17th Annual Scientific Meeting

COVID-19 CNS CLINICAL TRIAL METHODOLOGIES BLUEPRINT – ISCTM/ECNP Joint Working Group

Chairs:
Kemi Olugemo, MD
Dragana Bugarski-Kirola, MD
Gerard Dawson, BSc, DPhil

DISCLOSURES

Kemi Olugemo is an employee of Ionis Pharmaceuticals

Dragana Bugarski-Kirola is an employee of Acadia Pharmaceuticals, Inc.

Gerard Dawson is an employee of P1Vital LTD

ISCTM-ECNP Covid-19 Working Group

AGENDA	
Welcome and objectives for the working group	Gerry Dawson
Survey Results	Kemi Olugemo
hATTR-PN CASE EXAMPLE	Kemi Olugemo
COVID-19: A Site Perspective	David P. Walling, Ph.D.
Discussion Leader	Dragana Bugarski-Kirola

ISCTM-ECNP Covid-19 Working Group

ISCTM THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

ECNP neuroscience applied

Workshop Objectives

Indication	Country/region	Role (i.e., sponsor, CRO, site)	Rating Scales	Digital endpoints /PROs	Modification to Protocol and/or SAP
Mental Health • Depression • Anxiety • PTSD • Schizophrenia	Country and region-specific considerations	Role-specific considerations	Impact of the pandemic environment on item-level ratings and change with treatment Reward processing	Which assessments can be done virtually vs. in-clinic administration	Changes to study conduct as protocol deviations vs. amend the protocol
Dementia Neurodegenerative disease • AD • Cognitive Impairment • Parkinson's disease	Country and region-specific considerations	Role-specific considerations	Impact of the pandemic environment on item-level ratings and change with treatment	Which assessments can be done virtually vs. in-clinic administration Recruitment/retention issues	Treatment interruptions Safety considerations and capture of adverse events
Rare diseases/Pediatrics • Tourette's • Multiple sclerosis	Country and region-specific considerations	Immunomodulatory therapy Age-specific considerations	Age-specific considerations School closure impact	Age-specific considerations School closure impact	Exclusion of COVID+ patients Prolonged placebo treatment

Identify members of subgroups that may meet individually and report recommendations or trial adaptations to the core WG

