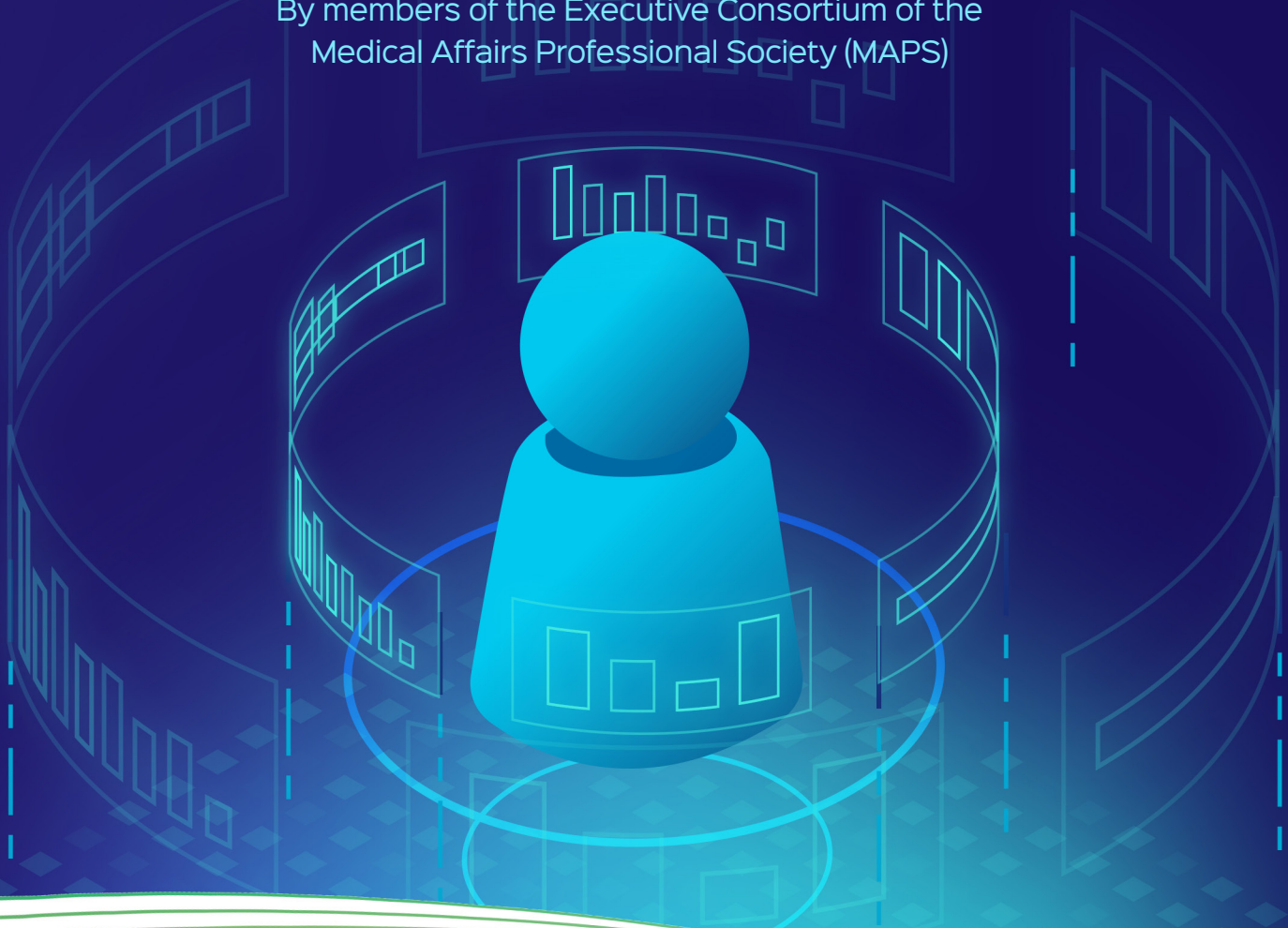
MAPS
FOR Medical Affairs Professionals
BY Medical Affairs Professionals

