U.S. FDA Investigational Device Exemptions

EMERGO
by UL

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Introduction

The U.S. Food and Drug Administration (FDA) requires evidence that a medical device is safe and either performs as intended (and therefore is likely to be effective) or is effective for its intended use. For some devices, only non-clinical data is necessary, but for other devices, clinical data must be included. Clinical data is required for approximately 5%-15% of premarket notifications (often referred to as 510(k)s), the vast majority of de novo submissions and all premarket applications (PMA) and humanitarian device exemption (HDE) submissions.

Requirements for clinical trials are primarily covered in 21 Code of Federal Regulations (CFR) §812, but certain requirements are covered in 21 CFR §50 (informed consent), §54 (financial disclosure), and §56 (institutional review boards [IRBs]).

Determining if a clinical trial requires submitting an investigational device exemption

If a company determines that clinical testing is necessary to support the safety and/or effectiveness of their device in order to place it on the U.S. market, before they start the trial, they must determine if the study would be considered exempt, nonsignificant risk or significant risk. For nonsignificant risk and significant risk trials, this must be confirmed by the appropriate Institutional Review Board (IRB), and IRB confirmation should be considered even for exempt trials. The appropriate actions depend on this determination.

The company should make an initial draft, or at least an outline, of their clinical trial. Then they should consider an initial evaluation in alignment with 21 CFR §812 and FDA guidance "Significant Risk and Nonsignificant Risk Medical Device Studies" to determine if the trial represents a significant risk, nonsignificant risk or exempt clinical trial.

- Significant risk trials are described in 21 CFR §812.3(m), which can be summarized as a trial that presents the potential for serious risk to the health, safety or welfare of a subject, including implants, life-supporting or life-sustaining devices, or devices of substantial importance in diagnosing, curing, mitigating, treating or preventing disease or impairment of human health. Significant risk trials must abide by all requirements provided in 21 CFR §812, including the submission and approval of an investigational device exemption (IDE), which allows a device, which is not cleared or approved for human use in general conditions to be distributed for use in a clinical trial.
- Exempt clinical trials are described in 21 CFR §812.2(c), which can be summarized as those that are not being conducted to determine safety or effectiveness for human use (such as testing for consumer preference only) or are for diagnostic devices that are noninvasive, do not require an invasive sampling procedure, do not introduce energy to the subject and is used with confirmation of the diagnosis by a medically established product or procedure.
- Nonsignificant risk clinical trials are those trials that don't meet the definitions of either a significant risk trial or an exempt trial. These trials are subject to abbreviated requirements, as described in 21 CFR §812.2(b). There is no need to submit to the FDA or to gain approval, but the FDA has the right to review documentation during inspections.

The guidance provides partial lists of devices for which a clinical trial would generally be considered to be nonsignificant risk and for which the clinical trial would generally be considered to represent a significant risk. This does not cover all established generic categories of medical devices and devices that require a de novo submission generally do not fit into an established generic category.

If there remains uncertainty regarding whether the clinical trial should be considered a significant risk or nonsignificant risk, a Study Risk Determination Q-Submission may be requested from the FDA. For additional details, please refer to Emergo's white paper "Early Communication with the FDA" and the FDA's guidance document "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

This white paper focuses on the IDE, which must be submitted and approved before beginning a significant risk clinical trial. For additional information related to clinical data in general, please refer to the White Paper "Clinical Data in Support of U.S. FDA 510(k) Submissions."

It is also important to note that a clinical trial is part of the design controls for a medical device. As such, it should be conducted in alignment with design controls within the company's quality management system. Additionally, documentation regarding evaluations, decisions and other information must be maintained.

Designing the clinical trial

When a company determines that its device requires one or more clinical studies, first, it should draft protocols for those studies. Two clinical trial types should be considered for a medical device: a pilot or feasibility study and a pivotal study. In many cases, both trial types are required for a device that will require a PMA or a de novo submission and will be done in sequence with the pilot/feasibility study first followed by the pivotal study. In many cases, only a single study will be required to support a 510(k) submission. Note that these are only generalities and do not apply in all cases. Careful consideration should be given to determining if one or both types of trials should be included for any specific device and should be conducted in alignment with any device-specific guidance documents, which are beyond the scope of this white paper.

