



ANALGESIC CLINICAL TRIAL INNOVATIONS, OPPORTUNITIES, AND NETWORKS (ACTION)

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Background: The Problem

- To this day, the most widely used analgesics are opioids, NSAIDs and acetaminophen
 - All have serious toxicities, even when used properly
- Development of novel analgesic products has been slow and challenging
 - Clinical trials frequently fail to show efficacy
 - Pharmaceutical industry is reluctant to undertake advanced development of novel analgesics due to hurdle of achieving successful outcomes in expensive clinical trials

Why ACTION?

- 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 sites

“The science base necessary to evaluate and predict safety and efficacy ... is different from the science that generates the new idea for a drug, biologic or device.

In general, the National Institutes of Health and academia do not perform research in this area, indicating the need to develop mechanisms and incentives to foster research directed at improving the scientific base for the critical path, for example, for analgesic drug development.”

ACTION: Objectives

- To conduct critical research to improve the success rates of analgesic trials and to guide the design of future trials.
- Includes reanalysis of existing clinical trial data, with ultimate goal of conduct of new & improved clinical trials and development of safer and more effective analgesic drug products

Why Establish a PPP?

- Will result in more timely and directed advancements in analgesic development
 - Avoid duplication of work
 - Identify and fill scientific gaps
- Will allow for leveraging of greater financial resources and scientific expertise
 - No single entity has the resources or expertise to answer all of the outstanding questions

Other FDA Public-Private Partnerships (PPPs)

- 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

Past and Current ACTION Projects

(none of these are currently under the PPP umbrella)

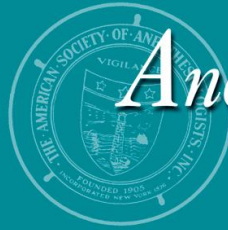
- Three projects
 - 1 data reanalysis project
 - 1 clinical protocol development project
 - 1 data transformation/standardization project
- Partners
 - Univ. Pennsylvania
 - SAS Institute/Executive Information Services (EIS)
- Funding: (All CPI money):
 - FY '07: \$50K; FY '08: \$250K; FY '09: \$500K

ACTION: Project #1 (U of Pennsylvania)

