FDA Webinar-Implanted BCI Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations Final Guidance

Moderator: Irene Aihie

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Coordinator: Welcome and thank you for standing by. Today's call is being recorded. If you have any objections, you may disconnect at this time. All participants are in a listen-only mode until the question-and-answer session of today's conference. At that time, you may press Star-1 on your phone to ask a question.

I would now like to turn the call over to your host. Irene Aihie. You may begin.

Irene Aihie: Thank you. Hello and welcome to today's FDA Webinar. I'm Irene Aihie of CDRH's Office of Communication and Education.

On May 20, 2021, the FDA published the Final Guidance, titled Implanted BCI Devices for Patients with Paralysis or Amputation, Non-Clinical Testing and Clinical Considerations.

This Webinar will describe non-clinical testing recommendations associated with implanted BCI devices for patients with paralysis or amputations with industry and stakeholders.

This Webinar will also recommend clinical trial design to provide a reasonable assurance of safety and effectiveness necessary to support a regulatory submission and translation of BCI devices from concept to assisting device users.

Today, Dr. Heather Dean, Assistant Director in charge of the Acute Injuries Advisory Team in the Office of Neurological and Physical Medicine Devices here in CDRH will share information about the final Guidance. Following the presentation, we will open the lines for your questions related to information provided during the presentation.

Now, I give you Heather.

Dr. Heather Dean: Thank you. So, first of all, I want to give a shout out of recognition to a member of my team who put together this presentation, Dr. Julia Slocomb. She was unable to be here today, but she really did the work in putting this together.

So, to get started, on May 20th, 2021, the U.S. Food and Drug Administration published the Final Guidance document, Implanted Brain Computer Interface – or BCI Devices – for Patients With Paralysis or Amputation, Non-Clinical Testing and Clinical Considerations Guidance.

The focus of today's Webinar is to share information and answer questions about the Final Guidance documents. During this presentation, I will provide an overview of the purpose and key components of the Guidance Documents

and highlight the differences between the Final Guidance document and the Draft Guidance document.

Before we begin, I would like to review a few important terms that will be used frequently during this presentation. Investigational device exemption – or IDE – is a mechanism which allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.

Q Submissions are a mechanism which you, as a researcher, can use to obtain FDA feedback on future IDE applications prior to their submission. It is typically used to review plan protocols, but not study data, which is addressed only in a formal submission.

For the purposes of this Guidance document, implanted brain computer interface, or BCI devices, are neuroprostheses that interface with the central or peripheral nervous system to restore lost motor and/or sensory capabilities in patients with paralysis or amputation.

Assistive effector components are a prosthetic limb, wheelchair, functional electrical stimulators applied to an intact limb, exoskeletons, or robotic systems or communication devices and computers.

The field of implanted BCI devices is progressing rapidly from fundamental neuroscience discoveries to translational applications and market access. This Guidance is a Leapfrog Guidance, a type of Guidance that serves as a mechanism by which the Agency can share initial thoughts regarding emerging technologies that are likely to be of public health importance early in product development.

This Leapfrog Guidance represents the Agency's initial thinking, and our recommendations may change as more information becomes available.

The purpose of this Final Guidance document is to provide recommendations to industry about the types of information to be included in your Q Submissions, and IDEs for implanted BCI devices for patients with paralysis or amputation.

It is important to note that non-implanted BCI devices are not within the scope of this Guidance, as the regulatory considerations of these devices may differ from those recommended in this Guidance document, depending on various aspects, such as, but not limited to the technical characteristics and indications for use or patient population. For feedback on regulatory considerations for non-implanted BCI devices, we recommend following the Q Submission process.

BCIs are used both in health care and home settings, but implantation and device training are always performed in health care settings. In health care settings, they are used by health care professionals.

We're seeing more and more submissions which involve home use by lay users, i.e., patients with paralysis or amputation, with or without assistance from caregivers. It is important to note that home use involves different considerations when preparing an IDE Submission. This Leapfrog Guidance impacts all stakeholders preparing Q Submissions and the IDEs for implanted BCI devices.

The Draft Guidance was issued on February 22, 2019. We received many comments through the docket during the 60-day comment period and further comments from outside stakeholders, not through the docket.

We used these comments as a basis for several significant changes to the Guidance, which are reflected in the Final Guidance. The Final Guidance was issued on May 20, 2021. Most of the recommended testing remains unchanged compared to the Draft Guidance.

However, in addition to minor changes in wording and grammar to improve clarity, important clarifications and additions were made to the sections listed here.

The Guidance includes recommendations for the sections shown here, which I will review in the remainder of my presentation.

We recommend that you include in your submission a device description, including 1) A complete description of every module of the device.

For example, BCI Systems typically consists of several modules including, but not limited to, the following modules: signal acquisition, for example, leads and recording electrodes; signal processing that includes software for decoding and encoding signals and providing stimulation, in some cases, and associated hardware; stimulation delivery, including internal and external stimulators and stimulating electrodes; assistive effector components, as defined earlier; sensor components for neural feedback, for example, sensors for restoring touch or recording other information, if applicable; and a programming module that consists of an operating protocol to control functions, such as turning the device on and off and switching between various outputs and programs.