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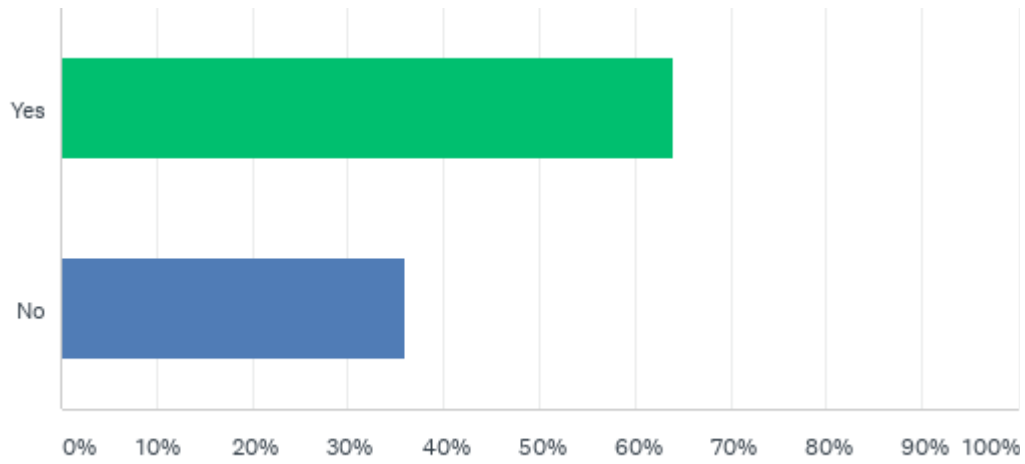
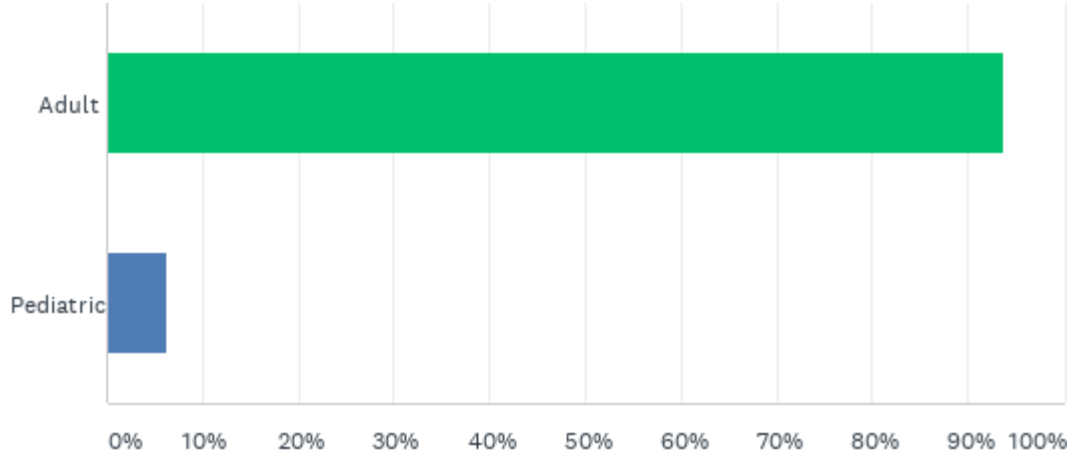
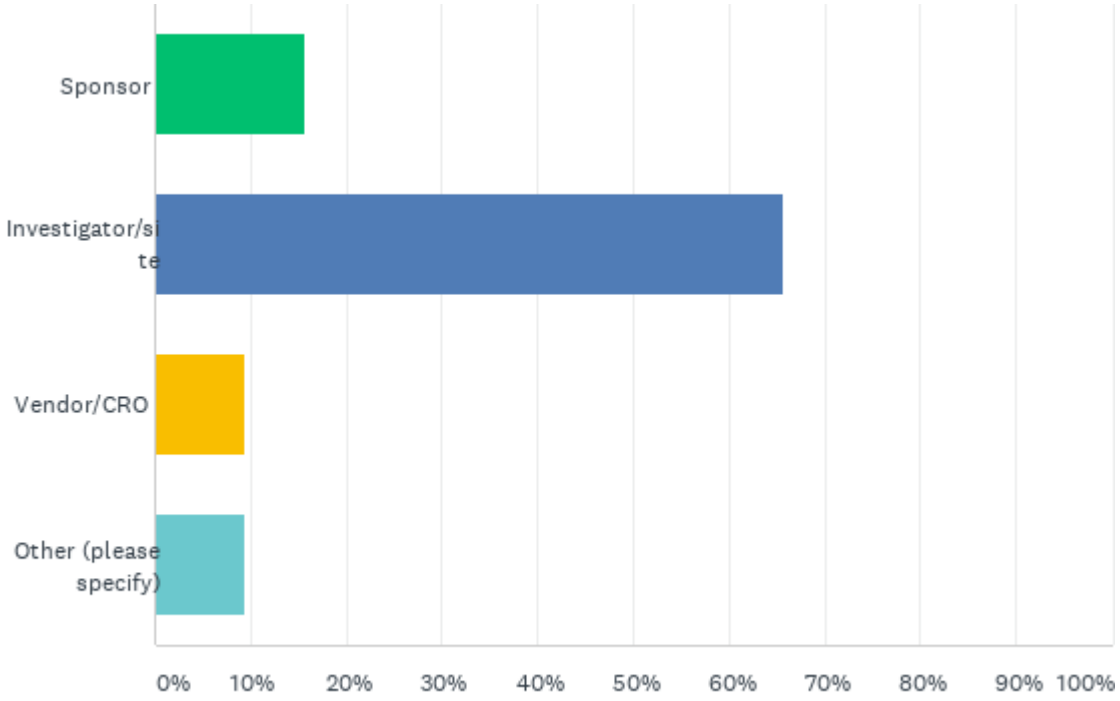
64% (39 of 61 respondents) are conducting or have conducted a clinical trial impacted by COVID-19