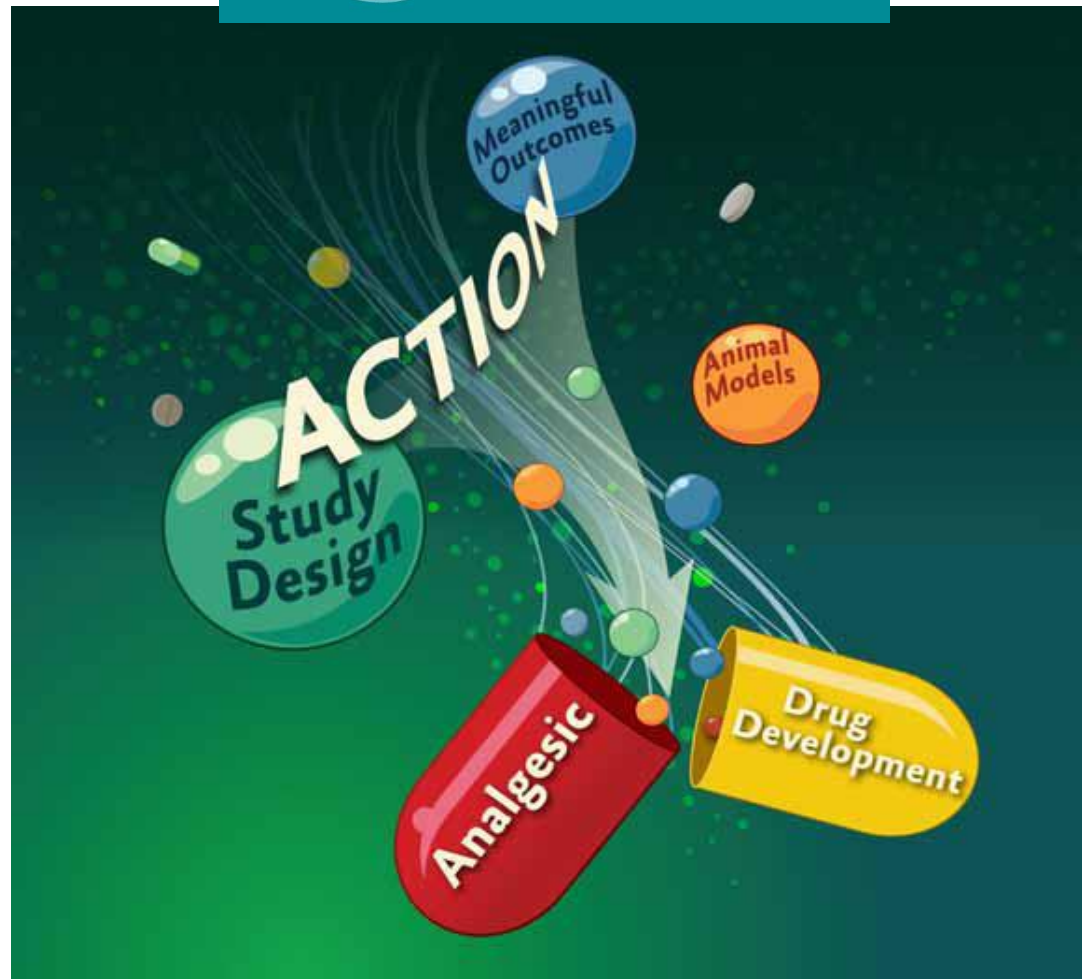
- Issue: In analgesic trials, the inability to show a difference between the test drug and the (placebo) comparator can be due to:
 - High placebo response
 - Methods used for data imputation (due to high dropout rates)
- Aims: This project is:
 - Exploring the factors that determine placebo response and will develop prediction models for response
 - Examining the effect of different imputation techniques on the cumulative proportion of responder analysis

ACTION: Project #2 (U of Pennsylvania)

- Issue: risk of chronic pain after surgical procedures such as thoracotomy and mastectomy
 - reports suggest that peri-operative administration of certain atypical analgesics may reduce the incidence and severity of chronic post-surgical pain
- Aim: Project is developing a sample clinical protocol to evaluate the safety and efficacy of select analgesics for prevention of chronic post-surgical pain; goal is publication
 - Initial publications from project-sponsored workshop published in *Anesthesiology* earlier this year



Anesthesiology



ACTION: Project #3 (Executive Information Services (EIS))

- Issue: Systematic analysis of data from across various analgesic trials is difficult because the data have been submitted in a variety of non-standardized structures and formats
- Project Complete: Confirmed that transformation of analgesic data into a uniform standard structure will require a large-scale and resource-intensive approach as individual sponsors report data very differently

ACTION PPP

- RFI issued on 12/18/09
- Responses reviewed and elements incorporated into ACTION RFP
- ACTION Initiative RFP issued on 7/22/10
- Elements of the RFP....

ACTION RFP

- Develop Strategic Plan in order to
- Identify and establish relationships with key experts in the field
- Create an Executive Committee with representation from key stakeholders
- Establish an independent scientific oversight body to coordinate the overall scientific mission of the ACTION Initiative
- Develop methodologies for the transformation of pooled trial data from multiple analgesic trials

ACTION RFP

- To determine relationships between assay sensitivity and metrics such as specific research designs and methodological features
- Assess FDA's clinical trial databases to develop alternative means of analyzing pain scores
- Co-led with FDA: hold scientific workshop to support the development of the Strategic Plan
- Development and publication of a report from the workshop.

