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# Example - Early Feasibility Investigational Device Exemption

## IDE Section:

Administrative Summary

# 1. Administrative Summary

This section contains:

## 1.1. Basic Administrative Information about this IDE

| | |
|---|---|
| Title of Investigation | "Early Feasibility Study of the Networked Neuroprosthesis for Grasp and Trunk Function in Spinal Cord Injury" |
| Type of Application | Original IDE, Early Feasibility Program |
| Name of Device | Networked Neuroprosthesis, NNP, NNPS, NNP-UE, NNP-T |
| Manufacturer | Case Western Reserve University |
| Name and Address of Sponsor | [redacted] |
| Sales Information | The NNP System will not be sold to the institutions or investigators involved in this study. The product will be paid for through research funding. |
| Participating Institutions | MetroHealth Medical Center |
| Name and Addresses of Investigators | [redacted] |
| Contacts for Administrative and Technical Questions | [redacted] |
| Institutional Review Board | [redacted] |

| | |
|---|---|
| | Chair: David Kuentz D.O. |
| Certification of Investigator Agreements | [redacted] hereby certifies that:<br><br>(1) All investigators who will participate in the clinical study protocol detailed in this IDE will have read and signed the Investigator Agreement and provided signed Certification prior to initiation of the study.<br>(2) The list of investigators includes the only clinical investigators who are anticipated to be participating in this study to date, and<br>(3) No investigators will be added to the study until they have signed the Investigator Agreement.<br>(4) None of the above listed investigators has been involved in a research investigation that has been terminated<br><br>Signed agreements will be kept at Case Western Reserve University, along with the investigators' CVs, which describe their relevant past experience. If any investigator has been terminated from a project, an explanation of the circumstances will also be filed, as well as statements of any financial conflict. |

## 1.2. Purpose of Early Feasibility IDE

**We are requesting 10 patients and 1 clinical site for this Early Feasibility IDE.** This Early Feasibility Study will utilize the "Networked Neuroprosthetic" (NNP) System to:

1) Explore the feasibility of providing multiple functions to individuals with cervical level spinal cord injury (SCI).
2) Use the learnings from this study to refine the NNP technology and inform the design of a future multi-center pivotal clinical trial. The results of the pivotal clinical trial are intended to generate the safety and effectiveness evidence to support a future marketing application to the FDA.

The specific goals of this early feasibility study include the following:

- Finalize technology design, particularly ergonomically-related design aspects.
- Optimize the recharging algorithm to balance the need for rapid recharging and the need to minimize heating due to power transfer.
- Evaluate and finalize the control algorithms that enable users to easily and intuitively control the functions of the NNP System.
- Finalize the implantation procedure.
- Finalize software features related to system customization with each subject.
- Finalize methods and procedures for most effectively training subjects in the use of the system.
- Establish clinical trial endpoints that are appropriate for a multi-functional system.
- Finalize the follow-up schedule, balancing critical data collection with the practical issues related to the participation of severely paralyzed subjects (e.g., travel considerations, attendant care, etc.).

## 1.3. Overview of the IDE

This Early Feasibility IDE will explore methods to provide hand grasp and release, overhead and forward reaching ability, and seated wheelchair stability to subjects with tetraplegia. Because the system involves both the coordinated activation of muscles and the integrated use of myoelectric control signals, this Early Feasibility IDE will be used to optimize and individualize these programmed settings, eventually resulting in improved instructions for use. If successful, this system will provide more motor function to these individuals than can be supplied through any other implanted system or rehabilitation modality, as noted in **3.0 Intended Clinical Use**.

This study will utilize the "Networked Neuroprosthetic" (NNP) System to provide grasp and reach for cervical level SCI, the technical details of which can be found in **2.0 Device Description**. The NNP System consists of a network of implanted modules that perform the electrical stimulation, signal acquisition, signal processing, powering, and communication functions necessary to implement a fully-implanted neuroprosthetic system. The network design is a critical advantage of the NNP System, allowing modules to be placed close to the target region of the body where function is required, and allowing new functional configurations to be added on over time.

As described in more detail in **8.0 Investigational Plan**, the proposed Early Feasibility study of the NNP System includes the screening, implantation and evaluation of up to 10

cervical level spinal cord injured individuals at one investigational site. Each subject will undergo training and functional evaluation to demonstrate the efficacy, safety, and clinical utility of the neuroprosthesis. Hand function and trunk stability will be compared before and after implantation; with and without the neuroprosthesis turned on; and with both functions evaluated separately and combined. Each subject will serve as his or her own concomitant control. Outcome measures to evaluate health, function, and quality of life will be assessed. Complications will be followed and complication rate will be determined. Subjects will be re-evaluated at six months and one year post implant. Two patients followed for six months will serve as the *minimum* data set before considering an expansion to a multi-center pivotal clinical trial.

As noted in **4.0 Prior Clinical Studies** and **5.0 Prior *In Vivo* Studies**, we believe sufficient information has been acquired through prior studies to demonstrate the enhanced functionality of the networked system. This first-in-man study is being conducted to evaluate if the NNP System can be used to restore grasp and reach function in individuals with cervical level spinal cord injuries. The functions to be provided, and the manner of generating those functions, are directly analogous to existing upper extremity neuroprosthetic systems that we are currently evaluating under IDE G950116. However, the NNP System offers significant advantages due to the modular nature of the NNP and the presence of implanted power and signal processing. These latter features free the user from the need for any externally worn components during daily use. We believe these advantages may ultimately result in increased functionality of the NNP System compared to previous neuroprosthetic systems.

