An Update on ACTTION:

Working Groups and Other Activities

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Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks

The mission o nesthetic, and Addiction Clinical Trial Translations, I ortunities, and Networks (ACTTION) public-private partne ited States Food and Drug Administration (FDA) is to identify, r, coordinate, and promote innovative activities — with a spec timizing clinical trials — that will expedite the discovery and improved analgesic, anesthetic, and addiction treatments fo he public health.

ACTTION is a r phase initiative that is closely aligned with the FDA's Critical is public-private partnership has been designed to streamline d development process for new analgesic, anesthetic, an cations and to more generally accelerate the development h improved efficacy and safety.

The key objectives of ACTTION involve initiating and supporting strategic collaborations among a broad spectrum of stakeholders — including, but not limited to, academia, the FDA and other government agencies, industry, professional organizations, patient advocacy groups, foundations, and philanthropic organizations — with the goals of sharing data and innovative thinking about the development of novel therapeutics. These strategic collaborations involve a wide range of research projects and other activities, for example, scientific workshops, consensus meetings, and in-depth analyses of clinical trial data to determine the effects of research methods on study assay sensitivity and efficiency.

ACTTION is intended to have benefits that are international in scope. To represent the bridges that ACTTION is establishing among its diverse stakeholders, this website is illustrated with watermarks of two bridges that

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October 11, 2012: ACTTION and APS to Spearhead the Development of a Comprehensive Pain Classification and Taxonomy

ACTTION and the American Pain Society will be collaborating on the development of a comprehensive taxonomy of acute and chronic pain conditions. At present, there is no consensus on pain classification and diagnosis, a major limitation that has impeded the development of improved treatments. An evidence-based pain taxonomy is essential to ensure that consistent and accurate diagnoses are used for clinical research and clinical trials, and to facilitate comparisons across research studies. A standardized and up-to-date classification system is also critical for evaluations of new drugs and other treatments by regulatory agencies. The aims of this initiative are to establish a coordinated framework for pain

Why have so many recent analgesic trials been negative?

1. Some of the drugs may have little or no efficacy at tested dosages in the conditions in which they were studied.

2. Many of these recent results are actually *false negatives*.
   - ~ 50% of depression trials of approved antidepressants fail...
   - placebo group patients improved "too much."
   - the optimal pain patients and pain phenotypes were not studied ("personalized pain medicine").
   - temporal changes in characteristics of patients enrolling in trials.
   - temporal changes in types of sites conducting trials.

ACTTION activities: assay sensitivity

1. **Development of comprehensive registry of analgesic trials available from government and industry websites and other sources (RReACT database).**
2. **Development of pain-specific CDISC database standard for retrospective pooling and for prospective database creation and submission of analgesic trials.**
3. **Meta-regression analyses of study-level data from published and publicly-available clinical trials: (1) neuropathic pain; (2) OA; and (3) post-operative pain.**
4. **Analyses of patient-level pooled data from analgesic trials made available by FDA and industry: (1) assay sensitivity; (2) development of novel composite outcome measures, including pain and physical functioning.**

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Topical review

A snapshot and scorecard for analgesic clinical trials for chronic pain: The RReACT database

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www.preclinicalpaintrials.org

www.humanpainmodels.org

ACTTION activities: assay sensitivity

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A standard database format for clinical trials of pain treatments:

an ACTTION–CDISC initiative

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4. Analyses of patient-level pooled data from analgesic trials made available by FDA and industry: (1) assay sensitivity; (2) development of novel composite outcome measures, including pain and physical functioning.

1. Investigate relationships between the methodologic features of clinical trials and their "assay sensitivity" (i.e., *ability to distinguish efficacious treatments from placebo or less efficacious treatments*)

   - e.g., are certain patient characteristics associated with greater assay sensitivity?

2. Determine whether assay sensitivity can be increased by modifying these study features

   - e.g., possibly by reducing placebo group improvement

Patient factors

- Minimum pain duration
- Maximum pain duration
- Baseline diary compliance
- Minimum mean baseline pain intensity
- Maximum mean baseline pain intensity
- Baseline pain variability
- Baseline pain consistency
- History of treatment failure(s)
- Sources of patient referrals
- History of psychopathology

