Preclinical Screening Platform for Pain (PSPP)

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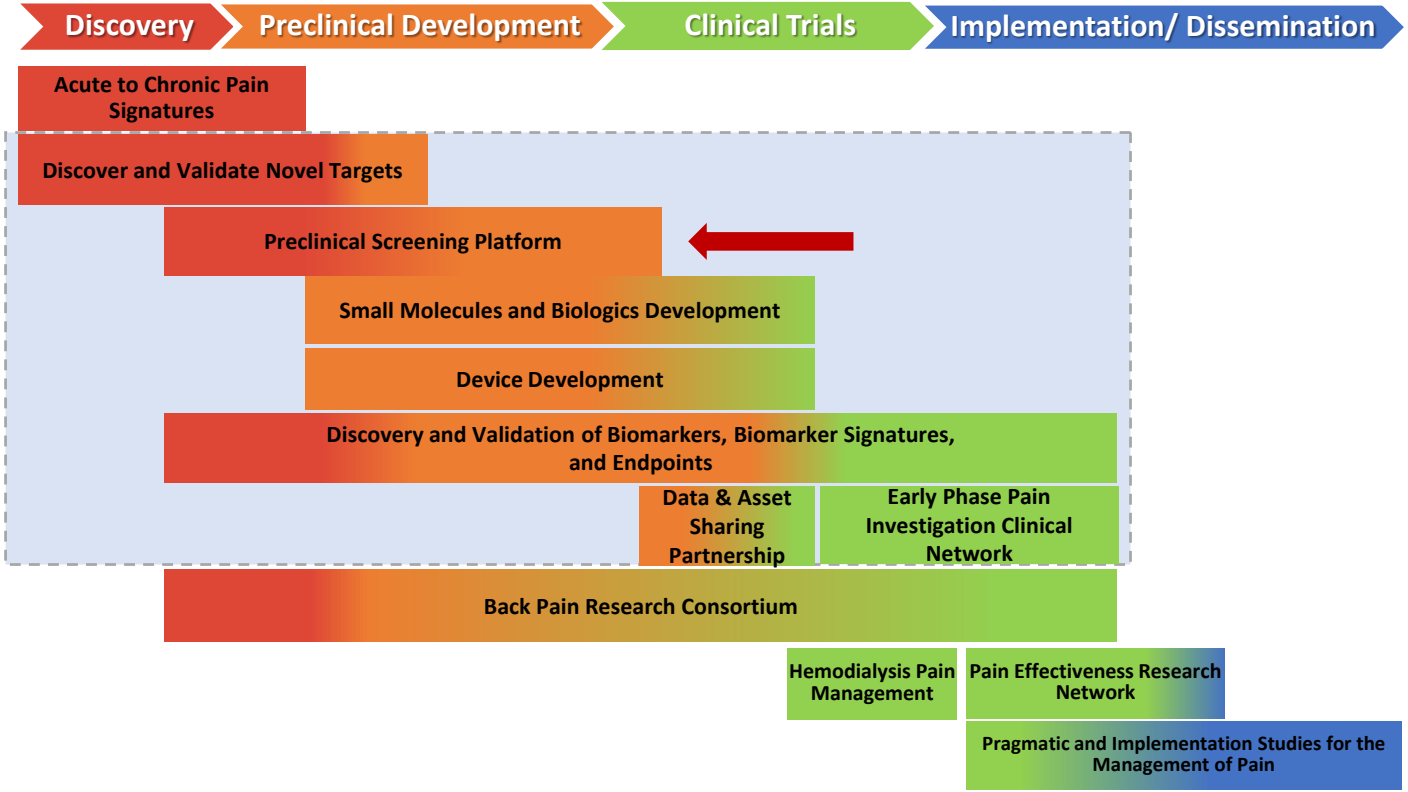
Mission and Strategy

