

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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REiNS Mini-symposium:

Consensus meeting to define the minimal set of outcomes to be reported for clinical trials of cutaneous neurofibromas

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Response Evaluation In Neurofibromatosis Schwannomatosis
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Objective

To avoid from the very beginning **lack of uniformity** in the outcomes reported in clinical studies of the treatment of cNF



To develop a **core outcome set (COS)**, a minimum set of agreed-upon outcomes to be measured in the coming clinical trials for the treatment of cutNF.



Will eventually allow to **compare treatment effectiveness** across trials.

Step 1: Identification of initial list of candidate items and potential domains

Systematic review for clinician and patient reported outcome domains

Focus group sessions for patient and physician reported outcome domains

WE
ARE
HERE

Two rounds
e-Delphi

International
consensus
meeting

Third round
e-Delphi

Final meeting

Step 2: Consensus process



Total of 31 candidate outcomes

Size and volume of cutaneous neurofibromas*†‡

Number of cutaneous neurofibromas*†‡

Body surface area covered with of cutaneous neurofibromas‡

Color of cutaneous neurofibromas*†

Texture and consistency of cutaneous neurofibromas*†

Shape of cutaneous neurofibromas+

Overall skin texture*†

Anatomic location of cutaneous neurofibromas *†‡

Visibility of cutaneous neurofibromas†‡

Pruritus caused by cutaneous neurofibromas*†‡

Pain caused by cutaneous neurofibromas*†‡

Irritation caused by cutaneous neurofibromas+

Recurrence of cutaneous neurofibromas*†‡

Stability of cutaneous neurofibromas†

Growth kinetics of cutaneous neurofibromas*+

Cosmesis related to cutaneous neurofibromas*†‡

Health related quality of life*‡

Physical functioning*‡

Psychological functioning*†

Social functioning*†

Stigma related to cutaneous neurofibromas‡

Self-esteem*†

Self-image†

Intimacy*†

Clothing restrictions*†

Perceived severity related to cutaneous neurofibromas*‡

Satisfaction with treatment*‡

Treatment burden*†+

Economic burden*†

Tolerability and adverse effects of treatments*†‡

Wound healing from interventional treatment *‡



* items generated in systematic review of literature

† items generated by patient, psychologist and nurse coordinator interviews

‡ items generated by NF1 experts

+ items generated by NF1 patients (ComPaRe e-cohort)

Methodology of the consensus meeting

1. Who are you?
2. What is a consensus?
3. Poll for each candidate outcome
4. Defining core domains



1. Demographics of participants



Demographics of participants

Characteristics		First round				Second round			
		NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
Total N (%)		71 (31.0)	130 (56.8)	28 (12.2)	229	48 (25.3)	118 (62.1)	24 (12.6)	190
Gender	Female	50 (70.4)	74 (56.9)	20 (71.4)	144 (62.9)	34 (70.8)	65 (55.1)	16 (66.7)	115 (60.5)
	Male	20 (28.2)	56 (43.1)	8 (28.6)	84 (36.7)	14 (29.2)	53 (44.9)	8 (33.3)	75 (39.5)
	Other	1 (1.4)			1 (0.4)	0			0
Age	Mean (SD)	46.6 (10.0)	48.6 (12.1)	48.0 (10.3)	47.9 (11.3)	46.6 (11.4)	49.6 (12.7)	51.0 (11.3)	49.0 (12.2)
	Median (IQR)	44.8 (40.3 to 52.6)	48.0 (39.8 to 57.3)	49.4 (39.7 to 55.1)	47.3 (39.8 to 55.8)	45.4 (40.5 to 55.6)	47.7 (39.7 to 59.1)	50.7 (42.3 to 57.3)	47.6 (39.9 to 58.0)
Geographic location	Europe	60 (84.5)	81 (62.3)	12 (42.8)	153 (66.8)	38 (79.2)	72 (61.0)	12 (50.0)	122 (64.2)
	United States or Canada	7 (9.9)	34 (26.2)	13 (46.4)	54 (23.6)	5 (10.4)	35 (29.7)	11 (45.8)	51 (26.8)
	Latin or South America	0	4 (3.1)	1 (3.6)	5 (2.2)	0	4 (3.4)	0	4 (2.1)
	Oceania	4 (5.6)	7 (5.4)	2 (7.1)	13 (5.7)	5 (10.4)	4 (3.4)	1 (4.2)	10 (5.3)
	Asia	0	4 (3.1)	0	4 (1.7)	0	3 (2.5)	0	3 (1.6)
Health care professional demographics	Genetic counselor / geneticist		3 (2.3)				6 (5.1)		
	Medical doctor		115 (89.1)				103 (89.6)		
	Nurse / Nurse specialist		8 (6.2)				6 (5.1)		
	Pharmacist		1 (0.8)				1 (0.9)		
	Psychologist		3 (2.3)				2 (1.7)		

Demographics of participants

And today ?