The description should also include, 2) A general overview of the BCI device as a whole system, including a description of how the different modules are

configured to comprise the whole system and, if applicable, a description of the different system configurations (for example, programming, calibration or testing configurations).

3) A complete description of key components of the device, including its function, relevant model numbers, material, location, implanted or external components, and dimensions or sizes that a user would need to know how to use the device properly.

The Final Guidance recommends that if any key components were previously cleared or approved, the pre-market submission number, i.e., 510(k) or PMA number, with a description of modifications to the cleared or approved device should be provided.

While I won't be reviewing the rest of the recommendations for the device description in detail here, I would like to note that the Guidance provides an outline of recommended information for a variety of specific components.

Our biggest concern is patient safety. So, we recommend that you apply risk management principles as detailed in the Guidance during the development of your device. We recommend that the risk analysis detail qualitative examination of the potential hazards (for example, hardware, software, non-clinical related and clinical related hazards) of the device from the perspective of the user.

We also recommend identification of hazards caused by single-fault conditions to ensure that the failure of any single component of the implanted BCI device does not cause an unacceptable risk during use.

The risk analysis should be provided in a tabular format and should analyze all potential causes for the identified risks.

Software in implanted BCI devices ensures that various components of the implanted BCI system, such as the signal processing modules, controllers, simulation hardware and assistive device, operate as intended and provide software mitigations when appropriate. Adequate software performance testing provides assurance that the device is operating within safe parameters.

Overall, software documentation should provide sufficient evidence to describe the role of the software included in the device, risks associated with the device, and performance testing to demonstrate that the software functions as designed.

We generally consider the software for implanted BCI devices to present a major level of concern. If you believe that the software in your device presents either a minor or a moderate level of concern as defined in the software Guidance, you should provide a scientific justification that supports your rationale for the level of concern based on the possible consequences of software failure.

For early feasibility studies, we recommend that you provide adequate software performance testing to provide assurance that the system operates within safe parameters. As appropriate, you should also provide information on the cybersecurity aspects of your device.

Human factors are also commonly referred to as usability and describe testing to understand how the device is typically used in real life. Use-related hazards are hazards resulting from failure modes tied to the use of implanted BCI

devices by end users (for example, patients, surgeons, prosthetists, caregivers).

They are a unique form of hazard in that use-related hazards can exist even if the device operates according to specifications. They generally do not involve specific failure modes associated with mechanical, electrical and software components that are previously known or reasonably anticipated.

These hazards might result from aspects of the user interface design that cause the user to fail to adequately or correctly perceive, read, interpret, understand, or act on information from the device.

Regardless of the severity of potential harm from a use-related hazard, it is important to understand and identify these hazards to ensure that you have designed a safe and usable device.

Human factors validation and evaluation is typically not needed to support feasibility study approval. However, it can be useful in demonstrating that home use is safe for users in an IDE application. Also consider that human factors data may be needed to support your future marketing submission to the Agency.

In order to address and mitigate use-related hazards in final device design, we recommend conducting usability evaluation (for example, cognitive walk-throughs, simulated use testing, satisfaction surveys) early in the device design process and iteratively throughout the device development and evaluation process.

If your device is still under development and you intend to pursue an early feasibility study for an IDE, the early feasibility study could be conducted to

obtain initial insights into human factors (for example, difficulties in comprehending procedural steps and sufficient training, et cetera).

Implanted BCI devices contain patient-contacting materials, which, when used for their intended purpose (i.e., contact type and duration) may induce a harmful biological response. You should determine the biocompatibility of all patient-contacting materials present in your device. If the components of your BCI device are identical in composition and processing methods to components with a history of successful use in the same or similar anatomical locations, you may reference previous testing experience or literature.

The type of tests that are applicable to your device may depend on whether the electrodes interface with the central or peripheral nervous system. Additionally, devices intended to be used in conjunction with the implanted BCI device (for example, components or surgical tools) may contact the patient in different ways and for different durations.

The Guidance provides the biocompatibility endpoints associated with four of the most common categories for implanted BCIs, which I will not detail today in the interests of time.

It is important to note that while there are many ways to mitigate risks without performing complete testing for skin contacting devices, the risks for implanted devices are greater and there are fewer ways to mitigate risk for these devices without performing complete testing.

Implants and BCI devices should be adequately sterilized to minimize infections and related complications. For implanted BCI components and surgical tools labeled as sterile, we recommend that you include the information listed in the Guidance, some of which is summarized here.

First, for the sterilization method, you should provide the following: A description of the sterilization method, chamber and site; in the case of radiation sterilization, the radiation dose; and for chemical sterilants, the maximum levels of sterilant residuals that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.

Second, for the sterilization method, you should provide a description of the method used to validate the sterilization cycle (for example the half-cycle method) as well as the sterilization and validation data.

