

Global Clinical Trials

Opportunities and Challenges



ISCTM

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Session 1: ISCTM Summer Meeting

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ISCTM

Conducting CNS Clinical Trials in the Developing World: Part I

Addressing Problems with Protocol Development to Regulatory Approval

**Summary of February 2007 meeting of ISCTM,
Washington DC**

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Summary of Issues on Global Clinical Trials Part I

- Thanks to Dr. JP Lindenmayer for preparing summary from Annual Meeting!
- Background and Issues for Session 1

Clinical Trials are a Global Reality: How are they tracked?

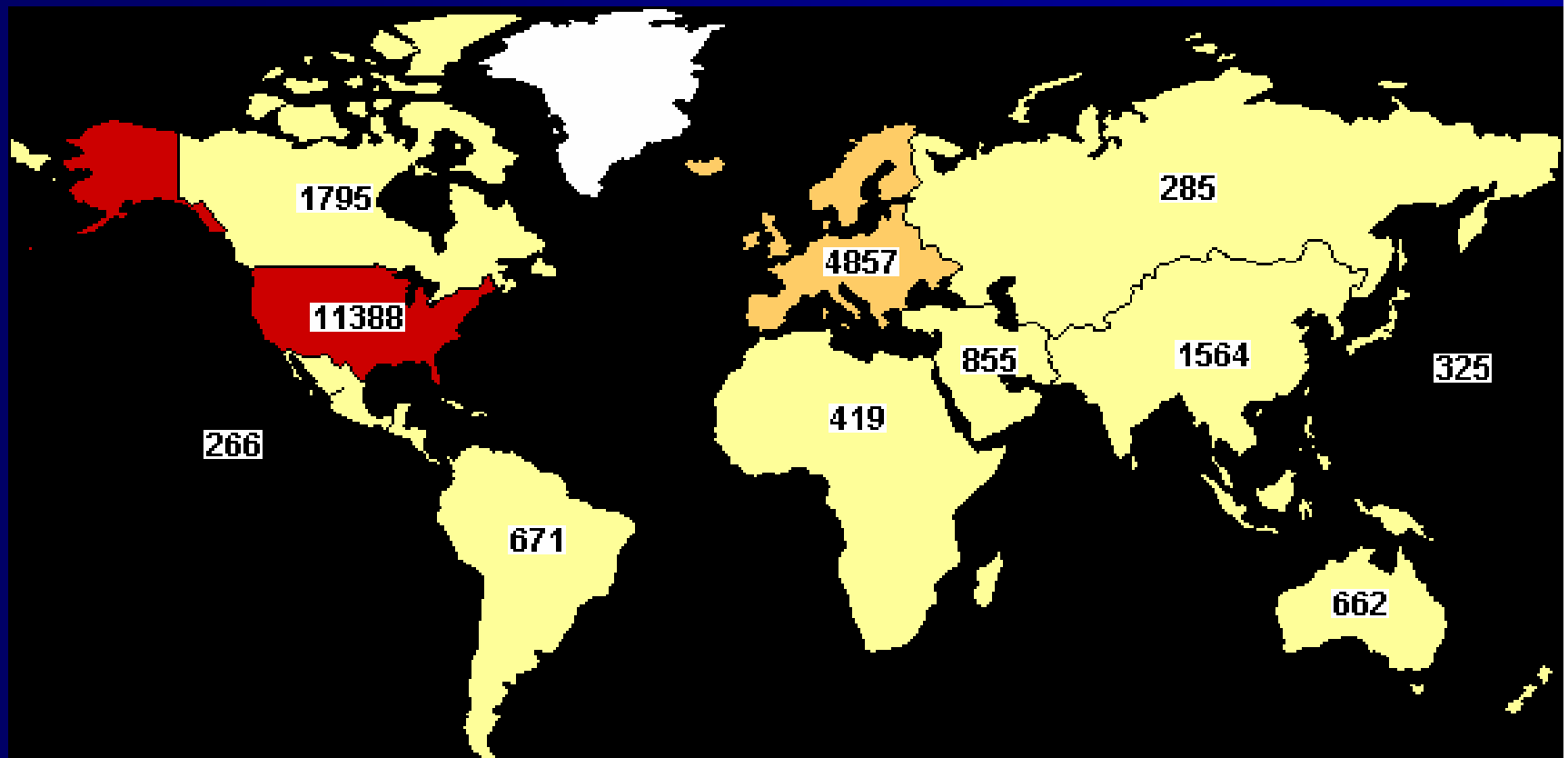
- How many trials are being conducted world-wide?
- INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM SEARCH PORTAL



