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Assessing Patient-Reported Outcomes (PROs) in Decentralized Trials

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National Cancer Institute

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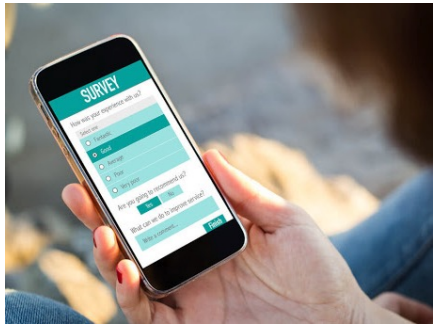
Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Is it time for remote PROs in NF clinical trials?

- FDA supports using PROs to document clinical benefit of treatment for regulatory approval
  - Endorses electronic capture of clinical trial source data over paper methods (FDA, 2009, 2013)
- Increasing availability of technologies to collect PRO data remotely
  - Use of bring your own devices (BYOD) in trials
- Validated electronic PROs (ePROs) are equivalent to paper (Griffiths-Jones et al., 2014)
- More accurate data with ePRO measures vs. paper (Stone et al., 2002; Ganser et al., 2010)
  - Higher compliance with expected completion times
  - Better integrity of data (less missing data and errors)
- More valid assessment of symptoms collected in real-time in the home environment (e.g., pain)
- ePROs currently are being conducted in NF trials



Is it time for remote PROs in NF clinical trials?

- Support for remote ePROs from qualitative studies
  - 65% of adults with NF1, NF2-related SWN, and SWN have smartphones (Wolters et al., 2023)
  - Most children/adolescents have a smartphone or access to WiFi-enabled devices
  - Majority of participants with NF preferred or were willing to complete the PRO measures electronically from home for a clinical trial
  - Important to have options (web-based or mobile platforms) for participants

I would like electronic.

A pain app would be really neat.

I would be willing to do that if I was on a trial.

I don't want an app for that on my phone.

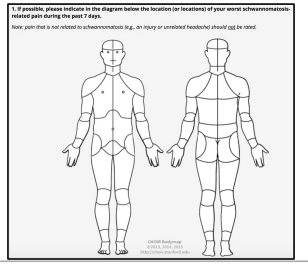
Medical trials with remote ePROs

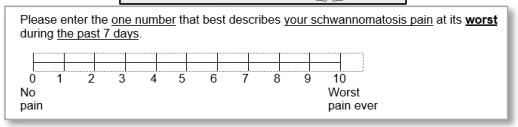
- Hybrid trial design
  - Worldwide randomized placebo-controlled Pfizer and BioNTech mRNA COVID-19 vaccine phase 2/3 trial (Polack et al., 2020)
    - In person: Vaccine or placebo injections
    - Remote: Primary outcomes of adverse events and pain/fever medication using ePRO diaries
      - Participants used own devices (79%) and provisioned smartphones (21%)
      - BYOD ePRO data used for regulatory approval and labeling claims

- Fully decentralized trial design
  - RCT to evaluate a treatment for heart failure (Spertus et al., 2021)
    - Primary outcome: Kansas City Cardiomyopathy Scale symptom score
    - All procedures done remotely: electronic informed consent; home delivery of study medication; completion of ePROs using a mobile app

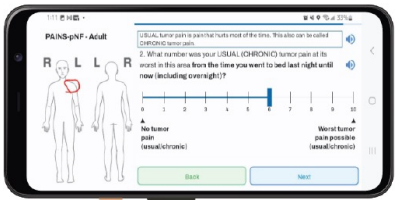
NF/SWN medical trials with remote ePROs

- Hybrid trial design
  - Phase 2 RCT evaluating effect of tanezumab (inhibits nerve growth factor) on pain in adults with SWN (PI: Plotkin)
    - In person: Injections of tanezumab or placebo and secondary PRO measures
    - Remote: Primary ePRO assessments of NRS-11 pain intensity and pain location by REDcap from home



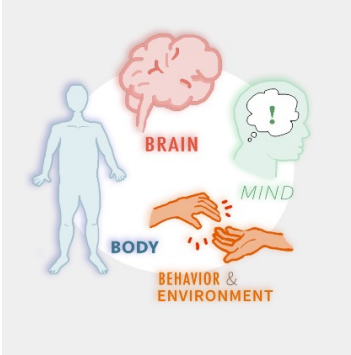


  - Randomized, placebo-controlled, phase III clinical trial to evaluate selumetinib for plexiform neurofibromas in adults (PI: Coyne)
    - In person: volumetric MRI of pNF and secondary PROs
    - Remote: daily administration of ePRO pain measure of pain intensity (PAINS-pNF) at home (key secondary)

