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# The emerging role of real-world data in advanced breast cancer therapy: Recommendations for collaborative decision-making

Paul Cottu [a, *], Scott David Ramsey [b], Oriol Solà-Morales [c], Patricia A. Spears [d], Lockwood Taylor [e]

[a] Department of Medical Oncology, Institut Curie, 26 Rue D'Ulm, 75005, Paris, France
[b] Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M2-B232, Seattle, WA, 98155, USA
[c] Health Innovation Technology Transfer Foundation, Aragó 60, E-08015, Barcelona, Spain
[d] 8605 Carolingian Court, Raleigh, NC, 27615, USA
[e] Epidemiology, Real World Solutions at IQVIA, 4820 Emperor Boulevard, Durham, NC, 27703, USA

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ABSTRACT

Among stakeholders and decision-makers in advanced breast cancer, the demand for insights from real-world data (RWD) is increasing. Although RWD can be used to support decisions throughout different stages of a breast cancer drug's life cycle, barriers exist to its use and acceptance. We propose a collaborative approach to generating and using RWD that is meaningful to multiple stakeholders, and encourage frameworks toward international guidelines to help standardize RWD methodologies to achieve more efficient use of RWD insights.


## 1. Introduction

The value of real-world evidence (RWE) generated using real-world data (RWD) (i.e., data collected outside of randomized controlled trials [RCTs]) is well recognized [1,2]. For patients with advanced breast cancer (aBC), the demand for RWE is increasing as stakeholders seek to understand unmet medical needs (e.g., what are the clinical fields where care improvement is urgently required?) and real-world product benefit and safety (e.g., what are the real-world outcomes of innovative therapies?). Additionally, real-world patients frequently differ from patients in clinical trials, including with regard to age, comorbidities, prior therapies received, and tumor features (such as hormone receptor [HR] status) [3,4]. However, barriers to the efficient development and use of RWD exist, as stakeholders have differing levels of comfort interpreting, accepting, and using RWD. Regulators and reimbursement decision-makers are often reluctant to consider non-RCT data, and manufacturers and academics may consider it unproductive to sponsor studies that collect RWD.

In aBC treatment, an increasing number of initiatives exist to standardize methodologies for generating RWD across stakeholders and geographies. This article will describe potential roles of RWD to support decisions throughout different stages of a breast cancer drug's life cycle [5] and offer recommendations to remove barriers to the use and acceptance of RWD.

## 2. Prior to a breast cancer drug's approval

Preapproval, RWE can elucidate the disease course in the

*Abbreviations:* aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; EHRs, electronic health records; EMA, European Medicines Agency; ER+, estrogen receptor-positive; ESME, Epidemiological Strategy and Medical Economics; HER2−, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; RCT, randomized controlled trial; RWD, real-world data; RWE, real-world evidence.

* Corresponding author. Department of Medical Oncology, Institut Curie, 26 rue d'Ulm, 75005, Paris, France.
*E-mail addresses:* paul.cottu@curie.fr (P. Cottu), sramsey@fredhutch.org (S.D. Ramsey), osola@fhitt.org (O. Solà-Morales), paspears88@gmail.com (P.A. Spears), lockwood.taylor@iqvia.com (L. Taylor).

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absence of or under current standard of care including treatment requirements to cover unmet medical needs, resource use, adherence, and differences between observed practice and clinical guidelines (Fig. 1).

Natural history studies are particularly useful to inform clinically meaningful endpoints and may serve as a source of controls for single-arm trials. For instance, the national French Epidemiological Strategy and Medical Economics (ESME) program has demonstrated how large, nationwide, retrospective cohorts help delineate critical medical needs in patients with aBC [6,7]. It is striking to observe that the long-term prognosis of patients with estrogen receptor-positive (ER+) aBC has not improved over the past 10 years. RWD studies can also help clarify the treatment preferences of patients, including the drivers of trade-offs between quality and quantity of life at some stages of the disease.

