D7.1 Report on the Consensus Definition of Current Challenges in NF

853966 – EU-PEARL

EU Patient-cEntric clinical tRial pLatforms

WP7 – Integrated Research Platform for Neurofibromatosis (NF)

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Definitions

- **Participants** of the EU-PEARL Consortium are referred to herein according to the following codes:
  1. VHIR. Fundació Hospital Universitari Vall D´Hebron – Institut de Recerca
  2. EATRIS. EATRIS ERIC
  3. SYNAPSE. Synapse Research Management Partners S.L. (Termination date: May 31st, 2020)
  4. MUW. Medizinische Universitaet Wien
  5. KU Leuven. Katholieke Universiteit Leuven
  6. KCL. King's College London
  7. USR. Universita Vita-Salute San Raffaele
  8. EMC. Erasmus Universitair Medisch Centrum Rotterdam,
  9. LMU. Ludwig-Maximilians-Universitaet Muenchen,
  10. Charité. Charité - Universitaetsmedizin Berlin,
  11. AP-HP. Assistance Publique - Hôpitaux de Paris
  12. CUSTODIX. Custodix NV
  13. i~HD. The European Institute for Innovation through Health Data
  14. BERRY. Berry Consultants LLP
  15. ECRIN. ECRIN European Clinical Research Infrastructure Network
  16. EPF. Forum Europeen des Patients
  17. UNEW. University of Newcastle upon Tyne
  18. EUROSCAN. EUROSCAN International Network e.V.
  19. PEI. Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Institut
  20. UOXF. The Chancellor, Masters and Scholars of the University of Oxford
  21. UMIL. Università degli Studi di Milano
  22. DocuMental. DocuMental OU
  23. UOM. The University of Manchester
  24. Janssen. Janssen Pharmaceutica NV
  25. Novartis. Novartis Pharma AG
  26. Allergan. Allergan Limited
  27. AZ. Astra Zeneca AB
  28. Novo Nordisk. Novo Nordisk A/S
  29. Otsuka. Otsuka Novel Products GmbH
  30. Pfizer. Pfizer Limited
  31. Sanofi. Sanofi-Aventis Recherche & Developpement
  32. Servier. Institut de Recherches Internationales Servier
  33. Teva. Teva Pharmaceutical Industries Limited
  34. CTF. Children's Tumor Foundation
  35. SpringWorks. SpringWorks Therapeutics INC
  36. TB Alliance. Global Alliance for TB Drug Development Non-Profit Organisation
  37. TEAM-IT. TEAM - IT RESEARCH SL (Start date: May 01st, 2020).

- **Grant Agreement. (Including its annexes and any amendments)** The agreement signed between the beneficiaries of the action and the IMI2 JU for the undertaking of the EU-PEARL project (Grant Agreement No. 853966).
- **Project**. The sum of all activities carried out in the framework of the Grant Agreement.

- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Part B; 3.1 to the Grant Agreement.
- **Consortium.** The EU-PEARL Consortium, comprising the above-mentioned legal entities.
- **Consortium** Agreement. Agreement concluded amongst EU-PEARL participants for the implementation of the Grant Agreement. The agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

Acronym/ Abbreviation	Meaning
ADHD	Attention-deficit/hyperactivity disorder
COVID-19	Coronavirus Disease 2019
CTF	Children's Tumor Foundation
ENFG	European Neurofibromatosis Group
ERN GENTURIS	European Reference Network (ERN) for patients with one of the rare genetic tumor risk syndromes (GENTURIS)
EU-PEARL	EU Patient-cEntric clinical tRial pLatforms
GIST	Gastrointestinal Stromal Tumor
IRP	Integrated Research Platform
LNHS	Longitudinal Natural History Study
LZTR1	Leucine-zipper-like transcriptional regulator 1 gene
MAPK	Mitogen-activated protein kinase
MPNST	Malignant Peripheral Nerve Sheath Tumor
NF	Neurofibromatosis
NF1	Neurofibromatosis Type 1
NF2	Neurofibromatosis Type 2
NFPU	Neurofibromatosis Patients United (Patient organization)
NRS	Numerical Rating Scale
NT	Need for treatment score
PI3K	Phosphoinositide-3 kinase
RAS	Rat Sarcoma genes and pathways
ReiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SD	Standard deviation
SMARCB1	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1 gene
SWN	Schwannomatosis
USA	United States of America
WP7	Work package 7

Publishable Summary

EU-PEARL is an international project that aims to create reusable and sustainable Integrated Research Platforms (IRPs). By creating an alliance between patients, health professionals and pharmaceutic companies, it will transform the current approach of performing single clinical trials into patient-centered, multi-center and multi-company IRPs in four disease areas. IRPs are more cost-effective and patient friendly by offering easier enrolment in active treatment arms, and will accelerate the development of new treatments. One of the four disease areas in EU-PEARL is Neurofibromatosis (NF) and looked after by Work Package 7 (WP7).

The term NF includes three conditions: Neurofibromatosis Type 1, Neurofibromatosis Type 2 and Schwannomatosis. All three are rare and hereditary conditions and have a high variability in expression and severity of symptoms. The underlying pathways have been researched in multiple studies, elucidating possible new drug treatments, making NF a good candidate for a disease-specific Platform Trial. The wide range of manifestations of NF (especially NF1) presents a challenge however when trying to create a framework for these future trials: a selection of manifestations will have to be made. The aim of Deliverable 7.1 – 'Report on the Consensus Definition of Current Challenges in NF' is to reach consensus on the most important manifestations of NF to select for clinical trials, and to share the findings with the wider scientific and medical community.

By performing a multi-staged modified Delphi procedure and consensus meeting for NF experts and a survey for patient representatives, EU-PEARL's WP7 has identified the most important challenges in NF. A large group of NF experts has reached consensus on how to group the various NF manifestations under the same platform trial, followed by a prioritization of these groups into a final selection of manifestations to be included into the IRP. Future efforts will be focused on peripheral benign nerve sheath tumors, sarcomas, cutaneous manifestations and high-grade gliomas for NF1, tumors for NF2, and pain for Schwannomatosis.

WP7 would like to thank all NF experts and patient representatives who collaborated with us by giving their input in the surveys and consensus meeting.

1. Introduction

Neurofibromatosis Type 1 (NF1), Neurofibromatosis Type 2 (NF2) and Schwannomatosis (SWN) are genetic disorders that predispose to the development of nerve sheath tumors (1, 2). These tumors are mostly benign with a low chance of malignant transformation but can cause significant neurologic morbidity due to their size and/or location. All three diseases are autosomal dominantly inherited, with a high de novo mutation rate (50% in NF1 and NF2) and characterized by a high variability in expression (1, 3, 4). There have been studies to elucidate the underlying pathways, resulting in multiple potential targets to find drug treatments for (5). Rare hereditary conditions with variability in expression like Neurofibromatosis (NF) require large, multi-center trials and multiple patient populations for a successful evaluation of new treatments. EU-PEARL is an international project that focusses on this issue, with its main objective being to create a framework for the future conduct of Integrated Research Platforms (IRPs)(6). Instead of conducting multiple separate clinical trials, the idea is that IRPs will accelerate the development of new treatments and will potentially reduce operational costs, something that is much needed in NF and healthcare.

Of the three diseases, **NF1** is the most common with a reported birth incidence varying from 1 in 2.000 to 1 in 3.647 (3, 7-9). It is caused by a mutation in the *NF1* gene on chromosome 17q11.2 (10, 11), resulting in the loss of a functional neurofibromin protein, inducing excessive stimulation of the RAS-pathway (12) which enables tumor growth. Being a neurocutaneous syndrome, its hallmark symptoms feature the skin and the nervous system (including cognitive impairment), but NF1 is a multisystem disease that can affect every organ system in the body.

For **NF2**, the *NF2* gene lies on the chromosome 22q11.2 (13, 14). Mutations in this gene cause a loss of functional merlin, a tumor suppressor protein (14). Similarly to *NF1's* neurofibromin, the loss of merlin stimulates activation of various mitogenic signaling pathways, including the RAS, phosphoinositide-3 kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways (15-17). It is a less common disease than NF1, with its incidence varying between 1 in 28.000 to 1 in 40.000 (3, 18, 19). Bilateral vestibular schwannomas are the characteristic defining manifestation of NF2. Besides these, manifestations like meningiomas and ependymomas may also occur (20-22).

Schwannomatosis is the third form of NF and the most rare. The reported incidence from one study is 1 in 68.956.(18) The genetic landscape of Schwannomatosis is less known than those of NF1 and NF2. Mutations in *SMARC1B* and *LZTR1* genes have been identified, which both are tumor suppressor genes (23-25). It is characterized by the development of multiple schwannomas, excluding bilateral vestibular schwannomas, and occasionally meningiomas. Its main symptom is extreme pain, which can be caused by a (growing) schwannoma, but the exact cause of pain in Schwannomatosis is not always clear.

The wide range of manifestations of NF (especially NF1) present a challenge when trying to create a framework for future IRPs. Since it would be impossible to include all manifestations, a selection will have to be made. Therefore, the aim of this study was to reach consensus on the most important manifestations of NF to select for clinical trials.

2. Methods

Design: We used a five-staged modified Delphi procedure, consisting of two questionnaires and a consensus meeting for NF experts, a survey and consensus meeting for patient representatives, and a final workshop for the selection of manifestations. (Figure 1)

2.1. Selection and contacting of the NF experts for the Delphi procedure

Potential Delphi participants were included from our contacts through a) the European Neurofibromatosis Group (ENFG), b) NF experts within ERN GENTURIS, and c) experts that participated in the development of the new diagnostic criteria(26). We also approached well-known NF clinicians or researchers from the USA, known for their experience in the field. We did not use a set definition of an expert, as this is arbitrary. There is no known method to calculate the needed group size for a Delphi procedure (27), since it is often researcher and situation specific(28). In most studies, samples sizes have been chosen dependent on availability of experts. We estimated that an approximate number of 40-50 NF experts would be a convenient sample size.

Fifty-two possible participants were informed by an introduction email on the reason for the study, an explanation about the Delphi procedure and the estimated time for filling in the questionnaires. We emphasized that the Delphi would consist of a minimum of two questionnaires, underlining the importance to fill in all surveys. They were asked to respond to this email with “Yes, I would like to participate”, or “No, I don’t want to participate because of (reason)”. Experts that responded with “Yes” were included into the Delphi questionnaire.

At the start of each questionnaire the participants received an announcement email, followed directly by a second email with a hyperlink to the questionnaire. The hyperlink was sent in a separate email because emails with links from an external source might end up in the Junk Folder of email programs. The deadline for completing the questionnaires was set at 2,5 weeks after launch. Non-responders were sent a general reminder after two weeks, and a personalized reminder email on the day of the deadline.

2.2. Selection and contacting of the patient representatives for the survey

Participants for the patient representatives’ survey were recruited though the patient organizations Children’s Tumor Foundation (CTF) (29) for the USA, and the Neurofibromatosis Patients United (NFPU) (30) for Europe. An invitation email with the link to the surveys was either send directly to known patient representatives or to other patient organizations, with the request to forward the survey to their patient representatives. The deadline for completing the surveys was set at two weeks after launch. General reminder emails were sent 1 week and 1,5 weeks after launch.