We are hoping for a significant participation of patients / relatives / representatives and professionals.

Should it not be the case, a separate consensus meeting will be held with patients / relatives / representatives.



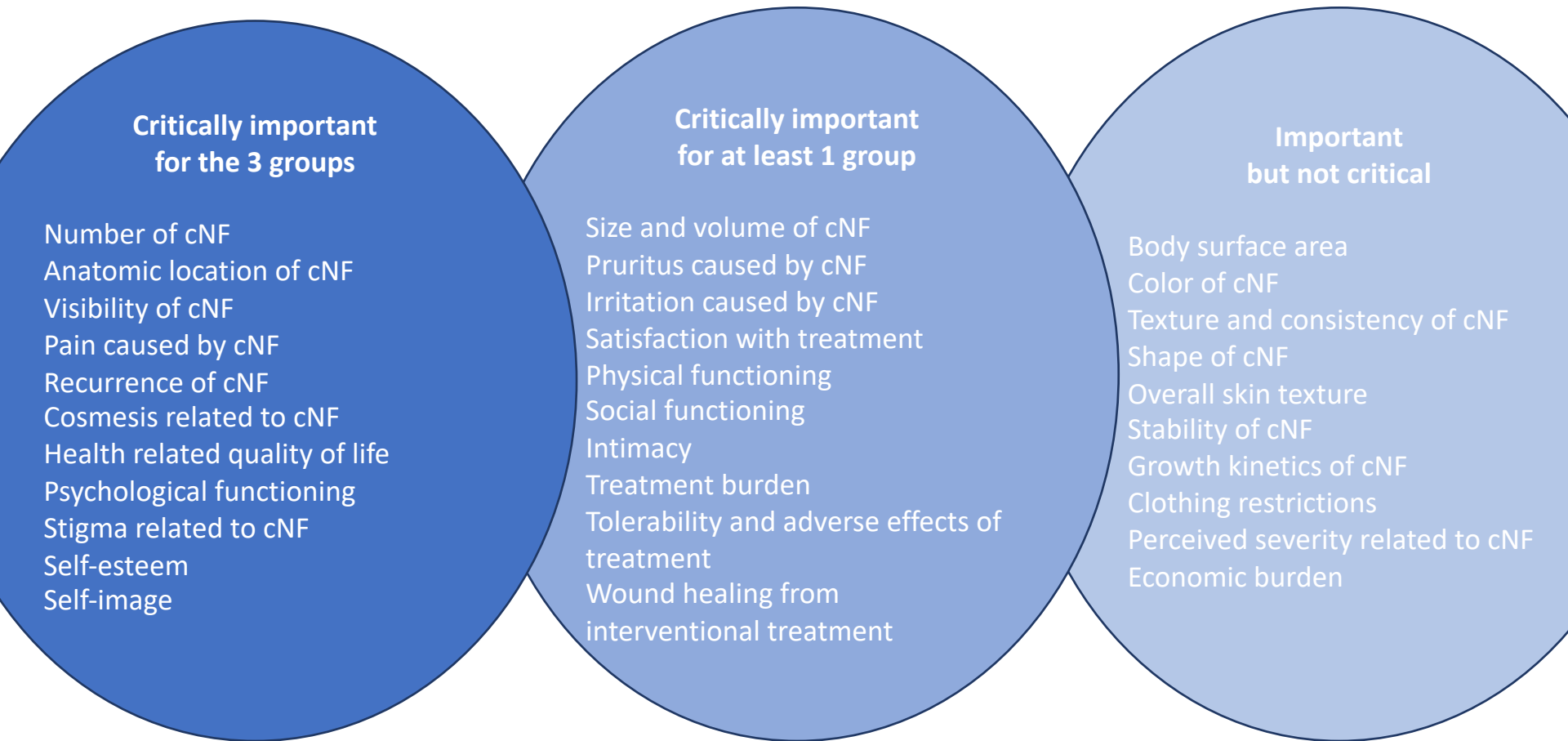
2. What is a consensus ?