If RWD is used to describe product safety or effectiveness in another country, where the product is already approved, or within the country where approval is sought for a different dose/indication, RWE may be considered to supplement RCT data. Such an approach may provide a holistic evidence package to support regulatory decision-making, particularly around endpoints relevant to regulators that are often not captured in RCTs, including overall survival, effectiveness in underrepresented patient populations, and surveillance for rare safety events [8].

## 3. Following approval of an advanced breast cancer drug

Once a drug is approved for aBC, RWE can support reimbursement decisions and treatment decisions by clinicians and patients. Recent RWE studies evaluated treatment patterns in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) aBC based on national guidelines recommending the use of cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) in first-line therapy. Interestingly, many patients with HR+/HER2− aBC do not receive a CDK4/6i in first-line treatment [9,10] even in those countries where these drugs are approved (i.e., no regulatory limitation to their prescription). These results raise two key questions that were not addressable in RCTs: Why do physicians not routinely prescribe a CDK4/6i in this setting? Is there an unidentified patient group in which patients are not candidates for or chose not to receive CDK4/6i treatment?

RWD can help to identify these patient groups by informing disease simulation models based on global and regional data [11–13]. For example, claims databases can be used to develop predictive models for identifying cases of ER+ and HER2− early and aBC; these claims-based models can have improved predictive value and sensitivity compared to models based on clinical insights alone [11]. In France, results from the personalized reimbursement model database involving more than 20,000 patients showed how recent advances of HER2-targeted therapies may benefit patients with early and advanced HER2+ breast cancer [14]. Using RWD instead of RCT data to inform population-based disease models can better reflect the clinical reality of treatment-eligible patient populations and improve physician engagement and patient experiences.

RWE can also provide data to support clinical guidelines regarding specific subgroups of patients not well-represented by RCT data. For example, for patients with early-relapsing (<12 months) HER2+ aBC, the American Society of Clinical Oncology (ASCO) recommended trastuzumab emtansine (T-DM1) instead of the combination of pertuzumab, trastuzumab, and a taxane based on RCT data from a very small subgroup of patients in the EMILIA trial [15]. More recent RWD describing treatment outcomes in this early-relapsing patient subgroup is now available from a retrospective analysis of real-world patient cohorts [16]—a clear example of how RWE may be useful in guiding clinical decision-making.

## 4. Mature breast cancer drugs

Once an approved breast cancer drug is in clinical use, RWD maintains value by describing long-term outcomes using national

