Advanced Clinical

INSIGHT BRIEF

Optimizing Protocol, Country and Site Feasibility Strategies: Best Practices for a Better Clinical Experience

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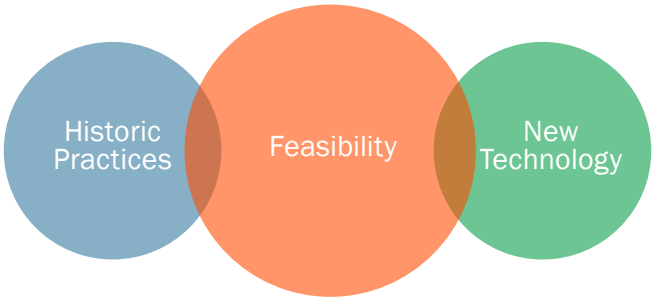
Introduction

In today's clinical research environment, many teams often rely on outdated or limited strategies for feasibility and assume this is a "one-and-done" activity that can be completed quickly within the request-for-proposal (RFP) process. Effective feasibility requires a robust, multi-channel strategy and a risk management feedback loop to monitor and mitigate risks throughout the project. Authored by Advanced Clinical experts, this paper explores the fundamentals of feasibility, the necessity of broadening approaches, the best way to leverage technologies and processes, and how a multichannel combination of techniques can deliver more actionable insights from feasibility assessments.

Feasibility Fundamentals

All feasibility methods and tactical elements add value, and over time, technology and approaches have evolved (Figure 1). Historically, many feasibility assessments relied on site feedback or past study metrics. Robust business intelligence tools then became available and allowed benchmarking based on actual study metrics. With the growth of social media, teams started using social listening to learn more about patient perspectives. Additional information can now also be derived from tools connected to electronic health records (EHRs).

Figure 1: The Evolution of Feasibility



In this environment, where patients can access their medical charts with an app and opt in to share health information, approaches to feasibility will continue to expand. With studies underway for novel therapies across therapeutic categories, the continued evolution of personalized medicine and a focus in rare diseases, creative approaches may be needed to assess data and predict outcomes. The best approach is a comprehensive and custom strategy built to fit each study.

As shown in Figure 2 (page 4), feasibility goals often focus on areas such as:

- Incidence, prevalence and countries of focus
- Enrollment duration and accrual rates
- Patient perspectives, needs and expectations, including family and caregivers
- Numbers of sites and enrollment goals
- Primary operational strategies

Strategic feasibility should also include areas that are requested less frequently, such as biometrics review, technology usage, principal investigator grant planning, recruitment and retention strategies, and the use of decentralized components. Strong and thorough feasibility outputs can be used for multiple purposes, such as budget planning, study budget creation, a starting point for site discussions, or to eliminate regions that may not support the goals of the study. Every Sponsor uses this information slightly differently.

Figure 2: Common feasibility goals

Feasibility goals are often as unique as the study.

- Vocalized feasibility goals often tend to focus on:


Incidence, prevalence & countries


Enrollment duration, accrual rate


Patient perspectives, needs & expectations


Number of sites


Primary operational strategies

- Strategic feasibility should include other areas not often specifically requested:
  - Biometrics review
  - Technology usage
  - PI grant planning
  - Recruitment and retention strategies
  - Components to decentralize

Approach to Feasibility

Typically, feasibility is assessed based on three primary areas of focus—protocol, countries and sites—all of which can help mitigate risk over the long term.

For protocol feasibility, key considerations are design, endpoints, the patient population, inclusion/exclusion criteria, investigator and subject acceptance and patient burden.

For country feasibility, areas for attention include regional differences in incidence/prevalence of the disease or condition of interest, standards of care, regulatory timelines and other country-specific requirements, availability of experienced sites and investigators, and the competitive landscape.

For site feasibility, major factors are the availability of the target patient population and the ability to recruit, investigator experience in the indication of interest, availability of qualified resources, and the existence of competing trials.

Tactical Solutions and Tools to Support Strategic Feasibility

There are tactical solutions and tools to support feasibility across these three areas of focus, yet their application requires creativity and persistence to minimize issues such as slow enrollment and non-enrolling sites. Strategy and tactics are complementary to one another. Feasibility cannot be successful if it ignores either one. Strategy is required to set the direction and destination of the feasibility and to clarify goals and how success will be defined. Tactics define the concrete actions that will need to be performed to achieve this success.

The clinical trials ecosystem will continue to evolve and require creativity to overcome challenges.

