



# ACTION

## Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks

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# Challenges in Analgesic Drug Development

1. Clinical trial design
2. Clinical trial design
3. Clinical trial design
4. Others

# Challenges in Analgesic Drug Development

- Others
  - Animal models and failure in preclinical studies
  - Limited funding for clinical research
  - Pain research not centralized/coordinated
- New perspective:
  - IPRCC
  - FDA
    - Consolidation
    - Scientific Workshops
  - NIH Pain Consortium/NIDA Drug Development
  - IOM Report: “Relieving Pain in America”
  - IMMPACT - Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
  - ACTION



Analgesic Clinical Trial  
Translations, Innovations,  
Opportunities, and Networks

# Background

- Clinical studies, particularly efficacy trials, notoriously flawed for analgesic drug development
  - Frequent failed studies with drugs known to be effective
  - Extremely small treatment effects even when successful
  - Multiple causes, e.g.:
    - Large placebo effect
    - Missing data
    - Study design flaws
    - Study analysis flaws
    - Investigator quality
    - Frequent use of foreign study sites

# Background

- Although somewhere between 60 and 180 million people suffer from chronic pain in US
- And the dangers of treating even acute pain with opioids, NSAIDS or acetaminophen are considerable
- Industry reluctant to put money into novel analgesic development with a low success rate of clinical trials

# Rationale

- IMMPACT has performed an enormous service in advancing the field of analgesic clinical trials
- But there's a wealth of data from failed analgesic trials in FDA files
- Initial FDA efforts under Critical Path Initiative:
  - Small contracts with academic investigators
  - Small contract to evaluate data standardization
  - Confidentiality agreements
  - Data access successful but limited
- Meanwhile – numerous investigators with similar goals working in silos
- Not to mention industry and other government agencies remaining untapped

# Rationale

- Previous experience working with Critical Path on a Public-Private Partnership (PPP)
- Why not bring all stakeholders under a single umbrella?
- PPP would allow for:
  - Bringing together the scientific experts
  - Data sharing
  - Closing the research gaps
  - And, leveraging resources
- Dr. Woodcock, Director, Center for Drug Evaluation and Research, completely supportive of proposal

## Other FDA Public-Private Partnerships

- Numerous PPPs have been established over the past few years
- Examples:
  - ECG Warehouse (housing over 4M digital ECG)
  - Cardiac Safety Research Consortium (CSRC)
  - Nanotechnology
  - Biomarker Consortium (administered by FNIH)
  - SmartTots (formerly SAFEKIDS)
- Some of these projects have already raised many millions of dollars

# Objectives

- Primary objective: develop novel analgesic drugs products
  - “broad spectrum”
  - Targeted
  - Additive and/or synergistic
  - And with less toxicity
- By exploring the flaws in current analgesic clinical trial designs
- Testing novel designs and analyses
- Standardizing data presentation to allow for more efficient exploration and analysis

# Objectives

- Raising the funds to support the research
  - Must come from the private partner
  - Sources include:
    - Private foundations
    - Government
    - Stakeholder organizations, e.g., patient advocacy groups, pain societies
    - Industry
- FDA provided seed funding
- And we hope to provide additional funds, if available

## ACTION in Motion

- Decision to select the University of Rochester as contractor, with Dr. Robert Dworkin as PI
  - will establish strong leadership team to manage all elements (scientific and administrative) of this massive undertaking
  - will leverage existing activities and expertise in the field
- One million dollar contract awarded in September 2010

## ACTION mission statement

To identify, prioritize, sponsor, coordinate, and promote innovative activities — with a special interest in optimizing clinical trials — that will expedite the discovery and development of improved analgesic treatments for the benefit of the public health.



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Review

## Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for ACTION

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# Current ACTION activities, I

- IMMPACT consensus meeting on “The Role of Biomarkers and Related Measures in the Development of Improved Analgesic Treatments” (June 2012).
- ACTION meeting on “**Preclinical** and Clinical Models and Methods for Accelerating Analgesic Drug Development” (October 2012).
- Meta-regression analyses of study-level data from published and otherwise publicly-available analgesic clinical trials: (1) neuropathic pain; (2) osteoarthritis; and (3) acute post-operative pain.
- Analyses of patient-level pooled data from neuropathic pain trials (John Farrar); also osteoarthritis, rheumatoid arthritis, and fibromyalgia trials (Farrar in collaboration with Europain).

