Bridging the Gap Plus (BG+)

Dr. Al Emondi
Program Manager
DARPA/BTO

Proposer’s Day
November 5, 2019
Bridging the Gap Plus (BG+) Program Vision

**DoD Problem:** Spinal cord injury causes devastating paralysis to warfighters and veterans

**Injury**

- **Acute Phase (0-2 days):** Preservation + Regeneration of Neural Communication
- **Sub-Acute Phase (2-14 days):** Track biomarkers
- **Chronic Phase (14+ days):** Restoration

**Goals:** Two classes of bidirectional devices to:
1. Sense the environment at the site of injury and provide intervention
2. Record from and adaptively stimulate the nervous system at key locations for recovery of function

**Acute:**
- blood pooling, reduced oxygenation, inflammation, spinal cord pressure buildup

**Sub-Acute:**
- expanding region of cell death, cell-cell connectivity loss, scar formation

**Therapeutic Blackbox**

**Bridging the Gap Plus (BG+) Program Vision**
**Bridging the Gap** from bench to bedside with an emphasis on strong transition partnerships

**Bridging the Gap** of injury with devices for stabilization, regeneration, and restoration of function

**Bridging the Gap** of clinical care between early and late phases of injury

**Bridging the Gap** of expertise between “cylinders of excellence”

Regen + Restore + Bio-markers + Machine learning + Research + Clinic ...

*Use today for teaming*
Spinal Cord Injury In The Military

Higher Injury Impact on Military

- Spinal Cord Injuries to military personnel are on average more severe than general populace
  
  *Furlan et. al., 2018*

- Higher rate of spinal cord injuries in recent operations (Iraq, Afghanistan) than in previous engagements
  
  *Schoenfeld et. al., 2013*

American Spinal Injury Association (ASIA) Scale

Below injury:
Grade A: Complete lack of function + sensation
Grade B: Some sensation
Grade C: <50% muscles cannot move against gravity
Grade D: >50% muscles can move against gravity
Grade E: All neurologic function has returned

Care for Veterans

Of 250,000 Americans with serious spinal cord injuries and disorders, about 44,000 are veterans (Veterans Affairs)

Morbidity up to 2x higher for those with spinal cord injury than general populace

System Dysfunction Leading to Increased Morbidity

- Bladder
- Bowel
- Respiratory
- Posture
- Movement
Technical Approach

Technical Area 1
Injury Stabilization and Therapeutic Stimulation

- Introduce intervention
- Track biomarker
- Interpret and provide response

Technical Area 2
Functional Recovery

- Record residual signals
- Decode signals and coordinate device response
- Stimulate nervous system
Technical Area 1: Injury Stabilization and Therapeutic Stimulation

Goal: stand-alone device for real-time biomarker tracking and therapy intervention at the site of injury

Biomarker Examples:
- Mean arterial pressure
- Oxygen levels
- Growth factors
- Inflammation markers

Intervention Examples:
- Therapeutic electrical stimulation
- Drug/biologic elution
- Cell therapy
- Physician intervention

Technical Challenges:
- Measuring key biomarkers
- Continuous sampling
- Tailoring adaptive intervention

TRACK specific biomarker signal

INTERPRET biomarker data using appropriate algorithms and suggest interventions

INTERVENE as necessary to address the issues signaled by the biomarkers
Technical Area 2: Functional Recovery

Goal: Repair the broken connection in the nervous system with functional stimulation

Functions of Interest:
- Movement with somatosensation
- Posture with proprioception
- Bladder, bowel
- Cardiovascular
- Respiratory

Technical Challenges:
- Selective neural recordings
- Selective neural stimulation
- Bidirectional functional restoration
- Large muscle activation
- Muscle fatigue

Graphical Representation:
- RECORD from residual neural circuits
- DECODE neural signals using appropriate algorithms and coordinate (networked) devices
- STIMULATE the circuits to encourage growth or restore function

