



# The Importance of Real-World Evidence Generation in Oncology

## Applications of Retrospective Chart Review Methodology

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### Background

The burden of cancer remains high, with an estimated worldwide incidence of 14.1 million new cases and 8.2 million deaths in 2012.<sup>1</sup> By 2025, the predicted global cancer burden is expected to exceed 20 million new cancer cases annually.<sup>2</sup> As technologies for early cancer detection improve, and effective and novel treatments emerge (e.g., immunotherapy, targeted therapy), progression-free survival rates and durations are anticipated to improve.<sup>3</sup> Though the number of cancer survivors will increase, these important advances in cancer care will continue to place significant economic burden on healthcare systems. The generation of real-world evidence that reflects the complexity of usual care patterns of oncology care, as well as clinical and economic outcomes, is foundational to successful market access and value demonstration.

While clinical trials are designed to demonstrate efficacy and safety under experimental and controlled circumstances,<sup>4</sup> payers and regulators require marketing authorization holders to undertake non-interventional

observational studies to generate evidence of burden of illness, treatment patterns, drug effectiveness, cost, and safety in usual care practice to demonstrate effectiveness, safety, and value *in the real-world setting*.

If in the context of a robust real-world data strategy,<sup>5</sup> it is determined that suitable secondary data, such as administrative/claims databases and electronic health records, are not available to fulfill evidence needs, a retrospective chart review methodology is a viable alternative solution as either a sole source of evidence or to resolve specific data gaps. Though more complex to operationalize than database studies, chart studies can be employed to build fit-for-purpose, patient-level databases that can be harvested to support a broad array of research objectives and questions. Retrospective chart review studies, like database studies, allow for the collection of naturalistic data free of the Hawthorne effect — the phenomenon whereby study subjects (in this case, healthcare professionals) inadvertently modify their behavior as a result of their awareness of being observed.

## Chart Review Studies in Oncology Why so Common Given the Availability of “Big” Healthcare Data?

Although some oncology-focused databases exist in the United States to facilitate real-world evidence (RWE) generation, existing databases in Europe are more frequently administrative in nature, and only a few (e.g., CPRD<sup>A</sup> in the United Kingdom and SIDIAP<sup>B</sup> in Spain) are linked to electronic medical records.<sup>6</sup> Such **databases typically lack two key components necessary for robust and fit-for-purpose oncology RWE generation: 1) clinical indicators** such as stage of disease, histology, or performance status; and, **2) hospital drug administration information** inclusive of treatment type, duration, and/or sequencing. These data are important when researchers characterize the patient population and try to understand why certain treatments were administered, whether specific populations may have better treatment outcomes, or why some patients had better or worse overall survival. Most oncology treatments are administered in hospitals, and the diagnosis-related group (DRG) systems used in hospitals do not allow for the identification of these treatments, even though they are essential data elements when research objectives include the evaluation of treatment patterns. Chart review studies permit the collection of a full range of patient-level data pertaining to cancer treatments; obtaining this data can allow an understanding of treatment sequencing, types of regimens being used, treatment duration, reasons for discontinuation, and treatment response.

### Timing Is Everything

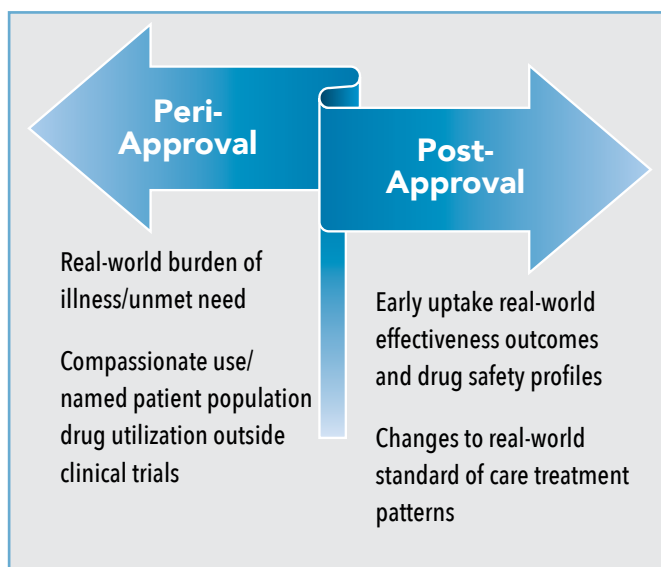
Prior to market launch, chart review studies can be used to generate RWE related to the burden of disease, and can effectively highlight important areas of unmet need in standard practice. Understanding contemporary treatment patterns, such as the sequencing of therapies in usual care, can illuminate where in a treatment pathway a new product can be most impactful. A detailed delineation of real-world resource utilization is a foundation for estimating direct costs of care, which can then be used for input into health economic evaluations and market access submissions.

