ISCTM
International Society for CNS Clinical Trials and Methodology

ISCTM Working Group:
Developing Strategies to Improve Recruitment for Clinical Trials Targeting Neuropsychiatric Symptoms (NPS) in Memory Disorders

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Disclosures Paul Rosenberg

- Research support
  - Lilly, Eisai, National Institute on Aging, Alzheimer's Association, Functional Neuromodulation (FNMI), Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Trials Research Institute (ATRI), Alzheimer's Clinical Trials Consortium (ACTC), Richman Family Precision Medicine Center of Excellence on Alzheimer's Disease
- Consulting/advisory boards
  - Acadia, Biogen, ExpertConnect, GLG, Guidepoint, HMP Global, Leerink, Lundbeck, Medalink, MedaCorp, Medscape, Novo Nordisk, Noble Insights, TwoLabs, Sinaptica Therapeutics
- DSMBs
  - Synaptogenix
- CME presentations
  - Neurology Week
- No royalties, patents, stock

Disclosures Moyra Mortby

- Research support
  - Dementia Australia Research Foundation

Plan for today's session

- Introductions
- Background:
  - Brief overview of challenges facing AD clinical trials
  - Experiences of challenges faced when conducting NPS clinical trials
- Goals of the Working Group
- Discussion

Introductions

- Name
- Where from
- Type of trials you work with

General Problems of Recruitment in AD trials

- Recruitment of participants into RCT is one of the biggest challenges faced by clinical research, with many trials failing to reach recruitment targets.
- A review of 24 multi-site phase II and II AD clinical trials found that only **one third of trials** were able to recruit sufficient participants within one year.
- Success of RCTs relies on **adequate and timely recruitment**
    - with delays resulting in additional costs and underpowering of clinical trials, which can threaten the empirical value of intervention research.

Reasons for poor recruitment into RCTs

- Prospective participants' understanding of trial processes (e.g. randomization)
- Hinderance identifying patients with mild-moderate AD due to diagnostic and care pathways
- Issues relating to access to up-to-date patient records and data access issues affecting screening processes
- Patient/health professional preferences for particular treatments
- Barriers to communication across trial sites
- Complex medication regimes that may exclude patients with advanced cognitive impairment
- Need to recruit study partners or companions alongside the patient for when disease progresses

Challenges of recruiting into NPS trials

- Despite NPS being a key hallmark of dementia and being associated with poor clinical prognosis, the evidence base for efficacy of interventions remains thing.
- A major practical challenge in NPS intervention trials is recruitment.
- Many recent trials have encountered significant challenges relating to recruitment, both in terms of identifying eligible and interested participants and recruiting diverse populations.
- Challenges include:
    - Issues relating to awareness and understanding of NPS as a hallmark of dementia.
    - Challenges relating to nomenclature, availability and use of diagnostic criteria in primary care, or a fear of stigma relating to diagnosing NPS.
    - Issues relating to the short window of opportunity to enroll participants into NPS trials (i.e. acute situations where enrollment into trials may be limited to just a few days/weeks).
    - Screening processes as recruitment into NPS trials generally require careful psychosocial assessments before enrolment.

Recent experience with NPS trial recruitment

ISCTM Scientific Meeting

Washington DC

February 21, 2024

Motivation for Discussion

- I specialize in clinical trials of interventions for neuropsychiatric symptoms (NPS) across the Alzheimer's disease (AD) spectrum
  - Drugs: sertraline, citalopram, S-citalopram, methylphenidate, THC (dronabinol), psilocybin, trazodone
  - Nonpharmacologic interventions: CBT for depression in MCI
  - Target symptoms: apathy, agitation, depression, insomnia
  - Adding objective measures to trials including actigraphy and home sleep testing
- Every trial has struggled for recruitment and many not met their targets
- A story I keep hearing across the field
- Moyra Mortby and I met at AAIC last year and agreed to convene a working group of investigators in the field to discuss experiences and strategies for improvement.