2.3. Preparation of the initial list of manifestations

Based on a literature search (21, 31) and the clinical experience within our work package group of EU-PEARL (WP7), we produced a list of the most common and important manifestations for NF1, NF2 and SWN that needed to be included into the first Delphi questionnaire.

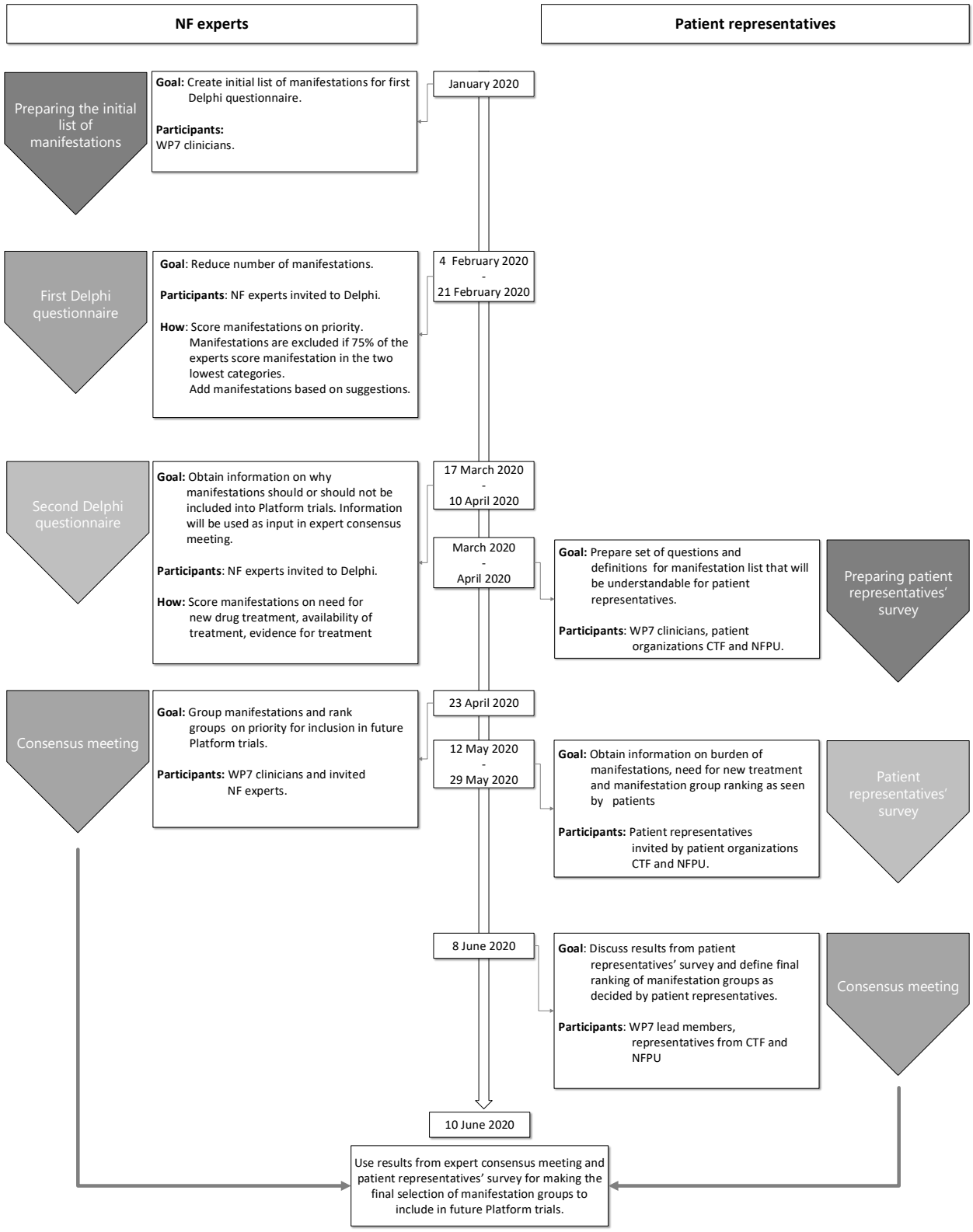

Figure 1. *A flowchart depicting the multiple stages of the study. The study consisted of two pathways, one for NF experts and one for patient representatives. The expert pathway consisted of two Delphi questionnaires and a consensus meeting, the patient representatives had one survey and a consensus meeting. The final selection of manifestations was done in a final workshop.*

2.4. Stage 1: First Delphi questionnaire for NF experts

The goal of the first questionnaire was to reduce the number of manifestations. Participants were first asked to declare their expertise on NF1, NF2 and SWN. Next, they were asked to score each manifestation on priority of including that manifestation into a platform trial. This was done on a 4-point Likert scale, allowing participants to choose between “No priority”, “Low priority”, “Moderate priority” and “High priority”. A manifestation was excluded from the second Delphi questionnaire if ≥75% of the participants rated the manifestation “Low priority” or lower.

The questionnaires were built and distributed using Google Forms. Participants were asked to fill in their name, so we knew who to send reminder emails to.

2.5. Stage 2: Second Delphi questionnaire for NF experts

The goal of the second questionnaire was to obtain additional information on why manifestations should or should not be included into a platform trial. This information would be used in the consensus meeting to create a ranking of manifestations. We identified three items that could influence this ranking: i) the need for a new drug treatment on top of already existing treatments, ii) the availability of already existing drug treatments, and iii) the available evidence for these treatments. Participants were asked to rate the manifestations on these three items. Need for new treatments and availability of drug therapies were scored on a 4-point Likert scale, and evidence for effectiveness of existing drug therapies on a 5-point Likert scale. For the items on availability and evidence, a “Do not know” option was provided.

2.6. Stage 3: Consensus meeting for NF experts

The consensus meeting was hosted virtually due to the COVID-19 pandemic and planned two weeks after the deadline of the second Delphi questionnaire (Meeting date: April 23rd, 2020). The consensus meeting had two goals: to group the various NF manifestations under the same platform trial where possible, followed by reaching consensus on a prioritization ranking of these groups. Participants consisted of experts within the European NF group, clinicians from the CTF clinical care advisory board and WP7 members.

Participants were supplied with pre-reading material before the meeting, which included the results from the second questionnaire presented as average scores with standard deviations and a table with the distribution of the scores in percentages. The consensus meeting started with a short presentation on the rationale for the Delphi study, explaining the need for future platform trials and the role of WP7 in identifying the main challenges in NF. Next, the pre-reading material was shortly discussed. The presentation ended with a slide on the two goals of the meeting (grouping manifestations and ranking of these groups), and this slide was also shown repeatedly during the consensus discussions to keep the discussion focused on the desired outcomes of the meeting.

The consensus discussions contained two separate discussions, one for NF1 and one for NF2/SWN combined. As a first step, participants were asked to discuss manifestations that could be excluded entirely. Remaining manifestations were then aggregated into main groups, based on either pathophysiology, targets for treatments, organ system, etc. Ranking on priority of inclusion into

platform trials was done for these main manifestation groups. Given the larger number of manifestations for NF1, this condition required a **third questionnaire**. It consisted of a question on feasibility to perform a platform trial for this group (easy vs. difficult) and participants of the consensus meeting were asked to rank the groups of manifestations.

2.7. Stage 4: Patient representatives' survey and consensus meeting

To include input of patients in our final selection of manifestations, a survey and consensus meeting was performed for patient representatives. Separate surveys were developed for NF1, NF2 and SWN in close coordination with the NFPU and CTF. Participants were asked to answer questions on three types of burden (physical, psychosocial and economic burden), disease severity and need for new drug treatments on a 4-point Likert scale. This was done for the manifestation list that resulted from the NF expert consensus meeting. A short explanation was provided for each manifestation. They were also asked to rank the groups of manifestations on priority for finding new treatments. The patient representatives did not know the results of the ranking from the NF expert consensus meeting. The deadline for completing the surveys was set at 2,5 weeks after launch. Results of the patient Delphi were discussed in a consensus meeting hosted virtually (Meeting date: June 8th, 2020). Representatives from NFPU and CTF were invited to share their view on the results and were asked whether they agreed or disagreed with the ranking of manifestation groups that resulted from the survey.

2.8. Stage 5: Final workshop

Using the outcomes of both the NF expert consensus meeting and the patient representatives' survey and consensus meeting, the WP7 group decided on a final selection of manifestations groups in a final virtual workshop (Meeting date: June 10th, 2020).

2.9. Data analysis

A thematic analysis was performed on the free-text comments of the second questionnaire for NF experts, by manually coding the comments and aggregating them under main themes.

Results from the second Delphi questionnaire for NF experts and the patient representatives' survey were analyzed by calculating the average score for each item. These average scores could range between 1 and 4, except for the average score of "evidence for treatments" from the second NF expert questionnaire, which could range between 1 and 5. For each average score, the standard deviation (SD) was computed. Next all items were analyzed for floor and ceiling effects by looking at the distribution of the respondents' answers, marking manifestations where 75% of the respondents appointed either the highest or the lowest score. For the NF expert consensus meeting and patient representatives' survey, average rankings were calculated with corresponding SD's. These average rankings could range between 1 and 8 for NF1, between 1 and 2 for NF2, and between 1 and 3 for SWN. A lower average ranking implies a higher priority for inclusion into future clinical trials.

3. Results

3.1. List of manifestations

We identified a total of 66 manifestations; 52 for NF1, 9 for NF2 an 5 for SWN. Manifestations for NF1 were grouped into subgroups, e.g. “Skin”, “Malignancies” and “Neurological”. Since the count of manifestations for NF2 and SWN were lower, grouping of manifestations was not deemed necessary. The list of these manifestations used for the first questionnaire can be found in the ANNEX I. Original manifestation list used in first questionnaire

