



Early Feasibility Studies

# Playbook

February 2026 | Pre-Release

# Early Feasibility Studies Playbook

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# Acknowledgments

The Medical Device Innovation Consortium (MDIC) would like to thank the following contributors for their insights in support of this playbook:

## Contributing Organizations

- 4C Medical
- Abbott
- Abel & Wolf
- Banner University
- Baylor University
- Columbia University
- Cornell University
- Criovalve
- Edwards
- Fire 1
- High Life Medical
- Hyalex
- Inight Medical Consulting
- Main Line Health / Lankenau Institute for Medical Research
- Medical University of South Carolina
- Medtronic
- Namsa
- Northwestern
- Oregon Health & Science University
- Piedmont
- Renata Medical
- Supira Medical
- Tricare
- Tricare
- University of Michigan Health
- Vdyne

## About MDIC

At MDIC, we work together to innovate for better health, transforming lives by accelerating access to medical devices. MDIC advances the scientific and technical disciplines that are fundamental to medical technology throughout the total product life cycle. Founded in 2012, MDIC is the premier public-private partnership convening medical device manufacturers, researchers, regulators, payers, patients, and health care providers as trusted collaborators to solve the industry's complex challenges. MDIC drives advancements in medical technology development, approval, coverage, adoption, and patient access in the core areas of quality design & manufacturing, evidence generation, digital health, and patient engagement.

## About Early Feasibility Studies

Medical technology developers frequently conduct feasibility studies outside the U.S., delaying patient access to new technologies. The FDA's Early Feasibility Study (EFS) initiative aims to promote early feasibility studies within the U.S., increasing patients' access to promising technologies and supporting device innovation. MDIC supports this initiative by developing tools and best practices to enhance EFS trials and collaborating with key partners to encourage studies to focus on the U.S.

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**For more information about the EFS initiative visit** <https://mdic.org/our-work/early-feasibility-studies/>

# Executive Summary

This playbook summarizes key considerations related to EFS regulatory and operational planning, site selection, site reimbursement structures and contracting, and broader ecosystem factors influencing early-stage device evaluation. Developed for sponsors, investigators, research institutions, and clinical partners and informed by insights from the past decade of EFS clinical trials, this resource aims to support the consistent, high-quality conduct of EFS programs across diverse organizational settings while ensuring that studies are executed in a manner that is both efficient and resource-conscious.

The FDA established the EFS program in 2013 in response to a decline in early clinical evaluations within the United States, driven by regulatory conservatism, legal concerns, and operational complexity. The EFS pathway enables sponsors to assess initial clinical safety, functionality, and feasibility in small-scale human studies, bridging the critical gap between preclinical development and pivotal trials. By establishing reasonable preclinical data expectations and strengthening communication between sponsors and the FDA, the program revitalized the U.S. environment for early innovation.

Internationally, parallel efforts, such as the European Union's HEU-EFS initiative, reflect a growing emphasis on harmonized early-stage evaluation and global collaboration. Alignment between U.S. and European approaches suggests movement toward a more unified global framework for first-in-human research, one that balances flexibility, safety, and scientific integrity.

Despite significant progress, several challenges continue to shape the EFS landscape. While the regulatory pathway for Early Feasibility Studies (EFS) is relatively streamlined, the data required to support IDE approval can be substantial and resource-intensive. Additional challenges include prolonged contracting and IRB review timelines, payer coverage limitations, enrollment barriers, and high screen-failure rates. . Additional gaps persist between the operational capacities of startups and strategics, as well as cultural tendencies that may constrain rapid learning and iteration. Recent reforms, such as the FDA's Total Product Life Cycle Advisory Program (TAP) and provisions in the 21st Century Cures Act, seek to address some of these issues by streamlining processes and encouraging the development of EFS-ready sites.

This playbook provides practical guidance for navigating these challenges. The chapters that follow translate regulatory expectations and industry lessons into actionable strategies for early feasibility work. Collectively, they present a systematic framework for advancing early-stage medical device innovation while maintaining the highest standards of safety, ethics, and scientific quality.

## Regulatory Foundations & IDE Approval

It is advised to engage the FDA early and iteratively through informational meetings and focused Q-Sub interactions to align expectations and prevent costly delays. Anchor all development planning in a strong Device Evaluation Strategy (DES) that provides the rationale for the testing needed to support IDE approval. Use the TPLC Advisory Program

(TAP), when appropriate, and experienced consultants to strengthen strategy, communication, and submission quality. Prepare a complete, well-justified IDE submission that addresses prior FDA feedback and avoids common deficiencies in testing, biocompatibility, and clinical study design.

## **CMS & Payer Considerations**

Centers for Medicare and Medicaid Services (CMS) coverage is critical for EFS enrollment, as Medicare beneficiaries often make up a large portion of eligible patients; however, CMS only considers reimbursement after FDA IDE and IRB approvals are in place. Understanding Category A vs. Category B classification is essential. Category A devices are experimental and reimbursement is not provided for devices; procedures and routine care are not reimbursed until clinical safety is proven in a minimal number of patients. Category B devices may qualify for device and routine care coverage, but only if CMS determines that the study will capture information important for their coverage decisions.

In addition, CMS timing is distinct from FDA timing. Premature submissions or assumptions about categorization can lead to delays. Sponsors should refer to their filing simply as a “CMS crosswalk submission” until their device categorization is confirmed. Coverage challenges remain a major barrier, especially for first-in-human procedures; alignment of regulatory, reimbursement, and startup timelines is critical to avoid delays in study startup and enrollment. Early payer engagement and a strong Payer Value Proposition (PVP), integrating clinical, economic, and patient-centered evidence, are essential for future reimbursement, including for commercial payers whose policies differ from CMS.

## **IRB & Site Administrative Leadership**

Institutional Review Board (IRB) partnership is essential for EFS, as boards must evaluate uncertain risk-benefit profiles, potential frequent protocol modifications, and limited early data; early engagement and clear communication greatly reduce delays. Making the case for EFS requires proactive IRB education, including explaining the unmet need, intended population, device rationale, and institutional priorities, ideally through direct involvement of physician-investigators and senior clinical leaders. Single IRB and rapid-activation pathways can dramatically accelerate approvals for multi-site or local EFS programs, especially when paired with pre-negotiated templates, parallel processing, and prioritized review channels.

Strong institutional support is critical, as administrative leaders must understand the risks, costs, and non-financial benefits of EFS—such as reputation, innovation leadership, and access to novel technologies—while ensuring appropriate infrastructure and preparedness to manage potential procedural risks and complications. A successful EFS culture requires transparency, coordination, and risk-tolerant leadership, with investigators, IRB leaders, and administrators aligned around ethical oversight, patient safety, and the shared responsibility of early innovation.

## **Site Selection & Qualification**

EFS site selection requires a distinct approach from clinical trial site selection. For EFS agility, communication, and real-time problem-solving represent more relevant site capabilities than over traditional performance metrics derived from prior pivotal and registry enrollments. EFS success depends on tailored, streamlined qualification processes that assess operational readiness, site responsiveness and access to patient population, and partnership potential. EFS site qualification must be a two-way evaluation, enabling sites to assess sponsor communication, expectations, protocol feasibility, resources,

and alignment with their portfolio and operational capacity. Selecting the right EFS site hinges on people and processes, including PI engagement, coordinator bandwidth, adaptability, clear communication pathways, and realistic assessments of patient access, startup timelines, and operational risks.

## **Budgeting & Finance**

EFS budgets must clearly distinguish Standard of Care (SOC) from research-only activities, with fair-market-value reimbursement for research only protocol-required tests, coordinator time, PI oversight, and prescreening efforts. Comprehensive budgeting includes one-time, annual, and per-occurrence fees, covering startup, IRB, pharmacy, monitoring, amendments, and specialty activities such as explant handling or source uploads. Transparent documentation aligned with case report forms (CRFs) ensures that all study-required procedures, follow-up schedules, and labor expectations are accurately captured and consistently reimbursed. Pre-screening and participant reimbursement require defined structures, including hourly or capped prescreen budgets, documentation of screen failures, and compliant travel/visit-related subject support. Given the inherently higher screen failure rates in EFS relative to pivotal trials, budgets should include defined prescreening reimbursement structures that recognize investigator time, coordinator effort, and diagnostic review for non-enrolled candidates. Budgets must also explicitly account for the higher expected screen failure rates typical of EFS compared with pivotal trials, ensuring appropriate reimbursement for prescreening effort, documentation, and investigator review. Clear negotiation and payment terms improve predictability and reduce administrative burden, including upfront nonrefundable startup fees, structured payment schedules, limited ad-hoc charges, and quarterly invoicing aligned with completed CRFs.

## **Contracting & Legal Considerations**

The MDIC EFS Clinical Trial Agreement (CTA) template<sup>1</sup> was created to reduce contracting delays, one of the biggest barriers to initiating early feasibility studies, by offering a standardized, pre-negotiated agreement accepted by both sponsors and sites. The template was designed to accelerate study startup by minimizing legal back-and-forth, reducing administrative burden, and enabling resources to be focused on study execution rather than prolonged contract negotiations. Sites benefit from fair, balanced terms, including intellectual property, indemnification, subject injury, and publication language, that have already been vetted across institutions, decreasing internal review time and enabling broader participation in first-in-human studies. Although designed as a single-use agreement, the EFS Clinical Trial Agreement (CTA) was developed through expert consensus among legal and operational specialists experienced in early feasibility studies, establishing EFS-specific language for provisions that are historically contentious. This approach promotes alignment between sponsors and sites, reduces negotiation friction, and helps accelerate the initiation of early feasibility studies—supporting timely patient access to innovative devices

## **Protocol Development & IDE Approval**

EFS should be designed for flexibility, clarity, and operational feasibility, balancing scientific rigor with the need for rapid learning, iteration, and safe early clinical use. Define the intended population and eligibility criteria with precision, focusing on anatomy and short-term survival rather than restrictive comorbidity exclusions, to support enrollment and meaningful early insights. Keep device descriptions

<sup>1</sup> Medical Device Innovation Consortium. Accelerate EFS Toolkit. Website: \_\_\_\_\_

high-level and adaptable, avoiding unnecessary technical specificity so sponsors can iterate through the FDA 5-day notification pathway without triggering frequent protocol amendments.

EFS should prioritize structured learning over formal hypothesis testing. While traditional pivotal endpoints are often unnecessary, data collection should capture comprehensive safety and technical performance insights—potentially more granular than in a pivotal trial, to inform device refinement and future study design.

Because Early Feasibility Studies are designed to generate early learning rather than test formal hypotheses, traditional pivotal-style endpoints are often unnecessary. Instead, data collection should be intentionally structured to capture detailed safety, technical performance, and usability insights, often including more granular information than would be required in a pivotal trial, to meaningfully inform device iteration and the design of subsequent studies.

Safety oversight in EFS should be strong, proactive, and fit-for-purpose. This includes clearly defined clinical mitigation strategies, timely and transparent adverse event reporting to enable rapid assessment and protocol or device modifications when needed, and the use of appropriate oversight mechanisms (e.g., an independent medical monitor or DSMB, when warranted). Operational flexibility, such as realistic visit windows and clear enrollment definitions, should support efficiency without compromising rigorous patient safety monitoring.

## **EFS Execution & Startup**

The MDIC's 60/60/60 framework serves as a practical benchmark for time to site activation and enrollment, targeting 60 days to contract, 60 days to IRB approval, and 60 days to first enrollment, with contracts, IRB review, training, and regulatory document collection run in parallel. Site activation is framed as an integrated workflow rather than a checklist, with tiered activation focused on core staff, early delegation of authority (DOA) development linked to training matrices and logs, proactive regulatory document collection, and a well-structured, audit-ready Investigator Site File (ISF) from the outset. Recruitment best practices center on EMR-embedded internal screening, strong sponsor–site collaboration, targeted referring-physician outreach, and a consent process that is patient-centered, transparent about FIH uncertainty, and attentive to equity, language access, and practical barriers to participation. Case execution requires detailed process mapping and logistics planning, including device shipment and storage, vendor credentialing, sterilization, pre-case readiness checklists, day-of huddles, tiered sponsor presence, and comprehensive debriefs, to ensure safety, efficiency, and continuous improvement. Rapid, high-quality electronic data capture (EDC) entry and image upload after each case enable real-time learning and cross-site feedback, while accumulated EFS data are used to determine when device design, patient selection, event rates, and operator performance are mature enough to justify a thoughtful transition to a pivotal trial.

## **Protocol and Device Modifications**

Amendments in EFS may involve device and/or protocol changes. Many amendments are minor and do not impact subject rights, safety, or welfare, while others require additional review depending on the nature of the change. When applicable, sites assess whether IRB review, updates to risk documentation, or confirmation of the risk–benefit profile are needed prior to continued enrollment. Sites maintain appropriate version control and device accountability—tracking shipments, segregating iterations as

required, and returning superseded versions—to support audit readiness and prevent inadvertent use of outdated products. . Any new device iteration or protocol change requires timely investigator and staff retraining, supported by clear sponsor-provided materials, to maintain compliance and operational continuity. Re-consent is required only when amendments meaningfully affect enrolled subjects, with the IRB determining whether updates warrant full re-consent, a consent addendum limited to the new or revised information, or no subject-facing communication. Effective amendment management depends on strong sponsor–site coordination, including transparent rationale, complete documentation packages, streamlined IRB pathways, and proactive planning to minimize study disruption.

## Choosing the Right CRO

Because Early Feasibility Studies are designed to generate early learning rather than test formal hypotheses, traditional pivotal-style endpoints are often unnecessary. Instead, data collection should be intentionally structured to capture detailed safety, technical performance, and usability insights—often including more granular information than would be required in a pivotal trial—to meaningfully inform device iteration and the design of subsequent studies.

Safety oversight in EFS should be strong, proactive, and fit-for-purpose. This includes clearly defined clinical mitigation strategies, timely and transparent adverse event reporting to enable rapid assessment and protocol or device modifications when needed, and appropriate oversight mechanisms (e.g., an independent medical monitor or DSMB, when warranted). Operational flexibility—such as realistic visit windows and clear enrollment definitions—should support efficiency without compromising rigorous patient safety monitoring.

Operational execution models should match the scale, maturity, and complexity of the sponsor. While some sponsors engage Contract Research Organizations (CROs) as strategic partners to help bridge engineering-led development teams, clinical sites, and regulators, CRO involvement is not mandatory for EFS. Early-stage companies may elect to internalize certain functions or work with smaller, device-fluent CROs tailored to early-phase needs. When CRO support is used, sponsors should prioritize EFS and device fluency, lean project planning, named team quality, and cultural fit—not price alone.

Effective EFS operational models—whether CRO-supported or internally managed—are lean and modular. They rely on tailored project plans (not rigid, pivotal-style SOP structures), pragmatic monitoring, streamlined data capture tools capable of accommodating device and protocol iteration, and clear governance structures that define execution responsibility, decision ownership, consultation pathways, and escalation processes. Across all models, successful EFS execution requires a mindset shift: from policing to partnering, from exhaustive to essential, from static plans to adaptive learning, and from uniform oversight to stratified monitoring aligned with site experience and risk profile.

## Emerging Challenges in the EFS Ecosystem

EFS progress is slowed less by science and more by structural gaps. Startups often lack regulatory and operational fluency, while larger strategics depend on them for the boldest innovation—creating a critical knowledge and resource divide that must be intentionally bridged. Although the regulatory pathway for EFS is designed to be streamlined, the volume and depth of data required to support early clinical investigation in the U.S. can be substantial. As a result, some First-in-Human (FIH) studies are initiated outside the U.S., with EFS programs increasingly taking on a global or hybrid structure.

Enrollment remains fragile, particularly once commercial therapies exist. Programs that deliberately prioritize EFS candidates and adopt flexible, learning-oriented inclusion criteria can reduce screen failures and preserve the exploratory purpose of early feasibility. At the same time, safety expectations (e.g., one-year mortality endpoints) and investor-driven conservatism may push sponsors toward overly restrictive protocols. Refocusing EFS on short-term safety, technical performance, and iterative learning better aligns study design with the intended goals of early exploration and device refinement.

Finally, EFS findings are often under-leveraged due to limited publication pathways and inconsistent dissemination. Establishing structured mechanisms for abstracts, conference forums, and rapid-communication formats would enhance academic value, strengthen investigator engagement, and accelerate cross-site learning across the innovation ecosystem.

Global execution of EFS adds complexity, regulatory divergence, geographic-specific requirements (such as MDR) and pressures, and data harmonization challenges. However, when planned carefully, integrating U.S. and outside US (OUS) feasibility efforts can strengthen the device credibility and prepare sponsors for pivotal trials while preserving domestic innovation. An examination of trends shaping the future of early feasibility research, including regulatory convergence, the impact of the FDA TAP program, emerging data-integration practices, and the importance of disseminating EFS findings to strengthen global evidence generation.

This playbook is intended to serve as both a practical resource and a strategic guide for organizations seeking to build or strengthen their EFS capabilities in an evolving global landscape. The chapters provided below present a systematic and detailed framework for advancing early-stage medical device innovation while upholding the highest standards of safety, ethics, and scientific quality.

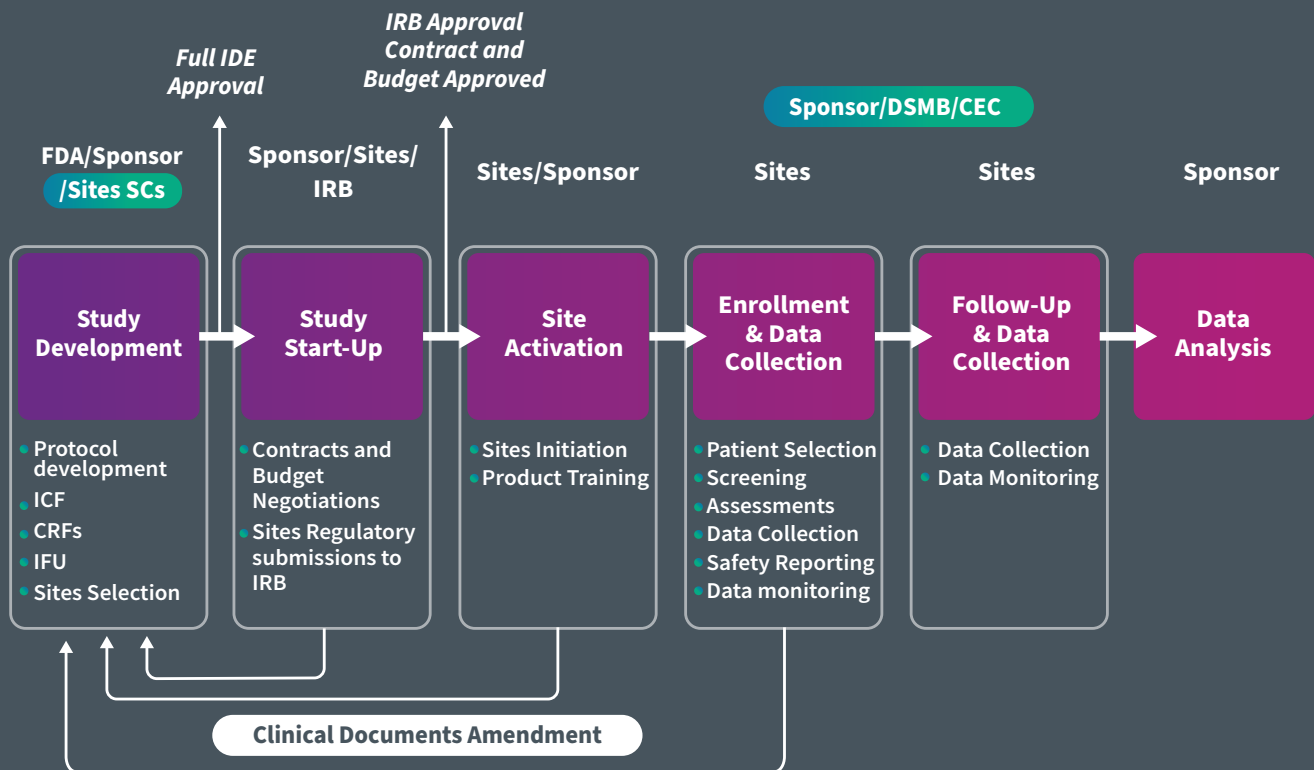


Figure 1. EFS/IDE Clinical Study Lifecycle: Roles, Milestones, and Key Activities

# Chapter 1 Introduction and Background

## Overview of Early Feasibility Study (EFS)

An early feasibility study (EFS) is a limited clinical investigation of a medical device early in development. It typically enrolls a small number of subjects, is used to evaluate the device design concept with respect to initial clinical safety and device functionality; and may guide device modifications.<sup>2</sup>

In the world of medical device innovation, the journey of a new technology begins long before it ever reaches a patient. The earliest phases are rooted in engineering and bench testing, where developers explore and develop foundational questions: ***What is the purpose of this device? What materials is it composed of? How does it function? Can it reliably perform the intended task? Who is the target population? Most importantly, how can we be confident that it is safe enough to consider testing in humans?***

Prior to initiating any testing in humans, new device development includes an early phase commonly referred to as non-clinical evaluation. However, device development is not centered solely on non-clinical studies. Early work encompasses a range of assessments and testing activities, including biocompatibility, bench testing, and animal studies, conducted alongside iterative engineering refinement, risk analysis, and design controls to support readiness for first-in-human investigation. This typically includes simulations, a variety of bench tests, and animal studies. But there is a fundamental limitation to this early testing: bench tests and animal models cannot fully replicate many of the human diseases or conditions that medical devices are meant to treat and are limited in their ability to predict outcomes in humans. Unlike drug development, where researchers can study systemic effects in animals with similar biological pathways, medical devices often target very specific human anatomical or pathological issues such as a blocked coronary artery or a failing heart valve that cannot be simulated on the bench or in animals. Device developers cannot always give animals the clinical problems they are trying to fix in humans. In some cases animal studies offer only limited insight and rarely provide a complete picture. Because of these limitations, testing devices in human subjects is ultimately needed to develop new therapies and establish whether they are safe and effective. For a novel device, when there may be questions regarding product performance in humans, sponsors often start with a small study that is termed a First in Human (FIH) study or an Early Feasibility Study (EFS). If an investigational device poses significant risk, whether brand new or being used in a novel way, sponsors must obtain Investigational Device Exemption (IDE) approval from the FDA to initiate a clinical study,<sup>3</sup> submitting an application with supporting data on safety, device design, testing results, and a plan to protect patients. If the FDA agrees that the study addresses a valid scientific question and that sufficient evidence exists to support it, approval is granted to begin the study. Following Investigational Review Board (IRB) approval, clinical sites may then begin enrolling patients under strict oversight with continued communication and reporting to the FDA throughout the study.

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<sup>2</sup> U.S. Food & Drug Administration. Early Feasibility Studies (EFS) Program. Website: [Early Feasibility Studies \(EFS\) Program | FDA](#)

<sup>3</sup> U.S. Food & Drug Administration. Investigational Device Exemption (IDE). Website: [Investigational Device Exemption \(IDE\) | FDA](#)

## The Shift Away from the U.S.

The United States has consistently maintained its position as a global leader in medical device and technology innovation.<sup>4</sup> Historically, much of the Intellectual property creation, engineering, venture investment, and enterprise development has taken place in the US.<sup>5</sup> Despite this, early clinical evaluation of novel devices in the U.S. began to decline in the early 2000s.<sup>6</sup> Data from ClinicalTrials.gov demonstrate that in 2004, approximately 87% of initial medical device clinical studies were conducted in the U.S., but by 2009 this figure had fallen to 45%.<sup>7</sup> A striking consequence of this trend is that the U.S. was only the 42nd country to approve transcatheter aortic valve replacement (TAVR) for clinical use.<sup>8</sup>

Over time, both the FDA and U.S. society became increasingly conservative regarding how much data was needed to approve an IDE for early human research. Over time, review team expectations for the information needed to support even initial clinical investigation in the U.S. have increased. As review teams have expanded to include additional scientific and technical expertise, the depth and rigor of data evaluation has correspondingly grown, resulting in more detailed information requests prior to first-in-human approval. The regulations themselves didn't change dramatically—but the way they were interpreted and applied did. As a result, the bar for non-clinical testing kept rising. Developers were required to conduct increasingly extensive nonclinical studies—bench tests for fatigue and durability, animal studies for biocompatibility—before initiating an EFS, all of which were expensive and time-consuming. And yet, many of these tests were not adequate to answer the most relevant questions around whether a product may work as intended in the clinic. In some cases, the scope and timing of preclinical testing expanded to the point that it slowed transition into early clinical investigation. Rather than reflecting device safety concerns, this often stemmed from uncertainty about how much data was necessary prior to first-in-human use. FDA's Early Feasibility Study guidance emphasizes a “right testing at the right time” approach, recognizing that certain questions are more appropriately answered through carefully monitored early clinical experience when nonclinical models have limited ability to fully predict human performance. Significant delays to regulatory approval stemmed from regulatory complexity, prolonged site contracting and IRB review processes, and uncertainty in payer coverage. In addition to delays, these complexities led to increased product development costs, and greatly impacted new companies' ability to partner with US sites. As a result, sponsors collectively pursued first-in-human (FIH) trials outside the U.S., leading to costly and inefficient development cycles which delayed access for American patients to groundbreaking technologies

Recognizing the need for reform, the FDA's Center for Devices and Radiological Health (CDRH) launched initiatives in the early 2010s to promote early-stage device evaluation within the U.S. These efforts culminated in the FDA's 2013 EFS Guidance, which formally defined an Early Feasibility Study as “a limited

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<sup>4</sup>Peter G. Peterson Foundation. U.S. Healthcare System Ranks Seventh Worldwide — Innovative but Fiscally Unsustainable. Website: [U.S. Healthcare System Ranks Seventh Worldwide](#)

<sup>5</sup>Research FDI. Why the US Leads the World in Entrepreneurship and Innovation. Website: [Why the US Leads the World in Entrepreneurship and Innovation - ResearchFDI](#)

<sup>6</sup>U.S. Food & Drug Administration. GUIDANCE DOCUMENT Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies. Website: [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies | FDA](#)

<sup>7</sup>Clinical Trials.gov. Trends and Charts on Registered Studies. Website: [Trends and Charts on Registered Studies | ClinicalTrials.gov](#)

<sup>8</sup>Clinical Trials.gov. Trends and Charts on Registered Studies. Website: [Trends and Charts on Registered Studies | ClinicalTrials.gov](#)

*clinical investigation of a device early in development, typically involving 10–20 patients, intended to gain initial insights into device safety and performance”*<sup>9</sup> The guidance emphasized that EFS were not intended to replace pivotal trials but to bridge preclinical testing, first in human (FIH) evaluation, and later pivotal studies. More importantly, the program allows for a staged and appropriate preclinical data package, recognizing that certain device performance questions cannot be fully addressed through nonclinical testing alone and may be more appropriately evaluated through carefully monitored early clinical experience.

The passage of the 21st Century Cures Act in 2016 further strengthened the EFS framework by modernizing regulatory processes and enabling better integration of real-world evidence (RWE), faster approval tools, and closer FDA-CMS alignment.<sup>10</sup> Between 2017 and 2021, FDA reported shorter IDE review timelines, with many EFS approvals granted within the first review cycle when submissions were developed collaboratively between sponsors and FDA.<sup>11</sup>

The agency also encouraged development of “EFS-ready sites”, institutions with dedicated infrastructure and standardized contracting templates designed to minimize start-up delays (MDIC, 2023). However, reimbursement continues to challenge program scalability. Under CMS policy, Category A IDE devices (considered experimental) are not eligible for device cost reimbursement, while Category B devices may qualify for both device and routine care coverage if sufficient evidence supports potential benefit (CMS, 2022). Commercial payers tend to be even more restrictive, frequently categorizing investigational devices as experimental and denying reimbursement.

## The Global Expansion of Early Feasibility Studies: Insights from HEU-EFS

While the U.S. FDA has refined its domestic EFS model, the HEU-EFS (Harmonized Approach to Early Feasibility Studies for Medical Devices in the European Union) initiative, launched under the European Commission’s Horizon Europe Programme, aims to build a harmonized pan-European approach for early device testing.<sup>12</sup> Coordinated by Bocconi University and multiple public-private partners, the HEU-EFS consortium is focused on reducing regulatory fragmentation, improving ethical and methodological consistency, and promoting a shared framework for early-stage device evaluation across EU member states.

*The HEU-EFS project’s objectives include:*

- Developing common regulatory and ethical review standards across Europe;
- Establishing pilot sites to conduct harmonized EFSs;
- Building stakeholder engagement networks among regulators, HTA bodies, clinicians, and patients; and
- Creating evidence frameworks to support decision-making and early payer dialogue (HEU-EFS, 2024).

<sup>9</sup> U.S. Food & Drug Administration. Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies Website: [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies | FDA](#)

<sup>10</sup> U.S. Food & Drug Administration. 21st Century Cures Act. Website: [21st Century Cures Act | FDA](#)

<sup>11</sup> U.S. Food & Drug Administration. (2021). Center for Devices and Radiological Health annual report. Silver Spring, MD: FDA.

<sup>12</sup> European Patient Forum. HEU-EFS. Website: [HEU-EFS](#)

Recent European research reinforces the importance of such alignment. A 2024 study by Ferrara et al. highlighted the global trend toward adaptive, risk-based, and collaborative feasibility frameworks to accelerate innovation while maintaining patient safety and ethical integrity.<sup>13</sup> The HEU-EFS initiative reflects this evolution—mirroring the FDA’s EFS goals of fostering early, data-driven iteration while strengthening patient protection.

### *A Global Workaround*

As expectations for the scope and timing of preclinical data to support first-in-human investigation increased, many companies began initiating their early feasibility or FIH studies outside the United States. By the 1990s, although the U.S. remained a global leader in device design and innovation, early clinical research activity expanded to regions such as Europe, Australia, New Zealand, and parts of South America, where regulatory pathways for early clinical evaluation were often more predictable in timing.

In some instances, devices designed in the United States entered clinical use abroad while U.S. IDE review processes were still ongoing. However, conducting early studies outside the U.S. was not a substitute for meeting FDA requirements. FDA appropriately requires adequate nonclinical testing to address specific safety and performance questions, and clinical data do not replace necessary bench or animal studies when those investigations are needed to answer defined scientific aims (e.g., histologic assessment or durability testing).

While non-U.S. clinical data may be incorporated into U.S. regulatory submissions, reliance on overseas early experience did not eliminate the need for appropriate supporting data. As a result, U.S. patients and physicians often did not have timely access to early investigational technologies intended to address unmet clinical needs.

### *A Turning Point*

Over time, FDA and stakeholders recognized the importance of ensuring that preclinical expectations were appropriately aligned with the stage of device development. This led to greater emphasis on whether sponsors were conducting the right testing at the right time—balancing the need for sufficient nonclinical evidence with the value of obtaining early clinical data under carefully controlled conditions. This was a particularly pressing issue for medical devices, which evolve rapidly. Unlike drugs, which often remain chemically stable, devices are constantly updated based on experience gained in their use. Each year brings improvements: smaller footprints, greater flexibility, better deliverability. Just like smartphones, each generation builds on the last. For instance, the evolution of TAVR (transcatheter aortic valve replacement) devices—from early models to the current SAPIEN 3—shows how iterative and fast-paced this field is.<sup>14</sup>

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<sup>13</sup>Ferrara, M., Piro, A., Martinelli, A., & Ciani, O. (2024). Therapeutic advances and early feasibility frameworks for medical device evaluation: A global perspective. *Frontiers in Medical Technology*, 6(2), 118-129. <https://doi.org/10.3389/fmedt.2024.011812>

<sup>14</sup>Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *New England Journal of Medicine*. 2016.

## **The Creation of EFS**

To improve the device innovation and early clinical study ecosystem, the FDA introduced the EFS guidance document and the EFS program,<sup>15</sup> which were designed to bring early device testing back to the U.S. by right-sizing expectations. It enables sponsors to begin small, closely monitored studies in humans earlier in development, once they've demonstrated:

- Basic safety.
- A sound scientific rationale; and
- Enhance clinical study mitigation strategies..

