



A Systematic Approach to Assessing Real-World Research Questions Supported by Digital Enablement

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Multiple strategies, each with their individual advantages and drawbacks, may be employed to answer a research question, but determining the optimal strategy – the one that will bring you to your answer in the most effective and efficient way possible – that is the true challenge in our industry. Identifying that optimal strategy requires the synthesis of science, operations, and increasingly, technology. That synthesis, with its balance and integration of so many elements, cannot be achieved with a scattershot approach. Our systematic approach allows us to consider all these elements, to create that required synthesis, and to find that optimal strategy for each research question. This comprehensive process engages and considers the needs of cross-functional and multi-stakeholder subject matter experts (SMEs), including internal client stakeholders, study design experts,

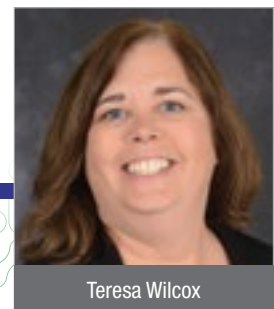
healthcare providers, external partners, other potential stakeholders, and most importantly, patients and their caregivers.

Our approach focuses on three key steps, including a two-step feasibility assessment and then a strategy confirmation.

- 1. Level One Feasibility:** An assessment of possible strategies to answer the research question(s) of interest, including:
 - ▶ Detailed and specific scientific considerations and questions
 - ▶ Review of what is vital to the return on investment (ROI) assessment (e.g., regulatory requirements, critical assessments, length of data collection, patient retention, budget constraints)
 - ▶ Assessment of the optimal data collection method

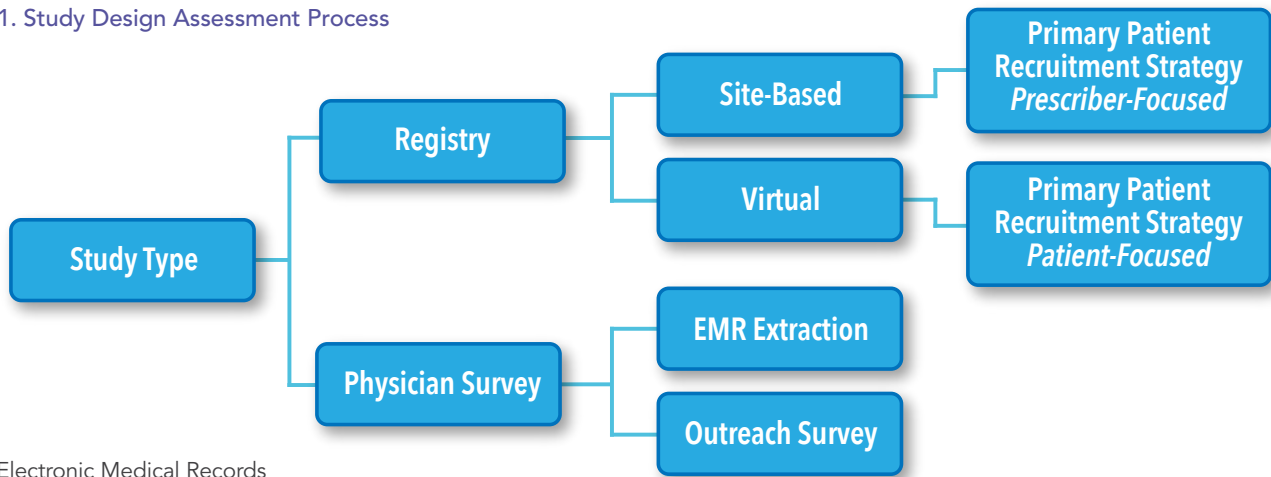


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Figure 1. Study Design Assessment Process



EMR = Electronic Medical Records

2. **Level Two Feasibility:** Refinement of strategy informed by stakeholder feedback, including:

- ▶ Analysis of study design options
- ▶ Assessment of execution options

3. **Strategy Confirmation:** Specific recommendations

The two-step feasibility assessment considers the benefits of digital enablement at each point of the evidence generation process. While technology enablement uses a tool to produce an outcome, digital enablement is choosing

the right technology to elevate and advance, in this case, evidence generation.

Level One Feasibility Assessment of Approach to Answer Research Questions

In Level One Feasibility there are key questions and possible frameworks to be considered for each study. Figure 1 illustrates the flow of how we assess the study design process. Table 1 and Table 2 list the examples of the key questions for assessing study design and operations options, and whether digital enablement can contribute.

