Note: some examples referenced in this white paper, including therapies, indications, and biopharmaceutical manufacturers, remain under review by regulatory agencies or health authorities; to preserve confidentiality, these are presented without identification.

Introduction
Evidence generation in oncology is at a key inflection point. Given the rapid pace of scientific innovation, historical approaches to drug development are increasingly burdensome, with randomized controlled trials remaining incredibly costly and time intensive to conduct, and having a low certainty of success. Biopharmaceutical companies will collectively invest USD 50 billion to support oncology research and development in 2018, with a ~3 percent probability of success for any individual product from preclinical through registration phases.\(^1\) Despite this investment, many completed trials fail to answer critical questions for payors and healthcare

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providers, exacerbating the wide evidence gap that already exists between clinical research and practice.

Patients, providers, and payors lack answers to fundamental questions – “What treatment is best for me?”; “How do patients treated in the ‘real world’ perform on this therapy?”; “What is the value of this therapy relative to other treatment options?” The evidence gap persists despite a richness of available data, novel analytic methods, and inexpensive computing and genomic sequencing power. Real-world evidence (RWE) – insights generated from data collected during routine clinical practice – provides a platform with which to close the evidence gap between clinical research and practice.

The role of RWE in drug development is expanding, driven in part by biotechnology and pharmaceutical manufacturers’ embrace of digital solutions to realize gains in speed and efficiency from innovation. RWE teams have taken root across the pharmaceutical industry with industry-wide investments in talent and technical infrastructure. Successful biopharmaceutical companies have coupled investment with the belief that RWE is a critical component of development and life cycle management, and committed to this by building RWE generation capabilities on a large scale. Providers have similarly embraced RWE to inform clinical practice, and clinical guidelines (e.g., National Comprehensive Cancer Network) increasingly incorporate RWE-generated insights. Recognizing the need for a more flexible framework for therapy evaluation, regulators are developing approaches to incorporate RWE in their decision making, as outlined in frameworks such as the 21st Century Cures Act. These changes are accompanied by the emergence of high-quality data providers, including those with distinct data sources and analytic approaches.

The potential for RWE is perhaps greatest in oncology. Cancer will soon overtake cardiovascular disease as the leading cause of death in the US,2 with a similarly increasing disease burden in other geographies. Governmental support for addressing the burden of cancer has increased, and includes record levels of federal funding (the National Cancer Institute is the most heavily funded of the 27 National Institutes of Health) and regulatory support through the creation of the Oncology Center of Excellence within the Food and Drug Administration (FDA).3 Clinical breakthroughs have led to the development of novel modalities of therapy (i.e., chimeric antigen receptor T (CAR-T)/cell therapy) that offer the potential for cure-like responses, but at financial costs that raise questions regarding the role and, ultimately, the value of such therapy. RWE is well positioned to help address these questions in a manner aligned with the interests of all stakeholders. Effectively deployed, RWE can accelerate the pace of discovery – and patient impact – of new oncology therapies.

How is RWE driving impact?

Robust RWE has applications across the entire drug development life cycle, presenting numerous opportunities for biopharmaceutical companies to shorten development timelines, reduce the costs of clinical trials, and improve the probability of technical and regulatory success (PTRS). There are several applications for RWE throughout clinical development, including:

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- **Early discovery.** Oncology development is increasingly personalized and precise, with narrower and more nuanced indications characterized by genomic alterations and signatures. RWE can de-risk elements of early discovery by focusing on identification of high-responding patient cohorts. Using robust genomic sequencing data and longitudinal clinical data, RWE analyses can identify biomarkers of therapeutic response and resistance to optimize a drug development strategy. For example, a top ten pharmaceutical company recently utilized a clinicogenomic database with tumor sequencing information from over 2,000 patients with advanced non-small cell lung cancer to identify and characterize genomic profiles of patients with rapid progression or otherwise poor prognosis. Application of such findings can inform biomarker targets of interest and, in the future, may support more targeted drug development.

- **Trial design and feasibility.** Targeted use of RWE derived from electronic health records (EHR) supports the design and optimization of clinical trials. RWE can be used to design a protocol that is generalizable to standard of care, assess the impact of eligibility criteria on trial feasibility, and inform the selection of trial sites. For example, a top five oncology drug developer designed a dosing study protocol with high external validity by using RWE to understand how standard of care was delivered in a metastatic cancer population in routine clinical practice. This included adjusting the frequency of assessments of diagnostic imaging and laboratory tests to match the patterns observed in the patient population in the real world. The resulting protocol was designed to be less onerous to patients and investigators, and to lower the cost to the sponsor while producing reliable evidence.