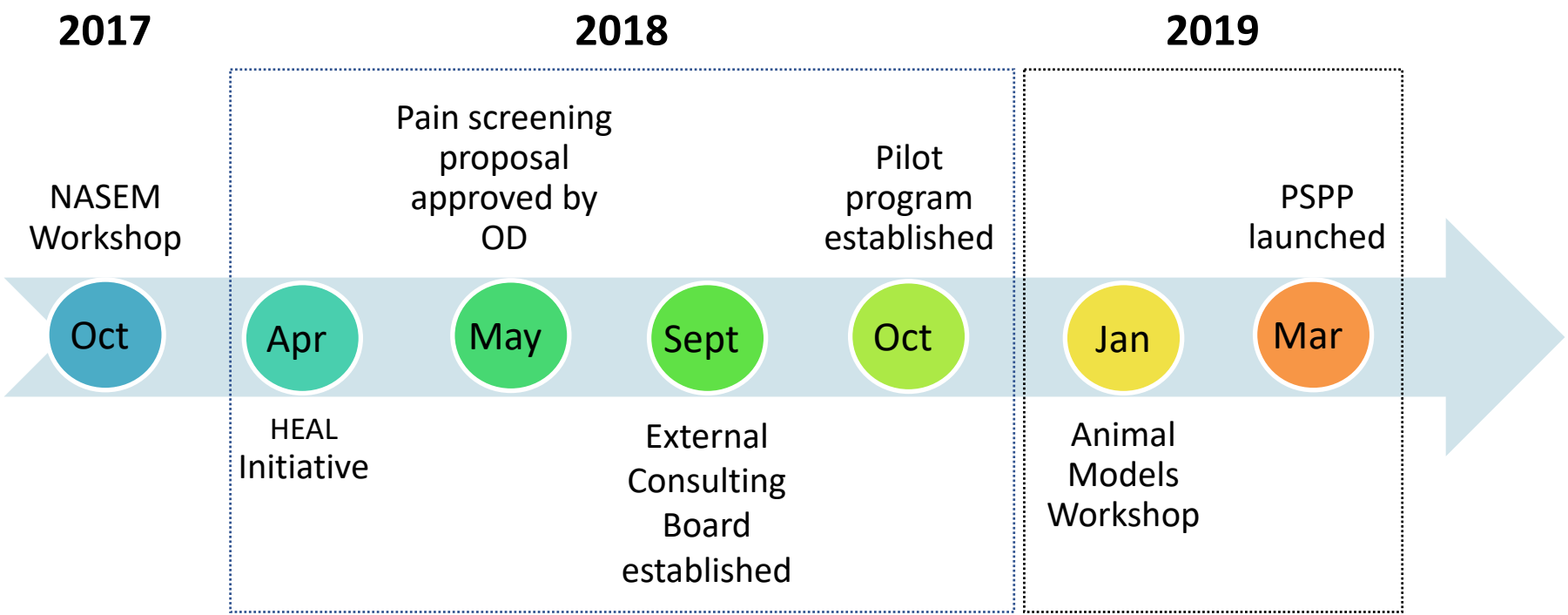
Accelerate the Discovery and Pre-Clinical Development of Non-Addictive Treatments for Pain

- The NIH HEAL Initiative aims to improve treatments for opioid misuse and addiction and to enhance pain management
- Build an understanding of the development and prevention of chronic pain
- Discover and validate novel targets for safe and effective pain treatment
- **Engineer a preclinical testing platform to identify and profile non-addictive therapeutics for pain**
- Support translational programs in therapy development, discovery and development of biomarkers
- Provide a robust clinical trials network to test new therapies for pain conditions in adults and children

HEAL Programs for Pain

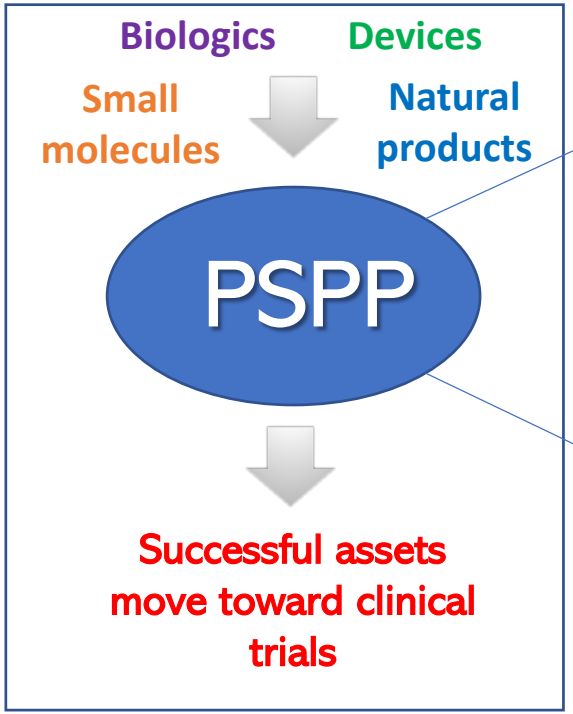


Timeline to Establishing PSPP



Preclinical Screening Platform for Pain (PSPP)

One-stop preclinical testing platform to accelerate discovery of non-addictive, effective therapies



