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Example - Early Feasibility Investigational Device Exemption

IDE Section:

Appendix C – Risk Analysis

C. Appendix C – Risk Analysis

This section contains:

C.1. Overview and Conclusions

Our methods of risk analysis are consistent with those described in ISO 149791. We followed a three-step process to assess risk associated with the NNP system and to prioritize areas of risk mitigation:

- A **Fault-Tree Analysis** allowed us to identify the factors that contribute to our Top Level Events, e.g., those associated with the highest-severity risks, defined as:
    - Loss of life;
    - Permanent impairment or life-threatening injury; or
    - Temporary injury requiring surgical intervention or hospitalization.
- A **Failure Modes and Effects Analysis** (FMEA) resulted in a list of identified device failures that could lead to the highest-severity events. These were reviewed by an informal data monitoring group, and assigned a severity and probability score.
- Based on the Severity and Probability scores of the failures, a **Risk Priority Number** (RPN) was calculated, allowing us to identify the most critical risks requiring mitigation.

The outcome of each of these steps is provided in the sections that follow.

From our Risk Analysis process, we conclude:

- The **highest *severity* risks** tended to be **lowest *likelihood*** and are fully mitigated through skilled surgical technique (for surgical risks) and engineering design (for risks associated with the technology).
- One event in the FMEA scored a Risk Priority Number (RPN) in the Intolerable region, therefore requiring mitigation: excessive heating during recharging. Multiple mitigations are used in this EFS IDE in order to minimize both the likelihood and severity of this event, as discussed in section C.4, below.
- Eleven (11) events in the FMEA scored in the ALARP region, and appropriate mitigations have been identified for each, as noted in section C.5, below.

C.2. Fault-Tree Analysis: Drivers of Highest-Severity Risks

The goal of the Fault-Tree Analysis was to identify the Top Level Events associated with the highest severity risks, and the contributors to those events. We used definitions of Severity and Probability of Occurrence (Po) consistent with ISO-14971, as shown in the tables, below.

TABLE C-1. DEFINITION OF SEVERITY

SCORE	SEVERITY	DEFINITION (ISO-14971)
5	Catastrophic	Results in loss of life
4	Critical	Results in permanent impairment or life-threatening injury
3	Serious	Results in temporary injury or impairment requiring surgical intervention or hospitalization
2	Minor	Results in temporary injury requiring minimal medical intervention (outpatient)
1	Negligible	Results in inconvenience or temporary discomfort

TABLE C-2. DEFINITION OF PROBABILITY OF OCCURRENCE

PO SCORE	PROBABILITY OF OCCURRENCE (PO) DEFINITION (ISO-14971)
1	Improbable: < 0.1%
2	Remote: 0.1 – 2%
3	Occasional: 2-10%
4	Probable: 10-20%
5	Frequent: > 20%

Top Level Events were those that resulted in risks of Severity Score 3 or higher, and included the following:

- **5-Loss of life**, due to:
  - Surgical complications,
  - Post-operative infection,
  - Anaphylactic shock,
  - Uncontrolled autonomic dysreflexia.
  - Late infection, or
  - Cardiac arrest
- **4-Permanent impairment or life-threatening injury**, due to:
  - Surgical scar tissue formation,
  - Burn,
  - Surgical injury,
  - Late infection, or
  - Tissue necrosis.
- **3-Temporary injury or impairment requiring surgical intervention or hospitalization**, due to:
  - Late infection,
  - Burn,
  - Broken bone, or
  - Need for device removal or premature replacement of components.

Fault-Tree Analyses were generated for each Top Level event, identifying the faults that could lead to each Top Level event and then identifying the causes for each fault. The

causes and faults were then connected using the logic gates of "and" or "or" as appropriate. The following tables present these Top Level events for Severity Scores of 3, 4, and 5.