Study design factors

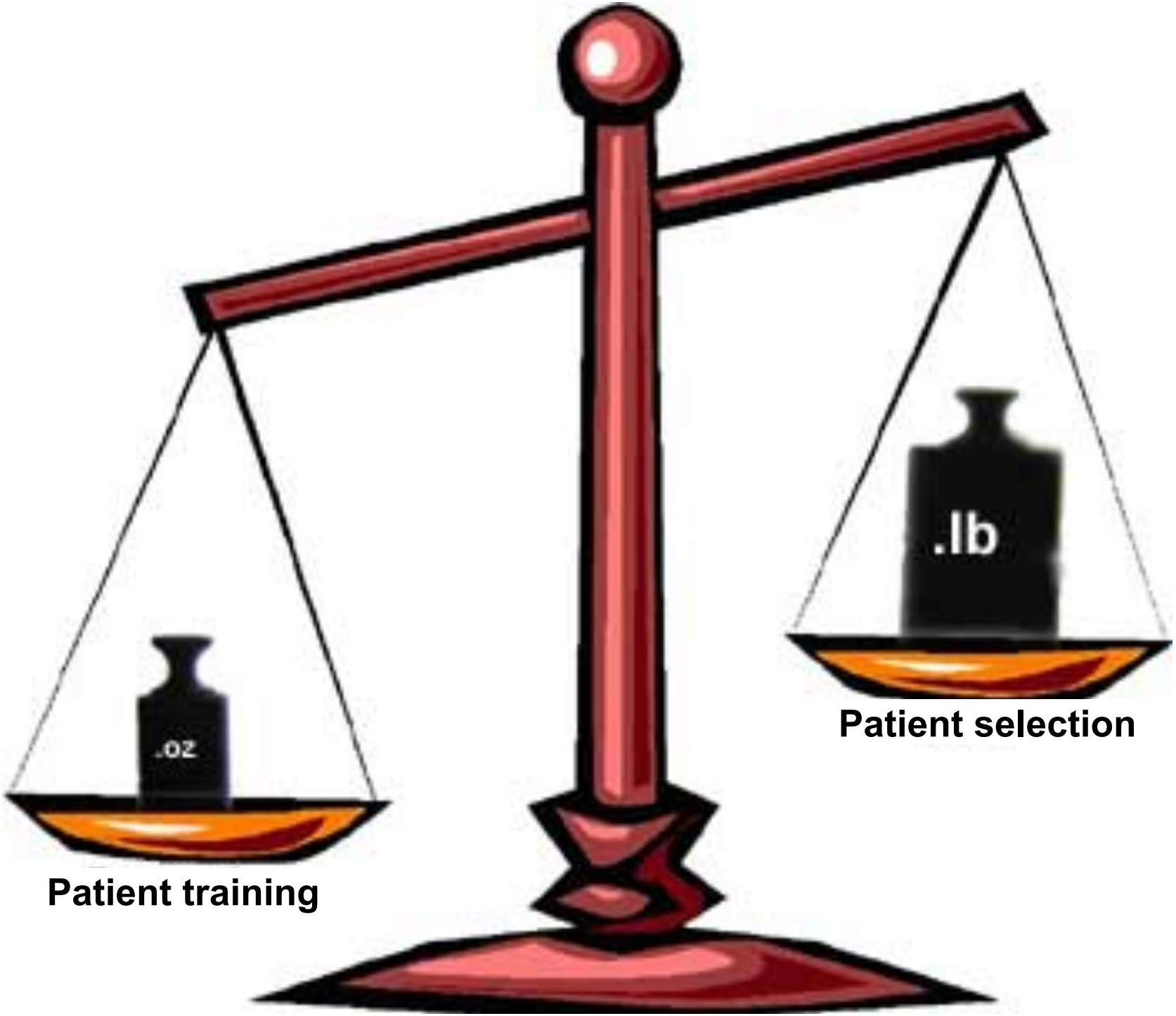
- Research design (e.g., parallel group vs. cross-over)
- Number of treatment arms
- Study duration
- Study quality
- Baseline period duration
- Titration period presence and duration
- Dosing strategy (e.g., flexible vs. fixed)
- Permitted use of rescue and/or concomitant analgesics
- Presence of active comparator
- Outcome measures
- Methods of data collection (e.g., paper vs. electronic)

Study site factors

- Sources of patient referrals
- Number of sites
- Site investigator and staff experience
- Site investigator and staff training
- Inclusion of patient training
- Methods for accelerating enrollment
- Geographic region

Can we improve the selection of patients for clinical trials?

Selecting subjects based on characteristics of their baseline pain ratings that might reflect rating "carefulness" or "thoughtfulness" is likely to be less efficient than providing training before the baseline so that fewer subjects will be excluded because of their baseline ratings.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Patient selection
Patient training

ACTTION activities: clinical trial conduct and reporting

1. **Development of patient and staff training system to increase assay sensitivity of pain ratings and other patient-reported outcomes, including studies of reliability, validity, and effects on assay sensitivity.**

2. **Systematic reviews of analgesic trials focusing on: (1) safety reporting, assessment methods, and data analysis and presentation; (2) pain outcome measure characteristics and reporting; and (3) reporting adherence to ICMJE standards.**

3. **Development of definitions, classification system, and rating scales for evaluating misuse/abuse in analgesic trials (modeled after FDA-sponsored C-CASA and C-SSRS for evaluating suicidality in clinical trials).**

Pain rating training system:

1. Educating the patient that it is very important that pain ratings be made in a conscientious and thoughtful manner because this is necessary for the study to succeed in determining whether or not the treatment is effective.

2. Identification of personal anchors and use of reminders for rating pain in a consistent manner throughout the study.

3. Missing data diminishes the scientific value of the study and of the other subjects' participation.

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2. **Systematic reviews of analgesic trial: (1) safety reporting, assessment methods, and data analysis; (2) pain outcome measure characteristics; (3) analysis and interpretation of multiple endpoints; and (4) authorship and contribution adherence to ICMJE standards.**

3. Development of definitions, classification system, and rating scales for evaluating misuse/abuse in analgesic trials (modeled after FDA-sponsored C-CASA and C-SSRS for evaluating suicidality in clinical trials).

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Adherence to CONSORT harms-reporting recommendations in publications of recent analgesic clinical trials: An ACTTION systematic review

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1. Reporting checklist for preclinical studies

2. Reporting checklist for human experimental studies

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3. **Development of definitions, classification system, and rating scales for evaluating evidence of drug abuse/ misuse in analgesic trials (modeled after C-CASA and C-SSRS for evaluating suicidality in clinical trials).**


DSM-III Diagnostic and Statistical Manual of Mental Disorders
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders
DSM-IV™ Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-IV-TR™ Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES

CHALLENGES AND OPPORTUNITIES

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES