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Assessing cutaneous neurofibromas in decentralized trials

Kavita Sarin, MD PhD, on behalf of the CNF Working Group

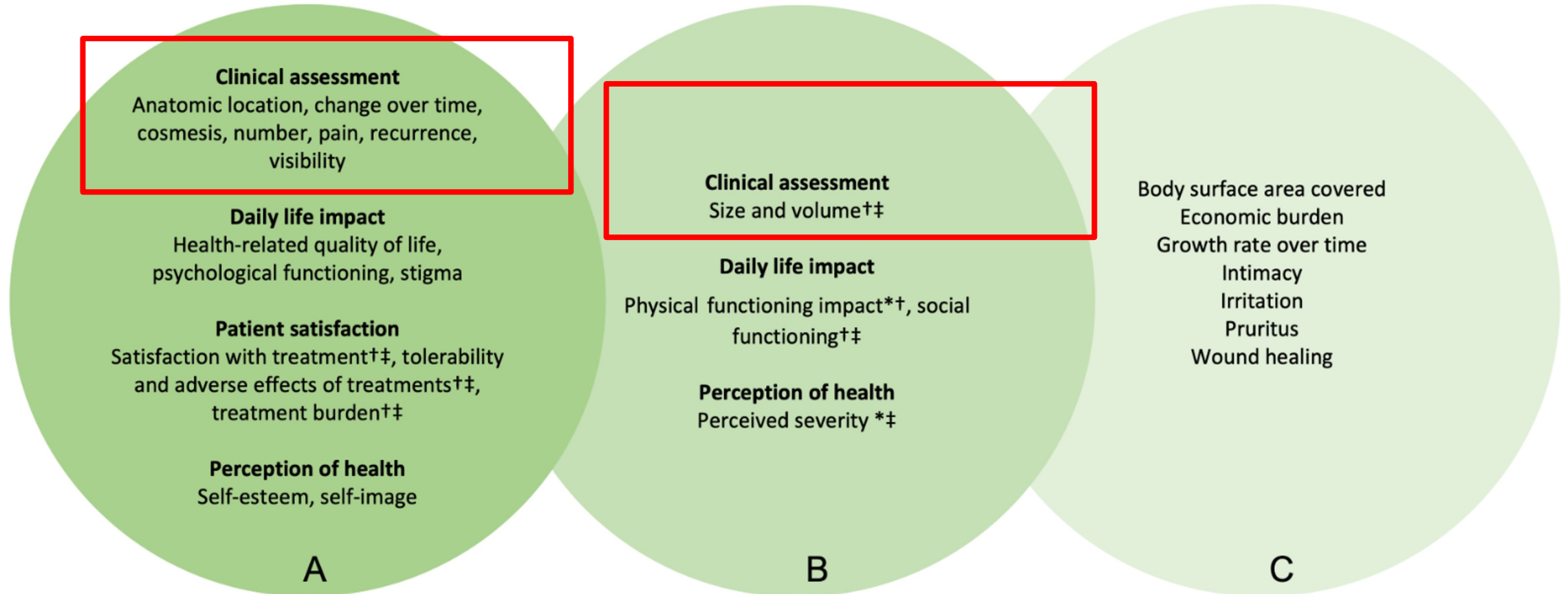Stanford University

December 3, 2023

Unique characteristics of cNFs for decentralized trials

- Three dimensional objects
- Different subtypes with variation in shape, compressibility and depth
- May have ill-defined borders
- Large range in numbers, color, and distribution
- Skin is very personal
- Location matters: cNFs can be in visible and sensitive areas
- Pain/sensitivity is variable
- Not static/ appearance and size can evolve change with time

- No validated measurement tools for cNFs in clinical trials
- Decentralized clinical trials in skin have not been used in pivotal trials for FDA approval

DermNetNZ.org

Core Domain Outcomes

Clinical assessment
Anatomic location, change over time, cosmesis, number, pain, recurrence, visibility

Daily life impact
Health-related quality of life, psychological functioning, stigma

Patient satisfaction
Satisfaction with treatment†‡, tolerability and adverse effects of treatments†‡, treatment burden†‡