Medical™ Affairs Professional Society

How the use of non-Registrational Evidence by Medical Affairs Improves Patient Outcomes

By members of the Executive Consortium of the
Medical Affairs Professional Society (MAPS)



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INTRODUCTION

In the biopharmaceutical industry, the organization's Research and Development (R&D) function manages a program including Phase 1-3 clinical trials that leads to regulatory approval. Concurrently and continuing after approval, Medical Affairs manages a program to answer questions not addressed in the regulatory filing, but that remain essential in helping healthcare providers and others within the healthcare ecosystem optimize patient benefit[1]. Will the drug work in patient populations beyond the narrowly defined clinical trial inclusion criteria? What about in patients with comorbidities? Or those taking other medications? How could an understanding of the natural history of a disease improve care paths and disease management? How do factors such as burden of disease and quality of life impact the decisions of payors and Health Technology Assessment (HTA) bodies, and what are the impacts on Healthcare Resource Utilization (HCRU)?

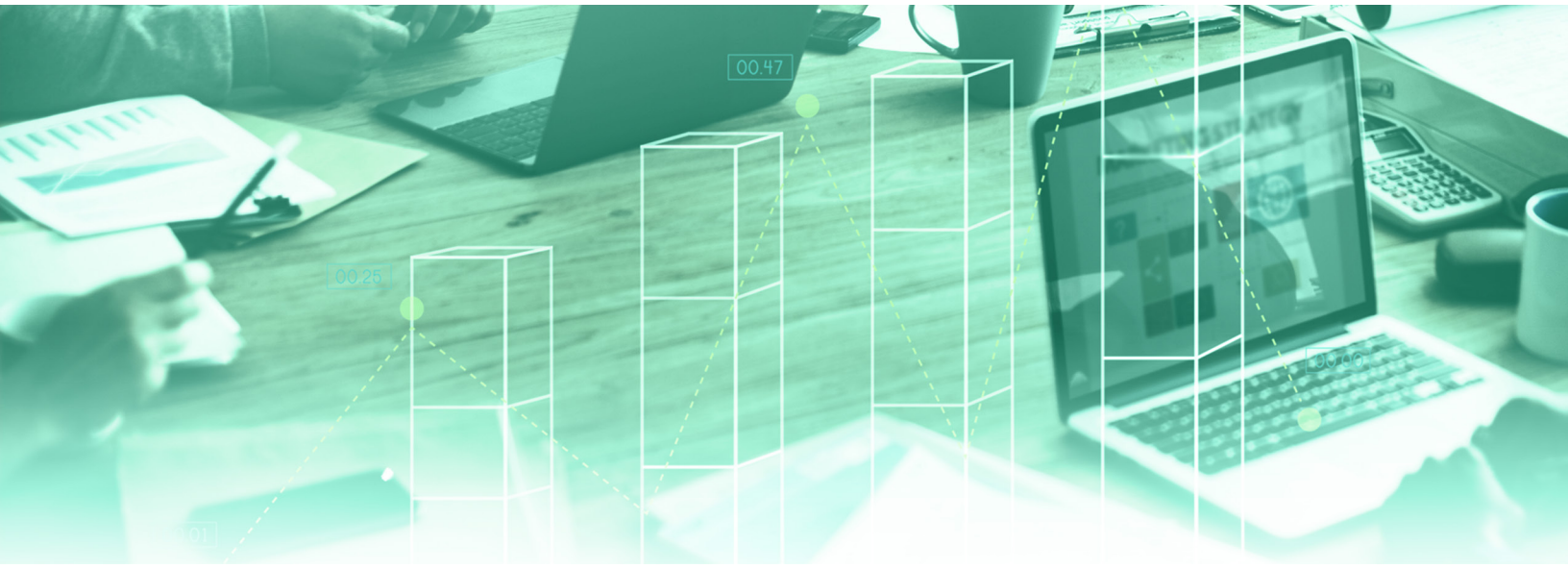
Answering these questions requires identifying/generating and interpreting non-Registrational Evidence (nRE)[2]. Very basically, the goal of nRE is to provide a framework for understanding how a drug functions in patient populations and real-world situations beyond those addressed in the regulatory filing. Along with the evidence from clinical development, nRE is included in the organization's cross-functional Integrated Evidence Plan (IEP).