Access to tools that collate, synthesize and analyze real-world data enables the detection of new connections and patterns at a volume and speed that would be difficult to achieve manually. This has created new opportunities to inform feasibility, with a multi-channel approach offering the best way to fully assess feasibility. Tactical components and tools include:

- **Past metrics and experience:** These are valuable for benchmarking, developing inclusion/exclusion criteria, addressing operational challenges, and start-up planning.
- **Site feedback:** This supports site centricity, harnesses the power of site networks, provides input on standards of care, helps overcome enrollment hurdles, and offers alerts about accrual rates.
- **Business intelligence:** Articles and other publications are helpful sources, along with enrollment benchmarking data, and comparison of inclusion/exclusion criteria, site participation, and planning of principal investigator grants and start-up.
- **Real-world data:** Sources include electronic health records (EHR), text and data mining using natural language processing, claims/insurance data, wearables and registries.
- **Epidemiologic data:** Examples include information on disease incidence and prevalence and projections for newly emerging diseases.
- **Social listening:** This enables the ability to tap into structured and unstructured sources linked to advocacy groups, consortiums, and patient groups helping to guide recruitment and engagement tactics and providing information on each country's clinical trial environment.
- **Patient journey planning:** This informs patient recruitment, education, awareness, engagement and retention needs.

The clinical trials ecosystem will continue to evolve and require creativity to overcome challenges. Current trends include increased use of decentralized clinical trial elements during the COVID-19 pandemic, increasing interest in targeted therapies, highly competitive markets and small patient populations.

The Future of Technology in Driving Feasibility Transformation

Clinical development efforts are challenged to keep pace with the ever-growing amount of information available, including real-world evidence, genomic details and data from biosensors. Competition for clinical trial participants is increasing, which is adding to the complexity of the recruitment process. Choosing the right sites and identifying suitable patients can improve the speed and efficiency of clinical trials. This can only be done by efficiently analyzing large amounts of data.

Artificial intelligence and machine learning (AI/ML) are already influencing the way data is processed during the feasibility process in areas including:

- Linking multiple data sources, combining de-identified data sets to create longitudinal patient records (EHR, claims, patient-reported outcomes, registries)
- Challenges in transforming raw data into research-ready data
- Natural Language Processing (NLP), which has great potential to help harvest information from unstructured records that contain crucial, clinical context
- Enhanced examination of structured data using NLP and AI to improve accuracy

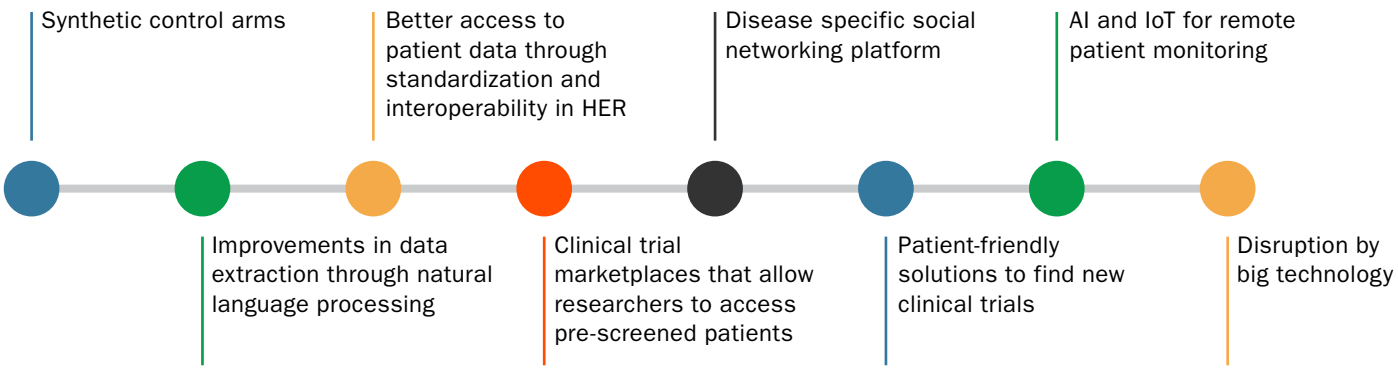
In trial design, AI/ML can help in: identification of eligible patients for clinical trials; patient selection, by reducing population heterogeneity and population enrichment; automated analysis of EHR and clinical trial digital eligibility data; integrating data from historical patients or trial participants with the aim of supplementing a placebo arm with a synthetic control, thus maximizing the number of trial participants who receive active treatment; investigator and site selection; and educating patients about the existence of clinical trials.

Despite much progress, wide applicability of AI/ML relies heavily on access to the appropriate type of data. Advances in mining unstructured data stored in data lakes and improvement of data analytics will play a key role. Recent developments in NLP allow for identification of patients with conditions not explicitly mentioned in EHR data, improving the match rate between patients and clinical trials. Data sharing is allowed under the Health Insurance Portability and Accountability Act (HIPAA) if the patient consents.

