

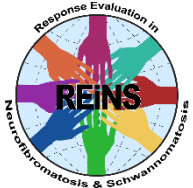
Response Evaluation In Neurofibromatosis Schwannomatosis INTERNATIONAL COLLABORATION

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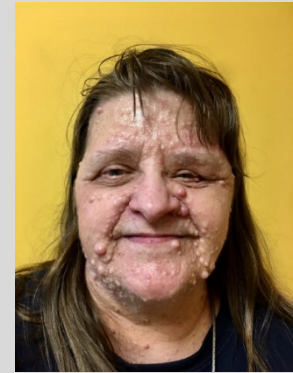
Assessing established PROs for cNFs: are these scales adequate for clinical trials?

Dominique C. Pichard, MD
on behalf of the cNF Working Group
September 22, 2019



Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

- cNFs affect more than 99% of adults with NF1
- No malignant potential but have significant negative effects on quality of life
- Current treatment is limited to surgical and destructive methods
- No validated tools to assess improvement on quality of life after treatment of cNFs

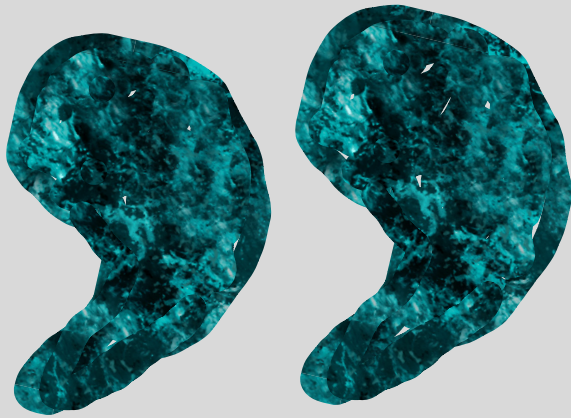


Patient-centered cNF research



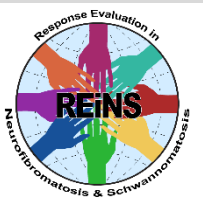
Lack of data concerning how patients assess morbidity related to cNFs and how they view current and potential cNF treatments

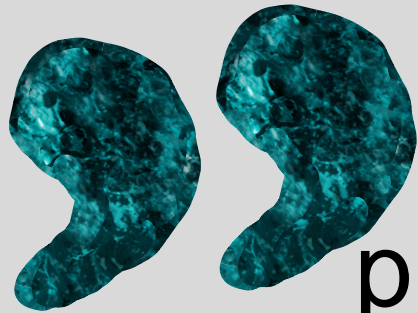




The patient-focused drug development meetings conducted to date have given FDA a deeper appreciation for the expertise that patients and caregivers can bring to the process and the value of incorporating their voice.

FDA Draft Guidance: Patient-focused drug development. June 2018.





A PRO instrument, like physician-based instruments, should be shown to measure the concept it is intended to measure, and the FDA will review the evidence that a particular PRO instrument measures the concept claimed”.



FDA Guidance: PRO Measures – Use in medical product development to support labeling claims. 2009

Process

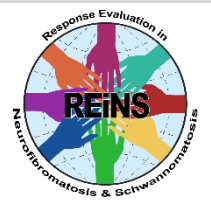


Review the literature for existing PROs that are specific for assessing the skin



1

- Review of the literature:
Skin specific PRO
instruments identified
 - Skindex & teen-skindex
 - Dermatology life quality index (DLQI) & CDLQI
 - *Adjusted NF QOL (Hilda Crawford)*
 - *Itch scales*
 - *Pain scales*



2

Rate PROs

Neurofibromatosis Outcomes Rating Acceptance Tool for Endpoints
 for REINS Committee use only

Disease-Specific QOL Pain Functional Disability _____

_____ Date: _____

Supporting its use in neurofibromatosis trials
 Information but needs more work
 Potential

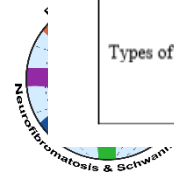
1= Limited
 0= No/poor data/information
 *Half ratings (.5, 1.5, 2.5) can be used if needed

