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COMMENTARY

Real-World Evidence Acceptability and Use in Breast Cancer Treatment Decision-Making in the United States: Call-to-Action from a Multidisciplinary Think Tank

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ABSTRACT

Complementing randomized controlled trials, real-world evidence (RWE) from observational analyses can extend clinical insights in oncology. While healthcare stakeholders have published rigorous RWE frameworks and resources, a multidisciplinary think tank was established to further advance acceptance and use of RWE in treatment decision-making, with the focus on breast cancer (while recognizing relevance in oncology more broadly). Members discussed perceptions of RWE from a clinical perspective, across domains of data, methodology, and mindset, and "calls-to-action" for stakeholders. Agreement was reached on a primary "call-to-action," to develop clinically-relevant, patient-informed, real-world endpoints, and secondary "calls-to-action": establish a multidisciplinary consensus forum; publish examples of unique RWE value; build upon existing frameworks and resources; and tailor an approach for exhibiting utility to guideline bodies.

Keywords: Breast cancer; Real-world data; Real-world evidence; Treatment decision-making

Key Summary Points

A multidisciplinary Think Tank on real-world evidence (RWE) in the US from Multiple Perspectives in Healthcare (TRIUMPH) was established to further advance acceptance and use of RWE in treatment decision-making, with the focus on breast cancer.

TRIUMPH identified perceptions of RWE acceptance and use in treatment decision-making from a clinical perspective, considered solutions for addressing perceptions that may prevent further advancement of acceptance and use, and developed "calls-to-action" to drive implementation of highest-priority solutions.

Based on critical perceptions, 13 solutions were prioritized (perceived impact; feasibility to implement); 5 were ultimately identified as highest priority to pursue

To address highest-priority solutions, a primary "call-to-action" was articulated, to develop clinically-relevant, patient-informed, real-world endpoints for all stakeholders.

Four secondary "calls-to-action" were identified: establish a multidisciplinary consensus forum; publish examples of unique RWE value; build upon existing frameworks and resources; and tailor an approach for exhibiting utility to guideline bodies.

BACKGROUND

While conventional randomized controlled trials (RCTs) remain the gold standard for evaluating efficacy of treatments, real-world evidence (RWE)—generated via analysis of real-world data (RWD) (relating to patient health status and/or delivery of healthcare [1]) collected from routine care—can further support evaluation of treatment outcomes. RWE may be incorporated into randomized trial design, such as with pragmatic trials that enroll heterogeneous patient populations from real-world clinical practice [2]. However, RWE generated from observational analyses (based on retrospective or prospectively collected RWD) can also extend clinical evidence around a disease state or treatment option, especially after market authorization [3, 4]. Recognizing that many patient populations are underrepresented in RCTs (e.g., elderly, patients with comorbidities, racial and ethnic minorities), such RWE can provide the necessary information to guide decision-making alongside RCTs, since it is both unrealistic and infeasible to conduct head-to-head trials in all potential patient populations. By analyzing data from routine care, RWE can broadly capture outcomes on patients while also characterizing specific subpopulations, allowing for greater personalization of treatment decision-making, which accounts for unique circumstances of individuals [5].

In oncology, RWE can be especially useful for a wide variety of applications, such as contextualizing rare tumors or subtypes with smaller populations (e.g., epidemiology, patient characteristics), and capturing outcomes (e.g., effectiveness, toxicities) that require long-term observation [6–8], thereby strengthening the body of evidence available to inform treatment decision-making (Table 1) [2–4, 9–17].

To date, significant progress has been made across healthcare stakeholder groups in advancing acceptance and use of RWE, by way of guidance, frameworks, resources, and tools (Fig. 1) [18–38]. The United States (US) Food and Drug Administration (FDA) continues to demonstrate interest in using RWE to support regulatory decision-making, with establishment of the Advancing Real-World Evidence Program (October 2022) and recent guidance for industry addressing standards for RWD submission, assessment of registries, and digital health technologies for remote data acquisition (December 2023) [18–21], as well as RWD reliability and relevance (March 2024) [22]. In addition, the FDA's Oncology Center of Excellence continues to publish thought leadership [23–25] alongside initiatives such as TEAM FoRWD [39] and QCARD [40]; likewise, the Sentinel Innovation Center developed PRINCIPLED as a stepwise process guide for non-interventional research [26]. The US Agency for Healthcare Research and Quality has also participated in ongoing dialogue, writing methods guides for effectiveness and comparative effectiveness reviews [27], such as a decision framework for selecting observational studies for comparing medical interventions [41]. Beyond the US health agencies, other notable organizations have also published guidance documents, such as the European Medicines Agency (EMA) RWE framework [42] and European Society of Clinical Oncology Guidance for Reporting Oncology Real-World evidence (ESMO-GROW) [43]. Through a joint task force, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) have released a series of good practices reports [28], including the HARmonized Protocol Template to Enhance Reproducibility (HARPER) [29] to improve consistency in conduct of real-world research.