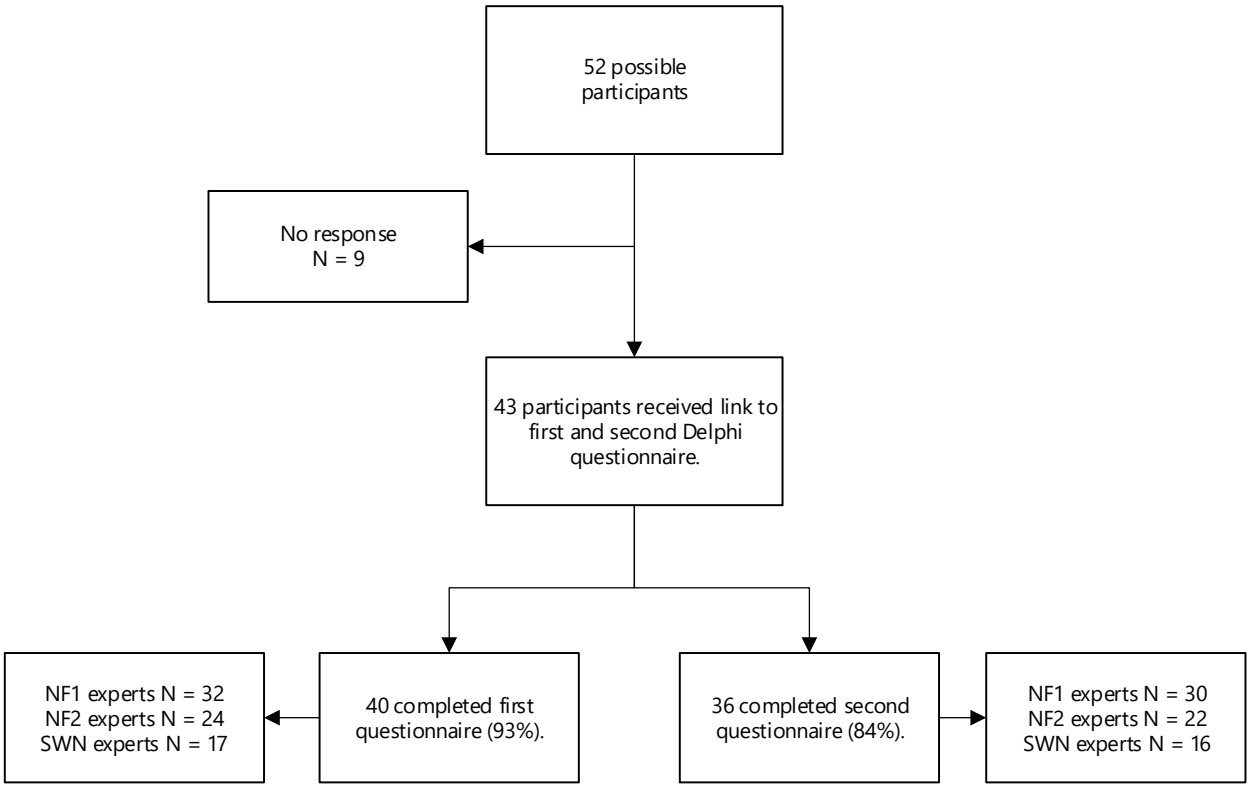

***Figure 2**. Flow-chart of the recruitment of experts for the Delphi and the response rate of the first and second questionnaire. Participants could belong to more than one expert group. NF1 = neurofibromatosis type I, NF2 = neurofibromatosis type II, SWN = Schwannomatosis.*

3.2. Stage 1: First Delphi questionnaire for NF experts

The initial group of possible Delphi participants consisted of 52 NF experts. Of the 52 invitees, we received 43 positive responses, 9 did not respond, (Figure 2) and 38 participants completed the first questionnaire in the given timeframe. The questionnaire was temporarily reopened for two days at the request of two additional respondents, achieving 40 respondents in total (93%). Of these 40 respondents, 32 reported expertise in NF (80%), 24 in NF2 (60%) and 17 in SWN (43%). A list of experts that participated in the Delphi questionnaires can be found in Annex III.

Fourteen NF1 manifestations were excluded using the pre-defined criteria. We received five manifestation suggestions for NF1, four for NF2 and three for SWN. There were seven propositions for rephrasing and/or splitting manifestations. After discussion within the WP7 group one manifestation was added for both NF1 (problems with motor skills and/or coordination) and NF2 (mononeuropathy). Four manifestations were rephrased, and for NF1, “brain or spinal cord glioma” was split into three separate manifestations: low grade brain glioma, high grade brain glioma and spinal cord low grade glioma. Thus, after the first questionnaire a total of 55 manifestations remained; 40 for NF1, 10 for NF2 and 5 for SWN (ANNEX II. Manifestation list as used for second questionnaire

3.3. Stage 2: Second Delphi questionnaire for NF experts

Due to the COVID-19 outbreak the original deadline of 2,5 weeks after launch was extended by 1 week. 36 participants completed the questionnaire (84%) (Figure 2). Full details of the results of the second Delphi questionnaire can be found in ANNEX I and ANNEX V.

For **NF1**, the manifestations with the highest average NT score were the malignant peripheral nerve sheath tumor (MPNST) (3,97 (SD 0,17), high grade glioma (3,85 (SD 0,36)) and plexiform neurofibroma (3,82 (SD 0,52) (Figure 3). The lowest average NT scores were appointed to hypertension (2,03 (SD 0,94)), vitamin D deficiency (2,06 (SD 0,95)) and precocious puberty (2,12 (SD 1,01)). There were 7 manifestations that displayed a ceiling effect, meaning that they were appointed the highest NT score by 75% or more of the respondents: (sub)cutaneous neurofibroma, plexiform neurofibroma, atypical neurofibroma, spine root neurofibroma, high grade glioma and MPNST.(ANNEX I) These manifestations all had average NT scores of 3,71 and higher, with SD’s of 0,65 and lower. A similar floor effect was not observed in NT scores.

In **NF2** the highest need for treatment scores were observed in all tumor types, all with small variability (SDs), with meningioma having the highest average score (3,86 (SD 0,47)) (Figure 4). The visual complications cataract and retinal hamartoma were appointed the lowest average NT scores, with scores of 2,18 (SD 0,80) and 2,41 (SD 0,96), respectively. Vestibular schwannoma and meningioma displayed a ceiling effect and were appointed the highest NT score by 75% or more of the respondents.

Pain received the highest average NT score for **Schwannomatosis** (3,88 (SD 0,33)) (Figure 4). It was also the only manifestation that was appointed the highest NT score by 75% or more of the respondents. The other manifestations obtained high average scores but showed much higher variability as reflected in their SDs being above 0,79.

For the **thematic analysis**, comments were aggregated into three main themes: treatment, phrasing and expertise. The treatment theme was divided into four subgroups, with comments concentrating on 1) the availability of treatments with limited effect, 2) availability of non NF-specific treatments, 3) availability of treatments other than drug treatment, and 4) the availability of drugs in routine care.

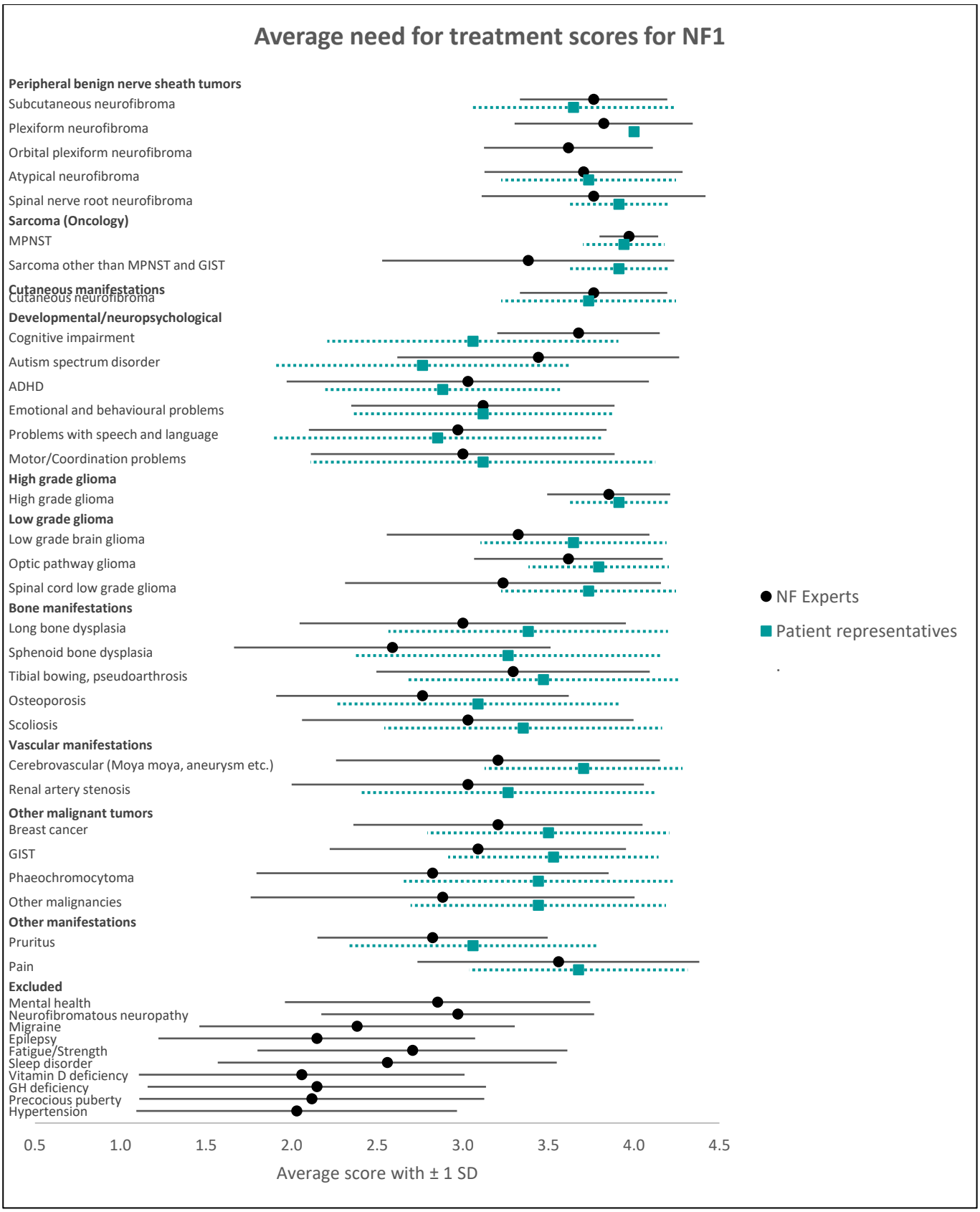

Figure 3. *Forest plot of the average need for treatment scores with ± 1 SD of the second NF expert questionnaire and patient representatives survey for NF1. This plot only contains valid answers from experts, "Do not know" answers have been excluded. Average scores could range between 1 and 4, a higher score implies a higher need for new treatment.*