The objective is not to reduce nonclinical testing, but to align it with the specific questions necessary to support early feasibility. Under a “right testing at the right time” framework, some uncertainties may be appropriately addressed in a controlled clinical setting. With strong oversight and predefined mitigation strategies, early human experience can inform iterative device development in a timely and evidence-based manner.

## **Reclaiming Leadership: A work in progress**

The introduction of the EFS pathway marked a critical step toward restoring the U.S. role in early-stage medical device innovation and clinical evaluation. Rather than lowering standards, the EFS approach aims to better align regulatory expectations with the realities of device development, recognizing that some questions can only be answered through carefully controlled early human use.

While still evolving, the EFS pathway is helping to rebalance safety and innovation, offering a structured way for sponsors to begin FIH studies earlier and with appropriate safeguards. It reflects a growing recognition that the road to meaningful clinical progress must be both scientifically rigorous and operationally feasible.

The effort to bring early research back to the U.S. and increase US patient access to novel investigational devices is ongoing. As more sponsors engage with the EFS framework, and regulators apply EFS principles, the pathway holds promise accelerate device development to address unmet clinical needs and ensure that transformative technologies reach patients not just faster but closer to home.

## **A Playbook for Advancing EFS**

This playbook is a collective summary of insights and lessons learned over the past 10 years. It reflects on the origins, impact, and future of EFS in the U.S., and offers a vision for how we can re-energize the process and expand access in the years ahead.

### **Target Audience: Startups**

The majority of EFS sponsors are small startup companies with limited financial resources and less experience running clinical trials. Rather than learning the hard way, through inefficient processes that can threaten a company's viability, this playbook aims to share knowledge and best practices from across the industry. By doing so, we aim to empower small companies to succeed and continue driving meaningful innovation in medical technology.

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<sup>15</sup>U.S. Food & Drug Administration. Early Feasibility Studies (EFS) Program. Website: [Early Feasibility Studies \(EFS\) Program | FDA](#)

## ***Target Audience: New Investigators and Sites***

To date, EFS activity has largely been concentrated in a limited number of high-volume, experienced centers. This concentration reflects the technical complexity, procedural demands, and data rigor required for early-stage investigation. Expanding EFS indiscriminately to inexperienced or low-volume sites may compromise data quality, enrollment efficiency, and patient safety.

This Playbook is therefore designed not to broadly decentralize EFS, but to support capable centers that are prepared to meet the clinical, operational, and safety expectations of early feasibility research. It provides practical guidance, shared insights, and actionable strategies to strengthen internal infrastructure, improve consistency, and reduce avoidable startup barriers while maintaining the rigor required for high-quality early-phase investigation.

Above all, EFS thrives in a collaborative ecosystem. The most successful efforts are those where clinicians, sponsors, regulators, and patients engage early and often breaking down silos and working toward a shared goal: bringing safe, effective, and innovative treatments to patients faster.

This playbook is a resource for everyone committed to advancing that goal. Whether you're a sponsor, investigator, coordinator, or part of a clinical operations team, you'll find practical strategies, lessons learned, and tools to support successful EFS implementation—from concept to execution.

***Let's build the future of innovation—together!***

## Abbreviations

Term	Definition
AE	Adverse Event
CDRH	Center for Devices and Radiological Health
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CV	Curriculum Vites
DES	Device Evaluation Strategy
DOA	Delegation of Authority
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
EFS	Early Feasibility Study
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
FIH	First in Human
GCP	Good Clinical Practice
HEU-EFS	Harmonized European Union - Early Feasibility Studies
IA	Investigator Agreement
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
LAR	Legally Authorized Representative
MDR	Medical Device Regulation
MSP	Medicare Secondary Payer
OR	Operating Room
ORA	Office of Regulatory Affairs
OUS	Outside U.S.
PI	Principal Investigator
PVP	Payer Value Proposition
RCT	Randomized Controlled Trial
RWE	Real World Evidence
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOC	Standard of Care
SOP	Standard Operating Procedures
SQF	Site Qualification Form
SQV	Site Selection Visit
SSQ	Site Selection Questionnaire
TAVR	Transcatheter Aortic Valve Replacement
US	United States
V&V	Verification and Validation

# Chapter 2 Regulatory Framework & IDE Approval

## Early FDA Engagement Strategy

Early interaction with the FDA is critical to the success of an EFS. Sponsors should approach this as a layered process, beginning with informal engagement and gradually progressing toward structured regulatory submissions. The Q-Sub process is a voluntary process through which companies can receive valuable FDA guidance and feedback prior to submitting, or during FDA's review of, applications for device marketing authorization.<sup>16</sup>

One of the most effective starting points is an informational meeting. A meeting may be conducted in-person (face-to-face) or virtually (by videoconference or teleconference) or as a hybrid of the two.<sup>17</sup> This type of meeting is highly recommended for sponsors developing novel or first-in-class technologies. The purpose is to introduce the device concept, mechanism of action, and intended clinical use in a one-way, non-binding format. Best practice in informational meetings is to focus on the device concept, clinical context, and unmet need rather than overwhelming reviewers with detailed technical data. Although at this stage, the FDA may begin digging in and asking technical questions that would clarify their understanding of the product; sponsors should be prepared to have those conversations.

Once the FDA has a clear grasp of the technology, sponsors should submit pre-submission (Q-sub) supplements to aid in aligning expectations for IDE submissions. The purpose of these interactions is to obtain FDA feedback on the sponsor's proposed Device Evaluation Strategy (DES), animal testing plans and protocol, biocompatibility assessment approach, and the clinical protocol. Generally, a clinical protocol synopsis and not the full protocol is submitted. Experienced advisors consistently view this step as essential; bypassing it often means losing opportunities to adjust course before costly mistakes are made. While each Q-submission does add approximately 70 days to the timeline, this upfront investment prevents costly setbacks and significantly increases the likelihood of first-round IDE approval.

### Case Example

One sponsor skipped pre-submissions and submitted a full IDE package directly to the FDA. The FDA issued a 38-page deficiency letter, citing inadequate animal study duration, inappropriate test articles for biocompatibility testing, and a poorly justified sample size. Correcting these deficiencies delayed their FIH enrollment by nearly a year and required additional expenses for repeating tests.

<sup>16</sup>U.S. Food & Drug Administration. Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program. Website: [Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program | FDA](#)

<sup>17</sup>U.S. Food & Drug Administration. Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program. Website: [Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program | FDA](#)

## Case Example

A sponsor pursuing a novel transcatheter valve structured its FDA engagement into four pre-sub: DES overview, bench testing, animal study design, and clinical strategy. By the time the IDE was filed, the FDA had already weighed in on every major component. The IDE was approved on the first review cycle, with only minor clarifications requested interactively.

A layered engagement strategy provides strategic benefits for both sponsors and regulators. It helps prevent common mistakes, such as conducting costly (time and money) animal studies without FDA input or designing inclusion/exclusion criteria that unintentionally limit enrollment. It also creates space for FDA to offer insights informally, without the constraints of binding feedback, which can often be more useful during early device development.

Finally, sponsors should avoid discussing clinical protocol details prematurely. Diving too deeply into trial design before addressing core device safety and engineering issues can distract from the foundational aspects of regulatory review. Worse, it may lock the sponsor into impractical study designs made without sufficient context. The most effective early engagement focuses on device fundamentals, risk mitigation strategies, and building FDA confidence, reserving detailed clinical discussions until later in the process.

## Case Example

In one EFS program, a sponsor spent its first pre-sub meeting walking through an overly detailed draft protocol. FDA reviewers redirected the discussion back to basic device safety concerns, and the clinical protocol had to be rewritten three months later. By contrast, focusing early conversations on DES and risk mitigation allows protocol design to be built on a stronger foundation of understanding the limitations of the device and its usage gleaned from the DES.<sup>18</sup>

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<sup>18</sup>U.S. Food & Drug Administration. GUIDANCE DOCUMENT Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies. Website: [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies | FDA](#)

## Sponsors new to EFS can learn from these strategies...

### ***Engage FDA Early & Often***

Use multiple Q-Subs, break up complex topics, and seek iterative feedback.

### ***Come Prepared***

Submit focused questions, bring decision-makers, and use meeting time efficiently.

### ***Document Agreements***

Document minutes, clarify binding vs. advisory feedback, and prevent scope creep.

### ***De-Risk via Pre-Subs***

Focus on animal studies, biocompatibility, and test duration to avoid IDE deficiencies.

### ***Design Flexible Protocols***

Design Flexible Protocols – Broad inclusion, optional assessments, and pre-approved ranges to limit amendments.

### ***Balance Speed & Compliance***

Use 5 -day notices wisely and consult FDA when uncertain.

### ***Align Global & U.S. Strategies***

Coordinate outside the US (OUS) and US studies to maintain consistency and avoid duplication.

### ***Communicate with Stakeholders***

Keep FDA, CMS, IRBs, and sites engaged with clear materials and timelines.

### ***Engage Constructively When Clarification is Needed***

Seek alignment on requests by referencing EFS guidance, scientific rationale, and alternative approaches.

### ***Plan Early for Pivotal***

Collect data to inform endpoints, event rates, and pivotal study design from the start.

Figure 2. Tips and strategies for sponsors that are new to EFS.

## The Importance of Choosing a Good Consultants

Selecting the right consultants is one of the most important strategic decisions a sponsor can make during an EFS. Experienced consultants bring specialized regulatory knowledge, industry perspective, and an understanding of how FDA engages with novel technologies. Their role goes beyond logistics; they help craft the overall regulatory strategy, determine what information should be submitted, and guide the timing and sequencing of submissions. Strong consultants also ensure that the narrative of the device and its value is clearly communicated, building confidence with FDA reviewers.

It is critical to distinguish between active and passive consultants. Active consultants collaborate closely with the sponsor, co-writing or refining pre-submission content, shaping the DES, and framing the testing rationale. They know how to “tell the story” Of the device in a way that resonates with regulators and are willing to push back or escalate when FDA feedback is unclear or inconsistent. In contrast, passive consultants simply compile sponsor input with little added perspective. This limited involvement can result in missed opportunities or regulatory missteps that may result in costly delays.

Another important role consultants may serve is helping sponsors clearly articulate how their development strategy aligns with regulatory expectations. FDA guidance documents, particularly for first-in-class technologies, often require thoughtful application to device-specific contexts. Experienced advisors can help sponsors communicate the scientific and risk-based rationale underlying their bench testing, animal studies, biocompatibility strategy, and clinical protocol design.

Rather than simply proposing an approach, effective communication frames the underlying assumptions, known limitations, and justification for the selected pathway. This enables productive dialogue, allowing FDA to evaluate the scientific reasoning and identify potential gaps or risks early—supporting refinement of the plan rather than default rejection based on incomplete context.

Consultants also contribute to relationship management with the FDA. Many trusted advisors have established rapport with agency reviewers, built over years of interactions. This familiarity can facilitate smoother, more candid discussions, particularly when the FDA has concerns. In some cases, the reputation of the consultant can lend credibility to the sponsor’s submission and help strengthen regulatory trust.

Most importantly, the right consultants can prevent costly mistakes. They help avoid premature or poorly framed IDE submissions, incomplete preclinical plans, or submissions that fail to address prior the FDA feedback. Poorly prepared IDEs can result in denials, long delays, or loss of trust, outcomes that can set a sponsor back months or even years.

The importance of selecting qualified consultants and advisors cannot be overstated. Having the right partner may be the difference between an efficient pathway to approval or unexpected delays.

**Choose wisely!**

### Case Example

A consultant incorrectly advised a sponsor to re-submit a failed 510(k) as a De Novo without adjusting the content, which led to additional delays

## Pre-Submission Preparedness, FDA Expectations, & Sponsor Challenges

Pre-submission meetings are not the place for brainstorming. Sponsors should arrive with defined questions, supporting data, and a clear strategy for discussion. Sponsors often underestimate the level of rigor FDA expects, even at this early stage. While EFS is intended to be exploratory, the agency may still apply mature standards—such as those used in pivotal studies (e.g., Mitral Valve Academic Research Consortium (MVARC) frameworks), to certain aspects of review. This creates natural tension; sponsors are seeking flexibility for early learning, while the FDA prioritizes patient safety and robust device evaluation. These dynamics are particularly challenging for novel or complex technologies, such as transcatheter mitral valve devices, where there is little precedent to guide expectations. Compounding this challenge is the limited pre-sub meeting time, which are typically one hour. If sponsors spend the time on unfocused presentations or tangential discussion, they miss opportunities to address critical questions. Professionalism, precision, and focus are essential for making the most of these sessions.

### Dos and Don'ts in Pre-Sub Meetings

#### Do:

- ✓ Arrive with a clear, prioritized agenda.
- ✓ Keep slides focused and streamlined (no data dumps).
- ✓ Bring decision-makers and subject matter experts who can respond in real time.
- ✓ Leave space for FDA questions and discussion.
- ✓ Capture key agreements in meeting minutes.

#### Don't:

- ✗ Spend the first 20 minutes on company history or marketing.
- ✗ Overload slides with technical details irrelevant to the meeting's goals.
- ✗ Assume FDA will guide the conversation if you stall.
- ✗ Talk over FDA feedback instead of listening.
- ✗ Walk in without alignment among your own team.

Figure 3. Advice for sponsor conduct during pre-sub meetings

Startups face unique hurdles in this space. Many smaller companies are unsure what information belongs in a pre-sub, and they often miss the opportunity to educate the FDA about their novel device. Others may not appreciate how collaborative the FDA can be, assuming the process is adversarial when in fact the agency is open to dialogue and encourages it.

Historically, there have been challenges that have stemmed from a legacy of mistrust and inconsistent FDA feedback. Sponsors sometimes perceive the FDA as changing requirements late in the process—for example, approving a performance goal in one pre-sub only to later request randomization. In most cases, these shifts are not due to official policy changes but rather reviewer turnover or differences in interpretation across divisions, or evolution in understanding and expectations over time. To manage this risk, sponsors should always ensure that agreements reached in pre-sub meetings are captured in the official meeting minutes; while technically non-binding, such feedback is often considered “binding in spirit” once documented. If the FDA later reverses course, those minutes provide a critical reference point to support escalation, and elevating the issue to senior staff (such as the Division Director) may be appropriate. Although sponsors are often reluctant to challenge the FDA directly, knowing when and how to escalate is backed by a clear record of prior agreements can be essential for keeping development timelines on track.

The variability of review teams also poses difficulties. Reviewers may handle multiple unrelated technologies, or they may be assigned to devices outside their primary area of expertise. Sponsors should never assume that FDA reviewers “know” their device simply because it has been discussed before. Clear, structured, and accessible communication is essential to bring new reviewers up to speed and to ensure that critical details are not lost.

A common but underappreciated risk in EFS is **scope creep**—the gradual expansion of study objectives beyond what is necessary for proof-of-principle. Unlike pivotal trials, the purpose of an EFS is not to provide definitive evidence of safety and effectiveness, but rather to generate early insights that guide device development and inform the design of larger studies. Scope creep often arises when investigators push for additional endpoints or procedures to satisfy academic interests, such as exploratory imaging, long-term follow-up, or secondary measures that are more appropriate for pivotal trials. While these requests may be well-intentioned, they can blur the purpose of the study, increase patient and site burden, and introduce unnecessary delays. Rather, sponsors should resist the temptation to overload an EFS with endpoints and instead keep objectives tightly focused:

- **Proof-of-principle:** Does the device function as intended in humans?
- **Initial safety:** Are there unexpected risks that preclinical testing did not identify?
- **Feasibility:** Can the device be delivered, deployed, and retrieved safely and reliably?

Keeping an EFS lean preserves its value as a developmental tool, accelerates learning, and allows sponsors to pivot quickly based on findings. Overly complex protocols, by contrast, slow progress and risk compromising both the efficiency and the clarity of the data generated.

## Avoiding Scope Creep: Keep EFS Objectives Focused

- EFS is designed for proof-of-principle and early safety insights.
- Investigators may push for extra and unnecessary endpoints to satisfy academic goals.
- Additional measures can blur the purpose of the study and slow progress.
- Stay disciplined: reserve complex or confirmatory endpoints for pivotal trials.
- A focused EFS = faster learning, cleaner data, and more efficient transition to pivotal studies.

Figure 4. Avoiding Scope Creep

## What a Well-Prepared Sponsor Looks Like

- Arrives with a clear, prioritized list of questions.
- Brings decision-makers who can commit to next steps.
- Submits structured briefing materials that are concise and accessible.
- Stays in “listening mode” to hear and integrate FDA feedback.
- Respects the one-hour meeting limit, focusing discussion on critical decision points.

Figure 5. Pre-Submission Sponsor Tips

## Device Evaluation Strategy Bridges Engineering, Safety, and Clinical Planning

Identification of the data necessary to support an early feasibility study should be based on a thorough device evaluation strategy (DES) that describes the device procedure, performance, and basic safety-related attributes and addresses the potential failure modes. The purpose of the device evaluation strategy is to facilitate FDA's understanding of the value of the leveraged information and why the information included in the Report of Prior Investigations is adequate to support IDE approval.<sup>19</sup> The DES is at the heart of an EFS pre-submission. More than a checklist, the DES serves as a narrative framework that explains how the novel features of a device will be evaluated to support early human use. It bridges engineering, safety, and clinical planning, giving FDA the context it needs to assess risk and feasibility.

A strong Design Evaluation Strategy (DES) does more than outline a bench testing program; it explains why each test, method, and sample size is appropriate for the device's intended use, technological characteristics, and innovation profile. The DES is typically focused on bench verification and validation activities. Biocompatibility assessments and animal studies, when applicable, are generally addressed in separate sections of the submission, each supported by their own risk-based scientific rationale.

Across all nonclinical components, FDA does not expect a simple inventory of tests. Rather, it expects a clear justification linking proposed evaluations to the specific risks, failure modes, and performance questions relevant to the device.

For first-in-class technologies, there is no universal template. Many EFS devices fall outside existing International Organization for Standardization (ISO) standards or FDA guidance documents. This should not be viewed as a disadvantage—FDA is often receptive to scientifically sound justifications for non-traditional evaluation approaches. In this way, the DES also functions as a storytelling tool, showing what is novel about the device, why traditional pathways may not apply, and how patient safety will be safeguarded. Experienced consultants can play a crucial role in shaping this narrative so that it aligns with FDA expectations and builds reviewer confidence.

The DES should also be treated as an iterative document. Many sponsors submit a focused DES pre-submission before launching expensive preclinical programs, giving FDA an opportunity to provide targeted feedback. This early input can prevent costly missteps, reduce the need for repeated studies, and ensure that the overall strategy remains fit-for-purpose as the device advances toward FIH use.

### From R&D to IDE: Determining Readiness and Transitioning to First-in-Human Trials

The decision to transition a device from research and development (R&D) into FIH or early clinical trials, such as an EFS (EFS), requires a holistic assessment rather than a strict formula. Readiness is judged by several interrelated factors. Foundational bench testing must be complete, demonstrating mechanical integrity, functional performance, delivery system usability, product sterility, and initial biocompatibility. During this early development period, FDA may exercise some degree of regulatory flexibility with the

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<sup>19</sup> U.S. Food & Drug Administration. Guidance for Industry and Food and Drug Administration Staff. Website: <https://www.fda.gov/media/81784/download>

numbers of test articles, select preconditioning or testing parameters, etc., which may also be true for GLP vs. GLP-like studies. Any deviation from standard expectations should be discussed or presented to FDA in a pre-submission setting. Appropriate animal studies are often needed to confirm in vivo safety and functionality, with number, scope and duration tailored to device type as negotiated with FDA.

The clinical need and taking a risk-based approach also matter when considering the path forward. When patients lack alternatives, earlier human use may be justified if paired with robust safety mitigations such as confirmation of bench characteristics, early understanding in known models, predefined monitoring plans, careful patient selection, and strong informed consent processes.

Sponsors need to assess whether their DES adequately documents critical attributes, completed testing, and potential failure modes. Ultimately, readiness means having enough nonclinical evidence to justify that anticipated benefits outweigh initial risks, while having a clear, risk-managed clinical plan in place.

## From Pre-Submission to IDE

One of the most critical junctures is knowing when to stop pre-submission discussions and move forward with a formal Investigational Device Exemption (IDE) filing. Signals of readiness include productive meetings where FDA provides specific expectations, complete submission materials with executable testing plans, and confidence that the device is sufficiently stable for FIH use. Importantly, readiness is not determined by patient numbers alone but by whether the device and sites are prepared for safe and effective enrollment.

Sponsors should avoid “pre-sub fatigue” which happens because of repeated cycles of submissions that delay progress and blur regulatory expectations. At some point, the right decision is to file the IDE. Protocol development should also run concurrently with engineering, ensuring that by the time testing is complete, the clinical design is ready for integration.

## IDE Approval Process

The IDE submission itself consolidates finalized testing, the investigational plan, and FDA feedback into a single application, which is the formal regulatory step that allows for initiation of human studies upon approval. In the past, the FDA sometimes granted conditional IDE approvals, but this practice has become increasingly rare following a policy change.

## Common IDE Submission Deficiencies

Even well-prepared sponsors often encounter setbacks during IDE review, many of which stem from common, recurring deficiencies. Understanding these pitfalls can help sponsors anticipate FDA expectations and strengthen their future submissions.

Animal studies are a frequent source of deficiency. Sponsors sometimes submit incomplete or poorly designed studies that fail to generate the level of evidence FDA requires for early human use. For implantable devices in particular, the absence of sufficient chronic data can be a major concern. Findings such as thrombus formation may be reported but not adequately addressed, leaving FDA uncertain about their clinical significance. Deficiencies also arise when studies are misaligned with FDA expectations regarding endpoints, study duration, or the choice of animal model.

Bench testing gaps are another common weakness. Submissions may lack critical validation and verification (V&V) data or fail to provide test protocols that justify the chosen methods. Inadequate rationales for test conditions, sample sizes, or acceptance criteria can also undermine FDA confidence in the testing program. Without this clarity, reviewers are left questioning whether the bench data truly supports the proposed clinical use.

A weak DES is often at the root of these problems. Some sponsors provide vague or incomplete test plans that fail to address key device risks, while others treat the DES as a simple list of tests rather than a cohesive narrative. The FDA expects the DES to integrate design features with test objectives and to clearly explain how the testing strategy mitigates risk in early human use.

Biocompatibility oversights are also frequent. Biocompatibility studies are needed for medical devices that come into direct contact or indirect contact with the human body. Such devices need to be evaluated for the potential for an unacceptable adverse biological response resulting from contact of the component materials of the device with the body. These include incomplete assessments, use of outdated standards, or omissions without justification. Sponsors may also fail to explain material changes or demonstrate equivalence to previously tested materials, gaps that can create unnecessary delays.

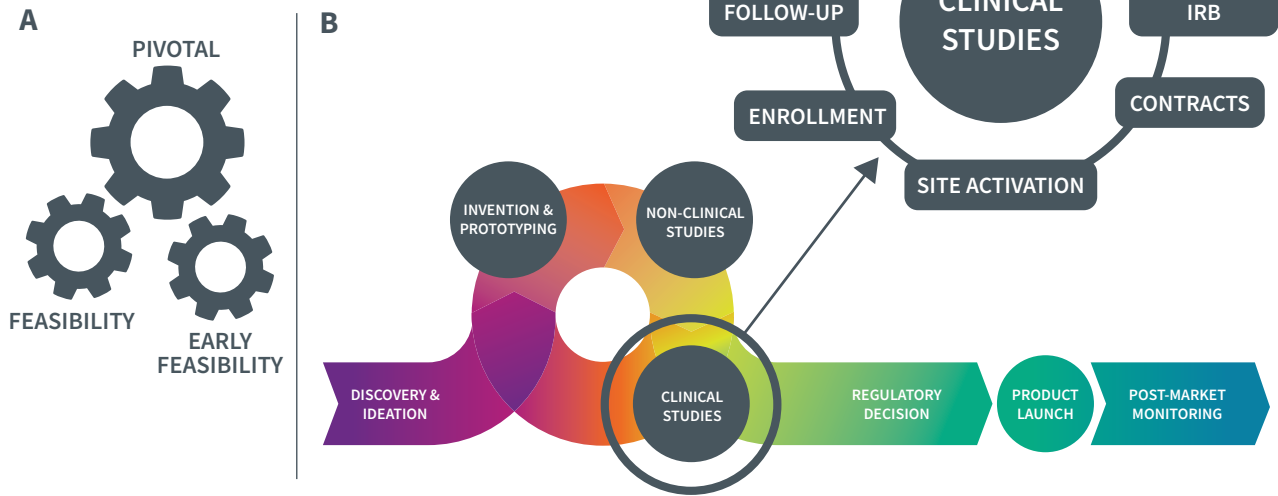
In the protocol or clinical synopsis, the FDA often sees overly ambitious or impractical inclusion/exclusion criteria that hinder enrollment. Other deficiencies include unclear primary objectives, vague endpoints, or missing follow-up plans. A frequent oversight is the absence of a safety monitoring strategy, such as Data and Safety Monitoring Board (DSMB) plans or stopping rules, which the FDA considers essential for patient protection in EFS.

Another recurring issue is the failure to explain how known risks will be mitigated. If preclinical studies or published literature highlight potential safety concerns, the FDA expects sponsors to describe how these risks will be managed in the clinical setting. Without a clear rationale for limiting patient exposure, IDEs are often delayed or denied.

Finally, sponsors sometimes submit IDEs that do not adequately address prior FDA pre-sub feedback. Ignoring or avoiding issues raised earlier almost guarantees further questions from the agency. Even if a sponsor disagrees with the FDA's position, the expectation is to provide a clear response and rationale, rather than leaving comments unresolved.

*Optional Note:* Many experienced reviewers also highlight administrative and formatting errors as a surprisingly common barrier. Missing Principal Investigator (PI) signatures, incomplete FDA forms (e.g., 1571, 3454/3455), inconsistencies across documents, or failure to organize submissions in the expected structure can slow review. While these issues may seem minor compared to scientific deficiencies, they often create a poor first impression. Even something as simple as spelling errors or inconsistent formatting can make the FDA more cautious in evaluating the submission. For many sponsors, avoiding these “easy” mistakes is the simplest way to distinguish themselves and build confidence with FDA reviewers from the outset.

## Central Illustration: Conducting EFS of Medical Devices in the United States



Holmes, Jr., D.R. et al. J AM Coll Cardiol. 2016;68(17):1908-15.

Figure 6. Conducting EFS of Medical Devices in the United States

## Chapter 3 Centers for Medicare and Medicaid Services

Centers for Medicare and Medicaid Services (CMS) beneficiaries often make up a substantial portion of patients enrolled in EFS, and CMS reimbursement is therefore extremely important. Generally, novel EFS devices are classified as experimental by CMS (category A); CMS may at their discretion, and consistent with their rules, cover reasonable and necessary costs associated with a category A device being studied in an EFS (but not the cost of the device itself). In contrast, for a category B device (nonexperimental or investigational), Medicare may cover the investigational device as well as the routine care and services.<sup>20</sup>

### Category A and B Device Classification

After receipt of an IDE application, FDA will determine whether the sponsor has provided enough information to support initiation of the clinical study. An IDE application is “approved,” “approved with conditions,” or “disapproved.” A study which has been approved or approved with conditions may be staged such that preliminary data can be reviewed prior to full patient enrollment. FDA uses specific criteria to assign a device to Category A or B when the IDE is approved or approved with conditions.

<sup>20</sup> ScienceDirect. The 21st Century Cures Act and Early Feasibility Studies for Cardiovascular Devices: What Have We Learned, Where Do We Need to Go?. Website: <https://www.sciencedirect.com/science/article/pii/S1936879818310926>

Category A (Experimental) refers to a device for which ‘absolute risk’ of the device type has not been established and the FDA is unsure whether the device type can be safe and effective. Category B (Nonexperimental/ Investigational) refers to a device for which the incremental risk of the device is the primary risk in question, or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA premarket approval or clearance for that device type.<sup>21</sup>

## Centers for Medicare and Medicaid Services and FDA Timing for EFS

Understanding the relationship between FDA approval and Centers for Medicare and Medicaid Services (CMS) review is critical for planning EFS. FDA designates the categorization of devices and CMS will only consider reimbursement for Category A or B devices once both the FDA has approved the IDE and the IRB has granted study approval. Until these prerequisites are met, sponsors cannot submit their CMS coverage crosswalk. Attempting to do so prematurely will result in rejection or delay.

The reason for this sequencing is straightforward: CMS requires confirmation that a study is both ethically and scientifically sound before it considers reimbursement coverage. FDA approval signals that the device is appropriate for human use in a controlled setting, and IRB approval confirms ethical oversight. Without these assurances, CMS will not evaluate the submission. Importantly, CMS is not looking for full statistical validation at this stage. Instead, it expects a plausible case that the device has the potential to provide health benefits to Medicare beneficiaries compared with available alternatives. Sponsors often over-interpret CMS requests, assuming they must present robust statistical proof, when in fact CMS is primarily seeking evidence of likely patient benefit to justify coverage during investigational use.

Sponsors should also avoid prematurely labeling their device as Category A or Category B. While a device may initially be expected to fall under Category A, FDA may later reclassify it as Category B based on its risk profile and available evidence, which would need to be submitted to CMS for Category B reimbursement. To prevent misalignment, sponsors should simply refer to their filing as a “CMS crosswalk submission” until the agency has formally confirmed categorization.

In most organizations, the CMS submission is managed by the contracting and reimbursement team, often with input from regulatory consultants. While this process is distinct from FDA review, it is closely tied to study startup timelines. Delays in coordinating FDA, IRB, and CMS submissions can slow patient enrollment and increase costs. For this reason, careful alignment of regulatory and reimbursement strategies is essential to keeping EFS programs on track.

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<sup>21</sup> U.S. Food & Drug Administration. FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions. Website: <https://www.fda.gov/media/98578/download>

## Common Misconception: CMS Requirements




-  **Myth:** CMS requires full statistical proof of safety and effectiveness before approving coverage.
-  **Reality:** CMS only needs a plausible case that the device could provide improved health outcomes compared with existing alternatives.
-  **Takeaway:** Do Not over-engineer the submission. Focus on demonstrating potential benefit for Medicare patients, not statistical validation.

Figure 7. Common myths and misconceptions of CMS requirements.

## CMS/Payer Chapter Summary

Optimizing CMS involvement in the regulatory pathways for novel medical devices is essential to ensuring that U.S. patients and providers have timely access to innovative technologies. Although the U.S. leads the world in intellectual property creation, engineering, venture funding, and company formation, the early device development process here has faced many challenges. Over the past two decades, there has been a sharp decline in the proportion of new device initial clinical studies performed in the U.S. ClinicalTrials.gov data show that in 2004, 87% of initial medical technology studies were conducted domestically, but by 2009 that number dropped to 45%.<sup>22</sup> Overall, device introduction in the U.S. has too often been characterized by costly and time-inefficient processes that drive early studies abroad, delaying access for American patients.

A critical enabler of EFS growth in the U.S. has been CMS's willingness to consider coverage for early-stage device studies. This represents an important step forward in supporting early innovation for patient benefit. However, coverage decision processes remain a barrier, particularly for FIH trials. CMS does not typically reimburse for true FIH procedures, meaning that initial data, often just a handful of cases, must be generated without reimbursement or conducted in countries with more flexible coverage or at lower cost. While some FIH studies will likely continue abroad, a refined CMS approach could help shift more early data collection back into the U.S., aligning with FDA's goal of ensuring American patients gain "first in the world" access to transformative technologies.<sup>23</sup>

There are also regulatory complexities around the Medicare Secondary Payer rule. Medicare Secondary

<sup>22</sup> Hwang et al., *Trials*, 2014; FDA IDE Guidance for Early Feasibility Studies, 2013.