Within breast cancer, RWE is already being used to support regulatory and clinical decision-making. In 2019, the FDA approved a palbociclib label expansion to include men matching the initially-approved indication for hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, supported in part by RWE [44]. In 2020, the FDA approved a label update for trastuzumab emtansine patients with metastatic disease previously treated with HER2-targeted therapies, including RWE on cardiac safety for those with low left ventricular ejection fraction, a population not included in the RCT [45].

Despite recent progress in the application of RWE in breast cancer research, substantial

Table 1 Key strengths and limitations of RCT and RWE, including select examples of studies in breast cancer

	RCT	RWE
Key strengths	High internal validity, supporting demonstration of causality, with generally even distribution of confounders via participant randomization	High external validity through inclusion of a more heterogeneous sample of patients
	Precise measurement of treatment efficacy and acute safety/tolerability	Potential to observe outcomes in general population, including those under-represented or excluded from RCT (due to age, gender, race/ethnicity, geography, etc.)
Key limitations	Low external validity due to highly-selected population via narrow inclusion/exclusion criteria	Variability in data availability, quality, and completeness
	Limited ability to measure long-term safety, including rare AEs	Potential confounding or selection bias due to lack of randomization in most study designs
	Highly-protocolized care potentially not representative of real-world practice	Evidence in specific geographic or economic contexts may not be generalizable to other contexts
Select examples in breast cancer	DESTINY-Breast04: Phase 3 trial of trastuzumab deruxtecan vs. chemotherapy in previously treated patients with HER2-low mBC	Use and outcomes of trastuzumab deruxtecan in patients with HER2 + and HER2-low mBC, including those excluded from RCT
	EMILIA: Phase 3 trial of trastuzumab emtansine vs. lapatinib and capecitabine in previously treated patients with HER2+ mBC	PRAEGNANT: Outcomes of trastuzumab plus pertuzumab followed by trastuzumab emtansine in patients with HER2+ mBC (sequence not investigated in RCT)
	PALOMA-2: Phase 2 trial of palbociclib and letrozole vs. placebo and letrozole in patients with ER+/HER2− mBC	P-REALITY X: Palbociclib treatment patterns and comparative effectiveness in patients with HR+/HER2− mBC aged ≥ 75 years

+ positive, − negative, *AEs* adverse events, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *mBC* metastatic breast cancer, *RCT* randomized controlled trial, *RWE* real-world evidence