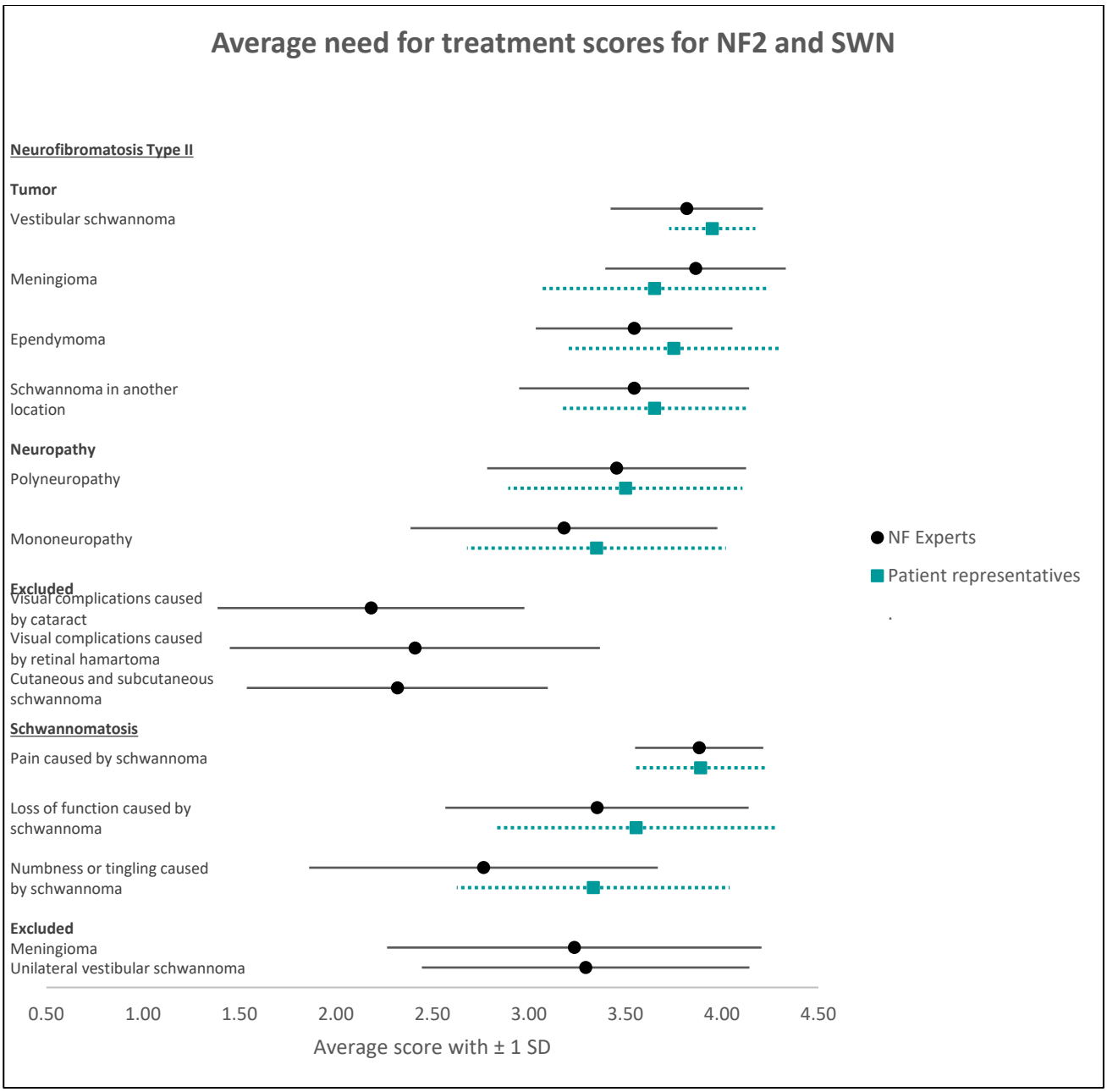

Figure 4. *Forest plot of the average need for treatment scores with ± 1 SD of the second NF expert questionnaire and patient representatives survey for NF2 and SWN. This plot only contains valid answers from experts, "Do not know" answers have been excluded. Average scores could range between 1 and 4, a higher score implies a higher need for new treatment.*

3.4. Stage 3: Consensus meeting for NF experts

A total of 7 external NF experts and 5 WP7 clinicians participated in the consensus meeting. In the NF1 consensus discussion a number of manifestations were excluded based on the availability of already existing effective treatments (e.g. vitamin D deficiency, precocious puberty, growth hormone deficiency), which was also reflected in their low average scores for availability of treatment and evidence for treatment (ANNEX V). Two manifestations were excluded due to limited feasibility to perform trials (fatigue/strength, sleep disorder).

The remaining manifestations were grouped into 10 main groups, based on e.g. pathophysiology, organ system, possible targets for treatment, and the feasibility to include them into platform trials (Table 1). It was decided that the groups “Other malignancies” and “Other manifestations” would not be included into the final ranking of the manifestation groups. For the malignancies, it would be more feasible to perform trials in the general oncology population, instead of a NF specific platform trial. For pain and pruritus, which are included into the “Other manifestations” group, the pathology is not sufficiently understood for the development of a platform trial.

Manifestations	*Average ranking NF expert consensus meeting (SD)* *Lower ranking = higher priority*	*Average ranking patient representatives (SD)* *Lower ranking = higher priority*	*Included in platform trials after final workshop Yes/No*
Neurofibromatosis type 1			
Peripheral benign nerve sheath tumors	2,33 (1,61)	4,38 (2,66)	Yes
Subcutaneous neurofibroma			
Plexiform neurofibroma			
Orbital plexiform neurofibroma			
Atypical neurofibroma			
Spinal nerve root neurofibroma			
Sarcoma (Oncology)	2,67 (1,67)	3,35 (2,21)	Yes
MPNST (Malignant Peripheral Nerve Sheath Tumor)			
Sarcoma other than MPNST and GIST (Gastrointestinal Stromal Tumor)			
Cutaneous manifestations	3,33 (2,15)	4,56 (3,23)	Yes
Cutaneous neurofibroma			
Developmental/ Neuropsychological abnormalities	4,08 (1,38)	6,18 (2,75)	No
Cognitive impairment			
Autism spectrum disorder			
ADHD			
Emotional and behavioral problems			
Problems with speech and language development			
Motor/Coordination problems			
High grade glioma	4,83 (2,21)	3,18 (1,75)	Yes
High grade glioma			
Low grade glioma	4,83 (1,47)	5,32 (1,87)	No
Low grade brain glioma			
Optical pathway glioma			
Spinal cord low grade glioma			
Bone manifestations	6,42 (1,38)	6,97 (1,91)	No
Long bone dysplasia			
Sphenoid bone dysplasia			
Tibial bowing, pseudoarthrosis			
Osteoporosis			
Scoliosis			
Vascular manifestations	7,5 (0,67)	7,29 (2,11)	No
Cerebrovascular - Moya moya, hemorrhage, infarction			
Renal artery stenosis			
Other malignant tumors	-		
Breast cancer			

Manifestations	Average ranking NF expert consensus meeting (SD) Lower ranking = higher priority	Average ranking patient representatives (SD) Lower ranking = higher priority	Included in platform trials after final workshop Yes/No
GIST			
Phaeochromocytoma			
Other malignancies			
Other manifestations	-		
Pruritus			
Pain			
Excluded	-		
Mental health problems			
Neurofibromatous neuropathy			
Migraine			
Epilepsy			
Fatigue / strength			
Sleep disorder			
Vitamin D deficiency			
Growth hormone deficiency			
Precocious puberty			
Hypertension			
Neurofibromatosis type 2			
Tumor	1	1,05 (0,22)	Yes
Vestibular schwannoma			
Meningioma			
Ependymoma			
Schwannoma in other location			
Neuropathy	2	1,95 (0,22)	No
Polyneuropathy			
Mononeuropathy			
Excluded	-		
Visual complications caused by cataract			
Visual complications caused by retinal hamartoma			
Cutaneous and subcutaneous schwannoma			
Schwannomatosis			
Pain caused by schwannoma	1	1,22 (0,44)	Yes
Loss of function caused by schwannoma	2	2,11 (0,78)	No
Numbness or tingling caused by schwannoma	3	2,67 (0,50)	No
Excluded	-		
Meningioma			
Unilateral vestibular schwannoma			

Table 1. *Grouping of the manifestations into main groups as decided in the NF expert consensus meeting, and the average ranking of the manifestations groups with corresponding standard deviations (SD's). Average rankings could vary between 1 and 8 for NF1, 1 and 2 for NF2 and 1 and 3 for SWN, and a lower average ranking implies higher priority.*

All NF experts and WP7 clinicians that participated in the consensus meeting completed the third and final questionnaire on the ranking of the 8 manifestation groups. Average rankings ranged from 2,33 to 7,5, and displayed large variability expressed by large SDs.(Table 1) The distribution of the rankings can be seen in more detail in Figure 5. The percentage of respondents that marked the feasibility to perform trials as easy was highest for the “Peripheral benign nerve sheath tumor group” with 92%, followed by the “Cutaneous manifestations” (83%) and “Sarcoma” group (75%). Lowest feasibility was appointed to vascular manifestations (8% of respondents marking feasibility as easy).

NF experts	Rank 1-3	Rank 4-6	Rank 7-8
Sarcoma/MPNST	10	1	1
Peripheral benign nerve sheath tumors	9	3	0
Cutaneous manifestations	7	4	1
Neurodevelopmental	4	8	0
High grade gliomas	3	6	3
Low grade gliomas	2	9	1
Bone manifestations	1	4	7
Vascular manifestations	0	1	11

NF patient representatives	Rank 1 - 3	Rank 4 - 6	Rank 7 - 8
High grade gliomas	20	11	3
Sarcomas/MPNST	20	9	5
Cutaneous manifestations	17	7	10
Peripheral benign nerve sheath tumors	16	10	8
Neurodevelopmental	8	10	16
Low grade gliomas	5	20	9
Bone manifestations	2	9	23
Vascular manifestations	2	8	24

Figure 5. Distribution of the rankings of NF1 manifestation groups as given during the expert consensus meeting and the patient representatives’ survey. A lower ranking means higher priority for inclusion in clinical trials. Manifestation groups are sorted to the number of votes in the highest priority rankings (rank 1-3).

For **NF2**, a total of 3 manifestations were excluded during the consensus meeting, either because effective (surgical) treatments are already available (cataract), or because the manifestations are rare and/or rarely cause significant symptoms (retinal hamartoma, cutaneous schwannoma). Although important to research in the future given its severity, it was decided that the manifestation orbital meningioma could be grouped under “Meningioma”. The remaining manifestations were grouped into a “Tumor” and a “Neuropathy” group, with the first group receiving the highest priority in future platform trials.

For **SWN**, unilateral vestibular schwannoma and meningioma were excluded for their rarity and availability of reasonably effective surgical treatment options. Pain was identified as the most important manifestation, given its severity and highest feasibility to perform platform trials for. Loss of function and numbness and/or tingling due to a schwannoma were also considered, but received a lower ranking than pain due to low feasibility and lacking clear outcome measures.

3.5. Stage 4: Patient representatives’ survey and consensus meeting

We obtained 34 responses of patient representatives for NF1, 20 for NF2 and 9 for SWN (Table 2). We calculated an estimated response rate of 80%. An exact response rate could not be determined, since it is not clear if all patient organizations responded, and how many patient representatives each patient organization provided. For NF1 there were more parent/caregivers of patients than patients, with quite an even distribution amongst representatives from Europe and the USA. In NF2 and SWN, there were more patients than parents/caregivers, and most of them were from Europe, especially in NF2.

No. of respondents		Age				Country		Role		
		11 – 20 years	21 – 40 years	41 – 65 years	66+ years	Europe	USA	Patient	Parent/ caregiver	Other
NF1	34	1 (2,9%)	12 (35,3%)	18 (52,9%)	3 (8,8%)	14 (41,2%)	20 (58,8%)	12 (35,5%)	18 (52,9%)	4 (11,8%)
NF2	20	2 (10%)	12 (60%)	6 (30%)	0 (0%)	14 (70%)	6 (30%)	13 (65%)	4 (20%)	3 (15%)
SWN	9	1 (11,1%)	1 (11,1%)	7 (77,8%)	0 (0%)	5 (55,6%)	4 (44,4%)	6 (66,7%)	1 (11,1%)	2 (22,2%)

Table 2. *Characteristics of the respondents of the patient representatives' survey. NF1 = Neurofibromatosis type I, NF2 = Neurofibromatosis type II, SWN = Schwannomatosis.*

Full details of the results of the patients' representatives' survey can be found in ANNEX VI.