TABLE C-3. TOP LEVEL EVENTS FOR LOSS OF LIFE (SEVERITY LEVEL = 5)

1. LOSS OF LIFE (SEVERITY = 5)					
1-1. Catastrophic Surgical Complication	1-2. Post-Operative Infection	1-3. Anaphylactic Shock	1-4. Autonomic Dysreflexia	1-5. Late Infection	1-6. Cardiac Arrest
	• Poor implant sterility, or • Poor sterile technique, or • Poor wound care	• Allergic reaction to materials	• Sensory stimulation that is not detected or managed.	• Infection contracted and patient delays treatment	• Leakage currents due to fault conditions, or • Current pathways across heart (electrode migration)

TABLE C-4. TOP LEVEL EVENTS FOR PERMANENT INJURY (SEVERITY LEVEL = 4)

2. PERMANENT INJURY (SEVERITY = 4)				
2-1. Scar Tissue Limiting Function	2-2. Tissue Burn Limiting Function	2-3. Surgical Injury	2-4. Late Infection	2-5. Tissue Necrosis
• Surgical injury	• Implant or external coil heating during charging, following multiple fault conditions		• Infection contracted and patient delays treatment	• Device failure

TABLE C-5. TOP LEVEL EVENTS FOR HOSPITALIZATION (SEVERITY LEVEL = 3)

3. SURGICAL HOSPITALIZATION (SEVERITY = 3)		4. OTHER HOSPITALIZATION (SEVERITY = 3)	
3-1. Premature Removal or Replacement Surgery Required	3-2. Broken Bone	4-1. Tissue Burn Requiring In-Patient Treatment	4-2. Late Infection
• Late Infection (infection contracted and patient delays treatment), or • Materials allergy, or • Any permanent failure of any system component (electrical, mechanical, software), or • Late surgical failure of any component (erosion, migration)	• Excessive limb motion, or • User accident	• Implant or external coil heating during charging, following multiple fault conditions, or • Heating due to MR use, following non-compliance with labeled contraindications.	• Infection contracted and patient delays treatment

C.3. Failure Modes and Effects Analysis (FMEA)

Once the FTA was completed for each Top Level event, each of the lowest level faults was analyzed for occurrence and existing mitigating design features. An initial team consisting of engineers was convened to elaborate on the failure modes that could lead to the potential hazards. A second review team consisting of engineers and clinicians provided the final scores with respect to Severity and Likelihood.

Results of the FMEA are presented in Section C.4.1.

C.4. Risk-Prioritization Number

A Probability of Occurrence score was assigned to each fault identified, and the Risk Prioritization Number (RPN) was calculated as the product of the Severity Score and the Probability of Occurrence Score. Per the chart, below, an RPN in the Intolerable region (> 10) warranted additional mitigation procedures in order to begin the Early Feasibility study. An RPN in the ALARP region (between 6 and 10) was considered borderline, warranting taking a cautious approach during the Early Feasibility study.

TABLE C-6. RISK PRIORITY NUMBER

Risk Priority Number (RPN) [Severity x Probability]					
5	5	10	15	20	25
4	4	8	12	16	20
3	3	6	9	12	15
2	2	4	6	8	10
1	1	2	3	4	5
Prob. / Severity	1 Negligible	2 Minor	3 Serious	4 Critical	5 Catastrophic

KEY:

BAR	Broadly acceptable region	ALARP	As Low as Reasonably Practicable	INT	Intolerable

Only one element resulted in an RPN greater than 10, excessive heating of the external coil during charging. Heating during charging is a known phenomenon, and the risk here relates to excessive heating of the skin sufficient to cause a burn that requires surgical intervention (Severity = 3). The likelihood of such an extreme event is unknown, but because recharging is a probable event (Probability = 4), the overall RPN was scored at 12.