The submission should also identify all relevant consensus standards used and identify any aspects of the standards that were not met. In the absence of a recognized standard, a comprehensive description of the process and the complete validation protocol should be submitted and reviewed.

You should state the sterility assurance level (SAL) of 10^{-6} for devices labeled as sterile. We recommend that you describe the sterilization process validated for each sterile configuration.

Pyrogenicity testing is used to protect patients from the risk of febrile reaction due to gram-negative bacterial endotoxins and/or chemicals that can leach from a medical device, for example, material-mediated pyrogens.

To address the risks associated with the presence of bacterial endotoxins, implanted BCI devices should meet pyrogen limit specifications. Additionally, we recommend providing the routine batch release limulus amebocyte lysate (LAL) monitoring procedures.

For devices intended to be labeled as non-pyrogenic, we recommend that both bacterial endotoxins and material-mediated pyrogens be addressed.

Shelf life testing is conducted to support the proposed expiration date through evaluation of the package integrity for maintaining device sterility and/or evaluation of any changes to device performance or functionality.

With respect to package integrity for maintaining device sterility, you should provide a description of the packaging, including how it will maintain the device's sterility, the protocols used for your package integrity testing, the results of the testing, and the conclusions drawn from your results.

We recommend that a package validation study include simulated distribution and associated package integrity testing as well as an aging process, which can be accelerated and/or real-time, and associated seal strength testing to validate package integrity and shelf-life claims.

We recommend you follow the methods described in the current edition of the FDA recognized consensus standards as listed here, or 11607–1, and ANSI/AAMI/ISO 11607–2.

With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the critical device properties to ensure it will perform adequately and consistently during the entire proposed shelf life.

To evaluate device functionality, we recommend that you assess each of the non-clinical bench tests recommended in this Guidance, and repeat all tests that evaluate design components or characteristics that are potentially affected by aging, using aged devices.

We recommend that you provide the protocols used for your shelf life testing, the results of the testing, and the conclusions drawn from your results.

We recommend all test samples undergo real-time aging to determine definitively the effects of aging on the maintenance, the sterility and the device performance.

Implanted BCI devices are medical electrical equipment and therefore may expose the operator and patient to hazards associated with the use of electrical energy or may fail to operate properly in the presence of electromagnetic disturbance.

Implanted BCI devices should be tested to demonstrate that they perform as anticipated in their intended use environments. We recommend that this testing be performed as described in the current FDA recognized versions of the standards for medical electrical equipment safety and electromagnetic compatibility shown here. If you have questions, please feel free to reach out to us via a Q-Submission.

In the design, testing and use of wireless medical devices, the correct, timely and secure transmission of medical data and information is essential for the safe and effective use of medical devices and systems.

BCI systems may utilize wireless connections to transfer neural signals, to control assistive technologies, or to drive electrical stimulation. If your implanted BCI device incorporates radio frequency wireless technology, such as Bluetooth, Wi-Fi, radio frequency identification (RFID) technology, or other wireless functionalities needed to perform the clinical function of your device, we recommend assessing the risk as described in the FDA recognized

version of AMII TIR 69: *Technical Information Report Risk Management of Radio Frequency Wireless Co-existence for Medical Devices and Systems*.

The selection of RF wireless operating frequency and modulation should take into account other RF wireless technologies and users that might be expected to be in the vicinity of the wireless medical device system.

These other wireless systems can pose risks that could result in medical device signal loss or delay that should be considered in the risk management process. If the risk management evaluation of the wireless function is found to be critical to the clinical function of the device, FDA recommends that you address your device's environmental specifications and needs as outlined in the current FDA recognized version of ANSI/IEEE C63.27.

MR imaging of a patient with an implanted BCI device poses a variety of potential hazards, including those shown here, which should be addressed in your IDE submission.

We recommend that you address the issues affecting safety and compatibility of your implanted BCI device in the MR environment as described in the FDA guidance, “Testing and Labeling Medical Devices for Safety in Magnetic Resonance (MR) Environment.”

In general, the typical duration of implantation should be considered when determining appropriate test methods for characterizing durability (for example, mechanical and electrical) of the components.

Testing should ensure that the device meets appropriate specifications that represent clinically relevant, worst-case *in vivo* conditions during device implantation and the expected life of the device.

When appropriate, we recommend that the testing simulate the effect of any body fluids on the device components that come in contact with such fluids (for example, after soaking in saline and before drying). We also recommend that you specify clinically justified acceptance criteria for testing.

We recommend that you include relevant information on the non-clinical bench testing provided in the form of test report summaries, test protocols, and complete test reports, as described in the guidance document, "Recommended Content and Format of Non-clinical Bench Performance Testing Information in Premarket Submissions."

We recommend that the non-clinical bench testing outlined in the Guidance be addressed in your IDE, but today I will provide a brief overview of some of the key testing we recommend in the Guidance.

Electrodes can be used to measure physiological signals or provide the stimulation to the brain, spinal cord, and/or peripheral nerves or muscles for eliciting movement and/or sensation.