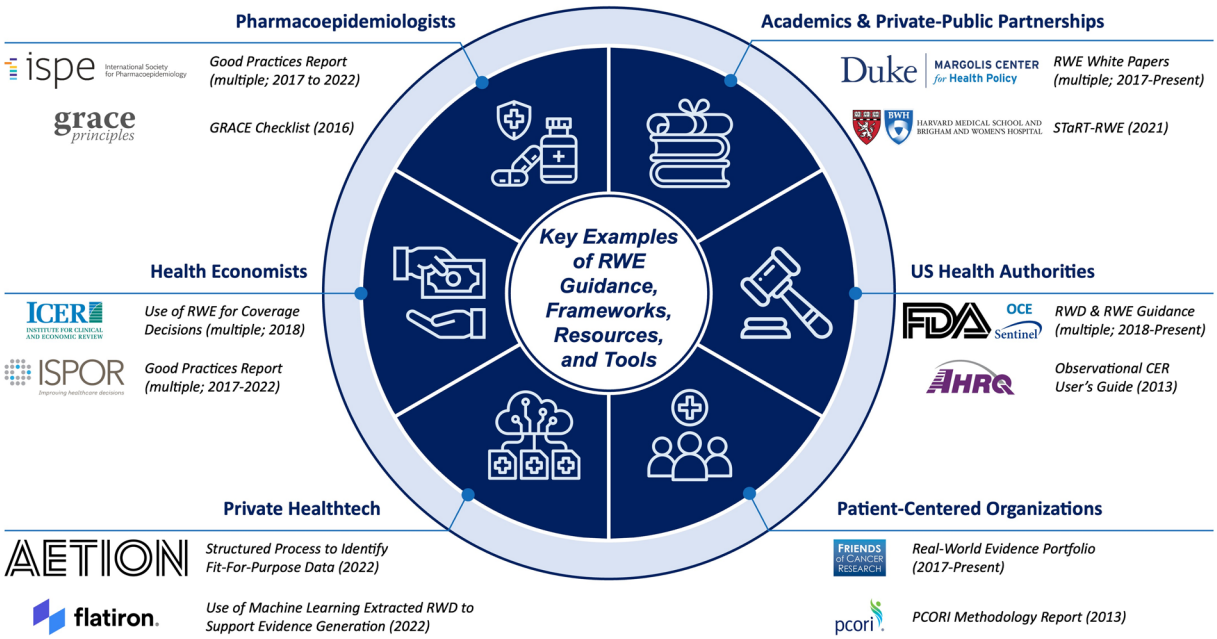

Fig. 1 Key examples of RWE guidance, frameworks, resources, and tools. *CER* Comparative Effectiveness Research, *GRACE* Good Research for Comparative Effectiveness, *PCORI* Patient-Centered Outcomes Research Institute, *RWD* Real-World Data, *RWE* Real-World Evidence

opportunities exist to further improve its acceptance and use. While the FDA supports the use of RWE in regulatory decision-making, there is still ambiguity about its use at the point of care, underscoring a broader challenge of achieving consensus on the value and applicability of RWE beyond regulatory approval processes and in direct support of treatment decisions. Clinicians and patients are engaging in shared decision-making and are calling for more granular clinical information about treatment effects for diverse patient populations, emphasizing the need to consider RWE alongside RCT data to help navigate the complexities of treatment selection. Similar exploration is already underway in other fields, such as low-risk differentiated thyroid cancer, where challenges exist in balancing clinical evidence with patient preferences [46]. Additionally, the integration and acceptance of RWE by US payors is increasingly recognized as essential for informed healthcare decision-making, especially to inform comparative effectiveness analyses and formulary placement [47, 48].

As proposed by Cottu et al., a multi-stakeholder, collaborative initiative has potential to greatly improve understanding and acceptability of RWE, particularly in breast cancer, where there is strong demand for additional evidence on unmet medical need and clinical benefit of therapies [49]. While initiatives may emerge ad hoc, thought leadership resulting from such efforts remains a persisting gap. To date, peer-reviewed literature, co-authored by stakeholders across disciplines and with intention of supporting a mindset shift around RWE, is limited. This absence is even more pronounced in the context of breast cancer specifically, despite the disease setting presenting great opportunity for further RWE adoption.

Ethical Approval

This article does not contain any new studies with human participants or animals performed by any of the authors. All members of the Think Tank were fully informed and consented to their thoughts being formulated into a manuscript,

and invited to contribute as authors on this article (of which, 13 of the 14 members accepted).

OBJECTIVES

A Think Tank on RWE in the US from Multiple Perspectives in Healthcare (TRIUMPH) was established to include 14 multidisciplinary stakeholders, representing oncologists, patient advocates, US regulatory policy experts, payor advisors, health economists, and real-world methodologists. Identification was informed by literature search, to confirm RWE expertise (based on publicly-available contributions to and teaching of the subject) and support multidisciplinary membership (i.e., avoiding biased representation towards one stakeholder group over another). Due to potential conflict of interest, individuals still currently employed by US federal agencies were not included. However, TRIUMPH members with US regulatory policy expertise provide perspectives that account for their prior experiences at such organizations, like the FDA and Centers for Medicare & Medicaid Services.