No manifestation received an average need for treatment score lower than 2,44.Table 1 (Figure 3, Figure 4) Generally, all manifestations were scored highly with relatively small SDs (Fig. 6 - 8, Annex VII). The highest average need for new treatment scores (NT) for NF1 were for the manifestations plexiform neurofibroma (4,00 (SD 0,00)), MPNST (3,94 (SD 0,24)) and spinal root neurofibroma (3,91 (SD 0,29)) (Figure 3). Lowest average NT scores were appointed to Autism Spectrum Disorder (2,76 (SD 0,85), problems with speech and language development (2,85 (SD 0,96)) and ADHD (2,88 (SD 0,69)). High grade gliomas reached the highest priority with an average ranking of 3,18 (SD 1,75), followed by sarcomas (3,35 (SD 2,21)) and peripheral benign nerve sheath tumors (4,38 (SD 2,66)). The vascular manifestations received lowest priority (average ranking 7,29 (SD 2,11)), followed by the bone manifestations (6,97 (SD 1,91)) and the developmental / neuropsychological manifestations (6,18 (SD 2,75)). (Table 1) The distribution of the rankings was different from the one from the NF experts (Figure 55).

Ten manifestations of NF1 displayed a ceiling effect on the need for new treatment item (more than 75% of the respondents appointed the highest score), including three manifestations of the peripheral benign nerve sheath tumor group, the two sarcoma manifestations (MPNST and other sarcoma) and high grade gliomas (ANNEX VIII). For NF2 vestibular schwannoma and ependymoma showed a ceiling effect on NT, and for SWN it was shown by pain.

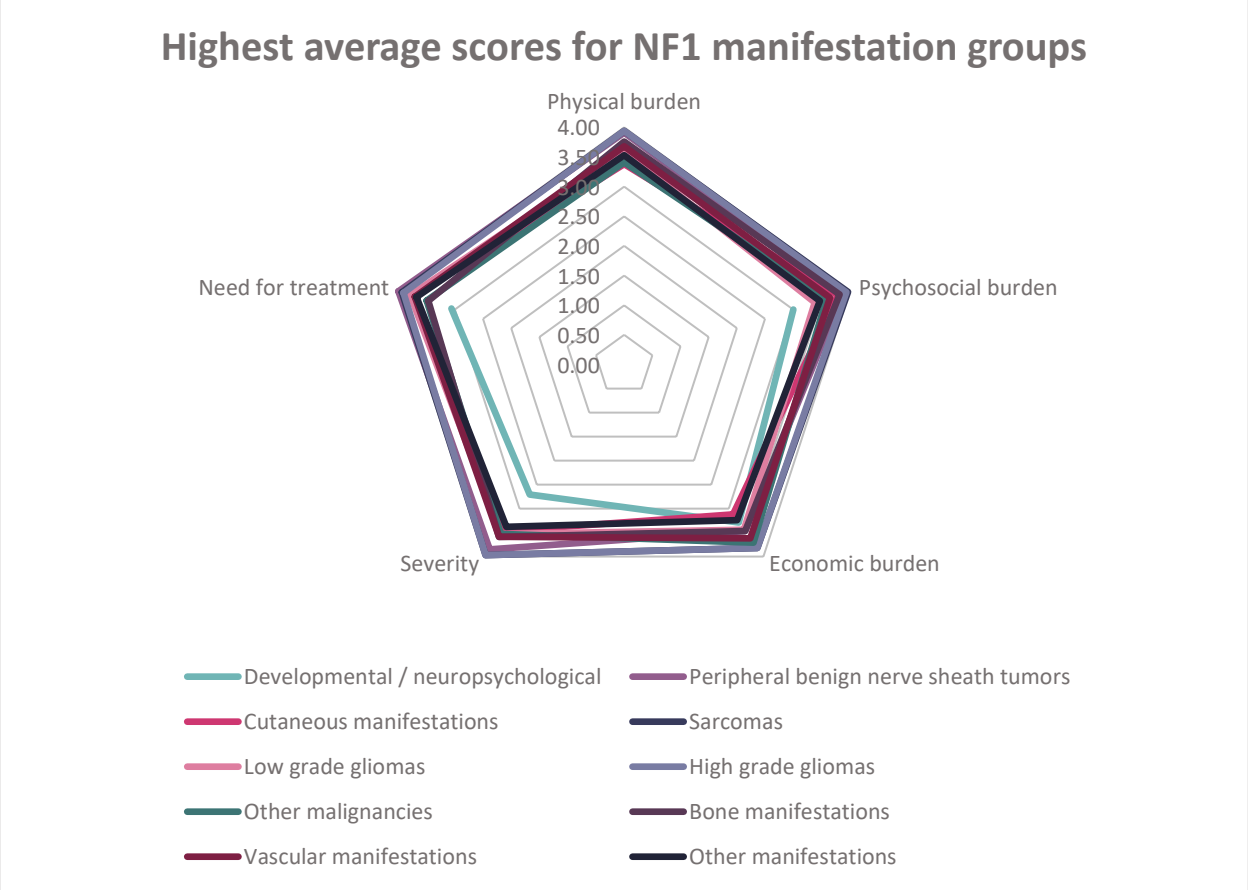

Figure 6. *Radar chart of the results from the patient representatives' survey for NF1. For each manifestation group the average score of the highest scoring manifestation within that group is displayed. A higher score implies more severe burden, higher severity and higher need for treatment. NF1 = Neurofibromatosis type I.*

For **NF2**, the highest average NT score was appointed to vestibular schwannoma (average score 3,95 (SD 0,22)), but all manifestations within the tumor group received high average scores with small SDs (Figure 4). Lowest average NT scores were seen in cutaneous or subcutaneous schwannomas (3,25 (SD 0,91)) and mononeuropathy (3,35 (SD 0,67)).

Average scores of all items were generally high and overlapping, and all have a distinct pentagon shape in the radar chart.(Figure 7) The tumor group was assigned the highest average ranking of 1,05 (SD 0,22), neuropathies received an average ranking of 1,95 (SD 0,22)) (Table 1).

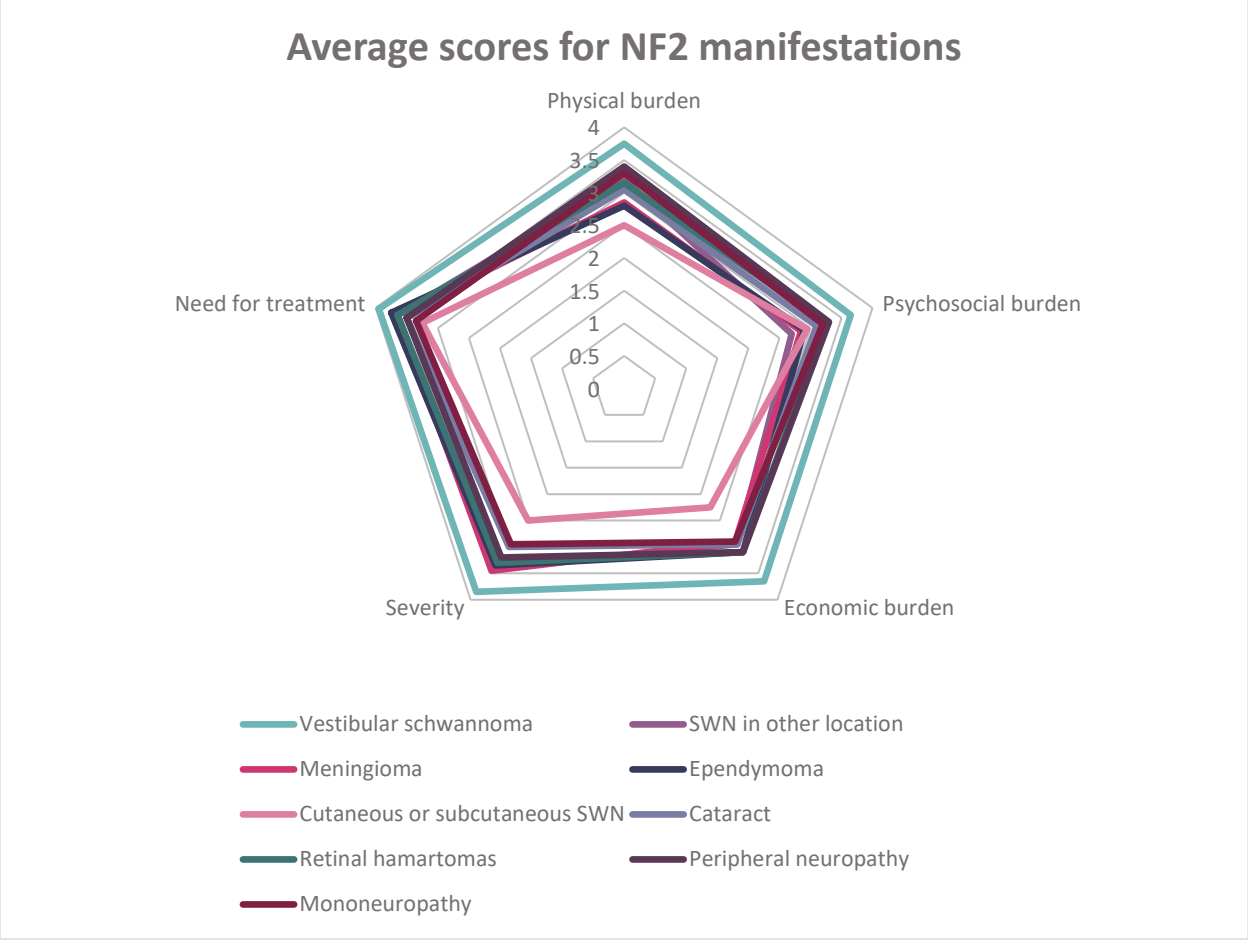

Figure 7. *Radar chart of the average scores of the patient representatives' survey for NF2. Average scores are depicted for each manifestation separately. A higher score implies more severe burden, higher severity and higher need for treatment. NF2 = Neurofibromatosis type II.*

In **SWN**, pain was the highest scoring manifestation, with the highest average score of all items (Figure 8). All three manifestations have roughly the same shape in the radar chart, and the lines do not overlap nor cross each other. Numbness and/or tingling caused by a schwannoma received the lowest average scores. Pain also received the highest average ranking of 1,22 (SD 0,44) (Table 1).