Neural interface
## Program Timeline

<table>
<thead>
<tr>
<th>Task</th>
<th><strong>Phase 1</strong></th>
<th><strong>Phase 2</strong></th>
<th><strong>Phase 3</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Device Development</strong> (18 months)</td>
<td><strong>Integration and Assessment</strong> (24 months)</td>
<td><strong>Clinical Studies</strong> (18 months)</td>
</tr>
<tr>
<td>Device development</td>
<td>PDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algorithm development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device integration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algorithm optimization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal safety testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA document preparation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA document submission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory approvals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject recruitment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical testing</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PDR:** Preliminary Design Review @ 12 months  
**CDR:** Critical Design Review @ 15 months

- **Φ1 Demo:** Animal demonstration of device subcomponent performance
- **Φ2 Demo:** Animal demonstration of integrated, fully implantable device
- **Φ3 Demo:** Clinical demonstration
Phase 1: Device Development

Phase 1 tasks
- Device development

- Algorithm development

- Design reviews
  - Preliminary Design Review (MAC 12)
    - Theory of operation
    - How to develop a system/systems to enact that theory
    - Details of how the metrics will be demonstrated
    - Description of system parameters
  - Critical Design Review (MAC 15)
    - Solidify PDR discussion and decision points
    - Describe established parameters
    - Describe Phase 2 system

Phase 1 demonstration: System subcomponent (sensors, stimulators, algorithms) performance in animal models.
Phase 2: Integration and Assessment

Phase 2 tasks
- System integration
- Algorithm refinement
- Safety and efficacy studies
- Prepare for system modularity (particularly for TA2)
- Pre-IDE/pre-IND submission(s)

Phase 2 demonstration: Integrated system performance in animal models.
Phase 3: Clinical Studies

Phase 3 tasks
- IDE/IND submissions
- Acquire regulatory approvals
- Recruit research participants
- Initiate clinical studies
- Refine SDK
- Substantiate relationship with clinical transition partner

Phase 3 demonstration: Performance of the final technology in a human research participant.
System Modularity

- The final TA1 deliverable is a system that includes one or multiple devices.
- The final TA2 deliverable is a ‘system of systems’. Each system addresses one function.

For both TAs:
- Proposals must describe a plan for allowing additional components to be added or removed from the system.
- Teams must provide open source standards for allowing others to use, modify, or interact with the technology.
- Statement of Work deliverables must include a software development kit (SDK) and a benchtop testbed that is amenable to testing by a third party, such an Independent Verification and Validation (IVV) team.
**Program Metrics**

<table>
<thead>
<tr>
<th>Technical Area</th>
<th>Phase 1 (18 Mo) Device Development</th>
<th>Phase 2 (24 Mo) Integration and Assessment</th>
<th>Phase 3 (18 Mo) Clinical Studies</th>
</tr>
</thead>
</table>
| **TA 1:** Injury stabilization and therapeutic stimulation | **Biomarkers tracked**  
  ≥ 3 | **Fully implantable device** | **Clinical transition**  
  ≥ 1 clinical sponsor |
|               | **Therapeutic stimulation channels**  
  ≥ 3 (e.g. electrical stim, drug elution) | **Sampling rate**  
  ≥ Nyquist for relevant biomarker | **External information channels**  
  ≥ 1 per biomarker |
|               | **Sensor accuracy**  
  Within ± 20% of ground truth concentration | **Therapeutic stimulation latency**  
  ≤ kinetics of the stimulation modality | |
|               | **Sensor precision**  
  Within ± 20% signal coefficient of variation | **MRI compatible implants**  
  Compatible with 1.5 and 3T | |
| **# of functions addressed in animals**  
  ≥ 3 | **System latency**  
  10 ms | **Clinical transition**  
  ≥ 1 clinical sponsor |
| **Full system channel count**  
  ≥ 64 ch | **Longevity studies**  
  Implanted components >10 year life | **# of functions addressed in humans**  
  ≥ 2 |
| **System latency**  
  50 ms | **Functional improvement in animals**  
  3x over baseline  
  (e.g. respiration: from 3 to 9 unassisted breaths/min) | **Functional improvement in humans**  
  3x over baseline |
Proposals must include an ELSI section.