<sup>23</sup> U.S. Food & Drug Administration. 2018-2020 STRATEGIC PRIORITIES Center for Devices and Radiological Health January 2018. Website: <https://www.fda.gov/files/about%20fda/published/2018-2020-Strategic-Priorities.pdf>

Payer (MSP) is the term generally used when the Medicare program does not have primary payment responsibility - that is, when another entity has the responsibility for paying before Medicare.<sup>24</sup> Medicare does not pay for services when another source, such as a sponsor, is expected to cover trial-related injuries. When sponsors agree to cover injury costs for privately insured subjects but not Medicare patients, CMS interprets this as liability insurance, which can trigger the MSP rule and block Medicare coverage. This has caused delays and inconsistent treatment across participants. Clarification is needed to determine whether sponsor coverage of injuries in EFS should be exempt from MSP liability insurance classification.

In addition to CMS's role, manufacturers must also be attentive to how broader payer perspectives shape evidence and coverage decisions. One central theme is the development of a Payer Value Proposition (PVP), a strategic positioning statement that defines the target population, identifies unmet clinical needs, and articulates the unique benefits of a device. Importantly, the PVP is not a marketing activity, but a tool to facilitate payer coverage and payment. To be effective, a PVP must extend beyond regulatory milestones and include evidence demonstrating the product's ability to address unmet needs, its comparative value against existing treatments, and its economic impact.<sup>25</sup> Manufacturers are encouraged to integrate economic and real-world outcomes into clinical trials to align with payer priorities, particularly long-term data (24–36 months) and real-world evidence (RWE). Payers value diverse forms of evidence, including peer-reviewed publications, randomized controlled trials (RCTs), and observational studies with diverse populations. Comparative data showing superiority or cost-effectiveness relative to current standards of care is essential, and inclusion of patient-centric metrics such as convenience, cost, and adherence can further strengthen the PVP.

Early and ongoing collaboration with payers during clinical trial development also improves alignment with coverage expectations. By engaging payers during trial design, manufacturers can ensure endpoints, study populations, and outcomes reflect both regulatory and reimbursement priorities, including patient outcomes, administrative costs, and health equity. Diversity in trials is another key priority, with FDA and CMS encouraging diversity action plans to ensure equitable access. The inter-agency agreement between CMS and FDA also provides opportunities for Medicare coverage of certain investigational devices under study, particularly Category B IDE devices.

Coverage for clinical trials remains complex and varies between CMS and commercial payers. CMS distinguishes between Category A and Category B IDE devices, with routine care costs generally covered for both, but direct device costs reimbursed only for Category B when criteria are met. Many commercial payers classify investigational devices as experimental and exclude coverage, although some, such as UnitedHealthcare, allow limited reimbursement for Category B IDE devices. Manufacturers are therefore encouraged to engage commercial payers directly, while also leveraging providers participating in clinical trials as advocates to support reimbursement. As payer interest in RWE grows, manufacturers should prioritize generating and presenting long-term effectiveness and economic data to strengthen their case for coverage.

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<sup>24</sup> CMS.gov. Medicare Secondary Payer. Website: [Medicare Secondary Payer | CMS](#)

<sup>25</sup> Medical Device Innovation Consortium. Framework for Patient-Centered Evidence Generation to Support Coverage and Payment Decisions. Website: [Integrating Real-World Evidence Into Evidence Generation Strategies To Expand Payer Coverage and Improve Patient Care - Medical Device Innovation Consortium](#)

The key takeaways for manufacturers are clear. Early integration of payer perspectives during product development and trial design increases the likelihood of alignment with payer evidence requirements and eventual coverage. A robust PVP should combine clinical, economic, and patient-centered evidence that demonstrates value relative to current treatment options. Familiarity with CMS and FDA pathways, including IDE classifications, can help navigate Medicare coverage opportunities, while tailoring strategies to the policies and concerns of individual commercial payers can maximize success. Collaboration with trial providers is equally important, as their advocacy can lend credibility and strengthen payer negotiations.

## Recommendations for CMS Engagement

### ***Parallel FDA–CMS Review*** ✓

Let CMS begin review once an IDE is submitted, so coverage and FDA approval run in parallel, not sequentially.

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### ***Tailored EFS Standards*** ✓

Create an EFS-specific coverage pathway focused on plausibility of benefit and unmet need, not statistically powered designs.

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### ***Pilot Coverage Models*** ✓

Allow conditional/time-limited coverage for small FIH cohorts, tied to safety oversight.

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### ***Transparency & Communication*** ✓

Build formal FDA–CMS–sponsor communication channels to avoid inconsistency.

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### ***Incentivize Domestic Participation*** ✓

Offer reimbursement or administrative relief for U.S. EFS to keep innovation domestic.

Figure 8. Recommendations for CMS engagement.

# CMS Coverage for EFS IDE Medical Devices

CMS coverage for EFS IDE studies depends on clinical maturity and relevance to Medicare beneficiaries.

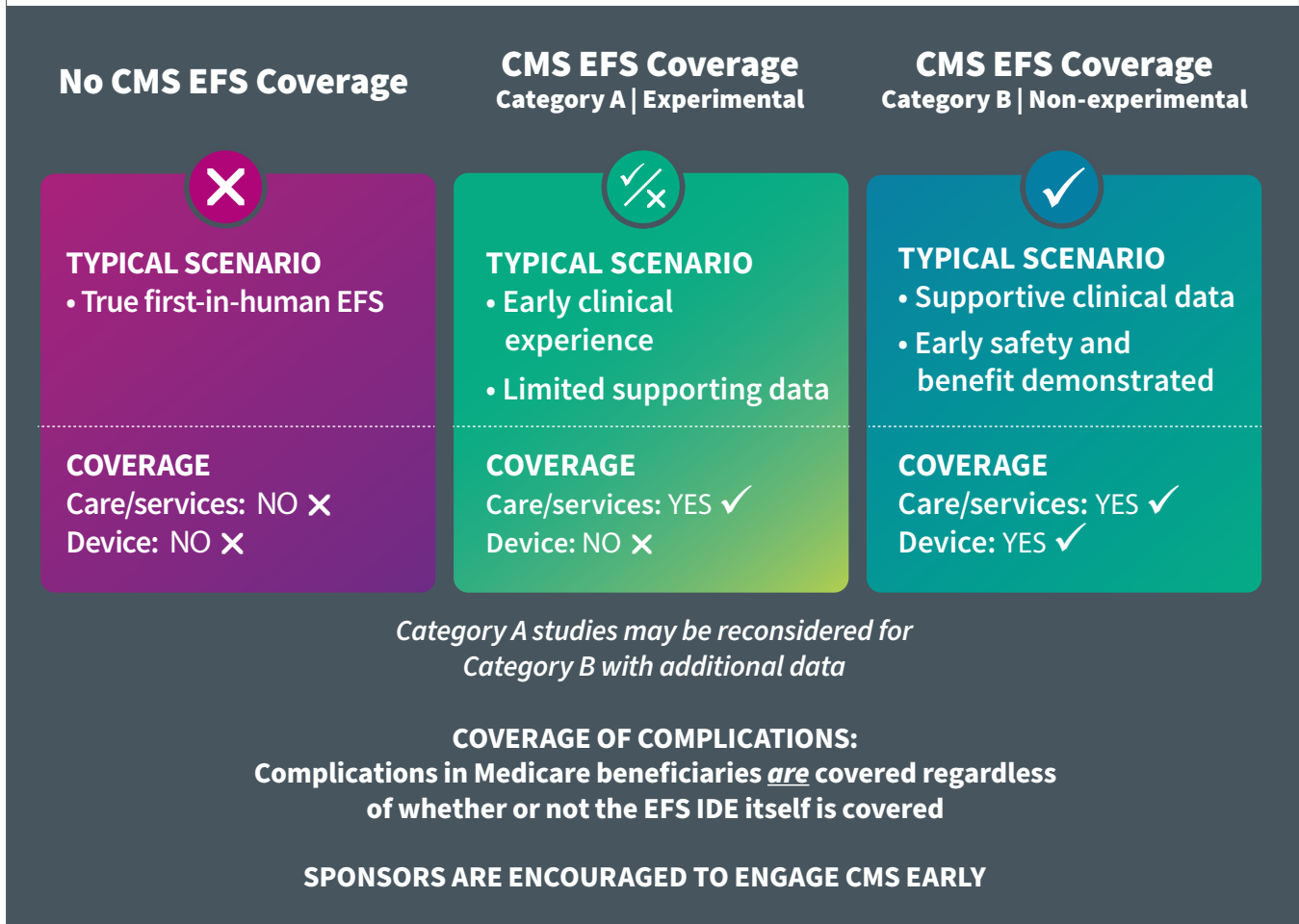


Figure 9. CMS Coverage Decision Table for EFS<sup>26</sup>

## Chapter 4 Site Institutional Alignment: IRBs & Leadership Buy-in

IRB EFS refers to the Institutional Review Board (IRB) oversight of Early Feasibility Studies. The IRB’s role is to ensure ethical guidelines are met, and the collaboration between the IRB and the study sponsors is critical for the success of these studies. Both IRB and administrative leadership support are critical for EFS success.

<sup>26</sup>Medical Device Innovation Consortium. Website: <https://mdic.org/wp-content/uploads/2022/09/SNIS-slide-deck-EFS-presentation.pdf>

## Making the Case for EFS to IRB

Institutional Review Boards (IRBs) play a pivotal role in reviewing and approving EFS protocols. While IRB review is often perceived as a bottleneck, in practice many delays stem from contracts and budgets rather than the IRB itself. Nonetheless, engaging the IRB effectively is critical because EFS protocols differ significantly from traditional pivotal trials. They involve more uncertain risk/benefit profiles, frequent modifications, and limited early data—all of which can challenge reviewers and slow approvals if not managed proactively.

A central difficulty for IRBs is evaluating risk when devices have not yet been tested in humans. Determining whether potential benefits outweigh unknown complications is complex, especially when commercial alternatives already exist, and investigators must justify why a new device is meaningfully different. EFS studies also evolve quickly; multiple amendments are often required as devices are refined. IRBs may be unaccustomed to this pace of iteration and may struggle with balancing oversight and efficiency. Informed consent reviews can also present challenges, with some boards focusing heavily on semantics rather than the integrity of the process itself. Adding to this complexity, institutional variability means that IRB questions and expectations differ widely across committees.

### Case Example: Large Academic Institution

During the start of the EFS wave, institutional leadership recognized the importance of securing IRB confidence in a study that carried significant procedural risks. Rather than relying on standard submissions, senior faculty personally presented the protocol to the IRB, highlighting both the clinical urgency and the scientific rationale for early human use. This direct engagement created trust, established shared responsibility, and led the IRB to expedite reviews when flagged as high priority. The institution's experience illustrates that treating the IRB as a partner—and positioning EFS as an institutional program rather than a single trial—can transform the review process into a collaborative effort rather than an obstacle.

Several strategies can improve the likelihood of success. Engaging IRB leadership early is critical. Meeting directly with the IRB Director to explain the institutional importance of EFS—how it contributes to reputation, scientific leadership, and patient access to innovation—helps secure buy-in. Emphasizing timeliness is also important, as slow U.S. reviews risk pushing innovation overseas. Involving physician-investigators directly in IRB meetings further strengthens communication, since clinicians can explain device rationale and patient need more effectively than administrators alone. Proactive communication also matters: notifying the IRB when an EFS protocol is coming, answering questions before formal meetings, and providing outcome updates during modifications or renewals reinforce the program's value and build trust. Above all, EFS patients should be framed as those with few or no alternatives, positioning the risk/benefit discussion around unmet need rather than comparisons to established commercial therapies.

Institutions must also prepare IRBs for iteration. Multiple amendments are inherent to EFS, and some boards may request interim reviews after several months or a small number of patients. While early outcomes are usually too limited to provide definitive insights, setting expectations upfront helps IRBs anticipate and manage these processes.

## Single IRB

Single IRB (sIRB) models can dramatically streamline approvals for multi-site EFS. In sponsor-driven approaches, commercial IRBs such as WCG<sup>27</sup> or Advarra<sup>28</sup> serve as the IRB of record, allowing subsequent sites to be added through simple administrative modifications—sometimes within five days. SMART IRB,<sup>29</sup> a national academic consortium, offers another pathway, though it tends to move more slowly than commercial boards. Even when relying on an sIRB, however, sites still conduct local feasibility checks for training, conflicts of interest, and compliance.

## Rapid Activation

At institutions that do not permit sIRB reliance, a rapid activation pathway can achieve similar efficiency. This approach involves early engagement with IRB leadership, pre-negotiated templates for consent and boilerplate language, and internal flagging systems to prioritize EFS submissions in the review queue. Parallel processing of contracts and budgets alongside IRB review prevents sequential delays, and encouraging the PI to attend meetings ensures that technical questions can be addressed in real time. Institutions that have implemented these pathways have reported turnaround times of two to three weeks—comparable to commercial sIRB reliance but with the benefit of maintaining local oversight.

Other case experiences reinforce this point. At risk-averse institutions, some EFS programs never launched when IRBs and institutional committees judged risk or conflicts of interest too high—for example, when the PI was directly involved in device development. By contrast, academic centers like Buffalo implemented hybrid “rolling review” models, where IRBs conducted interim evaluations every six months to balance oversight with speed.

From these experiences, several recommendations emerge. EFS should be positioned as an institutional priority, framed around benefits for patients, reputation, and innovation. Engagement with IRB leadership must begin early, and investigators should take an active role in discussions. Institutions should anticipate protocol amendments and maintain transparent communication, leveraging sIRBs whenever possible. Where reliance models are not permitted, rapid activation processes can prevent multi-month delays. Finally, risk/benefit discussions should always emphasize unmet patient need, and outcome updates should be shared regularly with IRBs to reinforce trust and support.

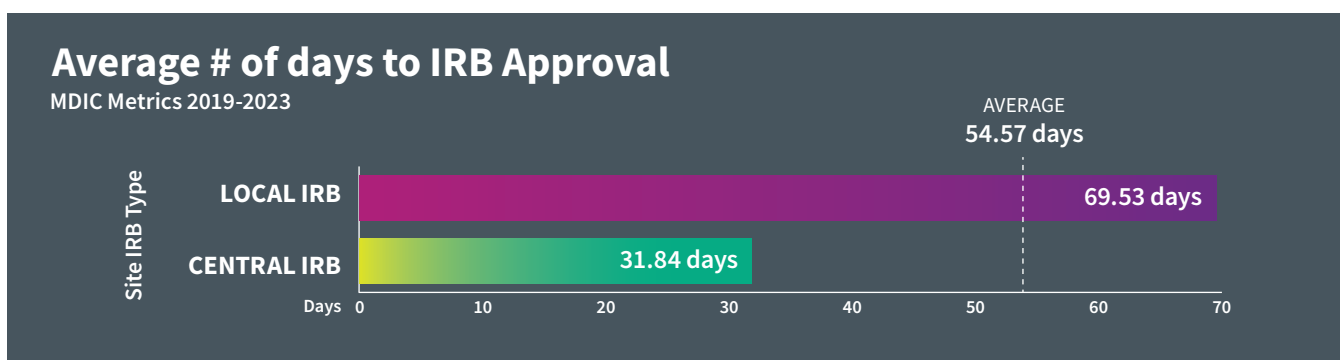


Figure 10. MDIC metrics for average number of days to IRB approval for timeframe 2019 to 2023

<sup>27</sup> WCG. IRB Review Solutions. Website: [IRB Review Solutions](#)

<sup>28</sup> ADVARRA. IRB Services Institutional Review Board (IRB). Website: [Institutional Review Board \(IRB\) Services - Advarra](#)

<sup>29</sup> SMART IRB. Website: [Home - SMART IRB | National IRB Reliance Initiative](#)

## Making the Case for EFS to Administrative Leadership

Securing institutional buy-in is critical for the success of EFS. These studies carry inherent risks and require leadership willing to balance potential complications against the opportunity to advance innovation and patient care. The right champions are not always the CEO or CMO; engagement should instead focus on leaders who understand the tradeoffs, such as clinical directors, IRB leaders, and senior research administrators. The goal is not to “sell” EFS but to explain it in clear, relatable terms: why the institution is uniquely positioned to participate, how participation differentiates it as a leader in innovation, and what benefits it brings in terms of reputation, access to novel technologies, and enhanced patient options.

The importance of institutional support becomes clear when looking at early experiences such as the first TAVR trials in 2002.<sup>30</sup> After only five patients, safety concerns forced the study to pause. At that moment, the institutional leadership played a critical role by prioritizing patient safety and supporting technical improvements before resuming. Their collective judgment, modeled on a “Heart Team” approach, was essential to navigating uncertainty and building trust. Just as FDA evaluates risk and benefit iteratively at each stage of device development, institutions must adopt the same mindset. Those lacking the risk tolerance, expertise, or infrastructure to manage this process will struggle to support EFS effectively.

Innovation inevitably carries risk, particularly when treating very sick patients who have no other options. Complications are expected and should be recognized as part of the process rather than as failures. Many devices do not advance beyond the EFS stage, but that reflects EFS’s purpose: to determine viability early and prevent costly missteps later. Because EFS often involves patients who are sicker or unrepresentative of pivotal trial populations, protocols should remain separate to preserve flexibility and avoid compliance burdens that can hinder early learning.

When approaching administrative leaders, investigators should be prepared to address their most pressing concerns. Liability from rare but severe complications, financial risk from unreimbursed care, and reputational exposure if adverse outcomes occur are all common worries. Mitigation strategies must be clear. Strong indemnification language in contracts protects the institution, while a robust informed consent process builds trust with patients and families. When patients understand the risks and feel respected, they are far less likely to pursue legal action in the event of complications. EFS should also be framed to patients and referring physicians as an option that advances future care rather than a guaranteed benefit: “This investigational therapy may help you, but it also helps us learn for future patients.”

Financial realities must also be acknowledged. FIH studies are rare in the US because CMS does not reimburse them, leaving hospitals or sponsors to absorb costs. Occasionally, institutions agree to cover a limited number of cases to secure prestige and position themselves as leaders in innovation. Administrators must understand that reimbursement is unlikely, risks are real, and unforeseen complications are part of the process. Yet participation provides powerful non-financial benefits: prestige, national reputation, differentiation, and early access to new technologies. Even without cost-effectiveness data, leaders can appreciate the potential for improved patient outcomes, reduced readmissions, and better long-term

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<sup>30</sup> New England Journal of Medicine. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. Website: <https://www.nejm.org/doi/full/10.1056/NEJMoa1008232>

value. Investigators should emphasize these future-oriented benefits, especially since many hospitals tend to focus narrowly on short-term financial performance.

Another cultural issue is publication. Many EFS results remain unpublished because sponsors fear reputational harm from early complications or incomplete data. This is a missed opportunity. EFS demands excellence and should be treated as a privilege. Only highly skilled and deeply committed teams should undertake this work, and institutions that embrace transparency and share lessons publicly will build credibility and advance the field as a whole.

Finally, building a culture of support requires preparing administrative leaders well in advance. Senior leaders must be educated and supportive before complications arise. This experience illustrates: senior physicians and administrators personally presented early high-risk work to the IRB, ensuring thoughtful review and avoiding later pushback. Complications are inevitable, but they should be viewed as learning events that guide future trial design and device development. Institutions that foster a culture of excellence, thoughtful innovation, and shared responsibility—rather than personal ambition or self-promotion—are best positioned to succeed.

EFS is not routine research; it is a privilege that demands an institution's A team across clinical, operational, and administrative domains, with leadership prepared to navigate uncertainty and treat complications as essential learning.

## Chapter 5 Site Selection & Qualification

### Why EFS Site Selection Requires a Different Approach

Site selection is the process of identifying and evaluating potential investigative sites to determine if they are suitable for participation in a clinical trial. EFS site selection, however, is fundamentally different from routine clinical trial site selection. While traditional studies emphasize infrastructure, staffing levels, and track record, EFS success often depends more on a site's "soft skills"—the ability to pivot quickly, manage uncertainty, communicate effectively with sponsors and key internal stakeholders (IRB/contracts), and problem-solve in real time. These attributes are harder to measure but critical in a FIH or early-device context.

Despite this, many sponsors still use the same generic Site Selection Questionnaires (SSQs) and Site Qualification Forms (SQFs) for EFS that they use for pivotal or late-phase studies. Standard forms, often developed by Contract Research Organizations (CROs), tend to be lengthy; exhaustive checklists focused on facilities and equipment, while overlooking the qualities that actually drive EFS success.

Best practice is to develop an EFS-specific site qualification process, streamlined to evaluate both infrastructure and partnership potential. This means assessing how well the site communicates, adapts to evolving requirements, and engages proactively with sponsor teams. Tailored tools not only reduce site burden but also generate more meaningful insights for sponsors, enabling them to select sites that can execute safely, compliantly, and efficiently in the high-stakes EFS environment.

## Current Industry Standards & Efficiency Impacts

In practice, many EFS site selections are still based on relationships or institutional reputation rather than objective readiness criteria. While this may appear efficient on the surface, it often results in inefficiencies:

- Delays in startup timelines.
- Mismatches between site capabilities and study requirements.
- Missed opportunities to expand into new or diverse regions.

These inefficiencies highlight a fundamental gap: current industry practices prioritize administrative completeness over operational readiness. For EFS in particular, this approach slows innovation, wastes resources, and frustrates sites without meaningfully improving study quality. Addressing these gaps requires a best practice workflow for site qualification—one that emphasizes clarity, efficiency, and two-way partnership rather than bureaucracy.

New sites, in particular, face steep barriers to entry. Without mentorship, clear expectations, or streamlined processes, they struggle to break into the EFS ecosystem. The result is an environment that favors established players while slowing innovation. Most site selection frameworks remain rooted in pivotal trial practices. These emphasize exhaustive qualification questionnaires, detailed feasibility assessments, and extensive administrative review. While appropriate for large-scale pivotal trials, such processes rarely align with the needs of EFS—where nimbleness, rapid activation, and close collaboration with a small number of highly specialized investigators are far more critical.

Adapting these processes within large sponsoring organizations is difficult. Site selection forms, contracting workflows, and qualification procedures are governed by rigid internal change control processes. Updates require multiple layers of approval—from regulatory, legal, quality, and compliance teams.

The burden is equally heavy on sites. Research teams are often required to complete the same lengthy qualification forms across multiple studies for the same sponsor, consuming significant time and resources. While sponsors view these documents as essential for compliance (e.g. they satisfy corporate obligations under anti-kickback statutes, the Sunshine Act, and other healthcare regulations), they rarely provide meaningful insight into whether a site is truly suitable for an EFS partnership. The risk-management rationale is clear: sponsors must demonstrate site selection is based on objective criteria, not investigator preference or purchasing influence. But in practice, the process often slows down study initiation and creates friction between sponsors and sites.

Without proactive adjustments, sponsors risk carrying forward procedures designed for pivotal trials into early-stage studies, where they add administrative burden without advancing study success.

## Common Site Pain Points in Current Site Qualification

### **Redundancy** ↙

Sites complete lengthy forms only to re-answer the same questions during qualification calls.

### **Non-savable systems** ↙

Online platforms often cannot be saved mid-completion, forcing coordinators to re-enter data and gather information in real time.

### **Sequential navigation barriers** ↙

Forms that require advancing one question at a time prevent sites from anticipating what information will be needed, leading to repeated starts and stops as staff track down answers across multiple systems.

### **Ambiguity** ↙

Poorly scoped questions create confusion (e.g., “How many research studies?”—per PI, per service, or institution? “Any FDA audits?”—at the PI, group, or institutional level?).

### **Box-checking vs. intent** ↙

Forms capture compliance evidence rather than assessing true site suitability for EFS partnership.

Figure 11. Common site pain points during site qualification

## Sponsor Goals of EFS Site Selection

### **Document due diligence for regulatory purposes.**

- Sponsors must demonstrate to FDA and internal quality teams that site selection was systematic, consistent, and evidence-based, in compliance with [21 CFR 812.43](#)<sup>31</sup>
- This requires maintaining complete records of the qualification process, including site feasibility questionnaires, investigator curriculum vitae (CVs), standard operating procedures (SOPs), training logs, and site visit reports.
- Documentation should clearly show that each participating site was vetted for safety, compliance, infrastructure, and capability before enrollment began.

<sup>31</sup> National Archives. Code of Federal Regulations. Website: [eCFR :: 21 CFR 812.43 -- Selecting investigators and monitors.](#)

### ***Assess infrastructure and resources.***

- Confirm the site has the facilities and equipment needed to safely conduct early-phase device work (e.g., cardiac catheterization lab/Operating Room (OR) readiness, imaging access, -80° freezers, investigational product (IP) storage).
- Verify adequate staffing, including PI engagement and coordinator capacity.
- Ability to effectively streamline study activities and approvals with the IRB, contracts office, and C- suite.

### ***Evaluate experience and expertise.***

- Review the site's prior experience with investigational devices, EFS, or high-risk early-phase research.
- Confirm familiarity with regulatory reporting, DSMB oversight, and device accountability.

### ***Gauge patient pool and enrollment feasibility.***

- Assess whether the site can identify and recruit appropriate patients, given inclusion/exclusion complexity.
- Evaluate projected enrollment and sources of patients (e.g. clinic population, referral networks, registries).
- Confirm the site's capacity to conduct screening activities, which may be time-intensive, involve screening a large number of patients, and result in a high screen failure rate.

### ***Confirm quality systems and SOP alignment.***

- Ensure the site operates under SOPs that meet Good Clinical Practice (GCP), FDA, and sponsor expectations.
- Assess training documentation, delegation processes, consent procedures, and safety reporting pathways.

### ***Establish monitoring and communication plans.***

- Set expectations for monitoring frequency, reporting requirements, and communication channels.
- Identify escalation paths for protocol deviations, safety issues, or enrollment challenges.
- Emphasize the importance of consistent communication between the site and sponsor, including scheduled check-ins and proactive updates to ensure alignment and timely issue resolution.

### ***Validate investigator commitment.***

- Confirm PI engagement, availability, and willingness to support the study.
- Ensure the PI understands study responsibilities, risks, and oversight obligations.

### ***Anticipate operational risks.***

- Identify potential barriers to enrollment (e.g., competing studies, resource constraints).
- Evaluate site flexibility and responsiveness to unanticipated EFS issues (e.g., protocol amendments, urgent reporting).

## Site Goals of EFS Site Selection

The site qualification process is typically structured as the sponsor interviewing the site to determine capability and readiness. However, sites can reframe this process as a two-way evaluation, —using it as an opportunity to interview the sponsor as well.

### *Evaluate portfolio fit.*

- Determine how the proposed study aligns with the site’s current and anticipated portfolio.
- Identify potential conflicts (e.g., competing studies, overlapping patient pools, resource bottlenecks) and opportunities for complementarity (studies that capture screen-outs from other protocols or fill therapeutic gaps).
- Ensure adequate bandwidth across investigators, coordinators, and procedure/lab schedules.

### *Assess partnership quality and communication expectations.*

- Clarify whether the sponsor approaches the relationship as a collaborative partnership versus a rigid compliance exercise.
- Confirm expectations for communication cadence, turnaround times for clarifications, escalation pathways, and flexibility in resolving operational challenges.
- Gauge the sponsor’s openness to site feedback, responsiveness, and respect for institutional SOPs.

### *Confirm safety, quality, and compliance readiness.*

- Demonstrate capability to manage early-phase device risk: Adverse Event (AE)/Serious Adverse Event (SAE) reporting pathways, investigational product controls, IRB processes, CV/licensure documentation, and SOPs for EFS oversight.
- Understand sponsor expectations for monitoring style (risk-based vs. exhaustive) and how findings will be communicated.

### *Stress-test protocol logistics.*

- Walk through an end-to-end patient journey (referral → prescreening → consent → index procedure(s) → follow-up).
- Flag impractical timelines, narrow visit windows, or dependencies (e.g., imaging availability, Cath/OR access, clinic scheduling).
- Propose pragmatic adjustments to enhance feasibility while preserving protocol integrity.

### *Clarify operational and resourcing assumptions.*

- Review anticipated screen-fail rates, staffing requirements, and budget coverage for unique EFS burdens (extra consenting visits, urgent clarifications, dual system maintenance).
- Ensure adequate startup support and realistic contract terms to sustain performance.
- Review screening committee logistics.

### *Build mutual confidence in study execution.*

- Establish a shared understanding of expectations, escalation pathways, and study priorities.
- Document agreements in writing (recap emails, operational assumptions, or checklists) to minimize downstream misalignment.

## Characteristics of an EFS Site

Area	Best Practices	Potential Pitfalls
<b>Champion PI</b>	Identify a PI who will act as a champion, driving startup across all aspects. Ensure transparency around resources, turnover, and site capabilities.	Lack of PI engagement or overcommitment can stall startup.
<b>Patient Access</b>	Validate patient availability with historical enrollment data or volume estimates. Consider factors such as institution size, referral networks (e.g., valve clinic), and the patient population's history with research participation.	Overestimating eligible patients due to poor or incomplete data.
<b>Infrastructure</b>	Conduct pre-selection visits (virtual or on-site). In-person assessments often surface critical details, foster dialogue, and help determine whether the site can perform at the level needed for EFS success.	Relying solely on written responses, which may not reflect operational realities.
<b>EFS-Specific Experience</b>	Prioritize sites with relevant device/procedure experience and a demonstrated mindset for pioneering early-phase research. Identify physicians eager to provide feedback. Review past contract/IRB metrics, request IRB SOPs, and obtain ICF templates to streamline submissions. Engage CRCs early, leverage their startup knowledge, and clarify IRB needs before submission.	Assuming general research or IRB experience automatically equals EFS readiness. Sites without specific procedural expertise (e.g., TEER at a low-volume TEER site) may struggle.
<b>Startup Timelines</b>	Request IRB metrics, SOPs, and ICF templates to anticipate timelines and streamline review. Partner with CRCs early, address questions proactively, and minimize back-and-forth with the IRB by resolving issues quickly.	Ignoring internal bottlenecks, staff turnover, or underestimating IRB/contract timelines.
<b>Collaboration &amp; Communication</b>	Assess site communication during feasibility. Involve PIs (post-NDA) in R&D calls and provide hands-on device training early to foster collaboration and feedback. Strong early engagement builds trust and accelerates issue resolution later.	Early warning signs—such as missed communications—often persist and can undermine trial conduct.
<b>Adaptability</b>	Select sites with demonstrated flexibility and willingness to adjust workflows for new or untested processes common in EFS.	Sites resistant to change may delay startup and enrollment.

## Themes & Considerations for Site Feasibility

When evaluating sites for EFS sponsors often request information across several key themes. Some elements remain consistent across studies and should be updated regularly (e.g., annually), while others are study-specific and tailored to the protocol.