Rating Criteria	Rating (0-3): use in NF trials
1. Patient characteristics: Age range (e.g., child, adolescent, adult) Normative groups (e.g., general, NF, oncology, other, # subjects)	
2. Used in published studies: Number and types of studies (e.g., descriptive, clinical trials)	
3. Domains assessed/Item content: Number/description (e.g., physical, social, emotional, cognitive)	
4. Scores available: Item response format (e.g., Likert scale, visual analog scale) Types of scores (e.g., raw, standardized, domain, total)	

5. Psychometric Data: Reliability (e.g., internal consistency, test/retest) Validity (e.g., construct, discriminative) Factor analysis	
6. Feasibility: Cost Length (number of items) Ease of administration Recall period assessed (e.g., 1 week, 24 hours) Availability in different languages/International use	
Overall Impression for use in NF Clinical Trials (Pros/Cons):	Total (mean):

Level of Acceptance (Committee decision):
 Primary outcome measure
 Secondary outcome measure
 Not acceptable at this time/further information needed (specify)
 Not acceptable (no further review)

Committee notes/comments/additional information needed/plan:



S K I N D E X

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?

	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
2. My skin condition affects how well I sleep	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
3. I worry that my skin condition may be serious	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
4. My skin condition makes it hard to work or do hobbies	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
5. My skin condition affects my social life	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
6. My skin condition makes me feel depressed	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
7. My skin condition burns or stings	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
8. I tend to stay at home because of my skin condition	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
9. I worry about getting scars from my skin condition	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
10. My skin itches	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
11. My skin condition affects how close I can be with those I love	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
12. I am ashamed of my skin condition	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
13. I worry that my skin condition may get worse	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
14. I tend to do things by myself because of my skin condition	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
15. I am angry about my skin condition	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
16. Water bothers my skin condition (bathing, washing hands)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
17. My skin condition makes showing affection difficult	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
18. I worry about side-effects from skin medications / treatments	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
19. My skin is irritated	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
20. My skin condition affects my interactions with others	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅



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S K I N D E X

HOW OFTEN DURING THE PAST 4 WEEK
DO THESE STATEMENTS DESCRIBE YOU?

NEVER RARELY SOMETIMES

- | | NEVER | RARELY | SOMETIMES |
|---|---------------------------------------|---------------------------------------|---------------------------------------|
| 21. I am embarrassed by my skin condition | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 22. My skin condition is a problem for the people I love | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 23. I am frustrated by my skin condition | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 24. My skin is sensitive | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 25. My skin condition affects my desire to be with people | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 26. I am humiliated by my skin condition | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 27. My skin condition bleeds | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 28. I am annoyed by my skin condition | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 29. My skin condition interferes with my sex life | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| 30. My skin condition makes me tired | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |

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Skindex PRO RATE

Overall impression: 2.54/3.0

PROS

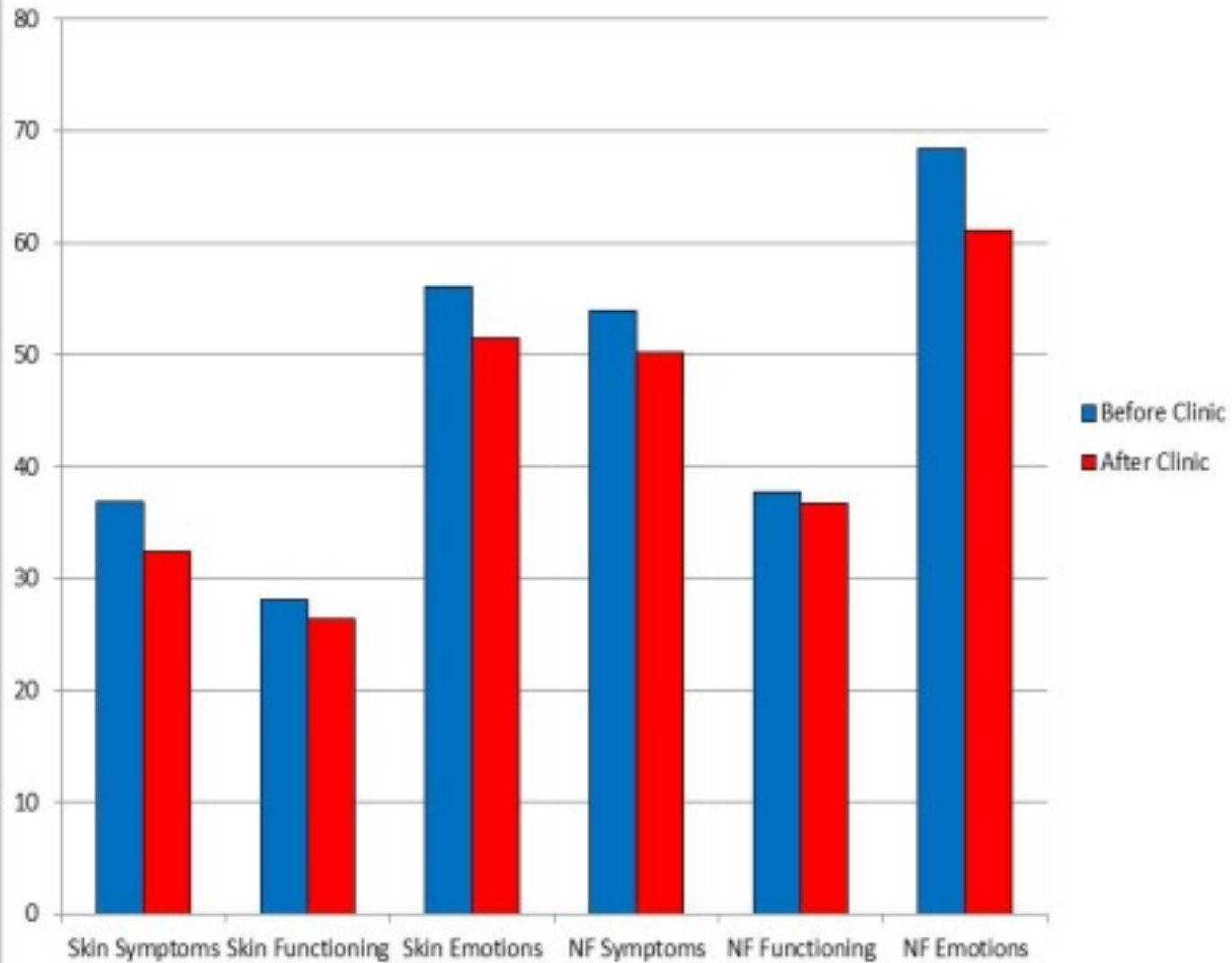
- Ages 12-17, ≥ 18
- Used widely in general dermatology.
- Questions appropriate for cutaneous nerve fiber disorders (cNFs)
- Feasibility

CONS

- No interventional trial data
- Questions not relevant to NF1
- “my skin condition”