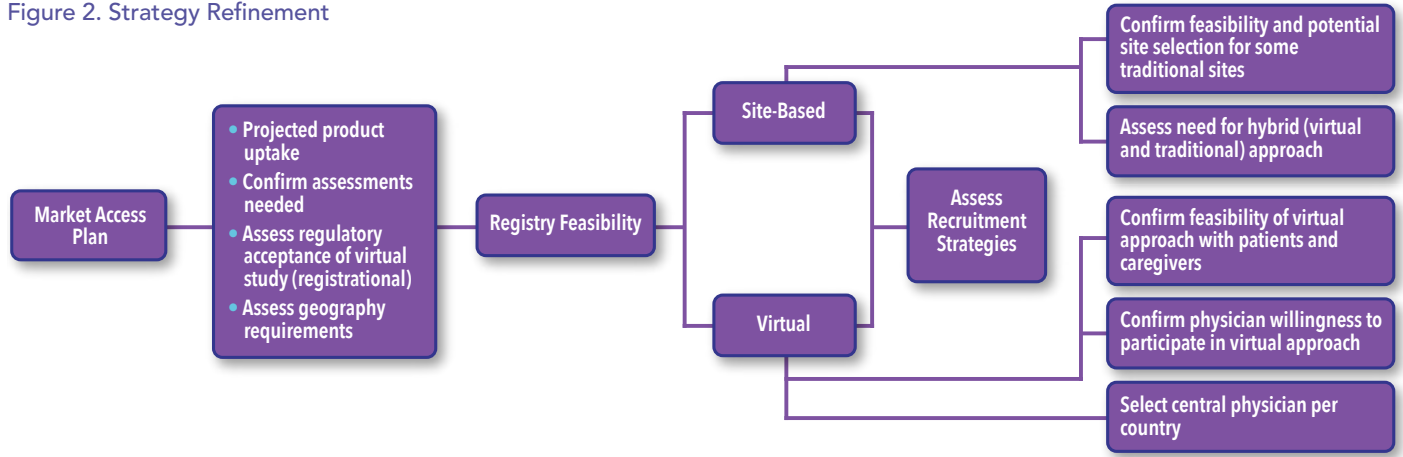
Table 1. Examples of Key Questions to Assess Study Design Options

Study Design Questions	Is Digital Enablement Available / Applicable?
Are there specific research questions/evidence requirements being requested by key decision makers?	N/A
Where is the point of care for the patient and for the dispensing/provision of the intervention (if applicable)?	Yes
Is the study data required for registration or regulatory purposes?	Yes
Do patients need to be recruited and/or can data be extracted from electronic medical records (i.e., assessments considered standard of care)?	Yes
In what geographical areas will this study be conducted?	Yes (digital enablement varies by geography)
Is data on multiple participants needed (i.e., pregnancy registry patient and newborn)?	Yes
Can some visits/procedures be decentralized?	Yes

Table 2. Key Questions to Assess Operational Options

Operational Questions	Is Digital Enablement Available / Applicable?
What sources are available for the cohort of interest?	Yes
Does the data collection plan account for the long-term follow-up (i.e., continuity of care, relocation)?	Yes
Can the report of measures be completed by the patient/caregiver? Is clinician confirmation required?	Yes
Where/how will patients be recruited? Are they recruited at sites or somewhere else? Where is follow-up being performed?	Yes
Could a virtual site be used?	Yes
Does electronic informed consent (eConsent) make sense?	Yes

Figure 2. Strategy Refinement



Level Two Feasibility Refinement of Strategy Informed by Stakeholder Feedback

In Level Two Feasibility our study approach is assessed based on key features of each study and considerations based on answers received from the Level One Feasibility, ultimately informing the recommended approach. The next step is scientific and operational assessment of a series of questions and factors that inform the final design and operational strategy (See Figure 2).

Critical Features to Assess

The following critical areas must be assessed when determining the best study design to answer a research question:

- Acceptability to Regulators, including 21 CFR Part 11 Compliance¹
- Alignment to the European Union’s General Data Protection Regulation (GDPR)²
- Representativeness
- Country-Level Factors
- Availability of Measures
- Appropriate Data Reporter (Clinician, Patient)
- Patient/Caregiver Burden
- Site Burden
- Recruitment and Retention
- Timelines
- Cost
- Challenges and Opportunities

Considering Decision Maker Needs in Solution Development

Example: Regulatory Guidance Regarding Use of RWE to Address PASS

Should the key audience for the study findings be a regulator(s), the evidence generation approach must consider their requirements.