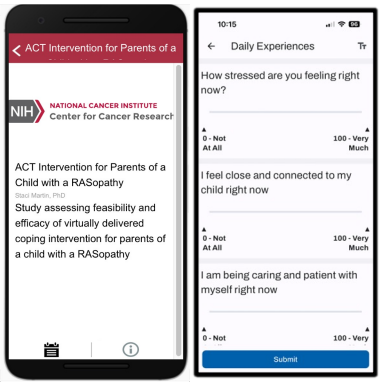


NF psychosocial trials with remote ePROs

- Fully decentralized trial design
  - RCT of mind-body skills training on quality of life for adults with NF (Vranceanu et al., 2023)
    - 8 virtual group training sessions
    - Primary outcomes: Physical health and psychological domains of the WHO QOL
    - ePRO assessments: Administered remotely via REDCap (sent 3 times with 1 call)
    - 80-85% PROs completed remotely at the 12-month evaluations



  - RCT to evaluate an ACT coping intervention for parents of a child with a RASopathy, including NF1 (PI: Martin)
    - 4 videochat ACT intervention sessions
    - Primary outcome: Parenting Stress Scale
    - ePRO measures completed using a mobile app
    - Ecologic Momentary Assessment: Brief set of items sent automatically 5 days/week



Remote ePROs currently are being implemented successfully in clinical trials including studies aiming for regulatory approval

Unique challenges for remote ePROs in NF trials

- Concerns from sponsors regarding use of patient's own devices (BYOD)
  - Limited trials with ePRO data using BYOD supporting product approval and labeling
  - Specifics of remote ePRO administration not well described in publications or labeling claims (Mowlem et al., 2022)
  - Potential security and privacy issues of collected data
- Adaptation of paper-based PRO measure to electronic
  - No substantial changes to measure content should be made (Gwaltney, et al., 2008)
- Sources of variability of PRO measures administered remotely
  - Learning disabilities and reading difficulties
  - Assessing children (assistance by parents)
- Resources
  - Personnel dedicated to managing ePROs
  - Devices, technology, and systems for conducting automated ePROs
- Cost of systems for remote ePRO data collection

Consideration of resources and costs

- Mobile technologies: reduce costs (6% - 14%) and improve efficiency/accuracy of trial data. Higher upfront costs can have downstream savings (Sertkaya , 2016)
- Research staff support: Fewer dedicated staff are needed with more advanced ePRO data collection of systems
- Remote ePRO systems and products (comparison example):
  - **REDcap:** secure web application for building and managing online surveys and databases for research
    - Institution provides infrastructure, staffing, tech support and develops measures
    - NCI cannot use REDcap as terms of service was not acceptable by a federal agency
  - **Digital health companies:** Provide mobile and web applications for surveys, infrastructure, staffing, tech support, and security measures (licensing for study approx. $5-10,000/year)

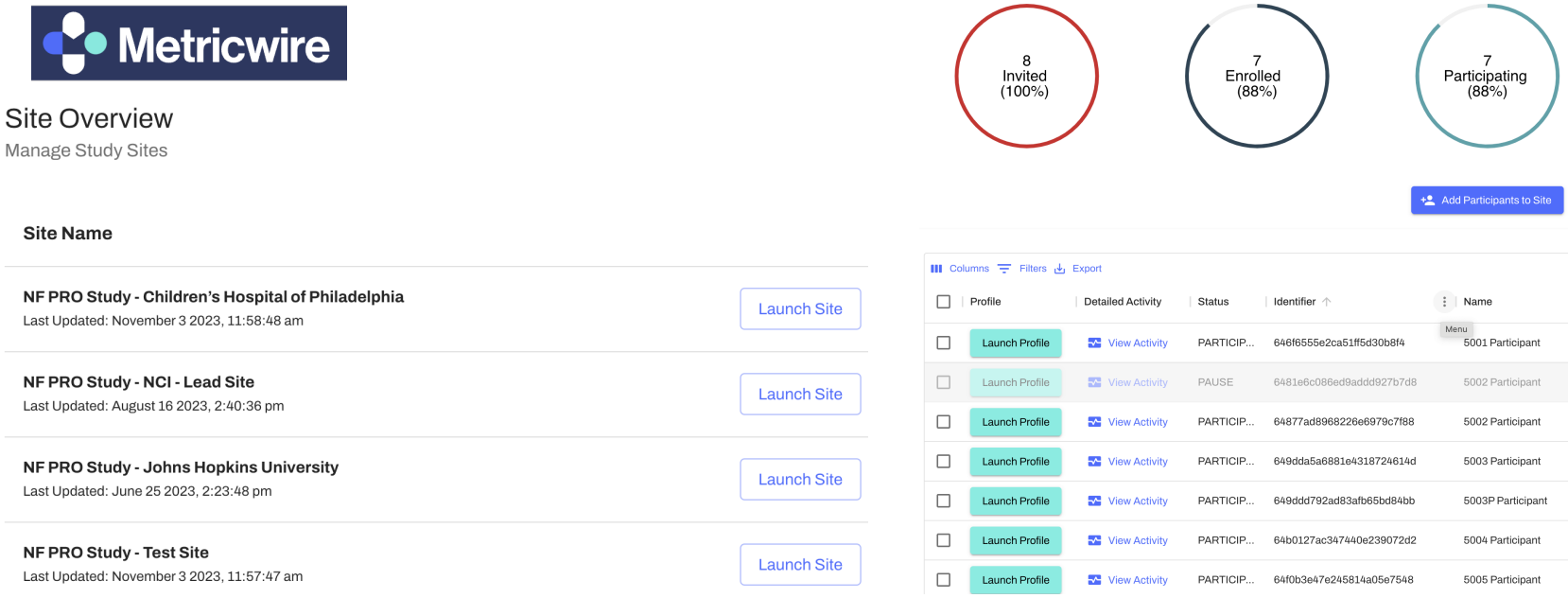
Solutions for using remote ePROs in NF trials