If the implanted BCI device includes electrodes, we recommend testing the following characteristics: dimensional verification and visual inspection, impedance, and accelerated lifetime testing.

Leads are used to connect electrodes to multiple components in an implanted BCI system, such as but not limited to, processing hardware and power modules. It is important that they function appropriately in the implanted BCI device system.

We recommend testing to characterize the following attributes: dimensional verification and visual inspection, leakage current, lead body and connector flex fatigue testing, connector insertion and withdrawal forces, tensile strength of lead, particulate matter hazards, corrosion resistance, and compliance with 21 CFR 898.12.

Electronics are often implanted, covered in a can or similar casing, which serve the process signals received from the leads and/or to provide electrical stimulation to the leads. We recommend you provide the testing listed here, which are detailed in the Guidance: hermeticity testing, environmental testing, header adhesion testing, and battery testing.

For devices that deliver electrical stimulation, it is important that the output stimulation delivered by the device and stimulation output limitations are appropriately characterized.

We recommend using methods described in ISO 14708–3: *Implants for surgery – active implanted medical devices - Part 3: Implantable neural stimulators*.

For each output mode, we recommend that you provide an oscilloscope trace describing the electrical output waveform under physiological loads that may be encountered. The Guidance outlines specific information that should be included with each trace. Traces should demonstrate ability to achieve maximum stimulation settings in each trace and remain within specification.

Simulation output results can be recorded in the format recommended in Appendix A of the Guidance. The Appendix includes a table which provides an example of how information may be organized for a variety of example output modes.

An output mode is defined, for reporting purposes, as a version of the waveform produced by the unit. For example, biphasic symmetrical and biphasic asymmetrical would be considered separate output modes. If multiple values are available for a given parameter within the output mode, then the manufacturer should provide the range and identify the different steps that may be selected in that range if not continuous.

For devices that deliver electrical stimulation to the nervous system and muscles, it is important that the output stimulation delivered to the tissue be safe for the intended use and stimulation duration. Excessive stimulation can produce tissue damage that could result in serious injury or death depending on the stimulation location.

We recommend that you provide scientific rationale (for example, literature and/or animal studies outlined in the Guidance) to support the safety of the stimulation output parameters (for example, maximum current, charge density, current density charge per phase, frequency and duration).

An analysis of the safety of the output stimulation parameters provides assurance that the risk of tissue damage is minimized during the use of the device.

Hardware used to program stimulation parameters or select different device modes are often called programmers or control units and may present risk to the patients if they do not operate as intended.

We recommend that programmers / control units be subjected to verification testing to assess electrical safety, functional, environmental, electromagnetic compatibility, software, and reliability performance. For programmers or

control units that can communicate with implanted electronics, testing demonstrating that the programmer or control unit is capable of communicating with and programming the implanted electronics should be provided.

If applicable, the transmitting and receiving antennae, transmitting distance, reed switch and magnet should be tested to ensure that they function as intended.

Radio frequency (RF) communication through a transmitter and receiver (such as through inductive coupling) is sometimes used for programming or controlling implanted components or recharging implanted batteries.

RF transmitters and receivers may present risks to the patients if they do not operate as intended. For example, inductive coupling may lead to tissue heating or tissue damage.

Testing for the RF transmitter should include information outlined for the programmer or control unit as described on the previous slide. In addition, we recommend that you provide the testing for the RF transmitter, including mechanical testing, electrical testing, and transmission distance and orientation between the external emitting antenna and the antenna inside the receiver.

Testing for the transmitter and receiver should consider the testing recommendations for wireless technology outlined in the wireless technology section of the Guidance. To adequately demonstrate protection from heating and ionizing radiation during the RF energy transfer, we recommend referring to the currently recognized version of ISO 14708–3: *Implants for surgery - Active Implantable Medical Devices- Part 3: Implantable neurostimulators.*

Many BCI device technologies have multiple components that may be interchangeable to achieve different and configurable clinical uses (i.e., a modular approach). Given the variability of individual patient needs, manufacturers may choose to develop BCI systems with individual components manufactured by different manufacturers, which allows a mix and match compatibility across several device makers.

Such individual components can be produced by different manufacturers and subsequently combined to make a complete system. A thorough understanding of how various components interact with one another, with the user and the patient, and with the environment is essential to demonstrate the safety and effectiveness of implanted BCI systems.

While each component of the system has characteristics that can introduce risks individually, new risks can arise when the components interact to perform as a system. To verify all system components operate together as set forth by the system specifications, FDA intends to evaluate the entire system and associated performance testing of the system. Electrical safety, electromagnetic compatibility, and wireless coexistence testing should be performed on the full, complete system for the proposed intended use.

In addition, you should identify specific criteria that demonstrate compatibility of the component with other device components and provide scientific or clinical justification for the criteria.

However, if system-level testing is not feasible, a rationale for the exclusion of system-level testing and description of how risk will be mitigated should be provided. All devices intended to be used in conjunction with the implanted BCI device (such as implantation tools, clips or belts for body-worn

components, or components from another marketed medical device) should be compatible.