A pilot or feasibility study is generally relatively small (usually less than 100 patients/samples) and is primarily focused on safety, although effectiveness is also usually evaluated. Generally, these studies are not statistically powered. They may be used to support 510(k)s submission on their own. Additionally, they are used to provide support that the device is likely to be safe and that a pivotal study may be conducted for PMAs and de novo submissions.

A pivotal study is larger (generally more than 250 patients/samples), is focused on both safety and effectiveness and is statistically powered.

When developing a clinical trial protocol, the company should consider general FDA guidance on clinical trial design.

The FDA offers guidance on:

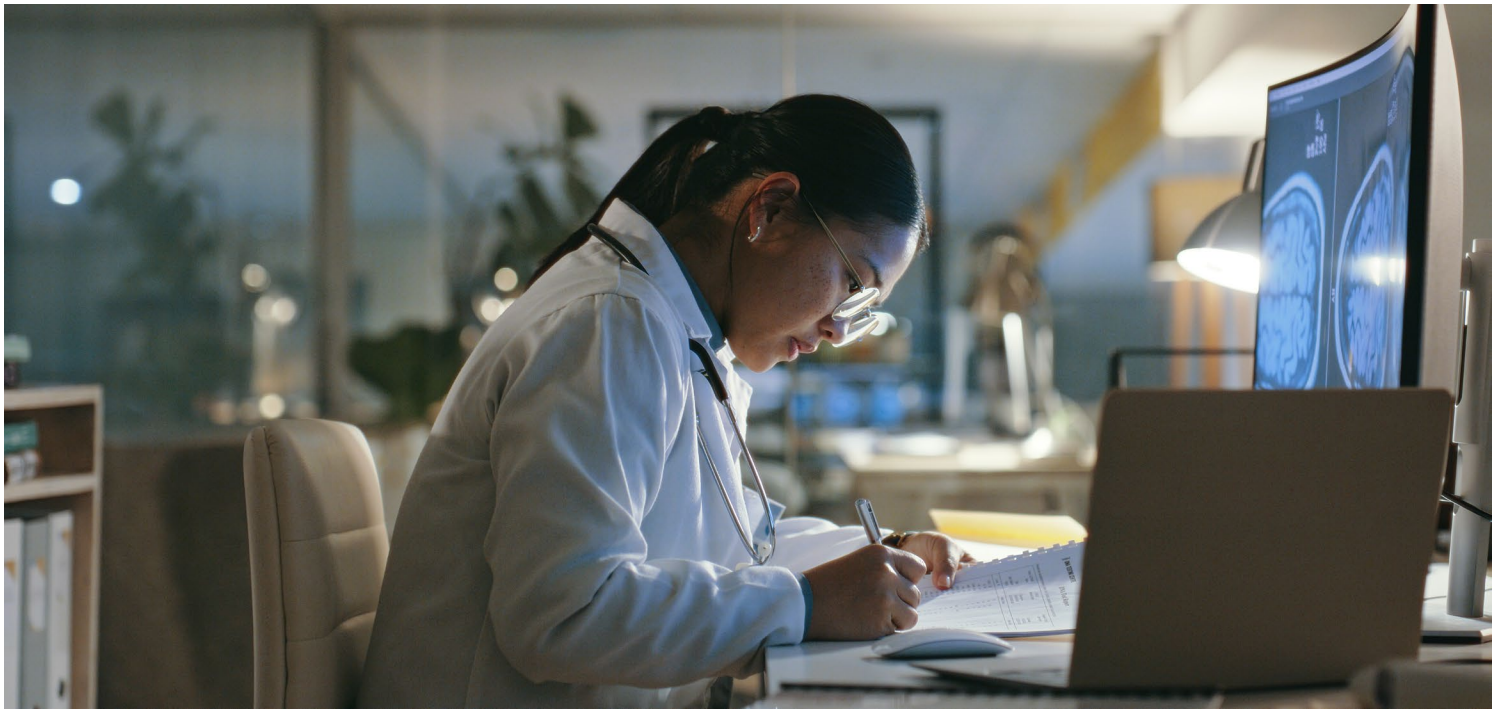
- **Collection** and **evaluation** of demographic information
- **Patient-reported outcomes**
- **Design considerations for pivotal clinical studies**
- **Statistical evaluation**
- **Informed consent**
- **Clinical trial oversight**
- **Clinical trial monitoring**
- **Use of electronic data**
- Responsibilities of **investigators, sponsors and IRBs**
- **Adaptive clinical trial design**

Additionally, for some specific device types, the FDA offers further guidance. The company should review current FDA guidance documents to determine if there is guidance specific to their device type.