Themes	Information Collected
<b>Site &amp; Contact Information</b>	<ul style="list-style-type: none"> <li>PI, sub-investigators, coordinator, regulatory, and contracts/budget contact info.</li> <li>Institutional affiliations and IRB type (central vs. local)</li> </ul>
<b>Clinical Research Experience</b>	<ul style="list-style-type: none"> <li>Experience with clinical trials (IDE, device trials, clinical indication, EFS)</li> <li>Number of ongoing studies and trial phases (enrollment vs. follow-up)</li> <li>History of FDA/OHRP inspections, 483s, or warnings</li> </ul>
<b>Patient Population &amp; Volume</b>	<ul style="list-style-type: none"> <li>Experience with device and interventional trials (IDE, TAVR, TEER, EFS)</li> <li>Number of ongoing studies and trial phases (enrollment vs. follow-up)</li> <li>History of FDA/OHRP inspections, 483s, or warning letters</li> </ul>
<b>Staffing &amp; Resources</b>	<ul style="list-style-type: none"> <li>Number and roles of staff (coordinators, nurses, regulatory, etc.)</li> <li>Staff certifications and experience (e.g., CCRP, RN, years in role, study-specific certifications)</li> <li>Availability of key personnel:</li> <li>PI availability for post-procedure discussions</li> <li>CRCs during monitoring visits</li> <li>Staff coverage for data capture during procedures</li> <li>Space for sponsor staff during cases</li> <li>Credentialing needs for sponsor monitors onsite</li> </ul>
<b>Infrastructure &amp; Capability</b>	<ul style="list-style-type: none"> <li>Availability of cardiac catheterization lab/hybrid OR, echo, TEE, CT, and imaging resources</li> <li>Electronic Medical Record (EMR) access for sponsor/monitors (critical for AE reporting and data verification; sites unwilling to provide EMR access are not recommended)</li> <li>Ability to upload/redact source documents for remote monitoring; clarify sponsor vs. site responsibilities in advance.</li> <li>Onsite secure storage capacity, temperature control, and separation from commercial devices to prevent mix-ups</li> </ul>
<b>Study Startup Logistics</b>	<ul style="list-style-type: none"> <li>IRB submission and approval timelines</li> <li>Central IRB use and willingness to defer.</li> <li>Ancillary committee reviews (radiation safety, COI, etc.)</li> <li>CTA/budget workflows, including dependencies (e.g., IRB vs. budget sequence)</li> <li>ICF review process and sponsor input before IRB submission.</li> <li>Activation process: Will sponsor issue a formal activation letter?</li> <li>SIV expectations: how training will be conducted and documented; site preferences for virtual vs. in-person training</li> </ul>
<b>Monitoring &amp; Data Management</b>	<ul style="list-style-type: none"> <li>Onsite vs. remote monitoring (onsite strongly preferred for EFS to ensure data completeness and AE safety review)</li> <li>EMR access processes and timelines</li> <li>EDC/data capture readiness</li> <li>PI/CRC availability for monitor meetings</li> <li>Monitoring visit timing and frequency (e.g., first visit, monthly vs. quarterly cadence, inclusion in SOW)</li> <li>Monitor credentialing requirements for onsite access</li> </ul>
<b>Competing Trials &amp; Enrollment Conflicts</b>	<ul style="list-style-type: none"> <li>Other ongoing or planned trials that may compete for the same patient population.</li> <li>Site processes for prioritizing studies and managing referrals (e.g., valve clinic workflow, consent practices, policies on multiple consents)</li> </ul>

Many of the questions asked during site feasibility (such as site contacts, institutional affiliations, IRB type, general infrastructure, and monitoring processes) do not change from study to study, yet sites are often asked to complete the same information repeatedly. To streamline startup and reduce burden, sponsors should rely on a standardized site information sheet for stable data elements, reference previously completed site qualification forms already on file, and provide abbreviated questionnaires for sites they have recently partnered with, requesting updates only for study-specific details such as procedure volumes, competing trials, or anticipated enrollment. This approach respects the site’s time and resources, accelerates activation, and strengthens sponsor–site collaboration.

## Step by Step Workflow

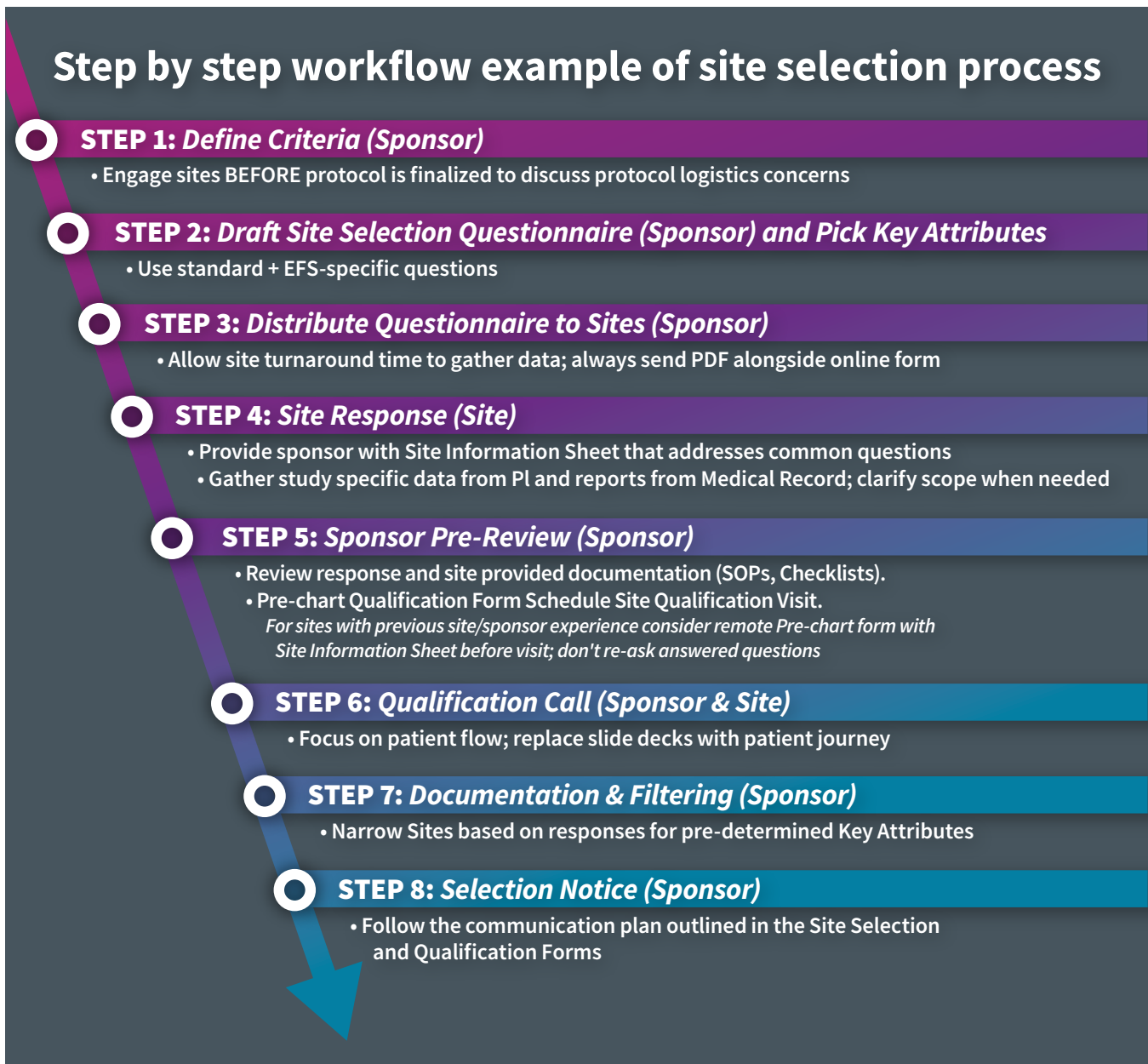


Figure 12. Step by step workflow example of site selection process

### Step 1. Define Criteria (Sponsor)

- Decide what makes a site “qualified”: infrastructure, PI experience, patient pool, agility, and EFS readiness.
- Define the key attributes required for study success and use them to systematically filter potential sites.

**Tip:** Publish the criteria internally before outreach so the entire sponsor team applies the same standards consistently.

### Step 2. Draft Questionnaire (Sponsor/CRO)

- Separate into two sections:
  - Standard Site Info: PI CV, IRB details, infrastructure, regulatory history, study volume. (Consider linking to MDIC’s EFS Site Platform as a resource.)
  - Study/EFS-Specific Info: Unique trial needs, patient population details, governance agility.

**Tip:** Keep the form under six pages and include only data points that will actually be scored.

### Step 3. Distribute to Sites

- Provide a realistic turnaround time ( $\geq 10$  business days) so sites can gather accurate information.
- Always send a fillable PDF or Word version alongside any online form for ease of use.

**Tip:** If the site already provides a standard information sheet, accept it as the “data block” response. Allow “N/A” checkboxes where applicable to reduce redundancy.

### Step 4. Site Response

- Site completes the form using PI input and IT database queries.
- Sites may request clarification of scope (e.g., “PI vs. department” for study counts).

**Tip:** Encourage use of Epic’s Slicer Dicer or equivalent tools to generate accurate feasibility data.

### Step 5. Sponsor Pre-Review

- Review site submissions before the qualification call.
- Do not re-ask questions already answered in writing.

**Tip:** Flag only true gaps or inconsistencies for the call—respect the site’s time.

### Step 6. Qualification Call

- Whenever possible, hold the call remotely; site tours can also be conducted virtually.
- Focus on patient flow and operational logistics (referral → screening → consent → procedures → follow-up).
- Clarify EFS-specific needs (ability to pivot, tolerance for ambiguity, availability of a multi-disciplinary team).
- Decide in advance which slides to cover at the SQV versus the Site Initiation Visit (SIV).

**Tip:** Replace lengthy protocol slide decks with a patient journey walkthrough to stress-test real-world feasibility.

## Step 7. Documentation & Scoring

- Apply the scoring rubric to site responses and call notes.
- Document due diligence internally for FDA compliance.

**Tip:** Reviewing AI-generated call transcripts can save time and serve as a defensible qualification record.

## Step 8. Selection & Notification

- Sponsor issues a formal selection notice (e.g., a “Congratulations” email or letter).
- Site begins preparing for the SIV.

## Tips from the Field

In the EFS world, the stakes are high, the timelines are tight. Here’s what our experience has taught us.

### What Works

- **Don’t confuse availability with capability.** Just because a site says “we can start next week” doesn’t mean they’re truly ready. Probe deeper—ask about bandwidth, competing studies, and historical startup performance.
- **Red flags show up early—believe them.** If a site takes 2 weeks to respond to an initial feasibility email, that communication lag will likely persist throughout the study.
- **Clarity is kindness.** Give sites a realistic picture of what’s expected—from patient volume and protocol complexity to post-procedure follow-up and documentation. If they can’t handle it, better to know upfront.
- **Remote qualification visits can be just as effective.** When done right, they save time. Just make sure the agenda is focused, and follow-up is prompt.
- **Match protocols to capabilities, not wishful thinking.** A site might be great for your next pivotal study, but not EFS-ready today—and that’s okay. Keep them warm for future studies.

### Common Pitfalls to Avoid

- **Copy-paste feasibility forms.** Sites hate answering the same 60 questions over and over. Use centralized data stored in MDIC and ask only what’s unique to your study.
- **Asking about basic research qualifications for known sites.** If you already know a site is running multiple IDE studies, skip the “Have you ever done research?” checkbox.
- **Skipping coordinator engagement.** Your PI might be all-in, but if the study coordinator isn’t looped in early, you’re in for delays and confusion.

### Pro Tips

- **Build trust early.** Sites that feel like partners will go above and beyond. Sites that feel like vendors... won’t.
- **Track site performance.** Start building a shared database of actual vs. projected enrollment, IRB timelines, and contract speed. Let transparent data talk and drive future feasibility.
- **Offer site feedback—even if they aren’t selected.** It builds goodwill and improves future engagement.

**Academic Site Realities: Academic centers play a vital role in EFS, offering clinical depth, experienced investigators, and access to complex patients.**

### *What Works at Academic Centers*

- **Engage early with clinical operations—not just the PI.** The PI might be excited, but they often don't control key bottlenecks like IRB submissions, contracts, or resource allocation. Meet the doers early: regulatory leads, research managers, department admins.
- **Simplify the process wherever possible.** Academic centers are flooded with feasibility requests. Use pre-filled templates, centralized documentation, and minimal back-and-forth. Don't make them chase down information they've given 10 times before.
- **Respect the pecking order.** Knowing who makes decisions—Chair, Department Admin, CTO, IRB, or someone's nurse coordinator—is half the battle. Map the internal ecosystem before you try to “move fast.”
- **Ask how research integrates with clinical workflows.** Academic sites can't disrupt patient care for your device. Understand cardiac catheterization lab access, post-op recovery workflows, and EMR touchpoints that support (or block) study logistics.
- **Support their ‘why.’** Academic investigators are driven by science, publications, training, and visibility. If your EFS aligns with those goals, say it loud. It's not just about being a site—it's about being a partner in innovation.

### *Pitfalls to Avoid*

- **Underestimating startup time.** Academic sites often juggle multiple IRB layers, internal budget reviews, and multiple committee approvals (radiation, device safety, COI, etc.). If you expect 30 days, budget for double and more.
- **Assuming institutional knowledge is centralized.** Even top academic centers have silos. The cardiology PI might not know their own budget office timelines—or even who their IRB contact is. Help connect the dots.
- **Disregarding coordinator bandwidth.** Many coordinators at academic institutions are split across multiple studies and have no say in prioritization. Confirm their actual availability, not just theoretical assignment.

### *Power Tips from the Field*

- **Send a clear, concise Site Fact Sheet.** Academic sites love a one-pager that says: What's the study, what's required, who's paying, and what resources are needed?
- **Pre-identify competing studies.** Institutions may prioritize pivotal trials or studies with major grant funding. Know what you're up against—and where your study fits into their portfolio.
- **Clarify patient flow.** Who identifies patients? Where do they get screened? Who schedules procedures? If this isn't streamlined, you'll get logjammed fast.
- **If it's their first EFS, handhold.** Academic centers are cautious with novel devices and FIH studies. Bring documentation, training, and compliance support to de-risk their involvement.

## Rethinking Site Qualification for EFS

If sponsors are primarily concerned about time and cost, they should consider developing their own streamlined process for documenting site qualification—rather than defaulting to the industry or CRO standard of a lengthy qualification form followed by an on-site visit. FDA regulations (21 CFR 812.43) require only that sponsors “select investigators qualified by training and experience” and “obtain from each investigator a signed agreement.” Nowhere is there a mandate for duplicative questionnaires or formal site visits.

# Chapter 6 Budgeting & Financial

## Budgeting Overview

Understanding the relationship between FDA approval and CMS (Centers for Medicare & Medicaid Services) review is critical for planning EFS. EFS budgets should provide a clear and comprehensive plan for all site-related costs, including protocol-required tests, research activities, and site personnel fees. Budget items should distinguish between Standard of Care (SOC) procedures and those required specifically for research, with fair market value assigned to research-specific activities. Protocol-required tests, follow-up schedules, and associated fees for Research Coordinators (RCs) and Principal Investigators (PIs) should be clearly documented and aligned with case report forms (CRFs). Potential study candidate identification and Pre-Screening activities may be reimbursed either on a per-hour or capped basis, with clear documentation of pre-screen failures and efficiency ratios.

## One-Time, Annual, and Per-Occurrence Fees

One-time fees include study start-up and site activation, IRB submission, and research pharmacy setup, while annual fees cover recurring IRB reviews and pharmacy maintenance. Per-occurrence fees address unpredictable but necessary activities such as protocol amendments, re-consenting, monitoring visits, audits, source documentation submission, and explanted device returns. Budgeting for these ensures flexibility and adequate reimbursement for site efforts while maintaining transparency for sponsors. Participant reimbursement, including travel and accommodations, should also be incorporated when relevant, ensuring compliance with study visit schedules without inducing participation.

## Budget Negotiation and Payment Terms

EFS budgeting should aim for predictability and minimize administrative delays by clarifying protocol guidance, establishing payment schedules, and limiting per-occurrence fees where feasible. Sponsors should define overhead and payment terms during site qualification visits (SQVs) and outline clear processes for amendments or post-CMS approval adjustments. Payments for start-up fees should be one-time and non-refundable, protocol-required fees reimbursed per completed CRF, and other services invoiced quarterly. A transparent budget ensures efficient site operations, supports timely study execution, and maintains strong sponsor-site collaboration.

## Chapter 7 Contracting & Legal Considerations

The MDIC Early Feasibility Study Clinical Trial Agreement (EFS CTA) was developed to address one of the biggest barriers to initiating early feasibility studies—contracting delays between sponsors and sites. Traditional contract negotiations can take months, slowing down studies that are already limited by small patient populations and the need to move quickly. The EFS CTA streamlines this process by providing a standardized, balanced agreement that reflects input from sponsors, sites, and legal experts.

For sponsors, the agreement offers clear benefits. It reduces costly and time-consuming negotiations, creates greater consistency across sites, and accelerates study start-up—allowing resources to be directed toward execution rather than legal back-and-forth. For sites, the template simplifies internal legal review and ensures fair terms on issues such as intellectual property, indemnification, and publication. This not only shortens contracting timelines but also enables more institutions to participate in first-in-human studies, expanding their role in advancing innovative technologies.

The EFS CTA was intentionally designed as a single-use contract specific to early feasibility studies, rather than a broad master agreement. The process begins when a sponsor proposes use of the MDIC EFS CTA at site initiation. Sites then review the standardized template, which has already been vetted across stakeholders, minimizing the need for major revisions. Once finalized, the agreement allows the study to move forward much more efficiently. Ultimately, the MDIC EFS CTA is intended to reduce friction in contracting, speed the launch of early feasibility studies, and foster stronger collaboration between sponsors and sites in bringing novel devices to patients.

## Chapter 8 Protocol Development & IDE Approval

### Overview

This chapter focuses on the development of Early Feasibility Study (EFS) protocols and Investigational Device Exemption (IDE) approval. It emphasizes the importance of balancing scientific rigor with operational flexibility to enable safe and efficient first-in-human (FIH) learning. We highlight the importance of designing EFS protocols and IDE submissions with flexibility, clarity, and operational feasibility to support early device learning and iteration while maintaining patient safety and regulatory compliance.

## Swim Lane

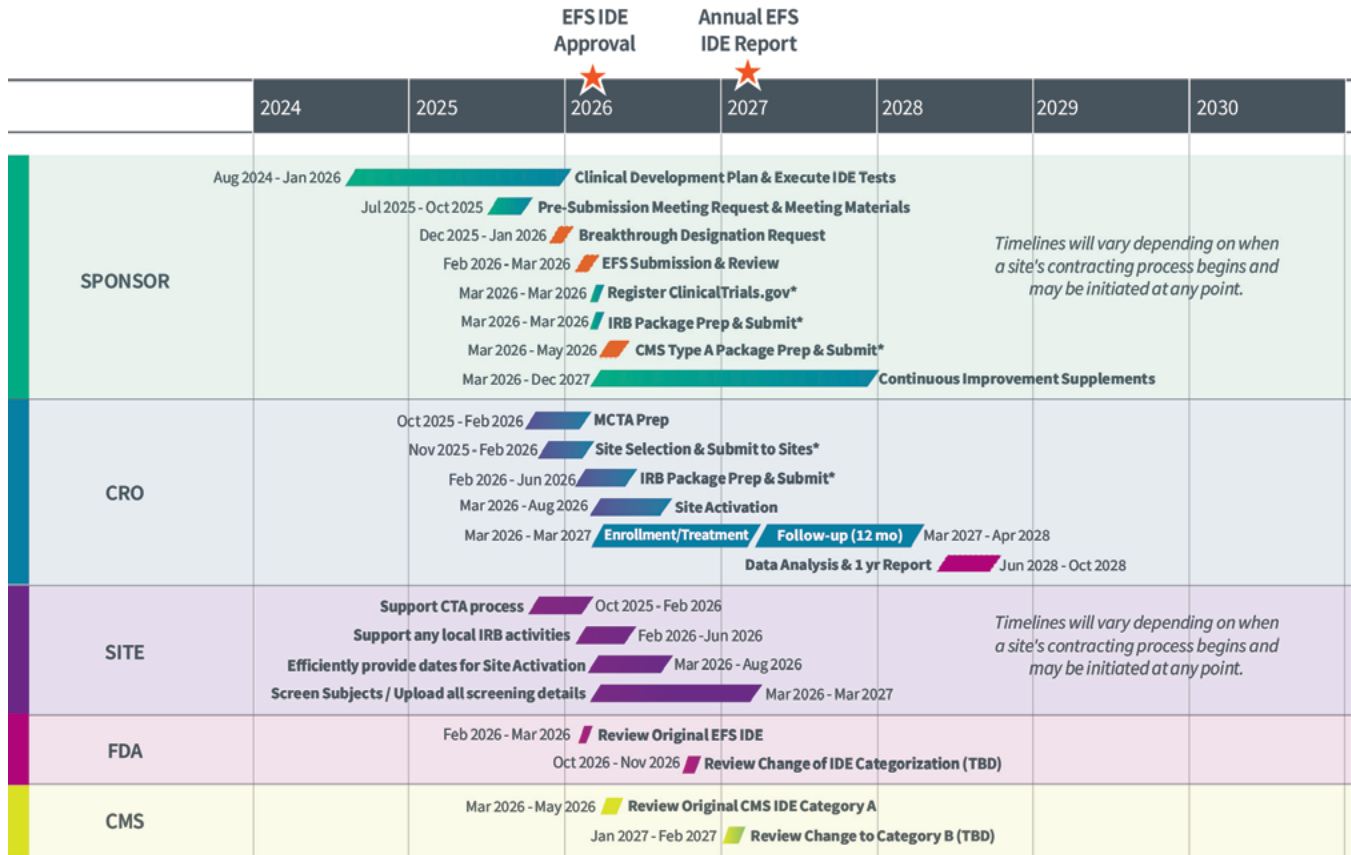


Figure 13. Example timeline and activities for EFS process<sup>32</sup>

## Intended Population and the Why

A well-written EFS protocol begins with a clear definition of the intended patient population—not just who the device is for, but *why* these patients are appropriate for early-stage investigation. EFS trials often target individuals with few or no treatment options, sometimes referred to as “no-option patients.” These patients may be too high-risk for standard therapies, or they may have exhausted existing alternatives. However, selecting a population that is too medically complex can obscure the ability to assess device safety or technical performance, especially when complications arise from comorbidities rather than the device itself. The challenge is to identify patients who are sick enough to ethically justify the use of an investigational device, but not so sick that the data become uninterpretable. This balance is one of the most critical—and nuanced—decisions in EFS protocol development.

Understanding and articulating the *why* behind the chosen population is equally important. It forms the clinical and ethical justification for the study, supports regulatory engagement, and helps sites assess feasibility. For example, a novel left atrial appendage occlusion device may offer procedural or safety advantages compared to existing options. In such cases, the sponsor must define not only the

<sup>32</sup> Atallah E. Eligibility criteria: too big, too small or just right? *Haematologica*. 2024;109(4):1021-1022.doi:10.3324/haematol.2023.283972 Creating the Informed Consent Document

population (e.g., patients contraindicated for anticoagulation) but also what differentiates the device's value proposition—such as ease of use, reduced procedure time, or improved anatomical fit.

Importantly, the intended population is not static. As the device evolves, and early outcomes become available, future protocol amendments or expansions may broaden eligibility criteria. A strong initial rationale helps ensure that these changes occur logically and are well-grounded in early safety and performance data. For regulators and IRBs alike, the intended population is the cornerstone of ethical acceptability. Getting this piece right is essential to the success of an EFS—not just for enrollment, but for generating meaningful insights that inform whether the technology should move forward

## Guiding Principles for Eligibility in EFS

Eligibility criteria in EFS should be lean, anatomy-driven, and survival-conscious, allowing for broad enrollment that accelerates device learning while avoiding unnecessary exclusions more appropriate for pivotal trials. Unlike pivotal trials, which are designed to confirm long-term safety and efficacy, the primary purpose of an EFS is to enable device learning and iteration. This includes defining anatomic limits, refining sizing boundaries, and identifying early procedural risks.

Patient selection in EFS should prioritize anatomy over ideal candidate profiles. While pivotal trials often seek lower-risk patients with longer life expectancy, EFS may appropriately include higher-risk patients if their anatomy offers important insights into device performance. Exclusions such as dialysis, cirrhosis, or oxygen dependency should be reconsidered, as they may unnecessarily limit enrollment. Instead, eligibility should be guided by two key principles: anatomical suitability for the device and reasonable short-term survival (typically greater than one year). Redundant exclusions should be avoided, as most comorbidities only matter if they directly limit survival or confound device learning. Similar arguments for broadening eligibility have been advanced in drug trials, where experts recommend minimizing restrictive entry criteria to improve inclusivity and representativeness. Others have shown that eligibility criteria are often either too restrictive or too liberal compared with known safety limits, underscoring the importance of designing criteria that are “just right” to balance patient safety with trial feasibility.<sup>33</sup>

A streamlined criteria framework is recommended. Inclusion should require only the target disease state and anatomic suitability for the investigational device.<sup>34</sup> Exclusions should be limited to anatomy incompatible with device implantation, clinical conditions that severely limit survival, or recent major events that confound outcomes (such as myocardial infarction or surgery within 30 days). This simplified approach avoids long, prescriptive lists of exclusions that do not materially impact the goals of early feasibility.

Endpoints and follow-up in EFS should align with the purpose of procedural learning. Thirty-day outcomes are essential to assess procedural safety and immediate device function, while longer-term follow-up at one year or beyond provides additional context. Preclinical data, such as animal studies or accelerated wear testing, can further support the rationale for minimizing long-term endpoints at the feasibility stage, though some stakeholders may still value them.

<sup>33</sup> Atallah E. Eligibility criteria: too big, too small or just right? *Haematologica*. 2024;109(4):1021-1022. doi:10.3324/haematol.2023.283972 Creating the Informed Consent Document

<sup>34</sup> Osarogiagbon RU, Merino Vega D, Fashoyin-Aje L, et al. Modernizing clinical trial eligibility criteria: Recommendations of the ASCO–Friends of Cancer Research Prior Therapies Work Group. *Clin Cancer Res*. 2021;27(9):2408-2415. doi: 10.1158/1078-0432.CCR-20-3854

Finally, start-up companies entering the EFS space should be cautious not to over-engineer eligibility. Attempting to mirror pivotal trial criteria can slow enrollment and undermine the learning purpose of early feasibility. Sponsors must also be mindful of fundraising pressures that encourage overly restrictive criteria, since this may limit enrollment and compromise the true intent of EFS: to identify device boundaries, understand risk profiles, and generate the knowledge needed to refine the device before advancing to pivotal evaluation.

## Device Description – Why It’s Different

In an EFS, the device description serves a unique and strategic purpose. Unlike later-phase protocols, where the device is typically finalized, EFS protocols must reflect the realities of early-stage development, where the design may continue to evolve in response to human use. As such, the device description should be clear and accurate—but intentionally high level. The objective is to convey what the device is, how it works, and what makes it meaningfully different from existing alternatives—without over-specifying components that may soon change.

This section of the protocol should emphasize how the device functions and what its intended benefits are relative to standard-of-care options or similar technologies. For example, a new vascular access device might differ in profile, deployment mechanism, or ease of use—but the description should focus on these differentiators conceptually, not on fine details like hub shape or connector type.

A common pitfall in EFS protocols is describing the device in such detail—through illustrations, technical specifications, or component-level drawings—that any future tweak, even a minor one, requires a formal protocol amendment. This creates unnecessary regulatory burden and can stall development timelines. To preserve flexibility, protocol authors should avoid locking in granular device details unless absolutely necessary.

A well-written, high-level description also enables the sponsor to take advantage of FDA’s 5-day notification process for certain modifications under the Investigational Device Exemption (IDE). This pathway allows minor changes—such as improvements to usability, material changes that don’t affect biocompatibility, or delivery system refinements—to be communicated to FDA without pausing the study for re-approval. However, this flexibility is only possible when the protocol avoids excessive specificity.

Ultimately, the device description in an EFS protocol must strike a careful balance: it should establish the novelty and purpose of the investigational device while protecting the ability to iterate quickly. A concise, thoughtful approach gives both regulators and sites the clarity they need—without boxing the sponsor into unnecessary amendments for every minor change.

## Endpoints and Assessments

Defining endpoints in an EFS requires restraint, clarity, and purpose. Unlike pivotal trials, which are designed to demonstrate efficacy through statistically powered outcomes, EFS protocols should focus on a limited number of endpoints that directly assess safety and technical performance. These endpoints form the core of the study’s objectives: Can the device be successfully delivered and deployed? Does it perform as intended? Are there unanticipated safety issues that arise with early use in humans? For example, a

technical performance endpoint might be the successful deployment of a valve without repositioning or retrieval, while a safety endpoint could include the absence of major procedural complications such as vascular injury, bleeding, or device embolization.

In addition to formal endpoints, secondary assessments or exploratory measures may be included, but should not be overemphasized. These can help generate signals for potential benefits—such as improvement in functional status or quality of life—but must not be confused with formal efficacy endpoints. Including too many endpoints or trying to simulate a pivotal trial framework too early often leads to protocol complexity, regulatory friction, and poor site compliance.

An important distinction in EFS design is between endpoints and measures. Endpoints are tied to study success or failure and should be tightly defined; measures are observations that may inform future study design but are not required to “prove” anything in EFS. For instance, a six-minute walk test or KCCQ (Kansas City Cardiomyopathy Questionnaire) score may be captured as part of clinical follow-up but should not be framed as primary or secondary endpoints unless directly aligned with the investigational intent.

Ultimately, the selection and framing of endpoints in an EFS protocol must reflect the study’s foundational goal: to determine whether the device is safe, works as intended, and warrants further investigation. Keeping the endpoints focused, feasible, and aligned with the early phase objectives ensures the protocol remains both actionable and appropriately scoped.

## Safety Oversight and DSMB Planning

Safety is the cornerstone of any EFS, and the protocol must include a clear plan for how safety will be assessed, monitored, and reported. Because EFS trials typically involve FIH use or early clinical experience with a novel device, risks may be poorly characterized, and the possibility of unanticipated complications is higher than in later-phase trials. Therefore, the protocol should describe both real-time safety monitoring procedures and independent oversight mechanisms, such as use of a medical monitor or a Data Safety Monitoring Board (DSMB). Use of a Clinical Events Committee (CEC) should also be considered.

A DSMB is often warranted in EFS, particularly when the study involves invasive procedures or potentially serious device-related risks. The protocol should define the DSMB’s scope, composition, meeting schedule, and what kinds of data will trigger review. In some cases, the DSMB may be asked to review outcomes after every case, or at regular intervals, depending on enrollment volume and device risk profile. Unlike in large pivotal trials, DSMBs in EFS may serve a more dynamic role: reviewing not just subject outcomes, or operator feedback to assess whether early safety signals suggest the need for protocol or device modifications.

In addition to acute safety monitoring, EFS protocols often include extended follow-up periods, sometimes as long as five years. This may seem disproportionate given the small sample sizes, but the rationale is twofold: first, to ensure that any late-emerging device complications (e.g., erosion, fracture, migration) are captured; and second, to align with FDA expectations that early device safety be assessed over time. Long-term follow-up also generates foundational safety data that can support future pivotal studies or premarket approval (PMA) submissions.

Ultimately, the safety section of an EFS protocol should convey a proactive and proportionate approach to monitoring risk, balancing the need for close oversight with the flexibility required in early-stage research. Strong safety planning not only protects participants, but also builds trust with regulators, IRBs, and investigators navigating the uncertainties of early innovation.

## Operational Aspects and Administrative Considerations

While clinical and technical components often take center stage in EFS protocol development, the operational and administrative sections are equally critical and frequently overlooked. These sections provide the blueprint for how the study will be conducted at the site level, how roles and responsibilities are assigned, and how compliance with local and international regulations will be achieved. In early-stage studies, where agility and clarity are essential, this part of the protocol must be simplified, aligned with regulatory expectations, and written with real-world site capabilities in mind.

One key consideration is geographic scope. If the intention is to run the study in multiple countries or regions (e.g., U.S. and outside U.S. (OUS) simultaneously), the protocol must be written to accommodate regulatory and operational differences across jurisdictions. This may include varying definitions of serious adverse events, differing consent processes, or country-specific data privacy requirements. In some cases, developing separate regional protocol versions or Appendix by country may be the most efficient way to avoid unnecessary complexity or redundant language. However, this should be anticipated and addressed upfront in the administrative sections to avoid delays in ethics approval and site activation.

The language in this section should be practical and proportionate. Overly prescriptive or sponsor-centric language often creates friction with IRBs, legal teams, or site staff. Avoid embedding sponsor SOPs or vendor-specific processes in the protocol unless they are legally or ethically required. When describing roles, document expectations for the sponsor, CRO (if applicable), investigators, and site staff in a way that reflects actual workflows, not aspirational ones.

## Building Flexibility into Protocols to Empower Enrollment

Flexibility in protocol design is essential to enabling efficient site enrollment in EFS. Investigators are obligated under 21 CFR 312.60 and 812.100 to protect the rights, safety, and welfare of participants, and to conduct studies in accordance with the investigational plan. Citing these regulatory responsibilities underscores that flexibility is not about “cutting corners,” but about designing protocols that align with existing obligations while remaining operationally feasible. When protocols are overly rigid and developed without meaningful site input, the result is not cleaner data, but a proliferation of unnecessary deviations, corrective and preventive actions, and substantial resource expenditures. The true risk of rigidity lies not in deviations themselves, but in the disproportionate time and effort sites must expend attempting to prevent them, effort that is diverted away from patient care, screening, and enrollment.