C.4.1. FMEA Table

NNP System FMEA - Risk Priority Number Assessment								
HID	Item/Function	Failure Mode	Effects of Failure	Severity	Cause(s) of Failure	Po	Current Control	RPN
1	FES implant surgery	Catastrophic surgical complication	Results in death	5	Death due to bleeding, anesthesia problems, or other catastrophic complications of surgery.	1	Skilled surgeons and highly competent facilities	5
2	FES implant surgery	Infection (within 30 days post-op)	Results in death	5	Non-sterile implant tools/implant/surgical field leads to an uncontrolled systemic infection with a resistant bacteria.	1	All implant tools sterilized using hospital sterilization processes	5
3	Implanted Components	Autonomic Dysreflexia	Results in death	5	Sensory stimulation results in severe AD event not detected/treated.	1	Careful observation during stimulation. Looking for unexplained nausea or sudden strong headache. If these symptoms reported, measure blood pressure. Training of staff to recognize the signs and treatment protocol.	5
4	Implanted Components	Arrhythmia/arrest	Results in death	5	Electrical stimulation current flow path inadvertently activates heart, resulting in arrhythmia/arrest.	1	Placement of electrodes and modules by knowledgeable surgeon and technical staff, observation of patient during stimulation. Measure heart rate if patient reports sensation of irregular heartbeat	5
5	Implanted Components	Arrhythmia/arrest	Results in death	5	Electrodes located too close to heart causing arrhythmia/arrest.	1	Electrode attachment mechanism and tissue encapsulation	5
6	Implanted Components	Arrhythmia/arrest	Results in death	5	System experiences abnormal operation, resulting in high currents, which cause arrhythmia/arrest.	1	System circuitry is protected from runaway operation through current-limiting fuses and magnetic (reed switch) interrupt of the Phillips ARM uP.	5
7	Implanted Components	PM capsule rupture	Results in death	5	Battery experiences runaway heating, resulting in capsule rupture, and vital organs are damaged.	1	Battery designed and tested to maintained controlled heating even under direct short or metal penetration conditions.	5

8	External Components	Arrhythmia/arrest	Results in death	5	Electrical shock due to current leakage through the external components (Control Tower, Computer).	1	Electrical isolation. Annual safety testing.	5
9	FES implant surgery	FES target muscle/tissue damaged	Results in permanent injury	4	During implantation, a tendon, nerve, muscle or other critical tissue is cut or damaged in a way that limits function.	1	Skilled surgeons and highly competent facilities	4
10	Implanted Components	Tissue loss due to infection	Results in permanent injury	4	Bacteria enters through cut on skin or pressure sore; patient fails to get timely treatment; results in septicemia.	1	Patient is trained to observe for this condition and to report any event of this type to the treating physician immediately. Components that erode through the skin are removed.	4
11	Implanted Components	Tissue loss due to burn	Results in permanent injury	4	PM capsule overheatsduring normal use.	1		4
12	Implanted Components	Tissue loss due to burn	Results in permanent injury	4	Internal battery malfunction causes heating of PM can.	1		4
13	Implanted Components	Tissue loss due to burn	Results in permanent injury	4	Recharge of implantable battery causes PM to heat up and produce internal burn.	2	Control Tower (Charger) output is hardware limited so that the maximum power delivery through the recharge coil does not result in excessive PM heating. Patient instructed to observe skin under recharge coil at frequent intervals.	8
14	Implanted Components	Tissue loss due to burn	Results in injury requiring medical intervention (surgery)	3	Patient undergoes MRI, causing heating of the components and internal burns.	2	Patient education regarding contra-indication for MRI; Caution card given to patient; MRI technicians contacting technical staff prior to imaging	6
15	Implanted Components	Power module failure requiring replacement	Results in injury requiring medical intervention (surgery)	3	Critical failures of Power Module (battery, circuit board, software, or capsule) result in malfunction requiring premature device replacement.	2	Engineering team will be vigilant in observing proper performance of all implanted components. Proper system performance will be characterized by the engineering team prior to implantation.	6

