Clinical Trials in the Age of Technology

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SCORE Seminar – 6/5/2018
Disclosures

I receive research funding from the American Academy of Neurology, NINDS, Michael J. Fox Foundation, and Greater Rochester Health Foundation
Go to:

pollev.com/christophert165
I have a personal smartphone

- Yes
- No

Obviously, how else would I be doing this poll?
<table>
<thead>
<tr>
<th>Which of the following technologies have already been incorporated into clinical trials?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smartphones</td>
</tr>
<tr>
<td>Telemedicine</td>
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<tr>
<td>Quantitative image assessment</td>
</tr>
<tr>
<td>Video-based home monitoring</td>
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<tr>
<td>Electronic consent</td>
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</tbody>
</table>
I have been involved with a study that incorporated technology-based assessments.
In 1 or 2 words, describe how you feel about the incorporation of technology into clinical trials
Objectives

1. Review the limitations of traditional clinical trials and investigator or coordinator-performed outcome measures

2. Describe the goals, expectations, and rationale for the use of technology in the conduct of clinical trials
   a) Virtual visits
   b) Technology-based outcome measures (digital biomarkers)

3. Discuss specific technologies that are already being incorporated into clinical trials

4. Discuss practical considerations for investigators, coordinators, sponsors, and participants when using technology in clinical trials
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Traditional clinical trial model: Successes

Centralized trial coordination centers

Trial networks and study groups

Safety monitoring

Adaptive trial design
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Traditional clinical trial model: Successes

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Adaptive trial design
Traditional clinical trial model: Shortcomings

- Complicated/unclear disease mechanisms
- Phenotypic variability
- Insufficient sample size in rare diseases
- Geographically limited and require travel
- Short trial duration
- Insensitive, episodic, subjective outcome measures
- Significant expense
- Failure to capture the patient experience
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Traditional clinical trial model: Shortcomings

Assessment of motor function in Parkinson disease

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.
1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one long arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

Serial imaging in multiple sclerosis
Traditional clinical trial model: Shortcomings

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Traditional phase 3 clinical trials in neurology have failed to replicate phase 2 findings

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Phase 2 Findings</th>
<th>Phase 3 Findings</th>
<th>N</th>
<th>Duration</th>
<th>Sponsor</th>
<th>Phase 3 Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idalopirdine</td>
<td>Alzheimer disease</td>
<td>2.1 points improvement on ADAS-Cog over placebo</td>
<td><strong>Failed</strong>, unchanged ADAS-Cog</td>
<td>2525</td>
<td>24 months</td>
<td>Lundbeck</td>
<td>~$600 million</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Alzheimer disease</td>
<td>1.9 points improvement on ADAS-Cog over placebo for lowest dose</td>
<td><strong>Failed</strong>, unchanged ADAS-Cog</td>
<td>2100</td>
<td>18 months</td>
<td>Eli Lilly</td>
<td>~$600 million</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>ALS</td>
<td>Safe and tolerable, staged design study</td>
<td><strong>Failed</strong>, no improvement in survival or rate of decline</td>
<td>600</td>
<td>12 months</td>
<td>NIH</td>
<td>~$60 million</td>
</tr>
<tr>
<td>Creatine</td>
<td>Parkinson disease</td>
<td>2.8 points improvement on total UPDRS over placebo</td>
<td><strong>Failed</strong>, study terminated early due to futility</td>
<td>955</td>
<td>5 years</td>
<td>NIH</td>
<td>~$25 million</td>
</tr>
<tr>
<td>Coenzyme Q₁₀</td>
<td>Parkinson disease</td>
<td>1.2-5.3 points improvement on total UPDRS over placebo</td>
<td><strong>Failed</strong>, study terminated early due to futility</td>
<td>600</td>
<td>16 months</td>
<td>NIH</td>
<td>~$14 million</td>
</tr>
<tr>
<td>Coenzyme Q₁₀</td>
<td>Huntington disease</td>
<td>0.34 point improvement on Total Functional Capacity over placebo</td>
<td><strong>Failed</strong>, study terminated early due to futility</td>
<td>609</td>
<td>5 years</td>
<td>NIH</td>
<td>~$22 million</td>
</tr>
<tr>
<td>Pridopidine</td>
<td>Huntington disease</td>
<td>1.0-1.2 point improvement on modified motor score over placebo in two trials</td>
<td><strong>Failed</strong>, no significant improvement</td>
<td>400</td>
<td>6 months</td>
<td>Teva</td>
<td>~$100 million</td>
</tr>
</tbody>
</table>

ADAS-Cog = Alzheimer’s Disease Assessment Scale – Cognitive subscale; ALS = amyotrophic lateral sclerosis

Sources:
- Dorsey ER, Papapetropoulos S, Xiong M, Kieburtz K. The First Frontier: Digital Biomarkers for Neurodegenerative Disorders. Digit Biomark 2017
- Atri A et al. Effect of Idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer disease: three randomized clinical trials. JAMA 2018
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Virtual visit basics