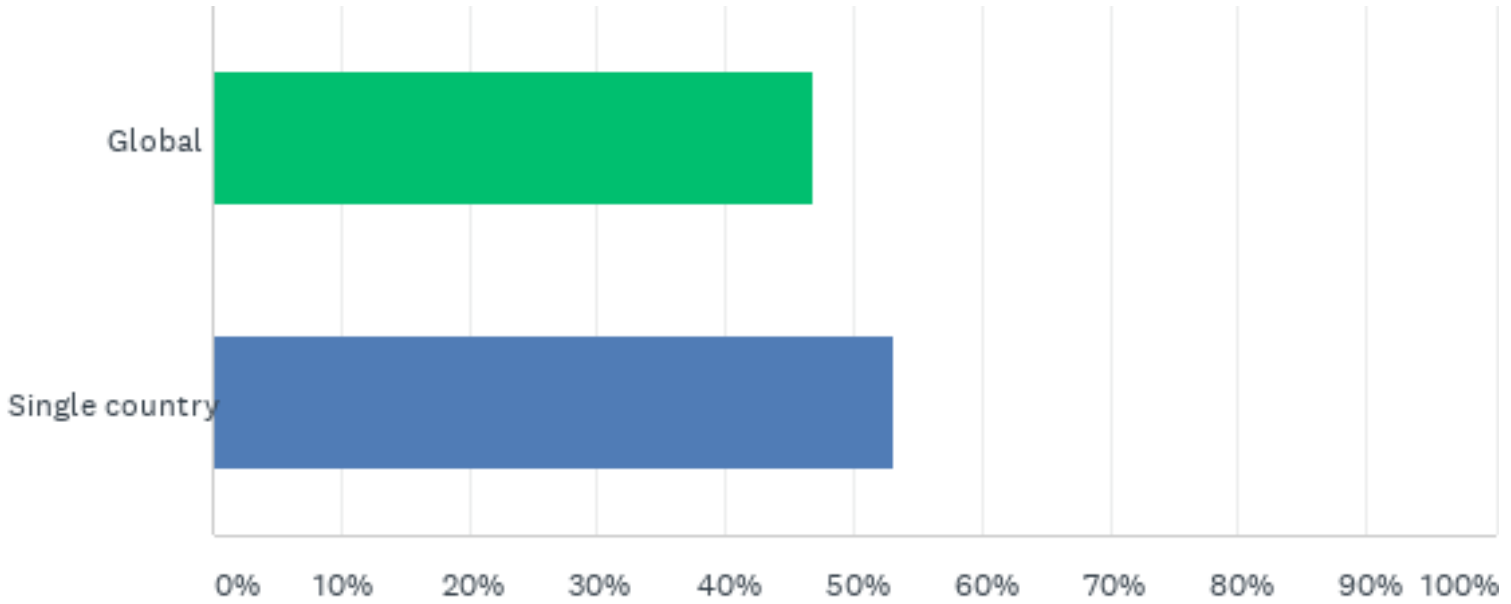
Distribution of roles



Answer Choices	Responses	
Sponsor	15.63%	5
Investigator/site	65.63%	21
Vendor/CRO	9.38%	3
Other (please specify)	9.38%	3
	Answered	32

