Developing Drugs and Testing Platforms for Pain, Addiction and Overdose in Collaboration with NCATS

Anton Simeonov, PhD

Scientific Director

NCATS pre-clinical HEAL initiatives involve both extramural opportunities and intramural collaborations

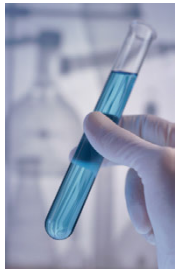
- Extramural funding opportunities
  - RFA-TR-19-005: HEAL Initiative: Biofabricated 3D Tissue Models of Nociception, Opioid Use Disorder and Overdose for Drug Screening
  - RFA-TR-19-003: HEAL Initiative: Tissue Chips to Model Nociception, Addiction, and Overdose
  - NOT-TR-18-031: HEAL Initiative: Announcement of the NCATS ASPIRE Design Challenges to Develop Innovative and Catalytic Approaches Towards Solving the Opioid Crisis
  - See https://ncats.nih.gov/heal for a full list of NCATS HEAL-Related Funding Opportunities

- Intramural collaborations with NCATS – to enable development of new experimental therapeutics
  - **Not an extramural grant – no funding provided to collaborator's institution**
  - Team-based: You (who have existing data, disease knowledge and novel therapeutic hypothesis) + NCATS (preclinical drug development expertise and laboratory capabilities)
  - Efficiency: state of the art technology and milestone-driven collaboration plans

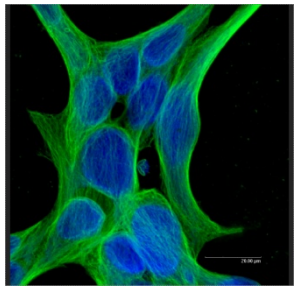
The Preclinical Translation Process

(using small molecule drugs as an example)

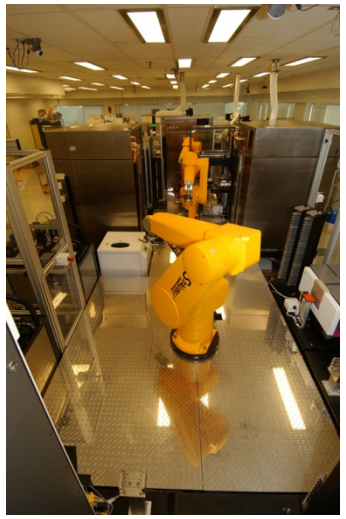
Identify disease mechanism → Create testing system → Test chemicals in system → Modify (chemistry) for human use → Test in animals → Test in humans



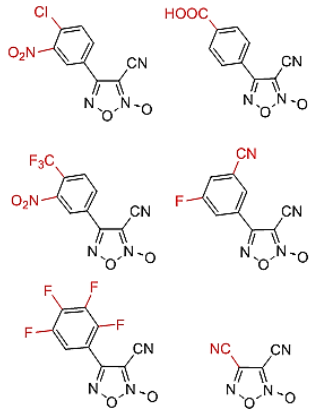
Basic Research



Assay Development

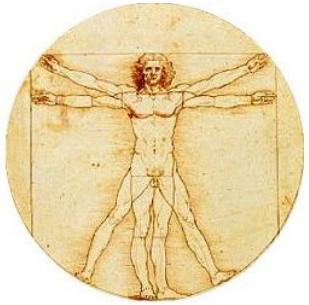


Screening



Medicinal Chemistry

Preclinical Development



Clinical Development

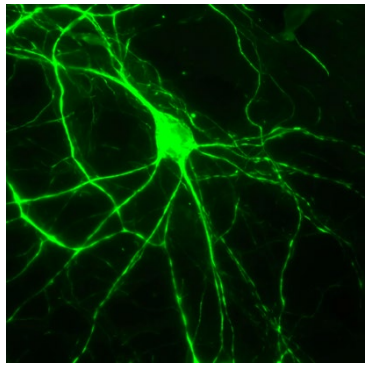
NCATS Division of Preclinical Innovation

National Center for Advancing Translational Sciences

Stem Cell Translation Laboratory

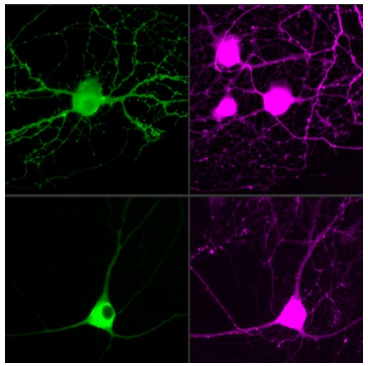
Collaborators can work with the SCTL to develop iPSC-derived cellular platforms for improved prediction of *in vivo* human effects of lead compounds

Capabilities



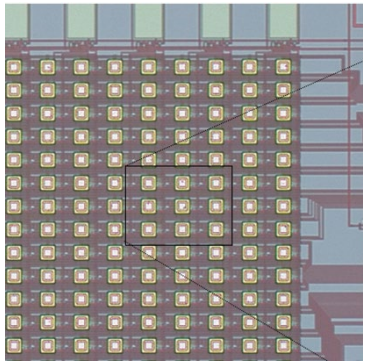
Access to relevant human cell types

Sensory neurons (nociceptors) and other neuronal subtypes



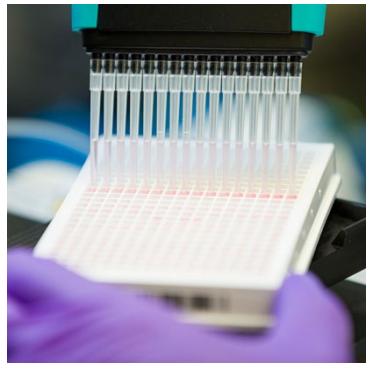
Advanced imaging technologies for functional cell characterization

High-content confocal, calcium imaging, optogenetics



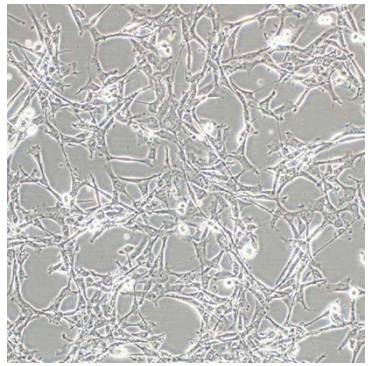
High-throughput electrophysiology methods

