



Response Evaluation In Neurofibromatosis Schwannomatosis INTERNATIONAL COLLABORATION

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Assessing functional endpoints for NF1 and SWN in decentralized trials

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December 4, 2023



Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Current REiNS Functional Evaluation Recommendations

Functional Outcome	Primary Endpoint	Secondary Endpoint(s)
Hearing	Maximum word recognition score	Pure-tone average
Facial Function	Scaled measurement of improvement in lip excursion analysis (SMILE)	House-Brackmann Scale
Muscle Strength	Handheld dynamometry	
Visual Function	Visual Acuity with Teller Acuity Cards	HOTV (age appropriate) Degree of optic disc pallor Visual quality of life using the Children's Visual Function Questionnaire
Pulmonary Function	Extrathoracic/upper airway lesions (using oscillometry) Airway resistance at 10 Hz (R10) Intrathoracic/peripheral airway lesions (using spirometry) Forced expiratory volume in 1 sec (FEV ₁) or 0.75 sec (FEV _{0.75}) for preschool children	Extrathoracic/upper airway lesions (using oscillometry) <ul style="list-style-type: none"> Airway resistance at 5 or 20 Hz Airway reactance at resonant frequency Airway reactance at 5, 10, and 20 Hz Intrathoracic/peripheral airway lesions (using spirometry) <ul style="list-style-type: none"> Forced vital capacity (FVC) Peak expiratory flow (PEF) Forced expiratory flows
Sleep	Apnea Hypopnea Index (AHI)	<ul style="list-style-type: none"> Oxygen saturation and hypercapnia during sleep End-tidal CO₂ Arousal index

Hearing Remote Evaluations:

- Remote "Maximum Word Recognition Score" Option:
 - "Digits in Noise" tests – ability to identify digits when spoken over background noise; identifies a "speech recognition threshold" where 50% of digits accurately recognized
 - Multiple platforms available, including WHO "hearWHO" app
 - Advantages: Quick to conduct, does not require device/headphone calibration
 - Limitations: Currently used as a screening test only
- Remote "Pure Tone Averages" Option:
 - Multiple platforms available
 - Advantages: Results provided appear similar to formal audiogram
 - Limitation: Requires calibration and sensitive to environmental noises

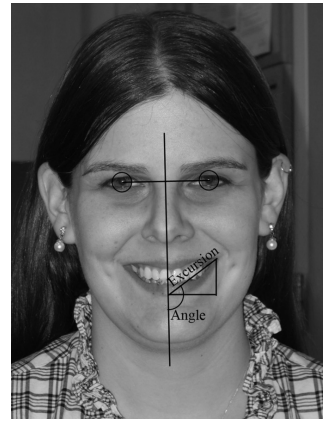


Download the app

(De Sousa 2021)

Facial Function Remote Options

- Scaled measurement of improvement in lip excursion analysis (SMILE)
 - Current analysis based on photographs which could potentially be done remotely
- Remote measurements being explored primarily for facial reanimation surgeries
 - Multiple computerized and machine learning approaches
- Fuzi et al developed a “SmileCheck” mobile app with excellent validity compared to manual methods (kappa 0.861) and good test re-test reliability (kappa 0.864)



(Fuzi 2023, Plotkin 2013)

Muscle Strength/Motor Remote Options



- Hand-held dynamometer needs to be administered by a trained provider
- Variety of wearable devices/activity trackers available
 - Advantages:
 - Ease of use
 - Get “real world” data over an extended period of time
 - Challenges:
 - Privacy concerns
 - Device cost and technical issues (e.g. battery life)
 - Large volume of data to be interpreted

Table 1 Examples of wearable sensors

Device type	Data collected	Examples
Wrist worn	Actigraphy, HR (Heart Rate), BP (Blood Pressure), EDA (Electrodermal activity)	Actiwatch Spectrum by Phillips, ActiGraph Link by ActiGraph, E4 by Empatica, ViSi Mobile by Sotera Wireless
Skin patch	ECG (Electrocardiography), actigraphy, skin temperature	BioStampRC by MC10, HealthPatch by Vital Connect, BodyGuardian by Preventice
Cuffs	BP, HR	Intellisense Digital BP Monitor by Omron Healthcare
Finger worn	HR, SpO2	iSpO2 Pulse Oximeter by Massimo
Clothing embedded sensors	HR, HRV (Heart Rate Variability), ECG, Breathing Rate, actigraphy	Smart shirts by Hexoskin
Headbands	EEG (Electroencephalogram), EMG (Electromyography)	EMOTIV EPOC by Emotiv, 4D FORCE by 4D FORCE