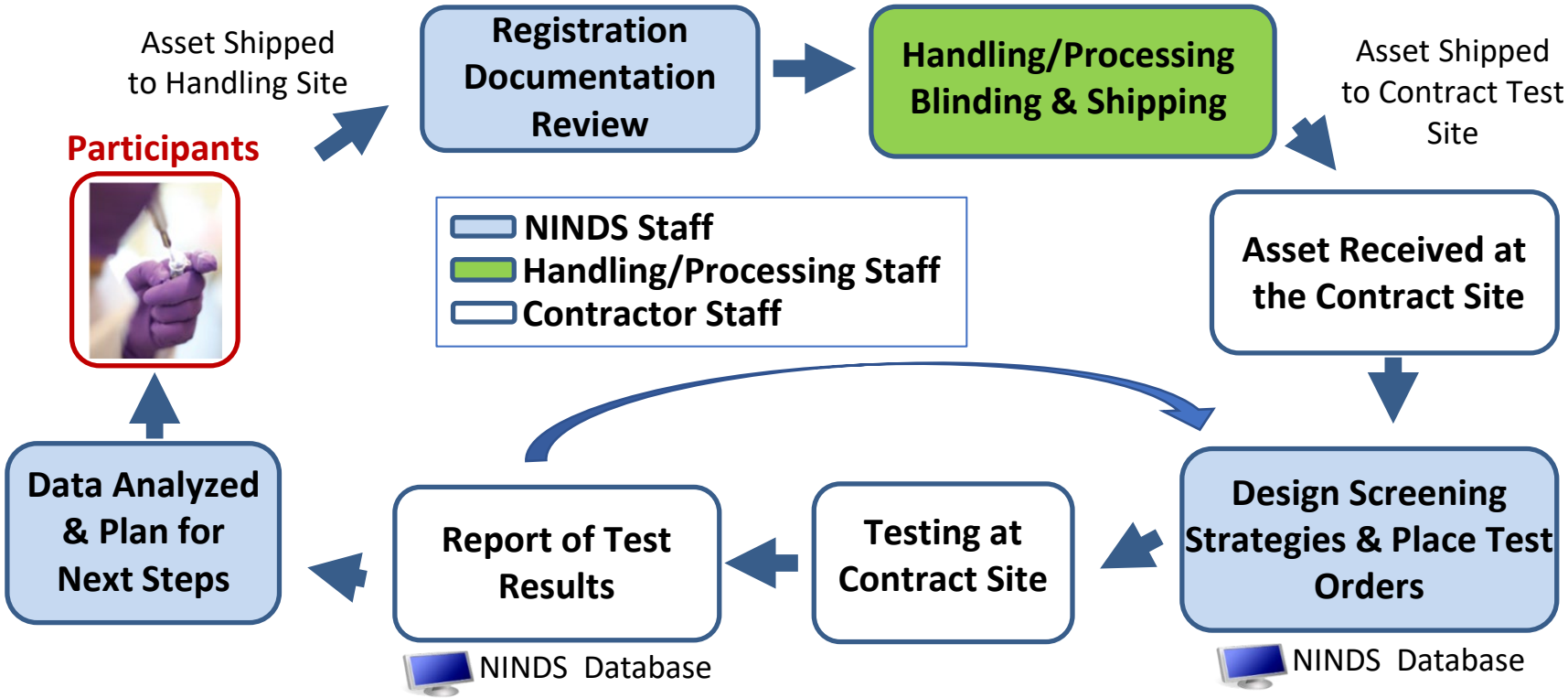
Efficient, rigorous screening resource

- Adhere to ARRIVE guidelines
- Testing is randomized, blinded, and both sexes are included
- Group size is determined by power analysis
- Testing site is blinded to asset
- Participant intellectual property protected
- Public database to highlight rigor and best practices

Participation in PSPP

- PSPP is currently accepting assets for evaluation continuously, on an ongoing basis
- Researchers from academic institutions or industry in the U.S. and internationally are eligible to submit assets for screening
- To start the process, participants contact us for more information and to discuss research goals, resources, and timelines
- A signed confidentiality agreement between NINDS and each potential participant is required before submission of agents for evaluation
- Under NINDS direction, preclinical screening of test candidates is performed by contract facilities on a blinded and confidential basis
- Since opening program up to participants two months ago, PSPP has had discussions with 20 parties

PSPP Sample Submission and Logistics



External Consulting Board (ECB)

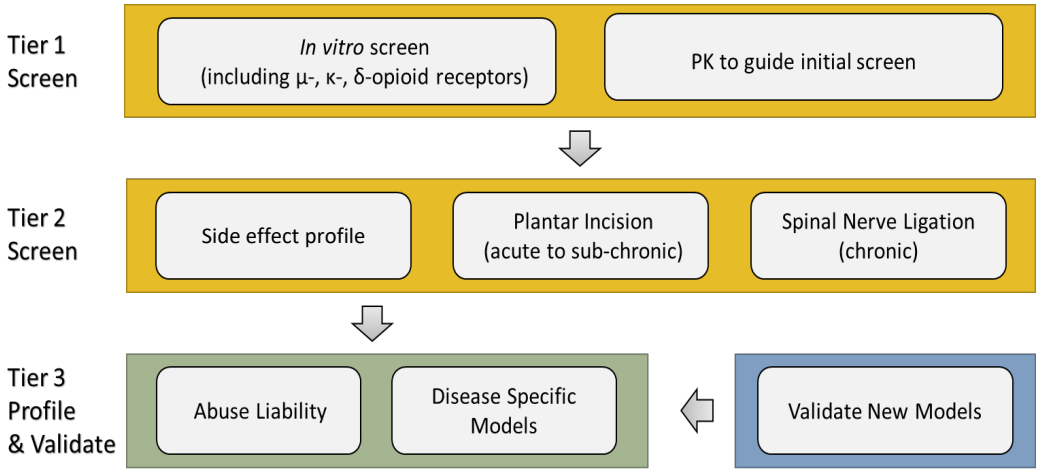
The ECB provides independent input and guidance on scientific and strategic priorities and implementation

