Considerations for the Review of Assets for EPPIC NET

HEAL Partnership Meeting

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Proposed Agenda for Today

- Present Application process - Template and Dossier applications
- Discuss outreach
- Discuss additional review & due diligence considerations
- Debate resources to enable/fix assets
- Discuss outreach
EPPIC NET Strategy – Building Infrastructure

1. Build a clinical network
   • Set up infrastructure
     o Clinical Coordinating Center (CCC)
     o Data Coordinating Center (DCC)
     o Hubs & Spokes
   • Recruit NINDS program officials
     o Oversight
     o Milestones

2. Generate asset entry and review process
   • Generate new application formats
     o Template
     o Dossier
     o Protocol
   • Generate review process
     o NIH special emphasis panel
     o Rolling review

3. Ratify new funding model – Other Transaction Authority (OTA)
   • HEAL funding for the network – cooperative agreements
   • HEAL funding for clinical trials – OTA
1. Clinical Coordinating Center:
   - Identify/Create centralized IRB and Master Trial Agreements
   - Match Hubs/Spokes to the proposed study/protocol
   - Identify site investigators
   - Standardize CRFs and methodologies
   - Train sites and staff
   - Work with DCC and create SOPs and quality controls
   - Distribute funds with NINDS oversight

2. Data Coordinating Center:
   - Receive and centralize data
   - Harmonize data from other studies
   - Monitor safety and provide reports to DSMB
   - Create and manage biorepository for samples and data

3. Hubs & Spokes:
   - Identify individual investigators
   - Conduct trials
   - Collect and report data to DCC and CCC

4. NIH:
   - Interact with all EPPIC-Net components to provide oversight of budget and milestones
   - Create DSMB of SMEs and other experts (e.g. Ethics, Stats)
EPPIC NET Application & Review Process

1. Applicant initiates research idea
   - Program outreach

2. Applicant submits template application

3. Program develops priority plan
   - Scientific review branch conducts review
   - Program develops priority plan

4. Program invites applicants to work with CRO to generate and submit dossier application

5. NIH council votes on priority plan

6. Clinical Coordinating Center delivers clinical protocol?

7. NIH provides funding

8. Scientific review branch conducts review
   - Program develops priority plan

9. H&S commence clinical trials
EPPIC NET Application & Review Process

1. Applicant initiates research idea
   - Program outreach

2. Applicant submits template application
   - >75 templates

3. Scientific review branch conducts review
   - Program develops priority plan

4. Program invites applicants to work with CRO to generate and submit dossier application
   - ~25 dossiers

5. NIH council votes on priority plan

6. Clinical Coordinating Center delivers clinical protocol?
   - ~10 protocols

7. NIH provides funding

8. Scientific review branch conducts review
   - Program develops priority plan

9. H&S commence clinical trial
   - 5-10 trials

10. 6-8 MO from application

NIH council votes on priority plan

NIH provides funding

H&S commence clinical trial

NIH council votes on priority plan

NIH provides funding

H&S commence clinical trial

NIH council votes on priority plan

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H&S commence clinical trial

NIH council votes on priority plan

NIH provides funding

H&S commence clinical trial

NIH council votes on priority plan

NIH provides funding

H&S commence clinical trial
1. **Manage diversity** - Assets (small molecules, biologics, and devices) are proposed by academia and industry

2. **Track rigor** - A non-grant/contract process to rigorously review all applications at multiple steps

3. **Level the playing field** - NIH provides free resources to assist applicants through the process

4. **Accelerate time to start** - Clinical trials are commenced within short time of initial proposal (6-8 months)
Initial Template Application is designed:
- To be filled out quickly online at no cost to the asset holder
- To collect the minimum information necessary for NIH to determine which assets should move forward to dossier stage
- We are seeking a balance between ease of initial template application (pipeline entry) versus obtaining adequate information to assess viability (go) and red flags (no-go)
EPPIC NET Template Application

1. Applicant information
2. Asset information
3. Freedom to operate
4. Biological rationale
5. Relevant prior studies (preclinical and clinical)
6. Proposed indication(s)
7. Treatment regimen and dosing
8. Outcomes measures (efficacy, biomarkers, and safety)
9. Competing products
10. Feasibility/logistics concerns
11. Relevant literature citations
Dossier Application - Challenges to Consider

- The Dossier Application is designed to be comprehensive addressing scientific merit and clinical trial readiness
  - Dossiers are designed to have all relevant information needed to be evaluated by the review to determine which proposals should proceed to detailed protocol development
  - Dossiers are tailored based on proposed modality
  - The participant will work with NIH contractor to complete a dossier
- There is a balance between ease of application versus information needed to assess protocol viability (go) and red flags (no-go)
Dossier Application – High Level Categories

1. Overview and scientific rationale
2. Biology, Pharmacology, and Physiology
3. Target Product Profile (TPP)
4. Preclinical data
5. Clinical data and trial plan
6. Asset readiness for clinical trial
7. Non-scientific considerations
1. Overview and Scientific Rationale

- Specific disease/condition/population to be studied
- Clinical unmet pain need
- Disease/condition/population specifics
  - Incidence/prevalence, including that for rare diseases
  - Morbidity, mortality, disability of condition and its associated pain
  - Currently available treatment/s for the disease and its associated pain.
  - State explicitly if there are currently no effective pain treatments
  - Epidemiological background, including known genetic and/or mechanistic pathways
  - Diagnostic criteria and how the disease/pain phenotype will be reliably characterized clinically for the study
  - Recruitment and logistics challenges
2. Biology, Pharmacology, and Physiology