This paper discusses the sources, uses and benefits to the organization, to society and to patients of nRE, and describes why Medical Affairs – as the bridge between the organization and external stakeholders – is uniquely positioned to lead and own the strategic plan for the generation and use of nRE.

DEFINITION OF NON-REGISTRATIONAL EVIDENCE (NRE)

Evidence Generation describes activities that generate the panoply of data that supports the optimal use of a product over its lifecycle. Certain aspects of that evidence are required for registration. Other aspects, while not required for registration, meet critical needs of healthcare external stakeholders. This is non-Registrational Evidence (nRE)[4].

Prescribers, patients, HTAs, patient advocacy groups and more groups within the ecosystem of external stakeholders all have informational and evidence needs that are not fully served by a drug's regulatory package – and it is the role of Medical Affairs to meet these needs with nRE. Traditionally, nRE referred to data generated by Medical Affairs through interventional Phase 4 studies; however, the definition of nRE has expanded to include Real-World Evidence (RWE) of the sort generated by observational studies using primary data collection or secondary data. Today, nRE is perhaps better understood not as a type of study or data, but by its purpose: The purpose of nRE is to answer the unmet scientific and clinical questions of external stakeholders regarding the real-world use of a medicine, diagnostic or device.



THE VALUE OF NRE

Medical Affairs uses nRE to generate the scientific body of evidence that supports the strategic goal of improving patient outcomes. When included as an essential element of the Integrated Evidence Plan, nRE contributes to a holistic view of evidence needs and priorities across stakeholders rather than the fragmented view of evidence by function, helping to determine in a more focused way the product value and differentiation. Whereas, registrational evidence answers the questions of efficacy and safety needed to bring a drug to market, nRE is used to answer the myriad questions that still remain. And just as it is valuable to know a treatment's effectiveness in a clinical trial population, it is also valuable to know a treatment's effects beyond this population. The following describes the value of nRE to various stakeholder groups.

The Value of nRE to Patients

With the changing portfolio towards more specialized treatments, fewer patients may be exposed to treatments in the pre-approval regulatory phase, requiring further evidence generation post-approval to truly understand the effectiveness and safety of treatments and meet the needs of external decision-makers[5]. This is especially true of treatments targeting rare diseases, for which registrational trials may include only a few dozen patients. Likewise, protocols for registrational trials often restrict participation to patients with narrowly defined criteria for age, comorbidities, and disease/treatment histories. This "clean" group of patients may be required to reduce bias in the clinical trial data that could otherwise obscure the signal of an investigational agent. However, once a drug obtains approval and becomes available to a much broader patient population, it can be unclear which patients with characteristics that would have excluded them from clinical trial participation will benefit. Is it safe to use a new neurology drug in patients who have diabetes? Can it be used in young people or the elderly? What is the risk of interactions with other medications? Will it work outside the careful treatment compliance monitoring of a clinical trial? Will patients be motivated to stay on treatment in the real world, beyond a strictly regulated and monitored clinical trial? Medical Affairs' use of nRE to answer these questions can help patients access and continue the best treatments for their conditions.

The Value of nRE to Physicians

For physicians, answering these questions of safety and efficacy in real-world patient populations is essential in optimizing the use of emerging treatments. For one example of many, take the case of oncology, in which a registrational trial may demonstrate the safety and efficacy of a new medicine against a genetic target – a common question is whether the same medication will work against cancers that share the same genetic driver but that occur elsewhere in the body than those studied during registrational trials. When an external stakeholder such as a physician reaches out to the organization to ask about emerging uses of new medicines in related populations or conditions, Medical Affairs may be positioned to provide nRE that offers context and rationale for treatment decisions. Answering these questions of related use may also influence the treatment paradigms issued by scientific societies. In other words, nRE may be able to efficiently offer guidance for healthcare providers seeking the best treatments for their patients, regardless of whether these patients would have been eligible for the treatment's registrational trial.