Evaluation of the NNP has proceeded through a risk-based approach, as summarized in **6.0 Device Evaluation**, in which design principles and prior testing are leveraged to permit an appropriately limited subset of testing for the NNP. Based on feedback provided by FDA (noted in the next section, below), we have completed that testing in order to fully characterize the NNP's safety and performance prior to our first human implant. More detailed reports can be found in **Appendices D – K**.

**We conclude from our Risk Analysis and our Device Evaluation Strategy that the current state of knowledge about the NNP renders it appropriate for a limited Early Feasibility clinical trial.** In other words, based on our Device Evaluation Strategy, we believe:

1) All risks of significance have been either addressed through formal engineering design, or characterized fully or partially through prior clinical, animal, and bench testing;
2) All remaining gaps in evidence have been identified, discussed with FDA, and there is agreement as to the level of characterization and mitigation that will be performed *at this stage*, versus what will be performed later; and
3) This Early Feasibility IDE is designed so that lessons learned from a small number of real-world clinical cases will allow us to further develop the technology and refine the investigational plan prior to conducting a pivotal clinical trial.

## 1.4. Response to Previous Issues

### 1.4.1. Summary of Response to IDE G110005

We previously submitted an original Investigational Device Exemption application (G110005) on January 3, 2011, requesting permission to initiate a clinical evaluation of the Networked Neuroprosthetic (NNP) System to provide grasp and trunk function for individuals with cervical level spinal cord injury: "Clinical Evaluation of the Networked Neuroprosthesis for Grasp and Reach"; Sponsor Investigator: [redacted]

A **disapproval letter for G110005** was received from the FDA Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices on February 4th, 2011.

**The issues raised in the G110005 disapproval letter are similar to, and superseded by, those discussed in detail under our pre-IDE application, I111144. In addressing the issues raised in the pre-IDE process we believe we have also addressed the issues raised in G110005.**

### 1.4.2. Summary of Response to Pre-IDE I111144

In its August 29, 2012 letter, FDA identified 33 issues to be addressed in our subsequent IDE submission. In this section, we have provided a high-level response to each of the issues, as well as references to the sections in our IDE where more complete answers can be found:

**FDA Response to Specific Questions:**
*Sponsor Question 1: Are the preclinical **biocompatibility studies** outlined in Section D.2.a adequate to proceed to an Early Feasibility Study?*

**FDA Response:**
1. After reviewing the information you provide in Section D and Appendix 7, we believe your general approach for demonstrating that your device is biocompatible is sound. In Appendix 7, you list the materials implanted in the body with direct tissue contact (Table 7-2) and identify past or current clinical use of each material (Table 7-3). However, for some materials listed in Table 7-3, you do not identify past or current clinical use (e.g., EPOTEK 301). For these materials, you need to provide one of the following types of information when you submit your IDE:
   - A reference to a previous FDA approval [e.g., PMA number, IDE number, 510(k)] for the material when it was used in a similar way (e.g., implanted in the body) and obtained from the same source.
   - A letter from the manufacturer of the material which gives us permission to look at their Master File.
   - The biocompatibility data for the materials according to ISO 10993-1.

**Sponsor Reply:**
**Please refer to *Appendix D - Biocompatibility*.**

**All patient-contacting materials used in the NNP have been identified and are listed in Tables 1-6 of *Appendix D - Biocompatibility*. Virtually all materials have a long history of prior use in our own previous IDEs, as noted in the tables. As agreed-to in our pre-IDE discussion, for those patient-contacting materials that are new in this application, we have provided right of reference letters for the materials Master Files filed with FDA. In addition, cytotoxicity testing was conducted for our remote module and power module, and the NAMSA test reports are provided in *Appendix D - Biocompatibility*.**

*Sponsor Question 2: Is our approach to **electromagnetic compatibility testing** adequate to proceed to an Early Feasibility Study? Our approach is outlined in Section D.2.c, and our proposed preclinical testing is described in Appendix 19.*

**FDA Response:**

2. Your strategy for electromagnetic compatibility (EMC) testing (i.e., as described in your email dated August 2, 2012) appears to generally address many of the EMC-related risk areas for your proposed early feasibility study. The results and findings from the testing should provide good insight into the expected performance of the NPP system device, though these cannot be assessed until the data and analyses are available. We recommend that you consult the latest list of FDA- recognized standards and note that the EN version of the IEC 60601-1-2 standard is not on the list, which might bear on your choice of reference standard. The following points are suggestions that are intended to aid you in the planning and reporting of the EMC testing.

   **Sponsor Reply 2:**
   **Please refer to *Appendix F – Electromagnetic Compatibility Testing*.**

   a. When the EMC testing is performed, please prepare a clear summary of all EMC testing (emissions and immunity) of your device system with the test results and data to support claims for the immunity to electromagnetic interference (EMI) of the device system. This should include when the testing was performed, the versions of software/firmware/hardware, and justification for how this represents the NPP system device that will be used in the study.

      **Sponsor Reply 2a:**
      **Please refer to *Appendix F – Electromagnetic Compatibility Testing*. Testing was conducted in both "Normal Mode" and "Charging Mode". Normal Mode included all the implanted components needed for a full hand and trunk system running in high-speed myoelectric recording mode while simultaneously stimulating at maximum levels. Charging Mode evaluated the Power Module (implant) running in charging mode with a maximum possible requested charge rate of 100mA per battery, while communicating with external system components. These conditions reflected a sufficiently challenging clinical scenario in terms of both hardware used in the configured set-up and functions evaluated.**

   b. The information should include a brief explanation of how each EMC test was performed and how the testing for each mode addresses the risks for EMI and demonstrates EMC for the complete device system and all components. This should include a clear statement about the device intended use correlated with its essential

performance as per the IEC 60601-1-2 standard you reference. Ideally, the EMC immunity testing should include the active wireless connections with traffic flow that simulates use conditions. The reported information should contain a brief explanation of how the testing addresses data connections, alarms, and the time for the device to perform its function.