Perception of health
Self-esteem, self-image

A

Clinical assessment
Size and volume†‡

Daily life impact
Physical functioning impact*†, social functioning†‡

Perception of health
Perceived severity *‡

B

Body surface area covered
Economic burden
Growth rate over time
Intimacy
Irritation
Pruritus
Wound healing

C

Clinical Assessment

- Individual features of cNFS: volume height, area, diameter, subtype change over time

- Global features of cNFS: number, distribution, change over time, global assessment of severity

- Cutaneous adverse effect of treatment (i.e. rash, erythema, ulceration, dermatitis)
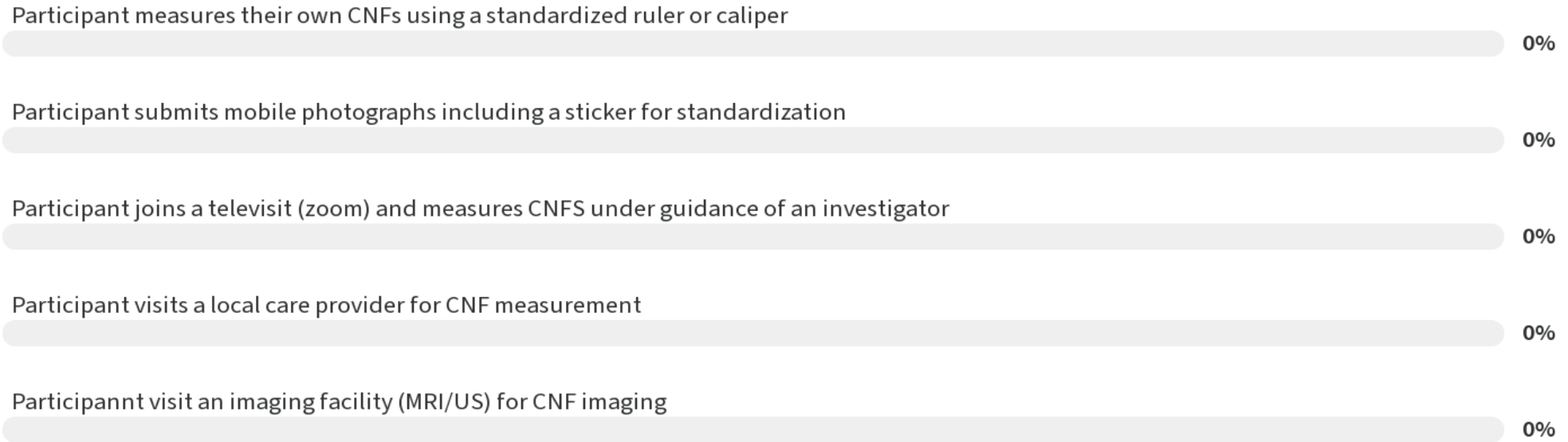
Methods of remote evaluation of cNFs

- Patient self measurements (sending calipers/rulers)

- Photographs based measurements

- Televisit measurements

- Visiting a local care provider for measurements / visibility scale

- Imaging based methods: ultrasound/ MRI

Measurement tradeoffs *examples

Method	Pro	Con
Self-measurement	Can be conducted at home Can measure all 3 dimensions	Participants may measure differently Requires training and may be more difficult to standardize
Photographs	Can be conducted at home Measurements can be done centrally Allows confirmation	Variable quality Some may feel uncomfortable Height measurement is difficult
Televisit	May help guide either self-measurement or self-photography	Time consuming
Local care provider	Can help with areas hard to measure. May be more appealing to participants	Feasibility: unclear if each site would need an IRB, Interrater and intersite variability
Imaging	Measures depth below skin	Costly, time consuming, unclear if accuracy is better than other measures Models may very across sites

Which method of CNF measurement do you think will be most accurate?

Which method of decentralized CNF measurement do you prefer?