The Value of nRE to the Organization

While Medical Affairs' actions remain driven by and focused on the needs of external stakeholders, generating nRE may also have cross-functional value to internal stakeholders. For example, Medical Affairs may work with patient advocacy groups to explore outcomes of interest that become the basis for new regulatory programs, or may work with datasets to help to define the burden of disease globally, regionally or locally that can help prioritize R&D studies. Then as a drug progresses toward a phase 2 investment decision, Medical Affairs can help to decide which questions become part of the regulatory package and which questions are explored in parallel through nRE studies. In this model, as R&D moves toward approval, Medical Affairs works alongside to build the surrounding framework of a product's scientific narrative. After launch, nRE can be used to validate the results from registration trials as per the U.S. Food and Drug Administration's RCT-DUPLICATE initiative[7]. Likewise, these nRE activities may guide future R&D activities also enrich a drug's scientific brand in way that may be useful for the Commercial function.

The Value of nRE to HTAs and Payors

Increasingly, nRE informs the decisions and actions of payors and HTA bodies. For example, nRE generated by Health Economics and Outcomes Research (HEOR) teams (which often but not always sit in Medical Affairs) may offer context for health systems seeking to optimize the use of new compounds in a decision landscape that includes cost, clinical burden, quality of life, caregiver impact, and other considerations not addressed by the regulatory filing.

The strategic role of Medical Affairs as the owner of nRE within the Integrated Evidence Plan
Medical Affairs is uniquely positioned as a two-way bridge of information leading from external stakeholders to the organization and also from the organization back out into the world. This dual internal/external perspective offers the opportunity for Medical Affairs to play an important strategic role within the organization. First, as previously described, Medical Affairs can identify external stakeholder knowledge gaps. Then in collaboration with cross-functional colleagues, Medical Affairs can ask and answer strategic questions such as "Why are we embarking on these projects and what are the needs we are filling?" and "How will answering this question benefit patients?" Importantly, Medical Affairs is also in a position to interpret and contextualize the results for the different key stakeholders. When the feasibility and outcome-based impact of nRE studies justifies their completion, they are included in the Integrated Evidence Plan.

This strategic approach requires the nRE plan led by Medical Affairs to be included alongside the Clinical Development Plan led by R&D in the cross-functional Integrated Evidence Plan (figure 3). Structurally, this means the Medical Affairs lead, Commercial lead, Market Access lead, Development lead, lead of Clinical Development, Communications lead and Regional leads to sit together on a committee designing the Integrated Evidence Plan. Just as the Development lead proposes the Clinical Development Plan and integrates the input of cross-functional colleagues, the Medical lead proposes and collaboratively designs the non-Registrational Evidence Plan.

The participation of Medical Affairs in a strategic role ensures the development of a product's scientific brand occurs in partnership with development of its commercial brand and that evidence supports the science behind the product.

COMMUNICATING THE NON-REGISTRATIONAL EVIDENCE PLAN

The external communication of data including nRE is at the end of the nRE value chain and has always been a staple duty of Medical Affairs (now with increasing use of many outlets included in the developing understanding of omni-channel engagement). However, for many Medical Affairs teams, it is not the external communication that is challenging, but communicating the impact of nRE activities to internal stakeholders, which is a prerequisite to evidence generation activities. One key to create internal alignment with the nRE Plan developed by a cross-functional team is to communicate nRE activities with the impact and outcomes in mind. The scientific perspective of Medical Affairs may lead teams to communicate nRE studies in terms of the study mechanics (the "what"), whereas internal stakeholders may conceptualize the need for nRE more from the perspective of outcomes (the "why"). When messaging nRE internally, consider why the study is needed and how data will be used to forward the organization's strategic objectives. In other words, when communicating the value of nRE and the nRE Plan, it is important to ask and answer, If you do the study, what is the value? Will it result in updated treatment paradigms, or HCPs making better decisions, or patients appreciating there is finally data for rare groups? Internal alignment is another reason why the nRE Plan should be designed in a cross-functional team rather than by Medical only, so that buy-in is likewise cross-functional and anticipated impact is embraced from the start.