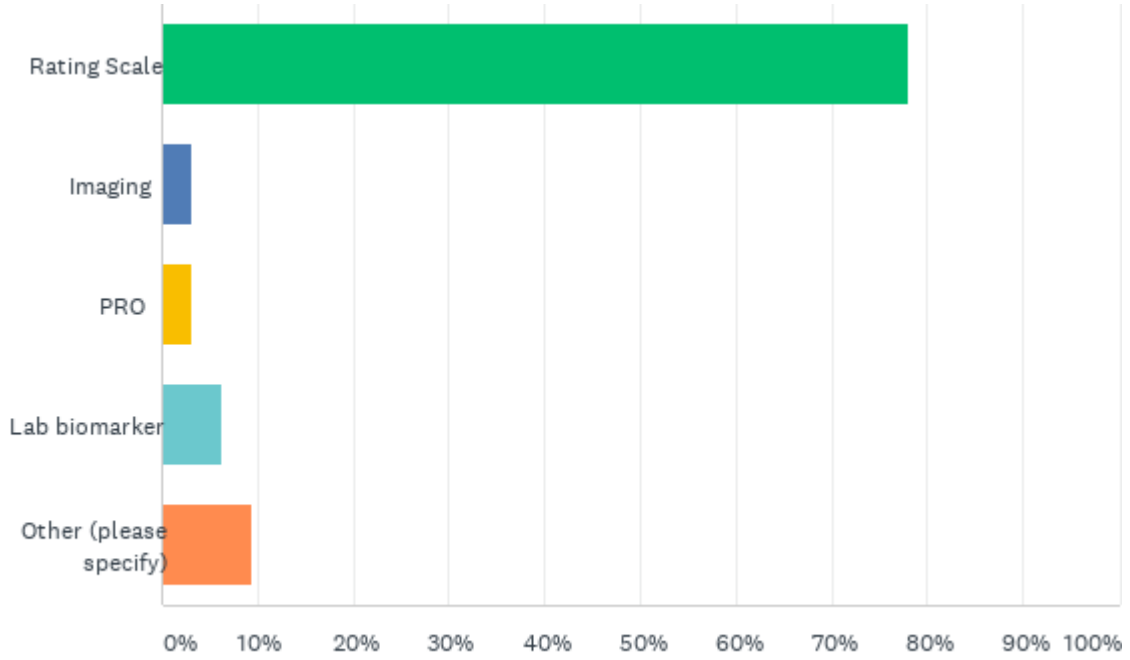
Other (please specify)
Director/Consultant/Advisor
Contractor (staff clinician/scientist)
Conceptualization / app development

Trial location



Please specify country:
Mostly USA (only) a few studies were/are global
Italy
Australia
Canada
Russia
Netherlands
United Kingdom
Sweden
Spain
Germany
italy
Denmark
United States
Morocco

