A company seeks to market a significant-risk investigational device.

THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS: WHEN IS AN IDE THE RIGHT CHOICE?

This fictionalized case study is the eighth in an educational series published by the U.S. Food and Drug Administration.

“Good morning, everyone,” Dr. Regie Cahn greeted his colleagues as he entered the conference room of CranialCare, LLC. The two newest employees, Mesa Lawsom, a veteran attorney specializing in medical device regulations, and Erin Clinette, a medical device clinical trials expert, greeted him warmly. The fourth meeting attendee settled for a wave followed by a yawn.

“Nice to see you out of the lab, Stacia,” Cahn chuckled as he took the seat beside his business partner and co-founder of CranialCare, Dr. Stacia Laup.

“As much as I love the lab, it is nice to be out of it for a few hours,” Laup responded. She picked up the mug in front of her and took a sip of strong black coffee, a tired, but content, smile on her face. “Putting my fatigue aside, we just finished the initial bench tests for the Crania-Deep prototype, and the results are looking very good!”

Laup was referring to CranialCare’s newest invention, a deep brain stimulation (DBS) device designed to safely stimulate target areas in the brain to improve symptoms of Parkinson’s disease (PD). (Exhibit 1)

Laup, a biomedical engineer specializing in magnetic and electrical stimulation, had lost her father to PD a few years ago. Motivated to find better ways to help those suffering with PD, she co-founded CranialCare with the help of Dr. Regie Cahn, a regulatory specialist with a Ph.D. in regulatory science and an MBA degree.

Since market research for the DailyStim, their first device invention to treat tremors in PD patients, gave promising results, Laup and Cahn had been able to expand the team at CranialCare and further their mission to develop device-based treatment approaches for PD. The purpose of this meeting was to discuss marketing pathways for their new device, Crania-Deep.

“That’s great news!” Cahn responded. “We timed this meeting perfectly. Mesa and Erin, do you want to begin walking us through the first steps of developing a roadmap to introduce Crania-Deep to the market?”

“Absolutely,” Lawsom responded. “But before we begin, could you explain the technological characteristics of Crania-Deep and how it works, Dr. Laup?”

“Sure, I’ll walk you through it,” Laup responded.

A High-risk Deep Brain Stimulation Device to Treat PD

“Deep brain stimulation, or DBS, stimulates certain target areas in the brain to improve PD symptoms without destroying the specific brain target,” Laup began. “The implantable portion of a DBS system consists of three components:

1. An electrode surgically implanted in the thalamus, the globus pallidus, or the subthalamic nucleus of the brain;
2. An implanted pulse generator (IPG) placed below the collarbone and the skin of the chest; and
3. Leads and extension wires that connect the electrodes to the IPG.

1National Institute of Neurological Disorders and Stroke: Deep Brain Stimulation for Parkinson's Disease Information Page
THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS:
WHEN IS AN IDE THE RIGHT CHOICE? CONTINUED

Exhibit 1: Parkinson’s Disease

Parkinson’s disease (PD) is a progressive disorder of the nervous system that results in the loss of dopamine-producing brain cells. It is estimated that PD affects up to 1 million people in the United States, and doctors diagnose as many as 60,000 new cases each year. The exact cause of PD has not been established, but environmental and genetic factors appear to play a role.5

British physician James Parkinson first described the disease as “the shaking palsy” in a paper in 1817.4 While tremors may be the most commonly known symptom of PD, others include rigidity (stiffness of the limbs and trunk), bradykinesia (slowness of movement), and postural instability (impaired balance and coordination). Many of these symptoms are due to loss of neurons in the brain that produce the chemical messenger dopamine. When dopamine levels decrease, it causes abnormal brain activity, leading to signs of PD.5 The signs and symptoms of PD vary greatly from person to person, and while there are treatment options that can improve the symptoms of PD, there is no cure for this disease.6

Medication is currently the most widely used method for PD treatment. One approach to medication attempts to increase the levels of dopamine in the brain.7 PD medication works very well for many when they start taking it, but over time side effects may develop and/or medication may become ineffective.8 One device-based approach to improve PD symptoms when medications are not sufficiently effective involves implanting a deep brain stimulator (DBS) to regulate certain regions of the brain.9

“Once activated, the IPG sends continuous electrical pulses to the target areas where the electrodes are implanted, and the stimulation blocks the electrical impulses in the brain that cause tremors in PD patients. Patients receive equipment they can use externally to turn the IPG on or off.2 DBS of the subthalamic nucleus and globus pallidus is effective for treating many symptoms of advanced PD, including tremors, slowness of movement, rigidity, and problems with walking and balance3,4,5 and DBS of the thalamus is effective for upper extremity Parkinsonian tremor. Our device stimulates the corpus striatum (CS), which experiences loss of dopaminergic innervation when affected by PD.”