**Sponsor Reply 2b:**
**Please refer to *Appendix F – Electromagnetic Compatibility Testing*.**
**EMC testing was conducted in accordance with the IEC 60601-1-2 standard, using simulated use conditions corresponding to functional use and charging. A high-challenge set-up was used involving a large number of active implantable components used both with and without communication to external units (see response to 2a, above). Each element of essential performance, as defined in IEC 60601-1-2, was documented with no observed degradations in performance. Other observations (not considered essential performance) were also documented.**

c. The information should include the specific pass/fail criteria for each of the EMC tests, justifications for these criteria, and how these were quantified and measured. For example, please clarify your ESD testing pass/fail criteria (p. 6 of document attached to August 2 email) and justify the allowance for failed components in terms of device safety and effectiveness. Typically, a failed component during such a test, that reveals a risk of additional surgery to repair or replace the implanted device, is considered to be a failed test.

**Sponsor Reply 2c:**
**Please refer to *Appendix F – Electromagnetic Compatibility Testing*. The Pass/Fail criteria for Immunity Testing were based on IEC 60601-1-2. No degradations in essential performance were noted in the Immunity test. The Pass/Fail criteria for Emissions Testing were based on FCC 47CFR15.109. The Emissions test passed the Class B (Industrial) limit; however, the Class A (Residential) limit was exceeded, indicating that the NNP is a weak emitter in a narrow range of Class A frequencies.**

**The methodology for ESD Testing of the *external* components was based on IEC 60601-1-2:2001, and all tests passed. This standard does not specify methodology to be used for ESD testing of *internal* components, however we chose to use similar methods and acceptance criteria. All tests passed. No failures were observed during ESD testing that would correspond to a clinical scenario in which an implanted device would have to undergo revision or replacement.**

d. The information should address any modifications to the NPP system that were needed in order to pass the EMC testing and any device changes subsequent to this testing. This should include a description of the modification or change, the effect on EMC of the modification/change, and EMC re-testing and findings. In addition, you should include a clear statement that all modifications will be incorporated into all the devices that will be used in the study.

**Sponsor Reply 2d:**

**Based on our Risk Analysis, our Device Evaluation Strategy and prior discussions with FDA, we do not intend to make modifications to our system to address EMC-related issues *prior* to embarking on the Early Feasibility study. Our test results indicate no safety-related effects: there were no degradations in essential performance in the Immunity test; in the Emissions Test, the NNP System complies with Class B (Industrial) limits on emissions, but is a very weak emitter in a narrow range of Class A (Residential) frequencies. If it becomes necessary to make modifications to address EMC issues in the future, we will submit an IDE Supplement along with a rationale for the proposed changes.**

e. While the information and labeling you provide address several common electromagnetic sources, it remains unclear how you intend to address EMI from sources such as diathermy, cellular telephones, and RFID. Please address the risks posed by these sources. A mitigation strategy for these risks could include appropriate labeling and training.

**Sponsor Reply 2e:**
**Please refer to *Section 13 – Draft Labeling*.**

- **Warnings and precautions have been added to the Patient Manual to address concerns about MRI exposure, other electrical stimulation systems, ultrasound, lithotripsy, x-rays, mammograms, and diathermy.**
- **Test results support safe use of the NNP with cell phones, and this is noted in the labeling.**

**User training will also emphasize the effects of sources of EMI.**

f. The information about emissions testing includes a proposal to evaluate use of the NPP system with powered wheelchairs. This seems like a reasonable preliminary approach to a potential source of EMI. However, the information you provide is unclear about the criteria for "incompatible operation" and what is to be done with the information and findings. You might wish to reference the ISO 7176 standard for powered wheelchairs, part 21 deals with EMC as does the ANSI/RESNA WC2 part 21 standard.

**Sponsor Reply 2d:**
**Please refer to *8.0 Investigational Plan*. Subjects' wheelchairs will be tested for compatibility with the system prior to being enrolled in the study. Incompatibility between the NNP system and the subject's wheelchair will be handled on a case-by-case basis and may form the basis for excluding a subject from the study.**

3. Your user's manual should contain the labeling called out in the IEC 60601-1-2 standard. In addition, the labeling and training should include information about recognizing and dealing with EMI if it is encountered. Some specific comments on the labeling related to EMC and wireless technology follow:

a. The labeling and training you provide should be augmented to include information giving a description of the wireless technology and its capabilities and limitations such as the quality of service needed, range, and latency limitations. This should include how to recognize and resolve wireless technology problems and where and how problems can be reported.

**Sponsor Reply 3a:**
**Please refer to *13.0 Draft Labeling*. The section entitled, "When to Call Us" now contains a statement, "If you experience any unusual performance of the system that may be caused by proximity to electromagnetic sources. Any unusual performance of the system should be reported so that we can trouble-shoot possible causes."**

b. In your user's manual, we recommend that you revise Point D under Contraindications to clarify that no active implantable or body worn medical devices should be located in the body area or electrical current pathways of the NPP system device. This should include specific examples of medical devices such as cardiac pacemakers, implantable cardioverter defibrillators, implantable neurostimulators, body worn insulin pumps, body worn patient monitoring devices (particularly those with wireless technology).

**Sponsor Reply 3b:**
**Please refer to *8.0 Investigational Plan*. Study subjects will be <u>excluded</u> if they have an "active implantable medical device with unknown or untested interaction with the NNP implant." We do not believe evidence supports a contraindication statement in the labeling at this time. Results of the clinical study and subsequent EM characterization will provide evidence necessary to support any contraindications for the system.**

c. The labeling should include markings according to the ASTM F2503-08 document "Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment". In the case of the NPP system it should be marked as MR unsafe.