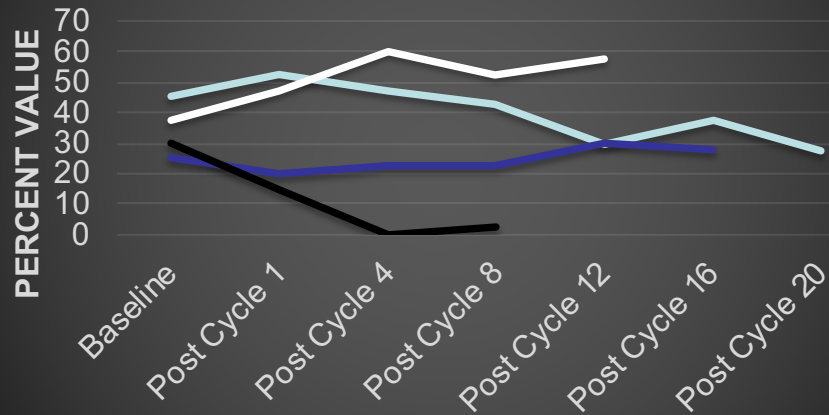


Effect of Treatment on Skin and NF related Symptoms

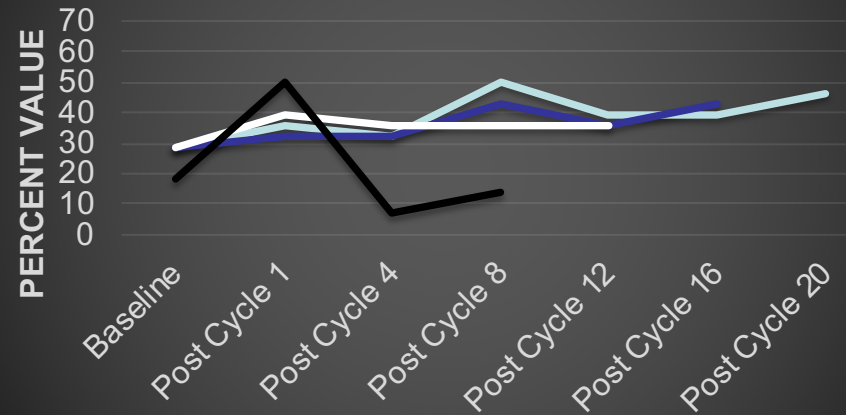


Skindex Scores

Emotion



Symptoms



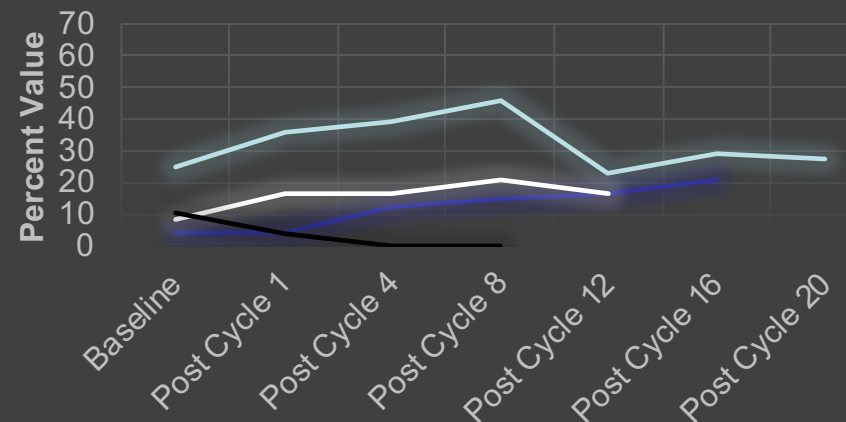
AL002-002

AL002-005

AL002-013

AL002-014

Functioning



D L Q I

- | | | |
|---|-------------------------------------|---------------------------------------|
| 1. Over the last week, how itchy , sore , painful or stinging has your skin been? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | |
| 2. Over the last week, how embarrassed or self conscious have you been because of your skin? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | |
| 3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 4. Over the last week, how much has your skin influenced the clothes you wear? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 5. Over the last week, how much has your skin affected any social or leisure activities? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 6. Over the last week, how much has your skin made it difficult for you to do any sport ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 7. Over the last week, has your skin prevented you from working or studying ? | Yes <input type="checkbox"/> | |
| | No <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| If "No", over the last week how much has your skin been a problem at work or studying ? | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | |
| 8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 9. Over the last week, how much has your skin caused any sexual difficulties ? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |
| | Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time? | Very much <input type="checkbox"/> | |
| | A lot <input type="checkbox"/> | |
| | A little <input type="checkbox"/> | |



Trouble with SKIN

The aim of the questionnaire is to measure how much your skin problem has affected you **OVER THE LAST WEEK**. Please tick ✓ one box for each question.

OVER THE LAST WEEK

Very much

Quite a lot

A little

Not at all



How itchy, 'scratchy', sore or painful has your skin been ?

Very much

Quite a lot

A little

Not at all



How much has your skin affected your friendships?

Very much

Quite a lot

A little

Not at all



How much has your skin trouble affected going out, playing or doing hobbies?

OVER THE LAST WEEK

Very much

Quite a lot

A little

Not at all



How upset or embarrassed, self conscious or sad have you been because of your skin?

Very much

Quite a lot

A little

Not at all



How much have you changed or worn different or special clothes/shoes because of your skin?

Very much

Quite a lot

A little

Not at all



How much have you avoided swimming or other sports because of your skin trouble?

C
D
L
Q
I



(C)DLQI PRO RATE

Overall impression: 2.5/3.0 (2.65/3)

PROS

- Ages 4-16, ≥ 16
- Used widely in dermatology. (>1000 pub)
- Qs appropriate for cNFs
- Feasibility

CONS

- No interventional trial data
- Multiple domains in single question
- Raw score, interpretation is not validated



Future directions

- Skindex: modifications to change wording from “my skin” to “my cutaneous neurofibromas”
 - Makes scale more specific to cNFs
 - Helps patients not rate skin AEs of a drug
- DLQI: modifications to the scale is more broad
 - Questions that have multiple domains need to be separated
 - Will require rewriting multiple questions and keeping the questionnaire an appropriate length and understandability
- ? Develop de novo cNF PRO



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groups