Incompatibility can result in device damage or other clinical adverse events. Therefore, we recommend that you identify and provide specifications needed to ensure compatibility between all modular components of the system in the protocol and any labeling provided to the operators or investigator.

Often, researchers submitting an IDE need to use another party's product (for example, material, sub-assembly or component) or use another party's facility in the manufacture of the device.

In this circumstance where a researcher chooses to leverage information related to the other party's product, facility, or manufacturing procedures in their submission, a device Master File may be referenced as part of the submission to FDA with a Letter of Authorization.

A Letter of Authorization is also required if referencing another researcher's IDE in your submission. If you are using a cleared or approved device within its approved indication, you do not need a Letter of Authorization to reference it in your submission.

But if you are using a cleared or approved device outside of its approved indications, then we will require a Letter of Authorization from the manufacturer.

Non-clinical animal testing is generally recommended to evaluate the *in vivo* safety of implanted BCI devices, particularly for new designs, significant device modifications, and new indications.

In most cases, we recommend that you conduct animal testing on a final finished device to support the assessment that the risk to the subjects do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained in a human clinical trial.

We do understand that devices evaluated in early feasibility studies are often undergoing modification, and in some scenarios, an animal study using a final finished device may not be needed if an adequate rationale is provided.

Keep in mind that due to the variability in components, device designs, targets, and benefits in implanted BCIs, you may need to customize your animal protocols to establish the data needed to support a future clinical study.

The Guidance outlines what to include in a typical animal study protocol, but I wanted to outline a few general points regarding animal studies for implanted BCIs.

The main purpose for conducting an animal study is to provide evidence of device safety. Animal studies may also provide evidence of device performance that cannot be adequately obtained from bench testing, including *in vivo* reliability over time.

However, alternative methods may be needed in situations in which animal studies may be inappropriate, such as cognitive assessments. When designing the study protocol, specific determinations of study variables such as the number of animals studied, the study duration, the type of animal model or the choice of controls depend on both the risks of the device and the existing scientific information that can be used to mitigate expected risks.

Existing scientific information with sufficient rationale may be leveraged to lower the burden associated with conducting animal studies (for example, a smaller number of animals or shorter duration of animal study) or justify why additional animal studies may not be needed.

Many BCI devices involve implanted multi-component systems designed for long-term use in human patients. For these devices, animal studies that address chronic *in vivo* evaluation of the final device system provide a greater degree of understanding of device safety than acute studies or chronic investigations of partial systems.

A full evaluation of device risks and available scientific evidence will allow for the determination of the appropriate protocol for a given BCI system. When describing the results of conducted animal studies, we recommend that you include a discussion of how the findings support preliminary safety of the device for your proposed clinical study.

Good laboratory practices – or GLP – for animal care and study conduct, as specified in 21 CFR Part 58,ensure the quality and integrity of animal data to support IDE applications.

Non-GLP study data may be used to support an IDE application only if the deviations from GLP are identified and justified and do not compromise the validity of the study results. I want to emphasize that we encourage you to submit a Q-Submission prior to initiating your animal study to discuss your animal model and study design.

The Guidance details some recommendations for an animal study design evaluating BCI devices. Notably, the Guidance includes that the choice of

animal models depends on the BCI device and may vary based on device type, indication and implant site.

We believe that the animal and its related environmental and physiologic attributes should provide a test system that offers the best attempt at simulating the clinical setting.

Animal models that can accommodate human-sized devices may be preferable, although the use of scaled devices might be acceptable in some circumstances if appropriate scientific justification is provided. Appropriate controls should be identified in the study protocol. Generally, non-implanted, contralateral tissue is an appropriate control.

We recommend histopathological or histomorphological evaluation of implanted tissue, including both structural analysis and evaluation of injury markers that are relevant to the neural tissue.

We recommend that you justify the use of specific histological markers and provide evidence that the histological protocol is adequate to capture major adverse reactions.

For devices involving a stimulation component, we also recommend that you provide experiments to establish the safety of stimulation. Behavioral and functional assays are recommended to better predict clinical adverse events.

For devices designed for chronic implantation, long-term device performance should be established in a biological environment unless scientific evidence for device performance *in vivo* has already been collected (for example, prior animal studies and/or published literature using the same or similar electrode configuration).

In vivo impedance of electrodes and stimulation components may be required to demonstrate and characterize the functionality of the device. The Guidance details recommended testing, which should be performed for studies of either acute or long-term stimulation. A detailed description of the implantation approach should be provided along with its translatability to human implantation.

For an IDE, a summary of any prior critical studies of the device used for the proposed intended use must be provided in the report of prior investigations. For early feasibility studies, although clinical data may not be available with the subject device for its proposed intended use, any relevant background clinical information should also be provided.

This information may come from clinical use outside of the U.S. (OUS), but you should justify its applicability to the patient population in the United States.

Certain components of the clinical study design are especially important when designing a clinical study intended to evaluate the performance of a BCI system. For each clinical study design component, scientifically supported and justified descriptions are essential to provide clarity and facilitate understanding.