- **Trial execution.** Of particular relevance to oncology is the adoption of external control arms which may reduce trial size (i.e., required number of patients), duration, and cost. In some scenarios, randomization of patients to standard of care will prolong recruitment, and may be difficult to recruit for if early signals show substantial benefit over standard of care. The traditional control arm, which provides a comparator to the experimental therapy, may evolve into an “external” control derived from historical or contemporaneous populations treated in a real-world setting. This opportunity is particularly striking in cases of rare malignancies where patient recruitment remains a challenge. External control arms may also serve as comparators to early phase single-arm trials used for registration purposes, as seen in 11 of the last 12 oncology-related approvals through the FDA’s Breakthrough Therapy Designation Pathway. Pfizer recently validated such an approach for a subset of clinical trial patients with HER2 negative/hormone receptor positive metastatic breast cancer. The real-world control arm replicated the clinical outcomes (progression-free survival and overall survival) observed in a subset of patients enrolled in a standard of care Phase III control arm. Important questions regarding experimental design, appropriate

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6 Huang Bartlett, Cynthia et al. Concordance of real-world progression-free survival on endocrine therapy as first line treatment for metastatic breast cancer using electronic health record with proper quality control versus conventional PFS from a Phase 3 trial [poster]. In 2017 San Antonio Breast Cancer Symposium, December 5-9, 2017; San Antonio, Texas, http://cancerres.aacrjournals.org/content/78/4_Supplement/P3-17-03.
use of external control arms, and role in the regulatory approval process remain to be elucidated.

As therapies move from investigation to regulatory approval and uptake, RWE can address additional evidence gaps. **Post-approval**, we see additional RWE applications, including:

**Post-marketing studies.** Real-world perspectives were first incorporated in the regulatory process through the mandate for post-marketing studies. These requirements have traditionally been satisfied through prospective patient registries or chart reviews, approaches requiring significant resources and time to enroll sufficient patients. As oncology therapies are increasingly approved through the FDA’s Breakthrough Therapy Designation Pathway, the number and scope of resource intensive post-marketing studies is growing. RWE derived from retrospective capture of high-quality data sources represents an alternative means of satisfying this regulatory requirement that is faster, cheaper, and more representative of real-world populations. A recent example of the increased regulatory role of post-marketing studies was the FDA’s Breakthrough Therapy Pathway designation and approval of osimertinib for second line or later EGFR T790M+ non-small cell lung cancer. Upon approval, the FDA requested that AstraZeneca provide overall response rate data from “one or more real-world cohorts of a minimum of 100 patients who have been selected for treatment on the basis of an EGFR T790M mutation positive result.” While the FDA has previously required post-marketing studies to assess effectiveness and safety in real-world populations, the approval of osimertinib is notable in that RWE is explicitly requested by name in order to maintain the label. A top ten oncology developer has gone a step further and adopted a portfolio-wide RWD approach using EHR data to track the effectiveness and safety of their on-market oncology products in near real time.

As regulators explore how to incorporate RWE into approval processes, the conditional approach taken with osimertinib may represent an emerging regulatory mechanism. For instance, regulators may increase the use of post-marketing requirements to address evidence gaps from traditional clinical trials as guidelines solidify the use of RWE in this setting. This approach would be of the greatest value in understanding therapy performance in populations typically excluded from clinical trials (e.g., mild chronic kidney disease, mild hepatic dysfunction, presence of brain metastases) where the risk-treatment benefit has not been studied.

Post-marketing studies are also critical in ex-US markets, and here too, RWE has been proven effective in addressing evidence gaps. For example, a European Health Technology Assessment authority recently requested data to evaluate the safety of a top five oncology therapy manufacturer’s new medication in patients with limited cardiac function. The patient population was excluded from the therapy’s registration trials, so a retrospective analysis of real-world patients was submitted to clarify the safety profile associated with the use of the therapy in this patient subset. This analysis informed the specific European country’s national regulations.

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coverage decision without the need for an additional costly trial. As the ability to generate high-quality RWE expands, providers will be able to understand the performance of therapies in specific population segments, allowing clinicians and governing bodies (e.g., guideline developers) to deliver more tailored therapy recommendations to patients.

**Indication expansion.** Oncology therapies approved for a specific indication are frequently used for the treatment of related malignancies. RWE provides a means of leveraging the series of natural experiments that occur as part of off-label use to clarify – and where possible, broaden – indications or guidelines for previously approved therapies. Using high-quality RWE to secure broader indications or coverage helps biopharmaceutical companies by reducing obligations for costly randomized controlled trials. In doing so, the impact and scope of biopharmaceutical companies’ development budgets is increased. Indication expansion has tangible benefits for patients who often depend on labels to ensure treatment coverage. Moreover, indication expansion via RWE also benefits providers by creating a richer evidence dossier that can inform clinical practice. The value of this benefit is demonstrated in Friends of Cancer Research’s recent efforts to promote label updates for generic therapies whose labels no longer fully reflect how a therapy is used in practice. In an example from a commercial setting, a top ten oncology drug developer recently submitted EHR-derived patient narratives – brief summaries of specific events experienced by patients during clinical trials – to support an indication expansion for a rare biomarker defined population. Aside from small populations, RWE can inform treatment in populations historically excluded from randomized controlled trials, including elderly patients and those with comorbidities.