High-density multi-electrode arrays 26,400 electrodes/well



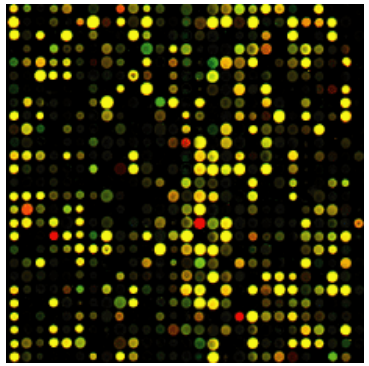
Measurement of signaling pathways, metabolism & specific targets

Cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism



Longitudinal tracking of cell behavior

Multiple measurements over days, weeks or months



Combined single-cell transcriptomic & proteomic analyses

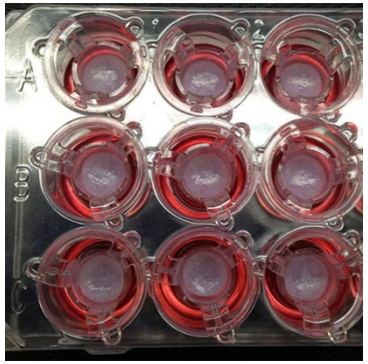
Drug response in individual nociceptors and other neuronal phenotypes

National Center for Advancing Translational Sciences

3-D Tissue Biofabrication Laboratory

Collaborators can work with the 3-D Laboratory to biofabricate multicellular functional tissues using human primary or iPSC-derived cells that are better models of human disease state and response to new drugs

Capabilities

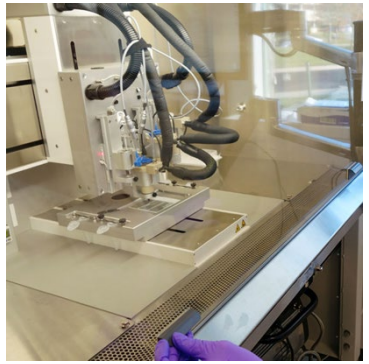


Tissue engineering technologies

Development of tissues-in-a-well

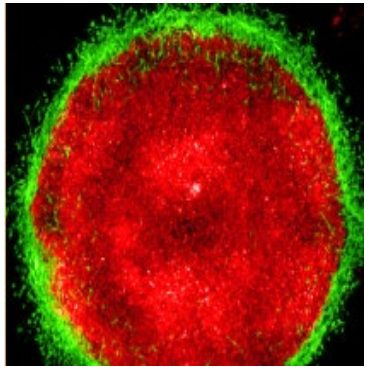
Automated production of iPS cell-derived cells

To reproducibly scale up production of human tissue relevant cells

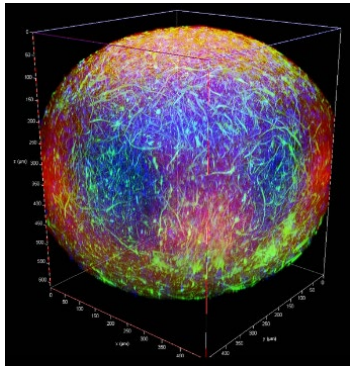


3D bioprinters

To create spatial cellular patterns in tissues, eg, neuronal circuits, neurovascular unit, innervated tissues

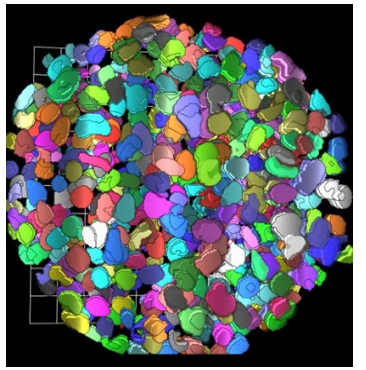


Spatially defined and physiologically relevant tissue models



Validation of 3D organoid cultures

Neural spheroids for compound screening



Assays using 3D tissue models

High-content confocal, calcium imaging, optogenetics, multielectrode,arrays, neurotransmiters biosensors

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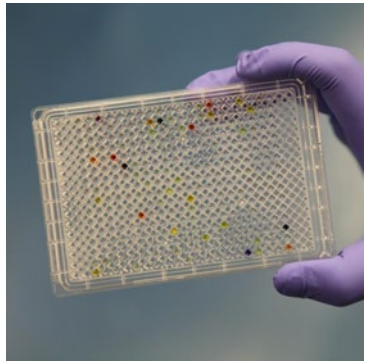
Pharmacological Probe Development

Use assay development and quantitative high-throughput screening to identify promising compounds to modulate novel targets; optimize compound properties to probe novel targets.

Capabilities

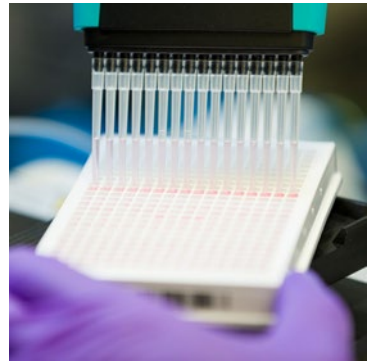
HTS assay adaptation, development

GPCR and ion channel assays and high-content image-based assays

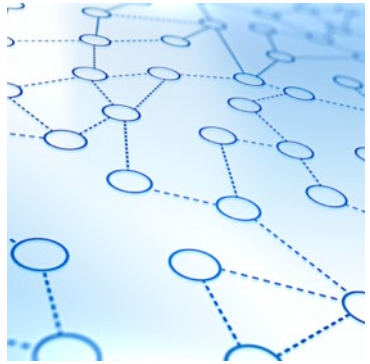


Drug repurposing libraries

All FDA approved compounds (>2,400), as well as >150,000 in annotated/diversity collections



Counterscreen & confirmatory assays



Cheminformatics platforms

Molecular modeling and docking, Machine learning, High content image analysis

Medicinal chemistry

Largest medicinal chemistry program at NIH, > 30 fume hoods, > 20,000 molecules made

ADMET Assays

Aqueous kinetic solubility, rodent & human liver microsomal stability & PAMPA permeability

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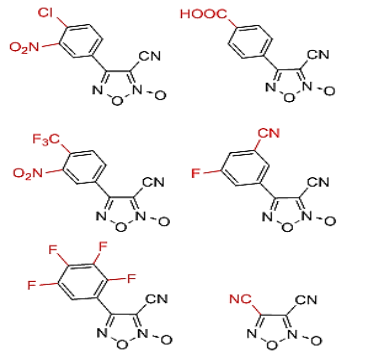
Enabling Investigational New Drug Applications