A critical yet frequently overlooked element in protocol development is the definition of the “no turning back” point. While enrollment is commonly defined at the time of informed consent, the concept of accrual is less well established in EFS. Because EFS trials are typically non-randomized and may involve lengthy intervals between initial consent and full study commitment, ambiguity around this milestone creates operational inefficiencies. Protocols should therefore provide clear guidance on when final

eligibility is confirmed and when patients are considered irrevocably enrolled. Such clarity minimizes redundant assessments and prevents unnecessary delays in patient follow-up.

Operational flexibility is also necessary in the conduct of follow-up and data collection. Protocols should explicitly permit the use of data obtained through routine clinical care when appropriate, clarify circumstances under which repeat testing is unnecessary, and incorporate realistic visit windows that accommodate patient logistics. Incorporating remote data collection options further reduces patient burden and enhances retention. In drafting protocol language, sponsors should critically evaluate the use of absolute terms such as “must,” “required,” or “do.” Each such requirement should be assessed to determine whether it is indispensable for device learning or mandated for regulatory compliance. Requirements that do not meet these thresholds should be softened to “should” or “may,” thereby preserving scientific rigor while permitting operational flexibility.

Adverse event (AE) reporting represents another domain where protocol rigidity can impose significant burdens without proportional benefit. Protocols should delineate reportable versus non-reportable events and define the appropriate initiation point for reporting, ideally beginning at the time of investigational product use rather than consent. During the initial year of follow-up, comprehensive reporting of all AEs may be warranted to ensure thorough safety surveillance. However, beyond this period, reporting should be narrowed to clinically relevant, device-related, or cardiac events. In addition, the definition of “site awareness” requires refinement. While current standards require entry within ten days of notification to any individual listed on the delegation log, in practice, many events are not recognized as adverse events until after review by the principal investigator, safety team, or monitor. Protocol definitions that align with these operational realities will reduce preventable deviations and improve data quality.

Finally, for those protocol requirements that must remain inflexible, it is important that sites understand the underlying rationale. Requirements designed to evaluate device performance or to capture potential safety signals should be explicitly communicated as such. Providing investigators and coordinators with clear explanations of the scientific or regulatory justification for key assessments promotes adherence and fosters greater site engagement. Flexible yet rigorous protocol design enhances efficiency, reduces unnecessary burdens, and ultimately strengthens the partnership between sponsors and sites, thereby facilitating the successful conduct of EFS.

## Prevention and Mitigation

Sponsors can reduce deviation frequency by:

- Designing simpler, more flexible protocols.
- Using broader, less restrictive enrollment criteria when safe.
- Allowing flexible time windows for essential assessments.
- Conducting remote assessments when feasible.
- Leveraging available data from the electronic medical record (EMR) prior to consent, provided the information remains clinically relevant and up to date.
- Eliminating nonessential activities.
- Avoiding over-restrictive prohibitions on brief, clinically appropriate medications.

Stakeholder engagement (trial participants, investigators, coordinators) during protocol design helps ensure feasibility and improves adherence. Risk assessments should be conducted before/during protocol development to identify elements that can be simplified or eliminated, and to flag critical safety/data elements that require strict compliance.

*Figure 14. Prevention and mitigation of deviations.*

### Creating the Informed Consent Document

Developing an informed consent document (ICF) for an EFS (EFS) requires special attention to how risk is communicated. Unlike later-phase studies, EFS protocols often involve novel devices or procedures with limited or no prior human experience. As a result, the consent form must strike a careful balance between transparency and participant comprehension.

In EFS, risk content originates primarily from the Risk Management Document (RMD), which is developed by the product development team in collaboration with engineering, clinical, and quality functions. The RMD outlines potential hazards, mitigations, and severity/frequency of harms associated with the investigational device.

The ICF itself is a downstream output of two core documents:

- The Protocol Synopsis, which provides a concise summary of the procedure and defines why a participant qualifies for the study.
- The Instructions for Use (IFU), which contains procedural and technical detail about device operation. Authored by the product development team, the IFU is often more detailed than the protocol itself in the EFS setting.

When including risk information, sites and sponsors should follow these principles:

- Risk percentages should only be included if required by the IRB. When needed, they should be based on comparable devices and presented as broadly as possible to reduce future amendment risk.
- The list of risks should be harmonized across the ICF, protocol, IFU, and RMD to maintain internal consistency.

All informed consent documents must comply with 21 CFR Part 50, Subpart B, which outlines the ten required elements of consent, including purpose, procedures, risks, benefits, alternatives, and the voluntary nature of participation. [Link to regulation](#)

Ultimately, the goal is to ensure participants are fully informed—not just about known risks, but also about the unique uncertainty and oversight associated with early-phase device studies.

## Creating the Instructions for Use (IFU)

In EFS, the Instructions for Use (IFU) is a foundational document that must be thoughtfully developed to guide investigational device use in a clinical setting. Unlike commercial IFUs, which are often static and well-validated, EFS IFUs are working documents that evolve as more is learned about device performance and procedural nuances.

The IFU is authored by the product development team, not just engineering, and should incorporate input from clinical, regulatory, and quality experts. Its development is informed primarily by simulated use and animal testing, with additional insight from the risk management process. These sources help establish an early understanding of procedural steps, potential hazards, and mitigation strategies.

Because EFS involves FIH use, the IFU often contains greater detail than the clinical protocol, including step-by-step procedural guidance, troubleshooting, anatomical considerations, and device-specific precautions. The IFU should also include extensive warnings and limitations, reflecting the uncertainties and safety considerations inherent to early-phase research.

Importantly, the IFU should be designed with flexibility in mind. Unlike the protocol or informed consent form, which often require formal IRB approval for changes, the IFU can typically be updated more easily as new insights emerge. This makes it an essential tool for iterative learning in early development.

When creating the IFU, teams must ensure that risk language is harmonized across the following documents:

- The IFU
- The Informed Consent Form (ICF)
- The Clinical Protocol
- The Risk Management Document (RMD)

Although these documents are intended for different audiences, they must convey a consistent understanding of device risks and mitigations.

In summary, creating the IFU for an EFS study is not simply a technical writing exercise—it is a cross-functional process that supports regulatory alignment, investigator training, and participant safety during the earliest stages of clinical investigation.

## Data Elements: Case Report Forms

In EFS (EFS), the goal of data collection is to gather just enough information to assess safety, technical performance, and the operational viability of the device—not to power a regulatory approval or answer every future research question. As such, Case Report Forms (CRFs) for EFS should be intentionally minimal, purpose-built, and directly aligned with the protocol’s objectives. Over-collecting data in EFS not only creates unnecessary burden for sites but can also slow down enrollment, introduce documentation errors, and inflate monitoring and database costs without adding meaningful value.

Each data element collected should map directly to a study objective, safety assessment, or critical operational insight. Sponsors should resist the urge to “pivotal-ize” EFS data collection by including exploratory or speculative fields that are not actionable in the context of a small, early-phase trial. Instead, the CRFs should focus on capturing: (1) subject eligibility and baseline characteristics, (2) key procedural details and device interactions, (3) safety events and protocol deviations, and (4) core follow-up assessments tied to primary and secondary endpoints.

CRFs must also reflect what sites can realistically capture within their workflows. Sponsors should engage clinical staff early to review draft CRFs and flag data points that may be difficult to obtain, inconsistently documented, or not routinely recorded in the medical record. Where possible, leverage existing clinical documentation and imaging systems rather than creating parallel data entry processes.

Another key consideration is flexibility. The CRF design should accommodate potential device or protocol modifications without requiring reprogramming of the entire database. Version control, audit trails, and clear guidance on which forms apply to which device iteration are essential in this evolving environment.

In short, good CRF design in EFS is not about collecting more—it’s about collecting the right data, in the simplest, most site-friendly way possible, to support rapid learning, regulatory alignment, and the eventual path to pivotal study design.

Example: Day of Discharge Data Collection	
<b>Protocol Requirement</b>	“The following study procedures will be performed at discharge or at 7 days post-procedure, whichever comes first: Chemistry Panel, ECG, TTE”
<b>Workflow &amp; Challenge</b>	Data required to be collected over the weekend when research team is not available to facilitate and limited clinical staff to obtain echo
<b>Site Corrective &amp; Preventative Actions</b>	<ul style="list-style-type: none"> <li>✓ <b>Adjust staffing to allow research coordinators to cover weekends, or pay overtime</b></li> <li>✓ <b>Collect data as close as possible to the required timeframe while ensuring clinical relevance. Protocol Deviation &amp; all its paperwork.</b></li> </ul>
<b>Suggested Language Change</b>	<p>“If the post procedure/pre-discharge assessments were performed &lt;48 hours post-implant but on the same calendar day as the discharge date, the same assessments do not need to be repeated.”</p> <p>“If discharge is expected to occur on a weekend or holiday, procedures may be performed on the last business day prior to discharge: Chemistry Panel, ECG, TTE”</p>

Figure 15. Example of writing protocols for operational compliance.

# Chapter 9 Execution

This chapter is dedicated to the execution of the EFS from estimating timelines using 60/60/60 goals, site activation, regulatory document preparation and collection, best practices for recruitment, the informed consent process, and site case support and logistics.

## 60/60/60 Goals

The 60/60/60 MDIC Metrics framework tracks three critical milestones in clinical trial startup: contract execution within 60 days, IRB approval within 60 days, and site activation within 60 days. A key factor in achieving these targets is ensuring that the contracting and IRB approval processes occur in parallel rather than sequentially, which significantly reduces delays. Capturing and analyzing this data provides visibility into common bottlenecks, enabling sites and sponsors to implement targeted process improvements. By benchmarking performance against these metrics, organizations can identify best practices, strengthen accountability, and establish greater predictability across trials. Ultimately, the 60/60/60 metrics help accelerate site activation and shorten the time to first patient enrolled, supporting both innovation and faster patient access to novel therapies.

### Definition of start and end of each metric

- **IRB:** Date of IRB Submission to Date IRB approved.
- **Contract:** Date FDA approved protocol received to Date Executed
- **First enrollment:** Date Activated by the sponsor to first Implant? Or first consent?

### Site Activation

Before a sponsor allows a site to enroll participants, a structured activation process must be completed. This includes collecting regulatory documents, executing contracts, securing IRB approval, and ensuring that all study staff are trained and properly delegated. A streamlined, parallel approach to these activities minimizes delays and allows sites to focus on finding and treating patients as soon as regulatory approvals are in place.

A best practice is for sponsors and sites to view activation not as a checklist of isolated tasks, but as an integrated workflow where regulatory documents, delegation of authority, training, and electronic trial master file (eTMF) readiness all move forward together. Quality checks should be ongoing as documents are submitted or obtained, rather than deferred until the end. This proactive approach prevents last-minute findings that can derail activation.

### Tiered Activation

Activating in tiers can help accelerate startup, as it is rarely practical for all site personnel to complete regulatory documents at the same time. Focus should be on the PI, primary research coordinators, and other mandatory staff needed to initiate the study. Additional Sub-Investigators and ancillary staff can be added post-activation as needed, provided they do not perform research activities until IRB-approved, trained, and delegated. This approach avoids bottlenecks while remaining fully compliant.

## Monitoring

Detailed monitoring procedures, appropriate for an early feasibility study, must be included in the Investigational Plan, as required by 21 CFR 812.25(e). Data Monitoring Committee (DMC) may be helpful to investigators, sponsors, and IRBs by providing independent, objective expert counsel. For certain early feasibility studies, a DMC may be composed of clinicians, scientific experts, and individuals with ethical expertise may be helpful in evaluating data relatively early in the course of the study and would provide an additional layer of human subject protection. Use of a DMC could be proposed by a sponsor as a risk mitigation strategy element, particularly for studies where additional independent oversight would be of value.<sup>35</sup>

## Regulatory Document Preparation & Collection

Best practice to have all templates ready at the time that your reg packages are released to avoid delays once a site reaches IRB approval. This includes FDF, IA, ITL, DOA, etc. and work in parallel with IRB submissions to train and collect documents. Have training plan ready to begin scheduling SIVs. Future proof the training plan to think long term – will there be amendments and how do we want to train to these; how will procedural training look; do we want oversight of image acquisition or do we NEED (not should, not want, NEED) to have techs trained as well; what is the minimum number of people we need trained and delegated to activate a site; what will activation look like.

Sponsors should initiate regulatory document collection in parallel with contract negotiation and IRB submission. Standard documents typically include:

- **Debarment Checks** (required in the U.S.)
- **Financial Disclosure Forms** (PI, Co-PI, Sub-Investigators)
- **Investigator Agreements** (country-dependent, e.g., FDA vs. Health Canada)
- **Good Clinical Practice (GCP) Certification** (provided by the site)
- **Curriculum Vitae** (signed/dated within 2 years of personnel activation)
- **Medical Licenses** (PI, Co-PI, Sub-Investigators with MD/DO; may also apply to NP, PA, BSN depending on scope/delegations). Sponsors should plan for ongoing collection and renewals, ideally using state systems where available.
- **Study-Specific Certifications (e.g., mRS, NIHSS, MoCA)**. Sponsors should confirm if sites already maintain these certifications, clarify if costs need to be covered in the budget, and establish portals or workflows to collect renewals.

Ongoing QA review of these documents ensures issues are caught early and avoids the common pitfall of missing or expired credentials at the time of monitoring or inspection.

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<sup>35</sup>U.S. Food & Drug Administration. Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies Guidance for Industry and Food and Drug Administration Staff. Website: <https://www.fda.gov/media/81784/download>

## Delegation of Authority (DOA)

The Delegation of Authority log is a critical regulatory document and should be developed in draft form *before* the PI officially delegates tasks. This proactive approach prevents non-compliance findings and reduces the need for retroactive corrections.

### Best Practices for DOAs:

- Use individual DOAs rather than group logs.
- Include site identifiers, personnel names and roles, delegated study-specific tasks, and signature fields.
- Ensure delegations are study-specific (e.g., “Perform NIHSS” vs. “Perform Study Assessments”).
- Include a system to add/remove delegations without requiring a new log.

DOA specificity strengthens compliance, clarifies expectations, and serves as the backbone of the training matrix.

Per ICH GCP 4.1.5, ancillary or intermittent care providers who do not make a direct and significant contribution to study data (e.g., PAs, phlebotomists, technicians, hospitalists, fellows) do not need to be listed on the Delegation of Authority log unless required by the protocol. These individuals may still receive protocol training or in-services as appropriate.

## Training Matrix & Logs

Training should be built in parallel with the DOA. Each delegated task should map directly to required trainings, which are documented in a site training matrix.

- **Training Matrix:** Maps delegations to training requirements and modalities (e.g., protocol training = instructor-led; amendment training = read & review). Each protocol version should have its own matrix.
- **Training Logs:** Capture details such as site identifiers, trainee names, training items, modalities, dates, versions, and signatures.

This dual system ensures traceability, aligns responsibilities with training history, and provides inspection-ready documentation.

## Training Materials

Sponsors should provide high-quality, version-controlled training materials, including:

- Protocol training slide deck (with supplemental role-specific decks)
- Investigational Device Instructions for Use (IFU)
- Imaging manuals
- CRF completion guidelines
- Monitoring and data management plans (internal documents)

Role-specific materials ensure training is not only documented but understood by the intended audience.

## eTMF Build and Execution

Use a good e-TMF that is well organized and easily searchable. Be consistent with metadata so that documents are easier to find. If possible, dedicate someone or a team to work on record management. During start up, so much is happening that it may be good to emphasize that document collection and organization is a very important part of being audit ready. Early collaboration between sponsor and site on building the eTMF ensures that regulatory documents, DOAs, training logs, and certifications are filed correctly from the start. Proactive, ongoing filing prevents delays caused by missing or misfiled records and reduces end-of-activation surprises.

## Regulatory Requirement Tracking

Proactive tracking of activation milestones at the personnel level is essential. Maintaining dashboards or trackers that display document status, training completion, and DOA updates helps:

- Communicate staffing plans clearly.
- Ensure compliance with IRB and sponsor expectations.
- Avoid unnecessary “Notes to File” that consume site time.

By reducing administrative burden, sites can redirect resources to the most important aspects of the study: recruitment, informed consent, and patient safety monitoring.

Roles	Personnel	IRB (Approved-Removed)	DOA (Added-Removed)	Protocol Training (Ver #)	EDC Training	Imaging MOP	Device Training	If Applicable Activation Date (Ver #)	CV/Expiration	Medical Licenses	FDF	IA	IBSP (Ver #)	PSP (Ver #)
<b>Investigators</b>														
PI														
Subl														
<b>Research Coordinators</b>														
Primary RC														
Back up RC														
<b>MDs TO BE ACTIVATED AFTER INITIAL ACTIVATION</b>														
Subl														
Subl														
<b>RCs TO BE ACTIVATED AFTER INITIAL ACTIVATION</b>														
Back up RC														
<b>Admin-on the IRB for Administrative purposes only. Will not proceed with activation or engage in research activity</b>														
Admin														
IRB														
Finance														

Figure 16. Personnel and Regulatory Readiness Tracker

## Key Takeaways

- Begin document collection in parallel with IRB and contract steps.
- Apply ongoing QA checks instead of relying on an end-of-activation review.
- Draft DOAs early and use them to drive training requirements.
- Implement tiered activation to prioritize essential staff.
- Build training matrices and logs that map directly to delegated tasks.

- Partner with sites on eTMF build to prevent regulatory bottlenecks.
- Track milestones proactively to support compliance and reduce unnecessary site burden.

By approaching activation as a proactive, integrated workflow, sponsors and sites can accelerate startup and devote more attention to the core objectives of early feasibility research.

## Recruitment Best Practices

### *Sponsor and Site Partnership*

Set up regular calls with the CRCs to allow them to share their lessons learned, tips and tricks, for enrollment. Share how information on the study has been disseminated to the relevant provider community and how the referral process works. Sponsor to consider providing recruitment tools to the sites that include referral letter templates, informational brochures or slide decks for HCP, informational brochures and/or posters for potential patients, and visual animations that can be used during consult visits. Sponsor should be aware that any site facing material will need to be reviewed and approved by the site's regulatory body. Additionally, the Sponsor may consider sending out a regularly produced newsletters with recruitment updates *and metrics, updates to study criteria, and tips and tricks to help expedite the screening process.*

Share how information on the study has been disseminated to the relevant participant population (as applicable) and what was most successful.

- ✓ **Collaborations with other sites/ Forums to discuss issues and share best practices for recruitment and retention.**
- ✓ **Share operational process and source templates including EPIC created templates that can be modified to site specific details.**
- ✓ ***Discuss updates to screening processes and screening criteria as these evolve during the course of the study***
- ✓ ***Create a forum for Q & A that can prevent screening errors across multiple sites***

The strategy emphasizes prioritizing internal screening over broad external campaigns, given that EFS are highly niche and criteria dense. Screening should be clinic-embedded and longitudinal, with weekly chart reviews in specialty clinics such as heart failure, electrophysiology, and neurovascular, and aligned with disease registries where available. Electronic medical record (EMR) tools play a central role: Epic's SlicerDicer can be used for phenotype queries, Chart Review filters for narrowing eligibility, and OBPA/flags or MyChart Messaging for targeted outreach when permitted. In addition, the enterprise data warehouse (EDW) can be leveraged to build and validate computable phenotypes and to generate refreshed lists for coordinators on a scheduled basis.

Ensure a clear understanding of the workflow currently being utilized for known disease treatment. There may be a regular work up that a patient goes through. Identify with the team (research and other members of staff) when the appropriate trigger is for research to approach the patient and ensure research has advance knowledge of the event. If this is a new treatment and a patient workflow is not

yet established, set up meetings with the PI to discuss how these patients will be identified. *Garner information on a site's referral network during their SQV to ensure that they have adequate access to the correct patient population.*

### **Referring Physician Network**

A successful network depends on targeted education and proactive “customer service,” with consistent updates on indications, inclusion/exclusion criteria, and study logistics. Adopting a “referrer-first” communication model ensures trust and efficiency. Collaboration should remain non-competitive, with shared care models that clearly define handoffs and follow-up responsibilities. Communication should be right-sized, avoiding hype that overwhelms coordinators with ineligible leads. Instead, concise one-page clinical criteria sheets should be used to ensure precision in outreach.

Education and outreach to referring physicians play a crucial role in this process, as many EFS studies target highly specific populations. Maintaining strong communication with referring physicians—emphasizing partnership rather than competition—encourages sustained referrals and long-term collaboration.

### **Equity, Access, and Patient Experience**

This often-overlooked area includes ensuring language access through multilingual consents, interpreter availability (in-person or remote), and translated instructions for home monitoring. Addressing transportation and social needs is equally critical, which can be achieved through resource support or partnerships for travel and lodging (which often the Sponsor is willing to support), as well as clustering visits to reduce patient burden. Community outreach should also be prioritized, engaging community cardiology and neurology practices and Federally Qualified Health Centers (FQHCs) to provide clear referral pathways and study guardrails.

### **Consents and Expectations**

The consent process should use plain language to explain FIH risks and available alternatives, incorporating a teach-back method to confirm patient understanding. Family involvement is encouraged, with caregivers present during training and engaged in post-discharge monitoring to ensure reliability and safety.

## **The Process of Informed Consent**

Informed consent involves providing a prospective subject, or their legally authorized representative (LAR), with adequate information to allow for an informed decision about participation in the clinical investigation prior to enrollment. Informed consent also involves facilitating the prospective subject's understanding of the information, providing adequate opportunity for the prospective subject to ask questions and to consider whether to participate, obtaining the prospective subject's voluntary agreement to participate prior to enrollment, and continuing to provide information as the clinical investigation progresses or as the enrolled subject or situation requires. Once a prospective subject is identified, and before research activities requiring prior consent occur, a person knowledgeable about the clinical investigation and capable of answering questions raised by the prospective subject should conduct a consent discussion.<sup>36</sup>

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<sup>36</sup>U.S. Food & Drug Administration. Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors. Website: [Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors](#)

## Screening Consent

In EFS, patient eligibility is often dependent on anatomy, making it difficult to know in advance which trial may be appropriate. To address this challenge, many sites maintain a separate IRB-approved protocol entitled “Screening for Eligibility to Participate in EFS Research.” The purpose of this protocol is to allow minimal eligibility determination, particularly anatomic review, before initiating the full enrollment process for a specific trial. This protocol does not replace or reduce the extensive informed consent that is required for participation in any individual study. Rather, it functions as a gateway step that streamlines enrollment, prevents unnecessary screen failures, and helps sponsors and investigators target the right population more efficiently.

This type of screening activity typically qualifies for expedited review by the IRB under 45 CFR 46.110, Category 5, as it involves the use of data and images collected for non-research purposes such as medical diagnosis and treatment. The risk profile is minimal and limited to potential breaches of confidentiality. Accordingly, strict safeguards must be in place and the screening consent original must be retained to comply with the IRB screening protocol and the subject charts to document the screening process. No repository of data is created, and only the principal investigator maintains the link between identifiers and medical record numbers.

For example: This practice has been successfully implemented in the structural heart EFS research space. Patients presenting to the valve clinic undergo standard diagnostic testing such as echocardiography, CT, or MRI. Their anatomy is then reviewed by the treating physician, who discusses standard of care treatment options alongside possible research opportunities. If the heart team deems the patient to be a potential candidate for the EFS study, the screening consent is introduced. Signing this consent authorizes the study team to send de-identified data and imaging to an industry sponsor for anatomic review. Information is transmitted through the sponsor’s electronic data capture system, as is the norm for all sponsored device studies. No additional procedures are performed solely for screening purposes.

The screening consent may be obtained in person during a clinic visit or remotely. When patients are not scheduled to return until the day of their planned procedure, coordinators may initiate the consent process by phone or video conference. The benefits of this approach are twofold. For patients, it reduces unnecessary office visits and allows them to make informed decisions without repeated travel. For sites and sponsors, it speeds up enrollment by confirming anatomical eligibility early and reducing wasted effort on patients unlikely to qualify. By combining efficiency with strong privacy safeguards, the screening consent protocol provides a practical and compliant pathway to advance enrollment in device-based EFS.

# Screening Consent Procedures

## Standard of Care Testing

Patients presenting to the valve clinic undergo standard of care diagnostic testing (labs, echocardiography, CT scans, and/or MRI). Their anatomical findings are key determinants of whether they may be eligible for device research in aortic, mitral, or tricuspid valve studies.

## Physician Review & Discussion

- Physicians review clinical findings and standard of care imaging.
- Standard of care treatment options and potential research studies are discussed.
- If research participation is considered, the patient is asked to sign the screening consent.

## Consent Process

- **In-person:** Patients sign the screening consent during their clinic visit after discussion with the physician/research team.
- **Remote/telephone:** In cases where patients will not return until the procedure date, the consent process may begin remotely.
  - The coordinator provides the consent via email, fax, or mail.
  - The consent is reviewed with the patient by phone or video conference.
  - Documentation follows standard short form/remote consent procedures.

## Data Transmission

Once the screening consent is signed:

- De-identified data and imaging are sent to the sponsor through an electronic data capture (EDC) system.
- Data are reviewed against protocol inclusion/exclusion criteria.
- No non-standard procedures are performed solely for research purposes.

## Benefits of the Screening Consent

- **Efficiency:** Streamlines enrollment by identifying anatomical eligibility before initiating full study consent.
- **Patient-centered:** Reduces unnecessary visits—patients may avoid an additional office trip if preliminary imaging suggests one study over another.
- **Sponsor collaboration:** Allows sponsors to review de-identified imaging early, improving study planning and allocation.

Figure 17. Screening Consent Procedures

## *Informed Consent*

Informed consent in Early Feasibility Studies (EFS) requires an approach rooted in authenticity, empathy, and transparency. The investigator's role is not to persuade or promote participation but to ensure that the patient fully understands what is known, what is unknown, and why the study is being conducted. Communication should be clear, non-promotional, and grounded in the physician's ethical duty to act in the patient's best interest. The discussion should reflect genuine enthusiasm for scientific discovery and potential patient benefit—while carefully separating that enthusiasm from personal ambition, institutional pressure, or financial motivation. Because patients cannot independently evaluate an investigational device's safety or efficacy, they rely on the physician's integrity and clinical judgment. Trust is established through honest dialogue, compassionate tone, and the use of accessible explanations. Simple language, visual aids, and opportunities for questions are essential, as is inviting family or caregivers into the conversation. The goal is not persuasion, but mutual decision-making based on clarity and comprehension.

When introducing a first-in-human procedure, investigators should help patients contextualize the innovation within established medical experience. For instance, while a new left atrial appendage (LAA) closure device may represent a novel indication, much of the procedural foundation—such as transseptal access and catheter-based delivery—is already well understood and widely practiced. The materials used in investigational devices are typically familiar biocompatible alloys and polymers with long-standing safety profiles in other cardiovascular implants. What remains uncertain are factors unique to the new device—such as its interaction with cardiac tissue, risk of thrombosis, arrhythmia, infection, or embolization. These uncertainties are inherent to early feasibility research but are counterbalanced by the clinical community's knowledge of how to anticipate and manage complications. Investigators should clearly distinguish between these known and unknown elements, framing the procedure within the continuum of standard, evidence-based practice. By doing so, the conversation reassures the patient that participation does not equate to venturing into uncharted territory, but rather contributes to carefully guided innovation built upon a solid clinical foundation.

The informed consent discussion should also prepare patients for the possibility of complications. While some events may be unpredictable, others—such as pericardial effusion or perforation during LAA closure—are recognized procedural risks that the care team is trained to manage. A well-conducted consent process ensures that patients and families are not blindsided when such events occur; instead, they understand that these possibilities were discussed openly from the start. Importantly, when complications do arise, the physician must be directly present to communicate with the patient and family, offering explanation, reassurance, and empathy. Delegating these conversations solely to research staff undermines the trust built during consent and diminishes the physician's ethical responsibility. True informed consent extends beyond a signature—it establishes a relationship of honesty and support that endures even when outcomes are uncertain.

Finally, informed consent in EFS should include discussion of preclinical data. Although human data may be limited or absent, the investigator can help patients understand the extensive laboratory and animal testing that precedes first-in-human use. Explaining how the device differs from existing technologies and what safety findings emerged during preclinical evaluation provides context and reassurance. For

example, if hundreds of successful animal procedures demonstrated no major adverse events and the relevant anatomy is comparable to humans, that information appropriately informs the patient’s understanding of potential risk. This transparency about both scientific rationale and data limitations allows patients to make decisions aligned with their values and comfort level. Ultimately, informed consent in EFS is an ethical conversation, not a regulatory exercise—one that reflects respect for patient autonomy, professional accountability, and the shared goal of advancing safe, meaningful innovation in medicine.

## Site Case Support and Logistics

The logistics of supporting an EFS case require process mapping, coordination, and early planning to prevent barriers and structured communication across every team involved in patient care and device oversight. Above all, patient safety and operational efficiency must guide each decision. Case logistics extend well beyond the procedure itself, encompassing pre-case preparation, training, credentialing, supply chain management, post-operative support, and patient discharge planning. This section provides practical guidance for sites and sponsors to anticipate common challenges and streamline execution for first-in-human or early feasibility procedures.

Sponsors play a critical role in ensuring seamless case support during Early Feasibility Studies (EFS). The early phase of clinical research is complex, resource-intensive, and highly collaborative. Success depends not only on the technology being tested but also on how well sponsors integrate into the site’s established workflows.

The goal for sponsors should be to fit within existing site processes as much as possible, minimizing disruption and administrative burden. Clear communication of expectations and proactive planning are key to ensuring that all required elements—regulatory, operational, and logistical—are in place well before the procedure date.

For many emerging companies or first-time EFS sponsors, the learning curve can be steep. Understanding what the site team must coordinate behind the scenes (regulatory approvals, credentialing, training, sterilization, logistics) helps sponsors anticipate needs and contribute effectively to a smooth, efficient case. The checklist below outlines the major tasks to complete prior to case support and provides a framework for maintaining readiness, communication, and accountability

### *Protocol and Process Mapping*

Process mapping should be initiated during the study start up process as it is a highly effective strategy during budget development and protocol activation. By translating the table of events and protocol visit into a step-by-step clinical and operational flow, sites can differentiate between standard-of-care and research-related tasks, anticipate bottlenecks, and allocate resources accordingly. The process map should follow the full patient journey—from identification and screening through consent, procedure, discharge, and follow-up—and should be revisited after each case to incorporate new learnings.

## *Flexibility and Anticipation in Early Feasibility*

A defining characteristic of EFS case logistics is that because so few cases have been performed—often first-in-human—it is impossible to anticipate every potential issue. Flexibility and proactive communication are critical. Everyone involved should understand from the outset that EFS cases are unique, with unknowns that require adaptability and rapid pivoting as challenges arise. It is essential that no one hears for the first time, on the day of the case, that something is being done for the first time. Sites should emphasize awareness and preparedness early in the study startup phase to minimize surprises.

Device management is one of the most complex aspects of EFS logistics. Depending on the sponsor, investigational products may be shipped in large crates, require locked or temperature-controlled storage, or involve components that must be logged, calibrated, or safety-certified. Academic institutions, particularly in dense urban areas, often face space constraints that make storage a challenge. Early identification of delivery requirements—including whether a shipment requires “white glove” service at the loading dock—is essential. Temperature monitoring, documentation of excursions, and confirmation that devices remained within the approved ranges per the IFU are all part of best practice. Components such as consoles, sheaths, and delivery systems should also be documented, logged, and stored securely.

Many EFS devices include software or electronic components that require additional oversight. Consoles must go through biomedical engineering review to confirm safety and functionality, while devices containing software must pass through institutional IT or privacy review (often through an ITPMO process) to ensure cybersecurity compliance. Understanding which elements are considered part of the investigational product—including implant cards, IFU booklets, and patient materials—is key to maintaining accountability and regulatory compliance.

