



**Blueprint for Early Feasibility Study Success:
A report of the Early Feasibility Study
working group of the Medical Device
Innovation Consortium (MDIC)**



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Preface

Over the past 2 decades, medical device companies have transferred a significant part of their initial clinical research activities and Early Feasibility Studies (EFS) overseas in response to a more stringent legal, regulatory, and financial environment in the United States. These EFS usually include a limited number of subjects treated with a device, which may be in its early development stage before the design has been finalized. As a consequence, patients in the United States may not have early access to these innovations, and U.S. investigators may continue to fall increasingly behind and lose their leadership position in the medical field if the trend persists.

United States policy makers and patient advocacy groups have attempted to reverse the current trends and incentivize EFS in the United States so that U.S. patients can benefit from early innovation. The U.S. Food and Drug Administration (FDA) has made EFS one of its top priorities in the past few years. The Medical Device Innovation Consortium (MDIC), through its unique private-public partnership initiative, has launched a number of initiatives to identify the barriers to EFS in the United States and, based on the barriers, propose possible solutions and tools to facilitate bringing these studies back to the United States. One of these initiatives is the release of this MDIC Blueprint report for EFS in the United States.

This report is intended for industry, academic centers, medical device innovators, investigators, clinical research personnel, and other individuals or organizations that have an interest in EFS to be conducted in the United States. The report was written by members of the MDIC Early Feasibility Working Group and reviewed by the Clinical Trial Innovation and Reform Steering Committee before its release to the general public for comment on April 13, 2016.

The Blueprint report is meant to provide a bird's-eye view of EFS in the United States. It includes general information one needs to know before starting an EFS. The report uses a casual language for easy access and simplification. It includes practical information to individuals or professionals interested in the execution of EFS in the United States. Whenever possible, the reader will be directed throughout the report to references that provide more details for each topic discussed in this report. This report is not meant to replace or substitute, in part or in totality, any guidance document provided by other

organizations, policy makers, the FDA, patient advocacy groups, Center of Medicare and Medicaid Services (CMS), ethics committees, or Institutional Review Boards (IRBs). This report is organized in 5 chapters. Except perhaps the Definitions section, each chapter represents a stand-alone section, and the reader can skip chapters or “jump” from one chapter to another in any order without affecting the comprehension of the report.

An initial draft of this report was released for general public review and comment between April 13, 2016 and May 31, 2016. The MDIC EFS Working Group appreciates the public feedback and has updated the report as deemed necessary with this current version. Any correspondence or comments about the current version should be directed to Stephanie Christopher, Program Manager, Medical Device Innovation Consortium (SChristopher@mdic.org).

On behalf of all the MDIC members, we would like to thank you for your support and interest in EFS.

Karim Benali, MD, MSc

Chair of the EFS Working Group, on behalf of all the Authors

1. Introduction

The medical technology industry plays a significant role in the lives of patients globally. The industry covers a large spectrum of applications including in-vitro diagnostics, electro-medical and electrotherapy, irradiation, surgical and medical instruments and supplies, surgical appliance and supplies, dental equipment, and ophthalmic goods.

Together with other segments of the healthcare sector, medical technology companies and academia have contributed to dramatic improvements in health. In a 20-year span, new diagnostic and treatment paradigms have helped drive the increase in U.S. life expectancy by more than 3 years, the decrease in annual mortality rates by 16%, and the decline in disability rates in the elderly by 25%.¹

The medical technology industry is responsible for generating almost 1.9 million U.S. jobs, over \$113 billion in personal income for U.S. workers, and \$381 billion in national economic output.² Internationally, the United States is the largest global consumer and the leading producer of medical device technology. Exports of medical devices grew at a compound annual growth rate of 4.5% between 2008-2013. Medical device technology is one of the few industries that has sustained a trade surplus. The United States achieved this position in part through decades of strong, sustained investment in research and development by U.S. medical device companies and the venture capital community.³

The medical technology ecosystem comprises academic and industrial research and development (R&D), large and small manufacturers, innovative start-ups, providers (hospitals, clinicians), payers (Centers for Medicare and Medicaid Services, private insurance companies), and regulatory authorities. The medical technology industry is heavily dependent upon innovation and thus shoulders a large amount of risk upfront. In addition to industry, the academic field contributes significantly to the medical innovation in the United States. Indeed, it is estimated that about 20% of the annual investigational device exemption submissions to the U.S. Food and Drug Administration come from

¹ "The Value of Investment in Healthcare", MedTap® International, www.Medtap.com accessed October 14, 2015

² "Economic Impact of the US Advanced Medical Technology Industry," March 2012, Batelle and Advamed

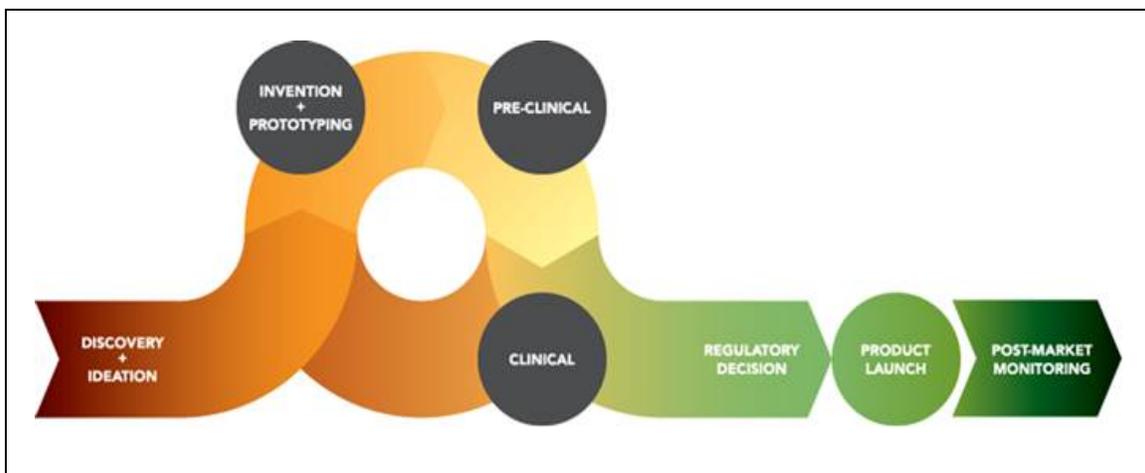
³ "United States Medical Devices", June 2015, Espicom, <http://www.espicom.com/usa-medical-device-market.html>

Accessed on October 14, 2015

academia. Therefore, any development that hinders the product development efforts can have profound negative consequences for the industry, the academia, and ultimately, for the patient.⁴

The development of a new product takes times. For instance, a life-saving innovation (Class III device) could take 10 years or more from the first prototype to its market introduction in the United States. Such innovation will have to successfully pass a series of phases from bench testing, to animal preclinical studies, to first-in-human or early feasibility study, to potential traditional feasibility study, to the pivotal study before market approval (Figure 1).

Figure 1: Device Development Cycle (Class III Device)



Graphic courtesy of FDA Center for Devices and Radiological Health

According to a 2010 report, it takes about 6.5 years and \$37 million for a company to bring a product from bench testing to completion of the feasibility study in the United States.⁵ Lengthy development times limit innovation and add a significant burden on the economy, especially on small businesses.⁵ Indeed, about 80% of the U.S. medical technology companies are relatively small with fewer than 20 employees with very limited capital and resources.⁶ Therefore, many of the innovations would never make it to market and many companies will not survive the economic burden if the development times are extensive.

⁴ “Medical Technology and Venture Capital: A Fruitful Yet Fragile Ecosystem,” June 2009, MDMA and NVCA

⁵ Statista (<http://www.statista.com/statistics/248687/us-medical-device-industry-projected-number-of-companies/>)

⁶ Dunn and Bradstreet, Inc. 2013

Put in simple terms, longer development times increase R&D costs and reduce the opportunity for returns needed to make investments that are financially viable. Everything being equal, longer development times reduces innovation incentives and results in missed opportunities for improving patient care and quality of life.

A survey of 200 medical technology companies revealed that unpredictable, inefficient, and expensive regulatory processes puts the United States at risk of losing its leadership position in medical technologies.⁷ Data from the survey indicated that European regulatory processes allowed new medical technologies to become available to patients more quickly and at a lower cost. Conflicting reports exist, however, on the potential possible risks to the patient with a quicker or less stringent regulatory process. Recent reports cited examples of devices approved in Europe that were later shown to be unsafe for the patients or ineffective when evaluated in the United States.⁸ Others have criticized the process used in Europe to bring devices to market and have requested that future device directives in Europe should be more stringent and require safety and clinical efficacy data in the device evaluation process prior to market release.⁹ However, a separate independent assessment of recalls between the United States and Europe does not suggest that different regulatory processes and quicker approvals in Europe increase the safety risks for patients.¹⁰

Because there is no clear evidence that a more stringent regulatory process and longer development time in the early phase of the product development cycle would improve safety and limit the risks to the patients, companies will conduct research and EFS overseas where the development ecosystem is more favorable than in the United States. As a consequence, early access to innovative therapies for U.S. patients will be delayed

⁷ “FDA Impact on US Medical Technology Innovation”, November 2010, Makower, Meer, Denend for MDMA and NVCA, independent data verification by PWC LLC

⁸ “Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform Report of a policy conference of the European Society of Cardiology”. Alan G. Fraser, Jean-Claude Daubert, Frans Van de Werf, N.A. Mark Estes III, Sidney C. Smith Jr, Mitchell W. Krucoff, Panos E. Vardas, and Michel Komajda, on behalf of the participants# European Heart Journal (2011) 32, 1673–1686.

⁹ Belgian Health Care Knowledge Centre, “The Pre-Market Clinical Evaluation of Innovative High-risk Medical Devices”, KVE reports 158 (2011). Article available at http://www.kce.fgov.be/index_en.aspx?SGREF=20267.

¹⁰ “Regulation and access to Innovative Medical Technologies: A comparison of the FDA and EU Approval Processes and Their Impact on Patients and Industry”, June 2012, Boston Consulting Group

and healthcare professionals will lose their leadership position in terms of knowledge, training, education, and applications of these technologies.