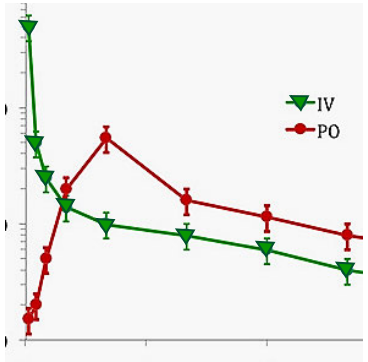
Joint project teams develop prototype therapeutics into IND-enabled small molecules, biologics, and gene and cell therapies ready for clinical testing

Capabilities

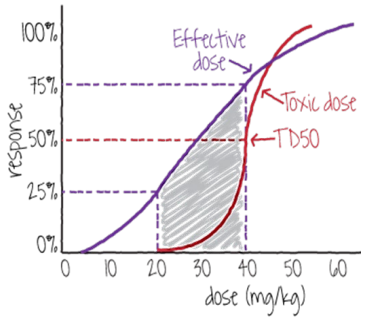


Target validation and lead optimization

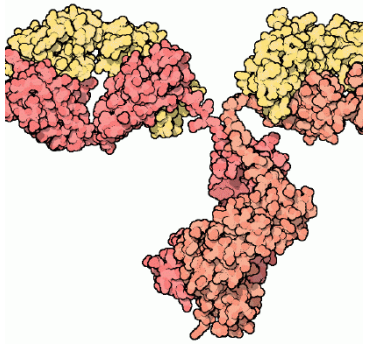
To finalize declaration of clinical candidates



Pharmacokinetics/ pharmacodynamics



GLP safety evaluation and toxicology



Therapeutic modality expertise

Including small molecules, biologics and gene and cell therapies

GMP manufacturing and formulation

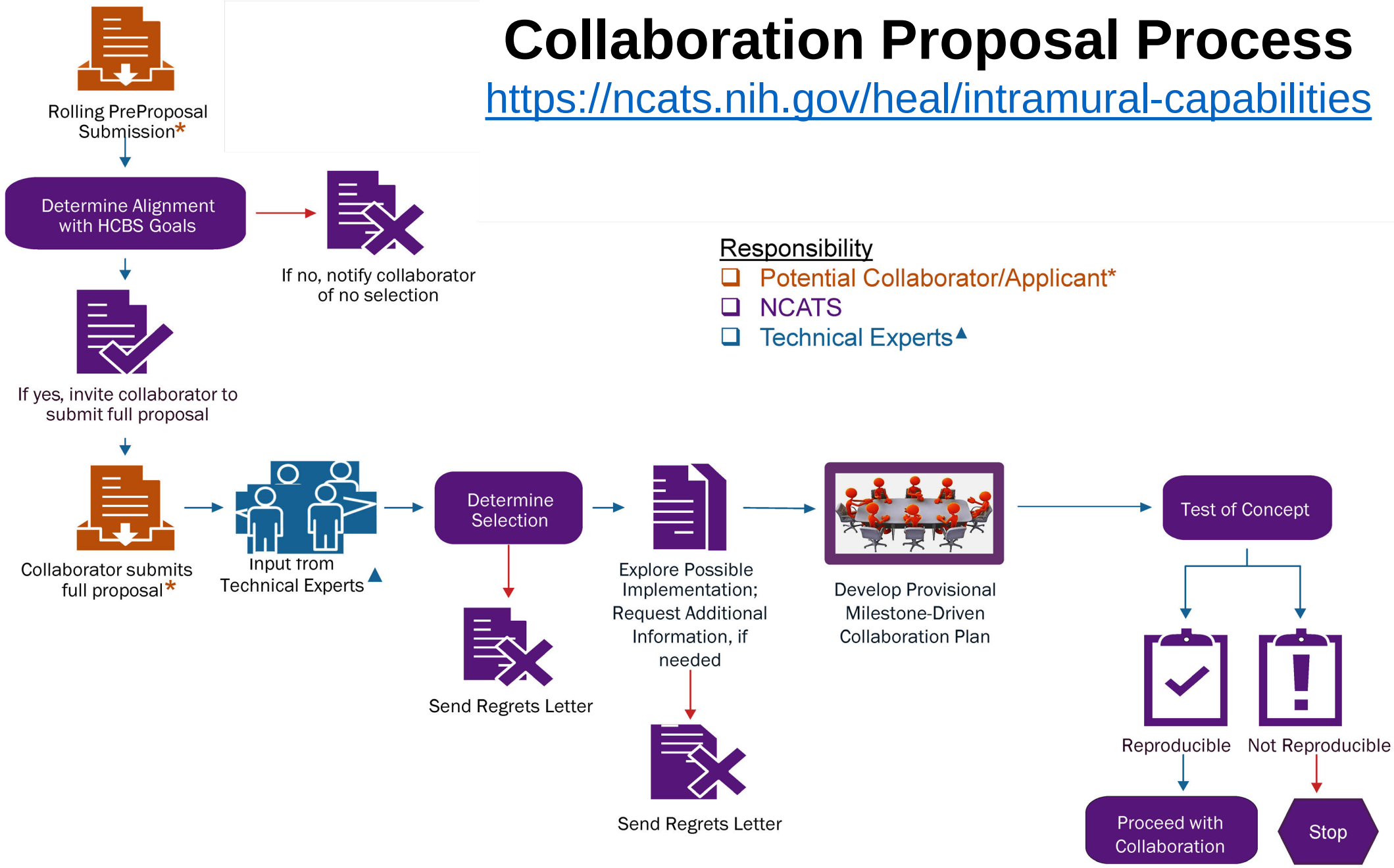
To scale up the production of the compound for clinical testing