ECB Member	Institution/affiliation
Daniela Salvemini, PhD	Saint Louis University
Ursula Wesselmann, MD, PhD, D.T.M.&H.	University of Alabama
Andrew Hershey, MD, PhD, FAAN, FAHS	Cincinnati Children's Hospital
Gregory Scherrer, Pharm D, PhD	University of North Carolina
Jeff Kennedy, PhD	Consultant
Stevens Negus, PhD	Virginia Commonwealth University
Donna Hammond, PhD	University of Iowa
Bavani Shankar, MBA	AstraZeneca

Testing Strategy: Screen, Profile, and Validate

➢ **Optimization based on ECB input:**

- Screening for opioid receptor binding & pharmacokinetic profiles
- Pharmacokinetics study based on stage of asset being tested
- Side effect profile assessed
- Assets are evaluated for abuse liability
- Need to identify appropriate non-evoked pain endpoints



PSPP Tier 3: Optimization Example

➢ **Tier 3: aim to optimize disease relevant models**

- For example, evaluation of migraine models:
  - Models:
    - Nitroglycerin, primed versus unprimed
    - Cortical spreading depression
    - Inflammatory soup
  - Test subjects:
    - rat vs mouse
    - male vs female
  - Endpoints:
    - plantar vs periorbital mechanical thresholds
    - validation of evoked (allodynia) vs non-evoked endpoints (e.g. photo/phonophobia)
  - Translatability

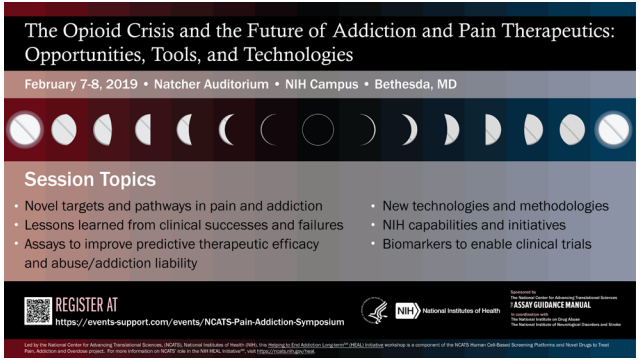
Non-Evoked Endpoints Evolving Debate: No Consensus in the Field

Endpoint	Pros	Cons	Translatability	Recommendations	Rank
Place escape / avoidance	Natural behavior; does not require training	Need to automate and structure differently for bilateral pain conditions			
Licking, biting, lifting, guarding behaviors	Natural behavior; can be automated	Not applicable to all models	Seems to translate		
Grimace	Automation being developed	Time and effort intensive (currently)	Not established	Needs further development; current scoring system has duplicative criteria	
Burrowing		Cannot be used alone			???
Wheel running				Confound: exercise can alleviate pain	
Nesting		Not applicable to rats			
Gait analysis				This is not a measure of pain	
Open field (rearing, horizontal, & vertical locomotion)	Adjunct test that can help interpret false negatives and false positives in other tests	Requires distance and pattern analysis			

Workshops Informing PSPP

Jan. 30-31, 2019

Feb. 6, 2019



Feb. 7-8, 2019

PSPP: Key Elements

1) Endpoint refinement/development to address gaps

2) Validated models configured into customized, asset-dependent flowcharts

3) Flexible decision-making process with input from participant

4) Rigor, confidentiality and IP protection

5) Commitment to appropriate data sharing

Timelines (2018-2023)

2018

- -Program approved
- -ECB formed
- -Market research conducted
- -RFP drafted
- -Workshops planned
- -Personnel identified
- -Pilot program established

2019

- -Workshops held
- -Personnel hired
- -Outreach activities
- -Initiate model and protocol development
- -RFP posted
- -Award contract
- -Enroll participants
- -Asset evaluation

2020-2021

- -Incorporate non-evoked endpoints
- -Optimize and validate disease specific models
- -Explore non-rodent species
- -Test new assets and complete profiling of existing assets
- -Establish testing paradigms for devices

2022-2023

- -Convene workshop
- -Evaluate initial goals and objectives and advances made
- -Determine next steps

Questions/Discussion