(Izmailova 2018)

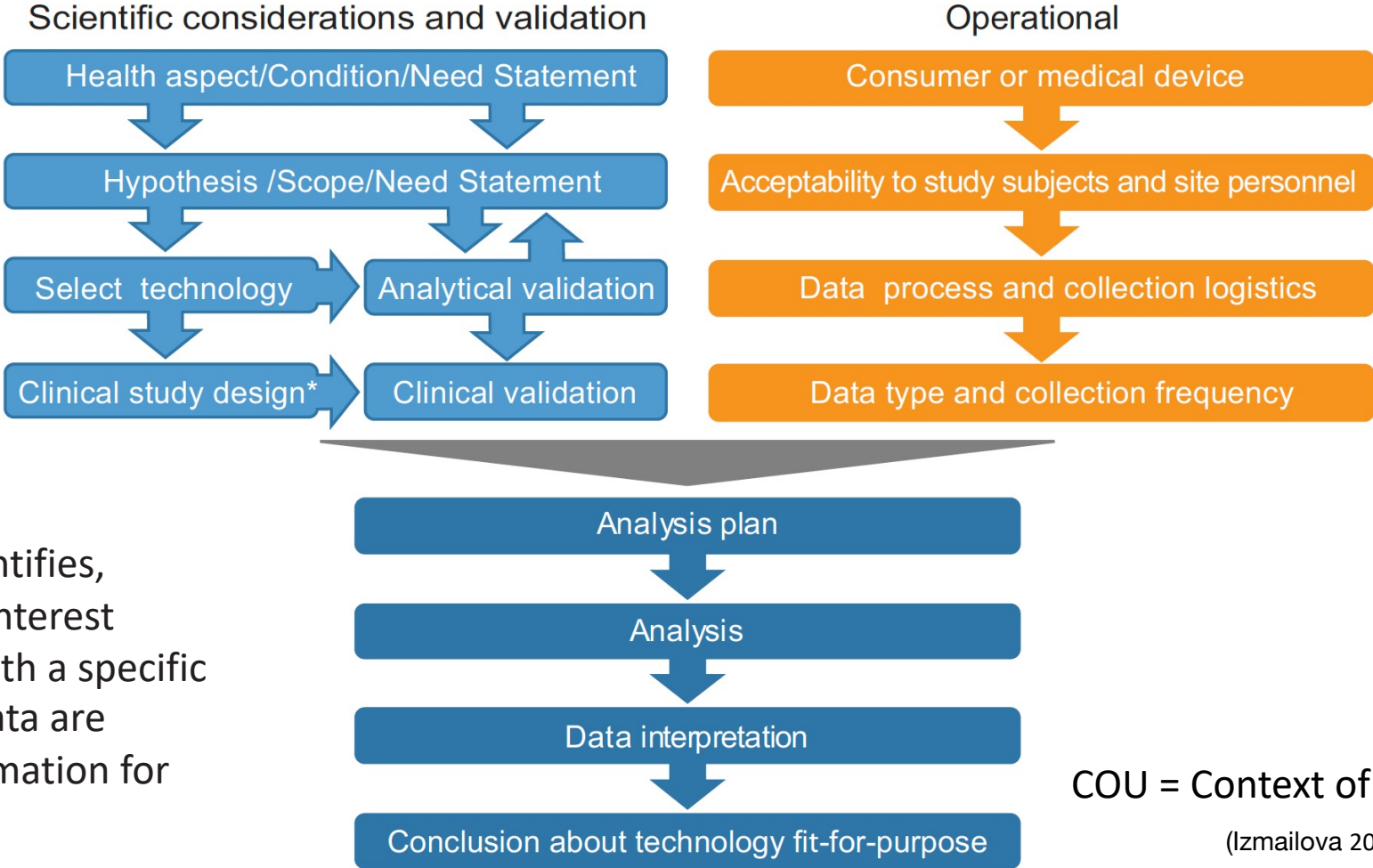
Wearable Devices & Clinical Trials

Analytical Validation:

- Establishes if device performance characteristics are acceptable by comparing device performance to a traditional tool for collecting the data or another device with well-established performance

Clinical Validation:

- Establishes that device acceptably identifies, measures, or predicts the concept of interest
- Includes establishing an association with a specific disease condition to make sure that data are interpretable and provide useful information for patient care management



COU = Context of use
(Izmailova 2018)

* Appropriate for COU and intended study population



Visual Acuity Remote Evaluation Options

- Multiple mobile apps and remote visual acuity assessments have been developed
- 2023 Systematic Review by Thirunavukarasu et al.
 - 3 apps DigiVis, iSight Professional or Peek Acuity were found to be comparable to clinic assessment

Stay tuned for a great talk about this from Dr. Avery!!