Sponsors should provide each site with a detailed list of ancillary devices and supplies needed for the procedure during study startup or the SIV. However, because activation and first-case timing often span months, these lists should be reconfirmed shortly before the case. A lack of timely communication can result in missing critical items such as frozen saline machines, specific catheters, or specialized hooks. Sites may find themselves borrowing from neighboring institutions—an avoidable scenario with early and detailed coordination.

Some protocols require testing or monitoring that is not part of standard care. Sites must ensure they have the proper instruments available at the correct location—for example, ACT devices on inpatient units if testing is required outside of the cardiac catheterization lab. Sponsors can provide loaner devices or assist with procurement, but planning must occur well before the case. Even with preparation, sites should expect that adjustments may be necessary during initial cases and build feedback loops to strengthen future readiness.

## *Awareness Campaign to Clinician that will be caring for the patients peripherally.*

Since these procedures are often novel and out of the normal routine care. Training must extend beyond the immediate procedural team to include the entire continuum of care—intensive care units, step-down units, anesthesia teams, physical and occupational therapists, and other ancillary staff. The depth of training should align with each team’s role. Awareness sessions can provide brief overviews for non-direct

care teams, while operational and proficiency sessions—lasting from forty-five minutes to several hours—should be conducted for those directly interacting with the device.

Depending on the complexity of the device and the human factors, patient and caregiver education must also be integrated into discharge planning, ensuring comprehension through bilingual materials and in-language support where applicable. For devices requiring continuous monitoring or data uploads, real-time technical and clinical support should be available 24 hours post-procedure to mitigate complications.

### *On-Site Sponsor Case Support*

Planning should begin eight to twelve weeks before the first case, ensuring that all necessary personnel are identified, credentialed, and equipped for their roles. Since these cases have never been done before or have been done infrequently sponsors want to send many representatives to the case to both support the case and teach their team for future case support. Sites to provide guidance and boundaries on limits to the number of sponsor representative that can attend and request the sponsor provided a be tiered plant to avoid overcrowding in the procedure room, Essential operators and technical staff in Tier 1, observers or secondary support in Tier 2, and remote or on-call experts in Tier 3. Limiting the number of sponsor representatives present in the room enhances safety, while remote viewing and post-procedure review sessions can offer training opportunities without compromising space or focus.

Once the sponsor staff supporting the case are identified, the site must work on access to the medical center either by undergoing credentialing or setting up visitor passes. For credentialing, it is critical, particularly when involving external or international personnel, and should be started well in advance of the case date.

### *The Day Prior to the Case*

Because EFS procedures often occur rarely, operator and sponsor training are intensive in the 48 hours before and after the first case. Dry runs the night before the procedure allows sponsors and teams to test room setup and workflows. Sponsors may bring mock models—such as a simulated beating heart—or 3D printed patient anatomy to visualize device deployment. The morning of the procedure typically includes a review of the patient’s imaging, procedural plan, and discussion of any anatomic or technical nuances. When feasible, sponsors often schedule multiple cases on the same day to maximize efficiency, though this creates long days for research teams. Sites should plan for coordinator workload, ensuring time for both patient-facing and data-entry responsibilities.

It is ideal for the research coordinators to develop and execute a pre-case readiness checklist the day before the procedure. This serves as the final confirmation that all logistical, regulatory, and operational requirements are in place. The checklist should include the following key elements:

- ✓ **Sponsor and visitor readiness:** Confirm that all sponsor personnel or vendor representatives have completed credentialing, obtained badges, and had appropriate scrubs or protective attire available on site.
- ✓ **Supply verification:** Check that all required investigational devices, ancillary tools, and disposables are on hand and accessible in the assigned storage area. Verify that backups are available for any single-use or limited-supply items.

- ✓ **Conference and briefing logistics:** Reserve a conference room or meeting space for the pre-case huddle and post-case debrief. Ensure audiovisual capabilities are available if remote participants will join.
- ✓ **Device accountability and documentation:** Confirm that investigational products have been logged, stored in secure and temperature-appropriate conditions, and that traceability documentation is up to date.
- ✓ **Safety reporting readiness:** Verify that the coordinator has the necessary access and time to report Serious Adverse Events (SAEs) or Unanticipated Adverse Device Effects (UADEs) promptly, with reporting channels to the IRB, sponsor, and FDA clearly defined.
- ✓ **Workflow clarity:** Ensure all staff understand the clinical flow, including which activities are standard of care (SOC) versus protocol required. Coordinators should communicate these expectations to the clinical team so that procedural staff understand what documentation, orders, or additional testing are required by the study. Whenever possible, provide the clinical team with the rationale behind these requirements. For example, if the protocol mandates two post-procedure cardiac enzyme draws at specific intervals to assess for peri-procedural myocardial infarction, explain that both are necessary for accurate endpoint assessment. Clinicians may otherwise assume the second order is redundant and cancel it, not realizing it serves a research-specific purpose. By sharing the “why,” coordinators can prevent errors, improve compliance, and strengthen collaboration with the clinical team.
- ✓ **Pre-case communication:** Send a summary email to the full care team (operators, nurses, anesthesiologists, sponsor reps, and research staff) confirming case timing, roles, and any special requirements such as imaging review or dry-run simulation.

### *Day-of-Case Operations*

On the day of the procedure, an interdisciplinary pre-case huddle is essential to review responsibilities, patient status, and contingency plans. Attendance should follow the predetermined tiers, and a designated point person should oversee equipment and device flow to maintain efficiency. Real-time sponsor support should be limited to a single technical lead at the field, while additional representatives can join remotely.

Following the procedure, a structured handoff should occur to ensure that the post-operative and step-down units are fully informed about device operation, patient monitoring parameters, and troubleshooting procedures. Patients discharged with devices should receive clear, accessible instructions, 24/7 support contact information, and confirmation that data transmission systems are operational.

### *Debrief, Safety, and Continuous Improvement*

Every EFS case should include both an immediate “hot debrief” immediately after the procedure and a more detailed “cold debrief” within 72 hours. These sessions allow the team to identify process gaps, update checklists, and refine workflows for subsequent cases. Documenting lessons learned and sharing gratitude with the multidisciplinary team fosters engagement and continuous improvement.

EFS procedures require close post-procedure surveillance. Adverse events often occur near the time of the procedure and must be reported promptly in the EDC, to the IRB, and to the FDA when applicable. Research coordinators should perform daily chart reviews to identify unreported events, maintain communication with treating clinicians, and ensure that reporting requirements are met. Because EFS

teams work long procedural days, workflows should include designated time for follow-up documentation and safety reporting to prevent fatigue-related errors.

### **Contingency Planning and Risk Mitigation**

Finally, contingency planning is essential in EFS case logistics. Unexpected challenges such as travel delays, missing equipment, or last-minute credentialing issues can jeopardize case execution. Sites should establish explicit “go/no-go” criteria and back-up plans, including pre-cleared alternate vendors and secondary case dates. Maintaining an adaptable mindset is key; flexibility and real-time problem-solving define successful EFS operations.

By documenting these workflows, sharing feedback openly, and planning ahead, research teams and sponsors can ensure that every early feasibility case advances both patient safety and scientific discovery.

### **Preparation Checklist**

- Regulatory Approvals** → Confirm FDA, competent authority, and IRB approvals are obtained.
- Insurance Coverage** → Verify that the required insurance policies are active and compliant before case scheduling.
- Vendor Credentialing** → Identify the site’s credentialing platform early and ensure all sponsor and vendor representatives are fully approved (“green”) before arriving on site.
- Training Confirmation** → Schedule and confirm training sessions with the site; verify that all required staff have completed both didactic and hands-on components.
- Device Shipment & Inventory** → Provide the site with the required device list and confirm all materials have arrived and are ready for use. If devices have temperature monitoring, verify integrity and ensure no compromise has occurred during transport.
- Sterilization Requirements** → Complete all sterilization needs in advance and confirm compliance with site sterilization procedures, documenting any special handling instructions
- Travel Logistics** → Finalize travel arrangements and confirm arrival schedules for all sponsor team members. Remain flexible and prepared for last-minute adjustments to case start times.
- Internal Device Requests** → If internal sponsor processes require formal requests or documentation for device shipment or release, ensure these are completed and approved prior to the procedure date.
- On-Site Support Coordination** → Connect with the site research team ahead of time to request scrubs, lead aprons, or any other vendor-specific needs required to support the case. Confirm access to storage, prep areas, and communication protocols for day-of logistics

## *Vendor Logistics*

Early identification of each site's vendor credentialing system is essential. Each hospital may use a different system—such as Vendormate, Green Security, or others—with varying requirements, such as completion of site-specific SOP reviews or submission of immunization records. Credentialing can be time-consuming, often taking several hours per individual, and must be completed for every sponsor representative entering the OR or cardiac catheterization lab. Because credentialing requirements vary by site, this process may need to be repeated multiple times across institutions. Sponsors should prioritize completion of this step early to avoid access delays on the day of the case.

## *Device accountability and delivery*

Device logistics can vary across studies and institutions. Some sponsors hand-carry devices to and from the site, ensuring that no investigational product remains afterward. Others may encounter sites requiring a “No Charge Purchase Order (PO)” for devices to be received on-site. These requirements should be identified and resolved early to prevent procedural delays. Clear communication between the sponsor, clinical site, and supply chain teams is crucial to maintain accountability and ensure that investigational products are handled appropriately.

## *Sterilization of Investigational and Ancillary devices*

New technologies often require unique ancillary equipment, and sponsors should provide a detailed list of all required materials—clearly distinguishing between items supplied by the sponsor and those expected from the site. This list should include detailed specifications, such as the exact length or type of guidewires, to prevent procedural interruptions. If any sponsor devices are reusable or require sterilization, early communication with the site's sterilization department is essential. For new or complex devices, a dedicated meeting with the sterilization team can be beneficial to explain handling requirements and address any concerns. Early engagement in this process is critical to avoid last-minute sterilization issues or delays in scheduling procedures. If the Sponsor requires components to be sterilized by the hospital's central sterilization department, that equipment should be provided approximately 2 weeks in advance. The sponsor should provide an IFU and in-servicing training to the sterilization department.”

## *Pre Implant Device Training*

Sponsors should differentiate between initial device training and subsequent refresher sessions. Initial training sessions, which may last two to three hours, typically include both didactic and hands-on components. These should be coordinated with the site to ensure that all relevant staff members are present and understand the learning objectives. Training may need to occur outside regular hours, depending on staff schedules. For subsequent trainings, sponsors should define clear criteria for when retraining is required. If a long interval has passed between cases, a comprehensive retraining may be appropriate, while shorter intervals may only require a brief didactic review or benchtop demonstration to reinforce procedural steps.

What Sponsors Can Do	
Action	Best Practice
✓ <b>Confirm Baseline Data Readiness</b>	Before each case, confirm with the research coordinator that all required baseline data have been collected per protocol.
✓ <b>Reinforce Protocol Compliance</b>	Gently remind the research coordinator of key timing or documentation requirements (e.g., lab collection windows, adverse event reporting).
✓ <b>Provide Template Source Tools</b>	When possible, supply a sponsor-prepared template source document that mirrors the <i>procedural flow</i> rather than CRF organization, allowing data to be captured in real time.
✓ <b>Share Cross-Site Learnings</b>	Communicate lessons learned from prior procedures—such as workflow improvements, documentation tips, or timing insights—to help sites avoid repeat issues.
✓ <b>Clarify Data Purpose</b>	Explain why specific data are collected (e.g., to demonstrate device function, assess safety, or evaluate procedural outcomes). Understanding intent enhances accuracy and engagement.
✓ <b>Support Post-Procedure Data Review</b>	Work collaboratively with the site team to ensure all in-hospital and early follow-up data points are captured and clarified while the case is fresh in memory.

Figure 18. What sponsors can do to support site data collection.

### Post Procedure Debrief

Post-case debriefs are critical, particularly in EFS, to capture lessons learned and strengthen the sponsor–site relationship. These debriefs should include both the sponsor and site teams and can take place immediately after the case to review procedural performance and any device observations. In the event of a device malfunction or adverse outcome, sponsors should consider conducting a more detailed root cause analysis with the site. This open communication fosters transparency, continuous improvement, and trust—key components of a strong EFS partnership.

## EDC Turn Around

Timely data entry and image upload are essential to the success of Early Feasibility Studies (EFS). Each case or patient treated provides valuable insights that inform the ongoing development of the device and deepen understanding of its risk profile. Rapid turnaround of data enables sponsors to analyze outcomes in near real time and share key learnings with other participating sites—an important distinction from the more rigid, retrospective data review process typical of pivotal trials.

Prompt submission of imaging and procedural data allows sponsors to conduct meaningful post-case debriefs, identify potential devices or procedural issues early, and disseminate best practices across the study network. This rapid feedback loop not only accelerates the collective learning curve but also provides critical input for device iteration and refinement. Early and accurate data entry helps sponsors assess whether performance or safety thresholds are being approached, guiding decisions on when modifications to the device design, protocol, or training approach may be warranted.

EFS cases are often long, complex days that demand significant time and energy from both the site and sponsor teams. However, a hallmark of a strong and committed site is the ability to prioritize timely data entry and imaging upload even after a demanding case day. By ensuring that information is quickly relayed back to study partners, these sites contribute to the greater good, helping the broader clinical community learn, adapt, and improve the technology for future patients. This spirit of collaboration and dedication to advancing innovation is at the core of what defines a high-performing EFS site.

## Transition from EFS to Pivotal Study

The decision to transition from an EFS to a pivotal study is one of the most critical inflection points in device development. It requires striking the balance between timely progression and ensuring that sufficient evidence exists to support a successful pivotal study. This decision is not based on patient numbers alone but rather on whether enough information has been gathered to finalize the device, establish safety and feasibility, and design a pivotal study that can be appropriately powered and executed at scale.

Sponsors should first confirm that the device itself is finalized, or at least highly stable, with clear documentation showing how prior iterations were refined to resolve earlier limitations. Equally important is the accumulation of preliminary clinical evidence: the EFS should demonstrate proof of principle, acceptable early safety signals, and functional performance in real-world clinical settings without evidence of unmitigated risks. The operator learning curve must also be considered; by the time of transition, investigators should be consistently performing the procedure with reproducible results across sites, minimizing variability that could compromise a pivotal study.

Another marker of readiness is a clear understanding of event rates and endpoints. Data collected during EFS should be sufficient to inform pivotal study design, including estimates of safety and effectiveness event rates, sample size calculations, and refinement of primary and secondary endpoints. Risk mitigation strategies should also be in place, encompassing training, monitoring, and oversight to ensure the safe expansion of the patient population. These measures provide reasonable assurance that the pivotal study can proceed safely and effectively.

## **Playbook Takeaway: When to Transition Pivotal**

Transition occurs once:

- Predictive sizing is well defined.
- Anatomic exclusions are clearly understood.
- Device iteration has stabilized.

At this stage, the sponsor can shift focus from procedural feasibility to clinical benefit, durability, and regulatory-grade outcomes.

### **Pitfalls:** *Lack of Iterative Focus*

Device iteration is the whole point of EFS, but some companies rush to “freeze” the design prematurely to impress regulators or investors.

If iteration is cut short, problems will surface in pivotal—which is far more costly and damaging.

Finally, alignment with regulators is essential. FDA typically confirms readiness to bridge through prior pre-submission discussions and ultimately through approval of an IDE supplement containing the pivotal protocol. Sponsors should recognize that device modification is acceptable during EFS but must cease in pivotal trials, where stability of the device design is a prerequisite.

## **Chapter 10 Modifications**

### **Modifications Overview**

Modifications during EFS—whether physical changes to the device such as design refinements, manufacturing updates, or the introduction of a new iteration, or process and protocol amendments—follow similar regulatory and operational processes as protocol amendments. The site submits a modification request to the IRB accompanied by updated **Instructions for Use (IFU)**, sponsor-provided rationale, and supporting risk documentation. The IRB evaluates all of these amendments to confirm that the risk-benefit assessment remains acceptable.

### **Risk-Benefit Evaluation**

Sites rely on the IRB’s review of updated IFUs, labeling, and sponsor justifications to determine the appropriateness of continued enrollment. The IRB ensures that device modifications do not introduce unmitigated risks and that investigator and participant information remains current and accurate.

## *Device Accountability and Version Control*

Sites maintain detailed device accountability logs that document shipment, labeling, and usage of all device iterations. Products are clearly identified in inventory systems, and outdated or superseded versions are promptly returned to the sponsor to prevent inadvertent use.

When possible, sites store distinct device versions separately and cross-reference them with applicable protocol versions in source documentation. This supports both audit readiness and operational clarity.

## *Investigator and Staff Training*

For new or modified device iterations, investigators and research staff complete all sponsor-required training prior to use. These may include in-person demonstrations, online modules, or competency attestations. Generally, there are no additional site-specific credentialing requirements beyond institutional or sponsor-mandated certifications.

## *Communication with Enrolled Subjects and Re-Consent*

When protocols or devices are amended after subjects have already been enrolled, a key consideration is whether and how to communicate these changes to those participants. The IRB will generally indicate whether they believe the new information rises to the level that requires re-consent.

If the amendment introduces changes that do not affect enrolled subjects—for example, adding an additional screening procedure for new patients—then re-consent is not typically required. In these cases, requiring re-consent can confuse participants who have already completed those stages of the study.

By contrast, if the amendment introduces changes that do impact enrolled subjects, re-consent is essential. This may include the discovery of an unanticipated risk, the introduction of new follow-up requirements, or modifications that alter the subject's ongoing participation. In such cases, subjects must be informed and provided with an opportunity to review and sign an updated consent.

It is best practice for the principal investigator to clearly state to the IRB whether they believe re-consent is necessary, and to provide rationale for their position. Depending on the significance of the change, the IRB may allow use of an addendum consent form that highlights only the new information, rather than requiring participants to re-sign the full original consent. This approach can reduce subject burden while ensuring compliance and transparency.

## *Sponsor Support Needs*

From the site's perspective, the most valuable sponsor support during device amendments includes:

- Non-technical explanations of the modification and its rationale, enabling coordinators and investigators to communicate confidently with staff and patients.
- Complete, well-organized documentation to facilitate rapid IRB review.
- Clear guidance on whether re-consent or retraining is required, to streamline site operations and avoid ambiguity.

✓ *Example of changes to the consent that would NOT warrant re-consent.*

- Correction of typographical or grammatical errors
- Reformatting for readability (font, spacing, layout)
- Re-ordering sections without altering meaning
- Updating page numbers or version control formatting
- Clarifications that do not introduce new information, modify study requirements, or change participants' understanding of risks or alternatives do not necessitate re-consent.

✗ *Example of changes that affect research activities the participant has already completed (e.g., re-consenting enrolled participants due to updates in screening procedures).*

- Adding an MRI substudy to patients that have already been enrolled and need a baseline MRI to be included in the sub study.
- Higher risk of bleeding post procedure

## Modifications of the Device

Device modifications present a distinct set of challenges. These amendments typically originate within R&D and quality functions rather than clinical operations, and any change requires verification testing before implementation. Although sponsors strive to avoid modifications during an EFS, they are often inevitable. When revisions are necessary, version control and documentation processes should mirror those used for protocol amendments.

If device changes alter the risk-benefit profile, sponsors must ensure alignment between protocol updates and patient-facing documents. In some cases, re-consent of patients may be required, particularly if substantive modifications occur prior to device implantation. While post-implant modifications (e.g., software updates) may not always require re-consent, transparent communication remains best practice.

EFS are designed to allow for iterative device development, including changes to design, materials, or software, based on early clinical experience. Unlike later-stage trials, EFS intentionally permits flexibility, recognizing that the device may not be finalized when first used in humans.

### *Common Modifications Include:*

- Size or shape adjustments (e.g., catheter diameter)
- Delivery system refinements
- Software or firmware updates
- Material or coating changes

- Minor usability enhancements
- These modifications must be predefined as possible in the protocol and carefully communicated to FDA and clinical sites.

The FDA's EFS guidance encourages innovation while protecting patients by allowing:

- Protocol flexibility (through a risk-based approach)
- Device modification plans to be submitted in the original IDE or via IDE supplements.
- Use of a risk assessment matrix to determine whether a modification requires formal FDA approval or only notification.

## *How to Streamline the Process*

### **Sponsors:**

- *Develop a Device Modification Management Plan*
  - Pre-define categories of anticipated modifications (ex. minor vs. significant)
  - Outline how changes will be documented, assessed, and reported to FDA and IRBs
- *Leverage FDA's Interactive Review Pathway*
  - Build rapport with the review team for faster feedback.
  - Use emails for minor clarifications, rather than waiting on formal supplements.
- *Coordinate with Clinical and Regulatory Teams Early*
  - Ensure engineers, regulatory staff, and clinical operations are aligned on what changes are permissible and how to track them.
- *Pre-Position Iteration Pathways*
  - Design protocols and manufacturing systems that allow for low burden iteration.

### **Clinical Sites:**

- *IRB Streamlining*
  - Use Central IRBs where possible.
  - Educate IRBs in advance about the EFS nature of the study and anticipated device modifications.
- *Communication Plan with Sponsor*
  - Set clear expectations with the sponsor for how and when updates will be shared.
  - Use shared tracking tools (like sponsor-supplied logs or cloud folders) to reduce confusion.
- *Site Training & Version Control*
  - Provide clear training on each device iteration.
  - Maintain clear documentation of which version was used with each patient.

## Modifications of the Protocol

When a protocol change is needed in an EFS, it must be carefully assessed and strategically managed to minimize disruption while maintaining regulatory compliance and patient safety. The first step is to determine the nature and impact of the proposed change. Not all modifications require the same level of oversight—some may trigger a full FDA review with a 30-day supplement,<sup>37</sup> others may qualify for a 5-day notice, and minor administrative changes may not require FDA notification or approval at all. Assessing whether the change impacts patient safety, study integrity, device use, or key study parameters is essential to identifying the appropriate pathway for submission. Early involvement of regulatory affairs is critical to navigating this process. Regulatory consultants can help clarify the reporting requirements, determine whether the change requires IRB approval at participating sites, and guide the documentation process.

In parallel, sponsors should proactively design EFS protocols with flexibility in mind to minimize the need for future amendments. This can be achieved by using broad timing windows, generalizable device descriptions, and carefully crafted inclusion and exclusion criteria that reduce the likelihood of operational barriers and frequent deviations. When a protocol amendment is necessary, give them the “why”. Sponsors must prepare a formal amendment that explains the rationale for the change, summarizes the specific modifications, and updates all relevant study documents, including the informed consent form, case report forms, and Instructions for Use, if applicable.

Site-level impacts should be a key consideration, as protocol changes typically require additional IRB submissions, staff retraining, participant re-consents, and re-activation letters. Sponsors should provide sites with detailed summaries of the changes, clear implementation instructions, and, when possible, support site training to facilitate the transition. Maintaining open communication with the collective sites is essential when managing protocol changes in an EFS. Frequent discussions with both the PI and the lead RC allow thoughtful discussion on proposed changes, assess their feasibility in clinical practice, and gather feedback on how modifications may impact workflows at the site level. Input from the front line can be invaluable in shaping amendments that are both clinically sound and operationally practical.

Sponsors are encouraged to design protocols with the intent of minimizing amendments. Because an EFS may enroll as few as 15 patients, pausing enrollment to revise the protocol can have outsized consequences. Once recruitment is interrupted, re-engaging sites often proves challenging—akin to “turning the Titanic”—and can result in months of delays.

When protocol amendments are necessary, sponsors must follow FDA’s five-day notification process or IDE supplement approval, then cascade changes to sites. Coordination with IRBs/ECs depends on the oversight model:

- **Local IRBs** – Research coordinators usually prefer to submit directly. Sponsors should allow them to manage the process.

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<sup>37</sup> U.S. Food & Drug Administration. GUIDANCE DOCUMENT Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies. Website: [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies | FDA](#)

- **Central IRBs** – This is the most efficient pathway, as amendments can be distributed quickly across participating sites.
- **CRO Involvement** – In ex-U.S. settings, CROs may handle IRB/EC communications, but in the U.S. many sponsors prefer to retain direct oversight.

Once approvals are in place, sponsors must ensure all investigators and site staff are trained on the revised protocol. Training should be documented, with records stored in the electronic trial master file (eTMF). Sponsors often use electronic data capture (EDC) systems and document control practices (e.g., protocol numbers with revision tracking) to ensure sites always work from the correct version.

### **Common triggers:**

- **Eligibility refinements** (over-stringent inclusion/exclusion; remove contradictions; reflect real-world signals).
- **Safety learnings** (exclude newly identified risk groups; add specific measurements).
- **Device/process changes** (e.g., catheter angle, sterilizer change).

And while the protocol is being modified assess patterns of frequent deviations, especially across multiple sites, that can indicate that specific protocol elements are misaligned with real-world practice. Use these trends to consider whether a protocol amendment would reduce non-compliance and improve study execution.

### **FDA 5-day notes vs 30-day notice**

- **Ask the safety question first.** If a change affects the rights, safety and welfare of patients design, consent, or risk analysis → 30-day supplement.
- **Err on the side of caution.** When in doubt, submit as a 30-day rather than risk a misclassified 5-day.
- **Keep a clean record.** Even non-submitted changes must be documented under 21 CFR 812.140.
- **Bundle updates.** Each change drives IRB amendments, site retraining, and CRO costs—group them whenever possible.
- **Plan ahead.** Build 30 days of lead time into project timelines for significant amendments.

## **Sponsor Process**

From a sponsor’s standpoint, anticipating and managing amendments during an EFS (EFS) requires careful planning and disciplined execution. Unlike pivotal studies, where larger enrollment may allow for more procedural flexibility, an EFS typically involves a very limited number of patients. This means that even a minor amendment can significantly disrupt study progress.

## ***Device Amendments Lessons Learned***

Across sponsors' experiences, several key lessons emerge:

- Protocol amendments might slow recruitment and, if enrollment must pause, can stall studies entirely.
- Proactive planning and tight protocol design are essential to reduce amendment frequency.
- Document control and version tracking prevent confusion across multiple sites.
- Communication and training must be prioritized to keep investigators aligned with the most current requirements.
- Device modifications must be carefully coordinated with quality systems, and their downstream impact on risk communication and patient consent should not be underestimated.

Ultimately, EFS sponsors emphasize that clear planning, rigorous control systems, and transparent communication with sites and patients are critical to navigating the inevitable challenges of amendments while keeping studies on track.

## **Site Process**

From the site perspective, protocol amendments and device modifications require coordination across multiple teams, thoughtful timing, and clear communication to minimize disruption to study conduct and patient care. Because EFS are conducted in real-world, high-acuity environments with rapidly evolving technologies, even minor changes can have broad operational, financial, and regulatory implications. This chapter outlines how academic and hospital-based sites approach the review, implementation, and communication of modifications during active studies.

### ***Notification and Initial Review***

When a sponsor issues a protocol amendment, the process often mirrors study start-up. Once the site is notified and revised documents are received, the research team submits a modification request to the Institutional Review Board (IRB). If the amendment impacts the study budget or contract, those teams are notified in parallel so that revisions and negotiations can begin. Early identification of operational impacts—such as workflow changes, new assessments, or altered visit schedules—helps ensure readiness across all functions.

### ***IRB Review Timelines***

Turnaround times for IRB approval vary based on submission volumes and institutional priorities. On average, sites report four to six weeks from submission to approval, although amendments tied to patient safety concerns can be reviewed on an expedited basis. Maintaining open communication with the IRB and submitting a complete package of materials are critical to minimizing delays.

## Common Challenges

Several recurring challenges arise when implementing amendments mid-study:

- **Visit Schedule and Procedure Changes:** Modifications to the visit schedule or testing requirements can be difficult to incorporate when participants are in the early, high-frequency visit phase. These changes require immediate updates to calendars, EMR order sets, and source documentation.
- **Contract and Budget Misalignment:** IRB approval often precedes finalization of the amended contract and budget. Because IRB approval authorizes immediate implementation, sites may be required to carry out changes before the financial terms are in place, creating reimbursement and compliance risks.
- **Concurrent Study Demands:** Coordinators balancing multiple active trials face added workload pressures to retrain, update documentation, and ensure version control across all systems and binders.

## Staff Notification and Retraining

Staff retraining is a critical step in amendment implementation. Once the changes are received and understood, sponsor-required training is distributed to all assigned study staff with the goal of completion prior to IRB approval to prevent interruptions in study conduct. Ancillary groups—such as cardiac catheterization lab staff, imaging teams, or pharmacy—are notified in advance of operational changes to ensure continuity.

At some sites, the research office maintains centralized amendment checklists that include documentation tracking, updated procedures, and confirmation of completion for all required training prior to reactivation.

## Tracking Deviations and Maintaining Compliance

During the transition between protocol versions, protocol deviations (PDs) may occur as teams adapt to the new requirements. Sites use internal participant tracking systems to record adverse events (AEs), PDs, and amendments, which enables reporting to the IRB at continuing review and supports proactive quality assurance. This systematic tracking ensures visibility across ongoing studies and supports institutional oversight.

## High-Impact Amendment Types

Certain amendment categories consistently present greater operational hurdles:

- **Eligibility Criteria Changes:** These may affect active screening pipelines and require updated prescreening logic in Research Electronic Data Capture (REDCap)<sup>38</sup> or Electronic Medical Record (EMR) systems.
- **Follow-Up Schedule Modifications:** These disrupt clinical workflows and require recalibration of reminders, visit windows, and data entry schedules.

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<sup>38</sup>REDCap. Research Electronic Data Capture. Website: [REDCap](https://www.redcap.org/)

- **CMS Coverage Adjustments:** Particularly in EFS, late introduction of Centers for Medicare & Medicaid Services (CMS) approval requirements can create reimbursement and operational delays if the study was initiated prior to CMS determination.

## Chapter 11 CRO Component

Early Feasibility Studies (EFS) sit at the intersection of pioneering clinical innovation, rapid iteration, and evolving regulatory expectations. They are uniquely complex: sponsors are often engineering-led startups navigating unfamiliar regulatory pathways; clinical sites are highly skilled yet risk-aware; and regulatory bodies require robust oversight while allowing for the flexibility needed to learn quickly. Contract Research Organizations (CROs) can serve as the connective tissue across this ecosystem—stabilizing operations, translating concepts into practice, and ensuring that both learning and compliance stay on track. When chosen and deployed well, CROs help sponsors accelerate development, avoid predictable pitfalls, and maintain the delicate balance between innovation and safety that defines EFS.

### Why CROs Matter in EFS

EFS demands operational precision at the same moment it requires iteration and flexibility. CROs help bridge those competing needs. They provide independent oversight to ensure quality, regulatory compliance, subject safety, and predictable study conduct, especially when sponsors are resource-constrained or navigating their first clinical investigation. Device development adds complexity: the regulatory pathways (IDE in the U.S., MDR 745/2017 in the EU, UKCA in the UK) are specialized, the operator learning curves are steep, and mid-study modifications are expected rather than exceptional.

Early feasibility programs often rely on regulatory consultants or specialty CROs with regulatory consulting arms to guide development of the Device Evaluation Strategy (DES), intended learning objectives, and risk mitigations in alignment with FDA expectations. CROs support execution by right-sizing operational processes—such as monitoring, data management, and site coordination—so that early feasibility studies remain nimble and are not burdened by pivotal-trial infrastructure. This model reduces variability across sites while preserving appropriate flexibility and provides operational continuity through sponsor and site staffing transitions.

While not every EFS requires a CRO, access to experienced operational support—whether through a CRO partnership or equivalent internal expertise—can be a significant accelerator. Early Feasibility Studies blend pioneering clinical work with rapid iteration, demanding executional rigor alongside flexibility.

## ***CROs can be the glue between small, engineering-led sponsors, risk-aware sites, and evolving regulatory expectations.***

Done well, CROs:

- **Translate concept to conduct:** turn an early idea and DES into executable study operations.
- **Right-size process:** apply compliance without importing the full weight of pivotal-trial bureaucracy.
- **Stabilize teams:** provide continuity across sponsor funding cycles and site turnover.
- **Standardize where it helps, flex where it counts:** consistency across sites, flexibility to iterate case-by-case.
- **Keep three lanes clear:** Sponsor, CRO, Site. Don't collapse responsibilities "just to be safe"

## **When and Why to Engage a CRO**

Sponsors should consider CRO engagement once they have begun forming their regulatory and clinical strategy and can clearly articulate how external operational support would add value. Early involvement can be beneficial in certain cases, particularly when a CRO has demonstrated experience with Early Feasibility Studies and device development.