Connect with video conferencing software

Enroll anyone with an internet connection
  • Connect in the home or an office setting

Consent online

Complete questionnaires and outcome measures that are done in-person
  • May need some modification to exam
  • Can coordinate with local providers

Currently used as a complement to in-person visits
Virtual visits offer benefits over traditional trial visits

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Traditional Model</th>
<th>Virtual Model</th>
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<tbody>
<tr>
<td>Geographic Reach</td>
<td>Determined by site location</td>
<td>Determined by internet access</td>
</tr>
<tr>
<td>Sites</td>
<td>Many</td>
<td>One</td>
</tr>
<tr>
<td>Institutional Review Boards</td>
<td>Many</td>
<td>One</td>
</tr>
<tr>
<td>Investigators</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Time to initiate study</td>
<td>Long</td>
<td>Medium</td>
</tr>
<tr>
<td>Time required for visits</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Variance in assessments</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Burden on participants</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$$$</td>
<td>$</td>
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Digital biomarkers can improve outcome assessment

**Digital biomarker:** objective quantifiable measure of biology or health measured through digital devices

- **Objective:**
  - Frequent or continuous
  - Sensitive

Objective severity scores derived from a smartphone application in Parkinson disease

Generating insight into home life with passive monitoring in Parkinson disease

Monitoring brain atrophy and white matter burden in multiple sclerosis
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Virtual Visits

Add-on study of 40 individuals concurrently enrolled in a disease modifying trial for Parkinson disease (STEADY-PD III)

Smartphone Technology

Involves development of App technology specific to disease state and/or study

- Recruitment and screening
- Assess and monitor disease-specific symptoms
- Track adverse events
  - Standardized questionnaires
  - Patient diaries
- Therapy delivery
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Brief report

*Smartphone data as objective measures of bipolar disorder symptoms*

Maria Faurholt-Jepsen, Mads Frost, Maj Vinberg, Ellen Margrethe Christensen, Jakob E. Bardram, Lars Vedel Kessing

*Psychiatry Research* 2014;217:124-127
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Adherence to antidepressant medications: a randomized controlled trial of medication reminding in college students.

BMJ Open  Behavioural activation versus mindfulness-based guided self-help treatment administered through a smartphone application: a randomised controlled trial
Kien Hoa Ly,1 Anna Träschel,2 Linnea Jarl,1 Susanna Magnusson,1 Tove Windahl,1 Robert Johansson,1 Per Carlbring,2 Gerhard Andersson1,2
Wearable Sensors

Accelerometers that allow objective assessment of motion and position

Particularly useful for mobility assessment

Can be adhesive or wearable like jewelry (e.g. Smartwatch, pendant)

Allows continuous assessment of function while worn
Passive Monitoring

Video, infrared, or radio-based activity monitoring in the home
  • Requires no active task completion
  • More detailed analysis of home activities
    • Walking
    • Time in bed or bathroom
    • Response to medication
    • Time in and out of the home
    • Socialization
    • Schedule regularity
  • Can monitor continuously for prolonged periods of time

12m radius
1,200 square feet on a single level
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Practical Considerations

Ensure adequate training on technology for investigators, coordinators, and participants

- Coordinators are often the first-line “experts” in troubleshooting problems

Technology may alter the roles of study team members

- Transition away from paper - electronic consent (eConsent) and electronic-only case report forms
- Fewer outcome measures assessments
- More “monitoring” of participants
  - Ensuring adherence/compliance
  - Active data monitoring for technological interventions
- May require new team members
Practical Considerations

Participant data privacy
- Ensure all technology used in human subject research is HIPAA-compliant
- Work with University IT and the IRB to ensure data storage security is adequate

Even “objective” measures need to be validated
- Studies with digital biomarkers today will include both “traditional” and technology-based outcome measures
- Ensure adequate testing of technology prior to agreeing to participate in study using it

Don’t forget the patient experience
- Ensure user-friendly technology that is “acceptable” to patients
- Incorporate patient-centered outcome measures into technology-based assessments to incorporate meaningful endpoints into research
Key Points

1. Success in traditional clinical trials has been limited by our reliance on geographically-limited research centers and subjective, episodic, and insensitive outcome measures.

2. Technology can address many of these concerns by expanding the reach of clinical trials and introducing novel, objective, digital biomarkers.

3. Technology is already being incorporated into clinical trials across the country, largely as a complement to traditional trial visits and outcome measures.

4. The role of technology will continue to rise in the coming years with virtual visits and technology-based assessments likely replacing many traditional trial procedures.

5. Adequate training on technology increases team versatility and limits frustration for investigators, coordinators, and participants.

6. Ensuring data privacy is exceedingly important in the incorporation of any technology into clinical research.

7. Always remember the patient experience.
Questions