“Thank you for explaining that, Dr. Laup,” Lawsom said. “Based on your description, I believe Crania-Deep might be a high-risk, Class III device. We’ll confirm if that’s the case shortly, but why don’t we begin our pathway assessment for Crania-Deep by looking at FDA’s five-step approach for marketing medical devices?” Hooking up her laptop to a projector screen, Lawsom pulled up a page on FDA’s website called “How To Study and Market Your Device.”

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1Florida Hospital: Statistics of Parkinson’s Disease
2Mayo Clinic: Parkinson’s Disease Causes
3WebMD: Parkinson’s Disease Health Center—What Causes Parkinson’s Disease?
4NIH Senior Health: What is Parkinson’s Disease?
5Mayo Clinic: Parkinson’s Disease—Definition
6Mayo Clinic: Treatment and Drugs
7WebMD: Drug Treatment for Parkinson’s Disease
8Parkinson’s UK: Side Effects of Parkinson’s Drugs
9WebMD: Is Deep Brain Stimulation Experimental?

2WebMD: Deep Brain Stimulation for Parkinson’s Disease
http://www.webmd.com/parkinsons-disease/guide/deep-brain-stimulation
Introducing Crania-Deep to the Market

“As you can see,” Lawsom nodded towards the screen, “there are five basic steps we will follow to get Crania-Deep to market:

- **Step One:** Classify Your Device
- **Step Two:** Choose the Correct Premarket Submission Type
- **Step Three:** Prepare the Appropriate Information for Your Premarket Submission to the FDA
- **Step Four:** Send Your Premarket Submission to the FDA and be Available to Interact with FDA Staff during Review
- **Step Five:** Complete the Establishment Registration and Device Listing

“Our first step is to identify the Federal regulation that classifies Crania-Deep, and then we’ll need to identify the premarket submission type required for that regulation. To identify the classification regulation, let’s look at FDA’s medical device classification database and search for a general term related to Crania-Deep or the disease or condition it is meant to treat.”

“Since the purpose of Crania-Deep is to treat PD,” Clinette spoke up, “could we try a simple search for ‘Parkinson’ on the database?”

“Good idea,” Lawsom responded. She typed “Parkinson” into the search field and pressed enter. The group took a few seconds to read through the query result.

“This product classification on the database sounds just like ours!” Laup said excitedly. She read out loud, “‘Product code NHL. Class III, implanted, electrical stimulator device for Parkinson’s.’ So what does this mean for us?”

“The class your device is assigned to determines, among other things, the type of premarket submission required for FDA approval and clearance to market,” Lawsom responded. “Device classification depends on the intended use and indications for use (IFU) of the device, as well as the risk the device poses to the user. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.”

“Why does this sound so familiar?” Laup looked at Cahn.

“Because we went through it before with the DailyStim,” Cahn replied. Looking at the result he said, “This product classification seems like the best match for Crania-Deep in terms of the technology used and the indications for use. Do you know of any devices currently on the market that fit into this classification?”

“No, but we can look into it and let you know if we find anything this afternoon,” Lawsom replied. The group ended the meeting after scheduling a time to talk later in the day.

Narrowing in on the Premarket Approach for Crania-Deep

In the afternoon, the CranialCare regulatory team regrouped to share their findings with Laup and Cahn. After displaying a comparison table on the projector screen, Lawsom began.

“Erin and I did some research and pulled together a quick comparison of key aspects of Crania-Deep and a comparable device we found in the FDA database that is already in the market, the Activa Parkinson’s Control System.” (Table 1)

“Because Activa was approved under a Class III regulation, and that device has the same technological characteristics and a similar IFU to Crania-Deep, I can say with certainty that we have a high-risk device that needs Premarket Approval (PMA),” the attorney announced.

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“That means we’ve completed Step 2 on the pathway to market, Choose the Correct Premarket Submission, and that we’re ready to move on to Step 3—Prepare the Appropriate
THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS: WHEN IS AN IDE THE RIGHT CHOICE? CONTINUED

Table 1. Comparison of Crania-Deep with Activa

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Activa Parkinson’s Control System</th>
<th>Crania-Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Medtronic, Inc.</td>
<td>CranialCare, LLC</td>
</tr>
<tr>
<td>Submission Number</td>
<td>P960009/S7</td>
<td>–</td>
</tr>
<tr>
<td>Product Code</td>
<td>NHL</td>
<td>–</td>
</tr>
<tr>
<td>Classification</td>
<td>Class III</td>
<td>–</td>
</tr>
<tr>
<td>Indication for Use</td>
<td>For bilateral stimulation of the internal globus pallidus or the subthalamic nucleus as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled with medication.</td>
<td>For bilateral stimulation of the corpus striatum (CS) as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled with medication.</td>
</tr>
<tr>
<td>Technological Characteristics</td>
<td>Uses an implantable neurostimulator to deliver electrical stimulation to the internal globus pallidus (GPI) or subthalamic nucleus (STN) of the brain. The device consists of the following implanted components: a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. External components include a physician programmer.</td>
<td>Uses an implantable neurostimulator to deliver electrical stimulation to the CS of the brain. The device consists of the following implanted components: a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. External components include a physician programmer.</td>
</tr>
</tbody>
</table>

Information for your Premarket Submission to the FDA.

