Decentralized trials in Neuroscience

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on behalf of the
eSIG Neuroscience working group on DCTs

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Overview

This presentation is on behalf of working group (WG) on Decentralized trials in Neuroscience

- WG created beginning of 2021
- WG part of the European SIG Neuroscience community
- WG is open to everyone
- WG explores options of decentralized trials in Neuroscience

Overview

WG members

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Executive Summary

Introduction

- Multi-stakeholder perspective on the value/challenges of Decentralized Clinical Trials (DCTs)
- Importance of DCTS in Neuroscience
- Review of the literature and gaps
- List of endpoints of interest

Methodology

- List of endpoints of interest
- Differences between at home and at site assessments
- Design of Simulations
- Results: What we learned from Simulations
- Conclusions/Summary

Why DCTs in Neuroscience

- Neuroscience heterogeneous therapeutic area of diseases with different endpoints and different development tools applied
- Traditionally, assessments in Neuroscience studies are site-based
- Endpoints are typically based on investigator or direct patient assessments
- Decentralization in Neuroscience may be different (and more complicated) as compared to other disease areas due to subjectivity of endpoints and vulnerability related to frame-of-mind
- Therefore, differences between on site and remote assessments expected
- However: Data obtained from at home assessments may be more relevant than on site assessments

Value of DCTs

- Decentralized clinical trials (DCT) are defined as studies “executed through telemedicine and mobile/local healthcare providers, using processes and technologies differing from the traditional clinical trial model.” (1)
- The opportunities and challenges of decentralized trials can best be understood using a multi-stakeholder approach

Patient	**Opportunities:** ● Location Agnostic (AP) ● Easily Assessable (CTTI) ● Reduced Travel Burden (AP) ● Part of daily routine (AP) ● Precise Subjective measurement ● Shift to Patient-centricity	**Challenges:** ● Use of unfamiliar technology ● Less interaction with site staff
Investigator	● Higher quality, faster, and more frequent data collection [Dockendorf] ● Reduced site burden ● Expanded/faster recruitment	● Verification of identity-replication of informed consent ● IRB concerns ● Requirements for licensure ● Change in business model

Value of DCTs

Sponsor	**Opportunities:** • Fosters research with less burden for patients • Enable higher quality, Less drop outs and missing data • Greater participation and diversity (AP) • More frequent measurement (even continuous), not restricted to clinic visits (AP)	**Challenges:** • Laws pertaining to shipment and accountability of Investigational drug products directly to trial participants (AP • Operational difficulty: Telemedicine/eCOA with operational aspects of DCT (e.g. telemedicine components) (AP) • Biostatistical concerns
Regulatory	• Patients can be recruited from anywhere: Accelerated enrollment (AP) • Greater “real world experience” potential more generalizable data • Better Diversity and Inclusion	• Validation that study defined activities are carried out consistently and rigorously despite varying site qualifications (staff qualifications) (AP) • Data rigor: reliability, integrity, traceability.

Literature

- There is a long list of literature on DCTs in NS
- Literature available is often connect with developing new endpoints for specific NS indications
- There is a gap in studies explicitly comparing **at home assessments** versus **on site assessments** using the same assessment tool
- Across Therapuetic Areas and disease states, there is limited data ***specifically*** comparing the impact of combining at home and in clinic assessments–to determine efficacy of a treatment

Potential Home-based Assessments

- We limited our evaluation to endpoints in 3 highly researched neuroscience conditions: We Alzheimer disease, Parkinson and MS
- Our assessment included identifying easily adapted endpoints for at home assessments and those that would be more challenging and would require changes when used at home