**Topics to consider:**

- **Animal research**
  - 3 R’s of animal research: Replacement, Reduction, Refinement
  - Animal research retirement where possible

- **Human subjects research**
  - Risk:benefit tradeoffs
  - Informed consent (especially for TA1 system)

- **Data security and privacy**

- **Embedding an ethicist in the lab:**
  - Could be a trained ethicist or a trainee (e.g. graduate student)
  - Embedded ethicist may attend/participate in lab meetings, experiments
Tech Transition Plan

Proposals must include a Technology Transition Plan.

- Transition plan can be for further technology development or a larger clinical trial
- Teams can describe a transition plan for the fully embedded version of the system or a less invasive approach

Things to consider including in the plan:
- Timeline for engaging early and often with the FDA, CMS and other relevant agencies
- Cost effectiveness of the final system
- Insurance considerations (consider the system as well as the potential for extra rehabilitation sessions)

Teams must substantiate a relationship with a clinical partner by the end of Phase 3.

Potential clinical partners may include Walter Reed and the Veteran’s Affairs. Representatives from these organizations will be invited to future program meetings and are here today.

Please network!
Teaming Revisited

Use today to:

- Find team members
- Initiate contact with transition partners

Teaming social and poster session: 5:30-7:30 pm
Bridging the Gap Plus (BG+)  
Doing Business with DARPA

Peter Donaghue  
Contracting Officer  
DARPA Contracts Management Office

November 2019
Abstract and Full Proposal Tips

Proposal Abstract Tips

- Abstracts are strongly encouraged, but optional.
- Abstracts are limited to 8 pages – must include components in BAA.
- DARPA will respond to abstracts with a statement as to whether DARPA is interested in receiving a full proposal.
- You may submit a full proposal even if you did not submit an abstract.

Full Proposal Tips

- Read the BAA carefully - Nonconforming proposals may be rejected without review.
- Technical Area (TA) 1 and 2 for all Phases (1, 2, & 3) proposal requirements listed in Sections 1.1 through 1.6 and under 4.2.2.
- Full Proposal Vol I is limited to 35 pages.
- You may submit a full proposal even if a proposal is discouraged in response to your abstract.
Cost Proposal

• There is **no page limit** to Volume II Cost Proposal.

• Cost break downs are outlined in the BAA:
  
  o By both TA (1, 2) and Phase (1, 2, 3) by contractor fiscal year
    
    o Ex: TA1 Phase 1 Base, TA1 Phase 2 Option, TA1 Phase 3 Option
  
  o Summary costs by each task for each TA 1 and TA 2 and phase
  
  o Projected funding required by month (account for early equipment needs)

• **Subcontractor** proposals **must** be prepared at the same level of detail as that required of the prime.

• **The Government strongly encourages that proposers use the provided MS Excel™ cost proposal spreadsheet in the development of their cost proposals**
  
  • Assists the Government in a rapid analysis of proposed costs and, if your proposal is selected for award, speeds up the negotiation and award execution process.

See BAA pg. 26-30 for details regarding the detailed cost proposal guidance
BAA Process: Teaming & Eligibility Information

- All responsible sources capable of satisfying the Government's needs may submit a proposal that shall be considered by DARPA.

- **Non-U.S. organizations and/or individuals**
  - Non-U.S. organizations and/or individuals may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances.

- **Government Entities & FFRDC’s: subject to limitations**
  - Government agencies/labs, FFRDCs cannot propose to this BAA in any capacity, **UNLESS** they can clearly demonstrate the work is not otherwise available from the private sector AND they also provide written documentation citing the specific statutory authority (as well as, where relevant, contractual authority) establishing their eligibility to propose to government solicitations.

- **Organizational Conflicts of Interest**
  - **DARPA policy:** Without prior approval or a waiver from DARPA, in accordance with FAR 9.5, a contractor cannot simultaneously provide scientific, engineering, technical assistance (SETA) or similar support (A&AS) and also be a technical performer.
  - **Must address in your proposal if providing SETA or similar support to any DARPA technical office(s) through an active contract or subcontract.**
Full Proposal Review-Awards Process

- No common Statement of Work - Proposals are evaluated on individual merit and relevance as it relates to the stated research goals/objectives rather than against each other.