TRIUMPH aims to further advance acceptance and use of RWE in treatment decision-making for breast cancer; however, members recognize that the RWE concepts discussed may be relevant in oncology more broadly, beyond breast cancer. In November 2023, members convened in Washington, D.C., with the following objectives:

1. Identify perceptions of RWE acceptance and use in treatment decision-making for breast cancer in the US, from a clinical perspective
2. Consider solutions to address perceptions that may prevent further advancement of RWE acceptance and use
3. Develop "calls-to-action" to drive implementation of highest-priority solutions

Recognizing continued lack of widespread acceptance and use of RWE ("perceptions of RWE") alongside opportunities for improvement

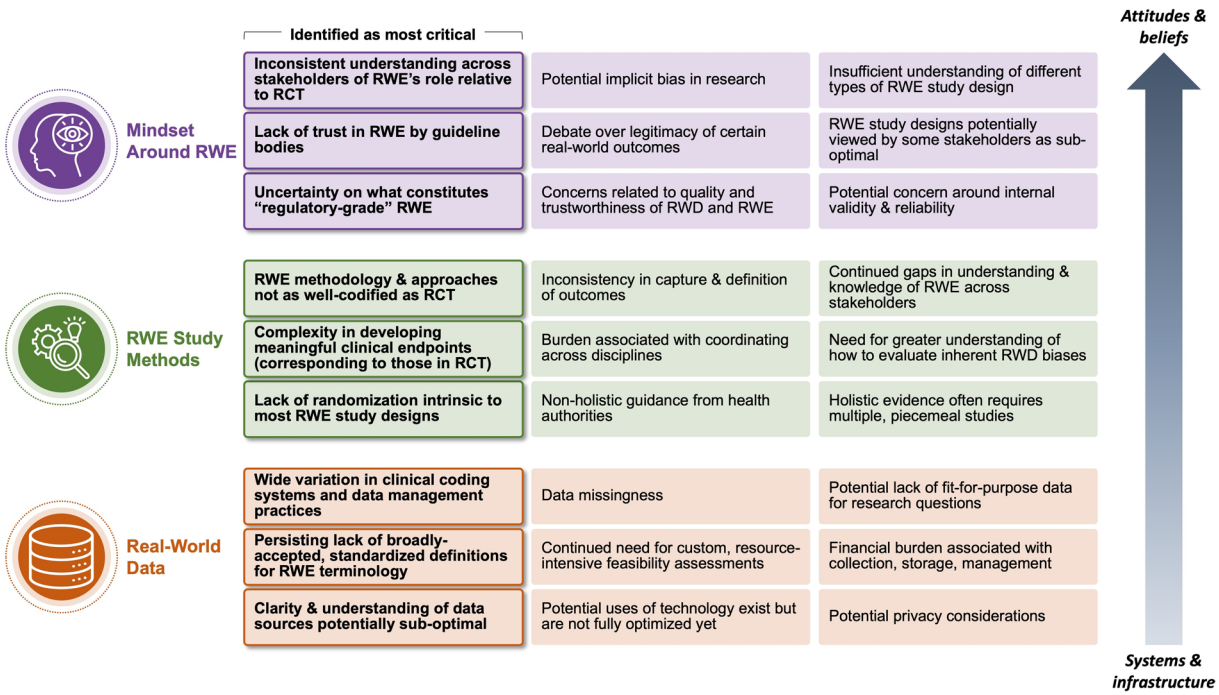

Fig. 2 Perceptions (most critical in *bold*) of RWE acceptance and use in treatment decision-making for breast cancer in the US, from a clinical perspective. *RCT* randomized controlled trial, *RWD* real-world data, *RWE* real-world evidence

("solutions"), we report findings and "calls-to-action" from the TRIUMPH members. As one of the first articles to address this topic in the form of a multidisciplinary white paper, we also aim to present our position to directly engage fellow healthcare stakeholders in further advancing RWE acceptance and use in treatment decision-making.

PERCEPTIONS OF RWE ACCEPTANCE AND USE FROM A CLINICAL PERSPECTIVE

TRIUMPH members identified common perceptions related to RWE acceptance and use in treatment decision-making for breast cancer in the US. Members reported perceptions (Fig. 2) across three categories—Real-World Data (including operational components), RWE Study Methods, and Mindset Around RWE—and reached group consensus on those most critical to address within each.

The most critical perceptions related to Real-World Data were wide variation in clinical coding systems and data management practices; absence of broadly-accepted, standardized definitions for RWE terminology; and potentially sub-optimal clarity and understanding of data sources. All similarly relate to an overarching lack of transparency and standard practices in data sourcing and management. This viewpoint is also consistent with FDA priorities, as demonstrated by recent guidance such as "Data Standards for Drug and Biological Product Submissions Containing Real-World Data" in December 2023 [20].