“Great job, team!” said Laup.

“Thanks, Stacia,” Clinette smiled, “but this is where the real work begins. To prepare for the PMA, we have to develop an investigational plan to generate data that proves the safety and effectiveness of Crania-Deep. Given the nature of this device, we’ll need more than the findings of nonclinical bench and animal testing to demonstrate to FDA that it’s safe. We’ll have to conduct clinical investigations with human patients.”

“That’s right,” Lawsom chimed in. “And since Crania-Deep is still an investigational device and has not been approved for use on patients, we’ll need to obtain an investigational device exemption (IDE) before we can conduct any clinical trials.”

Investigational Device Exemption

Seeing that his business partner looked a little lost, Cahn turned to Lawsom. “Mesa, could you give us a little overview of what an IDE is and what all it entails?”

“Sure. I’ll start by explaining the main aspects of an IDE application that are relevant to us, and then Erin and I will briefly discuss key points about how this will relate to your clinical study plan.”

“Perfect,” Laup said, relieved.
THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS: WHEN IS AN IDE THE RIGHT CHOICE? CONTINUED

“The purpose of an IDE is to encourage discovery and development of medical devices for human use that are consistent with standards created to protect the public health and safety of the population, while maintaining optimum freedom for investigators as they pursue these discoveries. Thus, as defined in the Code of Federal Regulations (CFR) Title 21, Section 812.1, an IDE is a regulatory submission that allows an investigational device to be used in a clinical study with the purpose of collecting safety and effectiveness data. These data are also required to support a marketing application (for example, a Premarket Approval [PMA], Humanitarian Device Exemption [HDE] submission, or a Premarket Notification [510(k)]]) by exempting the device from a number of regulatory requirements. Additionally, an IDE:

- Exempts sponsors from the Quality System (QS) Regulation, except for the requirements for design controls. (21 CFR § 820.30)

“...Continue...
a type of Q-submission\textsuperscript{11, 12} called a Study Risk Determination. Once FDA has made a determination, the IRB will not need to conduct an independent assessment of risk, as FDA’s determination is final.”

What to Include in Your IDE Submission

“Now I think we should review what material FDA expects to see in your IDE application,” Lawsom said as she passed around a list to the group (Appendix A). “Besides your contact information, FDA will be looking for:

- A report of prior investigations, including the bench and animal testing you have already performed;
- Your clinical investigational plan, which Clinica will help you prepare;
- A description of your manufacturing and processing methods and facilities;
- Information concerning your study’s investigators and the study site;
- Information about your IRB; and

Examples of your investigator agreements, informed consent forms, and device labeling.

“As we prepare and package these items, we can refer to the FDA website for tips on formatting our submission, common problems with IDE applications to avoid, and checklists to ensure our IDE submission is complete.”\textsuperscript{13}

Lawsom looked at the clock. “I think we’ve gone through enough for today. Erin, is it alright if we go over the plan for the clinical study tomorrow?” After receiving an affirmative nod, Lawsom ended the meeting.

Designing the IDE Clinical Study

The group convened the following day. “Now that we better understand what type of information we need to include in our IDE application,” Clinette began, “let’s talk about the plan for our IDE clinical study.

“First, I want to point out that as with any clinical investigation, our IDE study must be conducted\textsuperscript{13}.

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\textsuperscript{11} Early Collaboration Meetings Under the FDA Modernization Act (FDAMA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm

\textsuperscript{12} Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

\textsuperscript{13} How to Study and Market your Device: IDE Application http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm
THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS: WHEN IS AN IDE THE RIGHT CHOICE? CONTINUED

Table 2. Primary 21 CFR Regulations Governing the Conduct of Clinical Studies

<table>
<thead>
<tr>
<th>Investigational Device Exemptions</th>
<th>Protection of Human Subjects</th>
<th>Institutional Review Boards</th>
<th>Financial Disclosure by Clinical Investigators</th>
<th>Design Controls of the Quality System Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.</td>
<td>Provides the requirements and general elements of informed consent.</td>
<td>Covers the procedures and responsibilities for IRBs reviewing clinical investigations protocols.</td>
<td>Covers the disclosure of financial compensation to clinical investigators, which is part of FDAs assessment of the reliability of the clinical data.</td>
<td>Provides the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.</td>
</tr>
</tbody>
</table>

according to U.S. standards of Good Clinical Practice (GCP) and applicable regulations. Study site policies and procedures should also be followed.”14 (Table 2)

“The best place to start when designing your trial is your device’s intended use and indications for use.” Clinette looked at a copy of the comparison table she and Lawsom created. (Table 1) “In our case, that means the goal of our study would be to evaluate if using Crania-Deep as an adjunctive therapy is safe and effective to reduce movement disorder symptoms of advanced, levodopa-responsive PD that are not adequately controlled with medication. Am I correct?”