MDIC, through its public and private partnership, is uniquely positioned to work with the different stakeholders to identify the barriers to EFS in the United States and to potentially propose some solutions to the existing challenges. In an attempt to identify the barriers to EFS, MDIC recently conducted a survey through its members and other stakeholders.¹¹ The survey included 116 participants (29% C-level Executives; 49% Senior Management such as Functional Vice-Presidents, Directors; 12% Management; 10% Scientists/Engineers). Results of the survey identified the regulatory process as the most significant challenge to EFS in the United States. Additional challenges to EFS in the United States include Institutional Review Board (IRB) issues, legal issues, contractual issues, and reimbursement issues. These challenges remain significant and need to be addressed in order to promote EFS in the United States. There are other barriers that may not be as visible, such as the quality of an application, quality of the study design presented to the authorities, or lack of awareness or full familiarity regarding the obstacles embedded in clinical trial applications outside of the United States that may delay the regulatory progress and development times. According to the survey, the majority of responders said that they have conducted or plan to conduct their EFS overseas to avoid the stringent ecosystem in the United States. However, when asked if they would consider conducting their EFS in the United States if the existing ecosystem were to become more favorable, 63% said they would. The survey also identified a relative lack of information with respect to EFS and an opportunity for MDIC to provide more education and training for industry, investigators, and other stakeholders with an interest in conducting an EFS in the United States.

This report is one of the MDIC initiatives to address the existing barriers for EFS. The objective of this Blueprint report is to provide an education and an orientation for sponsors, investigators, and other interested audiences on the conduct of EFS in the United States.

2. Definitions and Assumptions

Before going further, it is important to start with definitions.

¹¹ The results of the survey can be downloaded here: <http://mdic.org/wp-content/uploads/2013/05/EFS-FIH-Study-Final.pdf>

2.1 What is an Early Feasibility Study (EFS)?

EFS is an informal designation. They have broad purpose and are designed to provide proof of principle and initial clinical feasibility and safety data. These studies are usually conducted on a small number of subjects (usually ≤ 15) at a limited number of investigational sites (to limit variability and maximize the learning curve). EFS are suitable early in the development process when further nonclinical testing methods cannot yield additional useful information to optimize the design, function, or deliverability of the device for the intended use and cannot provide additional insights into safety. In such case, it becomes required to collect clinical data to provide additional necessary information to advance the device's development.

EFS is critical because it represents the point of transition from research to clinical practice, and it is an opportunity to capture additional information for the intended use from the real-world setting that would not be possible in nonclinical methods (bench testing and animal studies). However, because most of these studies evaluate a device in the early stage of development, before the design of the device is finalized, or device for a new intended use, they carry greater unknown risks compared to traditional feasibility or pivotal studies. These studies must be justified by an appropriate risk-benefit analysis and adequate human subject protection measures (see sections below about regulatory and human protection requirements). That is why proper planning, taking into consideration the regulatory and ethical requirements, becomes important. It is critical for an EFS that the expectations are appropriately set and that communication is transparent between the different stakeholders including sponsor, investigator, the FDA, and the IRB so that there is a shared understanding of the EFS goals, risks, and potential benefits to the patient. Failure to do so may lead to unpredictable processes and subsequent delays in the study's execution.

Remember, the goal of an EFS is not to prove the device performs exactly as intended and requires no changes, but rather to provide information to help you make a better, more effective device. Changes to the device design, materials, procedure, instructions, and even patient population are to be expected.

2.2 Is an Early Feasibility Study Always Required For Device Development?

No. An EFS is not always needed to advance the device development process of a technology, as long as there is enough evidence that the design of the device is final or

near-final, the risks are mitigated for the patient, and the patient population for the intended use is adequate. In such cases a traditional feasibility study may be appropriate.

The data collected through an EFS may lead sponsors/innovators to change the design of the device, optimize the operator technique, modify the procedure and deliverability of the device, or refine the study population intended to treat. An EFS does not necessarily involve the first clinical use of a device. A new device or a prototype of a new device may have previously been used in a few patients outside of the United States, or the study may be for a new intended use of the device, and still be a candidate for the EFS program. Importantly, a device would potentially qualify for an EFS in the United States even if it has been used, is being used, or will be used concurrently outside the United States in a similar study or for a similar intended use.

2.3 What Happens After an EFS?

Different scenarios are available to the Sponsor/Innovator after completion of the EFS: 1) The Sponsor/Innovator in consultation with FDA may determine that further changes are necessary to optimize the device design, its deliverability, or technique of operation. In this case, an expansion of the EFS may be requested under the same Investigational Device Exemption (IDE); 2) The Sponsor/Innovator in consultation with FDA may determine that the design of the device is near-final or final, that adequate nonclinical data are available, and that the observations made in the EFS support the proof of principle that was aimed for with an acceptable safety profile. In this case, there might be enough information to provide a favorable benefit-risk profile to support the conduct of a traditional feasibility study. Of note, it may be appropriate to move directly to the pivotal study if the preliminary safety and effectiveness information is adequate to define the pivotal study population, the study endpoints, and that the benefit-risk profile is favorable. This decision should be reached in collaboration with FDA.

2.4 Early Feasibility Study (EFS) vs. First-in-Human (FIH) Study

An EFS is not necessarily a first use of the device in human. The device may have already been used for a different intended use or used a limited fashion for the same intended use outside of the United States and still be a candidate for evaluation under the EFS program in the United States. Although a FIH study aims at evaluating the device or the prototype for its first-ever application in human, a FIH study does not

always qualify for the EFS program. For instance, although the device is being used for the first time ever in human in a FIH study, FDA may determine that the nonclinical evaluation of the device is well-established and provides reasonable assurance that: 1) the risks to the patient are well-known and the potential benefits outweigh the risks; 2) the design is robust enough, near-final, or final; 3) the operator technique and deliverability are straightforward; and, 4) the study population is adequate. In such circumstances, FDA may agree that a traditional feasibility study or even a pivotal study may be the appropriate next step in the development process if additional clinical data are necessary prior to market release.

2.5 Early Feasibility Study (EFS) vs. Traditional Feasibility Study vs. Pivotal Study

EFS is suitable early in the technology's development process so that data gathered in the study help optimize or change the design of the device or a prototype, its function, or deliverability. It can also serve to optimize the operator technique or refine the patient population for the technology's intended use. A traditional feasibility study is usually conducted with a device that has reached a more mature level in its design. In general, the purpose of the traditional feasibility study is to collect some initial safety and effectiveness data. In general, the data will help the Sponsor/Innovator design a large pivotal study. The data may be used as well to support the market release of the product if there is evidence and a reasonable assurance that the use of the device does not carry a significant risk to the patient (Class II).¹² A pivotal study aims at establishing the safety and effectiveness of the device. Table 1 summarizes the differences between an EFS, a traditional feasibility study, and a pivotal study. The Table can be found in the FDA CDRH-Learn Module.¹²

¹² "FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions"

Table 1: Comparison Between an Early Feasibility Study, a Traditional Feasibility Study, and a Pivotal Study¹³

	Early Feasibility Study	Traditional Feasibility Study	Pivotal Study
Number of subjects	~15	Variable (but ≥ 15)	Determined by the statistical needs of the study endpoints
Purpose	Obtain initial insight	Capture preliminary safety and effectiveness information and plan an appropriate pivotal study	Support safety and effectiveness of the device for marketing application
Stability of device design	Changes may be anticipated	Near-final or final design	Design is final and there is significant information about the design, procedure, and intended use.
Justification for study initiation	Potentially more reliance on device design and leveraged information	Generally supported by more nonclinical (or prior clinical) data	Relevant and significant information from EFS and/or traditional feasibility study or prior pivotal study
Applicability	Always an option but most useful for novel technology or intended use	Generally useful	Help establish safety and effectiveness of the device

3. Prioritizing EFS Execution in the United States

Conducting EFS in the United States carries significant advantages for the patient, sponsors, innovators, regulators, and the entire healthcare system.

3.1 Potential Patient Benefits

Although the benefit of a specific technology may not be well defined at the time of the conduct of an EFS, U.S. patients can have earlier access to the technology. This could be beneficial especially in medical conditions that have limited or no alternative therapeutic options.

¹³ CDRH-Learn Module available at: <http://www.fda.gov/Training/CDRHLearn/>

3.2 Potential Benefits to Sponsor

High-quality EFS data may have greater impact on the company and its investors (or potential investors). The potential benefit may be more significant for small companies with substantial increase in the market valuation and access to additional sources of funding. Additional potential benefits to Sponsor include, but are not limited to:

- Assurance of patient protection
- Applicability of the device's use to U.S. patients
- Licensing of new innovation from/by academia
- Appropriate patient population and standard of care to support potential "poolability" of the results later
- Access to key opinion leaders
- Good and credible data
- Good clinical practice
- Shorter time to market if traditional feasibility study is not necessary

3.3 Early Regulatory Input

There are several technical risks in any product development program. One aspect of product development that is essential for success is early and frequent discussions with regulatory agencies. In addition to the advantage of providing the FDA with early exposure to the technology, these discussions enable a partnership, which allows the authorities to gain expertise and experience along with the manufacturer, leading to a more flawless development process through early interaction. Sponsor awareness and guidance on the appropriate data requirements for demonstrating relevant safety and effectiveness data greatly reduces development risks.

3.4 Expertise Development

The United States is host to a large number of experts, health care providers, physicians, and scientists. These technical experts and key opinion leaders provide critical inputs for product development and accelerate the advancement of innovation. Improved access to these experts can add valuable insights to the sponsors and manufacturers to drive innovation.

3.5 Appropriate Patient Population

Subject recruitment is a critical challenge in completing any clinical trial. The United States, with its large patient base and advanced health care system network, offers an ideal location for clinical trial execution ensuring the adequate population is enrolled to answer the research question that is intended by the study. The EFS also helps define the target patient population and ensure that the enrollment rate would be adequate for a larger feasibility/pivotal study (if needed).