The most critical perceptions related to RWE Study Methods were RWE methodology and approaches not being as well codified as those for RCT; complexity in developing meaningful clinical endpoints (corresponding to those in RCTs); and lack of randomization being

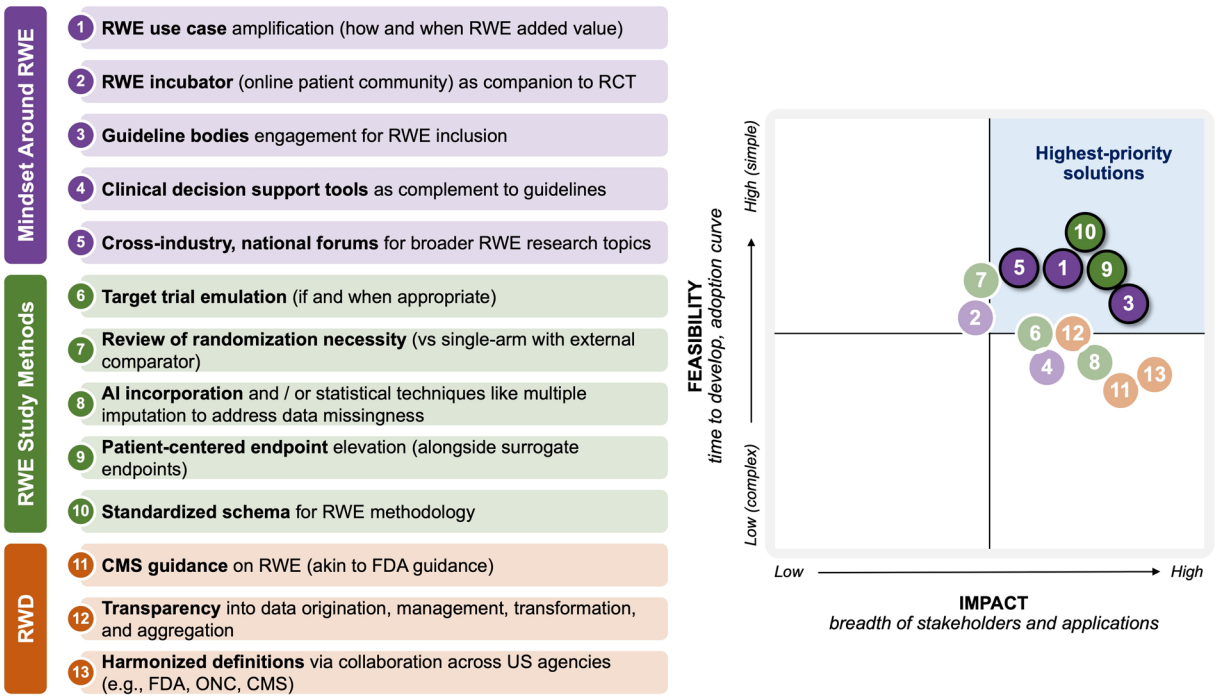

Fig. 3 Prioritization (based on average ratings) of potential solutions by TRIUMPH members, matrixed against impact and feasibility, with those in the upper-right quadrant considered highest-priority. *CMS* Centers for Medicare & Medicaid Services, *FDA* food and drug administration, *ONC* Office of the National Coordinator for Health Information Technology, *RCT* randomized controlled trial, *RWE* real-world evidence, *US* United States

intrinsic to most RWE studies. Although RWE entails a variety of study designs, these perceptions indicate a need for foundational standards (e.g., transparent reporting [50]) to account for methods specific to RWE studies.

Lastly, the most critical perceptions related to Mindset Around RWE were inconsistency in understanding role of RWE relative to RCT; lack of trust in RWE by guideline bodies; and uncertainty on what constitutes "regulatory-grade" RWE, despite ongoing guidance from the FDA [18–22] and EMA [42]. The complementary nature of RWE with RCTs [2] may remain unclear to some stakeholders, resulting in continued uncertainty and sometimes skepticism about the value of RWE, especially in the context of treatment decision-making.

SOLUTIONS AND "CALLS-TO-ACTION"

Based on the most critical perceptions, TRIUMPH members considered and then prioritized 13 solutions (e.g., tools, practices, resources, etc.). Each solution was rated across dimensions of perceived impact on RWE acceptance and use and feasibility to implement, with five identified as highest-priority to pursue (Fig. 3).

