



Early Access Programs Opportunities and Challenges for Real-World Data Collection

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What are Early Access Programs?

For patients with serious or life-threatening diseases who have exhausted all treatment options and who are not eligible for trial participation, early access programs can provide them with investigational treatments (pre-launch and/or prior to country approval).¹⁻³ Definitions and nomenclature of early access programs vary by country and many pathways exist for patients to gain early access to medicines. Each pathway is governed by different regulatory bodies; therefore, several guidelines exist around the approval, set-up, conduct, and structure of these programs. Early access programs may be implemented at different stages of the product life cycle, including prior to, during, and after the regulatory submission process for market authorization (*Figure 1*).

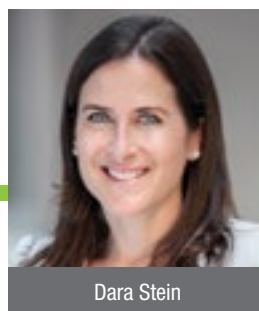
Since many countries have lengthy periods between initial marketing authorization and country approvals and reimbursement,^{1,4} the number of early access programs being initiated by pharmaceutical companies are increasing to bridge the treatment availability gap between clinical trials and market-uptake. Through early access programs, patients who have either already benefitted from clinical trial agents or patients who demonstrate unmet need can receive promising new treatments.

In addition to providing early access to treatment, these programs also offer a unique opportunity to evaluate clinical and safety outcomes outside of the clinical trial setting, without the constraints of strict inclusion and exclusion criteria. Data collected in these studies are viewed by some as proxies for real-world use because there is an opportunity to observe the potential benefits of an investigational treatment in a wider range of populations or for other indications.

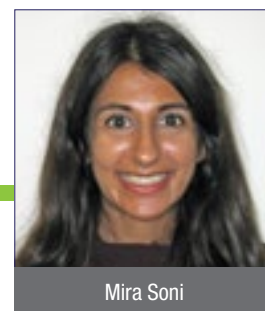
Data Collection within Early Access Programs

Guidelines for Data Collection Provided by Program Regulators

Data collection guidelines within early access programs tend to vary by country, and within the European Union (EU), they also vary by member state (*Table 1*). Across most types of early access programs, safety data collection is required, however, guidance on acceptable effectiveness data collection is limited.⁵ While the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) do not prohibit data collection beyond safety outcomes within their guidelines, they do state that data collected within these programs should not be a substitute for data collected in the trial setting.⁶⁻⁸