**Sponsor Reply 3c:**
**Please refer to *13.0 Draft Labeling*. The package label for implanted components will indicate that the device is MR Unsafe and will include appropriate markings to indicate MR Unsafe.**

d. A warning against exposure to diathermy should be included in the user's manual. In addition, in the absence of specific EMC testing for cellular telephones there should be a warning to keep the phones at an appropriate separation distance from the site of the active implanted portions of the NPP system. Many implantable cardiac pacemakers and neurostimulation devices have been tested for EMC with these RF sources and incorporate specific filtering and shielding. Because the NPP system has not been tested in this way, a reasonable solution would be to cite the separation distance recommended for the 1 to 3 W maximum output allowed for the cellular phones by the IEC 60601-1-2 standard.

**Sponsor Reply 3c:**
**Please refer to *13.0 Draft Labeling*. The Patient Manual has been updated to include a warning concerning exposure to diathermy. Our testing supports the safe use of cell phones, wifi, and cordless phones and this has been added to the labeling.**

e. The information on page 5 of your user's manual should include a warning about not using the magnet over any other medical device. As mentioned in comment 6, for the purposes of your study, we believe you should exclude patients with any active implantable device. The warning should nevertheless be included in the labeling as an additional risk mitigation.

**Sponsor Reply 3e:**
**Please refer to *13.0 Draft Labeling*. The Patient Manual has been updated to include a warning about pacemaker magnets.**

f. The list of restrictions on the use of the GT NPP system (page 6 in the user's manual under point A) should include welding equipment, high voltage industrial equipment, and RFID equipment and products. The information under point C. 3. on p.6 should be clarified to instruct the user to note the circumstances and any identifiable RF source (e.g., cell phone, portable radio transmitter) in the vicinity. The information under point C. 1. on p.7 should be revised to include security systems such as metal detectors and anti-theft systems like those in retail stores.

**Sponsor Reply 3f:**
**Please refer to *13.0 Draft Labeling*. The Patient Manual has been updated to include a caution about proximity to these sources.**

4. Your proposed testing to address wireless coexistence may not be adequate to fully address the risks related to this issue. While you offer explanations about the NPP system intended design performance, we generally recommend more inclusive testing to demonstrate wireless coexistence with RF emitters (e.g., cellular telephones, RFID, RF and microwave diathermy, and leakage from microwave ovens) that can be expected in most use environments. The information in your August 2, 2012 EMC strategy includes testing of like device systems at a separation distance of 1 m. If this testing is limited to the 1 m separation distance then this limitation should be included in the labeling and training. The testing and information in this area should include the NPP system device wireless specifications, characteristics, and functions, testing results, and acceptable tolerances for: data integrity (ensuring proper wireless function), data latency (ensuring functions occur in a timely fashion), and coexistence with other RF wireless products.

**Sponsor Reply 4:**
**Please refer to *Appendix F – Electromagnetic Compatibility Testing*. Based on the results of our formal testing, we conclude that no additional *formal* testing of the NNP System is warranted at this stage. Rather, *informal* testing with RFID readers used in the hospital and nearby retail providers will be performed and documented. If necessary, these potential threats will be identified as warnings in the User's Manual and during patient training, and a development plan for further mitigation will be established.**

5. We recommend that the labeling for the NNP System include a clear description of the wireless technology and information about how the system should be configured and operated, with details such as the needed quality of service, security requirements, and how to deal with risks and problems that may arise.

**Sponsor Reply 5:**
**A Product Specification Sheet will be developed as part of the system labeling prior to expanding this study to a multi-center pivotal clinical trial.**

6. For the purpose of the proposed study, we recommend that the exclusion criteria be more specific to avoid additional risks for users having active implanted, or body worn or mounted medical devices. In addition, use of the NNP magnet might inadvertently de-activate or affect such devices. Thus, we believe that the list of exclusion criteria should be augmented to include patients with any active implantable devices such as, but not limited to, implantable cardiac pacemakers, implantable cardiac defibrillators/cardioverters or cardiac rhythm devices, implantable neurostimulation devices, body worn or implanted drug or insulin pumps, body worn or implanted physiological or blood glucose monitoring devices.

**Sponsor Reply 36:**
**Please refer to *8.0 Investigational Plan*. Subjects will be <u>excluded</u> if they have an "active implantable medical device with unknown or untested interaction with the NNP implant."**

*Sponsor Question 3: Is our approach to addressing the **risks related to device heating** during recharge, as described in Section D.2.b, adequate to proceed to an Early Feasibility Study?*

**FDA Response:**

7. As we stated during our in-person meeting with you on July 16, 2012, your test method to address risks related to device heating during recharge is conservative when compared to *in vivo* conditions and we have no major concerns with your approach. However, in the following comments, we provide some additional recommendations regarding the description and testing of your implanted batteries.

   **Sponsor Reply 7:**
   **For Questions 7 – 13, please refer to *Appendix I – Battery Testing and Heating Characterization*. In our pre-IDE discussions, we outlined an approach to characterizing heating that was based on testing performed in open air, considered a worst-case condition. Since then, we have characterized implant heating in a saline phantom, which more closely simulates the clinical scenario. These tests demonstrated that the Power Module meets the criteria for safe temperature rises for both charging and discharging, exhibiting < 2 deg.C rise without software limits (e.g., single-fault condition). As discussed in our Early Feasibility IDE interactions, we are using the Early Feasibility IDE to fully develop the functional requirements for the charging feature, including potentially making modifications to the external recharging coil (see Question 8, below), as well as optimizing the recharge session duration and power transfer levels.**

8. You indicate that a hard plastic spacer will be attached to the external charging coil to prevent the patient from violating the minimum distance requirement that is required between the charging coil and the implantable charging system. Please provide a detailed description of this hard plastic spacer and a rationale for why you believe it mitigates the risk of device heating during recharge.