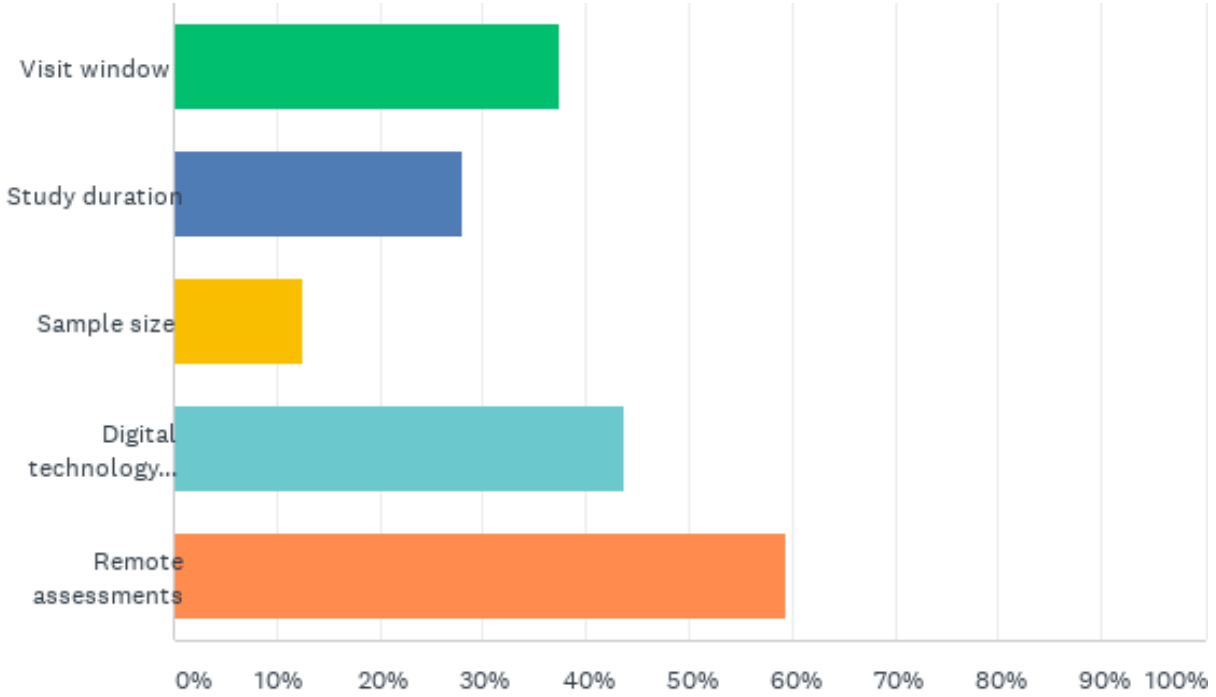
Primary Endpoint type



Answer Choices	Responses	
Rating Scale	78.13%	25
Imaging	3.13%	1
PRO	3.13%	1
Lab biomarker	6.25%	2
Other (please specify)	9.38%	3
	Answered	32

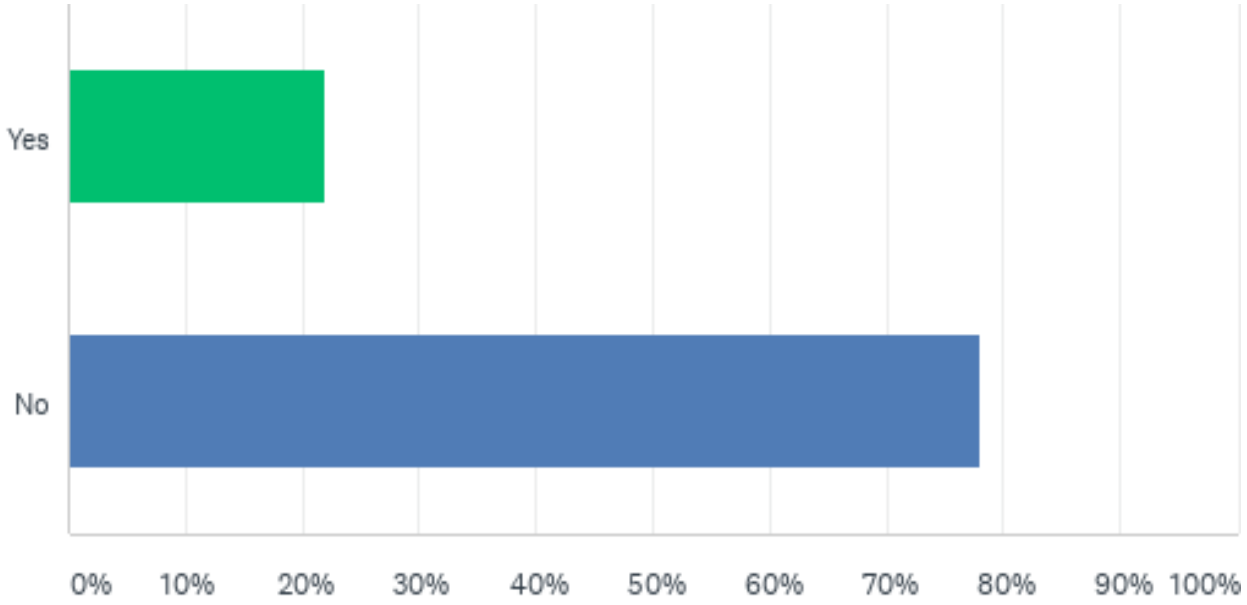
Other (please specify)
Safety with Rating Scales as Secondary
several endpoints - imaging, lab, linguistics
Both scale, imaging and biomarker