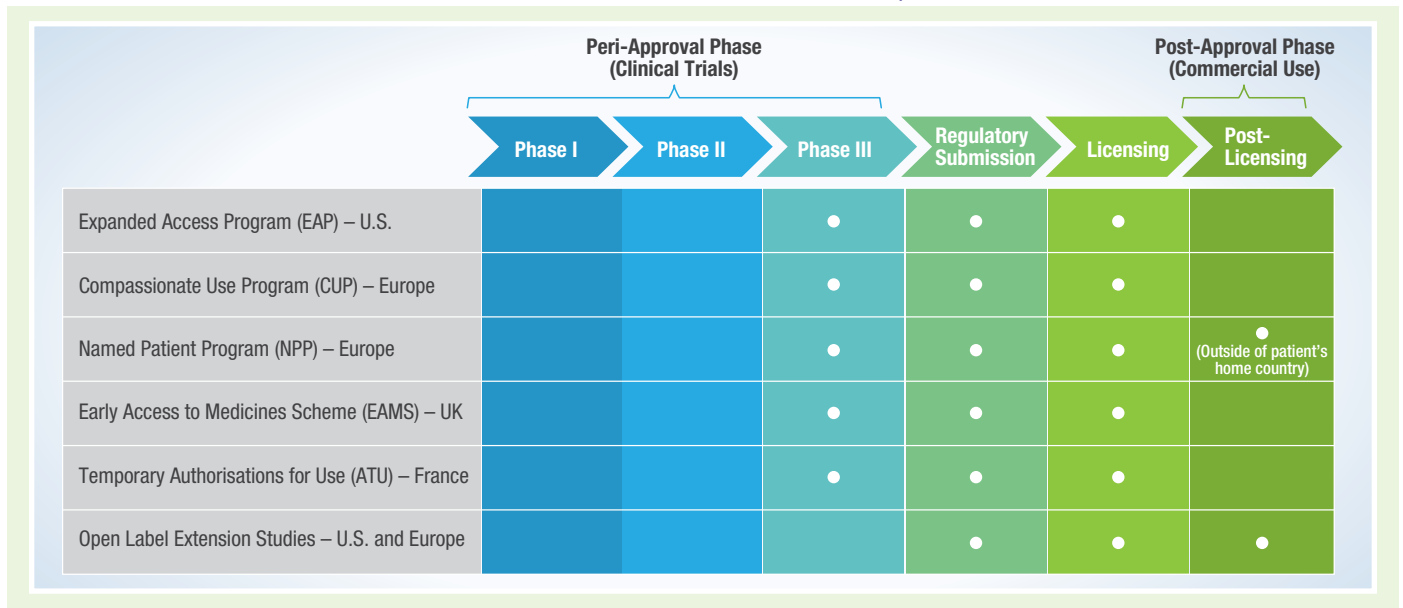


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Figure 1. Early Access Programs Throughout the Product Life Cycle (U.S. and Europe)



More recently, the Early Access to Medicines Scheme (EAMS) in the United Kingdom (UK), governed by the Medicines and Healthcare Products Regulatory Agency (MHRA), established in 2014, asserted the importance of collecting additional supporting real-world data to provide additional knowledge of product value outside of a clinical trial setting.⁹ The UK-based EAMS program is currently the only one of its kind to have issued guidelines for systematic collection of real-world data. The MHRA guidance highlights that data generated in EAMS can be used to facilitate National Institute for Clinical Excellence (NICE) Technology Appraisal. Additionally, these guidelines suggest that EAMS data collection must include, at a minimum, information on patient demographics,

disease characteristics, dose and duration of treatment, comorbidities, concomitant medications, adverse events, and other factors known to be strongly predictive of efficacy or other outcomes of importance. Requirements for additional data collection (e.g., quality of life) in EAMS must be agreed upon by all parties including clinicians and patients, on a case-by-case basis.¹⁰

Published Data from Early Access Programs

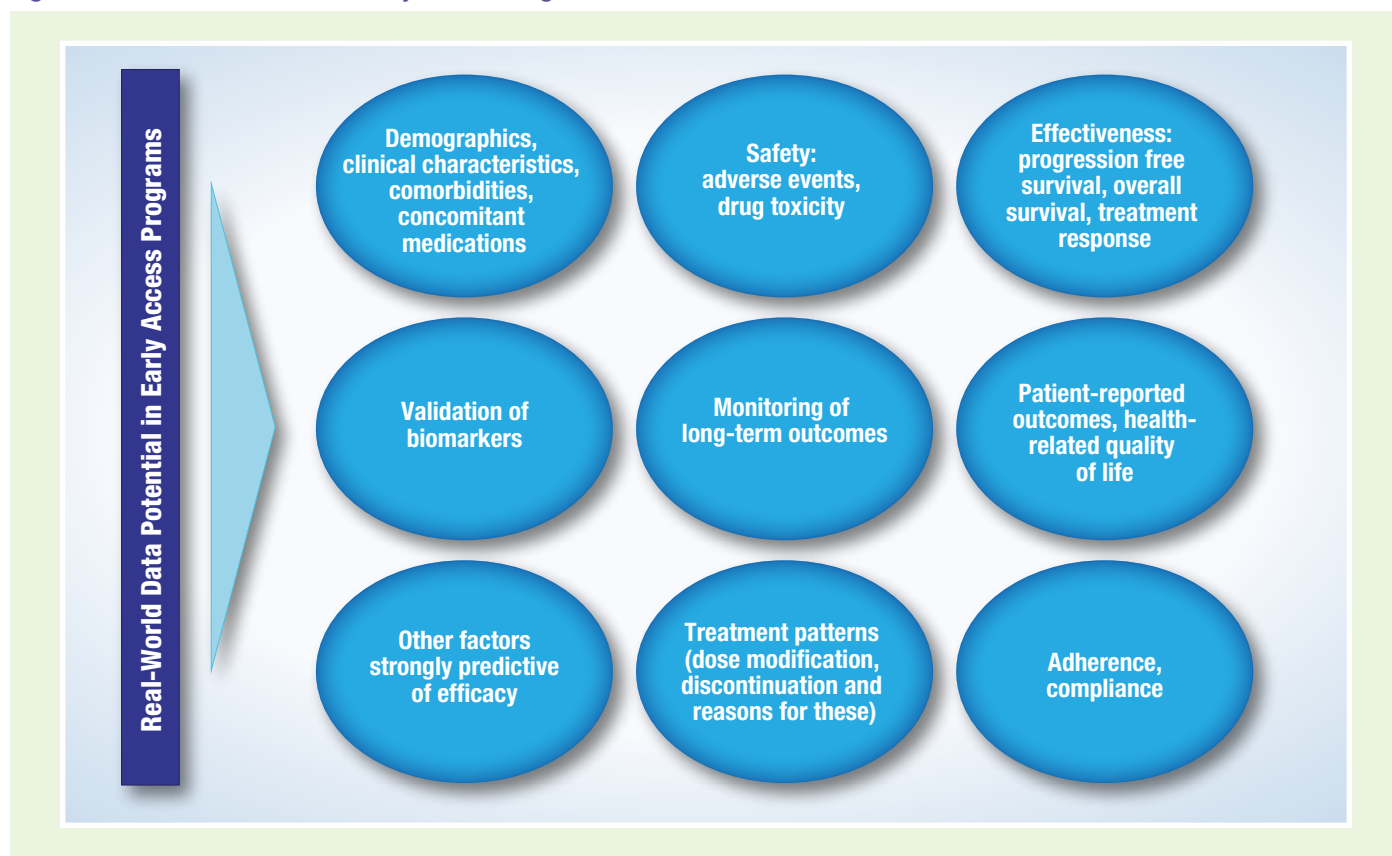
There is a breadth of published literature which summarizes the types of early access programs available and general overviews of these programs, including ethical considerations and operational challenges with set-up and conduct. To our knowledge, however, there is limited