- Various user-friendly options for devices, technologies, and systems for remote ePROs
  - BYOD (computers, smartphones, tablets) and/or provide devices
  - REDcap/Scribe/Mobile app systems
  - No need for Personal Identifiable Information in these systems
- Provide details of ePRO administration in publications and product labeling claims to support reliability/validity of using BYOD
- Collaboration between study team, ePRO system provider, and patient representatives
- Follow recommendations for ePRO measure development and implementation (C-Path Institute website)
  - Use voice (text to speech) instructions for patients with reading difficulties
  - Send automatic notifications/reminders to complete ePRO measures
  - Have back up plan if device cannot be used (e.g., phone call, website)
  - Training of staff and study participants in ePRO technology and measures
  - Build relationships and open communication with study participants
- Explore funding from grants, foundations, and pharmaceutical companies

Remote ePRO measures ready for NF trials

- BYOD
  - High percentage of participants have devices (smartphone/tablet/computer)
  - May need devices for participants who do not have their own
- Measures ready for remote administration
  - All REiNS recommended PRO measures suitable for remote assessment
  - PROMIS measures (short forms and computerized adaptive testing)
  - PedsQL generic and disease-specific QOL scales
  - PAINS-pNF and PII-pNF: new measures to assess pNF-related pain intensity and pain interference
  - Other measures can be developed in ePRO format using recommended strategies

ePRO mobile app example (PAINS-pNF & PII-pNF)



- *Mobile app and web-based platforms for multi-site trials; ePRO measures programmed to send at specific dates/times, with notifications, reminders, & rewards; no PII needed*

ePRO mobile app example (PAINS-pNF & PII-pNF)

Metricwire

Age Group

Select the adult, pediatric, parent or pediatric + parent version as applicable.

- Adult ≥18 years
- Pediatric 8-17 years
- Parents or Caregiver of pediatric patients 8-17 years
- Pediatric 8-17 years AND Parent or Caregiver using the SAME MOBILE DEVICE

PAINS-pNF Start Date for Adult Participant

This is the first DATE the adult participant will begin receiving the PAINS-pNF and PII-pNF

Select a date: 11/13/2023

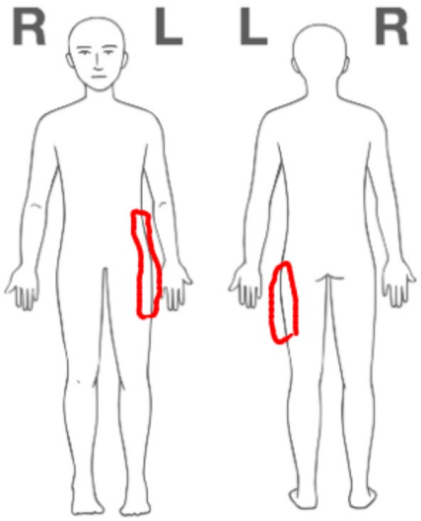
PAINS-pNF Preferred Time for Adult Participant

This is the TIME the pediatric participant will begin receiving the PAINS-pNF and PII-pNF on a given day.

Select a time: 08:00 PM

Adult Tumor Image Annotation

Please circle the location of the patient's tumor.



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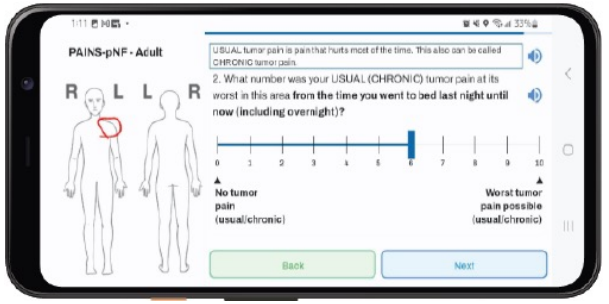

- *Mobile app and web-based platforms for multi-site trials; ePRO measures programmed to send at specific dates/times, with notifications, reminders, & rewards; no PII needed*

Next steps

- Start with one trial with few measures and only adult participants (patients or parents)
- Start with a currently available system in a single site trial or one NFCTC trial
- Meetings with researchers and patient representatives to develop feasible remote ePRO assessment guidelines (e.g., length, frequency, concerns)
- Consider various funding sources to help pay for remote ePRO administration systems and devices

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