Have modifications been made to the trial protocol as a result of the pandemic? Select all that apply:



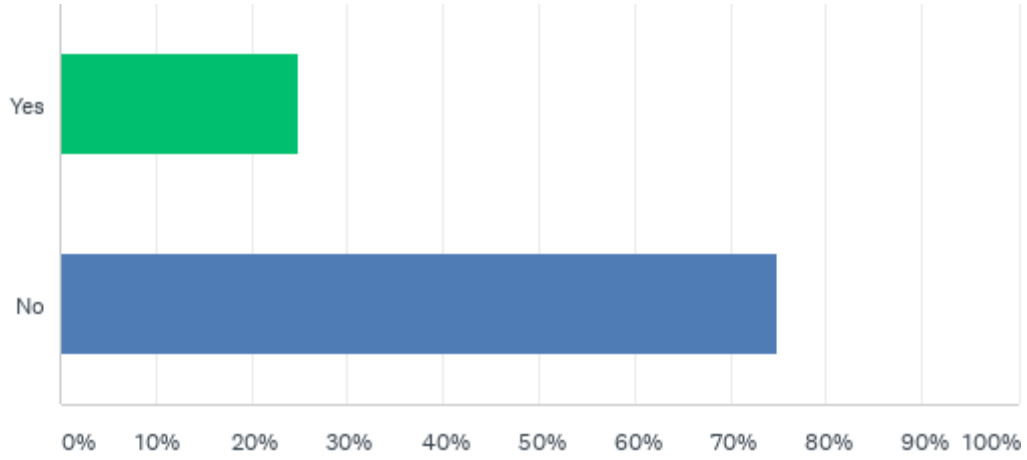
Other comments
Trial was put on hold and will re-commence in January. The trial duration will therefore be extended.
Mandated fewer outcomes' assessments and use of remote data entry and e-Diaries

Have modifications been made to the statistical analysis plan as a result of the pandemic?



If yes, please specify:
Commentary, as indicated
smaller sample size leading to reduced power
UNK as held by Sponsor
Pre- and post-pandemic (March 2020) as significant covariate for treatment level analyses
Proposition of the app

Have any changes been made as a result of regulatory or health authority interaction?



If yes, please specify:
PDCO, CHMP discussions
Practical procedures relating to treatment administration
Discussion concerning modifying some of the ratings to remote ratings
Per FDA guidance
Patients have been informed about the COVID-19 risks for visiting the hospital.
Trial will re-commence in January.
Fast track ethical committee

Proposed workstreams/subgroups that may meet individually and report recommendations or trial adaptations the core WG