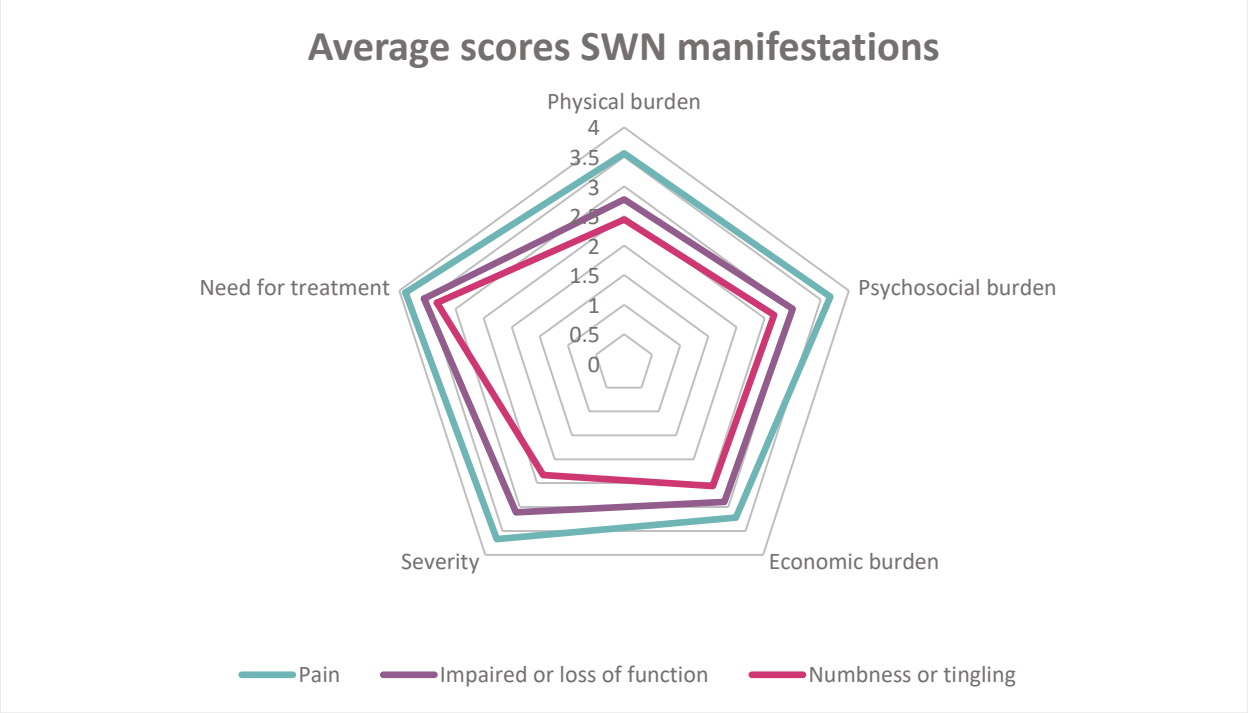

***Figure 8**. Radar chart of the average scores of the patient representatives' survey for SWN. Average scores are depicted for each manifestation separately. A higher score implies more severe burden, higher severity and higher need for treatment. SWN = Schwannomatosis*

The average ranking of the manifestations was discussed during the virtual consensus meeting for patient representatives. The representatives from NFPU and CTF agreed with the established ranking for NF1, NF2 and SWN as decided by the respondents of the survey, also confirming the findings from the NF1 survey that patients are generally very worried about high grade gliomas, since the prognosis is so poor.

3.6. Stage 5: Final workshop

The final selection of manifestation groups to include into future future platform trials was based on the results from the NF expert consensus meeting and results from the patient representatives' survey and consensus meeting. It was decided that for **NF1**, the following groups will be included into future platform trials: 1) peripheral benign nerve sheath tumors, 2) sarcomas, 3) cutaneous manifestations, and 4) high grade gliomas. The focus for **NF2** will be the tumor group. For **SWN**, the manifestation pain will be top priority.

4. Discussion

By performing a five-staged modified Delphi procedure, we reached consensus on the most important challenges in Neurofibromatosis as seen by NF experts and patient representatives. We identified four manifestation groups for NF1: peripheral benign nerve sheath tumors, sarcomas, cutaneous manifestations and high grade gliomas. For NF2, priority was assigned to the grouped tumor manifestations, although neuropathies were considered as well. For Schwannomatosis, pain has been selected as the absolute priority for future SWN platform trials.

Since platform trials can include multiple conditions in the same trial, either because of similar treatment and/or similar pathophysiology, manifestations could be aggregated into main groups. This allowed for a more extensive selection of manifestations that could be included. A similar strategy can be seen in a newly launched platform trial for NF2 in the USA, where different tumor types are encompassed in the same trial (https://clinicaltrials.gov/ct2/show/NCT04374305). It should be noted that this grouping of manifestations is susceptible to change according to new insights, e.g. the discovery of a new common drug target, or if the pathophysiology of a manifestation can be linked to the pathophysiology of another manifestation (group).

The selection of the NF1 manifestation groups peripheral benign nerve sheath tumors and sarcomas is in alignment with past and current trials in NF1, which have focused mainly on plexiform neurofibroma and MPNST (4). Although cutaneous manifestations have received less priority in clinical trials compared to these other two groups, there is a noticeable increase in (planned) trials for oral and/or topical drug treatments and laser/photodynamic therapy. The high priority assigned to cutaneous manifestations by both NF experts and patient representatives matches with qualitative studies in NF1 patients showing that the cutaneous manifestations are often considered as one of the worst aspects of their condition, causing great emotional distress (32, 33). Finding new therapies should therefore receive an even higher priority. For NF2, the high priority of vestibular schwannoma and other tumor manifestations agrees with the main focus of current NF2 trials on vestibular schwannoma and meningioma (4).

Until now, there has been limited information available on the comparison of expert and patient needs in NF. In a study by Lai et al. (34), which focused specifically on the concerns associated with plexiform neurofibroma in NF1 patients, it became apparent that experts and patients had different concerns regarding this manifestation. While patients and their parents placed greater emphasis on the psychosocial impact of the manifestation, experts focused more on the physical symptoms resulting from the location of the tumor.(34) This matches our findings of conflicting priorities of NF experts and patient representatives, underlining to the importance of including patient opinions in the planning, implementation, oversight and execution of trials, which is a key concept in EU-PEARL as well.

This study has several strengths. By using modified Delphi questionnaires for the NF experts, we were able to utilize one of the Delphi's greatest benefits: the involvement of large numbers of participants from all over the world while not needing face to face contact (35, 36). Additionally, the Delphi method avoids the possible dominance of particular individuals in reaching consensus through anonymity and the use of all answers when evaluating the results (37). The addition of the consensus meeting after the two questionnaires enabled discussion of the thematic analysis of the free-text comments. This discussion allowed reflection on the difference in interpretation of the questions of

the second Delphi questionnaire, which could be taken into account when ranking the manifestation groups. Another strength of this study is that we included both the opinion of NF experts and patient representatives in our final selection of manifestations, securing inclusion of patient needs from the very start. Respondents for both the NF expert Delphi as the patient representatives' survey are also geographically dispersed, representing NF experts and patients from all over the world, limiting country and culture-related bias.

Three main limitations of the NF expert Delphi can be identified. The Delphi method has no standard method for defining consensus. Choosing different exclusion criteria in the first questionnaire might have resulted in a different final set of manifestations (36). Secondly, while not requiring face-to-face contact can be advantageous in big international projects like EU-PEARL, the positive aspects of personal interaction are lacking, like discussing conflicting points and explaining chosen answers (36). By providing respondents room to give feedback in between questionnaires and the addition of the consensus meeting, we hoped to overcome this issue. The planned consensus meeting had to be turned into a virtual meeting as well due to COVID-19 measures, unfortunately. Finally, group consensus is not synonymous to "best results", again underlining the fact that our final selection of manifestations is not definitive and can still be changed along the way.

Partnerships between researchers and patients in the development and performance of clinical trials is increasingly recognized as a priority within the development of new drug therapies. We included the patients' opinion by performing a patient representatives' survey. Several limitations of the patient representatives' survey exist, one being the relatively small sample size. This can partly be explained by the rarity of the three diseases and our choice to only include patient representatives. Also, given the timeframe of this study, the survey was only offered in English, facilitating English native speakers in particular. This could have caused inclusion bias towards English speaking patient representatives. The non-native English speakers (38% of the representatives that completed the survey) however did not report important struggles with the survey not being in their native language, as questioned at the end of the survey. Results from the patient survey were very homogenous, suggesting a certain level of data saturation of the results, which probably would not have been changed by including a larger or more varied sample. Given the limitations of our patient representatives' survey however, a new survey with a larger population consisting of NF patients in general (instead of patient representatives only) is needed to get a more reliable view on burden, severity and manifestation ranking as seen by NF patients. The results from this survey could then be used in future NF research, outside the scope of EU-PEARL activities.

We chose to only include patient representatives rather than patients themselves, anticipating that they would be able to answer questions for all manifestations of their disease after a specific instruction at the start of the survey. Multiple patient representatives commented on the difficulty of estimating burden of manifestations that they themselves had no experience with, however. This may have affected priority of manifestations that had the highest prevalence in our patient representatives' survey, such as plexiform neurofibroma (prevalence 68%), subcutaneous neurofibroma (62%) and cutaneous neurofibroma (59%) in NF1. This by prevalence affected priority could be especially true for NF2 manifestations, where the tumor manifestations (highest prevalence 100% for vestibular schwannoma) were much more common than the neuropathies (highest prevalence 50% for peripheral neuropathy). In contrast, the high grade gliomas were scored very highly, while only 6% of the respondents had experience with this manifestation. While the results and final ranking of the patient representatives' survey should not be considered definitive due to the mentioned limitations,

we hope that they can serve as an indication on where patient priorities lie.

With the results of our study we conclude that NF experts and patients prioritize the development of future clinical trials for new drug treatments to be developed for peripheral benign nerve sheath tumors, sarcomas, cutaneous manifestations and high grade gliomas for NF1, tumor manifestations for NF2, and pain for Schwannomatosis. The findings of this study are mostly important and relevant to EU-PEARL, to aid the creation of the framework on which the future platform trials can be conducted. For other research, this study may serve as a guideline on what manifestation may have highest priority when trying to select a new topic to research.

Although high grade gliomas were not assigned much priority in the consensus meeting by the NF1 experts, the patient representatives scored this manifestation very high on all items, and it was selected as top priority by most respondents. This may be related to a great fear that patients have for this manifestation, which was confirmed by the representatives present during the patient consensus meeting. Although the NF expert group acknowledges the problems with designing a platform trial for high grade gliomas, such as its low incidence (risk of dying from a NF1-related malignant brain tumor ranging between a minimum of 3% and a maximum of 9% as calculated from the data of Uusitalo et al. (38)) and short life expectancy from diagnosis (39 - 41), this led us to reconsider our decision and to include the high grade gliomas in the final selection. So far, there has been little to no research on drug treatments in NF1-related high grade gliomas. The results from this study imply that more research for high grade gliomas is needed, especially given the bad response to current available treatments and lack of early detection methods (42, 43). It will also help to find methods to study the effect of treatment for rare complications in rare disorders with only very few patients available for study at a given moment.

Developmental and neurocognitive manifestations have not been included in our final selection of manifestations for the development of drug trials, despite the relatively high average ranking by the NF experts. One of the main reasons for this exclusion is the lack of a standardized set of endpoints for cognitive and behavioral manifestations, illustrated by the wide variety of tests and outcome measures that have been used in cognitive and behavioral studies in NF1 (44-46). There is a clear need for a set of reliable cognitive outcome measures that can be used across NF clinical trials. The ReiNS group (Neurocognitive Committee of the Response Evaluation in Neurofibromatosis and Schwannomatosis) is trying to achieve consensus on which outcome measures are the most fitting, and so far they have provided recommendations for the domain of attention (47). Until a clear set of cognitive and behavioral endpoints has been identified, it does not seem feasible to include developmental and neurocognitive manifestations into a large scale platform trial specifically designed for these manifestations. In addition to that, given the fact that neurocognitive outcome measures used in previous studies showed weak test-retest correlations over a 1-year period (48), neurocognitive manifestations require a distinct control group when trying to determine the effect of a drug treatment. Results from a longitudinal natural history study (LNHS) seem less valid to compare effects of treatments, requiring either a placebo group or comparison to another treatment arm. We believe that developmental and neurocognitive manifestations should be included as secondary outcome measures in other (platform) trials, given the high prevalence (up to 80% of NF1 children (49, 50)) and the effect they have on the daily life of NF1 patients (51, 52).

