The ACTTION public-private partnership: what is the FDA doing to accelerate the development of better analgesics?

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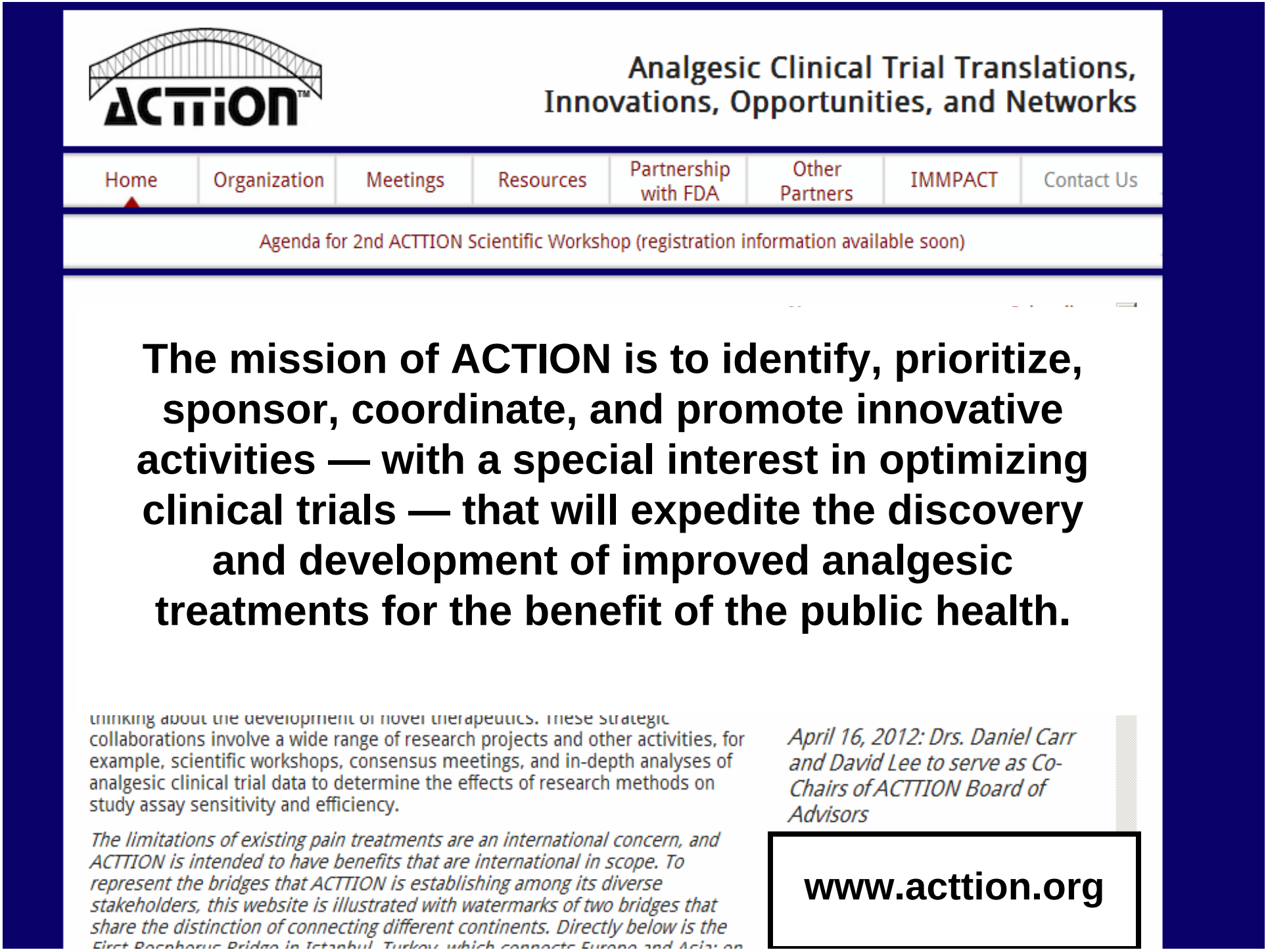
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Agenda for 2nd ACTTION Scientific Workshop (registration information available soon)
The mission of ACTION is to identify, prioritize, sponsor, coordinate, and promote innovative activities — with a special interest in optimizing clinical trials — that will expedite the discovery and development of improved analgesic treatments for the benefit of the public health.
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 analgesic clinical trial data to determine the effects of research methods on study assay sensitivity and efficiency.
The limitations of existing pain treatments are an international concern, and 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 share the distinction of connecting different continents. Directly below is the
April 16, 2012: Drs. Daniel Carr and David Lee to serve as Co-Chairs of ACTTION Board of Advisors
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Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy

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Innovative Therapies for Peripheral Neuropathies
2012 FPN National Research Symposium
The Foundation for Peripheral Neuropathy
Chicago
March 15, 2012

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 sites

Background

- Although somewhere between 30 and 60 million people suffer from chronic pain in US
- And the dangers of treating 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

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

Current ACTTION activities, I

1. **IMMPACT consensus meeting on "The Role of Biomarkers and Related Measures in the Development of Improved Analgesic Treatments" (June 2012).**
2. **ACTTION meeting on "Preclinical and Clinical Models and Methods for Accelerating Analgesic Drug Discovery and Development" (October 2012).**
3. **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.**
4. **Analyses of patient-level pooled data from neuropathic pain trials; also osteoarthritis and fibromyalgia trials (in collaboration with Europain).**

An evidence-based approach to analgesic clinical trial design

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

Current ACTTION activities, II

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

Current ACTTION activities, III

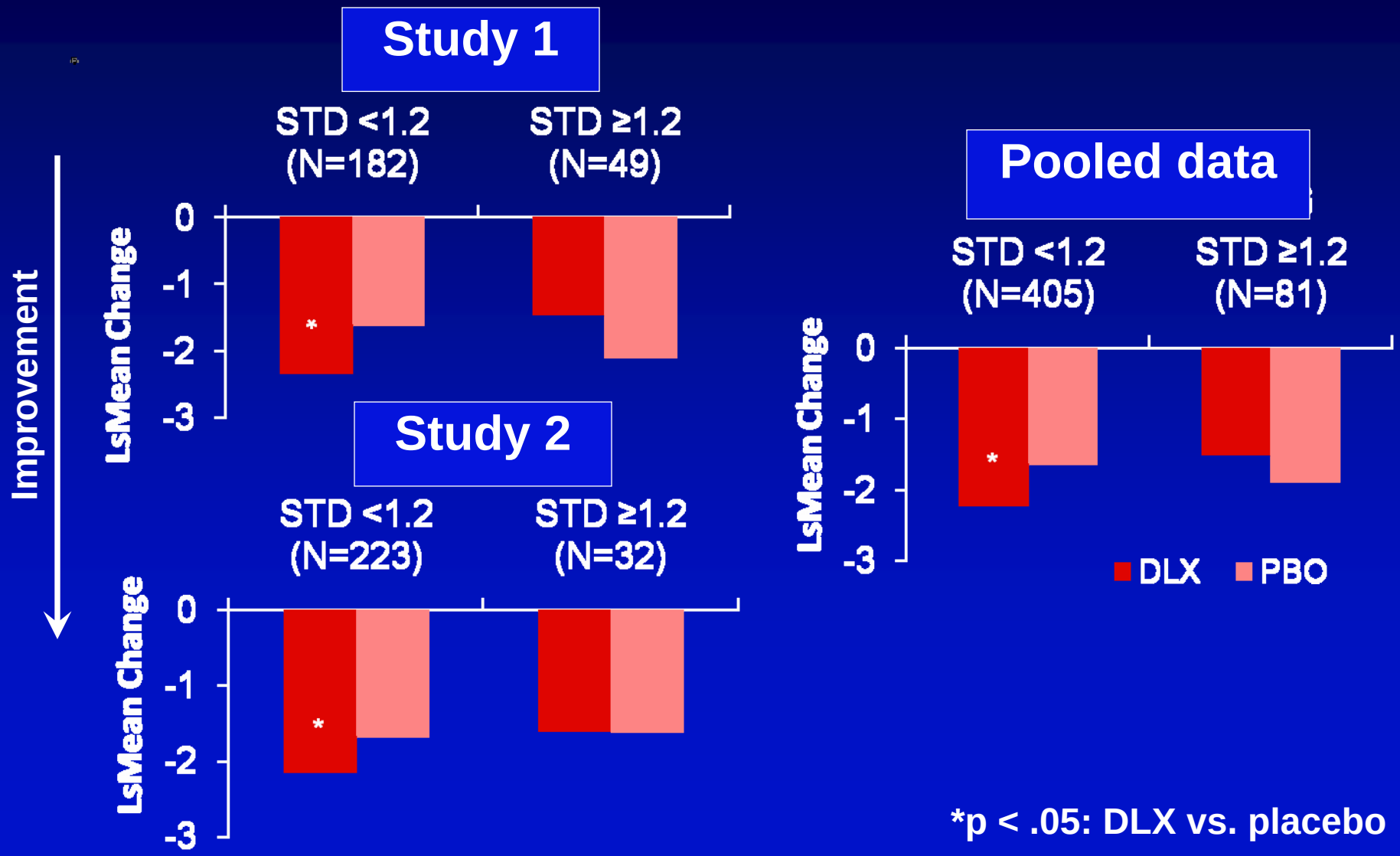
9. Development of patient and staff training programs to increase assay sensitivity of pain ratings and other patient-reported outcomes, followed by proof-of-concept trial to test hypothesis that the training increases assay sensitivity.