Alzheimers Disease	**Suitable endpoints:** ADAS-Cog, ADCS-ADL, CDR SB, MMSE, MoCA, Health Assessment Questionnaire-Disability Index (HAQ-DI) are all for on site and by telephone, hence also remote	**Challenging endpoints:** Other endpoints may be more difficult, like the Columbia Suicide Severity Rating Scale (C-SSRS)
Parkinson disease	UPDRS? (perhaps with some limitations especially in part 3 Motor examinations) CGI, PGI	UPDRS part 3 may be challenging to do it virtually due to the different detailed assessments of motor function
Multiple Sclerosis	Neurologic exam, 9-HPT, 25-FWT and SDMT can be done at home and on site	EDSS the main endpoint in trials only for raters at site. There might be a version which can be used for home assessment as well but is at the end a new endpoint

Differences between at home and at site assessments

- Endpoints in Neuroscience can often be easily adapted for home assessments (no major changes)
- Trials will become more complex when we have a mix between at home and on site assessments
- In neuroscience, we see challenges with inter-rater reliability, this may be compounded with in home assessments
- The expectation may be that the on-site assessment is more accurate, but in reality--the in home assessment may be more relevant when assessing real-world functioning
- This evaluation explores the concept of in-home versus on-site assessments by a set of simple simulations

Methodology

- Differences between at home and at site assessments
- Design of Simulations
- Results: What we learned from Simulations
- Conclusions/Summary

Aim of simulation study

1. Simulation of a set of (simple) scenarios assuming systematic and random differences in outcome between home and in-clinic assessments and patterns of visit types driven by patient choice

2. Evaluate consequences on treatment effect estimates in terms of bias and precision

Not covered:

- Optimisation of design with respect to home vs in-clinic visit schedules
- Impact of randomization of subjects to different visit schedules

Scope of simulation study

- Study design: balanced, parallel design, randomized (PBO-)controlled

Week	0	12	24	36	48 (primary endpoint)
Placebo					
Active					

- Type of assessment: taken at **home (H, ●)** or **in-clinic (C, ■):**
  - **location** and assessor are 100% correlated: home assessment through e.g. eCOA, central rater, ...; in-clinic assessment by site personnel
  - **same instrument** for H and C assessments

Scope of simulation study

- Considered potential effects on clinical outcome:
  - **Systematic difference** between H and C, due to e.g. assessment error, level of motivation, (self)perceived disease status, …
  - **Random difference** between H and C (idem)
  - **Patient choice** scenario's:
    1. Patient **choice for H or C** at some or all visits
    2. Patient may **miss next C assessment** after H assessment
    3. Patient may **reschedule H assessment when not feeling well (=poor clinical outcome)**

Simulation and analysis model

- **Simulation model**: two data generating models C_{ijk} and H_{ijk} are ”combined” to generate one observation per patient at each visit (i=subject, j=visit, k=treatment)
  - Clinic assessments*: $C_{ijk} = \mu + \beta_j + \tau_k + (\beta\tau)_{jk} + s_i^C + \varepsilon_{ij}$

    correlation ρ
  - Home assessments*: $H_{ijk} = \mu + \beta_j + \tau_k + (\beta\tau)_{jk} + s_i^H + \varepsilon_{ij} + \omega_{ij}$

- **Primary analysis model**:
  - Change from baseline: $X_{ijk} = \mu + \beta_j + \tau_k + (\beta\tau)_{jk} + b_i + \varepsilon_{ij} + \omega_{ij} h_{ij}$

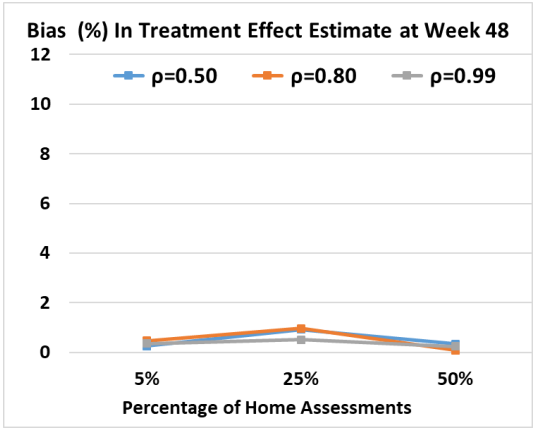
    standard MMRM model + adjustment assessment location
  - Primary endpoint W48