- 267 trials for schizophrenia now recruiting
 - 6 in India 25 in Germany
 - 5 in Japan 8 UK
 - 5 in Korea 2 China
- 294 trials for “depression” now recruiting
 - 1 in India 17 in Germany
 - 1 in Japan 14 in UK
 - 2 in Korea 4 in China

Clinical Trials are a Global Reality – but CNS is small percentage

- Clinicaltrials.gov website
- 9,053 studies have locations outside the USA



Recruiting studies in China listed under Schizophrenia

■ Clinicaltrials.gov

1. Effectiveness of Tropisetron Plus Risperidone for Improving Cognitive and Perceptual Disturbances in Schizophrenia
Conditions: Smoking Cessation; Schizophrenia
2. Identification and Treatment of the Liability to Develop Schizophrenia
Condition: Schizophrenia
3. Supervised Treatment of Schizophrenia, a Randomized Controlled Trial.
Conditions: Schizophrenia; Schizoaffective Disorders
4. A Study to Evaluate the Effectiveness and Safety of Risperidone for the Prevention of Mood Episodes in the Treatment of Patients With Bipolar I Disorder.
Condition: Bipolar I Disorder listed under schizophrenia

– WHO

1. Identification and Treatment of the Liability to Develop Schizophrenia
2. Effectiveness of Tropisetron Plus Risperidone for Improving Cognitive and Perceptual Disturbances in Schizophrenia
3. Study to Evaluate the Effectiveness and Safety of Extended-Release (ER) Paliperidone Compared With Placebo in Delaying the Recurrence of Symptoms in Bipolar I Disorder

R Anand: *Multi-National Trials in the Developing World: Conceptualizing the Trials—An Industry Perspective*

- What does it mean “Developing World”?
- Need to involve local PIs and local opinion leaders EARLY in the protocol design phase
- Need to focus on drug dosage issues, related to weights and metabolic issues; lack of Phase I data and especially preliminary MTD studies
 - Other variables by region that might affect drug pk or pd:
 - food drug interactions; example curcumin in India;
 - Issue of concomitant herbal medicine?
- Traditional outcome measures may not be applicable
 - Western pharmacoeconomic questionnaires may not be applicable

A Kalali: *Possible Advantages Gained by Conducting Global Clinical Trials*

- Accelerated local product approval
- Early local opinion leader development
- Availability of drug naïve patients?
- Improved patient retention rates?
- Better medication compliance rates?
- Stability of patient population facilitating long-term follow-up
- Are possible differences sustainable with time and success?

A Kiev: Multi-National Trials in the Developing World: Conceptualizing the Trials—An Academic Perspective

- Considerations in planning trials
 - Importance of awareness of local diagnostic traditions, care taking issues
 - Importance for inclusion of local PIs and physicians in protocol design issues; inclusion of anthropological expertise
 - Lower placebo response rates (purported)
 - Does that mean also higher study medication response rates?
 - Are there regional differences in defining treatment resistance?
 - Is investigator expectation a variably powerful force by region?

Regulatory Approval/Consent

- Informed Consent, patient capacity for consent
 - In local language and reviewed by independent observer
 - Concept of independent capacity evaluation; does it exist in all cultures?