Subsequently, to begin to address these highest-priority solutions, TRIUMPH members articulated a primary "call-to-action," specifically to "*develop clinically-relevant (and patient-informed) endpoints for the real-world,"* for all stakeholders, alongside four secondary "calls-to-action" (Fig. 4).

The primary "call-to-action" to *"develop clinically-relevant (and patient-informed) endpoints for the real-world"* was unanimously identified by TRIUMPH members as the foundation for enabling broader acceptance and use of RWE in breast cancer treatment decision-making. In RCTs, Response Evaluation Criteria in Solid Tumors (RECIST) enables a standardized and objective approach that can measure outcomes with both validity and reliability, requiring consistent imaging and testing over time. Currently, it is unrealistic to expect such research-driven standards to be similarly followed across routine clinical practice, and, when performed, such data may not be available, such as difficult-to-access radiographic images or specific measurements [51, 52]. Therefore, while meaningful,

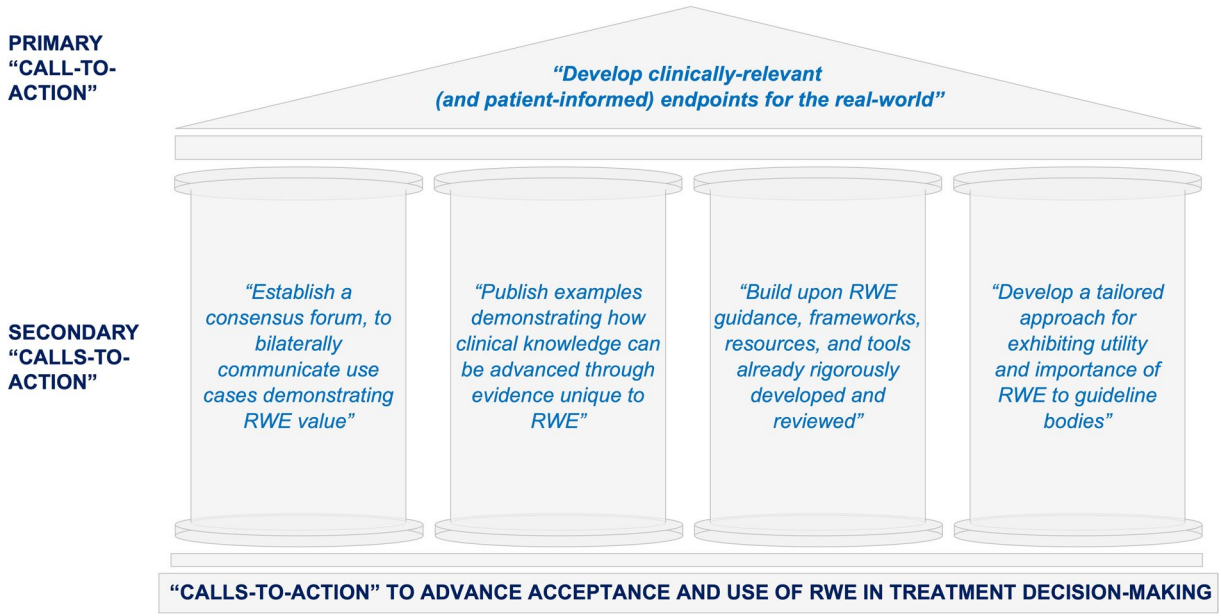

Fig. 4 Consensus-driven primary and secondary "calls-to-action" from TRIUMPH, to advance acceptance and use of RWE in treatment decision-making for breast cancer in the US. *RWE* real-world evidence

certain outcomes such as progression-free survival (PFS) are challenging to measure in the real world in a manner consistent with RCT practices [53]. Given findings from Friends of Cancer Research's multi-stakeholder real-world response pilot, aimed at understanding feasibility of treatment effectiveness evaluation based on clinician assessments within RWD [54], real-world PFS (rwPFS) should still be considered; however, researchers can also concurrently focus on development of clinically-relevant endpoints that are purposefully designed with pragmatic, real-world data collection in mind.