Peri-approval, compassionate use (or named patient programs), which provide access to medications for

<sup>A</sup> The Clinical Practice Research Datalink (CPRD) is a governmental, non-profit research service that provides anonymized primary care records for public health research.

<sup>B</sup> The Information System for the Improvement of Research in Primary Care (SIDIAP) generates research databases from computerized medical records of the primary health care setting within the Catalan Institute of Health.

Figure 1. Peri- and Post- Approval Chart Review Study Real-World Evidence Generation



patients with no other treatment options, can also provide a rich source of data on treatment effectiveness and safety of investigational products outside the clinical trial setting. Retrospective chart reviews in these patient populations may inform hypotheses related to their future real-world use and associated outcomes.<sup>7-10</sup>

Post-market approval, chart review studies can also be used to better understand emerging patterns of early drug uptake before available databases can compile and release their data. For example, if trial data are released only annually for commercial use, existing databases will experience a delay in providing that newer data. Chart review studies can be used to generate interim data that may improve the quality and extent of analyses when more data are ultimately available over time. For example, early data can also be fundamental for the characterization of patients considered “warehouse” patients — those patients for whom the standard of care treatment has not been effective and who await novel therapies.

### Real-World Patient Characteristics, Health Outcomes, Treatment Pathways, and Costs of Care Data are Foundational for Successful Market Access

Patients can be characterized by chart data in terms of demographics, disease characteristics, medical history, and treatment history, at different points in time such as at first-ever diagnosis, diagnosis of advanced/metastatic disease, and initiation of first and subsequent lines of therapy. Typical core study variables collected to

characterize patients include, but are not limited to, the following:

- Demographics: age, sex, race/ethnicity, height, weight
- Disease characteristics: primary tumor type and location, histology, stage, mutation status
- Medical history: family and personal history of cancer, comorbidities
- Treatment history: adjuvant/neo-adjuvant therapy, diagnostics, surgical removal of primary tumor, radiotherapy

Chart review studies can effectively evaluate and document the therapy sequences and regimen combinations being used in the usual care environment. Treatment patterns can be described for oncology patients who receive treatment and/or supportive care at different stages of disease. Chart data can help researchers understand which regimen types are being used in the neo-adjuvant/adjuvant setting, including time from diagnosis to initiation, duration of therapy, types of agents, reasons for discontinuation, and dosing. The delineation of lines of therapy can be challenging to decipher from a database, but indication(s) of changes in therapy and therapy line sequencing can be gleaned more easily from chart data. The use of radiation in combination with systemic therapy and/or between regimens, as well as information on surgical procedures, can be identified by reviewing the chart notes

Health outcomes and their associations with oncology treatments may also be determined from medical chart data. For example, while Response Evaluation Criteria In Solid Tumors (RECIST)<sup>c</sup> criteria are not generally followed outside of clinical trials, healthcare professionals do frequently assess disease status and treatment response

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<sup>c</sup> Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

<sup>d</sup> Eastern Cooperative Oncology Group (ECOG) Performance Status are scales and criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

<sup>e</sup> The Karnofsky Performance Scale Index is an assessment tool for functional impairment. It can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients.

<sup>f</sup> Common Terminology Criteria for Adverse Events (CTCAE) is a standard classification and severity grading scale for adverse events in cancer therapy clinical trials and other oncology settings, from the National Cancer Institute.

(complete or partial response, stable or progressive disease) by combining imaging and clinical judgment and documenting those results in patient medical charts, thus allowing the estimation of progression-free survival (PFS) or best overall response (OR). PFS can be measured from initiation of a treatment line to the earliest date of disease progression or death; best OR can be measured using the best documented response from initiation of treatment line until the initiation of any other regimens.

Performance status (Eastern Cooperative Oncology Group [ECOG]<sup>d</sup> and/or Karnofsky scales<sup>e</sup>) can be ascertained at diagnosis, at treatment initiation, and throughout treatment. Death status can be obtained to estimate overall survival, which can be measured from initiation of a treatment line to date of death.

Safety profiles for different usual care regimens can be evaluated by collecting data which may include: type of event, dates of onset/resolution, seriousness, severity (CTCAE criteria<sup>f</sup>), outcome of event, action taken with treatment (treatment modification/discontinuation), and documented relationship to treatment.