   **Sponsor Reply 8:**
   **Please refer to our response to Question 7; additional details are provided in *Appendix I – Battery Testing and Heating Characterization*. At the time of our pre-IDE submission in 2011, a hard plastic spacer was envisioned as a means of maintaining a minimum distance requirement for the external charging coil. Since then, our need for this feature is unlikely, given the results of our most recent heating characterization tests. Because battery recharge heating is a critical consideration for our system, but because we need to actually perform some of the characterization testing with our first human subject(s), we have not proceeded with a complete design of this feature. The spacer – if necessary – will be designed as part of the Early Feasibility IDE study following well-supervised, in-clinic recharging sessions. During this process, attention will be given to human factors as well as the choice of patient-contacting materials.**

9. Please clarify how your device signals the user that it is time to charge the batteries.

   **Sponsor Reply 9:**
   **At this time, the implanted system does not provide the user with any type of audible or sensory alert that the battery needs charging. Instead, the subject can interrogate the Control Tower, which is typically kept within easy reach on the**

**their wheelchair, in order to see the battery fuel gauge. This feature of the Control Tower is now better described in *2.0 Device Description*.**

10. In section B of the document attached to your email dated July 31, 2012 ("… NNP Power Module Battery Protection – v2"), you indicate that when the battery sinks a current of 6 amp to a resistive load, the battery cell temperature reaches a temperature of 115 degrees C. Please provide the case temperature for the power module in this situation. We are interested in knowing the case temperature of the power module because this test is also a good simulation of an internal cell short of the implanted batteries.

    **Sponsor Reply 10:**
    **Please refer to *Appendix I – Battery Testing and Heating Characterization*. To address this question, a test was performed under conditions simulating an internal short of one of the batteries. The maximum temperatures measured (referenced to body temperature) on the external surfaces of the Power Module capsule were 37.4 °C on the top surface, and 47.9 °C on the bottom surface. Temperature rises greater than 2 °C persisted for approximately 23 minutes in this test.**

11. Please provide reliability test data and any history (if available) of failure of your batteries in any other medical device or commercial product.

    **Sponsor Reply 11:**
    **We have no prior experience with this specific battery technology. A summary of published information about the safety of Li-ion rechargeable batteries can be found in *4.0 Prior Clinical Studies*. In addition, the performance of these Quallion cells can be found in *Appendix I – Battery Testing and Heating Characterization*.**

12. In Figure 3 of the document attached to your July 31, 2012 email (details of the battery terminal connections), you show that there are fuses in line with the battery terminals to prevent a direct short. Please provide the case temperature of the power unit when the maximum current (i.e., just below the trip current of the fuses) is drawn from the batteries.

    **Sponsor Reply 12:**
    **Please refer to *Appendix I – Battery Testing and Heating Characterization*. To address this question, a test was performed under conditions simulating the scenario when all three cells are sourcing current at a level just below the circuit protection threshold. The maximum temperatures measured (referenced to body temperature) on the external surfaces of the Power Module capsule were 41.7 °C on the top surface, and 40.2 °C on the bottom surface. Post experimental evaluation of the three cells showed no discernable physical or mechanical changes resulting from the high-current discharge.**

13. You identify the cells of the battery as Quallion QL0200I-A Product Specification, PS0006, 2003-Aug-13. Please clarify if this cell has a separator that closes its holes when a given temperature has been exceeded within the cell.

**Sponsor Reply 13:**
**Many of the design details of the QL0200I-A battery are proprietary to Quallion, Inc., and a 'separator' is not specifically called-out in the Quallion literature; however, the battery does contain a 'Self-Extinguishing Electrolyte System' that serves a similar purpose. This feature is described more fully in *Appendix I – Battery Testing*.**

*Sponsor Question 4: Is our justification for **considering software to be a "minor level of concern"** adequate, as described in Appendix 6 (and based on the Risk Analysis, Appendix 5)? We recognize that software operating an active implantable device is nearly always classified as a major level of concern. Our justification is based on the fact that our system is not life-sustaining and does not cause harm to the user in the event that it suddenly stops stimulating or continues to stimulate when it should stop.*

**FDA Response:**

14. We do not agree with your classification of the software as "minor level of concern" for the following reasons. First, the GT NNP system is a significant risk device, and according to our guidance document titled "Content of Premarket Submissions for Software Contained in Medical Devices", software in such devices should be classified as "major level of concern". Second, we acknowledge that you have implemented several hazard mitigations, many of them through hardware design, to reduce risks associated with your fully implanted software device. However, our guidance document calls for you to assess the level of concern "…as though you have not implemented hazard mitigations." (p. 6 of guidance document cited above). For these reasons, we believe the level of concern for your device should be classified as "Major." Please provide us with the appropriate documentation when you submit your IDE (i.e., as specified in Table 3 of the guidance document cited above).

    **Sponsor Reply 14:**
    **We have followed the above-mentioned guidance document and have concluded that our software is a Moderate Level of Concern, and have proceeded accordingly. Please refer to *Appendix H – Software Description and V&V* for our rationale.**

*Sponsor Question 5: Is our strategy regarding **proposed system modifications**, as described in Section F, adequate, i.e. does it fit within the intent of the Early Feasibility guidance, particularly as it relates to "a broader array of modifications to the device under 5-day notification"?*

**FDA Response:**

15. Yes, your strategy is adequate and we will judge the merits of each proposal when you fully explain each one in your IDE.