Example 1:
Alzheimer's Disease Methylphenidate Trial (ADMET 2)

- NIH-supported RCT of methylphenidate treatment (20 mg daily in divided doses for 6 months) for treatment of apathy in AD
- Follow-on to ADMET which was a positive pilot RCT (N=60, duration = 6 weeks)
- Target N=200
- 10 sites in U.S. and Canada
- Positive treatment findings and very benign safety profile
  - Mintzer et al., JAMA Neurol. 2021;78:1324-1332
- **We achieved target only by extending a 5-year study to 7 years!**
- Major barriers included
  - patient, family and clinician awareness of apathy
  - Pandemic lockdown
  - Need for EKGs, blood draw
- Mitigation included increased use of remote assessments for interim outcome measures

Example 2:
S-Citalopram for Agitation in AD (S-CitAD)

- NIH-supported RCT of escitalopram treatment (15 mg daily for 3 months) for treatment of apathy in AD
- Follow-on to CitAD which was a positive pilot RCT of citalopram (N=188)
- Target N=392
- ~25 sites in U.S. and Canada
- Trial completed recruitment, N=173
- **We extended a 5-year study to 8 years and only achieved 44% of target**

- Barriers
  - Clinicians started using SSRIs in the years between CitAD findings and startup of S-CitAD
  - Pandemic lockdown
  - Lack of knowledge about agitation among patients, families, and clinicians
  - Agitation is often a crisis
- Mitigation
  - Added sites on an ongoing basis
    - Results extremely varied from great to nonexistent
    - Need to vet sites carefully before engaging them
    - Junior faculty with fewer projects and busier clinics seemed to be more productive
  - Engaged consultant firm (at substantial expense)
    - Results very limited
    - Efforts may not have been optimized for narrow target of agitation in AD

Example 3:
Dronabinol for agitation in AD (THC-AD)

- NIH-supported RCT of dronabinol (10 mg daily for 3 weeks) for treatment of agitation in AD
- Dronabinol is FDA-approved for anorexia, repurposed for agitation
- Started at 2 inpatient sites
- Target N=80
- No minimum MMSE so included moderate to severe dementia
- Over time, morphed in outpatient trial at 4-5 sites
- **We extended a 5-year study to 8 years and are very near target (75 of 80)**
- **Ending 5/31/24**

- Barriers
  - Hospital closed one inpatient site (dementia unit)
  - Other inpatient sites not productive for recruitment
  - Difficult to maintain stable medication regimen on inpatient units
  - Pressure to discharge
  - Lack of knowledge about agitation in AD
  - Pandemic lockdown
  - Agitation is often a crisis
- Mitigation
  - Morphed to outpatient trial
  - Added 3 outpatient sites
  - Changed interim visits to remote
  - Engaged consultant firm (at relatively modest expense) too soon to tell

Example 4:
PEACE-AD (Prazosin for agitation in aD)

PEACE-AD Results (Elaine Peskind, Murray Raskind)

- Final total of 35 randomized participants
- 12-week study completers: 3 of 8 randomized to placebo group (38%) vs. 17 of 24 participants randomized to prazosin group (71%)

BLUF (Bottom Line Up Front) – all agitation and survivorship-based outcomes numerically favored prazosin

Primary outcome measure:

Clinical Global Impression of Change-Agitation (CGIC-A) – NS but 45% prazosin responders compared to 20% placebo responders

Key secondary outcome measure:

Neuropsychiatric Inventory (NPI/NPI-NH) - NS

Other secondary outcome measures:

