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Clinical Trial Methodology Challenges in a Device Used in Chronic Neurological/Psychiatric Disorders

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BACKGROUND

What kind of device?

- An implantable device for use in neurological and psychiatric disorders that provides continuous, intermittent, stimulation of certain neural pathways
- Its use in these disorders is in late (Algorithm) stages for chronic use
- Approval via PMA route (one prior indication)
- Small company with limited resources

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Early Phase Issues

What constitutes the right treatment?

- What is the right stimulus?
  - Stimulation, Inhibition, Disruption
  - Unilateral or bilateral?
- What is an adequate dose?
  - The best way to deliver the stimulus
  - At what levels? For how long?
- What constitutes adequate duration?
  - Continuous versus intermittent
  - Immediate effects versus modulating neural systems (and how long is required to do so?)

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Animal Models

- What are appropriate animal models for the Central Nervous System?
  - With pharmaceuticals, rats are often used and appear adequate for basic pharmacology
  - For neural devices, the complexity of the CNS is inadequate
    - Primates are closer to the human CNS (e.g. insular circuits, self awareness), but expensive
    - Some circuitry may be uniquely human

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Dose finding I

- What constitutes an adequate dose?
  - Transmission of stimulus to the neural circuitry
    - Charge density (Pulse width, current)
    - Frequency
    - Interuption vs stimulation vs pacing
  - Minimal effective dose vs suprathreshold
  - How can you be sure the “dose” is biologically relevant

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Dose finding II

What constitutes adequate duration?

- Time to first appreciable effects
  - Side effects do not connote beneficial effects are occurring
  - Biomarker proxies?
  - Do early effects predict long-term outcome?
- Time to adequate/optimal dosing
  - Does the neural circuit respond instantaneously?
  - If not, how long is required?

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Problems with surgery

- Surgery itself has risks
  - Adverse events
  - Poor placements
- In addition surgery:
  - Requires expertise in the proper placement of the device
  - Adds to the costs
  - Adds to the logistical/coordination load
  - Can complicate “placebo” arms
  - Makes interpretation of early adverse events more difficult

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Safety Issues

- How relevant is the previous safety of the device in the other disorder?
  - Are there unique safety issues in the new d/o?
- A new device with unknown (or incompletely known) mechanism of action leads to difficulties in assessing causation
  - “I don’t know that it doesn’t cause these things!” (e.g. skin cancer in Florida)
  - Early effects due to surgery or the device?
  - Need to properly educate/train in an environment sensitive to “coercion”

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Blinding/placebo

- Can it be “safely” done?
- Often difficult to provide an adequate “placebo” arm in device studies
  - Not turning the device on
  - Using a subthreshold dose
  - Using intermittent stimulation spaced too far apart to be effective
- Need for blinding the raters?
  - Programmers separate from the rater?

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Chronic Use

The problems of long duration trials:

- Inability to standardize conditions for all subjects
- Interference of other conditions
- Life events
- Use of medications/treatments
- How often should f/u occur?
- Does it decrease the effect of placebo?

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Late Algorithm Use

The implications of being used late in treatment algorithms:

- Can placebo treatment be safely used?
- "Add-on" trial design
  - Treatments were continued (but not controlled)
  - Usually on multiple treatments
  - Different illness durations and responsiveness
  - If subjects respond, can one then withdraw the treatment?

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The Registration Trial

Early results here were not as good as in the initial pilot study, why?

- By increasing the sites:
  - Adequate stimulation was lost
  - Quality of subjects decreased
- Other problems:
  - Different substudies at different sites
  - No attention paid to the timing of the pivotal outcomes versus the timing of substudy components

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Problem of Add-on Rx

The trial was designed as an "add-on" to "treatment as usual" (TAU)

- Beyond the initial time period of a few months, subjects were free to change Rxs
- How does one then know if subsequent changes in status are due to the device or to the change in the other Rxs?
- Confound of the need/desire to change Rx when things are not going well

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SUMMARY

- Animal models are often inadequate to fully anticipate human CNS responses and function
- Use an adequate “dose” for an adequate duration
- Take surgical issues into account
- Anticipate disorder specific safety issues
- Device trials often cannot easily compare with placebo treatment
- With this device special issues came into play because of the late stage use and need for long Rx duration
  - The use of multiple uncontrolled treatments over the duration of the trial