- Proposals are evaluated for strengths and weaknesses relative to the criteria published in the BAA, listed in descending order of importance:
  - Overall Scientific and Technical Merit
  - Potential Contribution and Relevance to the DARPA Mission
  - Cost Realism
  - Realism of Proposed Schedule; and
  - Plans and Capabilities to Accomplish Technology Transition

- Government reserves the right to select for award all, some (partial selection), or none of the proposals received.
- Government anticipates making multiple awards
- Contract negotiation timelines depend on each institution/organization’s responsiveness to the proposal requirements in the BAA.
- The contracting office will contact the selected performers and begin the contracting process.

See BAA pg. 35-37 for details regarding proposal evaluation
Bridging the Gap Plus
BAA Process Overview — BAA Inbox and Submission

David Swan III
BAA Coordinator
DARPA Biological Technologies Office

November 5 2019
BAA Inbox and FAQ

Direct all questions and communications to the BG+ BAA Inbox:

BGPlus@darpa.mil

Dr. Emondi cannot provide feedback or guidance on any aspect of your proposal, nor can any member of his team or the BAA Inbox. They can only clarify the content of the BG+ BAA.

A FAQ will be available on the DARPA Opportunities web page:


The FAQ will be updated regularly prior to the proposal submission deadline, however all questions must be submitted at least 10-15 days prior to the deadline in order to guarantee a response.
Before submitting a question, you should…

Understand that you’ll get a clarification, not an idea.

Understand that you won’t get any information from a competitor.

Understand that your question will likely be added to the FAQ.

Read the BAA **carefully** before submitting any inquiries.
Q: Does my team have to apply to both TAs?
A: Both technical areas must be developed concurrently over the duration of the effort. Proposals that fail to address both technical areas will be considered non-responsive.

Q: My research is not geared specifically to meet the BG+ program goals. Is there an alternate solicitation that I can respond to?
A: Yes. DARPA/BTO has an office-wide solicitation (HR001119S0048) for this purpose. Responses are being collected through April 23, 2020.

Q: How much funding is available? What is the expected size of an award?
A: DARPA has not predetermined award amounts. Proposers are required to provide a well-justified budget appropriate for the scope of the proposed work. Cost should be based upon how much money is required to perform the tasks you feel are necessary to meet the objectives of BG+. 
Submission Specifics

NO submissions via fax/e-mail

Cooperative Agreements – Grants.gov

All other Award Instruments – DARPA BAA Portal (https://baa.darpa.mil)

Start Today 😊

Only include attachments requested in the BAA
Final Submission Advice

Read the BAA over and over again and follow all instructions carefully

A conforming proposal addresses all aspects of the BAA

- Pay attention to “must”, “should”, “shall”, and “all” in the BAA
- Nonconforming proposals may not be evaluated

**DO NOT** try to shoehorn ongoing, but not applicable, work into the BAA

**DO NOT** submit a rewritten NIH or NSF proposal

**DO NOT** propose to do anything that is not directly relevant to the BAA

**DO NOT** submit an irrelevant or incomplete proposal in the hope we’ll fund it anyway

A proposal abstract is **HIGHLY RECOMMENDED**
Human Subjects Research at DARPA

Lisa Mattocks
STO ADPM/HSR Action Officer

Industry Day

DARPA
Use of Human Subjects in an activity constituting a systematic investigation designed to develop and/or contribute to
generalizable knowledge is considered Human Subjects Research, where:

The term “human subject” means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the
information or biospecimens; or
(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

**Intervention:** includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

**Interaction:** includes communication or interpersonal contact between investigator and subject.

**Private information:** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

**Identifiable private information** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

**Identifiable biospecimens:** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Any DARPA-funded research which involves humans as defined on this page MUST be considered HSR.
All DARPA human subjects research protocols must go through two reviews.