**Data generated assuming a mean progression over time for the control arm to be linear and mean change from baseline at W48 equal to 1; for each subject, outcome over time is the result of a combination of two random slopes models, one for home and one for clinic assessments*

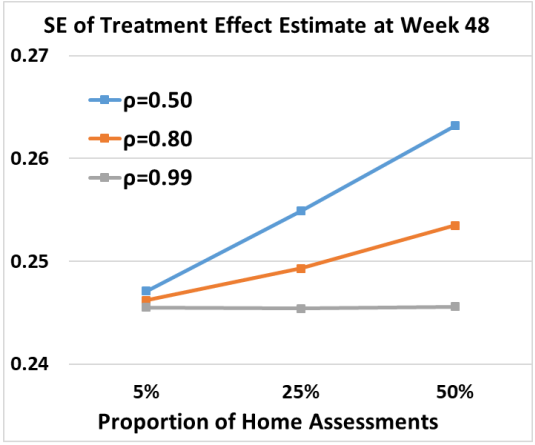
Patient choice for Clinic (■) or Home (●) Assessment at Each Post-BL Visit ("random choice for all post-BL visits")

Week	0	12	24	36	48
Placebo	■	■/●	■/●	■/●	■/●
Active	■	■/●	■/●	■/●	■/●

■ or ●: probability **(1-p) or p**



- Using the primary analysis model, at each visit, **estimates** of treatment effects and for «Home» vs «Clinic» differences are **unbiased**
- Increasing *p* of «Home» assessments (up to 50%) increases SE of treatment effect estimate at W48
- Increase in sample size (~10% here) also for high ρ (=0.8)* if 50% assessments done at home

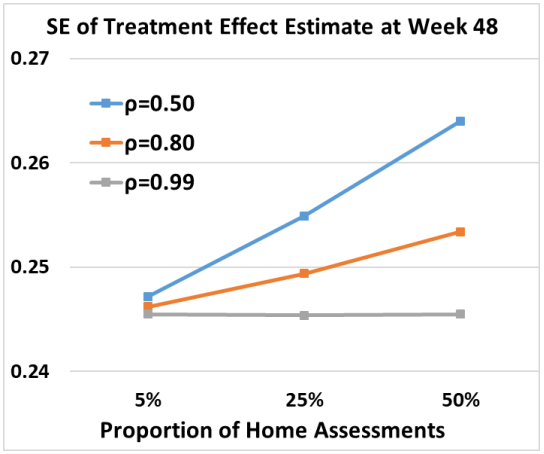


Patient choice for Clinic (■) or Home (●) Assessment at a Subset of Visits ("random choice for some post-BL visits")

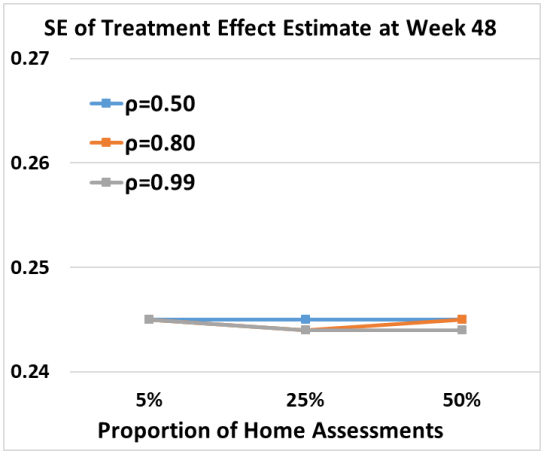
Week	0	12	24	36	48
Placebo	■	■	■/●	■	■/●
Active	■	■	■/●	■	■/●

Week	0	12	24	36	48
Placebo	■	■/●	■	■/●	■
Active	■	■/●	■	■/●	■

■ or ●: probability **(1-p) or p**



- Using the primary analysis model, at each visit, **estimates** of treatment effects and for «Home» vs «Clinic» differences are **unbiased**
- If Primary Analysis Visit is in clinic, standard errors of treatment effect estimates are unaffected by patient's choice at prior visits.