Detailed information pertaining to healthcare professional visits, emergency room visits, inpatient hospitalizations, surgical and non-surgical procedures, transfusions/infusions, and laboratory tests related or unrelated to oncology care can all be collected throughout the cancer care trajectory to estimate direct costs of care via post-hoc application of unit costs and analysis.

## Key Design Considerations

### Patient Identification

Despite protocol-driven selection criteria, the *process* by which sites can logistically identify and select a patient cohort from medical records will differ markedly. Understanding variations in medical chart access, storage, and retrieval infrastructure across study sites will facilitate the development of a flexible yet systematic and robust patient sampling frame. Sites may find it difficult to identify patients with advanced/metastatic disease who had an initial diagnosis of early stage cancer compared to patients with their initial diagnosis being advanced/metastatic disease. Ensuring clear procedures for the identification of either or both of these groups (where applicable) will reduce the risk of selection bias.

### Core Protocol and Case Report Form in Support of Multi-national Patient-level Data Repositories

In the context of strategic multi-national evidence generation, a common core protocol and core minimum dataset are essential to ultimately achieve a standardized database structure as well as a robust repository of

real-world evidence that can be pooled or compared across countries as appropriate.

## Key Operational Considerations

### Ethical Requirements and Data Protection

Ethics requirements differ by country and are constantly changing. It is important to consult with a regulatory expert knowledgeable about the ethics and regulatory requirements landscape for each country, region, and site included in the study to determine the requirements for ethics committee dossier submission. The sequencing of submissions and/or notifications to ethics committees and other health authorities may sometimes occur sequentially vs. concurrently; this will affect start-up and data collection timelines. National or regional ethics committees, for example, in European countries, review dossiers on their own schedules, which may be more or less frequent than other countries in the study. These variations in timing will affect when a study protocol may receive approval and ultimately study initiation.

It is also critical to ensure that all versions of a dossier, the master and all subsequent versions, are prepared in accordance with retrospective chart review regulations. The regulatory expert must be knowledgeable about retrospective data collection and the processes by which chart review studies are conducted, to ensure clear communications with the ethics committee and regulatory authorities. For example, these experts must convey that no personal health information (PHI) will be collected during the chart review study.

Data protection is critically important in these studies, so only de-identified data, void of PHI, is collected. If assurance of data privacy can be shown to an ethics committee, frequently a waiver of informed consent can be obtained. This is ideal as the data collection process remains unbiased (e.g., data for subjects who refuse consent or are deceased does not have to be excluded), and ensures more generalizable data inclusive of the patient sampling criteria. Recently, however, certain European countries' ethics committees have been requiring informed consent for any patient alive at the time the chart abstraction begins. To note, due to the strong and supportive relationships oncology practices have with their patients, the consent rate we have observed is typically  $\geq 95\%$  for these studies.

### Site Engagement

When collecting data in chart review studies, we rely on the site staff (e.g., investigator, study coordinator/nurse) to participate in study start-up activities – training, patient identification, data collection, and query

resolution. Utilizing site staff is ideal; they are employed by or under contract with the study sites and therefore have signed confidentiality agreements to keep patient privacy, they are usually experts in oncology, have relationships with the patients, and understand medical chart documentation. However, site staff do tend to have multiple and competing priorities from regular patient care to other studies/trials, making their time rather limited. It is important to ensure the aims of the study are clear, the data collection effort is streamlined, and the benefits to the site staff and their future patients are clear. Payment to study sites must also follow fair market values and compensate for their direct efforts needed to complete the study (as required by the Anti-Kickback Statute developed by the U.S. Department of Health & Human Services Office of Inspector General and the European Federation of Pharmaceutical Industries and Associations 2014 Code) by estimating total time for training, identifying patient populations, screening charts for enrollment, abstracting data, and responding to queries.

## Summary

Retrospective chart review studies are effective methodologies to generate robust patient-level repositories of data to facilitate overall and country-specific analyses as stand-alone studies, or as inputs into economic models/value dossiers. Chart review studies can support many client objectives and data needs.

Peri-approval, chart review studies can inform contemporary treatment patterns, healthcare resource utilization, and costs of care, thereby characterizing the burden of illness and/or unmet need.

Chart review studies in compassionate use/named patient program populations allow an early look at treatment effectiveness and clinical and safety outcomes outside trial settings, thereby informing future potential real-world use.

Post-market approval, chart review studies can be used to continue to generate evidence of a product's effectiveness and value.

Like database studies, chart reviews are not without their limitations, including issues with missing and/or poor quality data, representativeness, and generalizability. However, understanding the potential pitfalls of chart review studies and how best to employ them as part of a broader real-world evidence strategy<sup>5</sup> can contribute significantly to market access success.

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