3.6 Innovative Centers of Excellence

The United States is home to many world-renowned academic and business organizations that develop advanced device technologies and drive innovation. Information and knowledge derived from medical technology, from both academia and industry, can be leveraged locally to drive advancement of other sectors or specialties when appropriate, creating centers of excellence for research and innovations throughout the nation. For instance, this may lead to the development of spin-off technologies to treat other medical conditions and would lead ultimately to more EFS being conducted in the United States.

4. Getting Started with Early Feasibility Studies

4.1 Planning Phase

An EFS is intended to provide proof-of-principle information, as well as initial clinical and safety data to make the device development process more efficient and fluid. Because an EFS requires interaction between multiple stakeholders and organizations, it is critical that a well-developed and comprehensive execution plan is drafted prior to getting started. The plan should address the following:

- Strategic device evaluation roadmap (objectives, milestones, and timelines)
- Device development documentation (21 CFR 820.30)
- Regulatory requirements (when to approach FDA, expectations, investigational plan)
- Human protection requirements (IRB, informed consent)
- Clinical operation requirements (site selection, monitoring)
- Legal considerations (right to intellectual property, contracts)

- Resources, budget, and funding
- Insurance and reimbursement considerations

4.1.1 Strategic Device Evaluation Roadmap

It is the Sponsor/Innovator's responsibility to first determine if an EFS is necessary. Remember, EFS is not a regulatory requirement. It is up to the Sponsor/Innovator to determine first that clinical experience is necessary at this stage of the device's development cycle, and that nonclinical methods are neither available nor adequate to provide the information needed. It is helpful to have an overall device evaluation roadmap, which also includes a timeframe for traditional feasibility study (if any), pivotal study, and marketing application. The roadmap may be helpful to identify the level of information and testing required over the full product development cycle to avoid any potential delay. The roadmap should be aligned with the business goals and expectations.

4.1.2 Regulatory Considerations

You will be dealing with the Center of Devices and Radiological Health (CDRH) or perhaps the Center for Biologics Evaluation and Research (CBER) at FDA. You are encouraged to reach out to FDA very early in the process to minimize delay and improve your productivity (see Section 4.2.1). However, while FDA has encouraged Sponsors to contact the agency early in the device development process, you will maximize the outcome of these discussions by doing some homework prior to approaching the agency.

The FDA has acknowledged that initial clinical testing of novel products has moved to non-U.S. sites and product innovation may also follow overseas. Encouraging medical device innovation and facilitating clinical studies in the United States have become a CDRH priority. The need to focus on promoting public health and innovation is recognized in importance in conjunction with protecting public health.¹⁴ As a result, the FDA has undertaken a number of initiatives to make the process more flexible and dynamic. These initiatives include:

¹⁴ "Regulatory Reform Series #5 - FDA Medical Device Regulation: Impact on American Patients, Innovation and Jobs." Statement of Jeffrey Shuren, M.D., J.D. Accessed 2/15/2016. <http://www.fda.gov/NewsEvents/Testimony/ucm263491.htm>

- The release of a guidance document that outlines FDA's position and recommendations on EFS
- The nomination and training of EFS representatives in each Office of Device Evaluation (ODE) review division to assist sponsors and review teams
- The development of a toolkit of "CDRH-Learn modules" focused on EFS and pre-submissions
- The promotion of interactive review with sponsors

The EFS guidance document is a *"must read"* reference.¹⁵ It explains the FDA requirements to initiate an EFS in the United States. The document can be downloaded from FDA website using the link below. The document is intended for FDA staff, sponsors, innovators, investigators, and other audiences interested in EFS in the United States. The guidance document includes definitions, regulatory directions and recommendations, useful examples, and practical tools and templates for the conduct of studies under the EFS program. In addition, FDA has provided a series of additional educational materials and CDRH-Learn modules as well as a list of frequently asked questions (FAQs) that further explain and clarify different topics discussed or referenced in the FDA EFS guidance document. This information is available on the FDA website at <http://www.fda.gov/Training/CDRHLearn/> or accessed directly using the links below.

16, 17, 18, 19, 20

The FDA guidance document was developed to streamline the process of EFS in the United States under the IDE regulation to reduce the regulatory burden on Sponsors/

¹⁵ 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. <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

¹⁶ "Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies". Andrew Farb, MD and Dorothy Abel, BSBME. Office of Device Evaluation Center for Devices and Radiological Health (CDRH) Food and Drug Administration. <http://www.fda.gov/downloads/Training/CDRHLearn/UCM371840.pdf>. Accessed 12/1/2015.

¹⁷ Benefit/Risk Guidance available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>

¹⁸ FAQs available at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/UCM461286.pdf>

¹⁹ EFS IDE available at: <http://www.fda.gov/downloads/Training/CDRHLearn/UCM371840.pdf>

²⁰ Additional interactive CDRH-Learn module on EFS available at: http://www.accessdata.fda.gov/cdrh_docs/presentations/EFS/story.html

Innovators/Investigators. It clarifies how IDE requirements may be addressed in an EFS but also offers flexibility, both in the amount of nonclinical testing required as well as the manner in which changes are executed.

The EFS guidance document promotes the key principle of “Doing the Right Testing at the Right Time,” which means that approval of an EFS IDE may be based on less nonclinical data than would be needed to support the initiation of a larger clinical study of a more finalized device design. Indeed, the full battery of tests required in the product development cycle may not be required during the early phases of device development and may add cost and delay without significant return. Therefore, it would make sense to defer some nonclinical testing until the device design has been finalized. An example of testing done at the right time may be the use of batch release testing at the time of EFS instead of full validation testing, which may be required at a later stage. Testing that will not inform device performance at the EFS stage can potentially be eliminated or completed in parallel with the EFS. There should be specific reasons for deferring or eliminating any nonclinical tests and a justification should be provided to the FDA describing why the test strategy is appropriate. The use of clinical mitigations to further protect patients may be needed when information from nonclinical testing is not informative. The guidance recommends the use of device evaluation strategy (or DES) to identify the information needed to support study initiation. This may be presented in a variety of ways including the use of existing risk analysis and test plan documentation. Additional information about the DES, as well as an optional table template, are provided in the CDRH-Learn module.¹⁵ Further information regarding how to determine what testing is appropriate to start an EFS and examples can be obtained in the FDA webinar slides titled “An Update on the FDA’s Medical Device Clinical Trials Program - July 14, 2016.”²¹

To avoid unnecessary regulatory delays, the guidance also facilitates timely device and clinical protocol modifications during an EFS under IDE regulations, as described below:

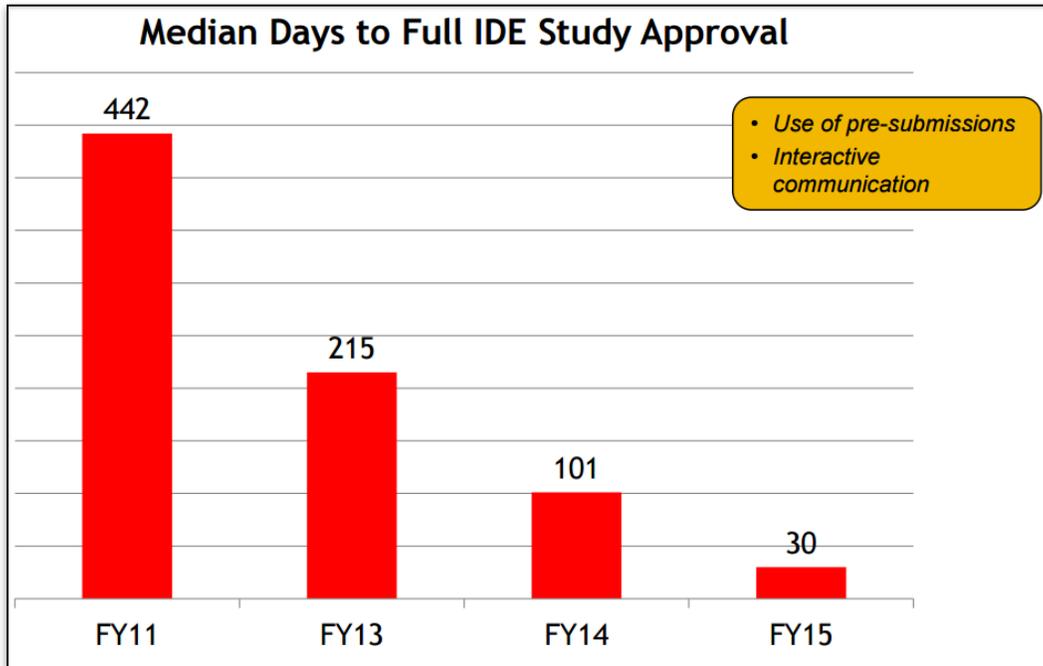
- Simple protocol and device modification can be made under a 5-day notification without prior FDA approval

²¹ Reference: “An Update on the FDA’s Medical Device Clinical Trials Program - July 14, 2016” (<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm509514.htm>)

- Contingent approval for more significant changes to the device or protocol can be obtained when supported with acceptable nonclinical test results
- For more significant changes, IDE supplements and amendments can be handled through an interactive review to avoid unnecessary delays

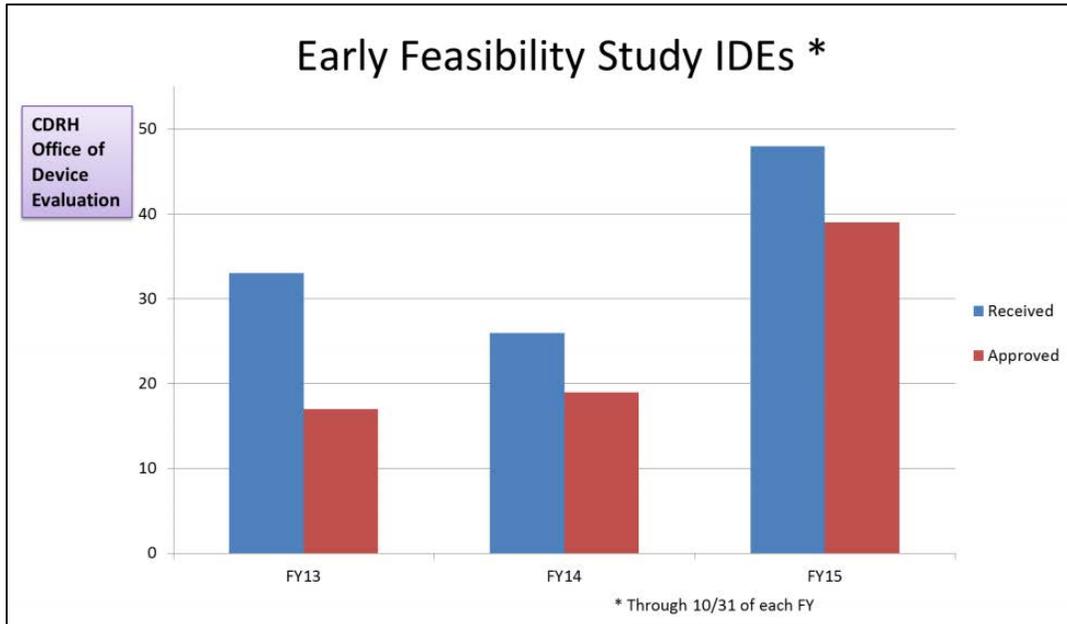
The initiatives proposed by FDA have been recognized and need to be applauded. While it is perhaps too early to determine if the recent improvement will have a positive impact on the EFS process in the United States, the preliminary results appear encouraging based on the positive trends seen in both median to full IDE study approval (Figure 2A) and the number of IDE submitted and approved by FDA under the EFS program over the past few years (Figure 2B)²².