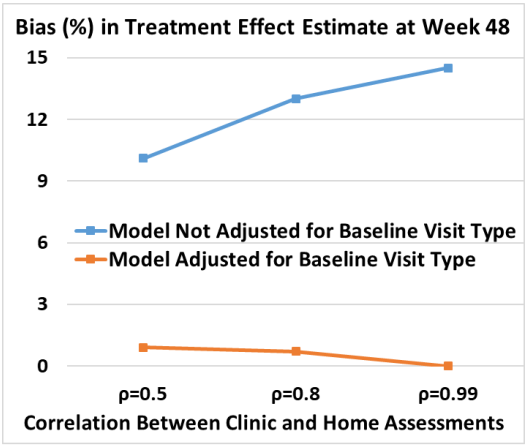


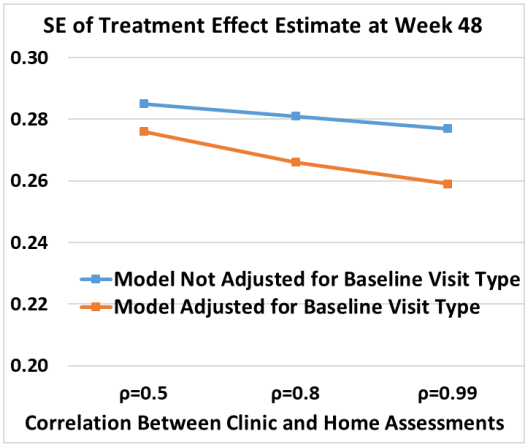
Patient choice for Clinic (■) or Home (●) Assessment at BL and Post-BL Visits ("random choice for all visits")

Week	0	12	24	36	48
Placebo	■/●	■/●	■/●	■/●	■/●
P(Home)	0.40	0.35	0.35	0.35	0.35
Active	■/●	■/●	■/●	■/●	■/●
P(Home)	0.60	0.65	0.65	0.65	0.65

■ or ●: probability **(1-p) or p**

- Adjusting for the Type of Visit («Home» vs «In Clinic») also at Baseline (secondary analysis model) is important to eliminate bias and reduce the standard deviation of the treatment effect estimates.

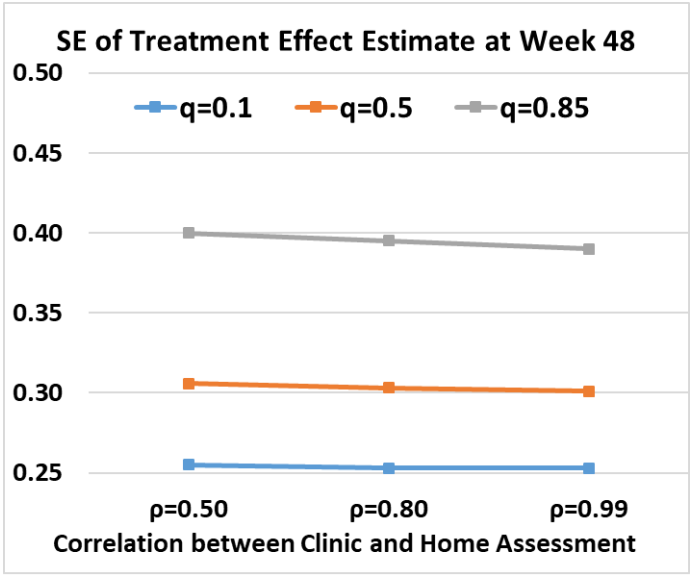




Patient may skip next Clinic Visit, after Home (●) Assessment at Week 36 ("random missingness at primary analysis visit")

Week	0	12	24	36	48
Placebo	■	■/●	■	■/●	■/□
Active	■	■/●	■	■/●	■/□

■ or ●: probability **(1-p) or p**
□ Missing Clinic Assessment with Probability q after Week 36 Home Assessment; Home Assessment possible with probability 0.8.