- the doctor is often looked upon as a person of greater stature and the patient may leave the decision upon the doctor if he should participate in the study or not
- taking informed consent thus becomes difficult

- Ministry of Health issues
- Ethics Committee issues
- Country specific issues
 - E.g. special rules on DNA samples

A Kalali: Setting Up and Implementing Protocols in the Developing World

- Need for adequate local CRO infrastructure
- Knowledge of local regulations
 - medication importing regulations, blood sample export regs, DNA sampling
- Availability of comparators, generic quality
- What about the site infrastructure?
 - Research pharmacists, research RNs, biostatisticians, cognitive psychologists?

JK Trivedi: Conducting Trials in Developing World

Language Issues

- India has number of regional languages and dialects. Apart from “Hindi” and “English” there are 21 other official languages which are recognized by the Indian Constitution
- It is difficult to translate the documents into the regional languages as the verbatim translation often loses its true meaning
 - e.g. No word in “Hindi” for placebo
 - The inter rater reliability is questionable because all the raters are certified/trained in instruments in English but the actual interviews are conducted in a regional language
 - Should rater training be in the regional languages?

S Khanna and JK Trivedi: Setting Up And Implementation in India: A Site Perspective On How To Adapt It For The Developing World

- Independence of research
 - Issue of funding being mostly by outside agencies
- Issue of validity of Western developed instruments; Diagnostics
- Differing social and functional normative standards
 - Inclusion of culturally sensitive social function scales
- Problems with inquiries of “taboo” subjects in rating scales and assessments
 - Sexual function
 - Birth control

T Sharma/ R Mohs: Case Studies: Evaluating Cognition In Multi-National Developing World Trials

- Computerized, paper and pencil tests are doable in other cultures
 - computer literacy may not be available in some countries
 - Exclusion of patients during screening
- Problems with the assessment of IQ in illiterate patients
- Cognitive tests are applicable, but may have to be modified (“what a normal person in that particular culture would know”)
- Maintain the concept of cognitive function tested and scoring rules
- What is the validity of the modified tests, particularly for regulators?
 - Test retest validity?

N A Khin: Reviewing Data from Multi-National Trials in the Developing World: FDA Perspective

- FDA can approve data conducted in non US countries without IND and use for marketing approval
- Possibility of FDA site inspections in non US countries
 - Low number of non US sites are FDA inspected; however when 'inspected' they have "comparable results to US sites in CNS studies"
 - Exception: lower reporting of AEs
- FDA will not rely exclusively on pivotal trial data from non US sources
 - FDA will accept data from long term placebo controlled non US studies
- For use of culturally adapted or modified assessment instruments....ask the Division before getting into it.

G Pons: Reviewing Data from Multi-National Trials in the Developing World: European Regulatory Perspectives

- **There is a regulatory EU frame work for the acceptance of clinical trials results from one Region to another Region, provided there are no intrinsic or extrinsic differences in the two populations:**
 - Need for a bridging study – variant of ICH-E5?
- **Are ICH-E5 guidelines really required, if so between which regions?**
- **Clinical trials data was accepted in a substantial number of trials/indications for new drugs in minors**
 - Significant numbers of completed GPC inspections
- **Most concerns came from sponsors and not from hosting countries**

Next steps for Part 'II'

- **Focus on challenges and solutions using specific case illustrations to the extent possible**
- **Extend the discussion to particularly focus on EU and Asia approaches to Global Trials**
 - Are the issues and remedies different for psychiatric and neurological indications v. medical indications?
 - Are the issues and answers different region by region?
- **What is the EU perspective on data from developing countries? How does it differ from the US perspective?**
- **Adverse events were identified as one area with significant regional differences**
 - How should this be addressed in future trials? In CNS?
 - How should pharmacovigilance and epidemiologic approaches to patient safety be approached?
- **We'll also discuss Asian Perspective and Biological and policy factors**