## Current ACTION activities, II

- Development of pain-specific CDISC database standard for retrospective pooling and for prospective database creation and submission of analgesic trials.
- Development of comprehensive registry of analgesic trials available from government and industry websites and other sources (Mike Rowbotham).
- Systematic review and meta-analyses of safety reporting in analgesic trials, focusing on adherence to CONSORT recommendations; assessment methods; and approaches to data analysis and presentation.
- Development of definitions, classification system, and rating scales for evaluating misuse/abuse in trials of analgesic drugs (modeled after FDA-sponsored C-CASA and C-SSRS for evaluating suicidality in clinical trials).

# Current ACTION activities, III

- Development of novel composite outcome measures for use in analgesic clinical trials, including: (1) pain and physical functioning; (2) pain and use of rescue analgesia; and (3) pain and adverse events (risk-benefit).
- Statistical modeling to examine: (1) treatment of missing data; (2) parametric vs. non-parametric methods of analysis; and (3) power and appropriateness of different analysis techniques, for example, landmark, time-weighted, and area under the curve.
- Development of patient and staff training programs to increase assay sensitivity of pain ratings and other patient-reported outcomes, followed by proof-of-concept trial to test hypothesis that the training increases assay sensitivity.

# Opportunities for ACTION

- Research
  - Facilitate collaborations among stakeholders
  - Sponsor analyses of pooled legacy data
  - Develop more efficient clinical trial designs
  - Reduce patient burden and study costs
  - Explore biomarkers and patient phenotyping

# Opportunities for ACTION

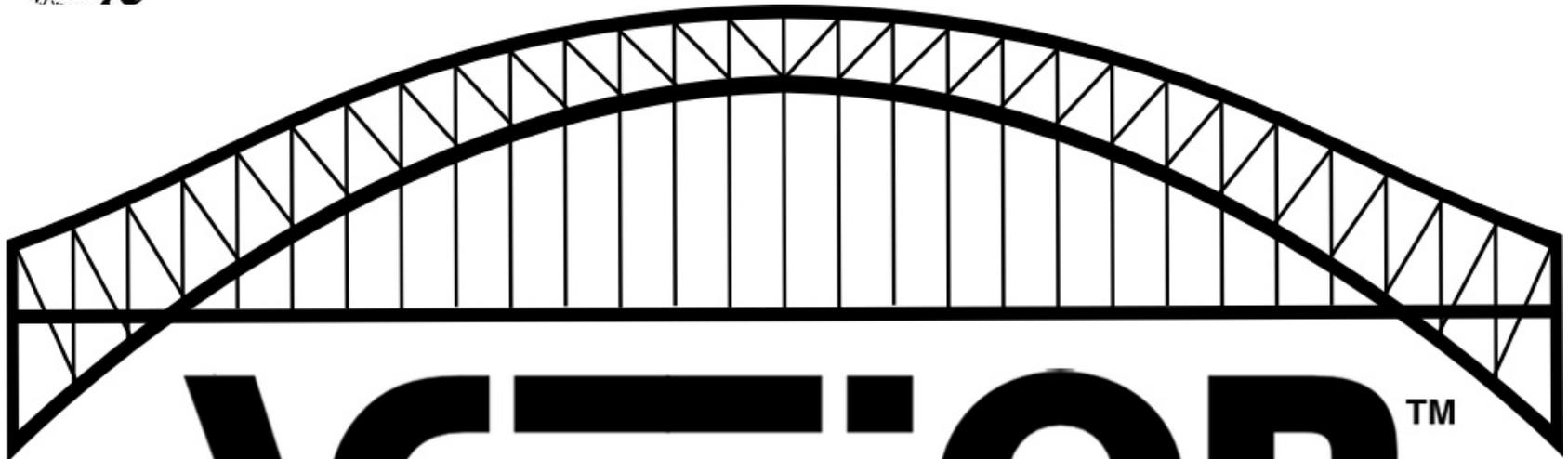
- Education
  - Provide research fellowships and grants
  - Conduct workshops and consensus meetings
  - Develop training materials for study subjects and study staff
- Treatment
  - Expand therapeutic armamentarium
  - Accelerate the development of mechanism-based treatments

## New ACTION RFP

- FDA issued an RFP for additional grant-type funding to be spread over five years
- The amount noted was up to \$1 million and last fiscal year we were able to provide \$500,000
- Hopefully, some additional FDA funding will be available each year, but
- The bulk of the funding for ACTION will need to come from fund raising efforts by the private partner



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# ACTION™

Other Stakeholders in Government, Industry, Patient Advocacy and Academia