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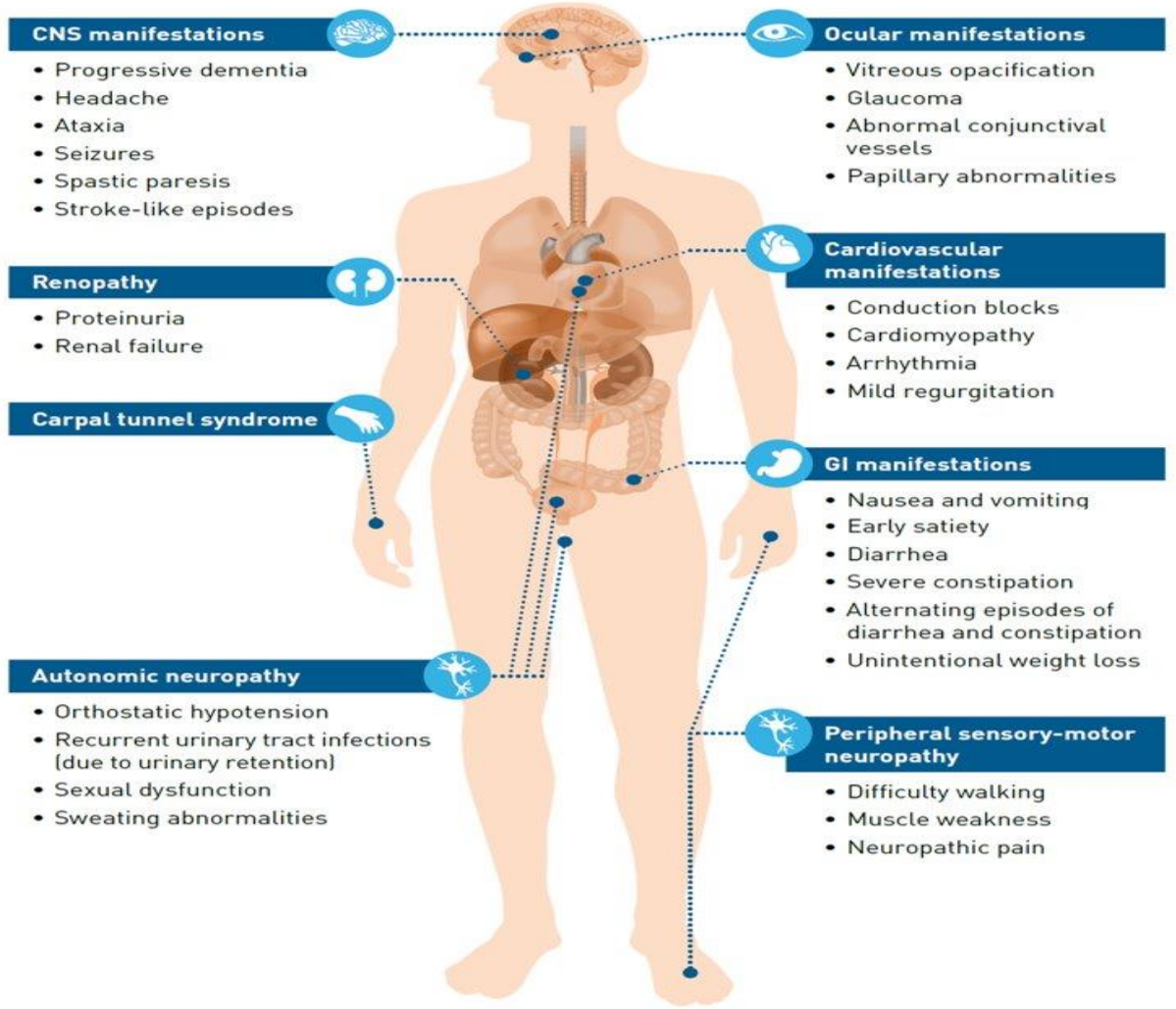
hATTR-PN CASE EXAMPLE

- Modified Neuropathy Impairment Scale (mNIS+7) is a complex composite scale comprised of 8 different components
- This composite is the key primary efficacy endpoint in a global, Phase 3 pivotal study
- The protocol required 2 Baseline assessments within 14 days prior to D1
- mNIS+7 training was conducted face-to-face pre-pandemic
- mNIS+7 training was a gating factor in site activation and patient enrollment

Indication: Hereditary Transthyretin Amyloid Polyneuropathy (hATTR-PN)

- Multisystem disease
- WW prevalence of 10,000
- Misdiagnosis common
- Difficult to capture full spectrum of disease due to heterogeneity
- Limited treatment options



Primary endpoint (mNIS+7) - Components

Composite included physical exam, rating scales, electrodiagnostic and autonomic testing

- QST (Quantitative Sensory Testing)
- HRDB (Heart Rate Deep Breathing)
- NIS (Neuropathy Impairment Score)
- LLF (Lower Limb Function test)
- NSC (Neuropathy Symptoms and Change Score)
- EMG/NCS (Electromyography and Nerve Conduction study)
- NIS (Neuropathy Impairment score)