Repurposing of approved therapies

National Center for Advancing Translational Sciences

Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities



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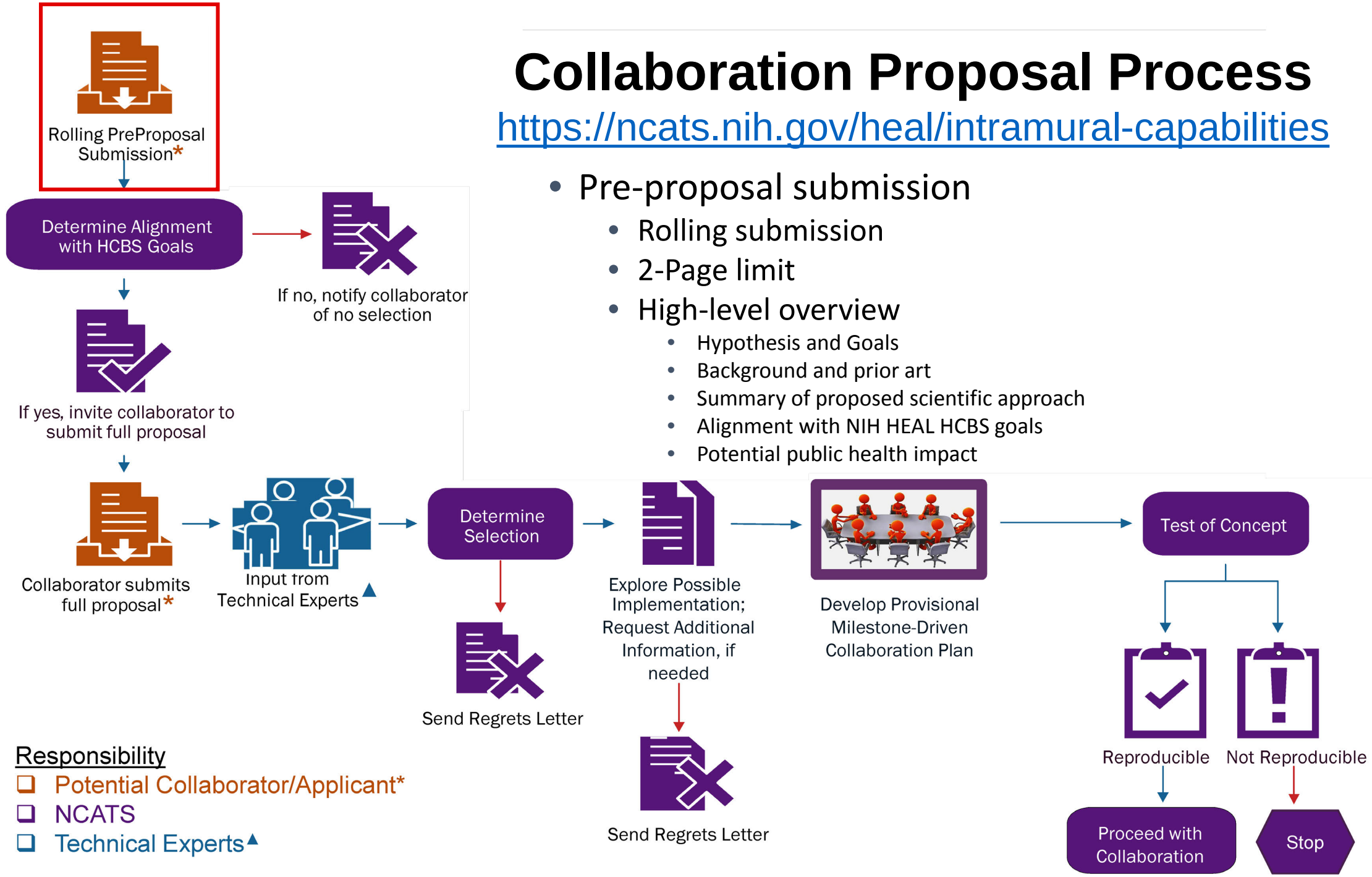
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Pre-proposal submission
  - Rolling submission
  - 2-Page limit
  - High-level overview
    - Hypothesis and Goals
    - Background and prior art
    - Summary of proposed scientific approach
    - Alignment with NIH HEAL HCBS goals
    - Potential public health impact



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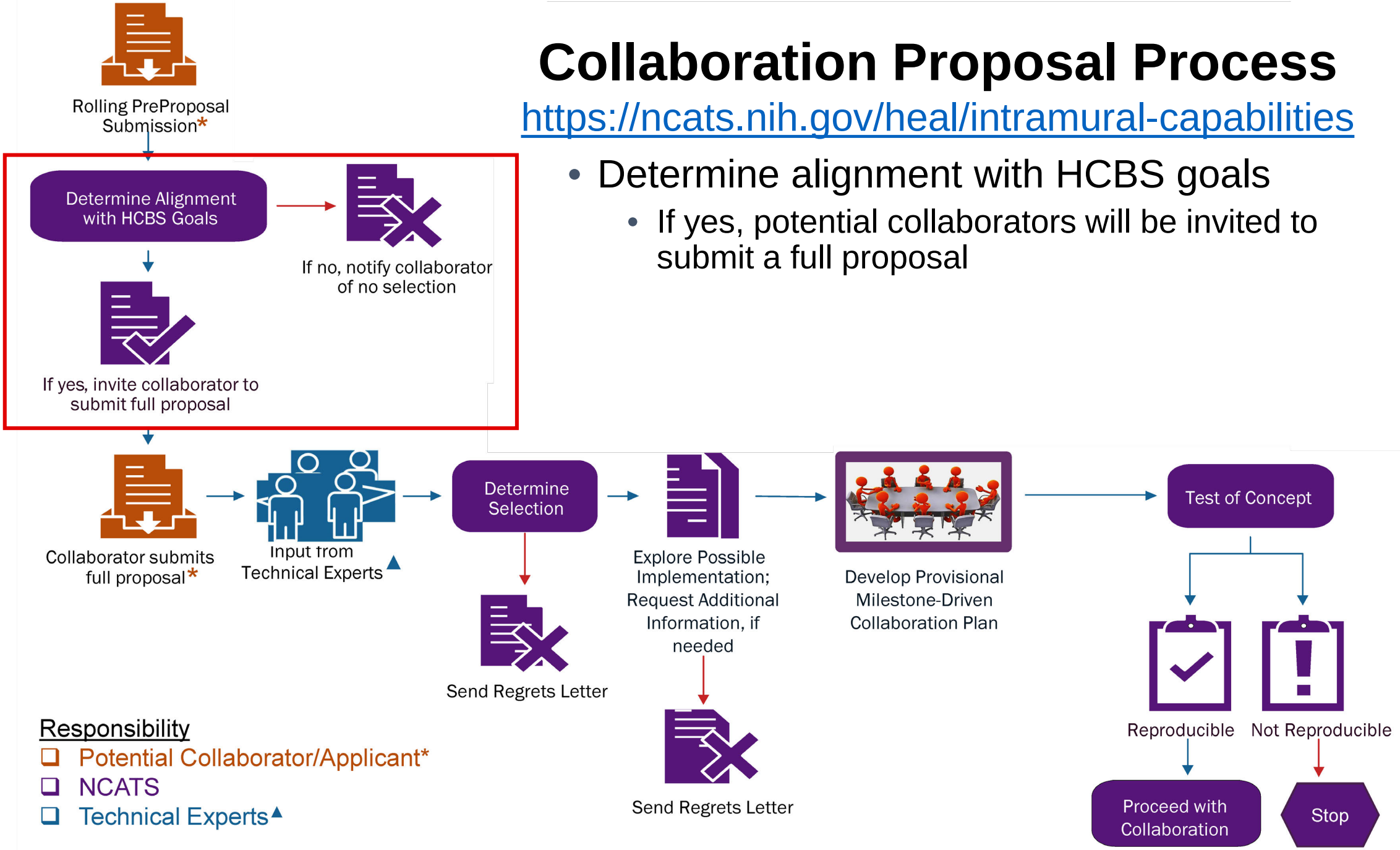
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Determine alignment with HCBS goals
  - If yes, potential collaborators will be invited to submit a full proposal