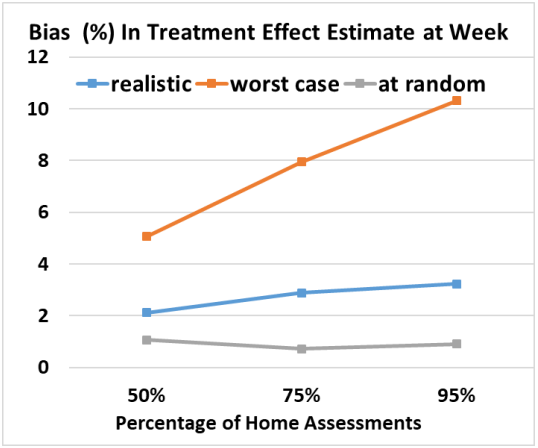
- Treatment effect estimates are unbiased
- Correlation between clinic and home assessments has no impact on standard errors of treatment effect estimates at week 48
- Increased proportion of missing values at week 48 leads to increased standard errors

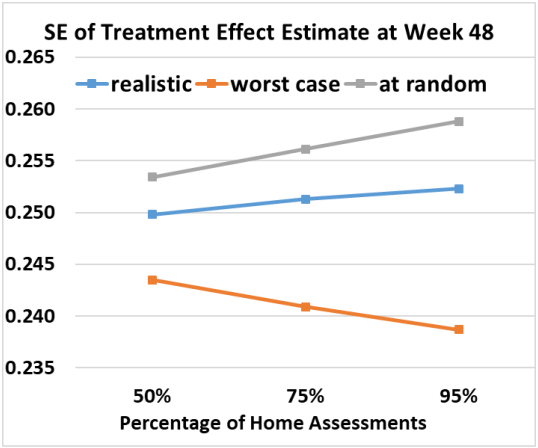
Patient may reschedule Home (●) Assessment if Not Feeling Well

Week	0	12	24	24R	36	48	48R
Placebo	■	■	■/●	●	■	■/●	●
Active	■	■	■/●	●	■	■/●	●

■ or ●: probability **(1-p) or *p***
24R/48R indicate rescheduled home assessments originally planned at Weeks 24/48.
Arrows indicate that home assessment may be rescheduled with probability *q*.

Response Category	Probability *q* for Visit Being Rescheduled		
$HR \le q_{70}$	0.05	0.01	0.30
$q_{70} < HR \le q_{80}$	0.30	0.01	0.30
$q_{80} < HR \le q_{90}$	0.35	0.01	0.30
$q_{90} < HR \le q_{95}$	0.40	0.99	0.30
$q_{95} < HR$	0.50	0.99	0.30
HR = Home Response; q_x = upper x% quantile of all Home Responses	«realistic»	«worst case»	«at random»





- Bias for treatment effect increases as probability of rescheduling depends more strongly on outcome
- This effect is stronger as proportion of home assessments increases

EFSPI

Conclusions

- Adjusting for type of assessment in the MMRM model is critical, but not always sufficient to avoid bias in treatment estimates
- If patient choice for having home visits is random:
  - treatment effect estimates are unbiased
  - power for detecting a treatment effect for the primary endpoint is reduced, if the primary visit includes a mix of home and in-clinic assessments across subjects
  - a strong within-subject correlation between home and in-clinic assessments can safeguard against a substantial loss in power
- If patients tend to miss in-clinic assessments after having had a home assessment at the previous visit, power for detecting a treatment effect is strongly reduced but no bias is induced.
- If patients reschedule home visits based on clinical outcome, bias and power may increase simultaneously and may result in statistically significant but erroneous conclusions on treatment effects