“Yes, that’s right,” Laup responded and Cahn nodded in agreement.

“Great, so we have our overall goal.” Clinette paused and handed two printouts to her colleagues. “Based on our previous conversations, I’ve developed an outline of the key elements we need to include in our investigational plan based on the regulations detailed in 21 CFR § 812.25. Where I could, I included details specific to Crania-Deep in italics,” she said, indicating the first handout (Table 3). Then she held up the second document and said, “And this is an overview of the IDE approval process.” (Exhibit 3)

“This is great, Erin!” Laup said after Clinette finished taking them through the list. “How soon can we get started on hammering out the details for our investigational plan?”

“Yes, if you like,” Clinette smiled. Laup and Cahn agreed, and the meeting adjourned so that the team could get to work.

A week later, CranialCare’s draft investigational plan was complete. Cahn had pulled together an impressive IRB to review their draft plan, and as further assurance, the team also put together a Pre-Submission for FDA to seek feedback on questions they had about their study design, safety, effectiveness, and potential adverse events.15 They were informed and on their way to submitting their first IDE application.

14Device Advice: Investigational Device Exemption (IDE) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm#
15Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff
Table 3. Key Items to Submit in the Investigational Plan for the Crania-Deep IDE Application

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Name of device: Crania-Deep</td>
<td></td>
</tr>
<tr>
<td>✓ I/FU of the device: For bilateral stimulation of the corpus striatum (CS) as an adjunctive therapy to reduce some of the symptoms of advanced, levodopa-responsive Parkinson’s Disease (PD) that are not adequately controlled with medication.</td>
<td></td>
</tr>
<tr>
<td>✓ Objectives of the study:</td>
<td>– To assess the safety and effectiveness of stimulation of the CS for the treatment of advanced PD&lt;br&gt;– To collect information on all adverse events (AEs) and serious adverse events (SAEs) that occur throughout 1 year&lt;br&gt;– To collect patient diary data to assess &quot;on time&quot; in patients with PD&lt;br&gt;– To assess Parkinsonian symptoms using the Unified PD Rating Scale (UPDRS) score</td>
</tr>
<tr>
<td>✓ Duration of the investigation: Duration of study will be from the time the first person enrolls, until the time the last person completes the study. In addition, the duration for which each patient should be followed should also be determined because the S&amp;E data for some minimum duration would be necessary to make a determination of reasonable assurance of S&amp;E for a permanently implanted DBS device.</td>
<td></td>
</tr>
<tr>
<td>✓ Clinette Note: The summary of safety and effectiveness data (SSED) and the approval letter for the Activa Parkinson’s Control System would be a good reference to get a sense of the possible duration of investigation for CraniaDeep.</td>
<td></td>
</tr>
<tr>
<td>✓ Describe the methodology that will be used in the study to collect the S&amp;E data:</td>
<td>– Suggested: Prospective multi-center randomized double blind sham-controlled study.(^8)</td>
</tr>
<tr>
<td>✓ A detailed description of the patient population that will be considered for inclusion in or exclusion from the study should also be provided. It should include information such as the number of patients, age, sex, and condition.</td>
<td>– Inclusion criteria: Aged 18 to 80 years; diagnosis of PD for at least 5 years; experiences at least 6 hours of “off time” per day; has history of improvement in PD symptoms by levodopa of at least 33 percent. &lt;br&gt;– Exclusion criteria: Not a surgical candidate; has an electrical or electromagnetic implant; requires MRI procedures; had prior surgical ablation for PD; has a history of seizures; is pregnant or nursing.</td>
</tr>
</tbody>
</table>

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**Notes:**

1. CFR Part 812: Investigational Device Exemptions
2. The examples provided here are hypothetical and should not be interpreted as FDA recommendations or guidance.
3. “On-time” is when a PD patient finds that their levodopa medication is having benefit, and their Parkinson’s symptoms are generally well controlled.
4. National Parkinson Foundation: PD Screening Instruments and Scales
5. Summary of Safety and Effectiveness Data for a Supplemental Premarket Approval Application: Medtronic Activa® Parkinson’s Control Therapy Device
6. FDA Approval Order Letter for Medtronic Activa® PMA
7. The study design should be scientifically sound to support investigation of the S&E of the device.
9. “Non-on time” or “Off-time” is when levodopa medication is no longer working well for the PD patient and their Parkinson’s symptoms have returned.
The Investigational Device Exemption (IDE) Process: When Is an IDE the Right Choice? Continued

Table 3. Key Items to Submit in the Investigational Plan for the Crania-Deep IDE Application\(^1\) Continued