16	Implanted Components	Remote module failure requiring replacement	Results in injury requiring medical intervention (surgery)	3	Critical failures of Remote Module (circuit board, software, or capsule) result in malfunction requiring premature device replacement.	2	Engineering team will be vigilant in observing proper performance of all implanted components. Proper system performance will be characterized by the engineering team prior to implantation.	6
17	Implanted Components	Power module failure requiring replacement	Results in injury requiring medical intervention (surgery)	3	Inadvertent overwrite of bootloader SW rendering PM inoperable and requires replacement surgery.	3	Engineering team will be vigilant in following proper software programming protocols when programming all implanted components. Programs will be tested on bench HW prior to programming implanted components.	9
18	Implanted Components	Electrode failure requiring replacement	Results in injury requiring medical intervention (surgery)	3	Electrode failure (movement from target area, mechanical interrupt, electrical interrupt) results in non- functional system.	2	Engineering team will be vigilant in observing proper performance of all implanted components. Proper system performance will be characterized by the engineering team prior to implantation.	6
19	Implanted Components	Network cable failure requiring replacement	Results in injury requiring medical intervention (surgery)	3	Network cable failure (mechanical interrupt, electrical interrupt) results in non- functional system.	2	Engineering team will be vigilant in observing proper performance of all implanted components. Proper system performance will be characterized by the engineering team prior to implantation.	6
20	Implanted Components	Biocompatibility issue requiring system/component removal	Results in injury requiring medical intervention (surgery)	3	New NNPS implantable materials in direct tissue contact cause a biocompatibility issue with patient.	1	Biocompatibility of all NNPS implantable components will be verified prior to implantation	3
21	Implanted Components	Infection results to system/component removal	Results in injury requiring medical intervention (surgery)	3	System becomes infected and infection doesn't resolve with outpatient treatments.	2	Patient is trained to observe for this condition and to report any event of this type to the treating physician immediately.	6

22	Implanted Components	User accident (clinical or home setting)	Results in injury requiring medical intervention (surgery)	3	Misuse results in broken bone or other injury requiring surgery.	2	Both user and clinical staff are trained to follow study protocol and question relevant PIs when things are unclear	6
23	External components	Skin burn from recharge coil	Results in injury requiring medical intervention (surgery)	3	During recharge, coils heats-up and burns the skin.	4	Patient is trained to observe for this condition and to report any event of this type to the treating physician immediately.	12
24	Implanted Components	Systemic infection	Results in injury requiring medical intervention (outpatient)	2	System becomes infected and requries outpatient treatments (antibiotics).	3	Patient is trained to observe for this condition and to report any event of this type to the treating physician immediately.	6
25	Implanted Components	User accident	Results in injury requiring medical intervention (outpatient)	2	Misuse in the patient setting results in bone fracture or other injury.	3	Patient is trained to follow study protocol and question clinical staff when things are unclear	6

C.5. Discussion of Risk Mitigations

Risks to subjects in the Early Feasibility IDE are mitigated in the following ways:

- Using good engineering design principles that reduce acute risks and assure long-term reliability of the technology;
- Using skilled surgical techniques that minimize acute and long-term procedural risks;
- Conducting the investigation in a way that allows both subjects and investigators to quickly identify problems and take actions to reduce harm; and
- Assuring appropriate screening, training, supervision and follow-up of subjects in the trial.

The specific "patient-centric" risk mitigation strategies are outlined in the table, below.

TABLE C-7. SUMMARY OF DIRECT PATIENT RISK MITIGATIONS

SCREENING	Subjects are carefully screened and will be excluded on the basis of health or medical issues that could exacerbate the safety profile of the system.
	The EFS IDE study is limited to fewer than 10 subjects.
INFORMED CONSENT	All subjects will be required to sign an informed consent document outlining the purpose of the study, the methods and procedures used, the risks and benefits of participating, and their rights as a subject.
USER RESTRICTIONS	Based on the results of our current testing, it does not appear necessary to restrict the environment of use for subjects. Nevertheless, training and consent documents will convey the need to potentially do this, based on experience with our first subjects.
USER TRAINING	Training for both subjects and clinical staff will emphasize safe use of the system in accordance with its design and labeling.
	Subjects will be educated through direct training on how to safely use the system, and how to identify certain device-related safety and performance events that should be reported as part of the investigation.
	Training for both subjects and clinical investigators / staff will include review of contraindications, warnings, precautions, and instructions.
SUPERVISED USE	In addition to being trained in how to use the system, subjects in the Early Feasibility IDE study will undergo sessions in which their independent use of the system is supervised by clinical investigators, prior to being discharged to use the system at home.
LABELING	Warnings and precautions are included in the Patient Manual to address concerns about risks posed by the investigational device.
	The section of the Patient Manual entitled, "When to Call Us" identifies key safety issues and events that should be reported to the FES Center investigators as part of the trial.
CLINICAL FOLLOW-UP	Subjects will be followed regularly as part of the clinical study, and every measure will be taken to assure long-term follow-up beyond the defined study duration.