To our knowledge, there have been no clinical trials for Schwannomatosis in the last 10 years, emphasizing the urgent need for new trials to be developed and performed. A good step forward is a

new phase II study that has recently started, researching the effect of Tanezumab on the worst experienced pain level as reported by patients, utilizing the frequently used Numerical Rating Scale (NRS-11) (https://clinicaltrials.gov/ct2/show/NCT04163419).

5. Conclusion

Through this study the neurofibromatosis work package of EU-PEARL (WP7) has made the important final step of identifying the most important challenges in NF. By using a modified Delphi approach, we have reached consensus amongst a large group of NF experts and patient representatives across Europe and the USA on how to group the various NF manifestations under the same platform trial. This grouping was followed by a prioritization of these groups into a final selection of manifestations to be included into the Platform trials as they will be conducted by EU-PEARL, focusing future efforts on peripheral benign nerve sheath tumors, sarcomas, cutaneous manifestations and high grade gliomas for NF1, tumors for NF2, and pain for Schwannomatosis.

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ANNEXES

ANNEX I. Original manifestation list used in first questionnaire

Neurofibromatosis type 1

Neurofibromas

- Cutaneous and subcutaneous neurofibromas
- Plexiform neurofibroma
- Atypical neurofibroma of uncertain potential

Visual

- Optic pathway glioma
- Glaucoma
- Lisch nodules

Orthopaedic

- Bone dysplasia - long bones, vertebrae, atlanto-axial dislocation
- Tibial bowing, Pseudarthrosis due to bone fractures
- Pectus excavatum
- Hypermobility
- Scoliosis (idiopathic/dystrophic)
- Stature disorder (short stature or gigantism)
- Osteoporosis

Neurological and Psychiatric manifestations

- Epilepsy
- Migraine
- Cognitive impairment
- ADHD
- Autism spectrum disorder
- Emotional and behavioral problems
- Mental health problems (anxiety and depression)
- Problems with speech and language development
- Multiple sclerosis
- Neurofibromatous neuropathy
- Aqueduct stenosis
- Brain or spinal cord glioma
- Malignant peripheral sheath tumor (MPNST)
- Spinal cord compression secondary to neurofibroma or kyphoscoliosis

Hormonal disorders

- Precocious puberty
- Growth hormone deficiency
- Vitamin D deficiency

Skin manifestations

- Café au lait spots
- Frecklings
- Pigmentation
- Pruritus
- Juvenile xanthogranulomas

Other tumors

- Breast cancer in < 50 years
- GIST
- Phaeochromocytoma
- Glomus tumor
- Liver hemangioma
- Other malignancies including lymphoma, leukaemia, bowel cancer, thyroid cancer
- Sarcoma

Vascular & cardiac disorders

- Renal artery stenosis
- Cerebrovascular – including moya moya syndrome, aneurysm, haemorrhage, occlusion and fistula
- Hypertension
- Congenital heart disease

Other manifestations

- Sleep disorder
- Fatigue
- Pain

Neurofibromatosis type 2

- Vestibular schwannomas
- Schwannomas in other location
- Meningioma
- Ependymoma
- Cutaneous or subcutaneous schwannomas
- Visual complications caused by cataract
- Visual complications caused by orbital meningiomas
- Visual complications caused by retinal hamartomas
- Peripheral neuropathy/Pain

Schwannomatosis

- Chronic pain caused by a schwannoma
- Impaired or loss of function caused by a schwannoma
- Numbness or tingling caused by a schwannoma
- Meningioma
- Vestibular schwannoma

ANNEX II. Manifestation list as used for second questionnaire

Neurofibromatosis type 1

Neurofibromas

- Cutaneous and subcutaneous neurofibromas
- Plexiform neurofibroma
- Atypical neurofibroma of uncertain malignant potential
- Paravertebral neurofibroma with compression of the spinal cord

Visual

- Optic pathway glioma
- Orbital plexiform neurofibroma

Orthopaedic

- Bone dysplasia - long bones, vertebrae
- Tibial bowing, Pseudarthrosis
- Sphenoid bone dysplasia
- Scoliosis
- Osteoporosis

Neurological and Psychiatric

- Epilepsy
- Migraine
- Cognitive impairment
- ADHD
- Autism
- Emotional and behavioral problems
- Mental health problems (anxiety and depression)
- Problems with speech and language development
- Neurofibromatous neuropathy
- Motor/Coordination problems

Hormonal disorders

- Precocious puberty
- Growth hormone deficiency
- Vitamin D deficiency

Skin

- Pruritus

Malignancies

- MPNST
- Breast cancer in < 50 years
- GIST
- Phaeochromocytoma
- Sarcoma other than MPNST
- Low grade brain glioma
- High grade brain glioma
- Spinal cord glioma
- Other malignancies including lymphoma, leukaemia, bowel cancer, thyroid cancer

Vascular & cardiac disorders

- Renal Artery stenosis
- Cerebrovascular – including moya moya syndrome, aneurysm, haemorrhage, occlusion and fistula
- Hypertension

Other

- Sleep disorder
- Fatigue/strength
- Pain

Neurofibromatosis type 2

- Vestibular schwannomas
- Schwannomas in other location
- Meningioma
- Ependymoma
- Cutaneous or subcutaneous schwannomas
- Visual complications caused by cataract
- Visual complications caused by orbital meningiomas
- Visual complications caused by retinal hamartomas
- Peripheral neuropathy/Pain
- Mononeuropathy

Schwannomatosis

- Chronic pain caused by a schwannoma
- Impaired or loss of function due to a schwannoma
- Numbness or tingling due to a schwannoma
- Meningioma
- Vestibular schwannoma

ANNEX III. NF experts that participated in the Delphi questionnaires

Only the NF experts that agreed to their name being published are listed here, so this list does not feature all participants.

A. A. Azizi, MD – Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Pediatric Intensive Care and Neuropediatrics, Medical University of Vienna, Austria

A. Bakker, PHD – President of Children's Tumor Foundation, New York, USA

I. Blanco, MD – Department of Clinical Genetics, Hospital Germans Trias i Pujol, Badalona, Spain

C. Cassiman, MD, PhD – Department of Ophthalmology, UZ Leuven, Leuven, Belgium

G. Evans, MD - Centre for Genomic Medicine, Division of Evolution and Genomic Sciences, University of

Manchester, St Mary's Hospital, Manchester, UK

R. E. Ferner, MD - Department of Neurology, Guy's and St. Thomas' NHS Foundation Trust London, UK

M. J. Fisher, MD – Division of Oncology, The Children's Hospital of Philadelphia, USA

D. Halliday, MD, Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Trust, Oxford, UK

J. T. Jordan, MD, MPH - Pappas Center for Neuro-Oncology, Massachusetts General Hospital, Boston, USA

M. Kalamarides, MD PhD – Department of Neurosurgery, Hôpital Pitié-Salpêtrière-APHP, Sorbonne université, Paris, France

M. Karajannis, MD, MS – Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, USA

H. Kehrer-Sawatzki, PhD – Institute of Human Genetics, University of Ulm, Ulm, Germany

M. Larralde, MD – Department of Dermatology, Hospital Alemán, Buenos Aires, Argentina

E. Legius, MD – Department of Clinical Genetics, UZ Leuven, Belgium

R. Listernick, MD – Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, USA

V. Mautner, MD – Department of Neurology, University Medical Center Hamburg-Eppendorf, Germany

V. Merker, PHD – Department of Neurology, Massachusetts General Hospital, USA

C. Moertel, MD – Department of Pediatrics, University of Minnesota Medical School, Minneapolis, USA

J. Ngeow Yuen Yie, MD – Cancer Genetics service, National cancer Centre Singapore, Singapore

R. Oostenbrink, MD – Department of Pediatrics, Sophia's Children's Hospital, Rotterdam, The Netherlands

R. J. Packer, MD – Center for Neuroscience and Behavioral Medicine, Children's National Hospital, Washington D.C., USA

L. Papi, MD – Department of Biomedical Experimental and Clinical Sciences, University of Florence, Italy

C. Potratz, MD – Department of Pediatric Neurology, Charité Universitätsmedizin Berlin, Germany

T. Rosser, MD – Department of Neurology, Children's Hospital Los Angeles, USA

H. Salvador, MD – Department of Oncology and Haematology, Sant Joan de Deu Barcelona Children's Hospital, Barcelona, Spain

M. J. Smith, PHD - Centre for Genomic Medicine, Division of Evolution and Genomic Sciences, University of Manchester, St Mary's Hospital, Manchester, UK

E. Trevisson, MD, PhD – Clinical Genetics Unit, Dept. of Women's and Children's Health

University of Padova, Padova, Italy

A. Varan, MD - Department of Pediatric Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey

K. Wimmer, PhD – Institute of Human Genetics, Medical University of Innsbruck, Innsbruck, Austria

P. Wolkenstein, MD – Department of Dermatology, Hôpital Universitaire Pitié-Salpêtrière (APHP), Paris, France

ANNEX IV. Results of the second Delphi questionnaire for NF experts

Table A1. *Distribution of the scores as appointed to the different manifestations by NF experts. Only valid answers from experts have been included, "Do not know" answers have been excluded. A higher score implies higher need for treatment, higher lack of available treatments and higher lack of evidence for treatments. Items where more than 75% of the respondents chose the highest scores are marked in green, items where 75% appointed the lowest score are marked in a grey color. NF1 = neurofibromatosis type I, NF2 = neurofibromatosis type II*

Manifestation	Need for new treatment				Available treatments				Evidence for treatments				
Score	1	2	3	4	1	2	3	4	1	2	3	4	5
NF1													
Peripheral benign nerve sheath tumors													
(Sub)Cutaneous neurofibroma	0 (0,0%)	0 (0,0%)	8 (23,5%)	26 (76,5%)	2 (5,9%)	7 (20,6%)	13 (38,2%)	12 (35,3%)	1 (3,3%)	2 (6,7%)	11 (36,7%)	7 (23,3%)	9 (30,0%)
Plexiform neurofibroma	0 (0,0%)	2 (5,9%)	2 (5,9%)	30 (88,2%)	9 (26,5%)	15 (44,1%)	9 (26,5%)	1 (2,9%)	15 (46,9%)	16 (50,0%)	1 (3,1%)	0 (0,0%)	0 (0,0%)
Orbital plexiform neurofibroma	0 (0,0%)	0 (0,0%)	13 (38,2%)	21 (61,8%)	7 (21,2%)	13 (39,4%)	12 (36,4%)	1 (3,0%)	6 (19,4%)	12 (38,7%)	9 (29,0%)	3 (9,7%)	1 (3,2%)
Atypical neurofibroma	0 (0,0%)	2 (5,9%)	6 (17,6%)	26 (76,5%)	1 (2,9%)	10 (29,4%)	9 (26,5%)	14 (41,2%)	3 (9,7%)	5 (16,1%)	9 (29,0%)	8 (25,8%)	6 (19,4%)
Spine root neurofibroma	1 (2,9%)	1 (2,9%)	3 (8,8%)	29 (85,3%)	1 (2,9%)	13 (38,2%)	11 (32,4%)	9 (26,5%)	4 (12,9%)	6 (19,4%)	11 (35,5%)	4 (12,9%)	6 (19,4%)
Sarcomas													
MPNST	0 (0,0%)	0 (0,0%)	1 (2,9%)	33 (97,1%)	6 (17,6%)	14 (41,2%)	8 (23,5%)	6 (17,6%)	5 (16,1%)	11 (35,5%)	8 (25,8%)	3 (9,7%)	4 (12,9%)
Sarcoma other than MPNST	1 (2,9%)	5 (14,7%)	8 (23,5%)	20 (58,8%)	7 (20,6%)	13 (38,2%)	7 (20,6%)	7 (20,6%)	6 (22,2%)	7 (25,9%)	5 (18,5%)	3 (11,1%)	6 (22,2%)
Cutaneous manifestations													
(Sub)Cutaneous neurofibroma	0 (0,0%)	0 (0,0%)	8 (23,5%)	26 (76,5%)	2 (5,9%)	7 (20,6%)	13 (38,2%)	12 (35,3%)	1 (3,3%)	2 (6,7%)	11 (36,7%)	7 (23,3%)	9 (30,0%)
Developmental / neuropsychological manifestations													
Cognitive impairment	0 (0,0%)	0 (0,0%)	11 (32,4%)	23 (67,6%)	0 (0,0%)	7 (21,2%)	13 (39,4%)	13 (39,4%)	3 (10,3%)	5 (17,2%)	7 (24,1%)	3 (10,3%)	11 (37,9%)