Recommended: Ensuring the clinical trial design is sufficient

When the FDA is evaluating an IDE, they are only evaluating it from the standpoint of if there is sufficient data to justify that the benefits likely outweigh the risks for the trial and that there are adequate human subject protection measures in place. During IDE review, the FDA does not evaluate if the clinical trial design will be sufficient to enable a successful marketing application.

Therefore, although not a requirement, both the FDA and Emergo by UL recommend a Q-submission with the FDA to align on the clinical trial protocol(s) and if it will be sufficient, assuming adequate results, to support the marketing submission (510(k), de novo, PMA, etc.). In particular, confirming that the numbers, the inclusion/exclusion criteria, the control, the acceptance criteria and the statistical analysis plan are critical to supporting the ultimate success of the marketing submission. A Q-submission may also be used to confirm if the nonclinical testing plan and risk analysis with mitigations will be sufficient to support the IDE. For additional details, please refer to Emergo's white paper **"Early Communication with the FDA"** and the FDA's guidance document **"Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program"**.



IDE overview

In alignment with 21 CFR §812, an IDE must be submitted to the FDA and approved prior to the enrollment of any patients in a significant-risk clinical study. The FDA has 30 calendar days to review an IDE from receipt, and may choose to approve, approve with conditions, or disapprove the study. If no decision is made at 30 days, the clinical trial can be considered to be approved, but it is best practice to confirm with the FDA before moving forward. After approval, periodic reports and a final report, as applicable, are required. In many cases, progress reports are required annually, and in cases of a clinical trial that lasts less than a year, only a final report may be necessary. Additional reports, as described in more detail later, may also be required.

Compiling and submitting an IDE

The primary sets of information that the FDA wants to review in an IDE are:

1. Basic description and similar information related to the device and its intended use
2. What is already known about the safety, effectiveness, and performance of the device
3. The details on the proposed clinical study

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The basic description and similar information include a description of the device itself, risk analysis with mitigations related to the device, basic manufacturing information and proposed labeling, including the instructions for use (IFU). This also includes a discussion of any prior interactions with the FDA regarding this device, such as any applicable Q-submissions.

2

For what is already known in relationship to the device, this needs to include a summary of all relevant information, published and unpublished, related to the safety, effectiveness and performance of the device. This generally includes bench/laboratory testing at a minimum. In many cases, it includes animal testing. It may also include market experience in other markets or other previous clinical experience, as relevant.

3

The details on the proposed clinical study include:

- The purpose of the proposed investigation
- The clinical protocol
- Intended monitoring procedures
- Any records or reports that will be collected during the investigation
- An example of the agreement to be signed by clinical investigators
- A list and any clinical investigators that have signed to be part of the clinical trial and their curriculum vitae
- Certification that all investigators have or will sign the agreement before being added to the study
- Information regarding the IRBs that have, are, or will review the trial
- Clinical trial site information
- Any amount that will be charged for the device and, if relevant, why charging does not constitute commercialization
- Informed consent form

The FDA provides a **webpage** with questions that must be answered to allow the IDE to be accepted for review by the FDA. We at Emergo recommend providing this completed checklist, along with references where in the submission to find that information, when submitting an IDE to maximize the chance that the IDE will be accepted for review the first time it is submitted. If the FDA does not believe that the information is complete, they may issue a refuse-to-accept (RTA) decision requiring additional information before starting their detailed review.

Responding to FDA questions

During the review process, the FDA may send an additional information (AI) request. In general, AIs during an IDE are relatively minor. If there is a major concern, the FDA will generally either issue an RTA or a disapproved decision.

Because of their limited review timeframe, the FDA generally expects a response to any AI request within a very short timeframe, such as two to three days, as communicated in the request. If responses are not received on time, in general, the study will be disapproved. Therefore, it is important to be ready to respond to questions at any time during the 30-day review period.

Possible FDA decisions

At the conclusion of their review, the FDA may issue one of three decisions:

Approved

If the submission is approved, the sponsor may begin to enroll subjects as soon as the appropriate IRB(s) have approved the study and clinical investigator(s) have signed the agreement. In some cases, the FDA may suggest modifications to improve the study and/or to ensure that the study will be adequate to support a future marketing application. If this happens, the sponsor should consider this feedback.