**Market access and reimbursement.** In the face of increasing therapy costs, payors are increasingly asking for evidence of clinical value before providing coverage. These pressures are more prominent in oncology, where multiple high-cost agents with similar mechanisms of action compete for market share. For example, the PD-(L)1 inhibitor class includes five on-market therapies and several under development. RWE provides a means for demonstration of value, ranging from confirming randomized trial benefits in real-world populations to a fuller characterization of resource impact. In the case of PD-(L)1s, RWE may be utilized as a means of differentiation. More recently, RWE has been used to facilitate value-based and other novel contracting structures by providing a mutually agreed upon measurement methodology for biopharmaceutical companies and providers. Novartis’ decision to utilize an outcomes-based pricing contract with CMS for their CAR-T breakthrough Kymriah illustrates this emerging trend.

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Defining quality RWE

While RWE promises to unlock significant value across the drug development life cycle, realizing its potential hinges on the quality of the data underlying RWE analyses. This raises the question of how stakeholders should define high-quality RWE. Poor-quality data risks leading to incorrect conclusions through noise and/or potential bias. Clearly defining what data are considered sufficient, and for what purposes, is necessary to ensure confidence in RWE. Data used for hypothesis generation or internal development decision making purposes may not require the same quality standard as data directly informing patient, provider, payor, or regulator behavior.

Regulatory grade RWE, or evidence derived from data and analyses intended for review by regulators such as the FDA and the European Medicines Agency, or for national payor reviews (Health Technology Assessment authorities), must withstand the highest level of scrutiny (i.e., potential review by the FDA Office of Scientific Investigations). Regulatory guidance regarding the specific aspects of high-quality data and analytics is still in development. In the absence of official guidance, principles suggested by others – traceable/auditable, complete, transparent, generalizable, timely, and scalable13 – provide a good starting point. Ideally, such standards will be developed in a collaboration between biopharmaceutical companies, regulators, and RWE data providers. FDA demonstration projects with RWE providers such as ASCO’s CancerLinQ and Flatiron Health, and industry roundtables through the Duke-Margolis Center for Health Policy Research RWE Collaborative represent ongoing efforts in this space.14 The FDA is accepting RWE as part of regulatory submissions prior to official guidance to, in part, inform such future guidance. Poor-quality RWE – reflecting data or analytic shortfalls – poses the greatest risk to its broader adoption. A thoughtful collaboration between relevant stakeholders can help define what best practices look like in the development and use of RWE.

Realizing the potential of RWE

Biopharmaceutical companies that have successfully leveraged the potential of RWE have done so by coupling high-value use cases with an operating model that enables large-scale impact. In leading organizations, RWE is championed by an RWE group with a broader mandate than traditional health economics and outcomes research (HEOR) groups. These RWE groups exist within a next-generation clinical development model that positions RWE as central to a broader evidence generation strategy, ensuring its integration throughout a product’s development and life cycle, and not simply geared toward satisfying a health technology assessment. Proactive RWE groups seek out “best-of-breed” data partnerships that go beyond the limitations of commercially available data. These range from traditional partnerships with academic medical centers to more oncology-specific data curated by dedicated RWE groups. In short, these organizations have moved away from the legacy HEOR model to drive RWE on a large scale across many of the use cases described above.

As RWE opportunities continue to expand and play a greater role in drug approvals, these biopharmaceutical companies will be best positioned to reap the benefits from RWE.

**Conclusion: RWE and a new drug development paradigm**

RWE, appropriately utilized, has the potential to dramatically improve drug development, inform clinical practice, and clarify the value of new therapies. With its rapid pace of drug discovery and clinical development, oncology will, by necessity, be at the forefront of how RWE impacts drug development. Early adopters recognize this and are positioning a comprehensive RWE capability as a central component of their drug development infrastructure, investing in robust real-world data and analytic capabilities. Biopharmaceutical companies that are slow to implement comprehensive RWE capabilities risk finding themselves significantly disadvantaged in an increasingly competitive therapeutic space, unable to benefit from the new drug development paradigm. By acting decisively and collaborating with relevant stakeholders, biopharmaceutical companies can actively shape the role of RWE in oncology drug development, accelerating the next generation of innovative therapies.