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
</table>
| Risk Analysis                             | ✓ Provide detailed descriptions and analysis of all increased risks to which patients will be exposed by the investigation:  
  – Suggested: description of possible surgical complications related to implantation of leads, lead extensions, and IPG; DBS complications related to programming; disease specific complications such as tremor, slowness of movement, rigidity, postural instability.  
  ✓ Describe how these risks will be minimized:  
  – Suggested: physician training, informed consent, device attributes such as ability to optimize stimulation settings to improve effectiveness and reduce AEs. |
| Description of the Device                 | ✓ Provide detailed descriptions of each important component of the device as well as their important characteristics and principles of operation:  
  – Suggested: include information on the maximum charge per phase and charge density of the device as this affects the safety of the stimulation output, verification testing including mechanical and electrical testing associated with both the implanted components (e.g., implanted neurostimulator, lead extensions, and leads) and external components (e.g., clinician and patient programmers), software testing, biocompatibility testing, sterilization, packaging, and shelf life.  
  **Clinette Note:** The device that is used in the IDE study should be identical to the device that will be marketed. However, if there are modifications to the device after the study, whether or not additional clinical or nonclinical testing is necessary would depend on the type of modification. For example, if a significant change is made to the lead, additional clinical data may be required. |
| Consent Materials and Labeling            | Include copies of all labeling as well as forms and informational materials that will be provided to subjects to obtain informed consent.\(^{10,11}\) |
| Additional Records and Reports            | Include a description of records and reports that will be maintained on the investigation in addition to those prescribed in 21 CFR Part 812, Subpart G. |
| Monitoring Procedures                    | Include procedures for monitoring the investigation as well as the name and address of any monitor. |
| IRB Information                           | List the names, locations, and chairpersons of all IRBs that have been or will be asked to review the investigation. Also include a certification of any action taken by any of those IRBs with respect to the investigation. |
| Other Institutions                       | List the name and address of each institution at which a part of the investigation may be conducted that has not been identified in the IRB information list. |

\(^{10}\)FDA. IDE Informed Consent.  
THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS:
WHEN IS AN IDE THE RIGHT CHOICE? CONTINUED

Exhibit 3: The IDE Approval Process

FDA has 30 days to approve, approve with conditions, or disapprove an IDE application.

Approval: FDA does not have outstanding issues that must be addressed to support the study of the patient population under the proposed investigational plan. An IDE application is approved if FDA has determined that sufficient data to support initiation of a human clinical study has been provided, no subject protection concerns preclude initiation of the investigation, and no additional conditions must be met.

Approval with conditions: FDA has identified issues that must be addressed in a timely manner, but they do not preclude initiation of patient enrollment in the clinical investigation.

An IDE application is approved with conditions if FDA has determined the following:

✓ Sufficient data to support initiation of patient enrollment in a human clinical study has been provided.
✓ No human subject protection concerns preclude initiation of enrollment.
✓ Additional conditions must be met to address other outstanding issues (for example, FDA may request additional information or data involving nonclinical testing issues that do not need to be resolved prior to initiation of patient enrollment).
✓ Clarification of procedures and assessment that relate to care of the patients in the late stages of the study is needed.

IDE amendments responding to each condition of approval raised in FDA’s approval with conditions letter must be returned within 45 days unless an extension is granted. Amendments may include scientifically valid alternatives to FDA’s request or scientifically valid rationales for why the information or modification(s) requested is not needed. FDA will contact sponsors with a decision within 30 days from the date of receipt of the amendment. During this time, sponsors and investigators may continue to conduct the study. If FDA determines that the issues have been adequately resolved, it will grant approval. If any issues remain, FDA may grant approval with conditions again and will communicate those outstanding issues to the sponsor by letter. In this case, sponsors may continue to enroll subjects in the study provided that, within 45 days, they address and respond to the remaining issues identified in FDA’s letter.

Disapproval: If FDA determines that resolution of outstanding issues may be necessary before initiating patient enrollment, the IDE will be disapproved. Patient enrollment in the clinical investigation may not be initiated until the sponsor responds to the issues identified in FDA’s letter and then receives an approval or an approval with conditions letter from FDA.

Scenarios in which FDA may issue a disapproval determination:

✓ Study plan contains elements that would expose subjects to unacceptable probable risks, or fails to adequately protect study subjects from probable risks (including adequate monitoring and review of the investigation).
✓ Available data suggest the device is ineffective for the use that will be evaluated in the proposed study.
✓ Insufficient information submitted to suggest that use of the device might result in patient benefit and/or the generation of knowledge adequate to justify the risks.
✓ Safety concerns (e.g., if the data and information provided are insufficient to adequately characterize the safety profile of the device and the data provided thus far indicate that human clinical investigation is not considered reasonable; specific safety concerns related to the need for additional basic device evaluation on biocompatibility, mechanical durability, or electrical safety).