**Sponsor Reply 15:**

**Please refer to *6.4.1 Device Evaluation – Anticipated Design Iterations* for a recap of our anticipated system modifications. Modifications to the NNP will be submitted as IDE/Supplements (either 5-Day Notices, or supplements requiring approval), as previously noted, and we intend to seek informal guidance from FDA on these modifications as they arise, prior to submitting.**

*Sponsor Question 6: Are our **risk mitigation strategies**, as outlined in Section E.2.a, appropriate for an Early Feasibility Study?*

**FDA Response:**

16. In general, the risk mitigation strategies you propose are appropriate and adequate. However, we recommend that you carefully consider our comments regarding the preclinical test plan you've designed to verify and validate the effectiveness of these mitigations.

**Sponsor Reply 16:**

**Please refer to *Appendix C – Risk Analysis*, and *6.0 Device Evaluation*. Following the guidance on Early Feasibility Studies and input from FDA on our pre-IDE, we have structured our Device Evaluation Plan to follow a risk-based approach. From these, we conclude that the remaining evidence gaps are appropriate for a limited Early Feasibility clinical trial. Based on our Risk Analysis and Device Evaluation Strategy, we believe:**

- **All risks of significance have been addressed either through formal engineering design, or characterized fully or partially through prior clinical, animal, and bench testing; and**
- **All remaining gaps in evidence have been identified, discussed with FDA, and there is agreement as to the level of characterization and mitigation that will be performed *at this stage*, versus what will be performed prior to any expansion of the study.**
- **This Early Feasibility IDE is designed so that lessons learned from a small number of real-world clinical cases will allow us to further develop the technology and refine the investigational plan prior to conducting a pivotal clinical trial.**

*General FDA Comments:* ***Sterilization***

17. You report that sterilization of the implantable NNP system components will be performed using ethylene oxide (EO) gas based on an overkill approach for a single lot release process at Ethox International (Rush, NY). Please provide the test report for validation of the EO sterilization process, including EO residuals testing in your IDE submission.

**Sponsor Reply 17:**
**Please refer to *Appendix G – Sterilization*. Please note, based on recent discussions with FDA (Carlos Pena and Felipe Aguel, email and telecon discussions, October, 2014), we are taking the following approach with our sterilization for the EFS IDE:**

**We agree that the single-lot batch release protocol will not result in a fully validated sterilization process required for routine sterilization. However, following exposure performed under the CWRU single-lot batch release protocol, the NNP system components will be considered sterile in accordance with ISO 11135-1:2007, and appropriate for human implant use if:**

- **An SAL of $10^{-6}$ is achieved, *and***
- **The EO residual levels are below the allowable limits per ISO 10993-7:2008(R)2012.**

**No devices will be implanted that do not meet these two criteria.**

**Please also see *Section 1.4.3 Response to FDA email dated 11/12/14*, below, for additional points.**

18. Please specify the validated EO sterilization and aeration parameters in your IDE submission.

**Sponsor Reply 18:**
**Please refer to our response to Question 17, above.**

19. Please describe the validated maximum load configuration, including dunnage configuration in your IDE submission.

**Sponsor Reply 19:**
**The following table from *Appendix G – Sterilization* shows the maximum content of a single sterilization batch:**

| Implantables Included in Sterilization Batch (Maximum Load) | Quantity in Batch | Quantity in Package (Double Barrier Tyvek Pouch) | Used in Single Surgery NNP Application |
|---|---|---|---|
| Power Module – PM1 + 4 Port Plugs | 3 | 1 | 1 |
| Stimulator Module – PG4 + 8 Port Plugs | 13 | 1 | 5 |
| Myoelectric Recording Module – BP2 + 8 Port Plugs | 5 | 1 | 2 |
| Network Cables - NC | 18 | 1 | 7 |
| Intramuscular Stimulating Electrode | 45 | 1 | 16 |
| Intramuscular Recording Electrode | 8 | 1 | 3 |
| Epimyseal Stimulating Electrode | 5 | 1 | 4 |

| | | | |
|---|---|---|---|
| Epimyseal Recording Electrode | 2 | 1 | 1 |
| Spare Port Plug | 5 | 5 | 0-5 |

20. Your Process Challenge Devices (PCDs: inoculated products seeded with $10^6$ Bacillus atrophaeus spores) were identified by earlier testing as the most challenging sterilization targets in your validation of the EO sterilization process. Please provide the test reports which demonstrate you inoculated the most difficult to sterilize locations on the PCDs.

    **Sponsor Reply 20:**
    **Please refer to our response to Question 17, above.**

21. Please provide your product adoption analysis per AAMI TIR28:2009. Please provide product adoption and process equivalence for ethylene oxide sterilization in a side-by-side tabular format, and comparative resistance testing used, to justify the adoption of your other system components into the validated EO sterilization cycle for each product family's master product.

    **Sponsor Reply 21:**
    **As noted in *Appendix G – Sterilization*, we are performing a new product sterilization validation protocol; this will not be an adopted product.**

22. According to ANSI/AAMI/ISO 10993-7:2008. Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals, "Consideration should be given for proportioning the limits downward if multiple devices with the residue of concern are used at one time". Your NNP system consists of a network of up to ten implanted modules, connected via power and communication cabling, that function together as one coordinated implanted neuroprosthesis. Table 21-1 in your pre-submission lists the specific components sterilized for implantation and the typical number of units utilized per surgery. Please establish your EO residual lot release specifications for the NNP system components based on the worst-case number of units utilized per surgery.