Participant measures their own CNFs using a standardized ruler or caliper

0%

Participant submits mobile photographs including a sticker for standardization

0%

Participant joins a televisit (zoom) and measures CNFS under guidance of an investigator

0%

Participant visits a local care provider for CNF measurement

0%

Participannt visit an imaging facility (MRI/US) for CNF imaging

0%

Adverse Effects Assessments:
Common Terminology Criteria for Adverse Events (CTCAE)

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death

Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.
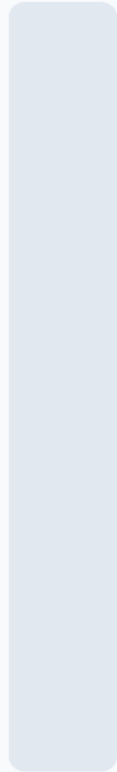
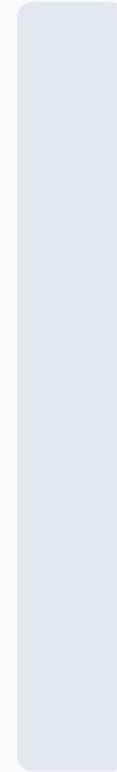# Do you think Adverse Effects could be evaluated removely

0%
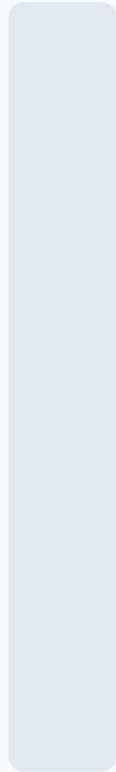
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Yes

No

Maybe

Can measurements of tumor height, area or volume be reliably obtained through photographs ?
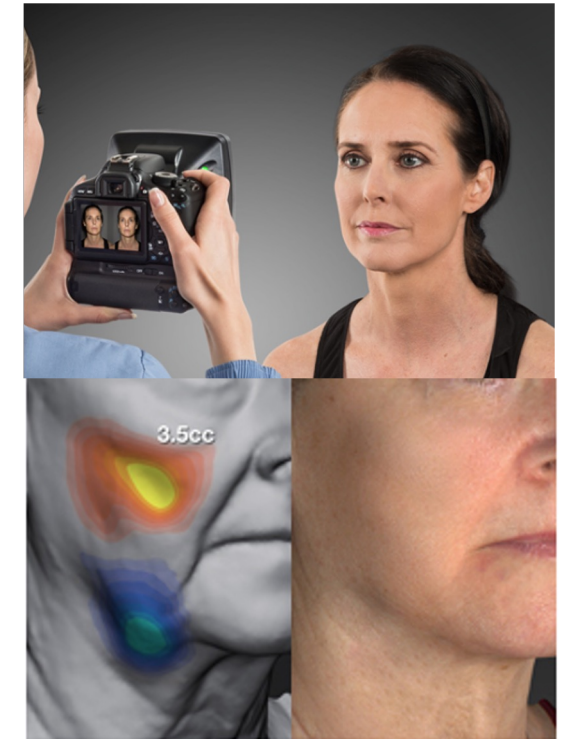

mobile   2D Full body   3D Full body   3D regional

Current studies with remote photographic evaluation of cNFs

- NF1 Genetic Study Cohort 5000 self-obtained photographs from 675 participants
  - 50 participants submitted both mobile photos (7 body sites) and also had in clinic full body photography
  - Drs. Sarin and Romo rated # of cNFS 1-10, 11-100, 101-500, > 500.
  - Number of cNFs had high agreement between mobile and clinic photos:
    - Kappa = 0.74 for, 1 within 1 level

- CNF Consortium Australian PI International recruitment: Patient photography and GWAS from saliva. 470 recruited but aiming for 2000. Working on AI to analyze photography from 3 body areas to determine cNF severity.