The internet of things (IoT)—the system of interrelated, internet-connected objects able to collect and transfer data over a wireless network without human intervention—is a major driver that is transforming clinical trials. Telehealth solutions and decentralized trials, which have advanced sharply during the COVID-19 pandemic, rely heavily on this. However, while AI adoption is widespread, limited digitalization and standardization in the medical field are still a notable challenge.

Thus, the future of feasibility is intimately connected with evolving technology, which holds the promise of decreasing costs and lowering the patient burden, and is increasingly accepted by regulators under the 21st Century Cures Act and recent U.S. Food and Drug Administration guidance on the use of real-world evidence in submission (Figure 3).

Figure 3: The Future of Feasibility



Feasibility Process: Best Practices

For benefits to be fully realized, teams need to adopt a new outlook on feasibility assessments by understanding the necessity of a multi-channel approach, allocating the time required to conduct a thorough and strategic assessment along with the overall value that proactive and continual planning brings to a clinical program. Important reasons why traditional feasibility assessments may fail include: basing plans on unreliable or partial information; tempering feasibility data from the site to account for possible overstatement of capacity to recruit; and neglecting to conduct due diligence to make use of all available information.

Feasibility best practices center around the team, taking a multidisciplinary and cross-functional approach to fully understand the patient population and its needs, attitudes and beliefs. Functions on the feasibility team should include:

- Feasibility management and local support
- Study start-up and contracts
- Clinical operations and patient engagement
- Medical
- Biometrics, among others

Feasibility is a complex process that should be data-driven and adaptive. It should start early and be customized to specific needs and milestone-driven. Starting when minimal necessary information is available rather than waiting for final documents allows for early progress. Availability of stable primary endpoints, inclusion/exclusion criteria, study design, number of patients, duration of treatment and information on comparators can be considered as a good start. The feasibility plan should take an adaptive, data-driven approach, exploring multiple options and potential impacts on the study timeline, and with early involvement of the full team.

Typical Feasibility Process Steps:

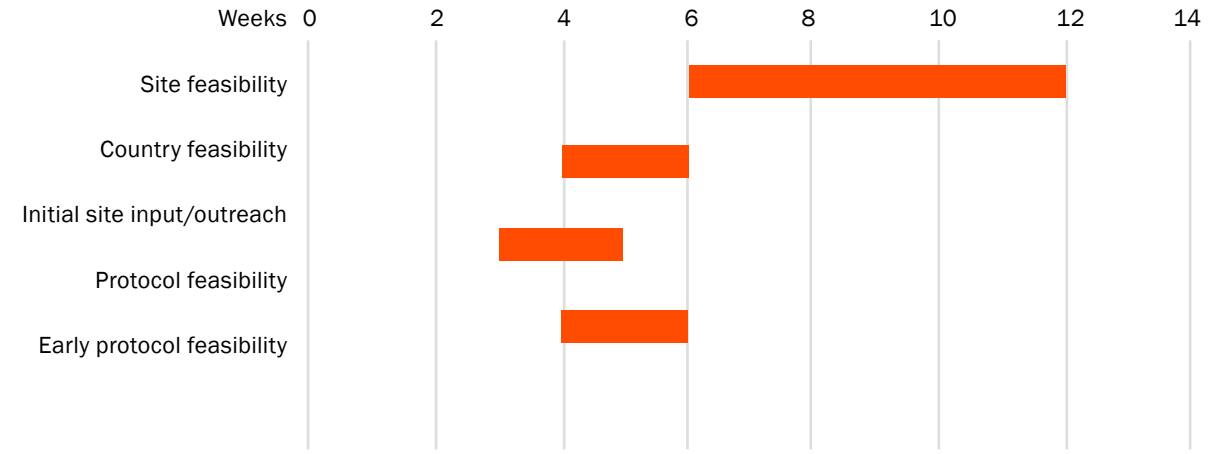
- Early Protocol Feasibility
- Protocol Feasibility
- Initial Site Outreach
- Country Feasibility
- Site Feasibility

A typical feasibility process comprises the following steps:

- **Early protocol feasibility**, the planning stage of the program, with the main purpose of gathering intelligence and developing an initial outreach plan
- **Protocol feasibility**, which should begin as soon as a draft synopsis is available and then be refined when the draft protocol is ready; regulatory agency input is particularly valuable during this stage
- **Initial site outreach** to a limited number of carefully selected sites
- **Country feasibility**, with target countries chosen based on a scoring system
- **Site feasibility**, which combines the results of a site survey with experience and business intelligence tools and data

There can be some overlap between these tasks, but no shortcuts can be made without the risk of comprising quality. The mean duration of the feasibility process is 12-16 weeks or longer (Figure 4). A key factor in overall timelines is the ability for all stakeholders to make timely decisions. One of the most frequent causes for delay is the choice of confidential disclosure agreement—including whose template should be used, who must sign, and levels of blinding vs. unblinding. Anticipating these issues can help avoid this delay.