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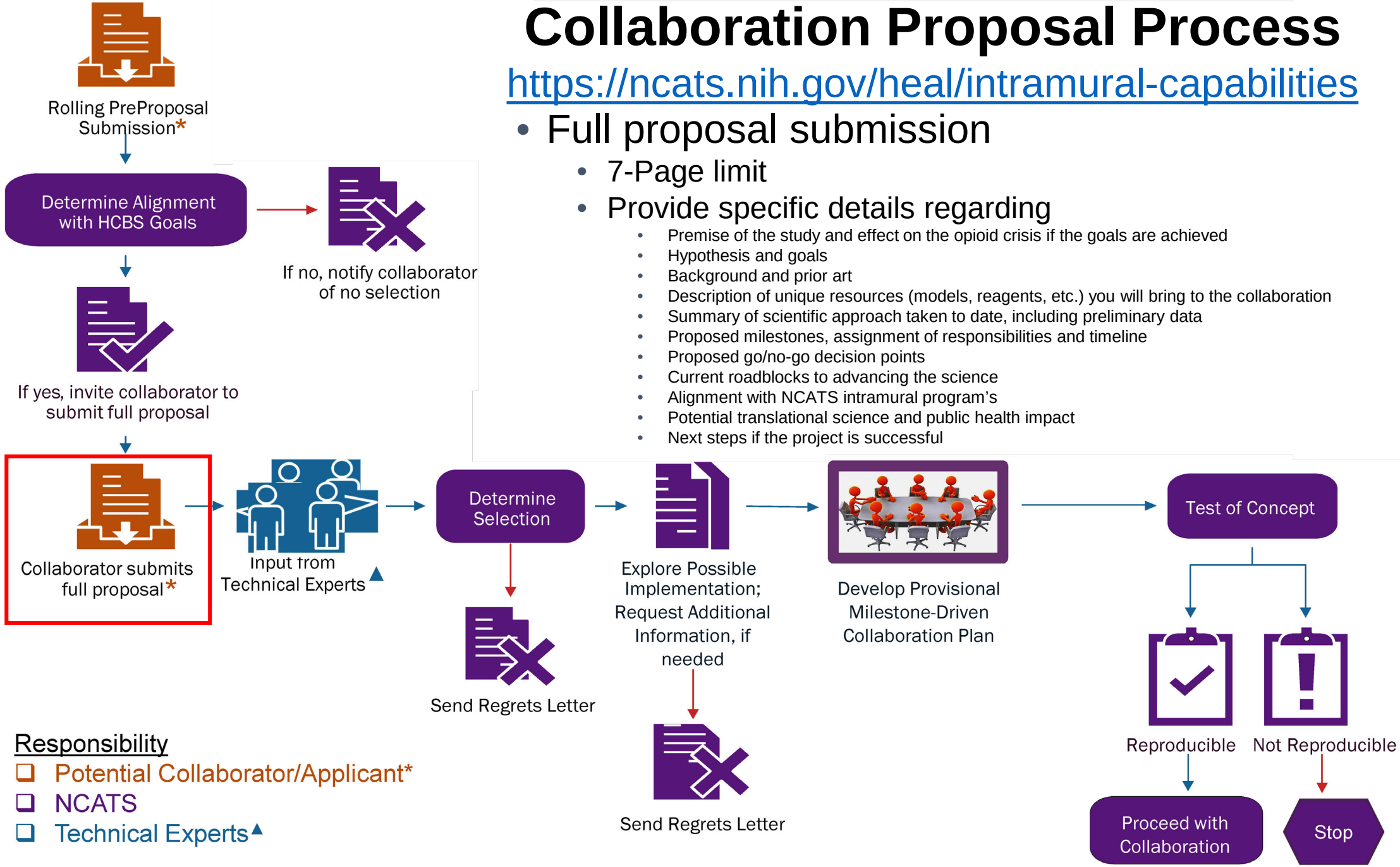
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Full proposal submission
  - 7-Page limit
  - Provide specific details regarding
    - Premise of the study and effect on the opioid crisis if the goals are achieved
    - Hypothesis and goals
    - Background and prior art
    - Description of unique resources (models, reagents, etc.) you will bring to the collaboration
    - Summary of scientific approach taken to date, including preliminary data
    - Proposed milestones, assignment of responsibilities and timeline
    - Proposed go/no-go decision points
    - Current roadblocks to advancing the science
    - Alignment with NCATS intramural program's
    - Potential translational science and public health impact
    - Next steps if the project is successful



