ACTTION

Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks

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March 27, 2012
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
  • ACTTION
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
ACTTION 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
ACTTION 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.
Review

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

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Current ACTTION activities, 1

- IMMPPACT consensus meeting on “The Role of Biomarkers and Related Measures in the Development of Improved Analgesic Treatments” (June 2012).
- ACTTION 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 ACTTION activities, I

- 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 ACTTION 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 ACTTION

• 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 ACTTION

• 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 ACTTION 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
Other Stakeholders in Government, Industry, Patient Advocacy and Academia