Approved with conditions/staged approval

If the submission is approved with conditions, that means that the FDA does not have immediate concerns with the safety of at least a portion of the trial, but does believe that something needs to be addressed. Therefore, the sponsor may begin to enroll subjects for at least the portion as outlined as appropriate in the FDA response as soon as the appropriate IRB(s) have approved the study and clinical investigator(s) have signed the agreement. In addition, the sponsor must respond to the FDA within 45 days, unless an extension is granted. The FDA will respond with approval, approved with conditions or by placing the study on hold (which would require that there be no additional patient enrollment and the submission of a new IDE). Some sponsors may wish to work out the conditions before starting enrollment to avoid the possibility of a study being placed on hold.

Disapproved

If the submission is disapproved that means that the FDA believes that there is at least one deficiency in relation to the safety of the trial or that they do not have enough information to adequately evaluate the safety of the trial. If a disapproval is received, the sponsor may still answer those deficiencies but may not begin enrollment in the trial. Alternatively, if the sponsor does not feel this is appropriate, they can request a regulatory hearing, but this is rarely the easiest or best pathway forward and therefore should be considered carefully. It is not required to respond to a disapproval, but the trial cannot proceed with a disapproval. A response will be reviewed again and a new FDA decision will be made.

It is also possible that the FDA does not respond within 30 days.

If the FDA does not respond within 30 days, then per the regulation, the IDE can officially be considered to be approved. However, it is best practice, and highly recommended, to wait until official approval from the FDA is received. It is appropriate to reach out to the FDA and check on the submission if 30 days has passed with no interaction or notification to obtain this official decision.

An overview of the IDE submission and review process is provided in the following figure 1.