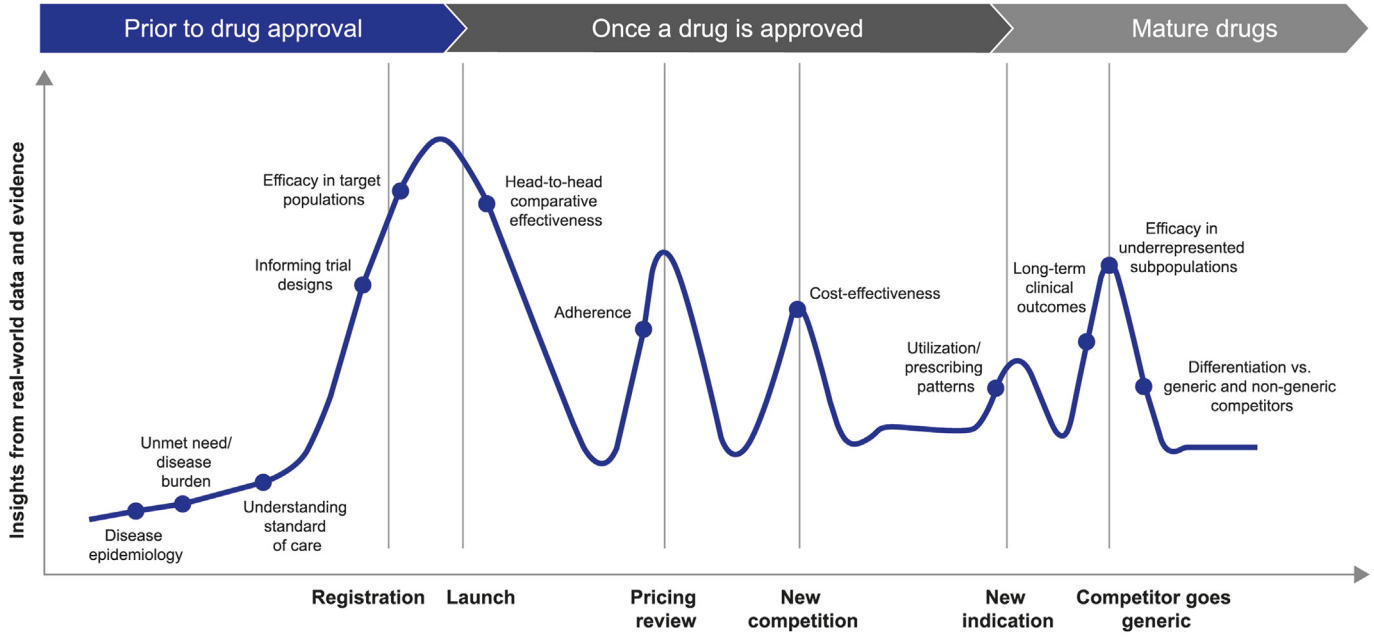


**Fig. 1.** Examples of insights provided by RWD and RWE throughout a breast cancer drug's life cycle. Adapted from: Innovative Medicines Initiative and European Medicines Agency [5].

databases or registries (e.g., the Surveillance, Epidemiology, and End Results (SEER) Program [17], ESME [18]). Outcomes informed by RWD include those related to overall survival, treatment/switching patterns, rare safety events, effectiveness in broader patient populations, and costs/resource utilization. The interconnection of electronic health records (EHRs) to genomic databases [19] is increasingly important to help understand future treatment pathways or to avoid preventable toxicities.

RWE can establish trust between the physician and patient and also result in new treatment paradigms that incorporate shared decision-making. RWD aids communication between physicians and patients by informing shared decision-making with regard to treatment options and available patient support programs [20]. In some cases, patients may prefer improved quality of life over an increased survival benefit, or may have concerns over specific toxicities [21–24].

It is important to educate patient communities about the impact of RWE on their care [25]. RWE can be used to demonstrate treatment benefit in broader patient populations, including populations that may be underrepresented in RCTs [26,27]; in aBC, these include men, older patients, younger/premenopausal patients, minority and underserved patients, as well as rare breast cancer subtypes (e.g., inflammatory or metaplastic disease). In male patients with aBC, for whom RCTs were not feasible, RWD supported the inclusion of this subpopulation in palbociclib's label [28]. It is also crucial to involve patients in the interpretation of RWE to prioritize outcomes most meaningful to them [29] and educate stakeholders on the relative value of different outcomes evaluated in RCTs or disease management programs [30].

## 5. How to overcome barriers to efficient development and use of RWD and RWE across stakeholders and geographies

There is a lack of clear guidance on what RWD sources and endpoints are most useful to inform decisions by regulators, clinicians, and patients, and there are substantial differences among countries in how RWD is collected and leveraged for reimbursement decisions. RWD are limited by the lack of unified endpoints across databases, and few resources exist to support real-world endpoint development and unification [31]. Furthermore, RWD is often not made available for use across stakeholders; it is crucial to share data and analysis methods, and establish a data governance policy prior to gathering and evaluating RWD.

Credible RWD-based models must account for population heterogeneity when making predictions. Heterogeneity can pose a challenge to making inferences and developing meaningful disease models as RWD is not uniformly available for all patient populations. For example, in the United States, data for individuals covered by Medicare may be easier to access than data for those covered by employer or commercial insurance. There is also need for reliable RWD cohorts that explore long-term outcomes among some patient subpopulations [32,33]. The ESME cohort in France has been able to establish that elderly patients with aBC, often underrepresented in RCTs, may be suboptimally treated [27].