    **Sponsor Reply 22:**
    **Please refer to *Appendix G – Sterilization*.**

*General FDA Comments:* ***Pyrogen Testing***

23. Please provide test reports in your submission for bacterial endotoxins testing, including methodology used, inhibition and enhancement testing, and endotoxins specification. Please be aware that FDA's 1987 Guideline for Limulus Amebocyte Lysate (LAL) testing is withdrawn. For guidance in this matter, you should refer to FDA's Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers, June 2012, which can be found at the following location: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/UCM310098.pdf. We recommend that you refer specifically to Question 11. What are the endotoxins limits for medical devices? and the response which includes the following: The Center for Devices and Radiological Health (CDRH) has adopted the USP Endotoxin Reference Standard and limits for medical device extracts expressed in EU/mL. USP Chapter <161> Transfusion and Infusion Assemblies and Similar Medical Devices provides the limits for medical devices within its scope. Therefore, the endotoxins limit is 0.5 EU/mL or 20 EU/device using the extraction volume recommendation of 40 mL for the NNP system implantable components, as discussed in our next comment below.

    **Sponsor Reply 23:**
    **Please refer to *Appendix G – Sterilization*.**

24. In response to Question 11 in FDA's Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers, June 2012, we recommend that during the same surgical procedure or placement in the same surgical site, multiple units of the same device from one manufacturer should generally meet the same endotoxins limit as a single device administered during the procedure. Applying this recommendation to your case means that all modules and cables implanted in a study subject, when combined and considered as a one device, should meet the overall endotoxin limit or justify any deviation from the limit identified in the guidance. Please establish bacterial endotoxins release specification and lot release procedures for the worst-case number of modules and cables utilized during surgery.

    **Sponsor Reply 24:**
    **Please refer to *Appendix G – Sterilization*. In developing the protocol with Moog Medical, we have considered the worst-case number of modules and cables used in surgery, per FDA's recommendation.**

*General FDA Comments:* ***Packaging and Shelf Life***

25. In your IDE submission, please indicate in your package description whether your device is packaged in a single or double sterile barrier pouch system and include descriptions of any protective packaging materials used to package your device.

    **Sponsor Reply 25:**
    **Please refer to *Appendix G – Sterilization*. Our package description now specifies that each of the implantable NNP System components are separately packaged in a Tyvek-poly peel double barrier pouch system.**

26. You state that given the limited distribution (1 site only) and tight control the Cleveland FES Center has of these investigational devices, additional shipping / storage testing is not planned at this time. We believe this rationale is inadequate justification for not performing simulated distribution and shelf-life studies on your packaged device components. Please include test reports for simulated distribution testing for all packaged device components. In addition, please provide shelf-life studies to establish expiration dating for your sterile device components in your submission.

    **Sponsor Reply 26:**
    **Please refer to *Appendix G - Sterilization*. Our packaging and sealing process and procedure is identical to that used in our prior IDEs G900108, G040214, G110018, where seal integrity and seal strength were evaluated by (then) Ethox International after applying a simulated ship test compliant to ASTM D4169. The IST System implantables used in our previous IDEs, are similar in size, shape, and weight to the NNP System components, and, as such, for this first-in-human EFS-IDE study in a maximum of 10 subjects will be enrolled, testing of the packaging procedure has not been performed. Such testing will be performed prior to expansion of the study to a pivotal clinical trial.**

*General FDA Comments:* ***Additional Comments***

27. You provide a table of maximum stimulation parameters for commercial and other human use devices (Table 4-1 in Appendix 4). Please revise this table to include the pertinent information for the GT NNP device (i.e., for all PG/electrode combinations). Please also add the 510(k), PMA, or IDE number(s) for the previously cleared/approved devices in the table.

    **Sponsor Reply 27:**
    **This table now appears as Table 4-2 in *4.0 Prior Clinical Studies,* Summary of Clinical Use of Electrical Stimulation, and has been modified to include IDE and PMA numbers (where known), as well as to indicate the stimulation levels used by the NNP. Stimulation levels for the NNP remain with the safe limits used by other devices studied under IDE or approved.**

28. You describe your hermeticity test plan in Appendix 11 and state that it is based on MIL-STD-883. Please explain why you chose this standard, and explain why you believe conforming to this standard demonstrates your implanted modules and feedthroughs are hermetically sealed.

    **Sponsor Reply 28:**
    **The MIL-STD-883 is a universally accepted test designed to determine the effectiveness of the seal of microelectronic devices with designed internal cavities, and is considered appropriate for medical microcircuits housed within an implantable case. It can be used to identify gross and fine leaks associated with welded titanium cases.**

29. Please explain in detail how you plan to test the subject device for DC leakage current.

    **Sponsor Reply 29:**
    **Please refer to *Appendix L – Control Tower System Testing*. Testing was conducted following methods described in IEC60601-1, Section 19.4g. Because the Control Tower System makes no intentional electrical connection to the user (such as EMG electrodes), DC leakage current testing was not characterized. The Control Tower System passed the normal condition and single-fault condition limits for all enclosure and patient leakage currents tested.**

30. Please provide a list of all electrical safety standards with which you plan to claim conformance.

    **Sponsor Reply 30:**
    **Please refer to *Appendix L – Control Tower System Testing*. We are not claiming full conformity to any recognized consensus standards at this stage. We did follow key elements of UL 60601-1:2003, IEC 60601-1-1:2000, IEC 60601-1-2:2001 and BS EN 60601-1-11:2010 to guide the design and testing of the Control Tower. The key elements are summarized in Table L-3 of Appendix L. As we are able to confirm performance of the system against these standards, we may claim conformance in a future application.**

31. Please explain why you believe that in an emergency situation in which the device needs to be disabled immediately, aligning the emergency shut down magnet in correct position is a reasonable requirement for the subject or caregiver to perform.