When engaged early, some CROs can provide operational input to FDA pre-submission planning, contribute feasibility and executional perspective during protocol development, and help anticipate downstream needs such as monitoring intensity, imaging logistics, safety management, and training requirements. Importantly, these capabilities vary widely across CROs and should not be assumed without careful scoping and confirmation of relevant EFS experience.

Startups, in particular, should define a minimum viable scope before initiating CRO discussions. This includes a high-level protocol concept, key endpoints, success metrics, safety thresholds, regulatory strategy, and anticipated case volume. Without this clarity, CRO conversations can drift into future-state hypotheticals that inflate budgets, dilute focus, and obscure the immediate objectives of the Early Feasibility phase.

### **CROs are especially valuable when:**

- Sponsors lack internal clinical operations infrastructure
- Device designs are expected to evolve mid-study
- Sites require intensive support
- Studies include imaging-heavy endpoints
- A small sponsor team must demonstrate quality and reliability to investors or regulators

While some sponsors defer CRO engagement until protocols are finalized, earlier engagement—when appropriately scoped—can support smoother transitions from feasibility concept to protocol development and operational planning.

## How CRO Relationships Begin: Engagement Pathways & Operating Models

### *How the Relationship Starts*

In medical device research—particularly structural heart, neuro-endovascular, and complex implantable devices—repeat experience and referrals dominate. The community is small, and reputation matters more than marketing. Sponsors often identify CROs through:

- Industry referrals and site recommendations
- Prior experience within the sponsor’s leadership team
- Thought leadership (conference presence, white papers, LinkedIn content)
- Review of historical EFS experience on ClinicalTrials.gov
- Networking among device engineers, regulatory consultants, and KOLs

Rescue projects constitute approximately 20% of CRO engagements, usually when sponsors underestimate the complexity of EFS or attempt to run studies internally without operational bandwidth. More common is a hybrid model where sponsors insource core operations and outsource specialized functions such as safety, data management, statistics, or imaging.

### *Operating Models*

CRO engagement sits on a spectrum from highly flexible to full service:

#### **A la carte / modular services**

- Protocol critique and DES advisory
- Regulatory guidance and pre-sub preparation
- Startup (IRB, contracts, training)
- Monitoring (central, on-site, RBM)
- Data management and EDC build
- Safety oversight and trending
- Imaging/core lab integration
- Biostatistics

#### **Hybrid or functional service provider (FSP)**

- Sponsor retains internal leadership; CRO provides select functions. This model supports agility and is popular among startups.

## Full service

- End-to-end execution from protocol to final clinical report.
- Most advantageous when the CRO has true device expertise and integrated imaging/statistical partners.

**EFS Principle** → Start lean.  
→ Avoid building a pivotal-grade machine for first-in-human unless necessary.

## Selecting a CRO for EFS (Sponsor Lens)

Selecting the right CRO for an Early Feasibility Study (EFS) is one of the most pivotal decisions a sponsor can make, often taking six to nine months from initial outreach to final contract. The process begins with internal readiness: sponsors must define their learning objectives and identify the minimum viable scope, outlining what is essential versus what would simply be nice to have. At this stage, it is also crucial to identify the decision makers, set a target budget range, and create a concise “CRO brief” that summarizes the device, endpoints, anticipated sites, desired start window, expected case volume, and special service needs such as core lab or statistical support.

Once internal alignment is achieved, the sponsor moves to long-list discovery. This stage typically involves identifying six to ten potential CROs through industry referrals, conferences, and prior EFS experience. Sponsors send a Request for Information (RFI) that focuses on the CRO’s fluency in early feasibility work, startup timelines by site type, monitoring model options, and access to subject matter experts or key opinion leaders. From these responses, the sponsor creates a shortlist of three to four CROs for deeper evaluation.

During the capability deep-dive, each shortlisted CRO presents how it would approach the study, with emphasis on designing a lean project plan, minimizing CRFs, adopting risk-based monitoring, supporting coordinator training, and providing clear escalation pathways. Sponsors request sample project plans and case studies from similar EFS experiences. The next step is issuing a targeted Request for Proposal (RFP) with varying levels of scope—from minimal core services to full-service models—to enable a fair comparison. It is essential that each proposal include named team members, not placeholders, along with assumption logs and draft pre-trial agreements for any at-risk activities.

Once proposals are in, sponsors should then perform due diligence and vendor qualification. This includes reviewing quality management systems, recent audit histories, and references, as well as hosting process-mapping workshops to see how each CRO translates a protocol into a real-world workflow. Sponsors then reconcile budgets and risk by comparing fair-market-value assumptions, defining monitoring intensity, and finalizing payment structures such as monthly screen-effort retainers or change-order thresholds that account for iterative device learning.

After due diligence, selection is based not only on price but also on team continuity, operational fit, and cultural alignment. Before final contracts are signed, the sponsor should approve the lean project plan, escalation matrix, and a 90-day startup plan that includes the proposed mix of academic and community sites. Contract execution follows, including the master service agreement, statement of work, and any pre-trial agreements covering early tasks before FDA approval.

The process concludes with a joint kickoff meeting to finalize the RACI, delegation of authority planning, and a scheduled first-case dry-run.

Throughout the process, sponsors can use a scoring matrix to objectively compare vendors on EFS track record, project plan design, team quality, coordinator support, data minimization, escalation structure, site network fit, budget transparency, and overall responsiveness. Red flags include bait-and-switch staffing, overbuilt processes more suited to pivotal trials, unrealistic timelines, or rigid change-control practices. Effective sponsors test these factors early by asking how the CRO would handle mid-study device modifications, manage change orders, and empower CRAs to escalate when templates conflict with site best practices.

Ultimately, the selection of a CRO for EFS is not a transactional decision but a partnership built on trust, lean execution, and shared understanding of risk. Sponsors that follow a structured yet flexible approach—balancing compliance with efficiency—are more likely to achieve first-in-human milestones faster, with fewer startup bottlenecks and stronger collaboration across the ecosystem.

### ***Decision Criteria (beyond the bid price)***

- Device & EFS fluency (not just “med-device,” but first-in-human nuance).
- Operational SME access (KOLs, senior QA/clin ops available to unblock edge cases).
- Team chemistry for a multi-year relationship; responsiveness > glossy slideware.
- Right-sized SOP culture (project-plan driven, not policy theater).
- Site network fit (ability to work with fast community centers and complex academics).
- Transparent risk management (what’s truly required vs. what’s habit or sponsor preference).

Stage	Purpose	What Sponsors Should Do	What to Evaluate	Outputs / Decision Points
<b>1. Internal Readiness</b>	Establish clarity before CRO outreach	<ul style="list-style-type: none"> <li>Define learning objectives &amp; success criteria</li> <li>Determine minimum viable EFS scope</li> <li>Identify internal decision makers &amp; SMEs</li> <li>Set target budget range</li> <li>Draft CRO Brief (device, endpoints, sites, timelines, volume, core lab/stats needs)</li> </ul>	Assess internal alignment and whether the scope is realistic for first-in-human	<ul style="list-style-type: none"> <li>Clear CRO Brief</li> <li>Target budget</li> <li>Defined “must-have” vs “nice-to-have” scope</li> </ul>
<b>2. Discovery &amp; RFI</b>	Build long list → short list	<ul style="list-style-type: none"> <li>Identify 6–10 CROs from referrals, conferences, PubMed, CT.gov, consultants</li> <li>Issue RFI tailored for EFS</li> </ul>	<ul style="list-style-type: none"> <li>EFS experience (# studies, device types, FDA interactions)</li> <li>Startup timelines</li> <li>Monitoring model options</li> <li>Core lab integration</li> <li>Data minimization philosophy</li> <li>Safety adjudication/trending</li> <li>Coordinator training strategy</li> <li>Escalation pathways &amp; SLAs</li> <li>Audit history</li> <li>Responsiveness and communication</li> </ul>	<ul style="list-style-type: none"> <li>Shortlist of 3–4 CROs</li> <li>Initial fit and chemistry assessment</li> </ul>
<b>3. Capability Deep Dive &amp; RFP</b>	Evaluate strategic + operational fit	<ul style="list-style-type: none"> <li>Conduct capability sessions</li> <li>Request sample project plans, case studies, named staff</li> <li>Issue structured RFP with tiered scopes (minimal → full service)</li> </ul>	<ul style="list-style-type: none"> <li>Lean, device-appropriate project plan</li> <li>Monitoring oversight, escalation, risk triggers</li> <li>Training and site engagement approach</li> <li>Quality of named team members (not placeholders)</li> <li>Realistic assumptions and timelines</li> </ul>	<ul style="list-style-type: none"> <li>Comparable proposals across CROs</li> <li>Clear understanding of team quality</li> <li>Draft assumptions &amp; scope options</li> </ul>
<b>4. Due Diligence &amp; Vendor Qualification</b>	Validate the CRO’s real-world operational strength	<ul style="list-style-type: none"> <li>Perform quality and compliance review</li> <li>Conduct process-mapping workshop</li> <li>Review audit and inspection history</li> </ul>	<ul style="list-style-type: none"> <li>Quality management system maturity</li> <li>Staffing stability &amp; turnover</li> <li>Regulatory expertise</li> <li>Ability to operationalize EFS</li> <li>Cross-functional integration (stats, imaging, safety)</li> </ul>	<ul style="list-style-type: none"> <li>Vendor qualification</li> <li>Confirmed operational strengths and gaps</li> </ul>

Stage	Purpose	What Sponsors Should Do	What to Evaluate	Outputs / Decision Points
<b>5. Final Selection &amp; Contracting</b>	Final alignment on scope, budget, and team	<ul style="list-style-type: none"> <li>• Compare proposals using scoring matrix</li> <li>• Finalize lean project plan</li> <li>• Finalize DOA/roles</li> <li>• Define 90-day startup plan</li> <li>• Establish escalation &amp; communication matrices</li> </ul>	<ul style="list-style-type: none"> <li>• Cultural fit &amp; team chemistry</li> <li>• Transparent budgeting</li> <li>• Realistic timelines</li> <li>• Clear escalation structure</li> <li>• Fit with sponsor's site network</li> </ul>	<ul style="list-style-type: none"> <li>• Signed MSA + SOW</li> <li>• Pre-trial agreement for at-risk activities</li> <li>• Confirmed team + launch plan</li> </ul>

## Key Considerations for Startups

### Early-stage medtech companies face unique constraints:

- Limited headcount
- Tight capital windows
- Pressure from investors to hit near-term milestones
- Need for rapid learning cycles

Large CROs may offer infrastructure but can be rigid or overbuilt for EFS. Smaller CROs may provide closer attention and device-specific experience but lack capacity or resilience to staff turnover.

### Startups should evaluate:

- Responsiveness and communication culture
- Clarity around change management
- Device-specific expertise
- Transparency in budgeting
- Ability to scale support as the study evolves

Sponsors should plan a 20% contingency for both budget and timeline, acknowledging that EFS change orders are not exceptions—they are a norm.

## Key Considerations for Startups

- EFS experience (therapeutic areas; # of EFS; FDA/Notified Body interactions)
- Start-up timeline ranges by site type; central vs. local IRB strategies
- Monitoring model options (RBM/central review/SDV sampling plans)
- Data Mgmt: CRF minimization philosophy; edit-check strategy for EFS
- Safety model (24/7 coverage, SAE adjudication, trending)
- Imaging/Core Lab integration approach (if applicable)
- Escalation path (CRA → CTM → PM → Exec sponsor) with SLAs
- Training approach for new coordinators and small sites
- Sample Project Plan table of contents
- Audit/inspection history and outcomes

## SOPs, Project Plans, and EFS Flexibility

CRO SOPs: intentionally general to remain compliant across many sponsors; rarely shared beyond qualification.

Project Plans: the operational “source of truth.” They should be short, living, and tailored for EFS.

### *EFS Project Plan — Lean TOC*

1. Study Overview & Objectives (EFS-specific learning goals)
2. Roles & Responsibilities (Sponsor/CRO/Site — avoid role creep)
3. Site Startup Strategy (central/local IRB, contracts, training sequencing)
4. Process Map: patient flow, consent ownership, data timing (by procedure flow, not CRF grouping)
5. Monitoring Plan (risk-based triggers; targeted SDV; central review cadence)
6. Data Management Plan (minimum CRFs, edit-check philosophy, rapid mid-study change control)
7. Safety Mgmt/Trending (EFS-appropriate thresholds; real-time feedback loop)
8. Escalation Pathways & Decision Rights
9. Change-Management (how device/protocol learnings update docs fast)
10. Communication Cadence (site ops huddle, sponsor/CRO leadership sync)

***EFS Principle*** → If an element doesn't accelerate learning, safety, or operational clarity, it probably belongs out of the plan.

## EFS Site Management (CRO Lens): Mix for Speed & Quality

Site success can largely depend on its study coordinators, who often vary in experience. It is not uncommon for sites to have high turnover in coordinators. Identifying sites with strong onboarding and continuous training are key performance indicators that are often overlooked by CROs and sponsors.

- ✓ **Avoid activation creep:** Some sponsors push 4-page activation checklists; this creates inefficiency and blurs responsibilities among sponsor/CRO/site. NAMSAs advocates assigning the right responsibility to the right party and trusting qualified sites.
- ✓ **Consistency for CRAs is vital;** flexibility comes via escalation, not ad-hoc local exceptions. Therefore, when sites push back, CROs should escalate to consider flexibility or a global communication/change.
- ✓ **Site mix guidance:** Criteria to favor nimble, experienced non-academic sites for speed, with a plan for adding academics later.

Refer to the Site Selection & Qualification (Chapter 5)

## Monitoring & Data Strategy for EFS

EFS data strategy must provide assurance without waste.

### Monitoring

Trust with verification: Experienced sites deserve a lighter touch with random checks, whereas newer teams may need closer support and training.

Consider a Risk Based Monitoring (RBM) for EFS. Depending on the logistics RBM might require more resources than 100% source doc verification.

- ✓ Critical data list; targeted SDV sampling fraction
- ✓ Central trend review after each case or small batch
- ✓ Random spot check policy (frequency by site maturity)

### Data Management using Electronic Data Capture (EDC)

EDC builds must accommodate:

- Evolving device characteristics
- Adaptive procedural parameters
- Nontraditional endpoints
- Rapid mid-study amendments

CROs should support:

- Minimal CRFs
- Rapid edit check execution

- Clear queries written in plain, direct language
- Cross-linking between imaging, safety, and device accountability datasets

### **Imaging and Core Lab Integration**

CROs help ensure:

- Consistent acquisition across operators
- Upload timelines that support real-time feedback
- Data structures compatible with FDA review
- Tight coordination between imaging labs and site operations

### **Budgeting, Contracting, and CRO Stability**

Budget transparency is essential; sponsors should receive detailed line-item budgets with clear assumptions. A ~20% contingency is recommended for monitoring, imaging, safety events, and logistics.

Sponsors should evaluate:

- CRO financial stability
- M&A risk
- Likelihood of team turnover mid-study
- Change-order philosophy and willingness to adapt scope

Rigid change-control systems built for pharma are incompatible with the dynamic nature of EFS.

### **Common Reasons for Sponsor/CRO/Site mismatch**

Mismatch often occurs when:

- CRO monitors lack device experience
- Communication between sponsor and CRO is inconsistent or delayed
- Sites struggle with high procedural or data burdens
- CRO escalation practices are slow or unclear
- Templates conflict with site realities and CRAs feel unable to escalate

Alignment at kickoff and continuous recalibration are essential to avoid drift.

## Evaluating CRO Quality, Fit, and Red Flags

<i>Technical &amp; Operational Indicators</i>	<i>Qualitative Factors</i>	<i>Red Flags</i>
<ul style="list-style-type: none"> <li>• Similar device class experience</li> <li>• IDE/PMA-facing expertise</li> <li>• Strong data management and imaging integration</li> <li>• Ability to support iterative device or protocol modifications</li> </ul>	<ul style="list-style-type: none"> <li>• Agility</li> <li>• Responsiveness</li> <li>• Transparency</li> <li>• Team stability</li> <li>• Cultural &amp; communication alignment</li> </ul>	<ul style="list-style-type: none"> <li>✗ Bait-and-switch staffing</li> <li>✗ Overbuilt processes</li> <li>✗ Reliance on inexperienced monitors</li> <li>✗ Poor documentation culture</li> <li>✗ Vague or slow responses to critical questions</li> </ul>

### Communication, Governance, and Oversight

Communication failures remain the most frequent root cause of partnership issues. Effective communication must be:

- Timely
- Professional
- Clear
- Well-documented

Joint governance structures—weekly PM calls, dashboards, risk trackers—reinforce alignment. Every decision, deviation, or concern should be documented.

### Best Practice for Sponsor/CRO/Site Partnership

Key principles include:

- Setting expectations early
- Using a RACI matrix (Responsible, Accountable, Consulted, and Informed) to define ownership
- Engaging sites early to understand operational realities
- Ensuring alignment in training and documentation
- Empowering CRAs to escalate when templates conflict with site best practices
- Conducting regular debriefs and root-cause analyses

A structured partnership supported by transparency, accountability, and mutual respect leads to faster enrollment and safer execution.

**RACI is a simple but powerful project management framework used to clarify roles and responsibilities across a team.**

The acronym stands for:

R	Responsible	The person (or people) who actually do the work to complete the task or deliverable.
A	Accountable	The one person ultimately answerable for ensuring the task is completed correctly and on time. (There should only be one “A” per task.)
C	Consulted	The subject matter experts or stakeholders who provide input or advice before or during execution.
I	Informed	Those who need to be kept updated on progress or decisions but aren’t directly involved in the work.

A RACI matrix helps define who owns each activity across the Sponsor, CRO, and Site.

Task	Responsible	Accountable	Consulted	Informed
Obtain IRB approval	Site	Site PI	CRO Regulatory	Sponsor
Monitor data quality	CRA	CRO PM	Site CRC	Sponsor
Manage device inventory	Site CRC	Site PI	CRO Logistics	Sponsor

**Lessons Learned from Real-World EFS Experience**

- Do not assume the CRO fully understands the protocol—verify.
- Audit early and frequently.
- Maintain alignment between CRO, sponsor, imaging core, and site teams.
- Establish infrastructure before activation.
- Trust must be built early; partnership culture predicts downstream success.
- Shift mindset from “policing to partnering,” from “exhaustive to essential,” and from “one-and-done to living plans.”

## Conclusion

CROs play a foundational role in the success of Early Feasibility Studies. Not merely operational vendors, they are strategic partners who help sponsors navigate uncertainty, manage complexity, and execute with precision. When aligned with the principles of lean design, rapid iteration, and transparent communication, CROs enable sponsors to reach first-in-human milestones faster, more safely, and with stronger insight to propel the device through pivotal and commercial development.

### Mindset Shifts for EFS Success

- ✓ From policing → partnering. Activate on the minimum compliant set and iterate together.
- ✓ From exhaustive → essential. If a data point won't change a device or safety decision, cut it.
- ✓ From one-and-done → living plan. Project plans and process maps must evolve case-by-case.
- ✓ From uniformity → stratified oversight. Match monitoring and training intensity to site maturity and track record.
- ✓ Pick CROs for EFS fluency, SMEs, chemistry, and lean plans—not just price.
- ✓ Build a lean, living project plan; keep SOPs in the background.
- ✓ Remodel SIV into a process-mapping workshop; record and auto-generate role-specific checklists.
- ✓ Use RBM with targeted SDV + central trend reviews; random checks for trust.
- ✓ Pay for screening work monthly; include pre-trial agreements for at-risk effort.
- ✓ Publish an escalation ladder and empower CRAs to escalate when templates clash with better, compliant site methods.
- ✓ Mix sites (fast community + selective academic) to balance speed and complexity.

# Chapter 12 Emerging Challenges in the EFS Ecosystem

While EFS are designed to foster innovation, investigators and sponsors continue to face recurring challenges that slow progress and discourage participation. These challenges are not always technical; often they reflect structural, cultural, and operational gaps across startups, strategics, regulators, and institutions. The following themes—drawn from recent investigator discussions—highlight the most pressing issues and opportunities for strengthening EFS in the U.S.

## Bridging Startups and Strategics: Closing Knowledge Gaps

Many early-stage companies enter the EFS space with limited understanding of the U.S. regulatory environment. Unlike large strategics, startups often lack the infrastructure, expertise, and resources to navigate complex FDA and institutional requirements. This knowledge gap makes them more likely to misstep, delay submissions, or design impractical trials.

At the same time, the ecosystem depends on startups to introduce the most novel concepts. Few survive beyond EFS, with most successful devices ultimately acquired and advanced by strategics. This dynamic makes it even more critical to support startups through guidance, shared resources, and institutional collaboration so that promising ideas can survive long enough to attract strategic partners.

## Prioritizing EFS Patients to Overcome Enrollment Barriers

Enrollment is typically strongest before the first device in a class is approved. Once commercial options become available, enthusiasm for trial participation often diminishes, slowing enrollment in subsequent EFS. Some programs have addressed this by explicitly prioritizing EFS patients over commercial cases—ensuring research devices are considered before moving forward with approved therapies. This approach keeps innovation central and preserves the momentum needed to test multiple novel devices within the same disease space.

## Reducing Screen Failures and Shifting Industry Culture

EFS has shifted from a learning-focused stage to a milestone for funding, causing companies to take a conservative approach that drives up screen failure rates. Tight inclusion/exclusion criteria and limited tolerance for iteration mean many patients are excluded unnecessarily.

A cultural shift is needed: broadening inclusion where safe, leveraging compassionate use, and sharing lessons across sites could reduce inefficiency while preserving safety. Refocusing EFS on discovery and iteration rather than short-term investor optics would realign it with its original purpose.

## Start Up Fear of Risk vs. Value of Learning

- Small companies worry that including sicker patients or tolerating variability will scare investors or harm their next fundraising milestone.
- This financial pressure leads to conservative protocol design, which “defeats the purpose” of EFS by avoiding the hard questions about device boundaries and risks.
- In reality, EFS should be the place to push boundaries before moving to a pivotal.

## Rethinking Mortality Endpoints in EFS

Current FDA emphasis on one-year mortality often prevents inclusion of high-risk patients, such as those on dialysis, who could still meaningfully benefit from investigational therapies. This rigidity narrows learning and stalls enrollment.

A more practical standard would emphasize 30-day safety and performance outcomes, aligning with the true purpose of EFS: early insights into device feasibility and patient impact. Shifting criteria in this way would expand access while keeping risk-benefit appropriate for early-phase work.

## Making EFS Data Matter: Publication and Dissemination

Despite their importance, many EFS remain unpublished. Sponsors are often reluctant to share results due to fear of reputational harm or incomplete datasets. However, lack of dissemination undermines academic value, reduces incentives for investigators, and limits collective learning.

Structured publication pathways—through conferences like New York Valve<sup>39</sup> or dedicated journal forums—would elevate EFS, making participation more attractive for investigators while advancing the field through shared insights.

A unique challenge in the EFS ecosystem is the financial fragility of early-stage sponsors. Unlike large strategics, many start-ups may fold mid-study if funding disappears, or milestones are missed. When this happens, sites are left with ongoing obligations: ensuring patient safety, managing device follow-up, and maintaining IRB and regulatory compliance, often without financial support. This places significant strain on institutions and can undermine trust in EFS participation. To mitigate the impact, sites and sponsors should plan proactively building contingency language into contracts, clarifying responsibilities for patient follow-up, and considering mechanisms for transition if a sponsor collapses. Even with safeguards, sponsor insolvency remains a systemic vulnerability that makes institutional alignment and risk tolerance essential for sustaining U.S.-based EFS.

## The EFS–Pivotal Data Divide

When considering whether to roll EFS data into a pivotal trial, sponsors must carefully weigh both statistical and operational challenges. While it may seem efficient to carry early data forward, this

<sup>39</sup> The Cardiovascular Research Foundation® (CRF). New York Valves. Website: [New York Valves 2025](#)

approach is often impractical. EFS studies are intentionally designed to be small, flexible, and iterative, with the primary focus on assessing feasibility, device performance, and procedural refinement—not on generating statistically powered safety or efficacy data.

As a result, the patient populations enrolled in EFS studies frequently differ from those in pivotal trials, both in clinical characteristics and selection criteria. The inclusion and exclusion criteria, procedural protocols, and even the investigational device itself may evolve significantly between the EFS and pivotal phases, making it difficult to justify that the two datasets are sufficiently similar to be pooled.

From a statistical perspective, the small sample sizes typical of EFS studies add limited value to the overall statistical power of a pivotal trial. Including these data can introduce unnecessary complexity into the statistical analysis, potentially complicating regulatory submissions without offering a meaningful contribution to study endpoints. Operationally, combining EFS and pivotal data can also be challenging for study sites. Pivotal trials typically involve more rigorous data collection, monitoring, and regulatory oversight, which may not align with the less stringent requirements of an EFS.

Maintaining separate datasets allows for clearer delineation of study phases, cleaner regulatory submissions, and more straightforward data interpretation. Overall, while the idea of rolling EFS data into pivotal trials may initially appear attractive, the practical and statistical limitations often outweigh the potential benefits. In most cases, it is more effective to treat EFS and pivotal trials as distinct phases, each contributing independently to the overall development pathway. At the same time, sponsors must balance strategy and execution: EFS should remain focused on learning and iteration, while pivotal trials demand rigor, stability, and scale. Clear boundaries between the two phases not only protect data integrity but also allow sponsors to optimize each stage for its intended purpose—building confidence in feasibility first, then executing efficiently at scale.

## Global Integration

### *Terminology and Regulatory Context*

Outside the U.S., the term EFS is rarely used. Instead, regulators and investigators typically refer to a *Feasibility Study* or *FIH* study. Regardless of terminology, the concept is similar: a small, exploratory clinical investigation designed to evaluate a novel device in patients for the first time.

When conducted solely in the U.S., these studies fall under FDA’s Investigational Device Exemption (IDE) regulations,<sup>40</sup> which outline specific expectations for safety reporting, device modifications, and protocol amendments. Expanding feasibility work to multiple countries introduces the challenge of navigating differing regulatory frameworks simultaneously. Regulatory authorities may have conflicting expectations, and when requirements diverge, sponsors can face delays or be forced to modify protocols to satisfy all parties.

Managing a single, unified global protocol can simplify documentation, training, and oversight by maintaining consistency across sites. However, this approach carries risk: what is acceptable to FDA may not satisfy European or Asian regulators, potentially forcing adjustments that delay timelines.

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<sup>40</sup>U.S. Food & Drug Administration. Investigational Device Exemption (IDE). Website: [Investigational Device Exemption \(IDE\) | FDA](#)

Alternatively, sponsors may choose to run separate protocols—one U.S. IDE and one Outside U.S. (OUS) feasibility study—to provide regulatory flexibility and avoid conflicting mandates. While this strategy can address country-specific expectations more efficiently, it substantially increases operational workload by duplicating start-up activities, submissions, monitoring, and reporting.

Data integration is central to this decision. If sponsors intend to use feasibility data to support a pivotal trial, they must demonstrate that patient populations, study designs, and data collection methods across regions are sufficiently aligned. Significant differences between U.S. and OUS sites may prevent FDA from accepting pooled data. A common compromise is a single global protocol with country-specific appendices, which allows for local adaptations without fragmenting the study structure.

The sponsor's size and resources often influence these choices. Startups may lack bandwidth to manage dual protocols and may favor a single streamlined approach. Larger strategics can handle greater complexity but still prefer harmonization to reduce risk and accelerate timelines. Ultimately, whether a sponsor pursues a U.S.-centric or global feasibility pathway depends on strategic goals. If the primary market is the U.S., sponsors may prioritize FDA approval and IDE alignment. If early global market penetration is essential, multi-country feasibility can build international experience and strengthen partnerships with global investigators.

### *Integrating U.S. and OUS Data*

When conducting EFS with both U.S. and OUS sites, global data integration presents unique challenges that must be addressed from the outset. Merging data from U.S. and international sites is not as simple as pooling results—it requires careful planning to ensure compatibility in study design, patient selection, and data collection methods. Regulators, particularly the FDA, will closely scrutinize whether OUS-generated data can be appropriately compared to U.S. results.

Consistency is key: if there are differences in device versions, procedural workflows, inclusion/exclusion criteria, or follow-up schedules, pooled analyses may not be acceptable for regulatory decision-making. Protocol execution and case definitions must remain harmonized across regions to support meaningful integration.

Another important factor is regulatory alignment. Countries may have conflicting requirements for safety reporting, device labeling, or procedural standards. Sponsors should anticipate these conflicts early and, where possible, use a single global protocol with country-specific appendices. This approach preserves study integrity while accommodating local variations.

Data quality is equally critical. Healthcare systems, clinical practices, and monitoring rigor differ across regions, and these differences can introduce variability. Sponsors must ensure OUS sites adhere to the same standards as U.S. sites through strong training and monitoring plans to support data integrity and comparability.

Finally, sponsors should clarify whether EFS data will inform subsequent pivotal trials. If pooled into pivotal datasets, patient populations must be demonstrably equivalent, and statistical requirements must be met. Given the small sample sizes and exploratory nature of EFS, this is rarely straightforward and requires proactive planning.

## ***The EFS Dichotomy: U.S. vs. OUS Approaches***

For many startups, conducting early feasibility abroad appears more feasible—cheaper, faster, and less administratively burdensome. A handful of cases (10–15) OUS can often be completed quickly, helping secure investor confidence and move toward a pivotal trial. However, this shortcut carries risk: OUS data are often less reliable due to limited follow-up, variable operator experience, and differences in patient populations. Devices that appear promising abroad may fail when tested under U.S. rigor.

By contrast, U.S. EFS is more expensive and time-intensive but produces higher-quality, more credible data. Rigorous follow-up, expert operators, and advanced imaging infrastructure strengthen confidence in outcomes and make U.S. data more valuable for acquisition, strategic partnerships, and regulatory progression. Sustaining domestic innovation requires emphasizing these advantages while building systems that make U.S. participation more accessible for smaller companies.

## ***EU MDR and Cross-Jurisdictional Challenges***

The implementation of the European Union’s Medical Device Regulation (MDR) has added further complexity to global EFS planning. MDR requires more robust evidence and post-market follow-up even for feasibility-stage devices, creating additional burdens for companies that once relied on Europe for faster early studies. Some startups are now reconsidering Europe as their default entry point, especially given long review timelines and reduced Notified Body capacity.

Cross-jurisdictional studies compound these issues. Differences in regulatory expectations across the FDA, EMA, and other global authorities can complicate protocol development, safety reporting, and device labeling. Without proactive harmonization, sponsors risk fragmented studies that produce non-comparable datasets. Successful strategies often involve early regulatory engagement in all jurisdictions, alignment on case definitions, and coordinated safety oversight structures that satisfy multiple agencies simultaneously.

## ***Balancing Strategy and Execution***

Global participation can provide valuable clinical insights and broaden exposure, but it also introduces operational burdens in contracting, training, submissions, and monitoring. Ultimately, sponsors must weigh the tradeoffs: lower-cost, faster enrollment abroad versus the higher credibility and regulatory impact of U.S.-based EFS. A thoughtful global integration plan—grounded in consistency, harmonization, and data quality—ensures that early feasibility findings contribute meaningfully to later pivotal studies and to the broader innovation ecosystem.

## **US Future Regulatory Climate**

With evolving FDA and CMS policies, there’s a potential opportunity to reduce regulatory burden and accelerate innovation domestically. Investigators and startups should encourage leadership to see EFS participation as a forward-looking strategy: by building capability and credibility now, institutions can position themselves to capitalize on future reforms that may streamline processes and attract even more novel trials.