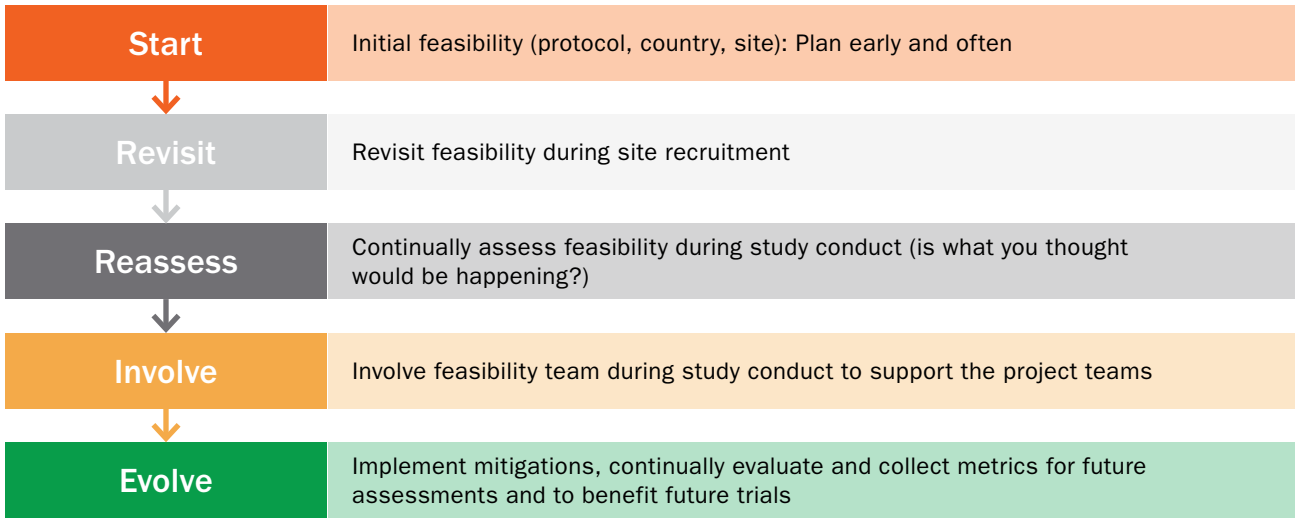
Figure 4: Feasibility Best Practices – Realistic Timing



Rolling and Adaptive Approaches to Feasibility

Traditional feasibility assessments are conducted at the beginning of a study. This is usually a one-time, static effort. Feasibility is not a "check-the-box" activity. Rather, it should be treated as a rolling and adaptive process that not only focuses on first patient in, but also helps to maintain enrollment performance until last patient in (Figure 5). This should take into consideration the ever-changing macro environment and other factors that may have an impact on a given study's feasibility and executability.

Figure 5: Feasibility Best Practices – Rolling Feasibility



Conclusion

Feasibility is both a science and an art with much to be gained from an optimized, multichannel, strategic approach. Sponsors should consider working with an experienced partner to ensure successful execution and associated benefits including:

- Actionable insights based on benchmarked data to appropriately prepare for study conduct
- Early identification and assessment of risk and development of mitigation strategies
- Confidence in study specifications for adequate budget planning
- An established infrastructure and solid basis for continued evaluation throughout the study

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Donna Hanson has been in the clinical trial industry for nearly 20 years. Donna has a comprehensive background, including leading teams in patient recruitment and engagement, feasibility and site engagement, bids and proposals and vendor management/outsourcing. Her passion is to enhance strategy and study optimization to expeditiously complete trials that provide access to cutting-edge treatments to those in need faster. Donna's experience spans multiple therapeutic areas with a large focus in urology, gastroenterology, rare disease, oncology and pediatric programs.

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Dr. Dan Sabou has worked in clinical research for over 14 years and is a board-certified physician, including university teaching experience. As a member of the Global Medical Services department, Dan provides medical and surgical advice to clients and within Advanced Clinical. This includes consulting on clinical development plans, protocols, KOL development, site networks and medical/safety monitoring (medical monitoring and safety management plans, medical monitoring and medical case review). He holds a Doctor of Medicine degree from Victor Babes University of Medicine and Pharmacy in Timisoara, Romania.

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