1FDA Decisions for Investigational Device Exemption Clinical Investigations: Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff
221 CFR § 812.30
APPENDIX A: MATERIAL TO INCLUDE IN YOUR IDE APPLICATION

1. Name and address of sponsor.

2. Report of prior investigations (21 CFR § 812.27): must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation. Specific contents of the report must include the following:
   ✓ A bibliography of all publications, whether adverse or supportive, relevant to an evaluation of the safety and effectiveness of the device.
   ✓ Copies of all published and unpublished adverse information.
   ✓ Copies of other significant publications if requested by an IRB or the FDA.
   ✓ A summary of all other unpublished information (whether adverse or supportive) relevant to an evaluation of the safety and effectiveness of the device.
   ✓ If nonclinical laboratory data are provided, a statement that such studies have been conducted in compliance with the Good Laboratory Practice (GLP) regulations in 21 CFR Part 58. If the study was not conducted in compliance with the GLP regulations, include a brief statement of the reason for noncompliance.

3. Investigational plan (21 CFR § 812.25): shall include the following items in this order:
   ✓ Purpose: the name and intended use of the device and the objectives and duration of the investigation.
   ✓ Protocol: a written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness.
   ✓ Risk analysis: a description and analysis of all increased risks to the research subjects and how these risks will be minimized; a justification for the investigation; and a description of the patient population including the number, age, sex, and condition.
   ✓ Description of the device: a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation.
   ✓ Monitoring procedures: the sponsor’s written procedures for monitoring the investigation and the name and address of each monitor.
   ✓ Additional records and reports: a description of any records or reports of the investigation other than those required in Subpart G of the IDE regulations.

4. A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device.
APPENDIX A: MATERIAL TO INCLUDE IN YOUR IDE APPLICATION

5. An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators. The types of information that must be included in the written agreement can be found in 21 CFR § 812.43.

6. Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study.

7. A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available).

8. The name and address of any institution (other than those above) where a part of the investigation may be conducted.

9. The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization.

10. Please note that an environmental assessment as required under 21 CFR § 25.40 or a claim for categorical exclusion under 21 CFR § 25.30 or 25.34 is no longer required. [21 CFR § 25.34(g)]

11. Copies of all labeling for the device.

12. Copies of all informed consent forms and all related information materials to be provided to subjects as required by 21 CFR Part 50, Protection of Human Subjects.

13. Any other relevant information that FDA requests for review of the IDE application information previously submitted to FDA in accordance with 21 CFR Part 812 may be incorporated by reference.

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1How to Study and Market your Device: IDE Application
THE INVESTIGATIONAL DEVICE EXEMPTION (IDE) PROCESS: WHEN IS AN IDE THE RIGHT CHOICE? CONTINUED

GLOSSARY

Approval: Approval of a medical device [or clearance for devices subject to 510(k), see below] must be obtained from the FDA by demonstrating reasonable assurance of safety and effectiveness, and that the benefits outweigh the risks for the intended patient population before it can be put into commerce. The term approval is generally used in the context of Class III medical devices.

In the case of investigational devices, approval or conditional approval of an Investigational Device Exemption (IDE) application must be obtained prior to starting an IDE study. An IDE application is approved if FDA has determined the following:

- The applicant has provided sufficient data to support initiation of a human clinical study.
- No subject protection concerns preclude initiation of the investigation.
- No additional conditions must be met.

Alternatively, if FDA has identified issues that must be addressed in a timely manner but do not preclude initiation of patient enrollment in the clinical investigation, the IDE will be approved with conditions.

Clearance: Clearance of a medical device not exempt from 510(k) must be obtained from the FDA by demonstrating that the device is substantially equivalent (SE) to its predicate device before the device is put into commerce.

Device Classification: FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to reasonably assure the safety and effectiveness of the device. The three classes and the requirements that apply to them are:

1. Class I General Controls
   - With Exemptions
   - Without Exemptions
2. Class II General Controls and Special Controls
   - With Exemptions
   - Without Exemptions
3. Class III General Controls and Premarket Approval

Effectiveness: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. [21 CFR § 860.7(e)(1)]

Good Clinical Practices (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a
way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

**Good Laboratory Practices (GLP):** A set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. GLP help assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

**Guidance Documents:** Documents prepared for FDA staff, applicants/sponsors, and the public that describe the Agency’s interpretation of or policy on a regulatory issue. These documents do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Draft guidance documents are for the public to comment on and suggest changes for, but are subject to change and are not for implementation. [See 21 CFR § 10.115 (b), (d), and (g)]

**Good Guidance Practices (GGP):** FDA’s policies and procedures for developing, issuing, and using guidance documents. Please refer to the following links for additional information:

- 21 CFR § 10.115
- Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency

**Humanitarian Device Exemption (HDE):** To obtain approval for a Humanitarian Use Device (HUD), a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.