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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www.elsevier.com/locate/pain

Review

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

Robert H. Dworkin^{a,b,c,*}, Dennis C. Turk^d, Nathaniel P. Katz^{e,f}, Michael C. Rowbotham^g,
Sarah Peirce-Sandner^a, Igor Cerny^h, Chekesha S. Clingman^h, Benjamin C. Eloff^h, John T. Farrarⁱ,
Cornelia Kamp^{b,c}, Michael P. McDermott^{b,c,j}, Bob A. Rappaport^h, Wendy R. Sanhai^h

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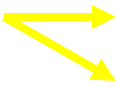
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ACTION Executive Committee Co-Chairs

- American Academy of Neurology
- American Academy of Pain Medicine
- American College of Rheumatology
- American Pain Society
- American Society of Anesthesiologists
- Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)
- International Association for the Study of Pain
- Outcome Measures in Rheumatology (OMERACT)
- *ACTION liaisons:*
 - EuroPain
 - German Neuropathic Pain Research Network

ACTION ongoing activities

1. Methodologically-focused meta-analyses of publicly-available randomized clinical trials
 - e.g., neuropathic pain, osteoarthritis
2. Methodologically-focused retrospective analyses of patient-level raw data provided by FDA and by industry
3. STandardized ANalgesic DAtabase for Research, Discovery, and Submissions (STANDARDS)
 - development of CDISC-compliant database format for retrospective pooling and prospective use
4. Request for Information  Draft Strategic Plan
Request for Proposals
5. Scientific Workshop at FDA White Oak facility (6/15/11)
 - identify obstacles and finalize Strategic Plan

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

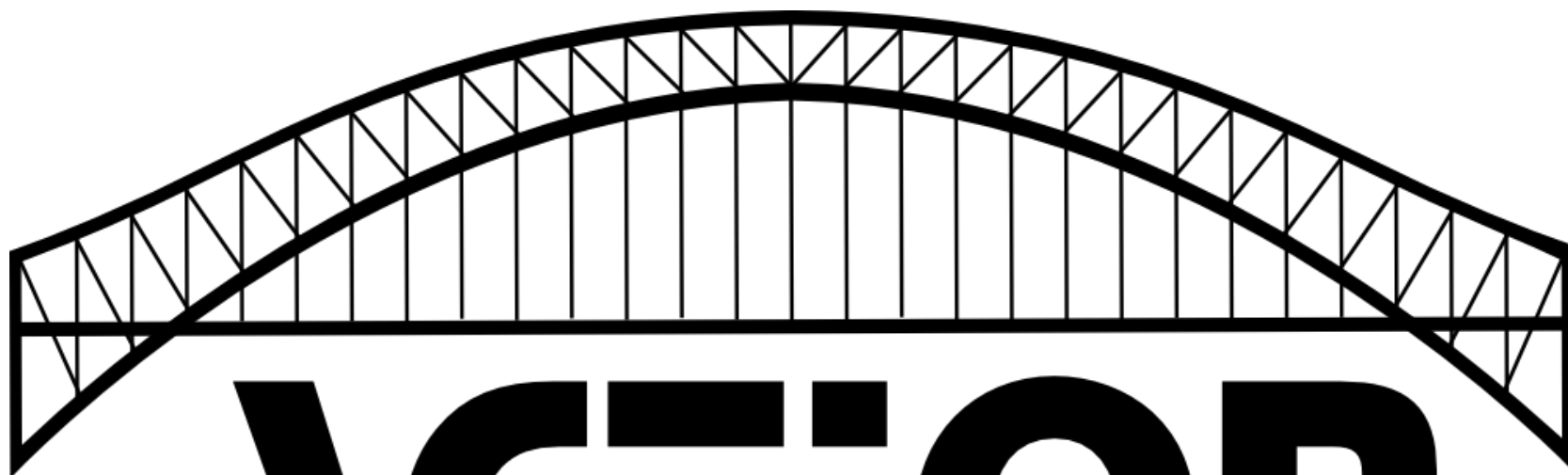
- Education
 - Provide research fellowships and grants
 - Conduct workshops and consensus meetings
 - Develop training materials for study subjects and study staff
- Treatment
 - Expand therapeutic armamentarium
 - Accelerate the development of mechanism-based treatments

Stakeholders

- Pain researchers and clinicians
- Government agencies
- Pharmaceutical and device companies
- Patients and patient advocacy organizations
- Non-profit foundations
- Professional organizations
- Society



UNIVERSITY of ROCHESTER



Action