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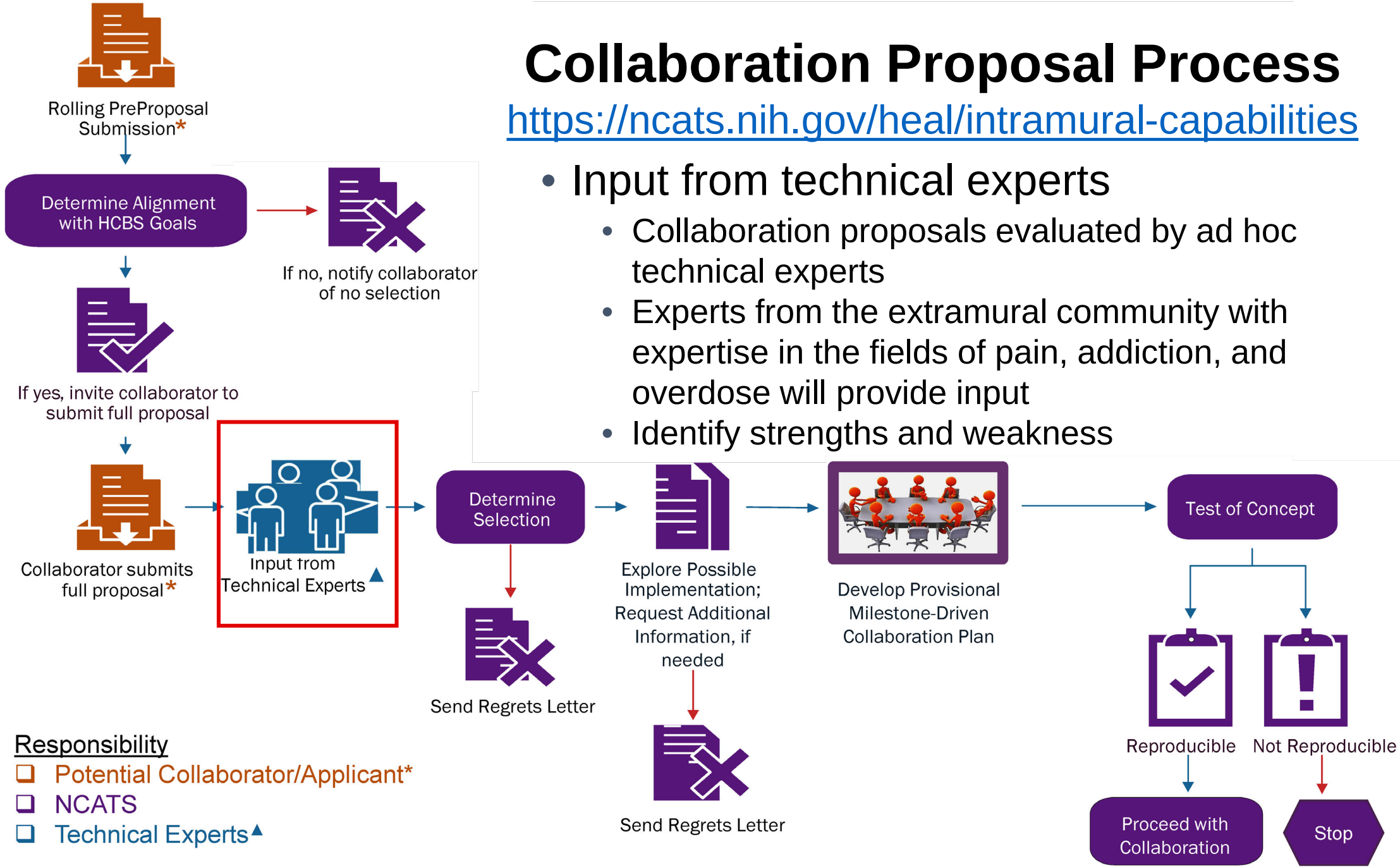
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Input from technical experts
  - Collaboration proposals evaluated by ad hoc technical experts
  - Experts from the extramural community with expertise in the fields of pain, addiction, and overdose will provide input
  - Identify strengths and weakness



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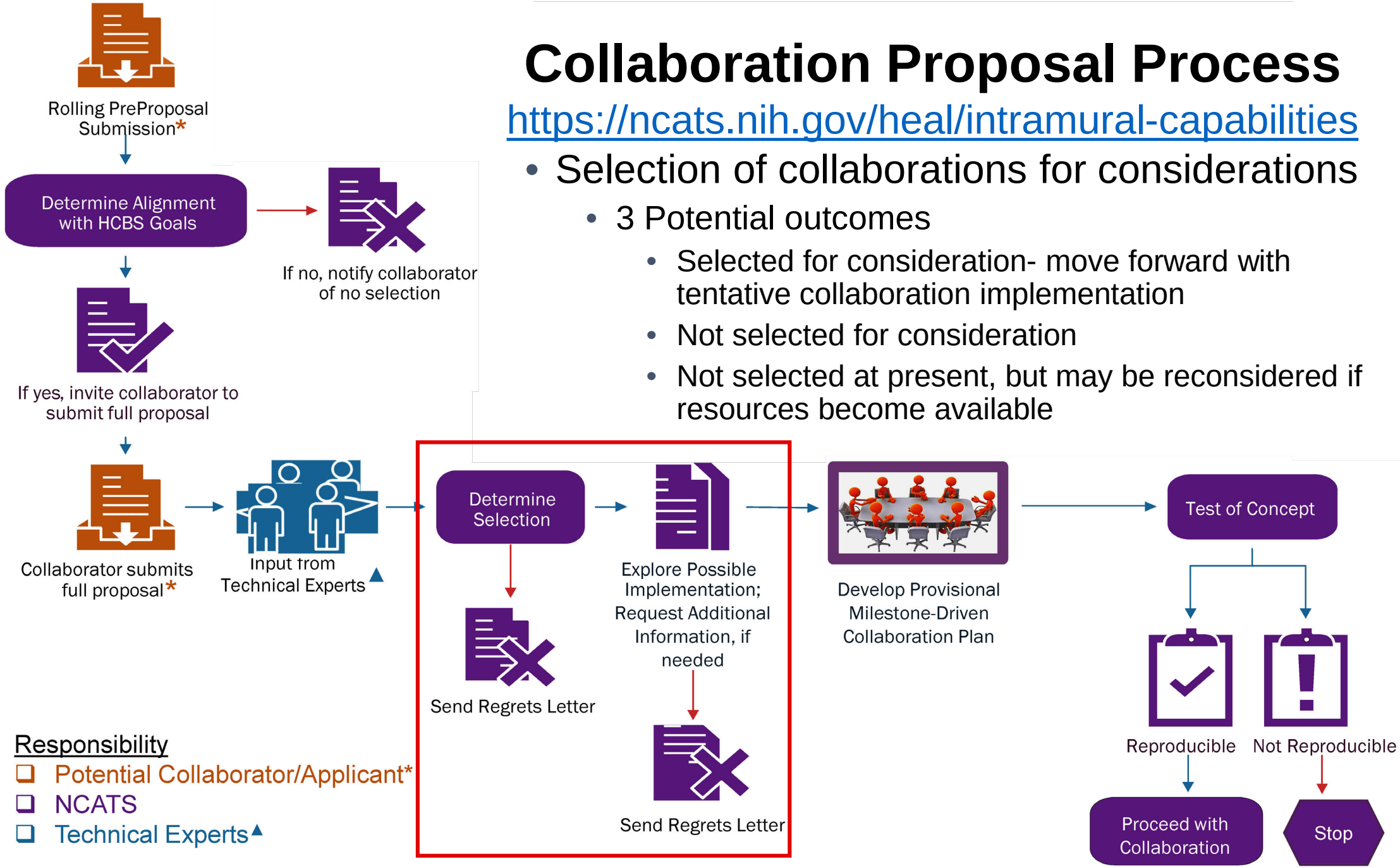
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Selection of collaborations for considerations
  - 3 Potential outcomes
    - Selected for consideration- move forward with tentative collaboration implementation
    - Not selected for consideration
    - Not selected at present, but may be reconsidered if resources become available