**Sponsor Reply 31:**
**Please refer to *2.4.4 Principles of Failsafe Function* for an explanation of this feature. Under normal operating conditions, stimulation through the pulse generator is under constant control from the software, and the "Stop Stim" command is the highest priority command of the system, interrupting all other commands. In a typical scenario, the subject would activate the "Stop Stim" command to turn off power to the implanted system. However, it is necessary to provide a rapid shutdown of the implanted NNP System components in the anomalous situation where the commands from the control unit fail to communicate, or when the modules stop responding to external commands. It is important to note that such a hypothetical situation would not be considered an "emergency," because of multiple other safety features that prevent harm to subjects. Locating, positioning and using the magnet in such a situation is considered reasonable. Use of the magnet should not require extensive repositioning or adjustment, based on bench tests to date.**

32. In Appendix 20, you provide a description of various tests intended to validate your software and ensure safe and proper functioning of your device system. Your descriptions, however, do not specify the pass/fail criteria against which the GT NNP will be tested. Please revise your validation/verification plan to include specific descriptions of each test, their respective pass/fail criteria, and a rationale for each specified pass/fail criterion.

**Sponsor Reply 32:**
**Please refer to *Appendix H – Software Description and V&V*.**

33. Your clinical plan is generally acceptable based on the broad outline you provide. However, we cannot provide specific comments without a formal, complete, clinical protocol and related documents (e.g., case report forms, informed consent forms, etc.).

**Sponsor Reply 33:**
**Please refer to the following sections for more complete information:**

- **8.0 Investigational Plan**
- **11.0 Informed Consent Document**
- **12.0 Case Report Forms**
- **13.0 Draft Labeling**

### 1.4.3. Response to FDA E-mail Dated 11/12/14

Below is a point-by-point response to the questions listed in the attachment to Michael Hoffman's email dated November 12, 2014. We are willing to work interactively with FDA during the IDE review to further resolve these issues, if the reviewers' time permits.

1. The protocol should address what actions would be taken in the event of any protocol deviations or failure to meet any of the pre-specified validation acceptance criteria.

   **Response: Please see p 14 of the Moog Sterilization Protocol (following Appendix G). Products are not released to CWRU unless pre-specified acceptance criteria are met. As noted throughout the document, process steps are requirements and must be met in order to result in a released lot. In several places (for example, as noted on p 13), deviations from monitored load conditions are a matter for discussion between Moog and CWRU.**

2. The acceptance/rejection criteria specifies that no devices will be implanted that do not meet the two specified criteria; however, it should also be specified whether devices may be resterilized.

   **Response: Please see p 4 of the Moog Sterilization Protocol (following Appendix G). Section 4.4 states that CWRU shall be responsible for considering the single lot release load sterile if the acceptance criteria of this protocol have been met. CWRU will not implant any components until they are sure that all of the protocol's acceptance criteria are met. Devices may be resterilized.**

3. The acceptance criteria should be revised to establish EO sterilant residual lot release specifications for the NNP system components based on the worst case number of components utilized per surgery.

   **Response: Please see p 12 of the Moog Protocol, where release limits are based on worst-case hardware surface areas for TCL. Since each article in the sterilization batch is individually packaged, the batch does not constitute a system as defined by ISO 10993-7:2008. We intend to implant components from each sterilization batch as appropriate to complete a functional implanted NNP System; this approach is similar to that used in our IDE G110018, which uses a validated sterilization protocol – Ethox Protocol # 2FES-1.**

4. The EO sterilization validation protocol should justify the number and type of test samples, and include the protocols for validated test methods that will be used for assessing presterilization bioburden, sterilant residuals, and endotoxin testing. Acceptance criteria should specify whether test samples are pooled and/or whether test results from individual test samples may be averaged.

   **Response: Please see p 13 of the Moog Sterilization Protocol (Following Appendix G). Table 5 specifies the number and type of product samples required for the bioburden testing, sublethal, ½ cycle, and full-cycle portions of the protocol. The justifications for these numbers can be found on pp 6, 7, 9 and 11. The test samples for each device type will be pooled.**

5. The validation acceptance criteria should address meeting load configuration and biological indicator/process challenge requirements.

   **Response: Please see the Moog Sterilization Protocol and Appendix G p 4 (table G-2). Load configuration, chamber configuration, and BI / PC requirements are all addressed.**

6. The CWRU single lot protocol would call out similar sterilization parameters to the currently validated Sterilization and Testing (S&T) protocol for Case Western (2FES1) and the following aspects of the processes will be the same: sterilization vessel, cycle, preconditioning and aeration times and temperatures. Differences between the currently validated 2FES1 protocol and the proposed protocol and processes that will be used by Moog Medical Devices should be identified.

   **Response: The starting point for sterilization parameters will leverage the knowledge gained during the validation of Ethox protocol # 2FES-1. Since the sterilization vessel, packaging, shipping, and intraoperative connection of multiple hardware components post-sterilization are the same as outlined in 2FES-1, we expect that the pre-conditioning and aeration times and temperatures, PCDs, EO residual levels, and sterilization parameters will be similar, if not identical, to those outlined in 2FES-1. Any differences will be identified and communicated to the FDA.**

7. The acceptance criteria do not establish product release specifications for batch release Limulus Amebocyte Lysate (LAL) testing to meet the required endotoxins specifications for the system components as part of the sterilization validation acceptance criteria. Additionally, the endotoxin release specifications should be based on the worst case number of units utilized per surgery.

   **Response: Please see pp 4, 11, and 14 of the Moog Sterilization Protocol (following Appendix G). Rabbit pyrogenicity testing will be completed in conjunction with LAL to demonstrate non-pyrogenicity of the NNPS hardware. This dual-testing approach will be performed following the Full-Cycle Sterilization Process. This single-batch release will constitute the first of dual-tests, with the remaining 2 performed as part of the additional 2 batch releases required for a validated sterilization protocol.**

8. Simulated distribution and shelf-life studies on packaged and sterilized NNP system components following EO sterilization are not addressed.

   **Response: Please see our response in *Appendix G – Sterilization*; section G.4 Packaging, Handling and Shelf-Life.**