**Humanitarian Use Devices (HUDs):** A HUD is a device that is intended to benefit patients with rare diseases by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year (may include medically plausible subsets for either the population or condition). HUDs are exempt from requirements to demonstrate effectiveness. Still, they must pose no unreasonable risks, or at least the probable benefits should outweigh the risks. Once approved, the device must be used under the guidance of an IRB.

Examples of HUDs include a fetal bladder stent, iris replacement device, radioactive microspheres for cancer treatment, and semi-constructed finger joints.

**Implant:** A device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants.

**In Vitro:** Outside the living body and in an artificial environment.

**Indication for Use:** Describes the disease or condition a device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

**Intended Use/Purpose:** The general purpose of the device, or what the device does. The intended use encompasses the indications for use. The use for which a product, process, or service is intended according to the specifications, instructions, and information provided by the manufacturer.

**Investigation:** A clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

**Investigational Device:** A device, including a transitional device, that is the object of an investigation.
Investigational Device Exemption (IDE): Refers to the regulations under 21 CFR Part 812. An IDE application is a regulatory submission to study a medical device in human subjects. An approved IDE means that FDA has approved the IDE study application. It permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.

Investigator: An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event of an investigation being conducted by a team of individuals, “investigator” refers to the responsible leader of that team.

Institutional Review Board: Any board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in Section 520(g) of the FD&C Act.

For additional information, please refer to:

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, “or accessory” that is the following:

1. Recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals
3. Intended to affect the structure or any function of the body of man or other animals
4. Does not achieve its primary intended purposes through chemical action within or on the body of a human or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes [Section 201(h) of the FD&C Act]

Monitor: A monitor (noun) is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor, a consultant to the sponsor, or an employee of or consultant to a contract research organization. To monitor (verb) means to oversee an investigation.

Nonclinical Investigation: A systematic investigation conducted to evaluate the safety and effectiveness of a medical device using non-human subjects or specimens, primary or secondary cell lines, or computational models.

Premarket Approval (PMA): The FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Any PMA application for a Class III medical device, including all information submitted with or incorporated by reference therein (21 CFR § 814.3). Class III devices are those that cannot be classified as Class I or Class II devices because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and either (1) are purported to be for a use in supporting or sustaining human life or for a use that is of substantial importance in preventing impairment of human health; or (2) present a potential unreasonable risk of illness or injury.

Premarket Notification—510(k) Clearance: Section 510(k) of the FD&C Act requires device manufacturers, who must register, to notify FDA of their intent to
When Is an IDE The Right Choice? CONTINUED

market a medical device at least 90 days in advance. This is known as premarket notification—also called PMN or 510(k). This allows FDA to determine whether the device in question is equivalent to a device already placed into Class I, Class II, or Class III requiring 510(k), or a legally marketed preamendment device. Thus, “new” devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified.

Specifically, medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the device design, material, chemical composition, energy source, manufacturing process, or intended use.

Requirements related to the methods used in, and the facilities and controls used for designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use.

Regulatory Pathways: Before a medical device that requires a premarket submission can be put into the U.S. market, manufacturers of medical devices have to submit evidence to demonstrate product safety and effectiveness to the Office of Device Evaluation (ODE) and to the Office of In Vitro Diagnostic and Radiological Health (OIR) of the Center for Devices and Radiological Health (CDRH) at FDA. There are various submission processes and respective applications for evaluation. PMA, PMA Supplement, Product Development Protocol (PDP), Humanitarian Device Exemption (HDE), IDE, IDE Amendment, IDE Supplement, and 510(k) are programs administered by ODE and OIR. They are also called regulatory pathways.

Sponsor: FDA defines a “sponsor” as a person or other entity that initiates but does not actually conduct the investigation. That is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of their own employees to conduct an investigation that they initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. The sponsor of an IDE must be located in the United States (see 21 CFR § 812.18).

Sponsor-investigator: An individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.
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Subject: A human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or who participates as a control. A subject may be in normal health or may have a medical condition or disease.

Transitional Device: A device subject to Section 520(l) of the FD&C Act and which FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.

Unanticipated Adverse Device Effect: Unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application. Or, any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