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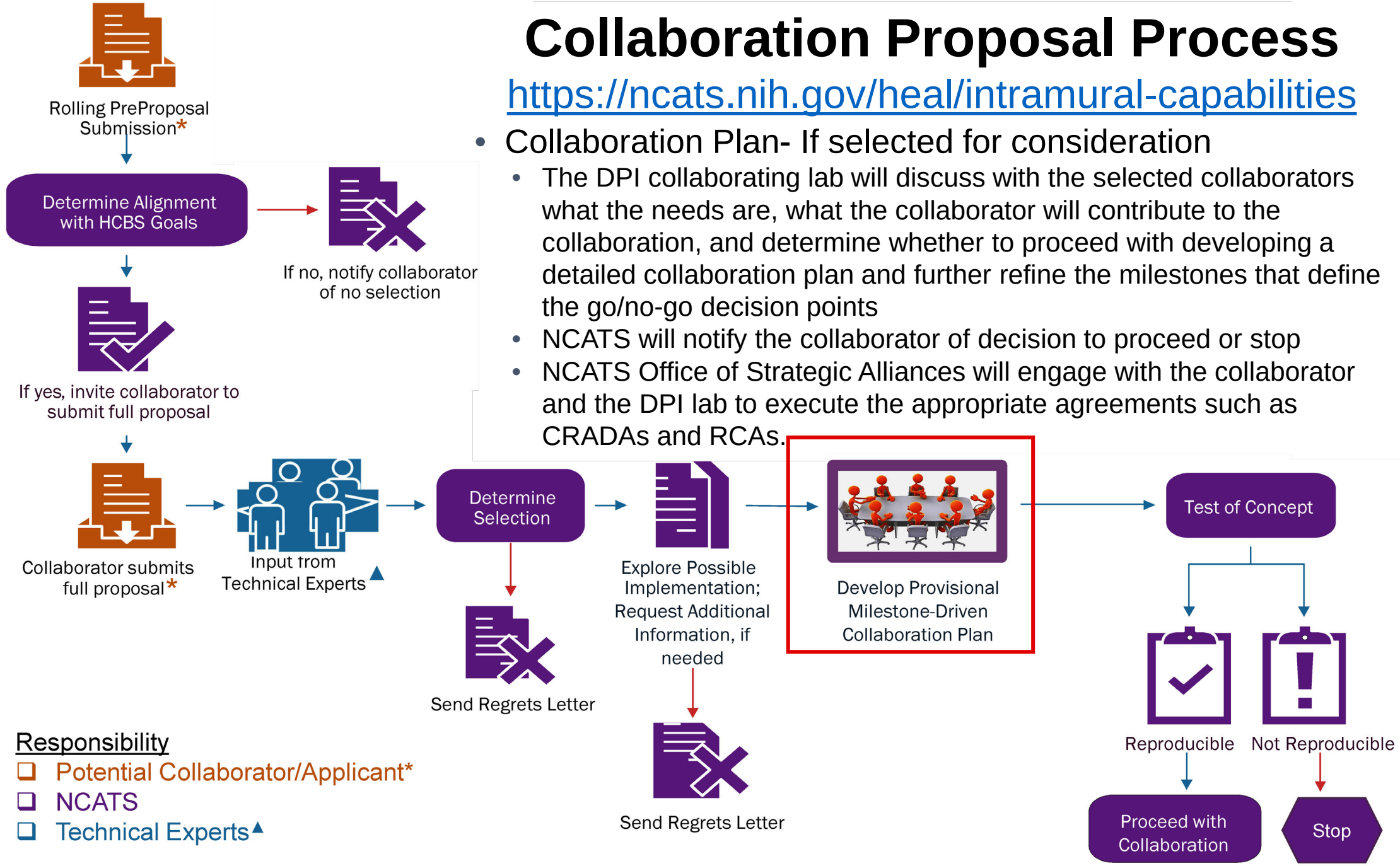
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Collaboration Plan- If selected for consideration
  - The DPI collaborating lab will discuss with the selected collaborators what the needs are, what the collaborator will contribute to the collaboration, and determine whether to proceed with developing a detailed collaboration plan and further refine the milestones that define the go/no-go decision points
  - NCATS will notify the collaborator of decision to proceed or stop
  - NCATS Office of Strategic Alliances will engage with the collaborator and the DPI lab to execute the appropriate agreements such as CRADAs and RCAs.



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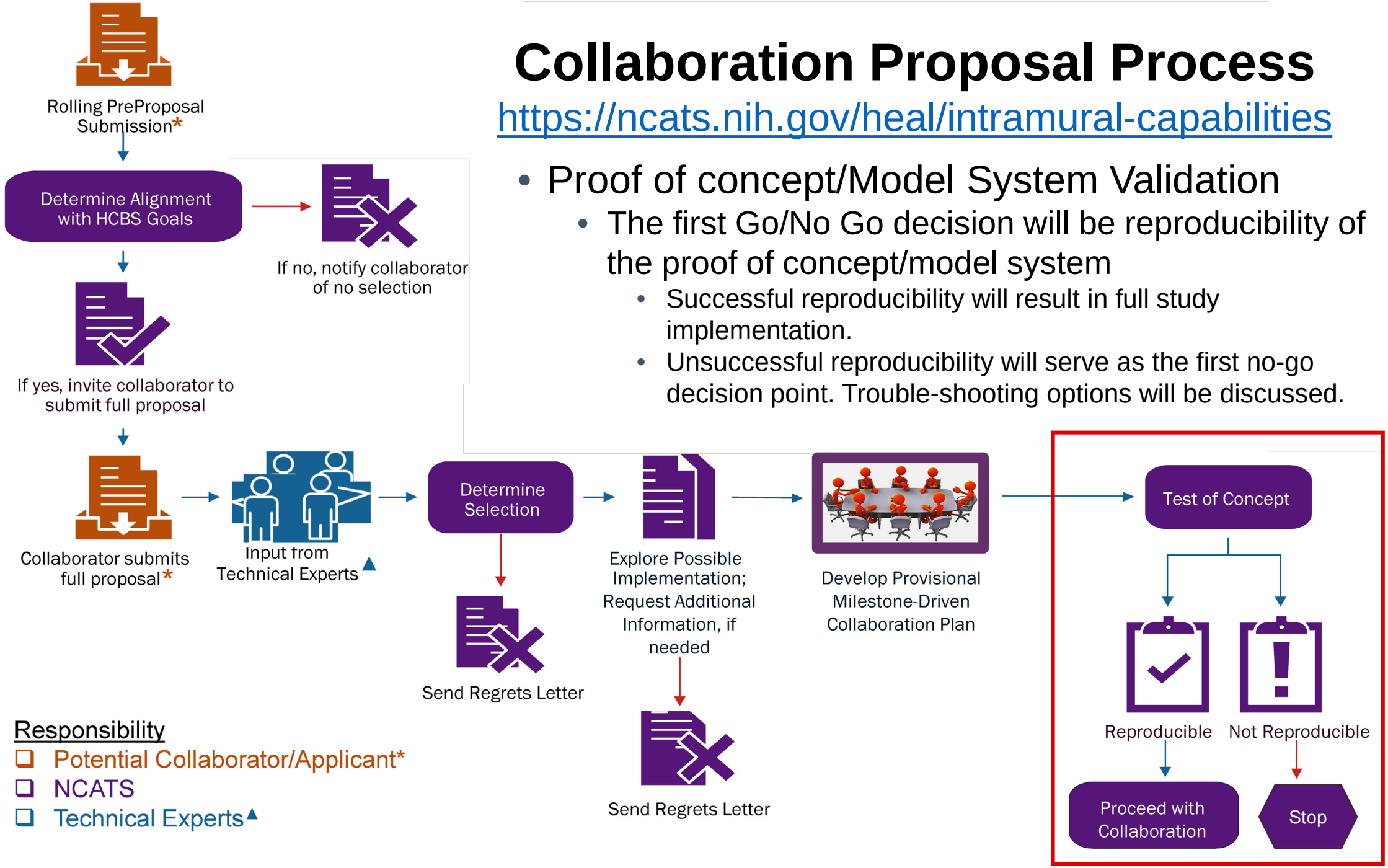
Collaboration Proposal Process