1st review
Local Level (local IRB)

2nd review
DoD HRPO Level (Administrative Review)
• Principal Investigator submits protocol to local IRB for review and approval
• HSR package is then submitted for DoD HRPO review and approval
  • Includes local IRB approval letter
  • Federal Wide Assurance (of institution performing research)
  • Informed Consent Document
    • ***Make sure informed consent document includes statement that the research is being funded by DoD and thus the DoD has access to the data***
  • Recruiting Materials
  • Biosketches/CVs
  • Training Certifications
• DoD HRPO reviews entire package
  • May go back to PI with comments/recommendations/changes
• Once DoD HRPO gives approval, HSR research can begin
• Note that protected populations (i.e. military, pregnant women, etc) have special regulations that need to be followed.

Note – DoD HRPO review and approval can take anywhere from 3-6 months. Do not delay in starting this process!
Helpful Hints/FAQs

• If possible, submit an IRB approval letter and/or a Draft HSR Protocol with proposal. Especially, in cases where humans are involved and you don’t know that the work is really HSR. Having an IRB already look at it will help you and DARPA in moving forward faster.

• If you do not have an internal IRB, you have one of three options
  • Hire a commercial IRB
  • Work with the Contracting Agent to determine if they have an internal IRB that could assist
  • If work involves collaboration with other performers, considering using their IRB

• If you have a contract involving subcontractors who are conducting HSR; they will also need to obtain HSR approval. Any performer including subcontractors must receive HSR approval through the local IRB and the DoD HRPO before start of their research.

• If you make changes to the statement of work, they also need to be approved. If the changes are to the HSR portion of the work, the revisions will have to go through the local IRB for review, as well as DoD HRPO review for approval and concurrence.
Points of Contact

**Government HSR and ASR Action Officer**
Ms. Lisa Mattocks  
Lisa.Mattocks@darpa.mil  
571-218-4424

**HSR POC**
Dr. Sahar Zafar  
Sahar.Zafar.ctr@darpa.mil  
703-362-3438
According to the DoD, an animal is:

- A living or dead *vertebrate*
- A larval fish or amphibian
- An egg-laying vertebrate is only an animal *after hatching*

Dead = killed for the direct purpose of conducting RDT&E or training
An animal is **NOT**

- An un-hatched egg
- An invertebrate
- Dead animals or parts of dead animals purchased at grocery stores or slaughterhouses
ALL Animal Research in the US Must Follow

1. Animal Welfare Act/Animal Welfare Regulations
2. Guide for the Care and Use of Laboratory Animals

DARPA animal research must also follow

3. DoD Instruction 3216.01 “Use of Lab Animals in DoD Programs”

These regulations are available on the web
DoD vet approval is needed **before** any funds can be used for animal research including purchase of animals and per diem costs for animal care.

**Allowable charges prior to DoD vet approval**
- Food
- Housing
- Equipment

**Prohibited charges prior to DoD vet approval**
- Animal Purchase and Care

Other questions about your contract? Contact your contract officer!
Review of the Protocol

All DARPA animal use protocols must go through two reviews:

1st review
Local Level (IACUC Review)

2nd review
DoD Level (Secondary Review)
The Reviews

- All animal use protocols in the USA must be approved by an IACUC
- International research must be approved by their IACUC equivalent

In addition, all DoD funded animal use must also be approved by a DoD vet

DARPA funded animal use protocols are reviewed by a DoD vet at MRMC
Animal Care and Use Review Office (ACURO)
ACURO Approval

Required Submission Docs
- IACUC approved protocol
- Evidence of IACUC approval
- Most recent USDA report
- ACURO appendix
  - Available on ACURO’s website

Approval Process
- ACURO reviews docs
- May ask PI for clarifications
- Sends to DoD vet for final review and approval

Approval takes 2-3 months

ACURO approval is good for the length of the award or length of IACUC approval
Significant amendments to protocols must also go through two reviews prior to implementation.