GENERATING NRE

Medical Affairs approaches evidence generation from an external perspective, though often with implications for internal strategy/actions. Broadly speaking, this requires identifying knowledge gaps and then generating the evidence needed to fill those gaps with the following two steps: 1) Identifying the questions to be answered; and 2) undertaking activities to answer them.

Identifying Questions

Medical Affairs responds to the scientific and clinical informational needs of external stakeholders. Thus, it is external stakeholders who generate information needs that may eventually become research questions answered by nRE. Questions may come from healthcare providers through the Medical Science Liaison or Medical Information functions; or questions may come from advisory boards, patient advocacy groups, HTAs, congresses, and, increasingly, from patients themselves.

It is the purpose of a cross-functional team led by Medical Affairs to choose questions to answer based on the significance and clinical impact of the knowledge gap. In alignment with Development and Commercial functions, the Medical-led nRE Plan included in the Integrated Evidence Plan prioritizes nRE studies from the perspective of outcomes – asking not only if a nRE study could be performed to fill a knowledge gap, but what the benefit to patients of filling this gap would be.

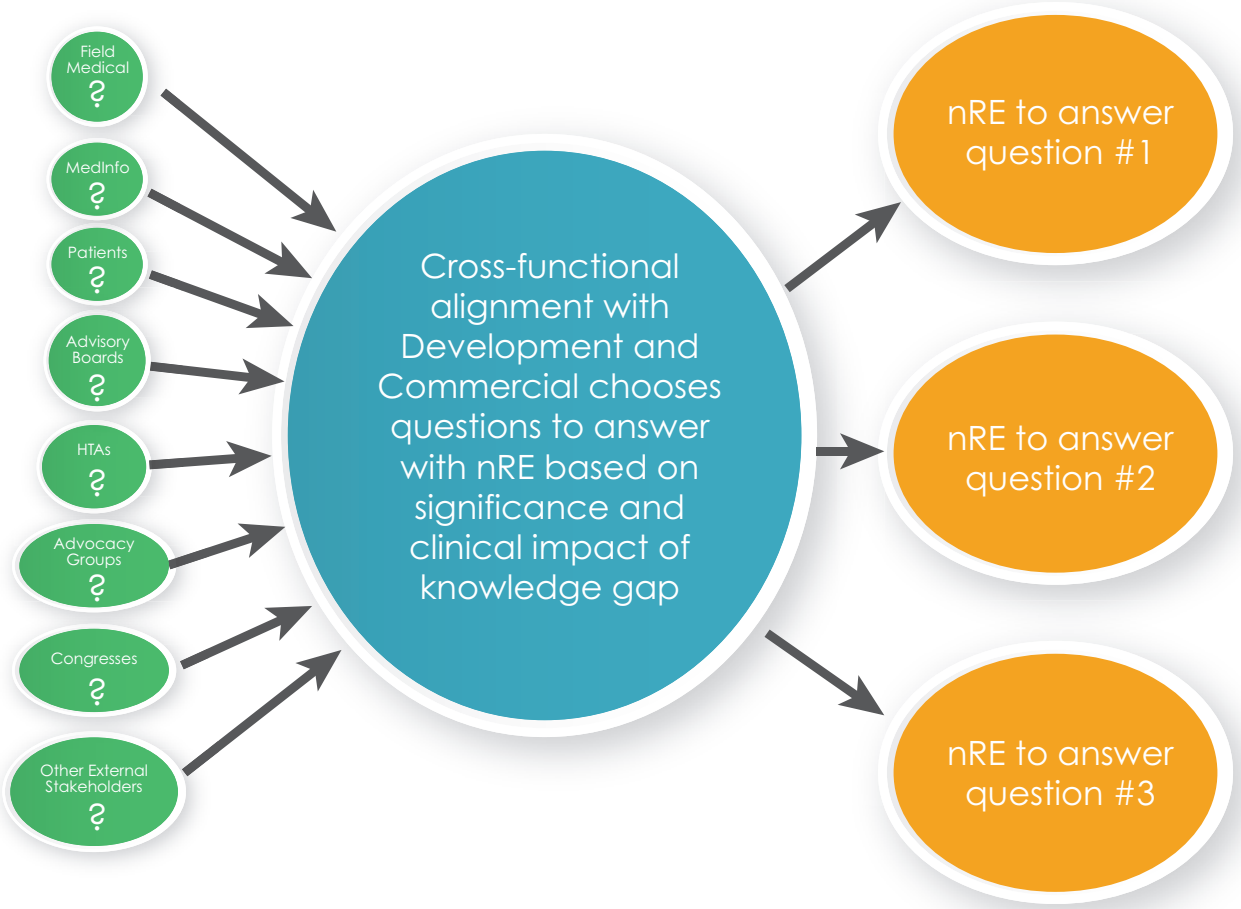


Figure 1. Identifying the External Stakeholder Questions to Answer with nRE

Answering Questions

Traditionally, R&D would pass the "baton" of evidence generation to Medical Affairs at the time of approval, with R&D using clinical trials to reach approval and Medical Affairs using a variety of nRE strategies to meet the information needs of external stakeholders after approval[5]. Now, the strategic use of nRE has expanded to include many types of activities to answer questions across the development cycle[6]. For example, in addition to performing new studies to generate nRE, Medical Affairs may be able to create knowledge from existing sources, such as by post-hoc analyses of registrational trial data or patient/disease registries, or through meta-analysis of previously performed studies (figure 2).