Figure 2: Regulatory Trends
 A: Median time to full IDE study approval over time
 (Reference: FDA communication MDIC Webinar – <http://mdic.org/wp-content/uploads/2016/03/Advancing-US-Early-Feasibility-Presentation-at-DMD.pdf>)



²² Reference: FDA communication MDIC Webinar – <http://mdic.org/wp-content/uploads/2016/03/Advancing-US-Early-Feasibility-Presentation-at-DMD.pdf>

B: Number of IDE submitted/approved by FDA under the EFS program
(Reference: FDA communication MDIC Webinar – <http://mdic.org/wp-content/uploads/2016/03/Advancing-US-Early-Feasibility-Presentation-at-DMD.pdf>)



Special considerations in planning for success also include a plan for clinical operations of the study, prioritization of the human protection measures, protection of the intellectual property, funding, insurance, and reimbursement. These topics will be covered in later sections.

4.2 Execution Phase

4.2.1 Regulatory: Your Interactions with FDA

Prior to reaching out to FDA, you will need to consult the FDA EFS guidance document and the EFS CDRH-Learn modules, referenced above. By doing so, you will be better equipped to ask the right questions and maximize the interactive review time. A provision for success includes the understanding of the EFS guidance concepts that are based on reasonable nonclinical data requirements and an increased flexibility in meeting the IDE regulatory requirements to minimize regulatory delays. **The primary goal for a Sponsor/Innovator is to reach an agreement with FDA on the nonclinical testing and investigational plan contents for the EFS as early as possible.**

As an example, a successful interaction with FDA would include 4 chronological steps, as outlined in the CDRH-Learn Module (Table 2).

Table 2: A Practical Example for Interaction with FDA under EFS Program

Steps	Goal
Step 1: Contact the FDA	Contact the FDA EFS Representative or someone from the FDA review branch (branch chief, lead reviewer) via email or phone (informally): <ol style="list-style-type: none"> 1. To introduce your program and device 2. To confirm that your device is suitable for EFS 3. To obtain potential additional information about EFS 4. To get the process started
Step 2: Submit Initial Pre-Submission	<ol style="list-style-type: none"> 1. To educate FDA on the device 2. To describe the clinical condition the device is supposed to address 3. To discuss the proposed test plan with rationale initiation
Step 3: Submit Additional Pre-Submissions	<ol style="list-style-type: none"> 1. To obtain feedback and reach an agreement on test protocols to be performed with the device 2. To obtain feedback and reach an agreement on the investigational plan (protocol, endpoints, monitoring plan, informed consent) 3. To confirm with FDA that your plan is sound and reasonable and that FDA does not have additional concerns
Step 4: Submit IDE	<ol style="list-style-type: none"> 1. Interact with FDA review team to address any questions about the IDE 2. Use the interactive review during the execution of the EFS to address any potential change in the device, the procedure, or the protocol

Step 1: Contact the FDA

Early and frequent interactions with the agency are fundamental to a positive EFS experience. The first step is informal. The initial interactions should begin at a point that allows the agency to participate in the development process. Typically, a project scope is defined and the development teams begin creating concepts that would meet the outlined requirements as specified in the guidance document. An ideal time to first reach out to the agency is when some design concepts are beginning to take form and you believe that you might qualify for the EFS program. Delaying your interactions much beyond this point will only hinder your chances for a successful review, as quality collaboration with FDA is the key to EFS success. In fact, the more novel your device, the earlier you need to reach out to FDA. You do not want to be performing nonclinical

testing that would not be accepted by FDA later or re-do expensive/time consuming testing that did not meet FDA expectations.

Most likely, the first interaction will be through the branch chief, the lead reviewer, or one of the EFS program leaders at FDA. Alternatively, you can directly contact the EFS representative of the division that covers your device. The contact list of the respective FDA EFS representatives and leaders at CDRH is kept up-to-date on the FDA CDRH website at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/UCM461288.pdf>.

During this initial contact, you may want to obtain additional information about the EFS process and then confirm that your device qualifies for the EFS program for the intended use you have defined.

Step 2: Initial Pre-Submission

Sharing your program goals through a conference call or web-based presentation will allow the FDA EFS review team to determine the best suitable team that should be assembled to provide good cross-functional feedback during the review process. Following the initial communication, having a face-to-face meeting is very helpful to provide the agency with a “hands-on” demonstration of the technology, as well as to discuss any areas of concern. This face-to-face meeting can be either informal or a formal pre-submission meeting. As a Sponsor/Innovator you should submit the 5 sections described below to the FDA to begin the discussion with the subject matter experts on the information that will be needed to justify study initiation. Suggested topics in the pre-submission should include:

- An introduction and background section that describes the medical condition the device is supposed to address, the device description, and operation
- Supporting evidence to justify EFS
- Development plan of the device including planned preclinical testing
- Development progress for the device
- Summary of the information you propose to include in the Report of Prior Investigations
- The questions you may have for the pre-submission

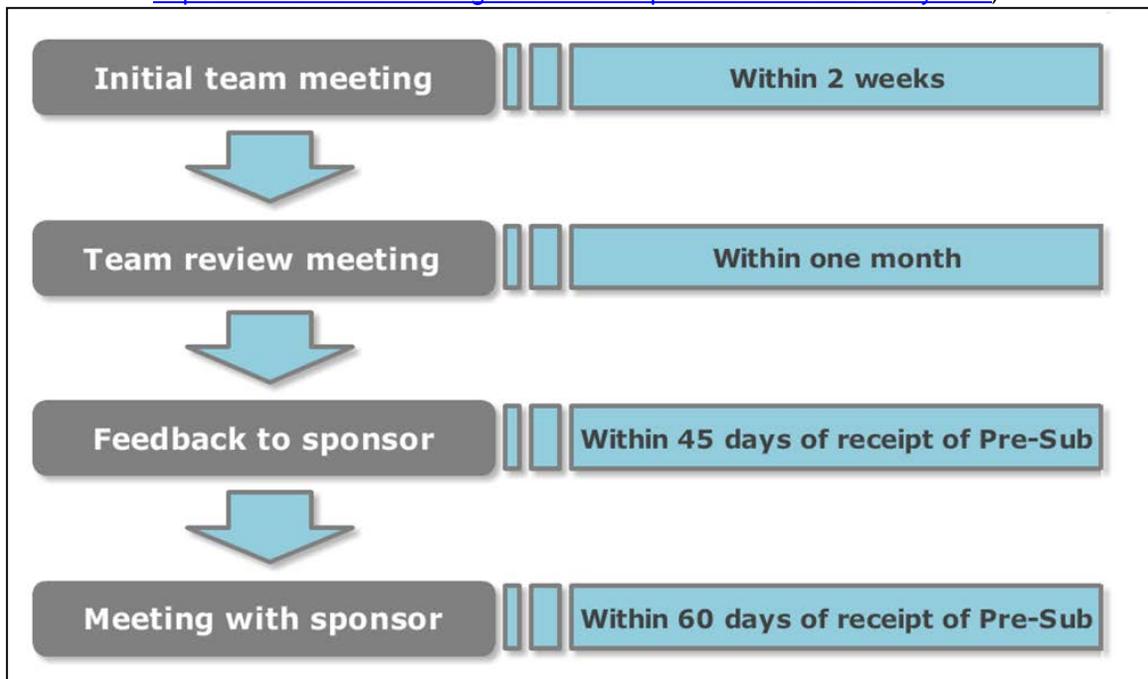
Once the agency is familiar with your device and agrees that the device is suitable for EFS for the intended use, you will need to make sure that the agency agrees on the information you plan to include in the Report of Prior Investigations, including the DES to support the study initiation. The EFS guidance document provides a very detailed outline for the Report of Prior Investigations under the EFS program (refer to Section 6 of the FDA EFS guidance document referenced above).

Step 3: Additional Pre-Submissions

After agreement has been reached on the information provided in the first pre-submission, you can then begin providing any further documentation that you would like feedback on to the agency. You can submit (optional) for FDA review the proposed nonclinical test protocols to be performed, the investigational plan, and the informed consent for the EFS for feedback. A pre-submission can be provided to get cross-functional feedback on items like sterilization validations, biocompatibility testing, animal study protocols, and/or clinical study protocols. This is a very interactive time and should be done before testing is started to maximize the interactions and feedback. It is also an excellent time to understand the agency's expectations on test durations (e.g., chronic animal studies, fatigue/durability tests). Additionally, ensuring agreement on your clinical study protocol patient population, follow-up schedule, and endpoints is crucial to a successful IDE submission. In summary, this is the time where you address any issues with the test plan and investigation plan, but is before the IDE is submitted. The intent of this process is to obtain agreement with FDA on your development plan before testing is completed (or even started). This may help avoid the potential need to do testing that you did not anticipate or to re-do testing already completed at the IDE stage. So, make sure you allow sufficient time to resolve questions and update or complete documents as planned. The goal is to try to avoid unexpected requests for new information at the time of IDE submission.

