oncology clinical decision making. These barriers are a result of structural and attitudinal factors that affect the way RWE is generated and utilized by healthcare stakeholders in emerging economies (Table 2). Key barriers identified include low availability of RWD, low RWD quality, RWD integrity issues, lack of regulatory engagement and entrenched HCP behaviors.

RWD availability

Experts confirmed that lack of commercially available secondary databases in emerging economies is perhaps the most acute contributing factor hindering widespread adoption of RWE. In the USA the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 led to the unlocking of EMRs as an RWD source [34]. Such legislation resulted in increased investment in healthcare IT and digitization of data. However, policy and legislation that may support RWE is either absent or in nascent stages in emerging economies. Furthermore, lack of such data collection hubs places the onus of RWD collection on practicing oncologists that are frequently leading studies without much technical support and sponsorship.

RWD quality

Lack of training and an understanding of data collection and entry methods can result in data missingness, errors and inconsistencies, thereby resulting in lower RWD quality. Additional factors that impact RWD quality in emerging economies include: the lack of regulatory RWE frameworks that promote data standards, and differences across data management systems (e.g., data structure, data format). Questionable RWD quality ultimately reduces the credibility of insights, resulting in mistrust of RWE [26].

Data integrity

Attacks on RWD are prevalent due to security vulnerabilities in emerging economies, further challenging a desired level of data integrity. For example, a Chinese regulatory (NMPA) report published in 2015 suggests data

manipulation in 30 RCTs conducted in China [35,36]. Beyond China, other countries in the Asia-Pacific region have also experienced breaches. In Latin America, 2.3 million health records of Mexican patients were breached in 2018 via inappropriate security protocols that opened access to identifiable patient information [37].

Entrenched behaviors

Entrenched physician behaviors and attitudes in oncology are generally prevalent on account of biases that physicians may have in viewing patient profiles and eligibility. In emerging economies, these behaviors, coupled with a conservative culture, play a role in impacting RWE adoption. At last, prior educational training focused on older therapies such as chemotherapy, accompanied by hesitancy of deviating from established treatment norms formed over decades of practice, may lower oncologist affinity to consider new therapies and treatment strategies [38,39].

RWE regulations

The voice of regulators is critical in creating momentum around RWE adoption and utilization. As discussed earlier, regulators in the USA and Europe have issued relatively detailed RWE guidance. In contrast, healthcare regulatory agencies in emerging economies, with the exception of China and Taiwan, are not markedly shaping the dialogue and definition around use of RWD/RWE [40,41,42]. This lack of regulatory guidance has resulted in an inertia for RWE research in emerging economies.

Call to action & future directives

Over the next 3–5 years, there is an opportunity for a societal contract in emerging economies to leverage RWE for oncology clinical decision-making. In particular, we propose three recommendations discussed below to catalyze the use of RWE in emerging economies.

Regulatory framework

Regulators in the emerging economies need to be engaged and play a proactive role as there is a critical need for RWE policy that accounts for regional considerations. Local RWE policy can be used to shape RWE dialogue and provide clear guidance on potential applications of RWE including for regulatory submissions. RWE policy guidelines also have the potential to promote rigorous data standards and governance procedures that can ultimately lead to improved data quality and integrity. Instituting policy will ultimately incentivize RWE adoption and build trust associated with use of RWE in emerging economies. As noted earlier, China and Taiwan are the only notable emerging economies that have provided RWE guidance in the public domain [40,41,42]. Consequently, it is no surprise that among the emerging economies, China and Taiwan have generated the largest share of RWE publications during the period of 2015 and 2019 (Figure 2; 803/1184 68%). Furthermore, health technology assessment (HTA) agencies in emerging economies also need to be engaged as these agencies impact how RWE may be utilized in clinical decision making for oncology. HTA guidance on RWE is established and robust in Europe. However, we are starting to see learnings from European HTA agencies applied to emerging economies such as Brazil and Argentina; and moving forward we expect HTA agencies to shape the dialogue even further.

RWE investments

Increased, systematic investments into RWD infrastructure (e.g., secondary databases, EMR, digital platforms) can be a cornerstone for accelerated local RWE generation. As stated earlier, lack of data standards and management is pervasive in emerging economies. Data integrity and manipulation are frequently cited issues, particularly in India and China [35,36,43,44]. Using widely accepted data standards and standard operating procedures such as those offered by the Observational Health Data Sciences and Informatics common data model, bring a structured approach to creating research ready, interoperable analytical data sets that may be used to power multiple studies. Data standardization needs to come hand-in-hand with clearly defined data governance rules, well-documented standard operating procedures and systems that ensure the strictest possible compliance. Together these investments are table stakes for setting up the foundation for RWE in emerging economies. In addition, there is an opportunity for the biopharma industry to collaborate with independent researchers to support data collection, statistical analysis and methods selected for RWE studies so that independent researchers are not conducting these in a silo.

RWE training

Even though oncology KOLs are driving the use of RWE in emerging economies, some oncologists remain unclear on how to best use RWE for clinical decision-making as well as how RWE is differentiated from RCTs. In such instances, RWE training imparted by KOL oncologists to oncologists practicing, both in community and center of excellence settings, can facilitate a paradigm shift from an RCT-only to an RCT-RWE hybrid insights model. Ideally, such training can be conducted through a train-the-trainer format and would begin with providing foundational RWE knowledge and progress to advanced topics such as innovative study designs and applications of RWE across the patient treatment journey. To execute RWE train-the-trainer programs, sponsors can take advantage of industry conferences such as International Society for Pharmacoeconomics and Outcomes Research China, European Society for Medical Oncology, Asia Congress, and oncology-specific medical conferences in emerging economies, such as the International Association for the Study of Lung Cancer Latin America Conference on Lung Cancer and the Asia-Pacific Gastroenterology Cancer Summit.

Conclusion

Despite RWE being a relatively nascent concept in emerging economies, we have seen evidence of increasing use over the past 5 years growing at 11% per year (Figure 2). That said, barriers specific to emerging economies need to be overcome through collaborative efforts, with regulatory agencies at the forefront. Regulatory engagement and sponsorship, RWE investments – both programmatic and one-off study sponsorships, and RWE training targeted at HCPs can harness the potential of RWE research in emerging economies.

Executive summary

Current scenario

- Increasingly, real-world evidence (RWE) is being used to guide clinical decision making in oncology in emerging economies. However, there are several challenges associated with RWE use in emerging economies.

Future directive

- The RWE challenges identified in this article can be addressed through regulatory engagement and sponsorship, RWE investments and RWE training targeted at healthcare professionals.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0425

Author contributions

All the authors equally contributed in conceptualization, research, and analysis of the results of the manuscript. C Ghai and A Pangilinan helped in writing of the manuscript.

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