Also, due to multiple factors, such as race, ethnicity, comorbidities, and social determinants of health, each breast cancer patient's treatment should be individualized and barriers to care should be addressed with an asset-based approach to tailored solutions. Patients want to understand what outcomes can be expected in the context of other patients similar to themselves, and clinicians often lack evidence to share beyond assuming that the average treatment effect from a RCT should be applied broadly across real-world patients. Achieving such insights can, though, be particularly challenging, as exclusion from RCTs is often due to possible vulnerabilities related to multimorbidity, polypharmacy, prior treatments, or age [55]. Combined, these factors necessitate development of clinically-relevant endpoints that measure outcomes in ways that are meaningful in routine clinical practice and for patients [e.g., patient-reported outcomes (PROs) such as those related to time toxicity, like days alive and out of hospital [56–58], or electronic PROs to characterize patient symptoms]. Organizations such as the Patient-Centered Outcomes Research Institute (PCORI) are beginning to address this need through provision of detailed resources that enable greater patient involvement in clinical research [59]. Such patient-centered endpoints in breast cancer may potentially be designed alongside advocacy groups, ensuring that selected outcomes are directly informed by patient experiences. Making RWE comprehensible and relevant to patients can better equip them to participate in discussing the totality of evidence (i.e., RWE and RCT data) with clinicians, ultimately supporting optimal shared treatment decision-making. And, from a health economic perspective, payors are continuing to demonstrate similar enthusiasm in considering clinical (including surrogate) endpoints with linkage to more patient-centric ones.

In addition to the primary "call-to-action," TRIUMPH recommended mobilization of four secondary "calls-to-action," as follows:

1. *"Establish a consensus forum inclusive of multidisciplinary experts, to bilaterally communicate use cases demonstrating RWE value."* Like TRIUMPH's multidisciplinary makeup but on a larger scale, a consensus forum with regular cadence (e.g., annually)—driven by organizations such as the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), National Cancer Institute (NCI), or PCORI, or cooperative groups focused on RWE generation—should bring diverse stakeholders together to discuss the value of RWE and further promote standardized ways of conducting RWE research. By uniting traditionally-siloed stakeholder groups engaged in RWE generation and/or use, such a forum may increase awareness around importance of RWE, highlight achievements and best practices to adopt, and enable more frequent and regular dialogue across stakeholder groups. In turn, these benefits can strengthen feasibility of implementing solutions for advancing RWE acceptance and use.
2. *"Publish targeted examples demonstrating how clinical knowledge can be advanced through evidence unique to RWE (e.g., "population-bridging," a short-hand term for evaluating treatment effects in populations not studied in RCT)."* Recognizing an increasing trend in the volume of RWE published, amplification of select RWE use cases is necessary, specifically those demonstrating unique value relative to RCTs, such as—but not limited to—outcomes in subgroups or local populations typically underrepresented or excluded from RCT, and confirmatory evaluation of efficacy or safety, as observed in the real world [5, 10, 60]. Subsequently, through various forums and communication channels (e.g., fireside chat, roundtable, podcast), clinicians can

lead amplification through dissemination of these select case examples. While seemingly simple, such efforts are still fundamental in establishing awareness around RWE to a broader set of healthcare stakeholders, especially those with minimal familiarity or prior exposure to it.

3. *"Build upon existing, established RWE guidance, frameworks, resources, and tools that have already been rigorously developed and reviewed."* With guidance as recent as March 2024 from the FDA on RWD reliability and relevance [22], several healthcare stakeholders have already, and continue to, issued credible RWE reference materials, with successfully validated methodologies, informed by supporting literature reviews and/or conceived by recognized RWE thought leaders. With such a wealth of RWE reference materials, researchers experienced in their use should drive broader utilization, as well as guide design and analysis of RWE studies, versus trialists experienced primarily in RCTs. Benefits of consistently using these materials will accrue over time and result in industry-wide, standardized RWE schema, accompanied by transparent communication around methodology, reduced misinterpretation, efficient and more informed review, and valid, reproducible research [36].
4. *"Develop a tailored approach for exhibiting the utility and importance of RWE to guideline bodies."* Generation of RWE has evolved over time, alongside increasing availability of evidence from multi-modal datasets, linkage between anonymized, patient-level datasets (e.g., between electronic health records (EHR) and claims), and access to unstructured datasets. Commensurate with this progress, the rigor and types of RWE available for consideration by guideline panels has also expanded. Integration of RWE into clinical practice guidelines may take different forms, such as incorporating new RWE findings into relevant sections, updating existing recommendations, providing additional context or caveats, or creating new sections altogether, in support of evidence-based medicine [61]. Study investigators may directly support this integration by generating hypothesis-driven cases that directly inform US guideline bodies like NCCN. Such RWE on outcomes in routine clinical practice can complement RCT data and support treatment recommendations: which to use (e.g., treatment patterns), when to use (e.g., optimal sequencing), and how to use (e.g., dose modification as part of adverse event management). NCCN has already made advances in providing accessible, credible education materials to providers and patients, through NCCN Frameworks and Evidence Blocks [62, 63]. By increasing emphasis on RWE within clinical workflows, NCCN has an opportunity to further enhance future treatment decision-making for breast cancer oncologists within both academic centers of excellence and community practices.