- French & Australian CNF outcome measure study: exploring 2D and 3D photographs for assessment of cNF response after procedures. 55 patients across 3 timepoints. Photography pre and post treatment. Challenges inherent in photographic series comparing appearance requires consistent photography.
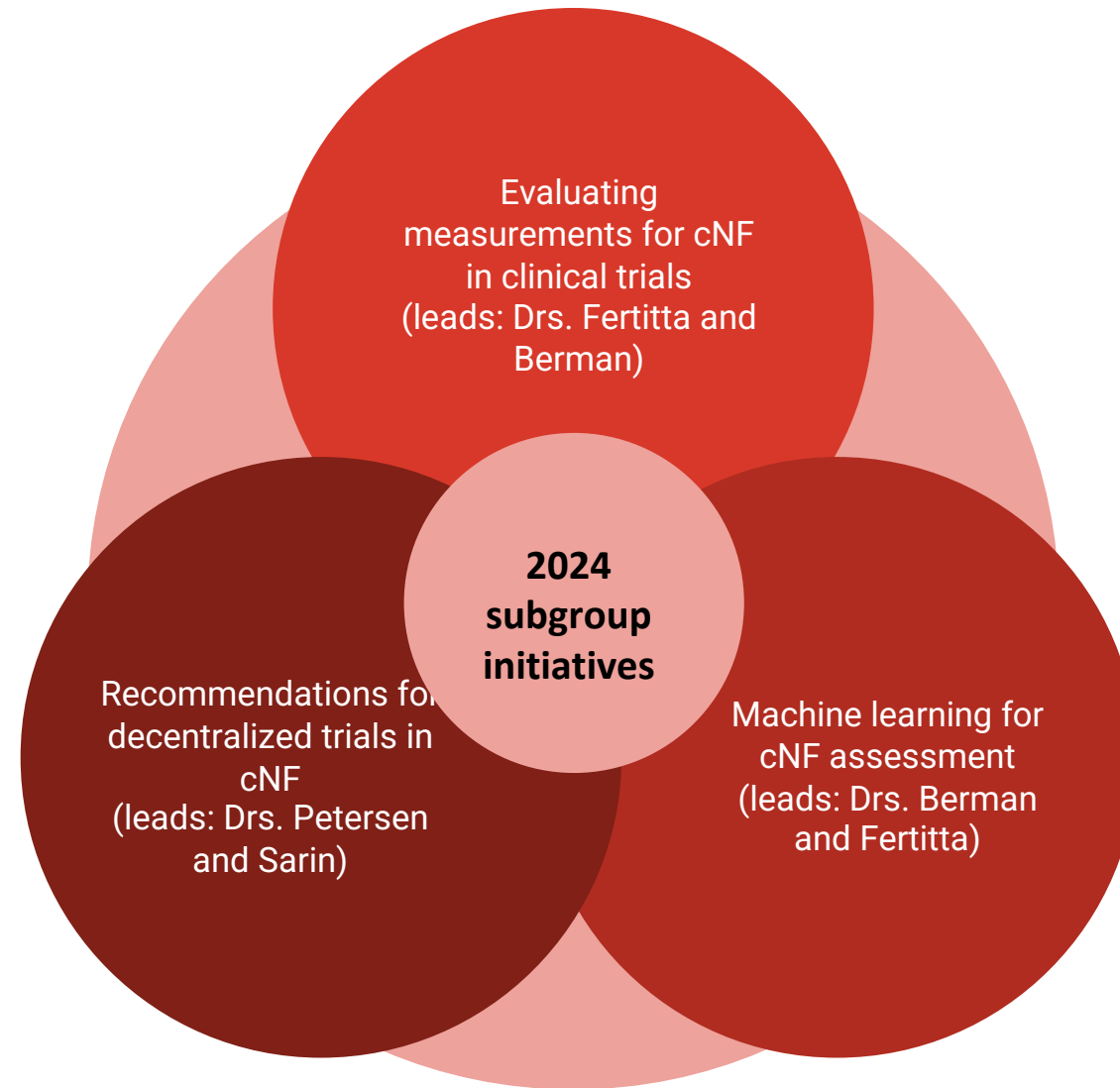
GAPS in implementing decentralized trials for cNFs

- No validated measurements for CNFS in clinical trials

- Lack of studies comparing accuracy of remote measurement methods

- Variability in Mobile photographs

Next Steps

Evaluating measurements for cNF in clinical trials
(leads: Drs. Fertitta and Berman)

Recommendations for decentralized trials in cNF
(leads: Drs. Petersen and Sarin)

2024 subgroup initiatives

Machine learning for cNF assessment
(leads: Drs. Berman and Fertitta)

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