Definition of consensus during e-delphi

Consensus classification	Description	Definition
Consensus in	The outcomes should be included in the core outcome set	$\geq 70\%$ participants scored 7 to 9 <u>AND</u> $< 15\%$ participants scored 1 to 3
Consensus out	The outcome should not be included in the core outcome set	$\geq 70\%$ participants scored 1 to 3 <u>AND</u> $< 15\%$ participants scored 7 to 9
No consensus	Uncertainty about importance of the outcome	Anything else



Candidate outcomes : levels of importance



None of the candidate outcomes was excluded during the first two rounds.

3. Poll for each outcome



Methodology

- 1. List of outcomes with high level of importance for the 3 groups:**
 - **Outcomes provisionally included**
 - **Answer the question** : should these outcomes be included in the core outcome set ?
 - **If there is over 30% of “no”**, time will be set aside for discussion

Critically important for the 3 groups, N=11

1. Not important
2. Important, not critical
3. Critically important

Items	Levels of importance	NF1 or related N= 48	Healthcare Professionals N = 118	Industrials / Editors / Researchers N = 24	Total No. (%) N = 190
Number of cutaneous neurofibromas	1	3 (6.2)	0 (0.0)	0 (0.0)	3 (1.6)
	3	37 (77.1)	97 (83.6)	19 (79.2)	153 (81.4)
Anatomic location of cutaneous neurofibromas	1	2 (4.3)	1 (0.9)	0 (0.0)	3 (1.6)
	3	36 (78.3)	96 (84.2)	20 (87.0)	152 (83.1)
Visibility of cutaneous neurofibromas	1	3 (6.4)	1 (0.9)	0 (0.0)	4 (2.2)
	3	37 (78.7)	104 (91.2)	19 (82.6)	160 (87.0)
Pain caused by cutaneous neurofibromas	1	10 (21.7)	0 (0.0)	0 (0.0)	10 (5.5)
	3	33 (71.7)	99 (88.4)	22 (95.7)	154 (85.1)
Recurrence of cutaneous neurofibromas	1	5 (11.1)	1 (0.9)	0 (0.0)	6 (3.3)
	3	33 (73.3)	88 (77.9)	20 (87.0)	141 (77.9)
Cosmesis related to cutaneous neurofibromas	1	3 (6.5)	0 (0.0)	0 (0.0)	3 (1.6)
	3	35 (76.1)	97 (85.8)	19 (82.6)	151 (83.0)
Health related quality of life	1	4 (8.7)	0 (0.0)	0 (0.0)	4 (2.2)
	3	35 (76.1)	109 (96.5)	23 (100.0)	167 (91.8)
Psychological functioning	1	4 (8.7)	0 (0.0)	0 (0.0)	4 (2.2)
	3	34 (73.9)	109 (95.6)	21 (91.3)	164 (89.6)
Stigma related to cutaneous neurofibromas	1	5 (10.9)	0 (0.0)	0 (0.0)	5 (2.7)
	3	36 (78.3)	106 (93.0)	21 (91.3)	163 (89.1)
Self-esteem	1	4 (8.9)	0 (0.0)	0 (0.0)	4 (2.2)
	3	32 (71.1)	98 (86.7)	19 (82.6)	149 (82.3)
Self-image	1	3 (6.7)	0 (0.0)	0 (0.0)	3 (1.7)
	3	34 (75.6)	102 (90.3)	20 (87.0)	156 (86.2)

Methodology

2. For outcomes that were not provisionally included:

- **Answer the question** : should the outcome be included in the core outcome set ?
- **If there is over 70% agreement (yes or no)**, the outcome will be **included or excluded**
- **Otherwise**, time will be set aside for **discussion**



Critically important for at least 1 group, N=10

Size and volume of cNF
Pruritus caused by cNF
Irritation caused by cNF
Satisfaction with treatment
Physical functioning
Social functioning
Intimacy
Treatment burden
Tolerability and adverse effects of treatment
Wound healing from interventional treatment

Size and volume of cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (10.4)	0 (0.0)	0 (0.0)	5 (2.6)
2	15 (31.2)	11 (9.4)	5 (20.8)	31 (16.4)
3	28 (58.3)	106 (90.6)	19 (79.2)	153 (81.0)