CONCLUSIONS

While RCTs remain the gold standard, RWE may complement and strengthen the body of evidence available to consider for optimal treatment decision-making, particularly accounting for inherent patient heterogeneity (including those not well represented in RCTs) in breast cancer and in the United States. Advances have already been made in RWE generation, such as creation of disease-specific databases, use and linkage between multi-modal datasets, and harnessing of unstructured data, for use in powering large-scale studies. Alongside these capabilities, healthcare stakeholders have significantly enriched RWE thought leadership through provision of guidance, frameworks, resources, and tools which serve as reference materials. However, a gap remains in the widespread acceptance and use of RWE in treatment decision-making. TRIUMPH identified the most critical perceptions of RWE acceptance and use across domains of data, methodology, and mindset (note, this article does not contain any new studies with human participants or animals performed by any of the authors.). Subsequently, potential

solutions were considered and prioritized, with a prominent "call-to-action" and four supporting "calls." The primary "call-to-action" was to *"develop clinically-relevant (and patient-informed) endpoints for the real-world*." The four secondary "calls-to-action" include *"establish a consensus forum inclusive of multidisciplinary experts, to bilaterally communicate use cases demonstrating RWE value"* to elevate RWE research nationally, highlight the uniqueness of RWE, and encourage standardized ways of conducting RWE research; *"publish targeted examples demonstrating how clinical knowledge can be advanced through evidence unique to RWE (e.g., population-bridging)"* to amplify how and where RWE adds value; *"build upon existing, established RWE guidance, frameworks, resources, and tools that have already been rigorously developed and reviewed"* to advance industry-wide, standardized RWE schema; and, *"develop a tailored approach for exhibiting the utility and importance of RWE to guideline bodies"* to enhance future treatment decision-making by increasing emphasis on RWE within clinical workflows. Beyond disseminating "calls-to-action" through this paper, TRIUMPH ultimately aims to continue growing awareness of the clinical utility of RWE among healthcare stakeholders, and to mobilize them to drive expanded acceptance of RWE use in breast cancer treatment decision-making in the US.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated and analyzed during the current study.

Declarations

Conflict of Interest. Sean Khozin is co-founder and Principal at Phyusion, LLC, providing advisory services to life sciences companies. Nancy Dreyer is Principal at Dreyer Strategies LLC and has received honoraria for consulting from Pfizer. Raymond Liu has received research funding (to institute) from AstraZeneca, Biotheranostics, Beigene, Exact Sciences, and Genentech. Peter Neumann has received honoraria for consulting from Pfizer. Nathan Nussbaum is an employee of and has equity ownership in Verily Life Sciences, and stock ownership in Roche. Joyce O'Shaughnessy has received honoraria for consulting and/or advisory boards from AbbVie Inc., Agendia, Amgen, Aptitude Health, AstraZeneca, BioNTech, Byondis, Carrick Therapeutics, Daiichi Sankyo, DAVA Oncology, Eisai, Fishawack Health, G1 Therapeutics, Genzyme, GlaxoSmithKline, Genentech, Gilead Sciences, LillyLoxo Oncology, Merck, Novartis, Ontada, Pfizer, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Roche, Samsung Bioepis, Sanofi, Seagen, Stemline Therapeutics, Taiho Oncology, and Veru. Debra Patt has received honoraria for educational consulting from Daiichi Sankyo, Inc. and Pfizer, and holds a leadership

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Ethical Approval. This article does not contain any new studies with human participants or animals performed by any of the authors. All members of the Think Tank were fully informed and consented to their thoughts being formulated into a manuscript, and invited to contribute as authors on this article (of which, 13 of the 14 members accepted).

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