“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”

NIH Clinical Trials: Intro

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Common Pitfalls

- Weak involvement of statistical/methodological expertise
- Too many “outcomes”
- Restrictive inclusion/exclusion criteria
- Insufficient resources
- Rush to efficacy vs. constant piloting

NIH Discussion Points

Why should it be done?

- Need, relevance, timeliness
- Expected impact on practice

Who is the target population?

- Disease, condition, subgroups
- Inclusion/exclusion criteria

"Phases" of trials: pilot to efficacy

- Study design
- Outcome measure(s)

NIH Grant Mechanisms

Trials require and consume resource$

- Individual research grant R01/U01
- Consortium/network
- Facilities: coordinating center
- Nesting: P50, P01, specific aim within an R01

All trials require human subjects safety monitoring

Submitting a Clinical Trial Application

- Protocol and operations manual finished
- Study personnel in place
  - Coordinator, statistician
- Sites lined up and screened:
  - Institutional Review Board (IRB), assurances
- Data/safety monitoring plan
  - Prospective design—stopping rules
  - Adverse events
- Focus on the outcome of interest

Human Subjects

- Make sure of your assurances (OHRP)

  http://ohrp.osophs.dhhs.gov
- Safety monitoring plan *required*
- Inclusion policies: women, minorities, children
- Data quality control
- Informed consent, vulnerable populations

Trial Design

- Phase II and NINDS Pilot Trials
  - Fixed sample size
  - Staged designs
  - Selection trials

  } Types of trials

  - **NOT** underpowered Phase III
- Phase III or Efficacy Trials
  - Safety/stopping rules/interim analyses
  - Large, simple trials
  - Primary outcome measure

Surrogate Markers

- When/why will they be used?
- Necessary for safety?
- Related to primary outcome?
- Measure>Analyze?
- All equally important?

- Imaging
- ICP/MAP/CPP/etc
- Biochemistry
- Neuropsychology
- Test batteries
- Worsen/improve
- Quality of Life (QOL)

Acute Traumatic Brain Injury

- Narayan et al. 2002. Clinical trials in head injury. J. Neurotrauma 19: 503

"why have all the trials failed??"

Treatments were ineffective under the conditions tested.

Bench to Bedside?

Animal Models

Treat within 1 hr

Single dose

Measure infarct size

Outcome at 3 days

No adjunct therapy

Inbred rodents

Clinical Trials

Treat within 8 hrs

Multiple doses

Measure Glasgow Outcome Score (GOS)

Outcome at 12 months

Multiple therapies

Variable populations

Translation

- **Obtain adequate preliminary data**
  - Animal models: diversity and replication
  - Pharmacokinetics and timing
  - Long-term outcome
- **Target appropriate mechanism**
  - Occurs in human disease
  - Realistic expectations

Priorities in Basic Research

- Preclinical development: multiple models, range of severities, dose and timing of intervention
- Create “animal clinic”: surrogate markers, drug interactions, treatment cocktails, secondary insults
- Long-term outcomes

Priorities for Clinical Studies

- Follow the preclinical lead
  - Timing/duration of target mechanism
  - Timing/duration of intervention
- Patient population(s)
- Monitor management
- Outcome measures that show a clinically significant effect

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