1st review
Local Level (IACUC Review)

2nd review
DoD Level (ACURO Review)

ACURO review and approval usually takes 1-2 weeks
ACURO categorizes amendments as **significant** (major) and **non-significant** (minor)

Significant amendments include:
- Change in Principal Investigator, species, or study objectives.
- Addition of procedures.
- Changes in anesthesia, analgesia, sedation, tranquilization, or experimental substances.
- Changes in euthanasia methods.
- Increase of animal numbers.
- Changes involving increased risk to personnel and/or animal safety (e.g. addition of hazardous agents)
- Changes in duration, frequency, type, or number of procedures performed on an animal.
- Change in housing and/or animal use location that is NOT overseen by the IACUC.
Review of Amendments

Non-Significant amendments include:

• Administrative changes, e.g. correction of grammatical and/or typographical errors, contact information, etc.
• Personnel changes, with exception of the Principal Investigator.
• Change of strain.
• Decrease in animal numbers.
• Change in housing and/or animal use location that is overseen by the IACUC.

Only significant amendments need to be reviewed by ACURO prior to implementation
All rewrites must be approved by ACURO

**Required Rewrite Docs**
- IACUC approved protocol
- Evidence of IACUC approval
- Most recent USDA report
- ACURO appendix
  - Available on ACURO’s website

**Approval Process**
- All rewrites must be submitted to ACURO within 30 days of expiration
- Previously approved work may continue on the protocol during review

*Approval takes 2-3 months*
Amendments and Rewrites

If significant amendments are implemented before ACURO review, the research is **NONCOMPLIANT**

If rewrites are not submitted to ACURO within 30 days of expiration, the research is **NONCOMPLIANT**

Noncompliance may be cause to stop work or cancel the contract!
Take Home Messages

1. If a protocol involves animal research, it must follow DoD animal use regulations

2. All animal use protocols require TWO approvals

3. All rewrites and significant amendments must be approved by ACURO
DARPA’s Animal Use POC is here to help with all aspects of animal research at DARPA including:

- Approval process
- Acting as liaison between PIs, PMs, agents, and ACURO
- Locating and understanding regulations
- Any other animal use questions or issues

Animal Use POC
Carrie Lewis
Carrie.Lewis.ctr@darpa.mil
703-526-1439
Moving Innovative Medical Devices to Patients
An FDA Staff Perspective

Bridging the Gap
Proposers Day
November 5, 2019

Michael Hoffmann
Associate Director for Regulatory Policy
Office of Neurological and Physical Medicine Devices (OHT5)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH), FDA
Michael.Hoffmann@fda.hhs.gov
301-796-6476
Disclosures

We have no financial conflicts to disclose
Disclaimer

This presentation is intended for informational purposes only and does not constitute legal or regulatory advice. Please see the Federal Food, Drug, and Cosmetic Act and 21 CFR Subchapter H for a full list of requirements by FDA.
Outline

1. Overview of Medical Device Regulation
2. Investigational Device Exemption
3. Early Feasibility Study
4. Considerations for Spinal Cord Injury
5. Presubmission
Introduction

• Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.

• The U.S. is the world’s leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety.

• U.S. post-market surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance.

• Devices are legally marketed in the U.S. and remain safe, effective, and of high-quality.

• Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make health care decisions.
Experience in Moving Neurological and Rehabilitation Medical Devices From Bench to Market

- Cognitive Function following concussion
- Deep brain stimulation
- ADHD Neurodiagnostics
- DEKA Prosthetic Arm
- Stent Assisted Coils For Aneurysms
- Microcatheters for the neurovasculature
A Risk Based Approach for Medical Devices since 1976

Increasing Risk
Classification determines extent of regulatory control (Risk Based)

**Class I**
*low risk*
- Generally exempt from premarket review
- In some cases require 510(k) / De Novo

**Class II**
*Moderate/Controlled Risk*
- Requires 510(k) to demonstrate substantial equivalence / De Novo if no classification exists

**Class III**
*High Risk*
- Requires PMA (Premarket approval)

**General Controls** [Electronic Establishment, Registration, Electronic Device Listing, Quality Systems, Labeling, Medical Device Reporting (MDR)]

**Performance standards**
**Special Controls** [Controls to address safety and effectiveness]

**Clinical performance data** (to support a reasonable assurance of safety and effectiveness)
Medical Device Classifications and Regulatory Pathways

• Class III: generally PMA (Premarket Approval)
• Class II: 510(k) (or premarket notification), if the intended use and technology are similar to something already classified
• De Novo: devices that aren’t comparable enough to something on the market. This generates a new device classification regulation, and will typically (but not always) be Class II
• Humanitarian Device Exemption (HDE): Regulatory pathway for products intended for diseases or conditions that affect small (rare) populations
Investigational Device Exemption

• And IDE is a regulatory submission that permits clinical investigation of devices.

• 21 CFR 812.1:

  “An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.”
Early Feasibility Study

IDE - Investigational Device Exemption
  • An IDE submission allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data

EFS IDE - A standard IDE except...
  • Small number of subjects (< 10) in the clinical investigation
  • Device is generally early in development
  • Device iterations are expected
  • Limited non-clinical data may be available
  • Enhanced clinical mitigations may be required

EFS is an informal designation
How can an EFS benefit you?

Permits A More Efficient Pathway to US Commercialization

- FDA feedback early in product development may help you improve your development strategy and reduce unnecessary testing
- Data collection in the US patient population may be easier to leverage to support later studies or marketing applications

Enables collection of high quality clinical data for:

- Optimizing device design or operator technique
- Refining the intended use population
- Refining nonclinical test plans
- Developing subsequent clinical study protocols
Key Principles of EFS and Additional Points to Consider
Just-In-Time Testing (JITT)

**Concern:** Comprehensive testing during early phases of device development may add cost without significant return

**EFS Approach:**
- Doing the right testing at the right time
- EFS should not take the place of informative nonclinical testing

**OHT5 Examples:**
- Long term durability testing may be deferred given criticality of short term benefit (e.g. glioblastoma, SCI, severe psychiatric disorders)
- Limiting use of a device to the hospital instead of a patient’s home may change testing strategy (e.g. EMC for electronic based assistive devices)
- Small number of devices may rely on single lot Ethylene Oxide (EO) sterilization versus full EO sterility validation (e.g. novel leads for spinal cord stimulation)
**Enhanced Risk Mitigation Strategies**

**Concern:** An EFS may carry greater unknown risks as compared to traditional feasibility and pivotal studies

**EFS Approach:**
- Enhanced clinical monitoring specified in the protocol
- More frequent/detailed reporting to the FDA
- Informed consent should highlight greater unforeseeable risk

**OHT5 Examples:**

<table>
<thead>
<tr>
<th>Risks</th>
<th>Mitigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation related adverse events</td>
<td>• Titrating therapy</td>
</tr>
<tr>
<td></td>
<td>• Turn device off and revert to standard of care</td>
</tr>
<tr>
<td>Novel endovascular stroke intervention</td>
<td>• Surgery performed at select sites with expert</td>
</tr>
<tr>
<td></td>
<td>surgical and clinical team</td>
</tr>
<tr>
<td>Infection caused by lead implantation</td>
<td>• Ongoing monitoring of implantation sites and body</td>
</tr>
<tr>
<td></td>
<td>temperature</td>
</tr>
</tbody>
</table>
Leveraging Existing Data

**Concern:** Applicable data may already exist in non-traditional formats (e.g., testing or literature from marketed products or earlier prototypes)

**EFS Approach:**
- Leveraged data can be used to provide information without unnecessary burden
- You should provide a leveraging rationale and a detailed discussion of differences (e.g., material, design, manufacturing) between the leveraged data and the proposed device

**OHT5 Examples:**
- Some biocompatibility endpoints could be leveraged from an animal study
- Data from published literature could support device safety (e.g. approved SCS parameters for novel PNS)
**Timely Device & Clinical Protocol Changes**

**Concern:** Devices studied under EFS are expected to change throughout the study and require timely device iterations.

**EFS Approach:**

- Contingent approval: device changes that are anticipated during the study may be executed without additional FDA action if the proposed change, supporting test plans, and acceptance criteria were agreed upon in an IDE or IDE Supplement
- Broader implementation of 5-day notice IDE supplements