CHALLENGE	MITIGATION	OPPORTUNITY
Previous study required 24 sites for 172 patients, whereas the current study needed 70 sites	Central Assessing Model Some sites were asked to send their patients to a geographically central site for consistency of evaluations	Modified central-rating paradigm
mNIS+7 training was a gating factor in site activation and patient enrollment	4-hour training video created with assessments to assess comprehension	Conversion of physician-rated and patient-reported outcomes to digital scales
Quality and oversight	Biweekly meetings with central raters, site staff and sponsors	Iterative peer-to-peer learning and risk mitigation
	Additional mitigations for the study	
Site closures from lockdown	Screening period and visit windows lengthened	Adoption of more patient-centric protocols
Confinement and COVID-19 exposure risk	Remote ICF administration adopted per locally acceptable methods	Adoption of more patient-centric protocols
Confinement	Use of home health services and telehealth to reduce mandatory in-clinic visits	Adoption of more patient-centric protocols

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Disclosures:
David P. Walling, Ph.D.
Grant/Research Support Disclosures

Novartis, J&J PRD, Sunovion, Janssen, Abbvie, Acadia, Alkermes, Allergan, Cerevel, Takeda, Otsuka, Noven, Indivior, IntraCellular, Lupin, Lyndra, Avanir, Lundbeck, Roche, SyneuRx, Sirtsei, Boehringer Ingelheim, Biogen

Consultant: Otsuka, Janssen, Boehringer Ingelheim, Biogen, Lyndra

COVID-19: A Site Perspective

- March 2020
  - Along with rest of country, California put on lock-down except for “essential businesses”
    - Both Healthcare and Pharmaceutical Industry were considered essential
  - Ongoing studies were placed on hold by a majority of large sponsors
    - Many small to medium sponsors kept studies enrolling
  - Communication became disjointed

Case Example: Unnamed Sponsor

- When Covid lockdowns began, sponsor alerted sites to screen fail subjects in screening for a difficult study
- Sites were also told to not have subjects come in for in-person visits
- Surveys were sent to sites asking about their current COVID situation – however, limited feedback provided back to sites
- Little guidance provided to sites for extended periods of time (by COVID standards)
- Re-start of studies with a “go now” approach

What Worked During COVID

- Implementation of safety strategies at the site level
  - Temperature checks for all staff, subjects and visitors
  - Use of PPE by all individuals in the facility
  - Limiting in-patient subjects to one subject per room
  - Limiting monitors to one per room or two per conference room
  - Ongoing testing of staff and all in-patient subjects

What Worked During COVID on the Sponsor Side

- A number of small to medium sized sponsors continued to run studies during the COVID lockdowns
  - Frequent communication between the sponsors and sites
  - Safety protocols required by sites continuing the studies
  - Tracking of ICU/Hospital bed capacities
  - Understanding if enrollment slowed down due to COVID related issues

What Did Not Work During COVID

- Some sponsors and CRO’s went radio silent with sites
- Guidance was often issued without consulting sites
- Went from a “we are your partner model” to a more directive approach

COVID-19 and Apex Response

- Our Policy and Procedures on managing COVID-19 risks are available online or by request.
  COVID-19 Policies and Procedures

- We have access to and utilize COVID-19 nasal swab and blood testing for all subjects.

- **We continue to operate and enroll healthy volunteers and patients into a variety of on the unit and outpatient studies.** If you have additional questions or concerns, please let us know.

- We have also been tracking our local hospitals' capacities to ensure that they are prepared to accept an EMS transfer for an SAE or Severe AE. Both in the New Jersey area surrounding our unit (HRI-Marlton) and in Los Angeles (CNS-Long Beach) they have ample beds and services.

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- Subgroup coordinators
  - Mental Health – Gerry Dawson (gdawson@p1vital.com)
  - Dementia/ Neurodegenerative disease - Dragana Bugarski-Kirola (dbugarski-kirola@ACADIA-Pharm.com)
  - Rare Disease/Pediatrics - Kemi Olugemo (kolugemo@ionisph.com)