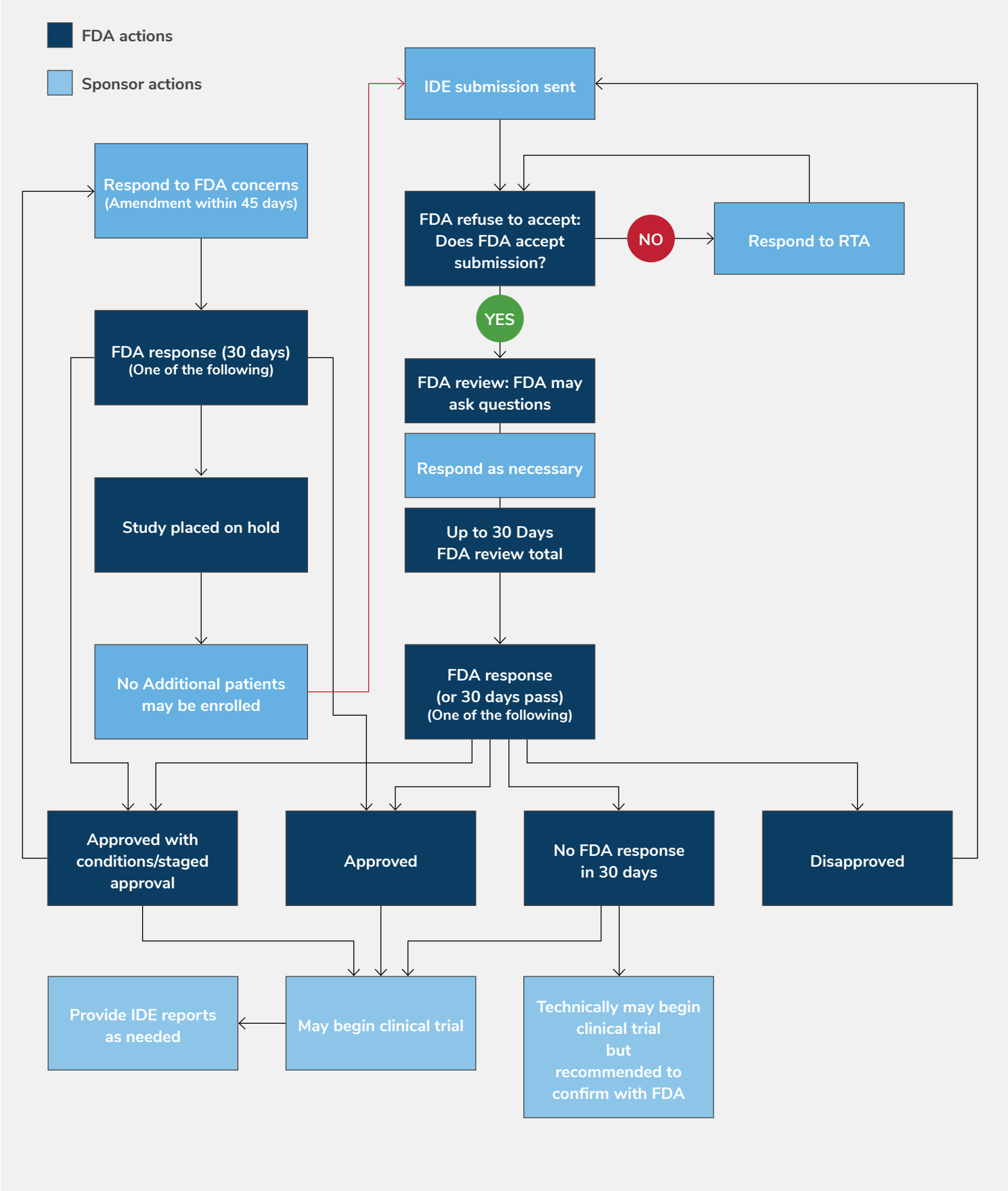

Figure 1: Overview of IDE submission and review process Source: Emergo

Registration with clinicaltrials.gov

Most clinical trials that require IDEs must also be registered on clinicaltrials.gov in alignment with 42 CFR §11. Exceptions include small trials intended only to determine feasibility and clinical trials that are intended to take place only outside of the U.S. For applicable trials, yearly updates must be made to clinicaltrials.gov and a final results submission no later than one year after the primary completion date. If there are significant changes, including in expected completion time, additional updates may be necessary, although these can sometimes be included in the annual updates.

Continued requirements related to an IDE

It is important to note that there are continued expectations after an IDE is approved.

First, any changes to the clinical trial need to be carefully evaluated. With the exception of minuscule changes (such as correction of typos), changes generally must be submitted to the FDA in a supplement to the IDE and must be approved by the FDA before implementation. This includes changes that are recommended by the FDA.

Second, the FDA requires reports for various situations and at various periodic times throughout the clinical trial.

The reports that are applicable to most reports include:

- Annual reports, also known as progress reports, regarding the current IDE trial status and any changes that have been made but have not been otherwise submitted to the FDA.
- Biannual investigator, site, and IRB information reports, providing current information.
  - Note that many companies include these in the annual reports instead of providing them separately.
- Completion of enrollment
- Completion of the study, including all follow-ups
- Final IDE report

Additional reports may be required depending on circumstances that arise during the course of the clinical investigation, including:

- Any failure to obtain informed consent
- Any emergency use of the device outside of the parameters of the trial
- Any compassionate use or live case use
- Any unanticipated adverse device effects

In alignment with 21 CFR §812.140, accurate and complete records relating to the clinical trial and the IDE must be maintained.

Conclusion

The U.S. FDA requires evidence that a medical device is safe and either performs as intended or is effective for its intended use. In some cases, one or more clinical trials are necessary to provide the evidence the FDA needs to make this determination and allow the device to reach the U.S. market.

Clinical trials can be divided into three types with different FDA requirements: significant risk, nonsignificant risk and exempt. In all cases, appropriate clinical trial design and documentation are critical, and it is recommended to engage with the FDA in a Q-submission meeting to address any potential FDA concerns before beginning the study to ensure that the clinical trial, when completed, can successfully be used to support the applicable marketing application.

For a significant risk clinical trial, an IDE must be submitted to the FDA and approved before the clinical trial can begin. Once an IDE has been approved or approved with conditions, enrollment may begin as soon as the appropriate IRB(s) have approved the study and clinical investigator(s) have signed the agreement. Most clinical trials must also be registered on clinicaltrials.gov. There are continued requirements related to IDEs and registration on clinicaltrials.gov, including annual reports and final reports.

About the author

Sarah Marie Fitzgerald leads U.S. regulatory services at Emergo by UL. She has 20 years of experience in medical device regulatory and quality affairs, primarily in the U.S. Fitzgerald has worked with a wide variety of medical devices and other regulated products. Her background covers global regulatory strategy, product support from concept to obsolescence, regulatory premarket submissions, product regulatory due diligence assessments, advertising and promotional support, auditing, and quality management system implementation and improvement. Fitzgerald is a member of the Regulatory Affairs Professional Society (RAPS), maintains a U.S. Regulatory Affairs Certification (RAC), and has a Master of Science in Regulatory Affairs.

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