1. Not important
2. Important, not critical
3. Critically important



Pruritus caused by cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	8 (18.2)	0 (0.0)	0 (0.0)	8 (4.5)
2	10 (22.7)	27 (24.1)	2 (8.7)	39 (21.8)
3	26 (59.1)	85 (75.9)	21 (91.3)	132 (73.7)

1. Not important
2. Important, not critical
3. Critically important



Irritation caused by cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	7 (15.2)	1 (0.9)	0 (0.0)	8 (4.4)
2	8 (17.4)	32 (28.6)	3 (13.0)	43 (23.8)
3	31 (67.4)	79 (70.5)	20 (87.0)	130 (71.8)

1. Not important
2. Important, not critical
3. Critically important



Satisfaction with treatment

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (11.9)	0 (0.0)	0 (0.0)	5 (2.8)
2	8 (19.0)	4 (3.6)	1 (4.3)	13 (7.3)
3	29 (69.0)	108 (96.4)	22 (95.7)	159 (89.8)

1. Not important
2. Important, not critical
3. Critically important



Physical functioning

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	7 (15.2)	3 (2.6)	1 (4.3)	11 (6.0)
2	9 (19.6)	13 (11.4)	3 (13.0)	25 (13.7)
3	30 (65.2)	98 (86.0)	19 (82.6)	147 (80.3)

1. Not important
2. Important, not critical
3. Critically important



Social functioning

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	6 (13.0)	0 (0.0)	0 (0.0)	6 (3.3)
2	8 (17.4)	8 (7.0)	4 (17.4)	20 (10.9)
3	32 (69.6)	106 (93.0)	19 (82.6)	157 (85.8)

1. Not important
2. Important, not critical
3. Critically important



Intimacy

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (11.6)	0 (0.0)	0 (0.0)	5 (2.8)
2	9 (20.9)	20 (17.9)	8 (36.4)	37 (20.9)
3	29 (67.4)	92 (82.1)	14 (63.6)	135 (76.3)

- 1. Not important
- 2. Important, not critical
- 3. Critically important



Treatment burden

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	6 (14.0)	0 (0.0)	0 (0.0)	6 (3.4)
2	12 (27.9)	14 (12.6)	3 (13.0)	29 (16.4)
3	25 (58.1)	97 (87.4)	20 (87.0)	142 (80.2)

1. Not important
2. Important, not critical
3. Critically important



Tolerability and adverse effects of treatment

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (11.9)	1 (0.9)	0 (0.0)	6 (3.4)
2	9 (21.4)	8 (7.1)	1 (4.3)	18 (10.2)
3	28 (66.7)	103 (92.0)	22 (95.7)	153 (86.4)

1. Not important
2. Important, not critical
3. Critically important



Wound healing from interventional treatment

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	4 (8.9)	2 (1.8)	0 (0.0)	6 (3.3)
2	13 (28.9)	24 (21.4)	5 (21.7)	42 (23.3)
3	28 (62.2)	86 (76.8)	18 (78.3)	132 (73.3)

1. Not important
2. Important, not critical
3. Critically important



Important, not critical,
N=10

Body surface area
Color of cNF
Texture and consistency of cNF
Shape of cNF
Overall skin texture
Stability of cNF
Growth kinetics of cNF
Clothing restrictions
Perceived severity related to cNF
Economic burden

Body surface area

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	3 (6.2)	0 (0.0)	0 (0.0)	3 (1.6)
2	13 (27.1)	35 (30.7)	13 (54.2)	61 (32.8)
3	32 (66.7)	79 (69.3)	11 (45.8)	122 (65.6)

- 1. Not important
- 2. Important, not critical
- 3. Critically important



Color of cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	6 (12.5)	42 (36.8)	4 (16.7)	52 (28.0)
2	36 (75.0)	64 (56.1)	20 (83.3)	120 (64.5)
3	6 (12.5)	8 (7.0)	0 (0.0)	14 (7.5)

1. Not important
2. Important, not critical
3. Critically important



Texture and consistency of cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	4 (8.5)	30 (26.5)	8 (34.8)	42 (23.0)
2	34 (72.3)	74 (65.5)	13 (56.5)	121 (66.1)
3	9 (19.1)	9 (8.0)	2 (8.7)	20 (10.9)

1. Not important
2. Important, not critical
3. Critically important



Shape of cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	6 (12.8)	24 (21.4)	8 (34.8)	38 (20.9)
2	29 (61.7)	75 (67.0)	13 (56.5)	117 (64.3)
3	12 (25.5)	13 (11.6)	2 (8.7)	27 (14.8)