The following design components should be considered and supported with the justification in your IDE submission when developing the clinical study protocol.

First, a variety of patient populations may benefit from BCI devices whose function is to augment their ability to interact with their environment and

improve communication. Such populations include patients with limb amputations or diseases and conditions, such as spinal cord injury, stroke, paralysis and neuromuscular disorders.

For an IDE approval, the potential benefit to the patient for any device should outweigh the potential risks, and these may vary based on medical condition. Therefore, you should consider a subject population with needs that are appropriately addressed by the device so that the potential benefits and risks are appropriately considered.

We are seeing more studies incorporating home use into the research. It is important to study BCI devices in realistic home-use environments, since lab conditions may not adequately reflect the possible risks and/or benefits the patients will experience during actual use in the environments in which the patient will be using the device.

Additionally, for home use, it may be necessary to have a caretaker who is willing, able and available to perform essential tasks related to the BCI system. Therefore, it is important to incorporate assessment of caregiver safety and their ability to assist the user (for example, time, attention, and physical ability) in the clinical study metrics.

To ensure safe use of your device in the home setting, we recommend that you specifically describe in your clinical protocol how subjects and caregivers will be trained to use the device at home.

We also recommend that you describe how you plan to assess the effectiveness of your training program. The BCI Guidance details how the investigational plan can be developed for IDE studies for implanted BCI devices.

The following is an overview of some of the key aspects of our recommendation.

First, the clinical protocol should begin with clearly-defined objectives and hypotheses and an overall statement of the purpose or objective of conducting the study, such as to evaluate the safety and effectiveness of the BCI device in the treatment of specific conditions as compared to a control.

In addition, the purpose should include a precise, medically-accepted definition of the condition to be treated and a scientifically sound rationale for the proposed clinical study.

For pivotal clinical studies, the null and alternative hypotheses for the proposed study should be stated in terms of the specific study endpoints, outcomes and parameters used to measure the success or failure of the system. The study should then be designed to test these hypotheses.

The Guidance details what your study design description should include, such as the basic elements I have listed here. You should describe whether your study is randomized; whether it is controlled, and if so, the type of control; whether the study results will be compared to performance goal, and if so, how the performance goals were derived; a description of the study success criteria; and a description of the patient success/failure if a responder analysis is being used.

Additionally, studies may include more than one treatment group, such as spinal cord injury, stroke or other conditions with proper justification as to why the different populations can be pooled. We recognize that many studies may not have well-defined performance goals or success criteria. And in those

instances, we recommend that you submit a Q-Submission to discuss this with us.

Next, study duration and follow up schedule.

In order to assess all safety and primary effectiveness outcomes sufficiently, the proposed study should include a sufficient amount of safety and an appropriate level of effectiveness data. A long-term follow-up period of at least one year is recommended due to the current lack of data regarding the long-term effectiveness of implanted electrodes and to identify any long-term safety signals.

Long-term clinical durability and reliability are important factors to long-term effectiveness of the implanted BCI device. For example, over time, implanted electrodes can lose their ability to detect signals due to physical or biological processes. Although some information on electrode durability and reliability can be obtained from animal studies, animal studies may not accurately predict long-term clinical performance in humans.

Apologies – give me just a minute to make sure that my computer is powered because it seems to be losing power. There we go – apologies.

The clinical study protocol should include sufficient information regarding the treatment parameters and protocol, including the implantation procedure, the post surgical recovery period and regimen, the treatment duration and any other surgical procedures anticipated, such as device removal.

The Guidance also provides recommendations relating to study endpoints and other outcomes. The study safety endpoints should include a characterization of all adverse events (or AEs) for all subjects, including, but not limited to,

subjects in both the treatment and control groups, if applicable, and adverse events related to the implant surgical procedure, the implantable device, and the assistive effective components.

The Guidance details information recommended with respect to safety endpoints, primary and secondary effectiveness endpoints and validation.

We note that for this family of devices in particular, patient engagement during clinical trial design may positively impact how an implanted BCI study is designed and conducted. Patient preference information may be an important factor, as previously mentioned, in the design and benefit-risk evaluation of the medical device, including implanted BCI devices.

Additionally, risk tolerance may vary depending on the severity of the disability. FDA recommends early discussion on a potential patient preference information study to ensure its regulatory relevance.

A patient-reported outcome measure can be used when the outcome of interest and desired intended use are best measured from the patient's perspective, such as pain reduction.

In such cases, it is important to select a scoring assessment that is validated by the appropriate context of use – in this case, subject, population and condition being treated – and desired intended use. Early discussion with FDA during the study design phase is important for studies of patient preference information and for studies using patient-reported outcome measures.

The informed consent document must include all required elements and be worded appropriately. We recommend ensuring that the document does not

include language that could lead subjects to overestimate the chance of personal benefit.

The statistical analysis plan will vary based upon the type of clinical trial. For example, a feasibility study may have a small number of subjects, and the clinical study protocol may be designed to lead to an understanding of the new therapy. Therefore, the statistical plan may be limited to descriptive statistics.