STUDENT ACTIVITIES

SESSION 1

I. Review the following materials before Session 1:

1. Background Information on Parkinson’s Disease (PD) and Treatments
   a. Statistics and Definitions
      i. Florida Hospital: Statistics of Parkinson’s Disease
         https://www.floridahospital.com/parkinsons-disease-pd/statistics
      ii. Mayo Clinic: Parkinson’s Disease—Definition
         http://www.mayoclinic.org/diseases-conditions/parkinsons-disease/basics/definition/con-20028488
      iii. NIH Senior Health: What is Parkinson’s Disease?
         http://nihseniorhealth.gov/parkinsons-disease/whatisparkinsonsdisease/01.html
   b. Causes
      i. Mayo Clinic: Parkinson’s Disease Causes
         http://www.mayoclinic.org/diseases-conditions/parkinsons-disease/basics/causes/con-20028488
      ii. WebMD: Parkinson’s Disease Health Center—What Causes Parkinson’s Disease?
         http://www.webmd.com/parkinsons-disease/guide/parkinsons-causes
   c. Treatment and Drugs
      i. Mayo Clinic: Treatment and Drugs
         http://www.mayoclinic.org/diseases-conditions/parkinsons-disease/basics/treatment/con-20028488
      ii. WebMD: Drug Treatment for Parkinson’s Disease
         http://www.webmd.com/parkinsons-disease/guide/drug-treatments
iii. Parkinson’s UK: Side Effects of Parkinson’s Drugs
   http://www.parkinsons.org.uk/content/side-effects-parkinsons-drugs

d. Deep Brain Stimulation Treatment
   i. WebMD: Deep Brain Stimulation for Parkinson’s Disease
      http://www.webmd.com/parkinsons-disease/guide/deep-brain-stimulation
   ii. WebMD: Is Deep Brain Stimulation Experimental?
       http://www.webmd.com/parkinsons-disease/guide/dbs-parkinsons?page=3#3
   iii. National Institute of Neurological Disorders and Stroke: Deep Brain Stimulation for Parkinson’s Disease Information Page

2. Medtronic Activa® Parkinson’s Control Therapy Device PMA Documents
   a. Summary of Safety and Effectiveness Data
      http://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S007b.pdf
   b. FDA Approval Order Letter for Medtronic Activa® PMA
      http://www.accessdata.fda.gov/cdrh_docs/pdf/p960009S7a.pdf
   c. FDA Recently Approved Medical Devices: Activa® Parkinson’s Control System P960009/S7 (accessed 03/01/2015)
      http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083894.htm

3. Mandatory Viewing/Reading
   a. CDRH Learn Materials:
      i. How to Market your Device—Clinical Studies/Investigational Device Exemption
         http://www.fda.gov/Training/CDRHLearn/ucm126230.htm
      Review the videos, slides, and presentations available in the following sections under Clinical Studies/Investigational Device Exemption:
      1. IDE Basics
      2. Strengthening the Medical Device Clinical Trial Enterprise New! 2/3/15
      3. Idea to IDE: A Medical Device in the Making
      4. IDEs for Early Feasibility Medical Device Clinical Studies, Including First in Human (FIH) Studies
      5. FDA Guidance: Design Considerations for Pivotal Clinical Investigations for Medical Devices
      6. Evaluation of Sex-Specific Data in Medical Device Clinical Studies
      7. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations
   b. Guidance and Regulations
      i. Guidance on IDE Policies and Procedures
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ii. Code of Federal Regulations (CFR)
Title 21 § 812.1

iii. 21 CFR § 820.30, Design Controls

iv. Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Non-significant Risk Medical Device Studies


4. Optional Reading
a. Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm

b. How to Study and Market Your Device—Step 1: Classify Your Device
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm#step1

c. FDA Product Classification Database: Stimulator, Electrical, Implanted, For Parkinsonian Symptoms

d. IDE-related guidance documents, forms, and templates
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm162453.htm

e. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

II. Answer the following questions—
Fundamental concepts:

1. Describe the following items for the neurological device discussed in the case study:
   a. Device Description
   b. Proposed Intended Use
   c. Indications for Use

2. After completing the mandatory viewing/reading assignments, define the following terms:
   a. Investigational Device
   b. Investigational Device Exemption (IDE)
   c. Study Risk Determination request
   d. Significant Risk Device
   e. Good Clinical Practices (GCP)
   f. Monitor
   g. Sponsor-investigator
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SESSION 2

I. In-class discussion (instructor guidance required):

1. Discuss the elements required for clinical evaluation of devices that have not been cleared for marketing.


2. Review the “IDE Application” page on the FDA website, and discuss the criteria that allow a sponsor of an IDE to modify a device and/or clinical protocol without approval of a new IDE application or an IDE supplement.

SESSION 3: TEAM PROJECT AND PRESENTATION

Note: This project may be used to satisfy, in part, an academic requirement such as a thesis, senior project, graduate project, technical writing assignment, or other special requirement.

I. Review the following material before beginning the team project:

1. Guidance on IDE Policies and Procedures

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm

II. Prepare an IDE Investigational Plan

Prepare an investigational plan for an IDE application. You may create a plan for a medical device you are working with on a class project, or prepare an investigational plan for the fictitious device discussed in the case study and use your responses to the questions raised in the before class activities as the base for your project.

As recommended in the IDE regulations, include the following sections in your investigational plan:

1. Purpose of the study:
   a. Device description
   b. Proposed intended use/indications for use
   c. Objectives of the study

2. Study design, including inclusion/exclusion criteria

3. Risk analysis

4. Consent materials and labeling

5. Monitoring procedures