- The European Medicines Agency’s guideline on good pharmacovigilance practices (GVP)³ acknowledges real-world evidence (RWE) approaches for post-authorization safety studies (PASS) for both primary and secondary data. Most PASS are observational studies and increasingly introduce other objectives, such as real-world utilization (in particular, to describe exposure in groups that have not been exposed in clinical trials) and effectiveness outcomes, on top of safety outcomes, drug utilization (42%), and effectiveness (30%).
- In the US, the use of RWE for regulatory decision making was mandated in the 21st Century Cures Act¹ of December 2016, and a framework for its incorporation into decisions is provided in the Framework for FDA’s Real-World Evidence Program⁴ of December 2018. Although additional regulatory guidance documents are under development, the Cures Act and FDA RWE Framework provide sponsors with an array of study design options for the post-approval setting.
- Beyond Europe and the US, which have been followed closely by Canada and Australia, Asian countries such as South Korea, India, Japan, and mainland China also now request post-marketing, real-world evidence to observe drug effects both in routine practice conditions and in larger and more diverse populations.

Engagement of the Patient in Solution Development

The 21st Century Cures Act has expanded the focus on patient centricity by introducing “Patient-Focused Drug

Development” and developing a plan to issue guidance on how to include the patient experience in drug development and regulatory decision making. The inclusion of patient centrality in drug development can involve a multitude of activities. One aspect is the use of patient-reported outcomes (PROs) to collect patient experiences; however, this remains infrequent with a recent study showing that only six out of 30 registries collected data on measures of quality of life.

A virtual approach to study execution potentially reduces timelines and cost, enabling patients and caregivers across the globe to participate in a study while minimizing burden. Through the virtual model, the emphasis on sites and in-person monitoring can be foregone for remote data collection and electronic communication between physician and patient. This provides the researchers, patients, caregivers, and other stakeholders and data providers the flexibility to ease trials into their everyday work and life.

Case Study Example

Overview of Study Design

In this hypothetical case study, we outline the above approach for a study with these characteristics:

- A non-interventional registry study

- Evaluating long-term safety and effectiveness of a medication as used in routine clinical practice in adult patients (18 years of age or older)
- Designed specifically to meet a post-approval safety commitment

Strategy Recommendations

For this study, we recommend a virtual approach to collect study data outlined. This approach provides:

- Involvement of fewer countries and sites
- Reduced burden of participation for sites and patients
- Long-term engagement and retention of sites and patients

Other designs discussed in Level One Feasibility: Assessment of Approach to Answer Research Questions were considered. While database analytics is acceptable to regulatory bodies for assessment of long-term safety risks, other key decision makers may be interested in comparative treatment effectiveness, which is not feasible using data analytics alone since current databases rarely have continuity over extended time periods. The clinician and patient assessments of treatment effect are rarely recorded in the medical record, neither as defined fields nor in text fields.

Table 3. Example of Critical Features Study Design and Operations Options

Critical Feature	Site-Based Registry	Fully Virtual Registry
Acceptability to Regulators - 21 CFR Part 11 Compliance	Acceptable	Minimal to no risk given data is collected as standard of care
Representativeness	Participant mix highly dependent on participating sites	Highly representative given patients do not have to be in proximity to a brick and mortar site to participate
Country-Level Factors	Standard approval based on country regulations	For each country, we need to assess virtual feasibility and selection of a virtual site investigator
Measure Availability	Measures available from standard of care visit data from participating physician	Measures available from standard of care visit data from participating physician and available by medical records release for patients at the virtual site
Site Burden	No additional burden as data will be collected from visits scheduled as part of routine clinical practice	Reduced burden as virtual sites will take on activities for many brick and mortar sites
Recruitment and Retention	High level of site motivation and effort required to enroll patients and keep them engaged over 10 years	Recruitment and engagement managed through technology; close follow up with patients/caregivers by virtual site staff
Timelines	Lengthy contracting and site activation processes can delay timelines	Fully virtualizing reduces to a single site per country equating to shortened total start-up timelines

Virtual Model

Given the procedures are all standard of care in this case study example, we proposed conducting the study as a fully virtual study. This provides:

- Reduced country footprint
- Reduced site footprint
- Reduced patient, caregiver, and healthcare provider burden
- Increased potential patient pool given a patient's ability to participate from anywhere
- Increased patient engagement through digital enablement of engagement strategies and data collection

Conclusion

Real-world evidence research questions can be answered in a myriad of ways. Each solution has benefits and risks that must be weighed. Whether it is the quality or quantity of the data or cost of the procurement of the data, these risks and benefits need to be methodically assessed. This assessment must include scientific study design questions, operational execution questions, and align patient centricity and digital enablement. When assessment is underpinned by experience and strong capabilities, the resulting solution ensures a well-thought out, key stakeholder engaged approach. ■

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***Virtualizing this study + applying the model assumptions above =
a 55% reduction in budgeted costs***

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