Many breast cancer real-world databases do not capture enough longitudinal data to comprehensively track changes in a patient's disease status and treatments over time, but provide a “snapshot” reflecting when the data was collected. Collecting patient data over time would improve the usefulness of real-world databases to decision-makers. A recent report by the European Medicines Agency (EMA) clearly established how data sources such as EHRs, registries, or sales and prescription data may be used in real-world studies [34]. The ESME results generated from EHRs and prescription data captured over a 10-year period have put forward the natural history of advanced ER+/HER2− breast cancer [35], underlining the unmet medical needs at different time points during the course of advanced disease.

To improve the availability and use of RWD in aBC, global stakeholders should collaborate in generating high-quality RWD, and in defining a common data governance, because decisions made by one stakeholder impact others. For example, reimbursement decisions affect prescribing behaviors, which in turn affect patients' access to therapies. The “Health Data Hub” effort currently developed in France [36] may exemplify these approaches, by combining all public health-related data on a single platform at a national level.

There is a need to implement and enforce international guidelines for the transparency and reporting of RWD, similar to established guidelines for the reporting of observational study results, like the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, which include study-design recommendations for cohort, case-control, and cross-sectional studies [37].

To adopt a more collaborative approach, such international guidelines might include standardized methodologies for generating RWD (e.g., more broadly accepted study designs, streamlined data collection, and integrated data sources). Ultimately, these guidelines would support increased transposability of RWD across geographies. The EMA has underlined how RWD is relevant to regulatory systems [38] and a recent review illustrated how RWD was critical for regulatory approval of innovative drugs [39]. Frameworks to help standardize methodologies would incentivize drug manufacturers to sponsor more studies to collect meaningful RWD, confident in its value to other stakeholders. However, we caution that these efforts to standardize RWD generation should not lead to excessive bureaucracy, which could impair the broadest collection of RWD. To ensure that the work of RWD generation is not entirely left to individual physicians, the involvement of dedicated RWE experts is required.

There is also a need for consensus on governance to assess and report the creation, maintenance, and quality of databases, to allow informed judgement around data reliability and relevance. Following the examples of the Consolidated Standards of Reporting Trials (CONSORT) statement [40] and clinicaltrials. gov [41], this could be enforced by requiring databases to be preregistered in a centralized register, and the ethics committees to require such preregistration.

## 6. Conclusions and proposed initiatives

A collaborative approach to generating and using RWD that is meaningful to different stakeholders could result in a wider understanding and acceptability of RWD and a more efficient use of its insights, improving our understanding of aBC and potentially bringing treatments to patients more quickly. For RWD and RWE to be meaningful to most stakeholders, collaborative frameworks toward international guidelines to help standardize RWD methodologies are encouraged.

To help pave the way forward, we recommend initiatives that address three key concepts. First, a stable framework for generation of RWD and interpretation of RWE must be endorsed, for use by both healthcare providers and regulatory authorities. Second, an enhanced, comprehensive process for sharing RWD among clinicians, data scientists, patients, and patient advocates must be established; such a process should include RWD generated from digital platforms outside of conventional health systems, such as those captured through social media. Third, we need to implement new, value-based pricing solutions that leverage RWD to directly incentivize its meaningful collection and use. Concrete initiatives in these areas will enable us to use RWD and RWE to assess not only

clinical and patient-centered outcomes, but also economic outcomes that demonstrate the RWD-based cost-effectiveness of individual treatment options.

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## Author contributions

All authors contributed to the viewpoints expressed in this manuscript. All authors contributed to the critical interpretation of data and drafting/revision of the manuscript content, have approved the final version of this manuscript, and take responsibility for the integrity of this manuscript.

## Declaration of competing interest

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