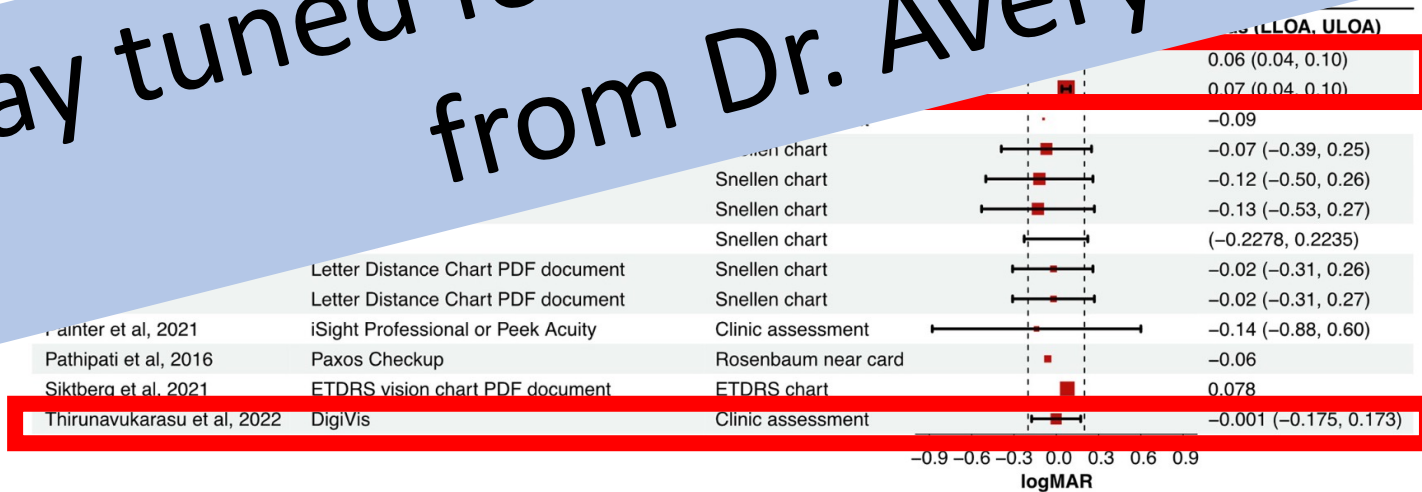


Fig 3. Forest plot summarising Bland-Altman analyses of accuracy. LLOA = lower 95% limit of agreement; ULOA = upper 95% limit of agreement; PDF = portable document format; ETDRS = Early Treatment of Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution.

(Thirunavukarasu 2023)



Sleep and Pulmonary Function Remote Options

- Polysomnography

- Variety of devices available for home testing – not as comprehensive as testing in a sleep lab (= Type 1 PSG)
- AHI can be measured at home
 - More sensitive with increased severity of Obstructive Sleep Apnea

- Pulmonary Function:

- Liao 2021 – Used remote PFT monitoring for patients after rib fracture; was feasible and showed improved outcomes in those who were compliant



(Liao 2021)