# The EFS Journey



**EFS Decision**  
(based on data)

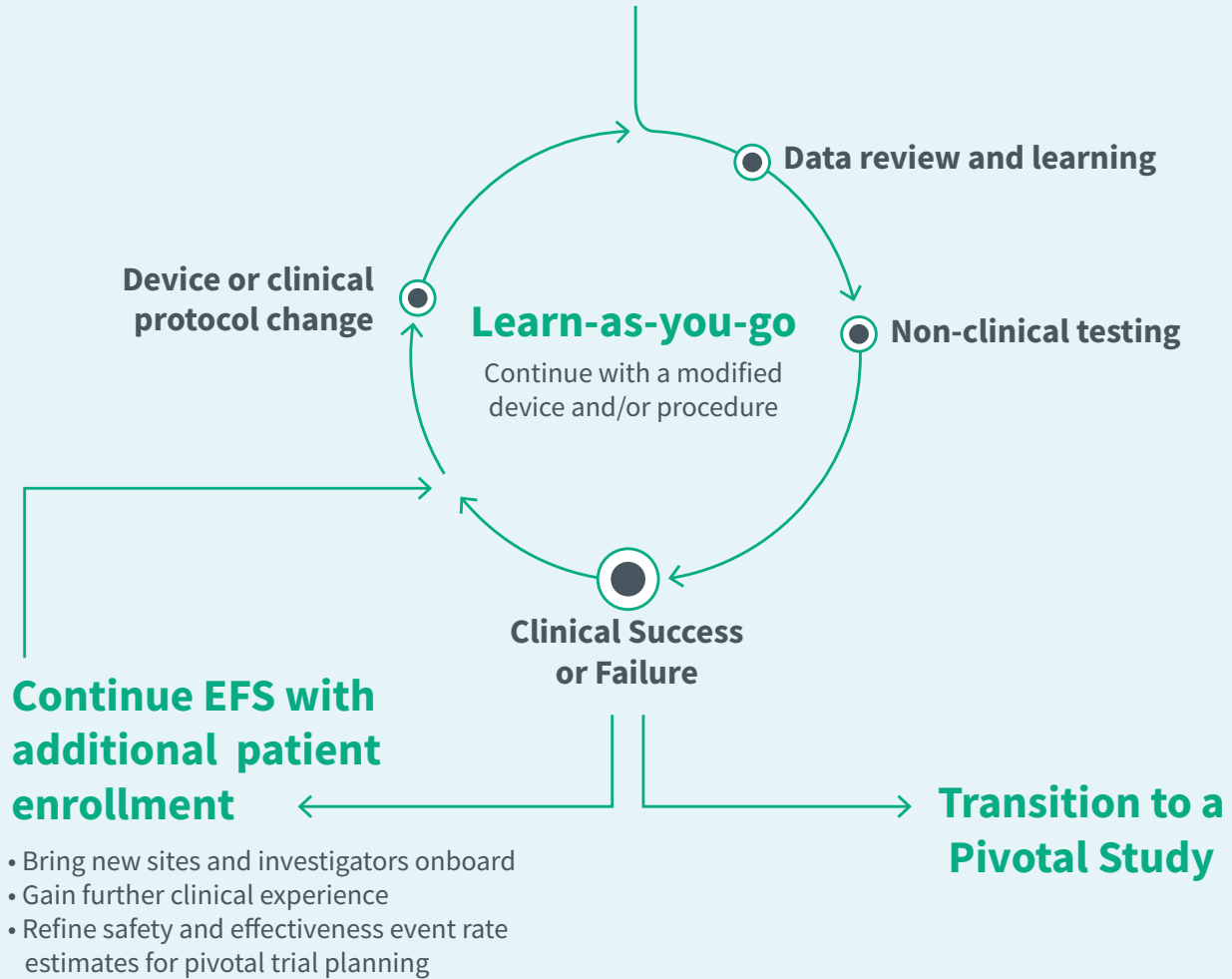


Figure 19. The EFS Journey

## Conclusion

This Early Feasibility Study playbook represents a modern reimagining of medical device development—one that values iteration, collaboration, and ethical learning as much as regulatory compliance. The lessons captured in this playbook underscore that success depends not on size or speed alone, but on alignment—between regulators and payers, sponsors and sites, clinicians, and institutions, and ultimately, innovation and patient need.

Although EFS exists to accelerate device innovation, recurring structural, cultural, and operational gaps slow progress and discourage participation. Startups—often the source of the most novel concepts—frequently lack the regulatory knowledge, infrastructure, and funding needed to navigate FDA and institutional requirements. Without targeted guidance, they risk delays, impractical trials, or insolvency mid-study, leaving sites with unfunded follow-up obligations. Supporting startups through shared resources, contingency contract clauses, and clear follow-up responsibilities is essential to sustain U.S. EFS.

By streamlining regulatory interactions, clarifying reimbursement pathways, professionalizing site readiness, and promoting cultural acceptance of iteration, the U.S. can once again make early device innovation a domestic strength. Through continued partnership among FDA, CMS, MDIC, and industry, EFS will remain the proving ground for safe, rapid, and equitable patient access to tomorrow's technologies. Together, FDA's EFS program and HEU-EFS signal a shift toward globally aligned early device evaluation—bridging preclinical testing and pivotal trials to accelerate patient access while maintaining safety, ethical integrity, and evidence quality. This Playbook captures lessons learned and practical strategies to support sponsors, new investigators, and diverse research sites in advancing EFS.

# Appendix

## Site Name SITE FEASIBILITY AND QUALIFICATION INFORMATION

This document supports site qualification and feasibility. Sponsors and CROs should use this information to populate feasibility forms or surveys and avoid duplicating requests. Any information not included here can be provided upon request.

**All study start-up communications & documents should be directed to the following distribution list:**

### List Names and Emails

Site Overview & General Capability		
<b>SITE INFORMATION</b>	Department	
	Street Address	
	Building	
	City, State, Zip	
	Phone	
	Website	
	<b>REGULATORY &amp; IRB CONTACT</b> Oversees regulatory Process. Should be included on all study specific and regulatory correspondence. Oversees all new study submissions, modification and maintenance of study protocols including renewals.	Name
	Title	
	Email	
<b>FINANCE CONTACT</b> Oversees Finance process. Primary liaison between sponsor and Clinical Trials Office. Should be included on all study specific correspondences.	Name	
	Title	
	Email	
<b>OPERATIONS CONTACT</b> Oversees all research operations and compliance	Name	
	Title	
	Email	
	Cell Phone	
<b>REGULATORY DOCUMENTS CONTACT</b> Primarily responsible for regulatory start up documents (CVs, ML, FDFs) pre SIV.	Name	
	Title	
	Email	
	Phone	
<b>CLINICAL RESEARCH MANAGER</b> Handles all activities from the SIV forward. Oversees the research coordinators. Should be included on all study specific correspondences	Name	
	Title	
	Email	
	Phone	
<b>PRINCIPAL INVESTIGATOR</b> Primarily responsible for regulatory start up documents (CVs, ML, FDFs) pre SIV.	Name	
	Title	
	Phone	

*PRIMARY RESEARCH COORDINATOR WILL BE ASSIGNED PRIOR TO THE SIV*

**Confidential Disclosure or  
NON-Disclosure Agreement  
(CDA/NDA):**

*EXAMPLE: Please send via email a word version of the CDA/NDA. The Start-up team will forward the CDA/NDA to our clinical trials office for review and execution. The Clinical Trials Office will reach out to you directly with redlines if necessary*

## START-UP FAQs

*What documents are required to begin start-up activities at your site?*

*EXAMPLE: Provide the final protocol, informed consent document(s), instructions for use and/or investigational brochure, case report forms, FDA approval or FDA conditional approval letter, a final or draft version of the CEC and/or DSMB charters as well as any imaging manuals if applicable. Once CMS approval has been received, we will need a copy of the CMS approval letter. In addition, we will need the NCT trial number published on Clinicaltrials.gov.*

*Are any internal committee reviews required in addition to IRB submission and approval?*

*EXAMPLE: Joint Radiation Safety Committee (JRSC) Approval for protocols that involve any form of radiation (cath lab procedure, x-ray or nuclear imaging, etc.)  
Submission to JRSC will be completed concurrently with the IRB Submission.*

*Does your site use an electronic system for management of regulatory documents?*

*EXAMPLE: We use a remote, centralized storage platform, Lab Archives, to provide direct access to standard regulatory documents including CAP/CLIA, lab normal, CVs & medical licenses*

*Can your site enroll subjects prior to receiving CMS approval for IDE studies?*

*What is the process to schedule Site Initiation Visit?*

*What is the address that study supplies should be shipped to?*

## CONTRACTS/BUDGETS

<b>LEGAL NAME &amp; ADDRESS OF INSTITUTION</b>	Institution/Site Name:	
	Street Address:	
	City, State, Zip:	
	Tax ID:	
<b>CONTRACT NEGOTIATION INFORMATION</b>		
<b>PAYMENT ADDRESS</b>	Payable to:	
	Attn:	
	Street Address:	
	City, State, Zip:	
	Email:	
<b>F&amp;A RATES</b> (Institution Overhead)	Federally Funded Trials:	%
	Industry-Sponsored Clinical Trials:	%
<p><i>How long on average does the contract and budget review /approval process take?</i></p> <p><i>Brief description of the process:</i></p>		<p><i>EXAMPLE: 6-8 weeks</i></p>
<p><i>How would the site and/or Institution name appear on the contract?</i></p>		
<p><i>Can the contract be executed prior to IRB approval?</i></p>		
<p><i>Are any other agreements needed at your institution?</i></p>		

## LOCAL IRB INFORMATION

<b>IRB Name:</b>	
<b>Director:</b>	
<b>Street Address:</b>	
<b>IRB City, State, Zip:</b>	
<b>Email Address:</b>	
<b>Contact Telephone:</b>	
<b>Website:</b>	
<b>Federal-Wide Assurance (FWA)#:</b>	
<b>IRB Fees</b> <i>(Effective 2025)</i>	Initial IRB Review:
	Continuing Review:
<i>Can your site use a Central IRB?</i>	<i>Only with NIH Funded Research</i>
<i>How often does your IRB meet?</i>	<i>EXAMPLE: The IRB schedule is attached or provide link if available online</i>
<i>How far in advance do IRB submissions need to be submitted prior to the meeting date?</i>	
<i>On average once all documents are submitted, how long does it take to receive IRB approval?</i>	<i>EXAMPLE: 6-8 Weeks</i> <i>Once we receive the full start up packet as described in item 4, we will begin the IRB application</i>
<i>From the IRB meeting date, what is the period of time expected for the IRB to provide approval documents?</i>	<i>EXAMPLE: 2-4 Weeks</i>
<i>Does your IRB require an executed Clinical Trial Agreement and Budget prior to IRB review or approval?</i>	<i>EXAMPLE: No but CTA cannot be executed until IRB approval</i>
<i>Can you provide a copy of the IRB rosters?</i>	<i>EXAMPLE: All rosters are available in Lab Archives Central Regulatory Folder</i>

## INVESTIGATIONAL PRODUCT-DRUG TRIALS

<b>RESEARCH PHARMACY</b>	Contact:	
	Street Address:	
	Floor/Room:	
	City, State, Zip:	
	Phone:	
	Email:	
	Website:	

<b>PHARMACY FEES</b> <i>(EFFECTIVE Date)</i>	<b>INDUSTRY SPONSORED</b>		
	<b>Start up \$ _____</b>	<b>Monthly Maintenance Fee \$____/Month</b>	<b>Dispensing Fees \$ _____ depending on route of administration</b>

## INVESTIGATIONAL PRODUCT-DEVICE TRIALS

<i>Does the site require a No Charge PO to receive product?</i>	<input type="checkbox"/> Yes, the site needs a No Charge PO per shipment. <input type="checkbox"/> Yes, use blanket study PO: <input type="checkbox"/> No
---	---

Delivery Address	Attention Line:	
	Street Address:	
	Floor/Room:	
	City, State, Zip:	
	Phone:	
	Email:	

Device Storage Location: <i>Brief Description</i>	
--	--

Vendor Credentialing process: <i>Brief description</i>	<i>EXAMPLE: Temperature-controlled and access-restricted storage if required. Separation from commercial devices to prevent mix-ups</i>
---	---

## GENERAL SITE FAQs

<i>What is the size of your study team?</i>	
<i>How many studies does a research coordinator typically have?</i>	
<i>When is a research study coordinator assigned?</i>	
<i>Does your site have high speed internet access?</i>	
<i>What is your site's approach to Monitoring Process? (onsite, remote, both)</i>	
<i>Will monitors have direct access to the EMR?</i>	
<i>Does your site have an established record retention and archiving practices?</i>	
<i>Do you have the ability to upload/redact source documents for remote monitoring</i>	
<i>Do you have a secure location to maintain study-related clinical materials (e.g., study binders, kits, research samples)?</i>	
<i>Can you process and ship samples to the core lab?</i>	
<i>Do you have access to a Centrifuge?</i>	
<i>Do you have access to a Freezer?</i>	
<i>Do you have access to a Refrigerator?</i>	
<i>Does your site have experience with web-based EDC?</i>	
<i>Can your site enroll subjects prior to receiving CMS approval for IDE studies?</i>	
<i>Has the FDA or any other governing body inspected this department?</i>	<i>FDA inspections and findings are publicly accessible. Please refer to: <a href="https://datadashboard.fda.gov/ora/cd/inspections.htm">https://datadashboard.fda.gov/ora/cd/inspections.htm</a> for up to date information.</i>
<i>Does your site require any language translations? documents related to</i> <ul style="list-style-type: none"> <li>• <i>Informed Consent</i></li> <li>• <i>Retention</i></li> <li>• <i>Adverse Events</i></li> <li>• <i>Monitoring</i></li> </ul>	<i>EXAMPLE: We serve a large number of Spanish-speaking patients. Therefore, the informed consent and HIPAA authorization, and any other patient facing research materials must be translated to Spanish. We have a local translation center approved by the IRB to complete this task.</i>

## PROTOCOL-SPECIFIC QUESTIONS

### Experience With Similar Studies

<p><b>Key similarities or relevant prior experience</b> Experience with studies of similar design, indication, or risk profile (IDE, EFS, Clinical indication)</p>	<p><i>Previous participating in clinical trials are publicly accessible on clinical trial.gov or search using MDIC EFS Explorer</i></p>
<p><b>Number of ongoing studies and trial phases</b> (study start up, enrollment, long term follow-up)</p>	

### Patient Population & Recruitment Feasibility

<p><i>Does the site have access to the target patient population?</i></p>	
<p><i>Estimated number of potentially eligible patients per month/year</i></p>	
<p><i>Anticipated enrollment rate for this study</i></p>	
<p><i>Competing trials or standard-of-care limitations that may affect recruitment</i></p>	
<p><i>Key inclusion/exclusion criteria that may limit enrollment at your site</i></p>	
<p><i>Ability to support screening, longitudinal follow-up, and retention</i></p>	

### Study-Specific Timeline Expectations

<p><i>Expected time to first patient enrolled</i></p>	
<p><i>The main factors that could realistically delay study startup, activation, or enrollment at your site for this specific protocol.</i></p>	
<p><i>Sponsor responsibilities that most impact this study's timeline:</i></p>	
<p><i>Site position on expedited startup requests for this protocol:</i></p>	

# EARLY FEASIBILITY STUDY (EFS) BUDGETING TEMPLATE

## 1. Study Information

- Study Name: [Insert Study Name]
- Sponsor: [Insert Sponsor Name]
- Clinical Protocol: [Insert Number and Version]
- Site Name: [Insert Site Name]
- Principal Investigator: [Insert PI Name]
- Study Start Date: [Insert Date]
- Estimated Study Completion Date: [Insert Date]

Note: if budget is attached to the clinical trial agreement (CTA), this information may be omitted.

## 2. Budget Overview

### 2.1. Protocol-required Tests Fees

Sponsor first should list all required tests and follow-up schedule from clinical protocol utilizing [Table 1](#) format. It is recommended that such required tests/schedule should also be aligned with case report forms.

Next, Sponsor to work with the site to:

- 1) Indicate what tests/procedures are Standard of Care (SOC) vs. have to be completed for Research (R) purposes at specific time points (e.g., follow-up visits).

For all R tests/procedures, add fair market value amounts (FMV). FMV will vary across sites. It is typical to observe regional and site-specific variability.

Note: Any SOC test that is repeated per study-specific requirements must be converted to R payment. For example: if echocardiographic imaging is SOC at baseline but it has to be completed per study-specific acquisition protocol that differs from SOC or has to be repeated due to tight compliance window required per clinical protocol that does not align with SOC.

Table 1. Protocol-required Tests Fees – extend table as needed to accommodate all study visits. Include study related costs at each required timepoint. Standard of Care (SOC) will have some variation across sites.

Budget Item	Baseline	Procedure	Discharge	Follow Up 1	Follow Up 2	Follow Up 3
Informed Consent	R - \$\$					
Inclusion/Exclusion	R - \$\$					
Medical History	R - \$\$			R - \$	R - \$	R - \$
Physical Exam	R - \$\$	R - \$\$	R - \$\$	R - \$\$	R - \$\$	R - \$\$
Medication Log	R - \$		R - \$	R - \$	R - \$	R - \$
Questionnaire 1	R - \$		R - \$	R - \$	R - \$	R - \$
Questionnaire 2	R - \$		R - \$	R - \$	R - \$	R - \$
6 Minute Walk Test	R - \$\$			R - \$\$		R - \$\$
Imaging E.g. echo, CT... (one per line - add lines as needed)	R - \$\$\$		R - \$\$\$	SOC	R - \$\$\$	R - \$\$\$
Add lines as needed						
12-Lead ECG	SOC		R - \$	SOC	R - \$	R - \$
Pregnancy Test	\$					
Blood work e.g. CBC, PT/PTT (one per line - add lines as needed)	SOC		R - \$	R - \$	R - \$	R - \$
<i>Pre CMS approval procedure/ hospitalization costs</i>		R - \$\$\$\$				
Research Coordinator (RC) Fees*						
Principal Investigator (PI) Fees*						

\* Includes time required to complete listed above activities per each visit and data entry/signing of corresponding case report forms (CRFs). Some sites prefer to combine RC and PI fees into one line item.

## Post CMS approval

- Category A – Medicare can be billed for procedure and hospitalization. Investigational device must be provided at no cost.
- Category B – Medicare can be billed for procedure, hospitalization and the investigational device.

Private payors may not align reimbursement with CMS determinations. Pre-authorization for services may be required.

## 2.2. Potential Study Candidate Identification/Screening Fees

To ensure proactive and efficient study recruitment, consider adding potential study candidate identification/screening fees as outlined in [Table 2](#).

Table 2. Potential Study Candidate Identification/Screening Fees

Budget Item	Description
Pre-consent Pre screening*	<p>Sponsor may choose to ask for designated number of charts to be reviewed by RC per week in effort to identify study candidates. Consider estimating the number of hours spent per week or month on such pre-screening activity (e.g., 20 hours/month of RC time).</p> <ul style="list-style-type: none"> <li>• A cap on hours is suggested to manage expectations and enhance productivity.</li> <li>• A log of de-identified screen failure potential participants with reasons for exclusion must be submitted to the Sponsor (suggest monthly) for reimbursement.</li> <li>• Sponsor may want to specify pre-screen to enroll ratio (e.g. per each 20 pre-screen failed patients at least 1 acceptable candidate must be identified) to ensure effectiveness of activity.</li> <li>• Modifications to the cap of hours or ratio can done with Sponsor’s written approval.</li> <li>• Quarterly or biannual invoicing is recommended.</li> </ul>
Post consent screen failures	Reimburse sites for research (R) activities completed per <a href="#">Table 1</a> .
Preparation of Screening Committee presentation	Intended to cover time spent by RC and/or PI to prepare PowerPoint slides and/or summaries required for potential study candidate presentation to Screening Committee. Payment per participant/ per presentation is recommended (typical range \$100 - \$500).

The alternative approach for pre-screening is to provide a one- time fee reimbursed at study commencement. This approach decreases the administrative burden but may not align compensation with the actual work.

### 2.3. One-Time and Annual Fees

All institutional review board (IRB) review fees should be charged as pass through. The cost at the beginning of the study can be obtained during the site qualification visit (SQV); however, **they are subject to change throughout the study and are non-negotiable**. These fees include:

- IRB initial review fees
- IRB annual review fees
- IRB amendment fee
- Additional IRB fees (e.g., serious adverse event (SAE) review, unanticipated adverse device effect (UADE) review, etc.)

It is recommended that budgets either exclude specific IRB fees—given their variability—or include estimated amounts with a note acknowledging that these fees are subject to change and will be treated as pass-through costs.

Additional one-time and annual fees are listed in [Table 3](#). All fees related to first year of study at a given site (defined as one year post CTA/budget execution) should be fixed. However, since some studies may require long-term follow-up, the budget must accommodate changes in annular fees that are expected at a later stage of the study.

Table 3. One-time and Annual Fees

Budget Item	Description	Amount (\$)
Study start-up fee	Covers time required to activate the site inclusive of training	
Coverage Analysis	These are <i>optional</i> but common fees required by most sites in United States (US) for assessment of fair market value of each study-specific tests/procedures.	
<b>IRB preparation fees</b>		
Initial review <sup>1</sup>	Preparation of initial study submission to local or reliance IRB. This fee also includes time required to address any IRB follow-up questions in order to receive initial study approval.	
Annual review	Preparation of study annual review submission to local or reliance IRB.	
Other	Site specific – determined at SQV	
<b>Research pharmacy fees (only applicable to combination products or study drugs)</b>		
Start-up	Covers site activation and meeting with Sponsor representatives to finalize logistics for drug/combination device receipt if used per protocol.	
Annual	Covers annual cost associated with maintaining the study at the site's pharmacy.	
Other	These fees are varies per site and may include dispensing fees, documentation fees, etc.	
Storage/Archiving fee <sup>2</sup>	Storage of study materials/data.	
Study close-out fee	Final data submission, any gap analysis required to ensure proper completion of the study at a given site.	

<sup>1</sup>If IRB preparation for initial study review is included in study start-up fees (that is common), this line item is not applicable.

<sup>2</sup>Storage fee for US sites typically is limited to two years post study completion as required by CFR 812. However, if some study protocol may require longer storage/archiving of the study documentation, then budget must be adjusted accordingly.

## 2.4. Per Occurrence Fees

After study is commenced at the site, there may be many incidences requiring RC and other site staff to spend time and effort to ensure compliance with the study requirements and applicable regulations – all these efforts should be reimbursed by the Sponsor. Some of these incidents are expected and will occur in any study (e.g., reporting of adverse events, transfer of images, etc.) and some may or may not occur (e.g., protocol amendment, reconsenting of the patients, etc.). Since the accurate number of such incidents is impossible to predict prior to study start, especially for EFS, they recommended to be paid and outlined in budget as “per occurrence”. This will provide flexibility to the site and Sponsors to accommodate a variety of possible scenarios. [Table 4](#) provides a comprehensive list of fees that are recommended to be paid per occurrence throughout EFS.

Since "per occurrence" fees add unpredictability to overall study budget, all efforts shall be made to limit such fees in the budget, where possible. This is especially critical for EFS conducted by the small start-up company with limited resources.

Table 4. Per Occurrence Fees

Budget Item	Description	Unit Cost (\$)
Protocol amendment <sup>1</sup>	Includes administrative support and activities required to ensure an amended protocol is implemented at the site. This fee also will include revision to the informed consent form (ICF) if it may be needed due to changes in clinical protocol.	
Protocol & device training after site activation <sup>2</sup>	On site - sponsor mandated: <ul style="list-style-type: none"> <li>Investigator - protocol and/or device re-freshers - up to a maximum of 4 hours for a total of \$500.00- \$700.00/per training the team of investigators. Invoice shall contain date, first &amp; last name of attendee and topic of training.</li> <li>Study staff - consider hourly or a one time fee to cover all team members</li> <li>Off site (may consider reimbursing): <ul style="list-style-type: none"> <li>Investigator - daily fee</li> <li>Coordinator - daily fee</li> </ul> </li> </ul>	
CTA and/or Budget amendment	Includes administrative support required to implement changes to CTA and/or budget per Sponsor request. <i>Note:</i> changes required per site (e.g., PI change) shall not be charged to the Sponsor.	
Reconsenting	In the event of ICF changes, re-consenting may be required. This is charge per patient/consent.	
SAE/UADE submission fee	Includes preparation of the SAE/UADE related documentation required for Sponsor and/or IRB notification.	
Death certificate	Upon request	
Image submission (optional)	If required per clinical protocol or requested by Sponsor, intended to cover RC time to de-identify and submit images to Sponsor, Core Laboratory, etc. This is charge per image.	
<b>Monitoring Visit</b>		
In-person visits	Intended to cover RC time required to support monitor (i.e., Sponsor or its representative) during in-person monitoring visit. It is recommended to utilize hourly rate (for actual hours spent by RC with monitor during the visit). However, some sites may not be able to accommodate hourly rate due to complexity associated with time tracking for variety of research staff required to complete dedicated tasks (data entry by one member, de-identification of the source documents by another member, checking on device accountability by the third member, etc.). In this case, the flat fee per visit will be negotiated.	
Remote visits	Intended to cover RC time required to support monitor during remote monitoring visit. Since there is a great variability of how much time RC may need to spend for each remote monitoring visit, hourly RC rate is recommended to be utilized.	
Audit	Intended to cover site staff time (RC, PI, etc.) for regulatory inspections. Per hour fees are recommended to be utilized (for the actual time spent during the audit); however, some site may prefer per day rate. <i>Note:</i> for cause audits are not chargeable to the Sponsor.	
Source documentation collection & submission (optional)	If required by Sponsor, intended to cover RC time to review, compile and de-identify source documentation. This is charge per requested set of source documentation per patient. <i>Note:</i> many Sponsors underestimate the amount of time required for such task.	
Return of explanted study device (optional)	If requested by Sponsor, the efforts associated with shipment of the explanted study device utilizing applicable biohazard procedures. This is charge per shipment (of one or numerous) study device(s).	

<sup>1</sup>Protocol amendment may necessitate an update to the CTA and/or budget.

<sup>2</sup>Training due to site's staff turnover or non-compliance cannot be charged to the sponsor.

## 2.5. Participant Reimbursement

Especially for studies with elderly patients, it is critical to offer participants reimbursement for accommodations required to ensure compliance with protocol's follow-up schedule. These costs may include but may not be limited to:

- Transportation reimbursement: travel costs for participants to get to and from site that can be either taxi, car service or reimbursement of car mileage.
- Hotel accommodation (for long-distance travel or multi-day visits).

Since there is a great variability in patient situations and geographical locations relative to site, it is strongly recommended to offer pass-through receipt-based reimbursement. Sponsor pre-approval above a set rate may be appropriate (especially in high-cost regions). Alternatively, patient stipends can be offered instead; however, careful analysis must be completed to ensure that stipend is intended to reimburse actual expenses and not induce patients to participate in the study via compensation. Additionally, ***participant reimbursement must be clearly outlined in the ICF.***

## 3. Considerations for Budget Negotiation

### 1. Ensure Predictability

- Clarify protocol guidance to reduce unnecessary charges.
- Be clear relaying payment terms i.e. one-time payment versus annual versus per occurrence
- Aim to limit "per occurrence" fees where possible.

### 2. Minimize Administrative Delays

- Schedule early discussions with key sites before finalizing the clinical protocol.
- Use phone discussions rather than email for faster resolution.

### 3. Plan for Amendments & CMS Approval

- If CMS approval was not yet obtained for EFS, include pre-CMS and post-CMS budget versions.

Note: if CMS approval is not received, the study index procedures (e.g., implant) must be covered by Sponsor and added as a separate line item to [Table 1](#).

- Clearly define amendment processes to allow flexibility; consider allowing additional study-related tests fees to be approved by Sponsor via email (as addition to agreed budget).

#### 4. Payment Schedule & Terms

It is critical for the Sponsor to determine institutional overhead during SQV:

- Discuss what items overhead should be applied for.
- Add overhead fees to budget (e.g., [Table 1](#), etc.)

The start-up fees should be paid by Sponsor as one-time, non-refundable administrative fee payable within sixty (60) days of CTA/budget execution. Protocol required fees should be reimbursed per completed CRF. For all other services unless clearly delineated, the site should be held responsible for invoicing Sponsor on a quarterly basis. The payment terms should specify where invoices shall be sent and include the following information:

- Bank name:
- Account name:
- Routing #
- Account #
- Tax ID:

## Purpose: EFS–FDA Engagement Checklist

This checklist is intended to serve as a practical planning and readiness tool for sponsors and innovators developing medical devices under the FDA Early Feasibility Study (EFS) Program. It is not a regulatory requirement, but a structured guide to help teams think strategically about when, why, and how to engage FDA throughout early development.

Specifically, the checklist helps teams:

- **Clarify/acknowledge the role of EFS in the overall development strategy**  
The checklist prompts sponsors to define what key uncertainties the EFS is meant to address, and how early data will support downstream decisions, including pivotal study design.
- **Plan proactive, continuous FDA engagement**  
The checklist reinforces the importance of engaging FDA early and often, particularly before committing to costly or long-lead testing, and ahead of major regulatory milestones such as IDEs, IDE supplements, or Breakthrough Device Designation requests.
- **Prepare for high-quality pre-submission interactions**  
The checklist outlines the core elements FDA reviewers benefit in seeing during early discussions, including clinical context, device evolution, testing strategies, risk mitigation approaches, and how EFS fits into the broader development lifecycle.
- **Strengthen technical and clinical rationales**  
By prompting teams to justify testing strategies, protocols, and acceptance criteria, and to reference applicable FDA guidance and standards, the checklist provides guidance for preparing comprehensive submissions.
- **Promote effective regulatory communication practices**  
The final section emphasizes principles that consistently improve FDA interactions, such as avoiding assumptions based on precedent, clearly telling the device development “story,” and maintaining continuity and documentation across review cycles.

Overall, this checklist is designed to reduce avoidable regulatory friction, improve the quality of FDA interactions, and increase the likelihood that EFS data meaningfully informs later-stage development, while maintaining patient safety and regulatory rigor. It reflects common challenges observed across early device programs and provides a shared framework for sponsors, sites, and regulators to align expectations.



# Early Feasibility Studies (EFS) FDA Engagement Checklist

Use this checklist as a planning and readiness tool for FDA interactions during medical device development.

## 1. Clarify/Acknowledge the Goals of EFS

- Identify insights needed to further device development
- Use EFS to de-risk a future pivotal clinical study
- De-risk overall investment in device development

## 2. Engage Early & Often With FDA

- Obtain understanding of FDA expectations for EFS IDE, pivotal IDE supplement, and future marketing applications
- Engage before completing expensive or long-lead testing
- Engage prior to major submissions (IDE, IDE supplements, Breakthrough Device Designation request)
- Plan for iterative data needs across development stages

## 3. Establish Context for Pre-Submission Discussions

- Define clinical context and unmet need
- Describe device design concept and evolution

## 4. Address Protocols & Rationales Under Pre-Submissions

- Outline device evaluation strategy, that is, justify selection of tests, parameters based on in-vivo conditions, sampling and sample sizes, and acceptance criteria, as well as clinical risk mitigation strategies, referencing relevant FDA guidances and voluntary standards
- Describe bench testing, biocompatibility, animal studies, sterility, packaging, and shelf-life plans
- Describe transition plan from EFS to later-stage studies with respect to non-clinical testing, including a description of how testing will be leveraged across development stages
- Identify long lead-time or unique testing needs and submit associated protocols
- Summarize prior clinical experience and proposed EFS clinical study synopsis

## 5. Address Protocols & Rationales Under Pre-Submissions

- Outline device evaluation strategy, that is, justify selection of tests, parameters based on in-vivo conditions, sampling and sample sizes, and acceptance criteria, as well as clinical risk mitigation strategies, referencing relevant FDA guidances and voluntary standards
- Describe bench testing, biocompatibility, animal studies, sterility, packaging, and shelf-life plans
- Describe transition plan from EFS to later-stage studies with respect to non-clinical testing, including a description of how testing will be leveraged across development stages
- Identify long lead-time or unique testing needs and submit associated protocols
- Summarize prior clinical experience and proposed EFS clinical study synopsis

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