Just as Medical Affairs is instrumental in identifying knowledge gaps and deciding which questions to answer based on clinical relevance, the function is essential in designing nRE studies to answer these questions. In part, this is due to the scientific expertise of the Medical Affairs function; and in part this is due to the ability of Medical Affairs to collaborate on evidence generation activities with external scientific experts. For example, Medical Affairs may be able to leverage relationships with independent investigators or collaborate with experts in patient organizations, who not only have access to data but also provide expertise and guidance on study design from the perspective of real-world patient outcomes.

Finally, when it comes to execution of evidence generation, Medical Affairs may utilize various resources, including outsourcing the project fully or partly to a contract research organization (CRO), outsourcing to an internal organization such as Clinical Operations or Data Management functions within R&D, or taking on evidence generation activities within Medical Affairs.

Examples of nRE use

After an organization earned approval for an antipsychotic, healthcare providers asked how the newly approved drug compared with existing treatment options. Registrational trials had shown similar effectiveness for many agents in the class. But the organization's Medical Affairs team used nRE in medical records to record dropout rates for patients taking a range of medications, finding a lower dropout rate for patients using the company's drug. By identifying and filling this knowledge gap, the Medical Affairs team were able to offer guidance to HCPs prescribing the new treatment.

At launch, an organization's oncology treatment was used primarily with patients who didn't respond to the current standard of care. However, patient advocacy groups wondered if the new drug should be used in a first-line setting. The organization's Medical Affairs team ran a phase 4 study with patients randomized to both drugs, showing the treatment was not inferior when prescribed first.

An organization brought a drug to market targeting a genetically defined subset of non-small cell lung cancer. Clinical trials would take years to determine its effectiveness in comparison with the existing first-line treatment.