ADCS-ADL for Severe Dementia - NS

Number of days of study survivorship - NS

Total mg rescue lorazepam – NS but very little use at all

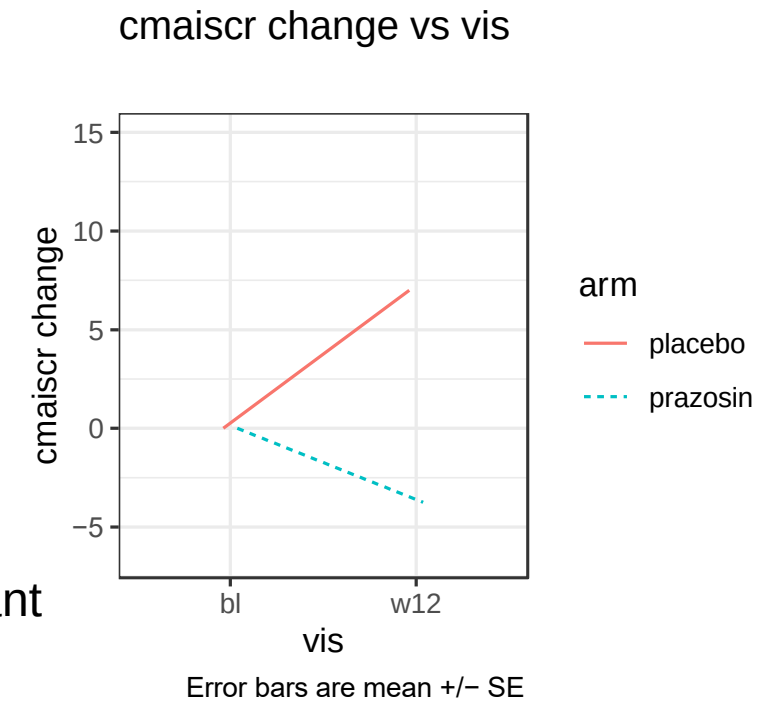
Exploratory outcome measures:

Subset of 5 NPI domains reflecting disruptive agitation:

Agitation/Aggression, Anxiety, Disinhibition, Irritability/Lability, Aberrant Motor Behavior - NS

Cohen-Mansfield Agitation Inventory (CMAI) – p=0.04

Change from Baseline in CMAI score (p=0.04)



Safety: significantly higher frequency of syncope/dizziness, nausea, and somnolence in prazosin group
With caveat of higher participant number and length of exposure in prazosin group

Conclusion, Lessons Learned, and Future Directions

- We had very limited power, but we believe that what has been achieved is a successful *pilot* study in home-based Alzheimer's victims with disruptive agitation that provides rationale for larger RCT
- Recruitment in LTCs can ONLY happen when a Site PI is also a treating clinician embedded within LTC
- Assisted living facilities appear *not* to have adequate staff support or supervision of participants to perform such a trial safely and with good compliance
- Alzheimer's agitation trials can be conducted in the outpatient/home-based setting, including *entirely* remotely if necessary
- These participants and their study partners CAN use technology for virtual visits with adequate support
- Two pilot studies of prazosin for disruptive agitation in AD: one in LTC, one in mostly outpatients provide rationale for larger placebo-controlled trial
- Murray drafting manuscript describing results of RCT and lessons learned
- Ben Boyarko and Guerry Peavy conducting individual responder analysis

Conclusions

- Several NIH-funded RCTs for treating NPS in AD had significant recruitment challenges
- Some did not meet target (S-CitAD, PEACE)
- Others met target but took many years longer than planned (ADMET 2, THC-AD)
- Common threads
  - Pandemic
  - Need for remote visits
  - Need for education of patients, families, and clinicians
  - Need to enroll rapidly in times of family crisis (agitation)
- Pharma studies rumored to have comparable challenges
- Caveat: I did not address diversity which was an issue for all the above trials.
- ***What is to be done?***

Goals of the Working group

- Bring together leading investigators, industry representatives and regulatory bodies to
  - Discuss the challenges
  - Brainstorm potential solutions
  - Develop a white paper to help address these issues

Points to stimulate discussion

- What are the **general problems** that you have experienced relating to the recruitment of participants into NPS/Dementia trials?
- What are the **specific problems** that you have experienced relating to the recruitment of participants into drug trials?
- What are the **specific problems** you have experienced relating to the recruitment of participants into non-pharmacological trials?
- What **challenges** have you faced relating to recruitment of diverse populations into trials?
- What **challenges** have you faced relating to the recruitment of participants into international/multinational trials?