1. Not important
2. Important, not critical
3. Critically important



Overall skin texture

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (10.6)	30 (26.5)	3 (13.0)	38 (20.8)
2	23 (48.9)	74 (65.5)	17 (73.9)	114 (62.3)
3	19 (40.4)	9 (8.0)	3 (13.0)	31 (16.9)

- 1. Not important
- 2. Important, not critical
- 3. Critically important



Stability of cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	4 (8.7)	2 (1.8)	0 (0.0)	6 (3.3)
2	16 (34.8)	61 (54.0)	9 (39.1)	86 (47.3)
3	26 (56.5)	50 (44.2)	14 (60.9)	90 (49.5)

1. Not important
2. Important, not critical
3. Critically important



Growth kinetics of cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	3 (6.5)	1 (0.9)	0 (0.0)	4 (2.2)
2	11 (23.9)	34 (30.1)	10 (43.5)	55 (30.2)
3	32 (69.6)	78 (69.0)	13 (56.5)	123 (67.6)

1. Not important
2. Important, not critical
3. Critically important



Clothing restrictions

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (10.9)	0 (0.0)	1 (4.5)	6 (3.3)
2	20 (43.5)	68 (60.7)	13 (59.1)	101 (56.1)
3	21 (45.7)	44 (39.3)	8 (36.4)	73 (40.6)

1. Not important
2. Important, not critical
3. Critically important



Perceived severity related to cutaneous neurofibromas

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	5 (10.9)	1 (0.9)	0 (0.0)	6 (3.3)
2	19 (41.3)	52 (46.4)	9 (39.1)	80 (44.2)
3	22 (47.8)	59 (52.7)	14 (60.9)	95 (52.5)

1. Not important
2. Important, not critical
3. Critically important



Economic burden

Levels of importance	NF1 / relatives / representatives	Health care professionals	Industrials / Editors / Researchers	Total
1	11 (23.9)	3 (2.7)	1 (4.3)	15 (8.4)
2	9 (19.6)	55 (50.0)	11 (47.8)	75 (41.9)
3	26 (56.5)	52 (47.3)	11 (47.8)	89 (49.7)

1. Not important
2. Important, not critical
3. Critically important



4. Defining core domains



Defining core domains

- For each core domain, we will set a poll to ask whether you agree with:
 - **The clustering of outcomes**
 - **And the names of the core domains**
- **If there is less than 70% agreement, time will be set aside for discussion**
- **Concerning the outcomes that we have just excluded, they will be removed from the core domains**



Proposed core domains

Clinical characteristics:

- Number
- Size and volume
- Color
- Texture and consistency
- Shape
- Anatomic location of cNF
- Body surface area
- Overall skin texture
- Visibility
- Perceived severity related to cNF

Progression of course:

- Recurrence of cNF
- Stability of cNF
- Growth kinetics of cNF

Treatment:

- Treatment satisfaction
- Treatment burden
- Tolerability and adverse effects of treatment
- Wound healing from interventional treatment

Symptoms:

- Pruritus caused by cNF
- Irritation caused by cNF
- Pain caused by cNF

Economic burden

cNF-related quality of life:

- Stigma
- Self-esteem
- Self-image
- Psychological functioning
- Physical functioning
- Social functioning
- Intimacy
- Cosmesis related to cNF
- Clothing restrictions
- Health related quality of life

Proposed core domains

Clinical characteristics:

- Number
- Size and volume
- Color
- Texture and consistency
- Shape
- Anatomic location of cNF
- Body surface area
- Overall skin texture
- Visibility
- Perceived severity related to cNF

Proposed core domains

Symptoms:

- Pruritus caused by cNF
- Irritation caused by cNF
- Pain caused by cNF

Proposed core domains

Progression of course:

- Recurrence of cNF
- Stability of cNF
- Growth kinetics of cNF

Proposed core domains

cNF-related quality of life:

- Stigma
- Self-esteem
- Self-image
- Psychological functioning
- Physical functioning
- Social functioning
- Intimacy
- Cosmesis related to cNF
- Clothing restrictions
- Health related quality of life

Proposed core domains

Treatment:

- Treatment satisfaction
- Treatment burden
- Tolerability and adverse effects of treatment
- Wound healing from interventional treatment

Proposed core domains

Economic burden

Join the REiNS cNF working group

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