What happens when short-acting beta2-agonist (SABA) inhalers are used chronically without inhaled steroids for asthma maintenance? A real-world study of more than 1 million adult patients, combined nRE secondary data sets with primary prospective data to show that SABA overuse was associated with more asthma exacerbations, contributing to the evidence base for changes to the Global Initiative for Asthma (GINA) guidelines.

Figure 2. Sources of nRE

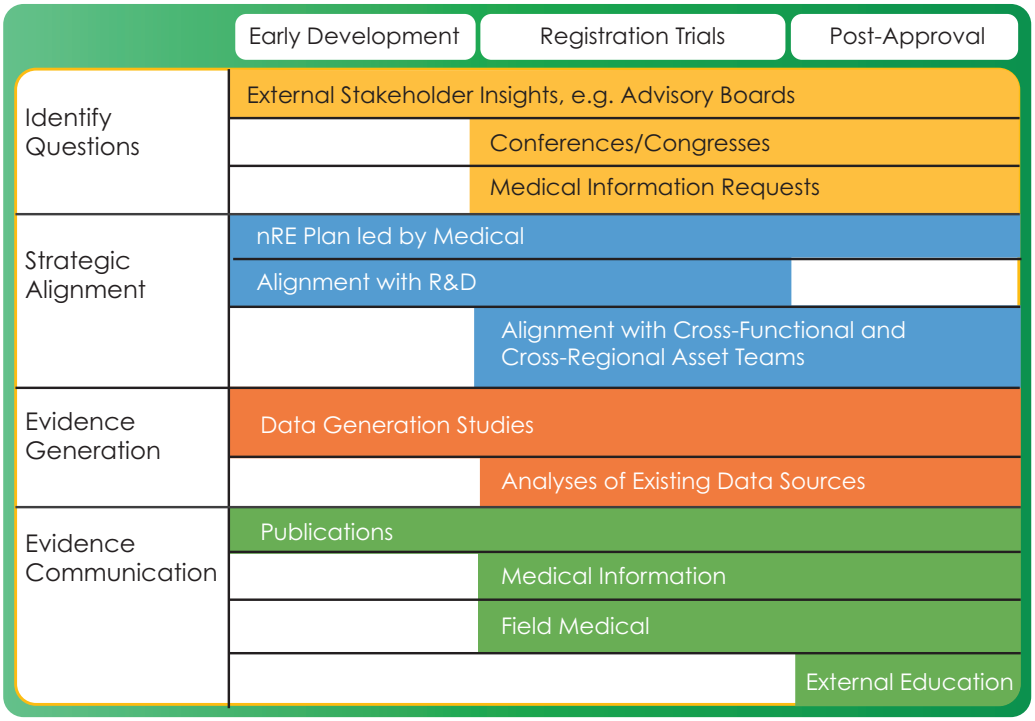


Figure 3. Timing of non-Registrational Evidence Activities Across the Lifecycle

CONCLUSION

Does a treatment work for patients who are ineligible for the registrational trials? What is the burden of a disease in various parts of the world? How does a new treatment support quality of life in comparison with the standard of care and across patient subsets? Do we meet the needs of payers and HTA bodies to make the right decision about our treatment? These questions are not necessarily answered through a treatment's regulatory approval but are essential in understanding the appropriate use of treatments as prescribed in the real world. Knowing who, when and how to use new drugs, devices and diagnostics improves patient outcomes.

External stakeholders ask; the Medical Affairs function uses nRE to answer; and through this dialogue, healthcare providers become able to more confidently use new medicines with the patients most likely to benefit, increasing the benefit to organizations, society and to patients who depend on pharmaceutical innovation for their wellbeing.

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ABOUT MAPS

MAPS is the premier nonprofit global Medical Affairs organization for Medical Affairs professionals by Medical Affairs professionals across all different levels of experience/specialty to engage, empower, and educate. Together with more than 6,300 Medical Affairs members from more than 220 companies globally, MAPS is transforming the Medical Affairs profession to increase its value to patients, HCPs, and other decision-makers.

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