Table 1. Data Collection Guidelines for Early Access Programs

	Expanded Access Program (EAP)	Compassionate Use Program (CUP) & Named Patient Program (NPP)	Temporary Authorisations for Use (ATU)	Early Access to Medicine Scheme (EAMS)
REGULATORY BODY	FDA	EMA/CHMP/EU Member States	ANSM	MHRA
DATA COLLECTION ↓				
Safety	✓ Required	✓ Depends on local requirement by member EU state	✓ Required	✓ Required and will be considered in regulatory submission
Effectiveness	✓ Allowed but not considered reliable evidence in regulatory submission	✓ Allowed but not considered reliable evidence in regulatory submission	• Patient characteristics and efficacy of medicinal product	✓ Allowed and will be considered in regulatory submission
Patient-Reported Outcomes (PROs)	• No clear guidelines	• No clear guidelines identified	• No clear guidelines identified	✓ Allowed subject to ethical approval. PROs will be considered in regulatory submission

ANSM=Agence Nationale de Sécurité du Médicament et des Produits de Santé; CHMP=Committee for Medicinal Products for Human Use; EMA=European Medicines Agency; EU=European Union; FDA=Food and Drug Administration; MHRA=Medicines and Healthcare Products Regulatory Agency; NHSE=National Health Service England; NICE=National Institute for Health and Care Excellence

Figure 2. Potential Outcomes in Early Access Programs²⁹



literature available which reports the findings of data collection within these programs. This is substantiated by a recent study (2017) which reported that only 2% (8/398) of early access programs registered in [ClinicalTrials.gov](https://www.clinicaltrials.gov) reported up-to-date results for real-world data (RWD)-related outcomes,¹¹ illustrating the need for more transparency in data collection. Reluctance to report data collected in early access programs may be due to concerns with reliability and validity of this data, as well as lack of information pertaining to the relevance and application of these data to marketing authorizations. Since patients in early access programs are likely to be sicker (due to lack of therapeutic options available), they may be at higher risk for adverse events and/or to having lack of clinical response, which may make sponsors hesitant to collect and report on outcomes in these patient populations.¹²

Although early access programs are not a substitute for data collection in clinical trials, they may be supplementary in addressing a variety of research questions...