The FDA suggested timeline to complete the EFS pre-submission is provided in Figure 3 (the timeline includes Phase 2 and Phase 3 above).

Figure 3: Suggested FDA Pre-Submission Review Process Timeline
(Included Phase 2 and 3 above)
(Reference: Available on the FDA CDRH website at
http://www.accessdata.fda.gov/cdrh_docs/presentations/EFS/story.html)



Step 4: IDE Submission

Once the interactive pre-submission is complete and your data package is complete, it is time to assemble your IDE. Essentially, the format and content of the IDE is no different than a traditional IDE in its requirements. First and foremost, be respectful of the review team at the agency. Also, establish good communication process with the review team at FDA. It is important to plan ahead to avoid any surprises.

Once submitted, the IDE goes through a 30-day review cycle. Since the 30-day review period is highly interactive, ensure your team is ready and available. This is critical for small companies operating with limited resources. It is likely that questions will come from FDA with a request for a quick turnaround. Another benefit of the interactive review is that you have a better chance of getting clarity on ambiguous questions preventing the back and forth that can commonly occur delaying the regulatory process.

After the IDE has been approved and the EFS has started, be sure to continue the interactions with FDA. Changes to the device design and/or materials, procedure, protocol, instructions, and even patient population are to be expected in an EFS, and

you will minimize the risk of regulatory delays by maintaining the interactions and promptly resolving issues as they come up.

With the completion of the EFS, several scenarios are possible. The Sponsor/Innovator may elect to expand the EFS to add additional patients if changes in the device design or the procedure occurred in the initial EFS and additional information is required to finalize the design. Alternatively, the Sponsor may decide that the design of the device is near-final or final and that enough information is available to perform a traditional feasibility study or even a pivotal study.

4.2.2 Investigational Plan

In general, the EFS investigational plan should follow the same requirements of a traditional feasibility study with some exceptions. Please note that the intent of the EFS is to gather initial insights into the safety and effectiveness of the device and to provide some proof of concept. Therefore, a statistical analysis is typically not conducted. Instead, the data are used to address the purpose of the study.

In the IDE submission, the study should be clearly identified as an EFS. Since the EFS is a small study (limited number of patients and sites), it does not require registration on www.ClinicalTrials.gov.

Table 3 provides information on the investigational plan's sections and corresponding contents.

Table 3: Investigational Plan Sections and Content

Section	Content
Background	<ul style="list-style-type: none"> - Should provide overview on the medical condition and healthcare problem the device is supposed to address - Should describe alternative treatments or standard of care if the patient were to use alternative treatments - Should clearly stipulate that this is an EFS
Device Description	<ul style="list-style-type: none"> - Should provide device description, its function, deliverability, management, procedure technique, and interaction with the human body
Patient Population	<ul style="list-style-type: none"> - Should describe the patient population targeted for the EFS - Inclusion criteria should be described clearly - Exclusion criteria should be described clearly with specific definitions of

	medical conditions that would be excluded
Number of Patients	- Frequently less than 15 patients
Number of Investigational Sites	- Frequently ≤ 5.
Study Outputs Defined	<ul style="list-style-type: none"> - Study outputs that are relevant to the purpose of the EFS should be described. This information may or may not be proposed as traditional study endpoints would. - While this is an EFS (classic safety and efficacy do not determine success or failure of the trial), primary and secondary endpoints can be useful in collecting information to assess potential efficacy endpoint to plan for future traditional feasibility or pivotal trial. The safety endpoint can be used as a benchmark to evaluate safety of the device to alternative treatments the patients may have access to if the device were not available. Endpoints should be clearly described and quantifiable if the intent is to use them to inform future clinical studies.
Adverse Events Definitions	<p>The information that is needed should be discussed with the FDA review team and may include:</p> <ul style="list-style-type: none"> - A comprehensive list of all clinical observations including adverse events (AEs) - A listing of all potential AEs that can be caused by the device or its interaction with human anatomical structures. FDA may ask that other AE be captured based on prior experience with other devices in the same field - Specifying a severity classification of the AE (unanticipated adverse events, severe AE, non-severe AE) - A definition of the relatedness of the AE to the procedure or the device
Reporting	- Because this is an EFS, more frequent reporting may be needed in case the review of the data requires prompt actions for safety reasons by the Sponsor (DSMC) and ultimately by FDA and IRB.
Monitoring Plan	- Should outline how the data will be monitored (on site), how often, by whom.
Data and Safety Monitoring Committee (DSMC) Also known as Data Safety Monitoring Boards (DSMB) or Data Monitoring Committees (DMC)	<ul style="list-style-type: none"> - While this is not required, a DSMC may be valuable to provide independent oversight of the study conduct and patient safety and can help the Sponsor make appropriate decisions with respect to the conduct of the EFS. FDA EFS guidance document provides more details about the DSMC. - Sponsor should have a charter in place that outlines the roles and responsibilities of the DSMC members so they can carry their mandate appropriately. - DSMC should include domain experts so they are familiar with the comorbidities of the patient being treated and also with the AEs associated

	with the medical condition.
Informed Consent Form Template	<p>Here are some important recommendations for the informed consent form. This list is not exhaustive and the Sponsor should refer to 21 CFR 50 for complete list of considerations and requirements about the informed consent form.</p> <p>The informed consent form should:</p> <ul style="list-style-type: none"> - Be written in simple language that the patient understands - Describe the device, function, interaction, and procedure - Describe the risks in order of severity - Describe standard of care or alternative treatments if patient were to decline - Mention the anticipated benefits, although these cannot be overstated <p>More details about the ICF can be found in the FDA EFS guidance document (Section 7.3) and below in the IRB section. A template of ICF is provided in Appendix 1.</p>
Institutional Review Board	<ul style="list-style-type: none"> - Protocol should mention the requirement to obtain IRB approval before initiating the site - More details about the IRB are provided below
Risk Analysis and Mitigation	<ul style="list-style-type: none"> - Should include a thorough analysis of the type and severity of the risks to which the patients will be exposed - Should include all measures taken to minimize the risks (e.g., training, patient selection, inclusion/exclusion criteria) - Should provide a rationale to support the claim that the anticipated benefits outweigh the possible risks. The anticipated benefits should not be overstated.

More details about the investigational plan can be found in the FDA guidance document (Section 7 of the EFS Guidance). An informed consent template is provided in Appendix 1 of this report.

4.2.3 Protection of Human Subjects: Your Interactions with Institutional Review Boards (IRB)

Do your homework before:

- The FDA 21 CFR part 50 regulations regarding Informed Consent are also applicable and should be used as a reference prior to IRB submission of EFS/FIH.

- The FDA guidance document includes important information about the Human Subject Protection Measures, IRB, and Informed Consent (Section 7.3). The document should be consulted.

Things that IRBs expect when evaluating EFS studies:

- IRBs will expect to see that the benefits outweigh the risk, especially in patients with limited treatment options. However, since this is an EFS, the potential anticipated benefits are *still uncertain and should not be overstated*. It is critical that the Sponsor moderates the language and sets realistic, objective, and reasonable expectations for the device's potential benefits at this early developmental stage. This is critical when writing the patient informed consent or other human subject protection materials for the FDA, the IRB, or the patient.
- IRBs will want to see that human subject protection was designed based on the device's risk level and the study's subject population.
- Procedures for ongoing review: EFS will require, at a minimum, annual reports to demonstrate a continuing review of the research study. They may request more frequent reports commensurate with the risk profile of the device. It is not uncommon that IRB may request to review the data of the first initial patients for high-risk devices to make sure proper oversight is conducted according to their mandate.
- IRBs will want to ensure that the Informed Consent Form (ICF) was designed with the 'unforeseeable risk' specifically addressed (Note: Appendix 1 of the above referenced guidance document contains additional information that sponsors may want to include in the ICF document for EFS).
- IRBs may want to receive additional information on the process for obtaining informed consent, who will be collecting informed consent, and the qualifications of staff delegated responsibility for informed consent collection.

Is the IRB of the study site you select qualified/experienced with EFS studies?

- When selecting sites for the study, the Sponsor will want to determine if the IRB of the study site has experience in EFS oversight.
- Feasibility assessment should contain specific questions on the requirements for IRB approval of EFS, including ongoing review.

- The Sponsor should also consider the experience of the investigative site with EFS as the IRB holds the responsibility for ensuring the investigator and his/her staff, and the facilities are appropriate for the research being conducted.

Central IRBs vs. local IRBs:

- The Sponsor should consider whether a central IRB may be more appropriate to evaluate EFS, depending on the sites selected and the site IRBs' comfort and familiarity with EFS.
- Depending on the size/number of sites/subjects, a Sponsor may choose to use a central vs. local IRB. This should be considered at the time the study is being designed.

Properly informed consent is critically important in EFS (ICF template in Appendix 1):

- The ICF is a critical document to FDA and IRB. The ICF should describe in simple language the device, its function, deliverability, and interaction with the human body. The intended use should be described as well (i.e., medical condition to treat).
- The ICF should clearly state that this is an EFS. The goals of the study should be described in simple terms.
- The ICF should provide information on any prior clinical experience with the device in prior studies (e.g., number of patients treated).
- Risks should be explained clearly and potential adverse events should be listed in the order of severity using simple language.
- Alternative treatment(s) should be provided if the patient were not to participate in the study.
- The ICF should stipulate that patients may choose to not participate or even change their minds at any time during the study to withdraw without any impact or consequences on the quality of care they would receive had they remained enrolled in the study.
- Potential anticipated benefits should be stated. While this may be important, especially in patients with limited treatment options, these cannot be overstated.

- The FDA EFS guidance document offers more details about the IRB and consent form on Section 7.3 and Appendix 1 of this report. The document should be consulted for further practical details.