10. 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).

11. 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.

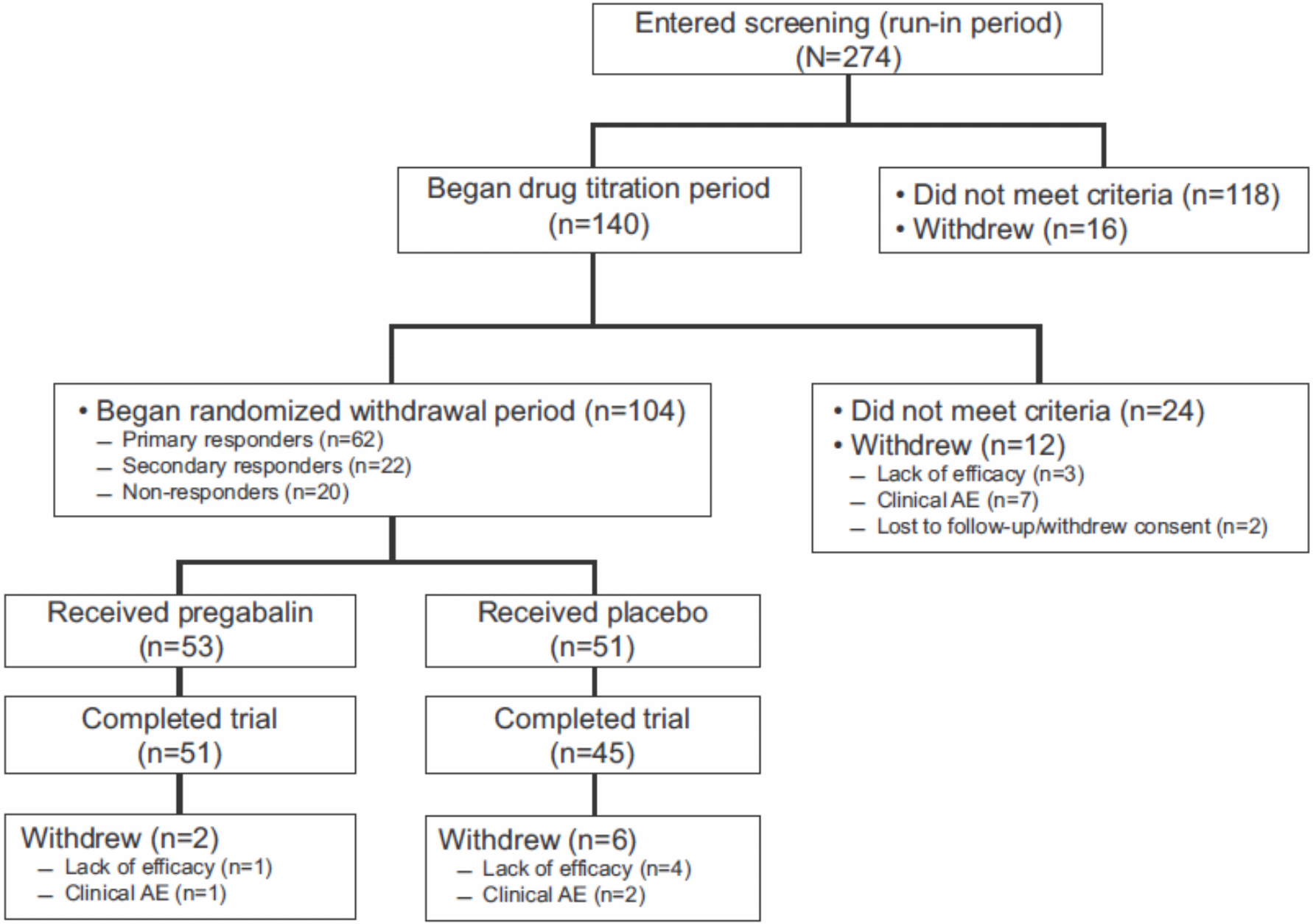
Can we improve the selection of patients for clinical trials?

Variability in baseline pain daily diaries and treatment vs. placebo differences in OA



*p < .05: DLX vs. placebo

Can we improve clinical trial research designs and methods?


Entered screening (run-in period)
(N=274)
Began drug titration period
(n=140)
• Did not meet criteria (n=118)
• Withdrew (n=16)
• Began randomized withdrawal period (n=104)
– Primary responders (n=62)
– Secondary responders (n=22)
– Non-responders (n=20)
• Did not meet criteria (n=24)
• Withdrew (n=12)
– Lack of efficacy (n=3)
– Clinical AE (n=7)
– Lost to follow-up/withdrew consent (n=2)
Received pregabalin
(n=53)
Received placebo
(n=51)
Completed trial
(n=51)
Completed trial
(n=45)
Withdrew (n=2)
– Lack of efficacy (n=1)
– Clinical AE (n=1)
Withdrew (n=6)
– Lack of efficacy (n=4)
– Clinical AE (n=2)

“Both investigators and patients were blinded to the following information: entry criteria for patients’ pain intensity, baseline pain intensity, definition of responder groups, visit at which randomization occurred, treatment during the withdrawal phase, efficacy failure criteria, and computation rules and time windows in the IVRS system used to calculate the baseline intensity and pain response.”

Hewitt DJ, et al. Pain 2011;152:514-521.

And what can be done about clinical trial study sites?