- For drugs and devices: Proposed target of asset activity
  - Target expression and distribution (e.g. molecular, tissue or organ target)
  - Mode of action
  - Potency and selectivity for target
  - MOA including target engagement assessment or assays and/or direct binding to target.
- For drugs:
  - Pharmacokinetic/pharmacodynamic information
    - duration of effect
    - elimination pathway
- For devices:
  - Mode of use (observational or interventional, implanted or external, transient or permanent)
  - onset of effect
  - duration of exposure
  - duration of effect
3. Target Product Profile (TPP)

- Online Template Application
- Formal Dossier Application
- Clinical Protocol
- EPPIC NET Clinical Trial

- Indication(s) and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Drug Abuse and Dependence
- Overdosage
- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- References
- How Supplied/Storage and Handling
- Patient Counseling Information
4. Preclinical Data

- Product optimization information
- Therapeutic target evaluation and selection process
- How was the proposed therapeutic/device optimized
- Summary of key relevant preclinical testing for drug/device efficacy and safety, including GLP animal studies
  - Replication studies

For drugs:

- Therapeutic index and toxokinetic data
- Ames test for bacterial mutagenicity, *in vitro* micronucleus assay for mammalian clastogenicity and/or aneugenicity
- Broad ligand profiling using a standardized CEREP panel or the equivalent
- The most sensitive preclinical toxicology species for preclinical development
- Potential drug interactions, including CYP analyses
5. Clinical Data and Trial Plan

Online Template Application

Formal Dossier Application

Clinical Protocol

EPPIC NET Clinical Trial

- Overall design, methodology
- For drugs: Drug dose, route of administration, timing, and duration of exposure.
- For devices: Device use methodology, timing and duration of exposure for an interventional device. Device use parameters/settings.
- Rationale for selected design "is the MAD design adequate to support the proposed phase II design?"
- Efficacy outcome measures
- Safety outcome measures
- Preliminary power analysis and proposed sample size to support feasibility
- Specific drug considerations: PK, major metabolites, adverse effects/safety concerns, both on- and off-target, MTD if previously determined, Tolerability, drug-drug interactions, addiction potential
- Specific Device considerations: Prior IDE and human experience, proof-of-concept studies, efficacy, safety
- Biomarkers
6. Asset Preparation for Clinical Trial

For drugs:
• Scale-up, manufacture, and resources
• Structure of proposed therapeutic and the analytical methods
• Measures of purity and release criteria
• Stability storage, shipping, handling, and usage information.
• Manufacture and scale-up history – including how many lots have been produced and in what quantity. State the largest production to date
• Estimated asset cost, including drug cost, shipping, storage, and use

For devices:
• Device schematic
• Measures of manufacturing, controls, safety standards
• Shipping, storage, maintenance and use information
• Estimated cost of device, shipping, setup, use and maintenance
6. Asset Preparation for Clinical Trial

For drugs and devices:

- Information on sterilization and Packaging Validations; relevant standards and safety testing (ISO, IEC, IEEE, etc.)

- FDA considerations
  - Pre-existing IND/IDE for the asset and the indication
  - Identify stage of IND/IDE application, if any
  - Pre-existing IND/IDE for the asset and other indications
  - Additional preclinical or biomarker validation studies that will be required by the FDA to support the proposed clinical trial

- For devices: Identify if there is an existing NSR designation available for the proposed indication

- Competitive analysis
  - Other therapies in use or development for same indication
  - Other therapies in use or development with the same mechanism of action
  - Advantages of this asset over, or differentiation from, the competition (regardless of whether novel or not)
7. Non-scientific Considerations

- Can the proposed be conducted without HEAL funding
- Further development plan if the project is successful
- Commercialization considerations
- Conflicts of interest and patent state
Further Considerations - 1

- Strategies for outreach to potential asset holders who can benefit from the network?
Evaluate high priority assets within the Preclinical Screening Platform for Pain (PSPP) program

- **Preclinical Screening Platform**
  - *In vitro* µ-opioid receptor screening
  - Acute pain models
  - Chronic pain/disease models
  - Large animal models
  - *In vivo* addiction screening

- Successful compounds/devices move on toward clinical trials

- **Compound handling Processing**
  - Small molecules
  - Biologics
  - Devices
  - Natural products

- **Confidential database**
- **Public database**
Hypothetical Testing Paradigm

In vitro Screen (Opioid, etc.)

Acute Pain  Inflammatory Pain  Neuropathic Pain  Observation Screen

Specific Pain Models

Abuse Liability
• Which asset(s) warrant additional resources so that they can be ready for early clinical trials?
• What resources should we consider? Phase I trials, CMC, regulatory, etc.
Therapy Development Beyond PSPP

Program Announcements Published December 2018
Optimization of Non-addictive Therapies to Treat Pain

UG3 Phase (Optimization)
- Anticipate ~6-8 projects
- <$500K Direct Cost/yr

UH3 Phase (Final Optimization/Development)
- Anticipate ~2-3 projects
- <$1.5M Direct Cost/yr

Goal: ≥ 2 INDs