For a pivotal clinical study designed to demonstrate effectiveness, the study protocol should include a detailed pre-specified statistical analysis plan that includes plans to evaluate, to the extent possible, key assumptions that were made in the design of the study.

The predefined statistical analysis plan should be adhered to in analyzing the data at the conclusion of the study to support the usefulness of the evidence generated by the study.

While we understand that interest in performing ad-hoc sub-analyses in some studies, note that they are not viewed in the same way and that these should be used only to inform future studies. We recommend that you talk to us in advance about your statistical analysis plan in a Q-Submission.

The recommendations in this Guidance should be used going forward to assist in the development and submission of new IDEs, IDE Supplements and Q-Submissions. We would like to emphasize that this Guidance is not all-inclusive. Our recommendations will likely shift and evolve over time as the field and technology advance. We encourage you to contact us through the Q-Submission process with any questions about this Guidance and how it applies to your studies or devices.

I've included links to the Final Guidance and where you can submit comments and suggestions to the Agency regarding the Guidance. I've also provided links to the pertinent Guidance documents for anyone who would like more information pertaining to Q-Submissions and IDEs.

At the bottom of the slide is a link to the FDA's 2016 paper in Neuron about the regulation of neurological and physical medicine devices, which may be of interest to you as well.

And with that, I will open it up to questions.

Vivek Pinto: Hey, Heather, This is Vivek Pinto. Thanks for giving the presentation. For the folks on the Webinar, I'm the Director for Division 5B, the Division of Neuromodulation and Physical Medicine Devices.

Just to start off the questions, you know, Heather, could you describe our organizational unit as an Office and Division and also give some feedback for the audience about when they submit a review, you know, what should their expectations be? Like, how does it go through the review process for, let's say, Q-Submissions and IDEs?

Dr. Heather Dean: Sure, thanks, Vivek.

So, we're located within CDRH and OHT5, which is the Office of Neurological and Physical Medicine Devices, which has two Divisions – Divisions A and B. You know, as you mentioned, you're the Division Director for Division B – Division of Neuromodulation and Physical Medicine Devices, which has four teams – two that are focused more on neurostimulation and two that are focused more on rehabilitation.

This particular team that that covers many of the BCI devices is on the rehabilitation side. It's a team of about 10 people. And when a submission comes in, that is routed to us and assigned to one of the Lead Reviewers. And a Lead Reviewer in the team – you know, they come from a variety of backgrounds, engineering and science – you know, especially neuroscience.

And they will then put together a team of experts to review that submission. If there are detailed biocompatibility questions, they will tap biocompatibility consultants within the Center, generally, within the Division, to serve as a consultant on that file.

If there are detailed questions about sterility testing, we have consultants to cover that. We also have our colleagues in the Office of Science and Engineering Laboratories for many of the questions on the details of the scientific studies or animal studies.

So, the Lead Reviewer puts together this team of experts to answer your questions or review the marketing submission or IDE. And then, the Lead Reviewer is the main contact with the sponsor – which is that we call anyone who puts in a submission – the sponsor.

And then that Lead Reviewer is generally the conduit for questions from the review team to the sponsor. Does that answer your question?

I'm going to go with Yes. And are there additional questions?

Coordinator: As a reminder, if you would like to ask the question over the phone lines, please press Star-1 from your phone, unmute your line, and speak your name clearly, when prompted. Your name is required to introduce your questions.

We ask that you please limit yourself to one question to allow time for all questions to be addressed.

To withdraw your question, press Star-2. Again, to ask a question over the phone lines, please press Star, then 1.

One moment as we wait for any questions over the phone lines.

Our first question over the phone lines comes from (Allison Kuwayama). Your line is open.

(Allison Kuwayama): Hi, thanks so much for taking my call, and thanks so much for this Webinar. This is insanely useful, and I appreciate FDA's efforts in this field.

My question is about biocompatibility. I know that the Guidance document, as well as the slides, mentioned using (ISO-10993). I just want to know if FDA is open, based on my understanding of it being a recognized standard, of the use of ASTM F2901. I think it's -19 is the one that's recognized, and that's the *Standard Guide for Selecting Tests to Evaluate Potential Neurotoxicity of Medical Devices*. Is that one an acceptable standard to use in evaluation of these devices?

Dr. Heather Dean: That question is really beyond the scope of this particular Guidance document. I would have to talk to one of those specific biocompatibility consultants that I mentioned to answer that question.

But if you follow up with, you know, by writing to us, you can reach us either by writing to the Division of Industry and Consumer Education, or you can reach out to directly to me. My email address is

Heather.Dean@FDA.HHS.gov. And you can ask a question any time, and I will try to get back to you.

(Allison Kuwayama): Awesome. Can I ask one other question? I'm sorry, I can jump back, I'm...

Dr. Heather Dean: Sure.

((Crosstalk))

Dr. Heather Dean: And the other thing I was going to say is to go directly to the biocompatibility Guidance document, which you've probably already looked at as well.

