International Regulatory Landscape
Neuroscience Trials of the Future
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Thomas Laughren, M.D.
Director of Regulatory Affairs,
Massachusetts General Hospital
Clinical Trials Network and Institute

Active Consulting Relationships with Pharmaceutical Companies and NIMH, and Employment Relationship with MGH CTNI

- Part time employee of MGH CTNI
- Consultant to NIMH
- Consultant to Acadia, AgeneBio, Alcobra, Alzheon, Axovant, Axsome, Biohaven, Braeburn, Camurus, Cerecor, Corcept, CoMentis, DAvia NS, Durect, Edgemont, Fabre Kramer, Forum, Janssen, Lilly, Lumos, MAPS, Marinus, Medgenics, Neurolifesciences, Noven, Omeros, Pfizer, Reviva, Sunovion, Taisho, Teva, Tonix, Transition

Major Themes from Yesterday's Sessions

- Moving beyond DSM
  - Domains within DSM
  - Biomarkers within DSM
  - RDoC
- Advancing clinical trials methodology
  - Novel designs
  - Novel approaches to patient selection, assessment, ensuring adherence, large simple trials, endpoint selection
- Data standardization
- Data sharing

Fundamental problem facing psychiatric drug development

- Lack of biological understanding
- Plato: “successful theories should carve nature at its joints”
- Given lack of biological understanding, we instead “apply a cookie cutter to the dough of nature”
- Multiple iterations of DSM
  - A phenomenological classification system

Fundamental problem facing psychiatric drug development (continued)

- DSM V released in May, 2013 (with considerable controversy)
- Irony: Even though few find DSM optimal, we all rely on it (drug developers, academic researchers, regulators, clinicians, payers, lawyers, etc)
- Major challenge facing our field: Finding better approaches to carving up the psychiatric illness space (i.e., moving beyond DSM)

Moving beyond DSM for Psychiatric Drug Development

- Phenomenological Domains (with or without biological understanding)
  - Within accepted DSM diagnostic entities
    - e.g., CIAS (cognitive impairment associated with schizophrenia)
  - Across diagnostic entities
    - e.g., agitation, impulsivity, a specific cognitive deficit (e.g., working memory), anhedonia
- Biological subgroups (defined by biomarkers, with or without clinical understanding)
  - Could be based on any of the many different types of biomarkers that have been proposed
  - As with phenomenological domains, could be applied within or across DSM diagnostic entities
- Research Domain Criteria (RDoC)
  - Might think of as way of combining biology and phenomenology
  - Not yet ready for prime time

Possible Topics for Regulatory Session

- Challenges in moving beyond DSM (gaining regulatory acceptance and defining clear pathway for integrating new concepts into drug development)
  - Phenomenological domains within DSM (e.g., CIAS, CI in MDD)
  - Biomarker defined subgroups within DSM entities (setting up hypothesis testing)
  - Defining a clear regulatory pathway has been a challenge
- Challenges in gaining regulatory acceptance of novel designs and other novel methods
  - Usually can get discussed only in context of particular IND
  - Drug Development Tool Qualification Process
    - Intended primarily for “qualifying” biomarkers, clinical outcome assessments, and animal models
    - Theoretically useful, but practically very challenging

Possible Topics for Regulatory Session (continued)

- Other ideas that would likely need regulatory perspective:
  - Use of internet, including social media, for patient recruitment and assessment
  - Virtual trial sites (geographically dispersed patients)
  - “Wearables” as a source of clinical trials data
  - Alternative “clinically meaningful” endpoints