**OHT5 Examples:**

- 5-Day notice: device changes that do not constitute significant changes to the design or principal of operation (e.g. ergonomic modifications)
- Contingent Approval: adjust stimulation parameters, interchange prosthetic devices/components
Key IDE information

• Population being treated – inclusion/exclusion criteria
• Study Protocol
• Clinical procedure
• Safety monitoring
• Preclinical testing
  – Sterility
  – Biocompatibility
  – Animal testing
• Risks to subjects and risk mitigation
• Concomitant therapy
A few points to consider

SCI - Intervention

• Comparison to Natural Recovery & A Well Controlled Study
• Injury Stabilization and Therapeutic Stimulation
• Clinically Meaningful Change
• Patient Population
• Preclinical testing
  – Animal testing
• Benefits and Risks of product and procedure
• Adequate Monitoring for safety issues
A few points to consider
SCI - Rehabilitation

• Functional Recovery
  – What functions?
  – What is clinically meaningful?

• Tracking normal or expected recovery

• Variability in level and severity of injury

• Benefits and Risks of product and therapy

• Concomitant Therapy
Benefit Risk Considerations

Several considerations when evaluating Benefits and Risks:

- **What are the probable benefits?** Type, magnitude, duration, etc.
- **What are the probable risks?** Type, severity, probability, duration, etc.
- **Additional Factors**, such as:
  - Uncertainty
  - Patient tolerance for risk and perspective on benefit
  - Alternative therapies and their risk profiles

GUIDANCE: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications
http://www.fda.gov/RegulatoryInformation/Guidances/ucm267829.htm
Presubmissions

- An opportunity to obtain **FDA feedback** prior to IDE or marketing submission
- Obtain feedback on proposed clinical and/or non-clinical test protocols and proposed regulatory paths

- Meeting (optional) within 75 days after submission
- Written feedback by day 70 or 5 days in advance of meeting
- Meeting may be canceled if there are no questions with FDA feedback

Presubmission Guidance
When to submit a Pre-Sub?

- When preparing a submission for a new device that does not clearly fall within an established regulatory pathway

- Prior to initiating long-term preclinical studies or before submission of an IDE

- When planning a study that does not require an IDE
  - Studies that are outside the US, exempt, or NSR

- Before submission of a marketing application to:
  - Apprise FDA review team on specifics of device and clinical study if there have been changes since initiation of the IDE
  - Obtain feedback on preferred data presentation
  - Gain insight into potential hurdles for approval or clearance
Involving FDA Early in the Process

• Early collaboration allows you and FDA to get on the same page. This in turn can shorten the timeline

• Provides a way to get feedback early
  – For example concerns over how an animal study is conducted can be discussed during the planning stage instead of afterwards so that a costly animal study isn’t repeated.

• Identify intended patient population early and design appropriate studies to evaluate risk / benefit profiles
  – Usability Studies are becoming increasingly important
Contact Information

• Center for Devices and Radiological Health
  – Xiaolin Zheng, PhD (Xiaolin.Zheng@fda.hhs.gov)
    Director (Acting), Division of Neurosurgical, Neurointerventional, and Neurodiagnostics Devices
  – Vivek Pinto, PhD (Vivek.Pinto@fda.hhs.gov)
    Director (Acting), Division of Neuromodulation and Rehabilitation devices

• Office of Combination Products (combination@fda.gov)
It’s About the Patients

Thank You

Michael Hoffmann
Associate Director for Regulatory Policy
Office of Neurological and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health, FDA
Michael.Hoffmann@fda.hhs.gov
301-796-6476
Resources

- Early Feasibility Study (EFS) Guidance
  https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103
- IDE Submission Information
  https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/default.htm
- Breakthrough Devices Program
- Benefit Risk Guidance for PMA and De Novo Submissions
- Patient Preference Information in Premarket Submissions Guidance
- Leveraging Real World Evidence in Premarket Submissions Guidance
- Design Considerations for Pivotal Clinical Investigations Guidance
- Pre-Submission Guidance