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

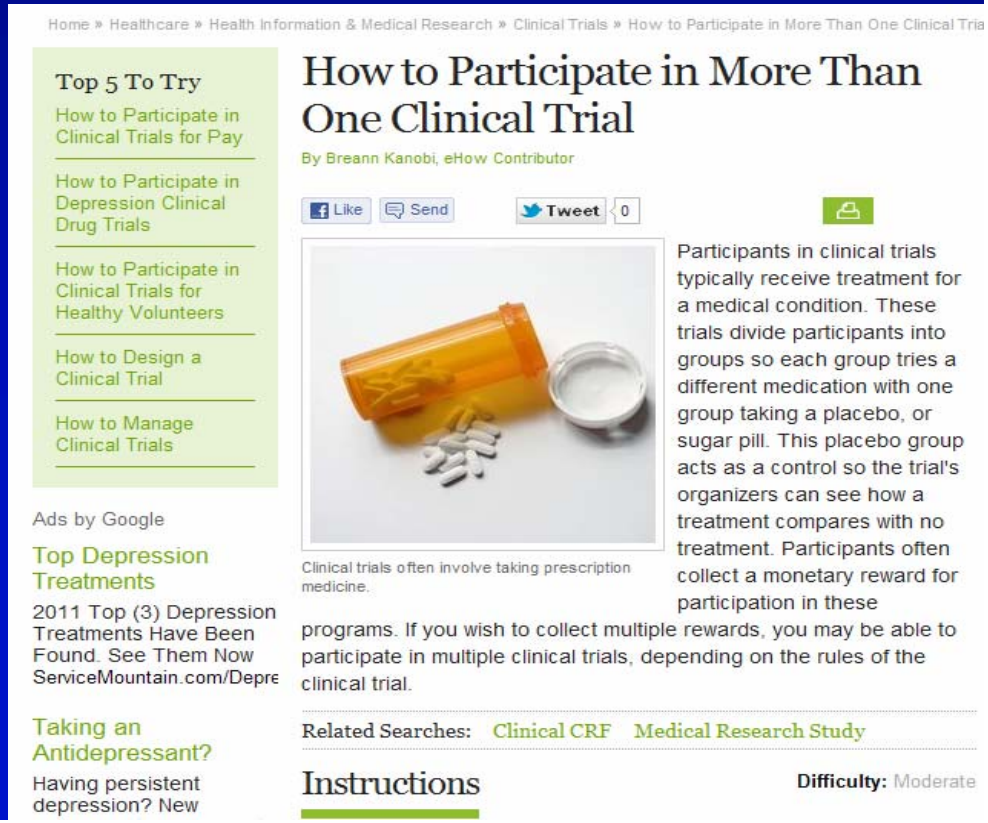
TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES

CHALLENGES AND OPPORTUNITIES

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

The IOM report describes the existence in psychiatry trials of "professional patients" — individuals who participate in multiple trials as a source of income and medication — noting the example of a 300 patient schizophrenia trial in which 30 subjects were found to have been randomized to the same study by multiple study sites.



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- How to Participate in Depression Clinical Drug Trials
- How to Participate in Clinical Trials for Healthy Volunteers
- How to Design a Clinical Trial
- How to Manage Clinical Trials

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Top Depression Treatments

2011 Top (3) Depression Treatments Have Been Found. See Them Now ServiceMountain.com/Depre

Taking an Antidepressant?

Having persistent depression? New

How to Participate in More Than One Clinical Trial

By Breann Kanobi, eHow Contributor

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Participants in clinical trials typically receive treatment for a medical condition. These trials divide participants into groups so each group tries a different medication with one group taking a placebo, or sugar pill. This placebo group acts as a control so the trial's organizers can see how a treatment compares with no treatment. Participants often collect a monetary reward for participation in these programs. If you wish to collect multiple rewards, you may be able to participate in multiple clinical trials, depending on the rules of the clinical trial.

Related Searches: Clinical CRF Medical Research Study

Instructions

Difficulty: Moderate

Concerns about the clinical trial enterprise have provided the impetus for a proposal made by Dr. Janet Woodcock in the IOM report that the US should develop a clinical trial infrastructure.

This infrastructure would provide a permanent network of resources (e.g., sites, investigators, staff), expertise, and funding that would replace the ad hoc manner in which clinical trials are currently conducted.

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Review and recommendations

Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations

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