Keep the IRB informed on the progress of the study, as more burden is put on the IRB for safety monitoring in EFS:

- With the new FDA guidance for EFS, the Sponsor can make small changes to the device or the protocol under a 5-day notification to FDA without requiring pre-approval. While this important advance provides more flexibility, some IRBs may feel that more burden is transferred to them to monitor the safety of the device. As noted above, an IRB will require, at a minimum, annual reports on the study. The IRB may request more frequent reviews. As per the FDA EFS guidance document “Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies,” “This may include, for example, continuing review on a more frequent basis than annually, continuing review after a small target number of subjects have been studied, and/or graduated enrollment based upon a safety analysis of the preceding subjects.”

Avoid usual pitfalls that may delay the study approval:

- By considering the risk of the proposed study, the experience of the investigator and site, as well as the IRB to be used for review, Sponsors can avoid pitfalls by preparing IRB packages that are comprehensive, complete, and commensurate with the risk of the device.

4.2.4 Legal/Intellectual Property Considerations: Your Interactions with Study Institutions and Investigators

Intellectual property (IP) rights are important. IP helps generate breakthrough solutions to medical problems by encouraging innovation and rewarding entrepreneurs. As such, IP rights often represent a significant investment by the study sponsor and deserve careful protection, especially in the setting of public evaluation of a new technology or treatment at study institutions by physician investigators. For this reason, it is extremely important to do your homework (confirm the site legal/IP policies and discuss with your legal representative to ensure alignment of expectations) before selecting your investigative site(s) in order to avoid lengthy legal discussions later. One should:

- Obtain a copy of the IP policy of the Study Institution, if there is one, to determine the Study Institution's stance on IP rights, including ownership and licensing requirements associated with any ideas, modifications, or improvements to the study device that may be generated during the study.
- Determine if the Study Institution is flexible or requires owning any modifications or improvements to the study device, if a Study Institution employee or the PI has had input into the modification or improvement. It is more common for Academic Institutions to have written IP policies, as compared to other medical institutions. Nevertheless, expectations and policies regarding IP rights should be thoroughly understood.
- Determine if there are distinctions regarding IP rights made relative to an IDE study as compared to other studies. There may be more flexibility with IP rights and licensing demands in certain instances.
- Determine whether the Study Institution (academic or medical) is associated with the state or federal government; these institutions may be subject to additional state and/or federal regulations and control that may affect the ability of the Institution to negotiate terms (e.g., confidentiality, indemnification, IP rights) and may limit flexibility. Such an institution may be subject to open records laws and requirements.
- Determine if a confidentiality agreement/non-disclosure agreement is required prior to discussing the study, study device, protocol, etc., with the Investigator/Study Institution.
- Determine patent strategy (e.g., provisional patent applications, utility patent applications; United States only, foreign patent applications, PCT patent application). U.S. provisional applications provide some IP protection for 1 year; a U.S. utility patent must be filed within a year of filing the provisional application. Consult IP counsel for determining patent strategy and timing, which among a number of considerations, may take into consideration costs and desired geographic coverage. There is no "international patent" but country-by-country applications or a PCT application and nationalization country by country. Consider filing any and all patent applications prior to discussions regarding conducting a study. Consult IP counsel.
- Determine the Investigator's willingness or ability to assign IP ownership to the study sponsor. You should know if the Investigator(s) is (are) legally obligated to

assign any IP rights to their Study Institution or another Institution. You will need to know whether this is a requirement or negotiable, and if IP assignment depends upon the type of study being conducted. For EFS/FIH, it is likely that the study device represents new technology and the sponsoring company needs to retain full IP rights, including rights to any modifications or improvements suggested during the study, to benefit from commercialization.

- Ensure your assignment of IP rights outside the United States (OUS) includes moral rights.
- Determine the Study Institution IRB's level of receptiveness to EFS given their risk/benefit profile.
- Identify any country-specific issues, such as:
 - The risks you may have OUS (you do not have U.S. protections)
 - The laws regarding confidentiality, IP protection, and patient rights, as these may differ country by country
 - If the study is performed OUS you must still determine where you will file the patent applications
 - Determine what is customary in the particular country/geography as compared to the United States. Is reference to U.S. patent law acceptable?

Specific legal considerations in EFS to be included in the contract(s) – [site, PI, co-investigator, research coordinator]:

- Extended timeframes for publication of study results by sites may be needed if technology is still in its infancy. Twelve to 18 months after study completion is typical for a pivotal trial.
 - If there are multiple investigators, consider publishing recommendations from the International Committee of Medical Journal Editors (<http://www.icmje.org/>)
 - Consider registration of the study on Clinicaltrials.gov
 - Consider copyright ownership of publications; assignment by authors to publisher and retention of some reprint rights or derivative works rights.
- Define acceptable time/content limits on presentation of EFS technology publicly.
- Be aware that liability insurance may be more difficult to obtain for an unproven significant risk technology in an EFS.

- Determine if there are any specific issues to the ICF for your EFS. Legal should review all ICFs to ensure consistency with Clinical Contract terms.
- Determine who will pay for the EFS device.
- Understand subject injury coverage, especially how it relates to third-party payers. For more information, see Medicare regulation 310.1 (<https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&bc=BAABAAAAAAAA>)
- Consider submission for approval to CMS or local providers. For more information, see Medicare Coverage Related to Investigational Device Exemption (IDE) Studies (<https://www.cms.gov/Medicare/Coverage/IDE/>)
- Understand that primary/secondary payer rules can come into play inadvertently in your EFS. For more information, see Medicare Secondary Payer information at (<https://www.cms.gov/Medicare/Coordination-of-Benefits-and-Recovery/Coordination-of-Benefits-and-Recovery-Overview/Medicare-Secondary-Payer/Medicare-Secondary-Payer.html>)

Intellectual Property FAQs:

- Is due diligence needed? Yes. Perform due diligence prior to the selection of study institutions and investigators to determine their expertise and long-term value to your program. Determine whether evaluation of the technology requires Centers of Excellence. Identify what related work has already been performed at each institution under consideration.
- Are there special considerations when selecting study institutions? Yes. Each institution is different. Obtain the written IP policies for the institutions under consideration. Be aware that many state universities have additional regulations and restrictions related to IP generation, ownership, and assignment.
- What confidentiality agreements are required? Obtain your template from Legal and execute a non-disclosure agreement prior to detailed discussions of the technology or study protocol with potential investigator(s). Understand what pre-existing knowledge is provided by the institution or potential investigator, as this may drive what each party would own or need to protect. There can be significant differences in language regarding “reduction to practice” as it relates to IP ownership; consult Legal at each encounter regarding:
 - Full ownership

- Joint ownership implications
- PI ownership options

Clinical Study Agreement:

The clinical study agreement between the Sponsor and the investigational site should codify the partnership between the two parties. The clinical study agreement should reflect both parties interest. The agreement is study-specific and is proposed by the sponsor to the site for review and approval. After consultation (and negotiation), the study agreement is signed prior to the commencement of any study related activity at the study site. A clinical study agreement may cover all of the (but not limited to) topics:

- Study Goals and Scope of Work
- Definition of Sponsor, Principal Investigator, and Co-investigators
- Facilities
- Subject Enrollment and Informed Consent
- Compensation
- Financial Disclosure and Reporting
- Study Device
- Records, Reports, and Regulatory Assistance
- Audit and Review
- Regulatory Inspections
- Ownership of Materials, Intellectual Property, and Work Product
- Confidential Information
- Privacy and HIPAA
- Publication and Use of Study Results
- Indemnification, Insurance, and Limitation of Liability
- Term of the Study
- Termination of the Study
- Disclaimers

Again, the clinical study agreement is study-specific and reflects Sponsor and site priorities and needs. For instance, the needs may be different if the Sponsor is a Company (Business) versus Academia. Similarly, a study site needs may be different if the site is a large hospital versus a community hospital or a physician office practice. Clinical study agreement templates are publicly available through organizations like Accelerated Clinical Trial Agreement (<https://ctsacentral.org/tools/acta>). The reader is encouraged to seek legal advice on the appropriate needs. A more detailed clinical study agreement template is provided as a courtesy in Appendix 2. The agreement may contain more details than required and should be tailored and adapted to the study needs to reflect both parties' interest.

Privacy:

- Local privacy laws and Safe Harbor considerations: You may consider seeking Safe Harbor certification, as it provides a guideline for requirements regarding the use of international data in the United States (<http://www.export.gov/safeharbor/>). However, if you choose this route, you may risk government involvement/ownership of the data.
- Understand Health Insurance Portability and Accountability Act (HIPAA) requirements regarding patient health information in the United States (<http://www.hhs.gov/ocr/privacy/hipaa/understanding/summary/>).
- Consider whether your company constitutes a Business Associate under HIPAA.

4.2.5 Insurance and Reimbursement

Insurance coverage of clinical studies in the United States from both private and government payers can be a distinct and often overlooked obstacle in the regulatory product approval process. Further challenges are presented in insurance coverage of FIH/EFS due to the inherent technical questions that remain in the device development process. Information is provided below on the current coverage landscape for both the Centers for Medicare and Medicaid Services (CMS) and private health insurers.

Centers for Medicare and Medicaid Services

Beginning on January 1, 2015, CMS instituted a centralized review process for coverage of investigational device exemption (IDE) clinical studies in the United States. CMS uses

clinical study criteria and the device category that is designated by the FDA to assist with the coverage decision. However, other factors may affect coverage, such as whether there is an existing national coverage or non-coverage decision for a device and/or procedure.

The CMS clinical study criteria include relevance of the device to Medicare beneficiaries and how well the study is designed among other items. The following link describes factors that CMS will consider when evaluating IDE coverage requests.
<https://www.cms.gov/medicare/coverage/IDE/index.html>

The device category as designated by the FDA reflects whether or not the device is considered to be experimental (Category A) or non-experimental/investigational (Category B). Medicare may cover only routine care items and services furnished in an FDA-approved Category A IDE study, *but not the device itself*. However, Medicare may make payment for an investigational device and routine care items and services furnished in an FDA-approved Category B IDE study. The FDA category designation may change as more information becomes known about the safety and effectiveness of the device. The FDA released draft guidance on how devices are categorized in June 2016.

Device manufacturers should contact CMS to obtain a definitive coverage decision through the IDE submission process.

For any EFS receiving a positive coverage decision from CMS, device manufacturers should educate sites on the requirements for properly coding the clinical study claims to ensure compliance with Medicare IDE coding requirements. These requirements can be located in the Medicare Claims Processing Manual, Chapter 32 – Billing Requirements for Special Services (<https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c32.pdf>).

The Medicare Secondary Payer rule, as it relates to clinical studies in general, has been debated in the past and device manufacturers financially supporting an EFS should seek counsel regarding the degree of financial liability during and after the study.

Private Health Insurers

With the introduction of the Affordable Care Act in 2010, most private health insurance companies adopted legislative language within their medical policies outlining coverage of routine clinical study costs for studies involving cancer or other life-threatening diseases. However, this language generally does not extend to coverage of services the health insurer deems experimental or investigational, as these services are not considered medically necessary for the beneficiary. As such, device manufacturers should not expect widespread insurance coverage, if any coverage at all, from private payers for FIH/EFS.

4.2.6 Site Selection and Other Study Operations

4.2.6.1 Site Selection: Are the sites you select skilled or technically equipped to execute the planned EFS?

A famous investigator, world-renowned hospital, or a state-of-the-art facility does not mean that a site is qualified for your EFS. In other words, each EFS requires its own assessment of the type of investigator and site that will fit that study's specific needs and potential outcomes.

Before vetting a site for an EFS, it is important for sponsors to ask and answer the question of “What could possibly go wrong?” and then determine the investigator characteristics and site features needed to attend to these issues.

Know Your Needs: Critical Criteria for an EFS Site

The fundamental question to consider here is: “Is this site—including the investigator, staff, and facilities—fully equipped, communicative, and flexible enough to handle the unknowns and ‘what ifs’ associated with EFS?”

Investigator

The experience and attitude of the investigator is the single most important factor influencing site selection. The best EFS *won't* go according to plan, but will instead provide information on how to improve the device and minimize risk. The investigator is a partner, not an independent party. The investigator must be flexible, forward thinking,

and available (or at the very least she/he should not also be running 10 studies simultaneously).

On a basic level the investigator should have:

- Experience in the clinical condition the device is intended to be used in the target population
- Experience with the type of device to be used in the study. One way to assess this is by having the investigator conduct animal and/or cadaver studies.
- Prior experience working on both EFS in general and also in the indication of interest (consider it an added bonus if you have worked together before).
- The motivation and time to complete the study. Key opinion leaders may be overcommitted.
- Access to the proper patient group and not be involved in any competing studies that may delay or prevent enrollment.
- A patient enrollment philosophy that complements the sponsor's and the nature of an EFS. Investigators who are quick to enroll may compromise future patient safety by not allowing enough time to assess device performance in the first few patients.

Site and Facilities

A great investigator also needs the right type of facility. It is about understanding all possible risks for noncompliance with good clinical practices and study protocol and having a facility that mitigates them as best as possible. Some questions to ask when assessing the facility include:

- Does the site have the proper processes in place to consent EFS/FIH patients? Do they have the IRB structure that can process and expedite an EFS/FIH program?
- Is the site centrally located in terms of manufacturer or Clinical Research Associate (CRA) access? Can someone from your staff quickly reach the site if something goes wrong or if the investigator needs to make a change to the device/procedure? Troubleshooting and risk management may be difficult for remote sites.

- Does this site have access to required services (e.g., is a cardiac intensive care unit or has an operating room available for a study on a percutaneous cardiac device)?
- Does this site have an onsite laboratory, flexible clinic hours, and proper equipment for device storage or maintenance?
- Is there a mechanism for reliable and prompt access to data, as well as communication between investigator and support staff?

Site Staff

The perfect investigator still needs a great support staff with experience in EFS. Staff assessment criteria should include an understanding of the following:

- Does the staff understand the nuances of EFS/FIH? Can they properly explain these to patients? EFS require distinctive additions to traditional informed consent forms. Study staff must understand and communicate the distinctive aspects that make these studies riskier than traditional feasibility or pivotal studies: the study is based on a smaller amount of nonclinical data than would normally be required for a larger study, there are potentially more unknown risks, and the chance of personal benefit is lower and should not be overestimated.
- Does the staff have a record of following protocol? EFS require regular follow-up assessments to monitor subject safety and device effectiveness at more frequent intervals than pivotal studies. These studies also require timely reporting of adverse events as they occur.

Useful Tools For Site Pre-selection

There are thousands of clinical research sites in the United States and it may be difficult to select one, especially if you are executing an EFS for the first time. Here are some resources available to build a list of 10 to 15 potential (pre-selected) sites for consideration.

Databases

[Sitetrove](https://citeline.com/products/sitetrove/) (https://citeline.com/products/sitetrove/) is a subscription service that tracks and maintains data on nearly 400,000 investigators and more than 100,000 clinical trial sites. It is useful for searching for investigators and sites by indication, access to specific

patient populations, and clinical trial experience. www.Clinicaltrials.gov is free and should not be overlooked as a key resource for understanding the caseload of a particular investigator or site. Disease foundations and associations may also have a searchable investigator and site directory.

CROs

CROs experienced in medical device and EFS studies will have a wealth of internal data on investigators and sites with whom they have previously worked. These data can include metrics on quality, startup timelines, and audit histories. From these data, CROs have likely built their shortlist of preferred sites. When choosing a CRO for feasibility work, it is important that the CRO not only has a device-specific feasibility department, but also documented experience in early feasibility medical device studies.

Your Own Due Diligence

The references provided above may be useful to you but the process may be overwhelming if you have to go through every site. Sites or investigators “speak” usually for themselves and leave a trail of records that you can access. So, you may want to use an intuitive approach based on “the records” of the site or investigator in the field of interest for your device. You can either ask several investigators you trust (i.e., no vested interest or conflict of interest with your EFS) to name a few investigators/sites in the field of your interest who would be suitable for your EFS. You can learn a lot through these informal interviews and conversations.

Another approach is to perform a literature search using The National Center for Biotechnology Information PubMed website (<http://www.ncbi.nlm.nih.gov/pubmed>). Use keywords that relate to feasibility studies and therapies used in the medical condition your device targets (or competitive devices such as yours). An investigator who has significant and published experience in the conduct of EFS in the field of your interest will bring considerable value to your program and will save you a lot of time, money, and effort. Facts and records matter in this space.

Selecting the Site

After you have obtained a pre-selection list of 10-15 sites, it would make sense to rank them in order of preference so you can approach your site in that order. You will

ultimately select one or two sites that you feel most comfortable with for your EFS, based on your “gut feeling.” However, it would be wise (and a good practice) to use some objective criteria to compare and rank the sites so the process is more rationally and less emotionally driven.

One way to do that is to use a weighted Pugh Matrix (Table 4). The Pugh-matrix template can be downloaded from the MDIC website under EFS section (Appendix 3). The technique is simple and uses a quantitative approach to rank different options (sites) based on multidimensional criteria (aspects that matter to you). The more important the criterion, the higher the weighting it should be given. You may use, for instance, an exponential scale for weights such as 1 (low/poor), 3 (medium/fair), or 9 (high/strong) to force the discrimination between the different criteria and options. Each of the sites will then be scored as well (1, 3, or 9 for each criterion), and the score will be multiplied by the weight. Each site obtains then a total that would be the sum of the products that the site scored for each criterion multiplied by the weight of that criterion.

Table 4: Pugh-Matrix Example for Site Pre-Selection

Site Pre-Selection			Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Site I	Site J
	Definition for criterion's score	Weight										
Investigator's expertise in the field	1=Poor, 3=Fair, 9=Strong (Elite)	9	3	9	9	9	1	9	9	3	9	9
Commitment of Investigator/Passion	1= None, 3= Dedicated, 9=Partner	9	3	9	9	1	9	1	3	3	1	3
Availability of the Investigator	1=Limited, 3=Fair, 9=Available when needed	9	9	9	9	1	9	1	9	3	1	3
Site's research staff	1=<=2 people, 3=3-4 people, 9=>5 people	1	9	3	1	9	1	3	9	3	1	3
IRB's experience with EFS	1= None/poor; 3= modest; 9= multiple reviews/year	3	1	3	3	9	1	9	9	3	1	9
Volume of procedure/month	1= <3/mo (low), 3=8-12/mo (medium), 9= > 12/mo (high)	3	9	3	9	9	1	1	3	3	3	3
Proximity of the site (travel time)	1= F>4hours (poor), 3= 2-4 hrs (fair), 9= <2 hours	3	9	1	9	9	9	3	3	9	3	1
Notoriety of the site	1=Limited, 3=Fair, 9=Prestigious (High)	1	9	1	1	9	1	3	9	3	9	9
Record for Site Start-up time	1=>6months; 3=4-6months; 9=<4months	3	1	9	9	1	9	3	9	3	9	1
Total Score			240	298	362	228	260	162	288	168	166	192
Ranking			5	2	1	6	4	10	3	8	9	7

For instance, it may be much more productive for you to work with an investigator from Site C (ranked #1), who has a proven expertise in the field, will commit to your device and mission, will be approachable and available, and can get the study started in a very short period of time although he has a limited research staff and comes from a site that has “no prestige,” instead of working with a very experienced investigator who comes

from a prestigious site with large research staff but has no time or particular commitment to your mission (Site D). The scores and weights are relative. Scores for each criterion are attributed based on what you believe is low (poor), medium (fair), or high (strong) for that criterion. The value given to each weight is relative on depends on what you would consider the least important (1), moderately important (3), or critically important (9) for your mission and EFS.

Please remember, the Pugh-Matrix process does not make the decision for you. It just helps provide a more objective display of subjective opinions and thoughts. Again, ultimately, you may still decide to go with Site D, for instance, for strategic business reasons, and that is your decision.

After developing the pre-selection list and ranking, it is time to contact sites in the order you chose to assess interest and suitability. Have the Investigator sign a Confidential Disclosure Agreement (CDA) before disclosing confidential information.

Investigator Q&A: Know Your Needs: Critical Criteria for an EFS Site

Run the investigator through the same set of questions posed in the earlier Investigator subsection (page 39). This can be a verbal or written exercise. Provide a copy or outline of the study protocol and ask the investigator to review it. Study the investigator's comments with a critical eye. Are they asking the types of questions that demonstrate expertise? Do they anticipate problems with a surgical procedure? Did they suggest a protocol modification that would make the transition to a pivotal study more seamless? Those are the investigators you want leading your study.

Investigators can be further vetted by asking for their comments on the device evaluation strategy—information required as part of an EFS IDE. Useful comments made regarding the device attributes, risk assessment for the procedure and device usage, potential failure modes, or clinical mitigation strategies likely demonstrate a thorough understanding of the device design and purpose.

Check the Facts and Records

In addition to assessing the suitability of the site via the investigator Q&A, be sure to perform a robust set of due diligence checks. Many red flags can be discovered via a

basic search of FDA compliance and medical license websites. If working with a CRO, have it query its Investigator database for a QA audit history.

A risk mitigation service such as World Check by Thomson Reuters can scan and aggregate publicly available information for violations of the U.S. Foreign Corrupt Practices Act, the 2010 UK Bribery Act, media coverage on significant fraud and malpractice, and any other information that suggests a risk of corrupt practices.

Pre-Study Visit

Once a site has been pre-qualified via the above processes, a CRA should perform a Pre-Study Visit (PSV) to inspect facilities, including supporting labs and pharmacies, to discuss the protocol, and to ensure all study requirements are met. Final selection of the site is confirmed following review of the PSV report and confirmation that it meets all criteria to conduct the study.

4.2.6.2 Metrics and SOPs

Custom effectiveness metrics are useful for screening sites and assessing preparedness for the study. To assess a site's potential for enrollment, perform a retrospective analysis that compares a site's anticipated recruitment rate to how the number of eligible patients who were actually recruited for that study over a given period of time. When possible, create metrics to evaluate timeliness and quality in your interactions with potential sites. For example, how long does it take for the investigator to sign and return the CDA and complete the Q&A? How long does it take the CRA to schedule and complete the PSV?

Internal metrics are useful for assessing the effectiveness of your company's site selection process. For example, how many sites respond to the initial contact? Of the sites that make the shortlist, how many met all the additional criteria (investigator Q&A, due diligence, PSV) to qualify for final selection? Poor performance may indicate the need to rethink certain aspects of your site selection strategy.

Excellence in site selection also requires preparedness on the part of the sponsors. The sponsor should create SOPs for adverse event reporting and device modifications (including an outline of those modifications requiring advance FDA approval), as well as EFS-specific consent forms and patient outcome assessments.

4.2.7 Support and Funding Opportunities Through the National Institutes of Health (NIH)

The mission of the NIH is to seek fundamental knowledge about the nature and behavior of living systems, and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. The NIH consists of 27 Institutes and Centers, each with their own mission and research agenda, which often focus on particular diseases or body systems. At any given point in time, Institutes or Centers may have their own active Funding Opportunity Announcements (FOAs) to promote device translational research, or participate in multi-Institute trans-NIH announcements to foster translational device research. Quick links to the individual website for each of 27 Institutes and Centers are available at <http://www.nih.gov/institutes-nih/>.

Another resource for those interested in obtaining NIH funding for a translational device project is NIH Reporter, which can be found at <http://projectreporter.nih.gov/reporter.cfm>. NIH Reporter is a public database, which can be searched to identify currently funded NIH research by investigator, organization, or topic area. Information provided by the database includes an abstract of the funded work, NIH Institute or Center supporting the work, and a link to the FOA under which the work was submitted. This is not only a useful tool for identifying appropriate funding mechanisms for your project, but is a resource to research what relevant projects are being actively pursued in your topic area prior to this research being published. This information can be critical for placing an applicant's idea in terms of the current state-of-the art, which is important for formulating a credible grant application for peer review.

There are several FOAs that are appropriate for funding the nonclinical testing necessary to enable an FDA Investigational Device Exemption for an EFS or traditional feasibility study, and the subsequent clinical study. Many NIH Institutes and Centers continue to support these endeavors through the Bioengineering Research Grants (set to be re-issued, see: <http://grants.nih.gov/grants/guide/notice-files/NOT-EB-16-001.html>) and Bioengineering Research Partnerships (see: <http://grants.nih.gov/grants/guide/pa-files/PAR-16-116.html>). Individual NIH Institute/Center websites include currently active FOAs, as well as contact information for Program Staff. Potential applicants are encouraged to reach out to NIH Program Staff prior to submission of an application to

discuss project goals and identify the most appropriate funding mechanism or program, as Institutes and Centers may vary significantly.

Of particular note for EFS are 3 unique NIH Programs. The first is the National Institute for Neurological Disorders and Strokes (NINDS) Cooperative Research to Enable and Advance Translational Enterprises (CREATE) Devices Program, launched in July 2014 (http://www.ninds.nih.gov/funding/areas/translational_research/CREATE-Devices.htm), and consisting of multiple FOAs relevant to specific device regulatory paths. This program includes 2 FOAs, PAR-14-297 and PAR-14-300, tailored specifically to support early feasibility “style” studies for therapeutic devices to treat neurological disorders. The latter announcement is part of the congressionally mandated NIH program to support research and development conducted by small businesses.

The second relevant Program is part of the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative (see <http://braininitiative.nih.gov/> for details), and consists of 2 FOAs, RFA 15-006 (<http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-15-006.html>) and RFA 15-008 (<http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-15-008.html>), to support translational and clinical studies for recording and/or stimulating devices to treat nervous system disorders and better understand the human brain. These FOAs were developed with feedback from the FDA and are also intended to support early feasibility “style” studies.

Finally, the NIH Common Fund’s Stimulating Peripheral Activity to Relieve Conditions (SPARC) program (see <https://commonfund.nih.gov/sparc/> for more details) supports translational studies through RFA-RM-16-009 (<http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-16-009.html>) for testing existing neuromodulation devices in support of new market indications. While this FOA is focused specifically on nonclinical studies to enable IDE submission, future FOAs will support follow-up pilot clinical studies.

The NIH recognizes that the leap from animal studies to humans is large, and initial clinical studies are often necessary to address critical scientific questions about the function of a device in human patients and/or inform a final device design suitable for eventual FDA market approval. Initial demonstrations of novel device function in humans have become increasingly required to encourage the industry and venture capital investment necessary to develop a final safe, reliable, and efficacious device that can be

manufactured at scale suitable for regulatory approval, yet at a price point sufficient for sustainable commercial market given insurance reimbursement.

4.2.8 Perspectives From a Patient Advocacy Group

As device companies are planning to begin EFS, it is important to consider cultivating relationships with the patient advocacy organizations relevant to their clinical area of interest. Informing, listening, and potentially collaborating with these groups at an early stage in the clinical trials process can be invaluable; whereas not seeking their input may be risky, particularly with respect to patient recruitment for clinical trials and ultimate clinical adoption of new technology.

The relationship between device companies and patient advocacy groups can be mutually beneficial. There are several ways in which device companies can and should engage with patient advocacy groups. These include the following:

- Brief advocacy groups on their technology/research so that these groups are prepared to manage patient/caregiver inquiries
- Provide group leadership (or larger “focus groups” from their network of patients) with the opportunity to review study design, enrollment criteria, etc.; for example, an aspect of the trial design may hamper patient recruitment, and if this is identified early, it may be able to be altered
- Help support patient group education and outreach through donation of funds or other in-kind measures
- Invite advocates to meet with executives to provide personal perspective/insight on patient needs; they may even have ideas for new products/enhancements

In turn, once the relationship is established, patient advocacy groups can provide many levels of support for device companies, particularly in patient recruitment efforts and awareness building that is critical for the ultimate widespread clinical adoption of their new technology and treatments.

- Provide access to patients to gauge their input during trial design (e.g., focus groups)
- Educate patients about new technologies on the horizon

- Promote clinical trial information to their network of patients via website, newsletter, email, webinars, information sessions with physicians, local support group meetings, etc. (e.g., it is useful to have key opinion leaders available at local chapters of patient support organizations so they can answer questions about the procedure)
- Encourage patients to enter clinical trials; communicate the importance of EFS to increased patient access to new and potentially better treatments
- Promote clinical trials finder; many organizations have this on their website (e.g., [Fox Trial Finder](#))
- As early studies are completed, they can help raise awareness of the results published/presented at conferences and perhaps help in raising funds for promising approaches

When engaging patient advocacy organizations, it is important to understand the rules and regulations concerning study promotion to patients. All promotional or educational materials given to patient advocacy groups, for dissemination to their network of patients, are under the same scrutiny as those used for general advertisement of the clinical trial. Promotional materials cannot make non-FDA-approved claims about the procedure. Materials mentioning trials at specific sites will need IRB approval from those institutions.

While there might be anticipated benefits with the new device being tested, especially in patients with limited or no alternative therapeutic options, these potential benefits cannot be overstated. As per CDRH website, “advertisements should be reviewed and approved by the IRB to assure that they are not unduly coercive and do not promise a certainty of cure beyond what is outlined in the consent and the protocol. No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device. FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection processes.” This includes flyers, website information, or other promotional material disseminated to patients by patient advocacy groups. More details on these guidelines can be found in the following:

["IRB Information Sheets - Recruiting for Study Subjects"](#).

[Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects](#)

5. Conclusion

Considerable efforts have been invested from government, patient advocacy groups, industry, and other stakeholders to reverse the current trends and bring back the EFS to the United States so U.S. patients and investigators benefit from early access to novel technologies. This Blueprint report was written by volunteers of the MDIC EFS Working Group to help those interested in device development advance the program of EFS in the United States. We hope the information included in this report was useful and insightful to you. Remember, an effective good EFS should provide you with sufficient information to pursue your path to market and hopefully offer this technology to many patients soon. So, maximize your learning experience and have fun while doing so. It is a unique opportunity and a memorable experience.

6. Appendices

1. Informed consent template
2. Study site contract template
3. Pugh-Matrix for site pre-selection