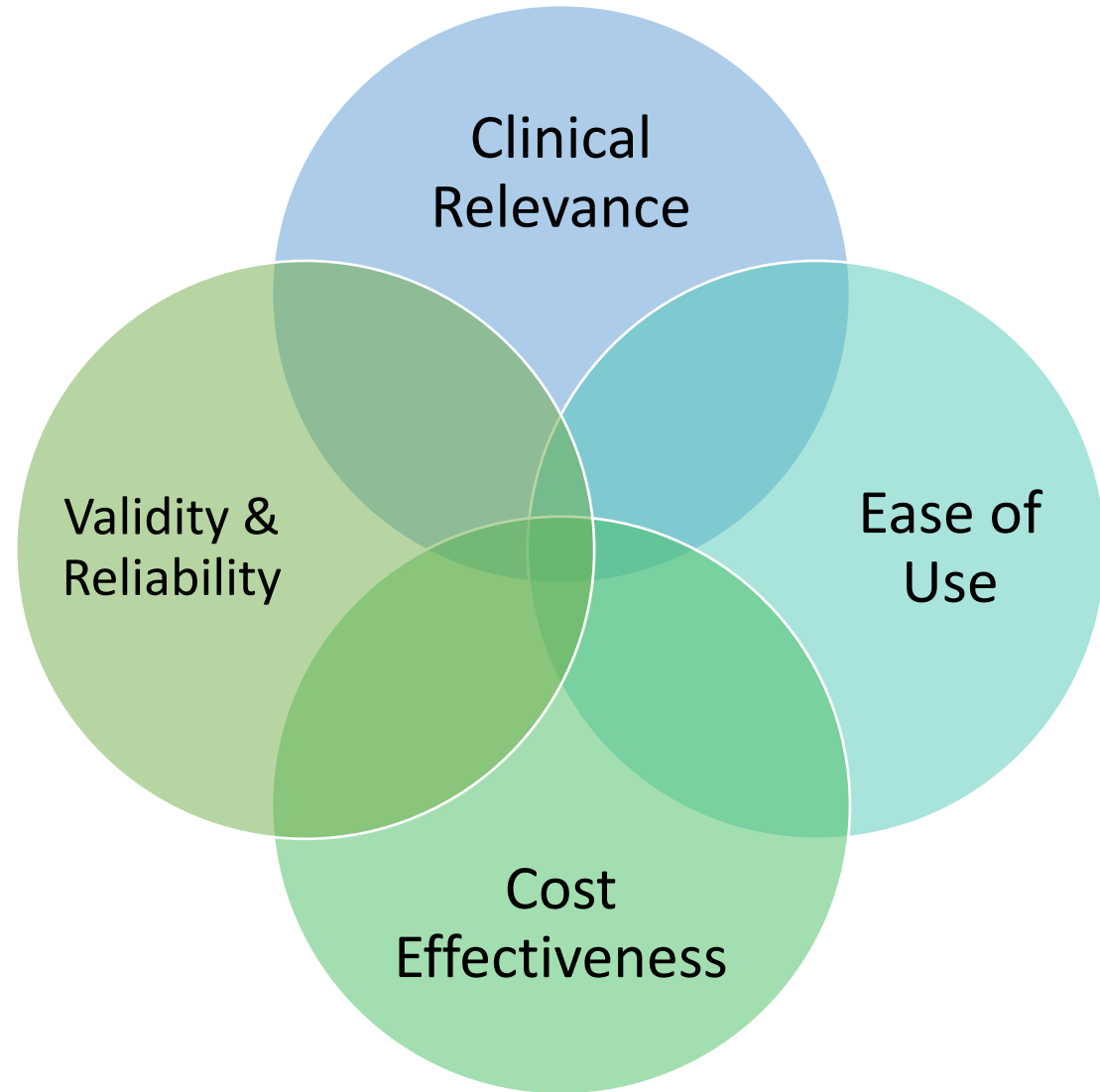
Costs?

- Likely significant costs associated with wearable/remote devices
- HOWEVER may overall be less expensive than in-hospital assessments (e.g. sleep study)
- Increased volume of data for analysis



What other remote endpoints would you like to have?

- In a perfect world, what would be possible in a decentralized trial?
 - LOTS of options – current challenge/gap is determining which of the assessments to use



Functional Group Proposed Next Steps

- Prioritize which functional endpoint most amenable/needed for upcoming clinical trials
- Consider systematically reviewing remote options for specific functional outcomes as part of “revisit” of prior REiNS recommendations?



THANK YOU to the REiNS FUNCTIONAL GROUP!!

- Andres Lessing
- Beverly Oberlander
- Brigitte Widemann
- Brittany Simpson
- Dave Viskochil
- David Stevenson
- Gareth Evans
- Heather Thompson
- Herb Sarnoff
- Jonathan Rios
- Kaleb Yohay
- Kelly Carpenter
- Laura Klesse
- Michael Fisher
- Miranda McManus
- Nicole Ullrich
- Noelle A Larson
- Renie Moss
- Scott Plotkin
- Srivandana Akshintala

...and more!!



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