In available publications of data collected in early access programs, some studies incorporated data collection from inception of the program,¹³⁻¹⁹ while others implemented data collection via retrospective chart review once the program was complete.²⁰⁻²⁶ In the majority of these studies,

data were used as supplements to clinical trial findings in a real-world setting. For example, retrospective chart review studies in oncology CUP and NPP patient populations demonstrated similar effectiveness and safety profiles relative to the trial patients.²¹⁻²⁴ A recent chart review study in the U.S. also found that lung cancer patients enrolled into a clinical access program after having benefited from an investigational drug within a prior trial were able to see clinical benefit from investigational drug use through the program for more than 10 years.²⁵⁻²⁶

A review study conducted in 2017 compared the efficacy endpoints for anti-cancer drugs observed in CUPs versus clinical trials (U.S. and Europe); efficacy endpoints included overall survival, progression-free survival, and overall response, and over half of CUPs (5/9) reported better or equal efficacy compared to that reported in clinical trials.²⁷

Research Questions in Early Access Programs

Although early access programs are not a substitute for data collection in clinical trials, they may be supplementary in addressing a variety of research questions, which could be informative for multiple stakeholders, including regulatory bodies, payers, clinicians, and patients. RWD collection in early access programs (Figure 2) has the potential to provide preliminary insight into:

- Whether the safety profile of the drug administered via early access program is similar to that observed in a trial setting and whether any new safety signals occur.²⁸

- Treatment effectiveness (e.g., treatment response, overall survival) outside of the trial setting, including in sub-populations not included in clinical trials (children, older adults, those with comorbidities).
- Knowledge of the impact of the drug on quality of life in the pre-approval or peri-approval phase. This is relevant given the increasing importance placed on these outcomes in the post-approval phase.

To increase the reliability and validity of observational data collected in early access programs, the primary research questions and feasibility of data collection should be explored prior to implementation of the program. Furthermore, limitations of this data (e.g., uncontrolled exposures, potentially sicker patient population), should also be considered in regulatory submissions for market approval.

Considerations and Recommendations for Set-Up of Observational Research in Early Access Programs

Ethical Approval (for the Observational Study Component of the Early Access Program)

Since early access programs are not considered traditional research studies, they follow different rules and regulations for obtaining ethical approval. Ethical approval processes will also vary by country (Figure 2).⁶⁻⁹ If additional data collection is needed within an early access program, a protocol outlining plans for data collection will most likely need to be submitted to an ethics committee following the same pathway that would be used for an observational study. This protocol should be submitted in parallel with seeking approval for the launch of the early access program. Due to the unique nature of data collection in early access programs, it is essential to identify a key stakeholder contact to discuss the data collection plans and seek feedback on the ethics review and approval process to identify any uncertainties or hurdles that may arise.

If the ethics committee reviewing the observational study application is not able to fully understand the nature of the early access program and the plans for data collection, this may negatively impact the outcome of the ethics submission. Furthermore, ethics approval is time sensitive based on when the early access program will open. If stakeholders are not approached in a timely manner, then there is a risk that ethics approval may not be put in place in time for the opening of the program, limiting the potential for data collection.