(Allison Kuwayama): Yes, I have. It just doesn't make any mention of that standard. And I know that one is recognized by FDA for any neuro-touching devices. So, I just didn't know that one was one that was acceptable.

My guess – my, just my follow-up question was I didn't quite follow the – or understand the Right to Reference of one that's applicable. You had mentioned that one – that if the device is cleared or approved, that they don't need the Right to Reference Letter. I just I kind of missed the statement. Do you mind restating it?

Dr. Heather Dean: Sure.

(Allison Kuwayama): Thanks.

Dr. Heather Dean: So, for example, you might be using – within the indications – a prosthetic device or surgical tools, and for those we don't need a Right of Reference Letter.

But if you are using something that goes beyond the indications – for example, if an electrode array is cleared for use up to 30 days, and your study intends to implant this device for longer than 30 days, that is outside of the indications for use. And it does require a Right of Reference Letter from the manufacturer.

(Allison Kuwayama): Got it.

Dr. Heather Dean: Does that answer your question?

(Allison Kuwayama): That's helpful. It does. Thank you so much, Heather. Appreciate your help.

Dr. Heather Dean: Absolutely.

Coordinator: Our next question comes from Thomas Oxley. Your line is open.

Thomas Oxley: Hi, this is Tom. Can you hear me?

Dr. Heather Dean: Yes.

Thomas Oxley: Thank you very much, Heather. That was extremely helpful.

I had a question; I don't know how much information you can provide around the pivotal trial design, particularly for pivotal trials for Class 3 implantables. Numbers are very large.

And I wonder if you've had any discussions internally about general numbers you're expecting to see in pivotal trials, compared to what you might normally see from Class 3 implantables?

And further to that, you mentioned the term, control. Around study design for a neuroprosthesis control is quite challenging, obviously. So, I wonder if there's any broad Guidance you can provide on those issues. Thank you.

Dr. Heather Dean: No – great questions. We have not, because these devices can vary so, so much, and then the patient populations can vary so much. And your ability to recruit patients can also vary greatly, depending on the indications and the device itself.

And so, I can't give you a number – a specific number for something like that. What I would recommend is that you talk to us early and often in Q-Submissions to get an idea what we might expect in terms of, you know, patients recruited in order to collect data sufficient to demonstrate the safety and effectiveness of their device.

You can obviously put in a pre-submission at any time and talk to us and put in multiple pre-submissions.

Thomas Oxley: Thank you.

Dr. Heather Dean: You're welcome.

Oh, and what was the second part of your question? Remind me again?

Thomas Huxley: You mentioned the term, controlled, in the study design for pivotal, and that's a bit of a challenge for neuroprosthetics.

Dr. Heather Dean: It is, it is. And again, that that is going to really depend on the device design. And we need some scientific evidence that a device is effective for the indication.

So, if it's stimulation involved in rehabilitation, say, after stroke, then we might need that patient population compared to another patient population. And we'd have to very carefully look at how that is designed to make sure that there aren't confounding factors.

I don't think that we could give any general Guidance on something like that. We'd have to talk to you in a pre-submission about the details.

Thomas Huxley: Thank you very much.

Dr. Heather Dean: Absolutely. I highly recommend – you know, for things like that, before starting any study, discuss with us your controls, because the last thing you want is to collect data and spend a lot of time and money and then find out the control, you know, has some confounding factors so that we can't tease out the effect of the device.

Coordinator: We have no additional questions over the phone lines at this time. As a reminder, if you would like to ask a question, please press Star-1 from your phone.

Irene Aihie: Thank you. Before I close, Heather, would you happen to have any other closing remarks while we stand by and see if there are any other questions before we close the Webinar?

Dr. Heather Dean: I am very excited to see what happens in the next few years in this field. I am very interested. I'm a neuroscientist by training myself, and I find it incredibly exciting to see what is coming down the pipeline.

And I hope that all of you that are working in this field engage with us early and often. We want to be your partners in making sure that these devices get to the patients that need them. We do not intend to be a roadblock. We are here to help you, and we welcome questions, informally and formally.

You can reach out to us any time, and just let us know what you're thinking – what we can expect. My email is always open for questions. I am definitely interested to see where this goes in the next few years. So, thank you for being our partners in all of this.

Irene Aihie: Thank you so much.

Well, it seems like we don't have any more questions, so I'll go ahead and close. Thank you to all of our participants for your participation and thoughtful questions.

Today's presentation and transcript will be made available on the CDRH Learn Web page at www.FDA.gov/training/CDRHLearn by Friday, August 6th.

If you have additional questions about today's presentation, please use the contact information provided at the end of the slide presentation.

As always, we appreciate your feedback. Following the conclusion of today's live Webinar, please complete a short 13-question survey about your FDA CDRH Webinar experience. The survey can be found at the www.FDA.gov/CDRHWebinar immediately following the conclusion of today's live Webinar.

Again, thank you for participating. And this concludes today's Webinar.

Coordinator: Thank you for your participation in today's conference, you may disconnect at this time. Speakers, please stand by for post-call.

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