https://ncats.nih.gov/heal/intramural-capabilities

- Proof of concept/Model System Validation
  - The first Go/No Go decision will be reproducibility of the proof of concept/model system
    - Successful reproducibility will result in full study implementation.
    - Unsuccessful reproducibility will serve as the first no-go decision point. Trouble-shooting options will be discussed.



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Collaboration Proposal Process

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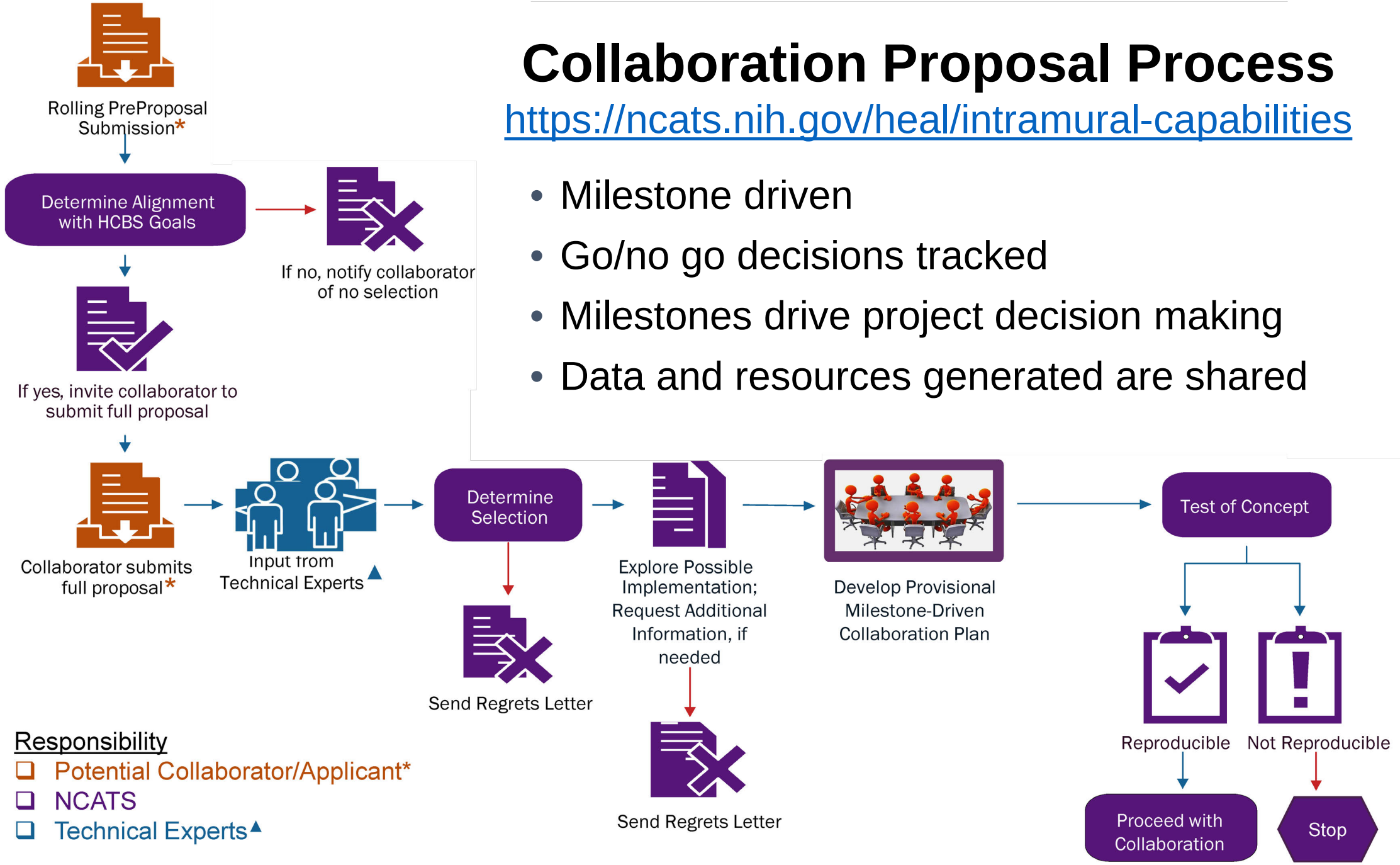
- Milestone driven
- Go/no go decisions tracked
- Milestones drive project decision making
- Data and resources generated are shared



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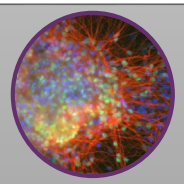
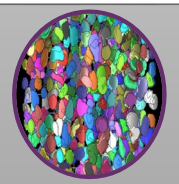
Summary

Human Cell-Based Platforms for testing new treatments



iPSC-Derived Neurons for Pain and Reward Pathways



3-D Bioprinted Tissue Models

Model Complexity

Cells — **Multi-organ**

Accelerating Translation of Novel Compounds for Clinical Testing

Development of Pharmacological Probes for Novel Targets

Development of Investigational New Drugs for Clinical Testing

Preclinical Development

Early — **Late**

Clinical Testing and Trials

More Information:

NCATSDPIHEALCollab@nih.gov

https://ncats.nih.gov/heal/intramural-capabilities

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