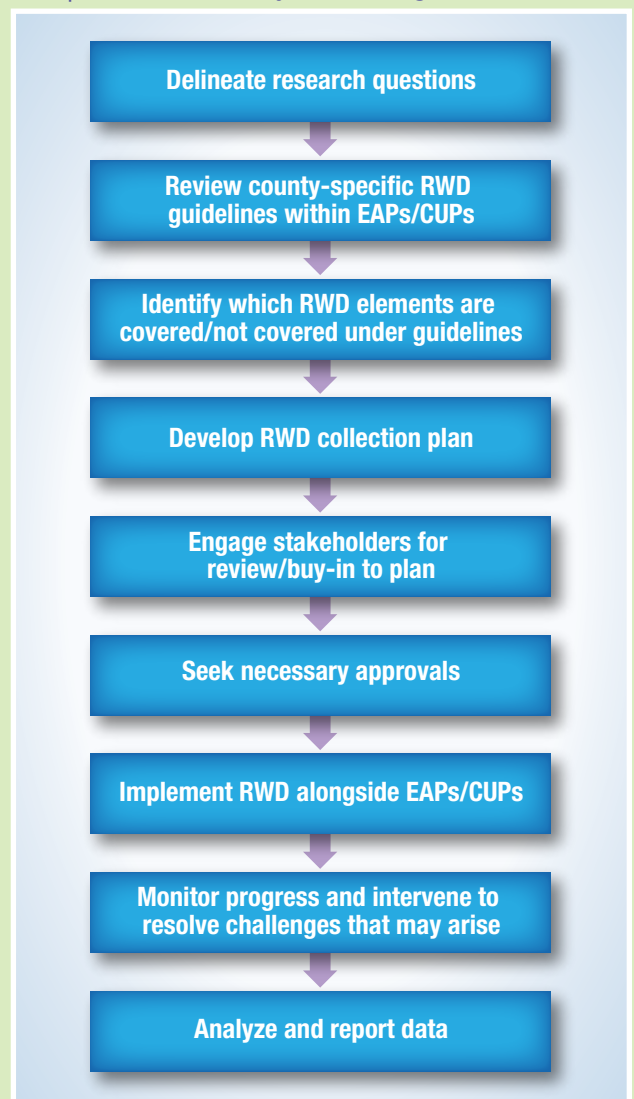
Patient Consent

Different options for how to obtain patient consent for the additional data collection should be explored based on what is most feasible for the study. The consent form should clearly define all aspects of the data collection, including privacy, data elements to be collected, data

Spotlight Case Study Incorporating Data Collection into Early Access Programs

To better understand the benefits of drug X in the pre-approval phase, Evidera recently collaborated with a pharmaceutical company to design and implement an early access program that integrated real-world clinical effectiveness and quality of life outcomes. During development of the data collection framework within this program, it was observed that published guidelines on the incorporation of data collection were lacking. Therefore, the process of framework development included the exploration and validation of the approach with key stakeholders (regulatory authorities, ethics, hospital systems). Figure 3 represents an overview of the steps taken, which led to successful approval and implementation of data collection within this early access program.

Figure 3. Recommended Steps to Successfully Incorporate RWD in Early Access Programs



source(s), timing of collection, and purpose of data collection (e.g., publication, HTA submission). It should be emphasized that the patient's ability to take part in the early access program overall is not contingent on whether or not they choose to take part in the observational research component of the program.

Data Collection Elements

It is important to determine which additional variables will be added to the study, what the data source will be, who will collect it, how it will be collected, and the timing for collection. Careful consideration for how the data will be used and challenges this may impose (that could negatively impact the program) is essential. Once the data elements are delineated, stakeholder feedback and approval from the regulatory authority that governs the early access program is needed. Secondary feedback and endorsement from clinician and hospital governing bodies is also recommended.

Site Set-Up and Training

Most often in early access programs, the request for drugs are patient/physician led, meaning that it is not possible to know in advance the hospitals or patients who will participate in these programs. This contrasts with observational studies wherein sites, patient population, and sample size are known prior to study initiation. This can add a complexity to setting up the RWD collection component of the study and may require special circumstance procedures for set-up of the study at the hospital and training of clinical staff.

In our experience, combining observational training with the early access program training was well received and efficient. In cases where set-up of the observational study

at a site cannot happen in parallel to initiation of the early access program, sites should be reassured that they can proceed as planned with the early access program and without the additional data collection. This is important for ensuring that data collection does not hinder the patient receiving early access to the investigational drug.

Site and Patient Involvement

The level of effort and workload needed to collect the data must be carefully considered. Data collection from patient medical records should be kept to a few key outcomes measures (e.g., disease progression, survival status). Having physicians enter observational data through the same data collection tool as that required for other aspects of the early access program may be able to reduce data entry burden at sites.

Summary

Data collection within early access programs allows for generation of RWD prior to and after marketing authorization in patient populations with unmet need. RWD generated in the pre-approval phase could be used to supplement primary clinical trial outcomes in submissions for market approval and is useful for informing future real-world use. Additional guidance by regulatory bodies on how to enable and ensure consistency in data collection in early access programs is needed to improve validity of this research for regulatory submission. Data collection approaches must be scientifically robust, practical, and ethical. As the number of early access programs and the use of RWD to inform market access continues to grow, so will the benefits of collecting RWD in these programs. ■

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