Manifestation	Need for new treatment				Available treatments				Evidence for treatments				
Score	1	2	3	4	1	2	3	4	1	2	3	4	5
Autism spectrum disorder	1 (2,9%)	4 (11,8%)	8 (23,5%)	21 (61,8%)	2 (6,3%)	7 (21,9%)	7 (21,9%)	16 (50,0%)	3 (11,1%)	4 (14,8%)	4 (14,8%)	5 (18,5%)	11 (40,7%)
ADHD	3 (8,8%)	9 (26,5%)	6 (17,6%)	16 (47,1%)	17 (51,5%)	9 (27,3%)	5 (15,2%)	2 (6,1%)	16 (53,3%)	7 (23,3%)	5 (16,7%)	0 (0,0%)	2 (6,7%)
Emotional and behavioural problems	1 (2,9%)	5 (14,7%)	17 (50,0%)	11 (32,4%)	4 (12,1%)	14 (42,4%)	7 (21,2%)	8 (24,2%)	7 (23,3%)	7 (23,3%)	6 (20,0%)	3 (10,0%)	7 (23,3%)
Speech and language development problems	3 (8,8%)	4 (11,8%)	18 (52,9%)	9 (26,5%)	0 (0,0%)	5 (15,6%)	6 (18,8%)	21 (65,6%)	1 (3,6%)	5 (17,9%)	4 (14,3%)	3 (10,7%)	15 (53,6%)
Motor/Coordination problems	2 (5,9%)	7 (20,6%)	14 (41,2%)	11 (32,4%)	0 (0,0%)	6 (17,6%)	8 (23,5%)	20 (58,8%)	1 (3,4%)	4 (13,8%)	6 (20,7%)	2 (6,9%)	16 (55,2%)
High grade glioma													
High grade glioma	0 (0,0%)	0 (0,0%)	5 (14,7%)	29 (85,3%)	9 (26,5%)	11 (32,4%)	7 (20,6%)	7 (20,6%)	9 (31,0%)	6 (20,7%)	6 (20,7%)	3 (10,3%)	5 (17,2%)
Low grade glioma													
Low grade glioma	0 (0,0%)	6 (17,6%)	11 (32,4%)	17 (50,0%)	12 (35,3%)	16 (47,1%)	5 (14,7%)	1 (2,9%)	15 (46,9%)	11 (34,4%)	4 (12,5%)	1 (3,1%)	1 (3,1%)
Optic pathway glioma	0 (0,0%)	1 (2,9%)	11 (32,4%)	22 (64,7%)	22 (64,7%)	9 (26,5%)	3 (8,8%)	0 (0,0%)	18 (54,5%)	12 (36,4%)	3 (9,1%)	0 (0,0%)	0 (0,0%)
Spinal cord glioma	1 (2,9%)	8 (23,5%)	7 (20,6%)	18 (52,9%)	6 (17,6%)	10 (29,4%)	9 (26,5%)	9 (26,5%)	7 (25,0%)	4 (14,3%)	6 (21,4%)	4 (14,3%)	7 (25,0%)
Bone manifestations													
Long bone dysplasia	3 (8,8%)	6 (17,6%)	13 (38,2%)	12 (35,3%)	0 (0,0%)	7 (21,2%)	7 (21,2%)	19 (57,6%)	0 (0,0%)	3 (10,0%)	5 (16,7%)	5 (16,7%)	17 (56,7%)
Sphenoid bone dysplasia	4 (11,8%)	12 (35,3%)	12 (35,3%)	6 (17,6%)	0 (0,0%)	3 (8,8%)	4 (11,8%)	27 (79,4%)	0 (0,0%)	2 (6,7%)	3 (10,0%)	3 (10,0%)	22 (73,3%)
Tibial bowing, pseudoarthrosis	1 (2,9%)	4 (11,8%)	13 (38,2%)	16 (47,1%)	0 (0,0%)	8 (23,5%)	9 (26,5%)	17 (50,0%)	0 (0,0%)	3 (9,7%)	8 (25,8%)	5 (16,1%)	15 (48,4%)

Manifestation	Need for new treatment				Available treatments				Evidence for treatments				
Score	1	2	3	4	1	2	3	4	1	2	3	4	5
Osteoporosis	2 (5,9%)	11 (32,4%)	14 (41,2%)	7 (20,6%)	15 (44,1%)	12 (35,3%)	4 (11,8%)	3 (8,8%)	11 (35,5%)	10 (32,3%)	6 (19,4%)	2 (6,5%)	2 (6,5%)
Scoliosis	3 (8,8%)	6 (17,6%)	12 (35,3%)	13 (38,2%)	2 (5,9%)	5 (14,7%)	4 (11,8%)	23 (67,6%)	2 (6,9%)	3 (10,3%)	3 (10,3%)	3 (10,3%)	18 (62,1%)
Vascular manifestations													
Cerebrovascular (Moya moya, aneurysm etc.)	3 (8,8%)	3 (8,8%)	12 (35,3%)	16 (47,1%)	4 (12,1%)	3 (9,1%)	3 (9,1%)	23 (69,7%)	3 (10,0%)	2 (6,7%)	3 (10,0%)	4 (13,3%)	18 (60,0%)
Renal artery stenosis	4 (11,8%)	5 (14,7%)	11 (32,4%)	14 (41,2%)	2 (5,9%)	4 (11,8%)	5 (14,7%)	23 (67,6%)	2 (6,7%)	4 (13,3%)	2 (6,7%)	2 (6,7%)	20 (66,7%)
Other malignancies													
Breast cancer	1 (2,9%)	6 (17,6%)	12 (35,3%)	15 (44,1%)	19 (55,9%)	10 (29,4%)	3 (8,8%)	2 (5,9%)	19 (63,3%)	1 (3,3%)	6 (20,0%)	2 (6,7%)	2 (6,7%)
GIST	2 (5,9%)	5 (14,7%)	15 (44,1%)	12 (35,3%)	7 (21,2%)	15 (45,5%)	5 (15,2%)	6 (18,2%)	6 (22,2%)	7 (25,9%)	7 (25,9%)	2 (7,4%)	5 (18,5%)
Phaeochromocytoma	4 (11,8%)	9 (26,5%)	10 (29,4%)	11 (32,4%)	5 (15,2%)	8 (24,2%)	5 (15,2%)	15 (45,5%)	3 (12,0%)	4 (16,0%)	5 (20,0%)	5 (20,0%)	8 (32,0%)
Other malignancies	5 (14,7%)	8 (23,5%)	7 (20,6%)	14 (41,2%)	15 (44,1%)	9 (26,5%)	6 (17,6%)	4 (11,8%)	12 (44,4%)	3 (11,1%)	5 (18,5%)	2 (7,4%)	5 (18,5%)
Other manifestations													
Pruritus	0 (0,0%)	11 (32,4%)	18 (52,9%)	5 (14,7%)	9 (27,3%)	14 (42,4%)	5 (15,2%)	5 (15,2%)	1 (3,7%)	6 (22,2%)	13 (48,1%)	3 (11,1%)	4 (14,8%)
Pain	2 (5,9%)	1 (2,9%)	7 (20,6%)	24 (70,6%)	13 (38,2%)	15 (44,1%)	4 (11,8%)	2 (5,9%)	13 (40,6%)	6 (18,8%)	11 (34,4%)	0 (0,0%)	2 (6,3%)
Excluded													
Mental health	3 (8,8%)	7 (20,6%)	16 (47,1%)	8 (23,5%)	20 (58,8%)	9 (26,5%)	4 (11,8%)	1 (2,9%)	17 (53,1%)	9 (28,1%)	4 (12,5%)	1 (3,1%)	1 (3,1%)
Neurofibromatous neuropathy	0 (0,0%)	11 (32,4%)	13 (38,2%)	10 (29,4%)	2 (5,9%)	6 (17,6%)	11 (32,4%)	15 (44,1%)	3 (10,7%)	5 (17,9%)	8 (28,6%)	1 (3,6%)	11 (39,3%)
Migraine	6 (17,6%)	13 (38,2%)	11 (32,4%)	4 (11,8%)	23 (67,6%)	8 (23,5%)	2 (5,9%)	1 (2,9%)	21 (63,6%)	8 (24,2%)	3 (9,1%)	0 (0,0%)	1 (3,0%)

Manifestation	Need for new treatment				Available treatments				Evidence for treatments				
Score	1	2	3	4	1	2	3	4	1	2	3	4	5
Epilepsy	9 (27,3%)	14 (39,4%)	8 (24,2%)	3 (9,1%)	28 (82,4%)	4 (11,8%)	2 (5,9%)	0 (0,0%)	26 (78,8%)	4 (12,1%)	3 (9,1%)	0 (0,0%)	0 (0,0%)
Fatigue/Strength	3 (8,8%)	11 (32,4%)	13 (38,2%)	7 (20,6%)	2 (6,1%)	7 (21,2%)	6 (18,2%)	18 (54,5%)	3 (11,5%)	2 (7,7%)	7 (26,9%)	5 (19,2%)	9 (34,6%)
Sleep disorder	6 (17,6%)	9 (26,5%)	13 (38,2%)	6 (17,6%)	11 (32,4%)	13 (38,2%)	4 (11,8%)	6 (17,6%)	9 (30,0%)	9 (30,0%)	6 (20,0%)	3 (10,0%)	3 (10,0%)
Vitamin D deficiency	11 (32,4%)	13 (38,2%)	7 (20,6%)	3 (8,8%)	29 (85,3%)	4 (11,8%)	1 (2,9%)	0 (0,0%)	24 (75,0%)	5 (15,6%)	3 (9,4%)	0 (0,0%)	0 (0,0%)
Growth hormone deficiency	9 (26,5%)	16 (47,1%)	4 (11,8%)	5 (14,7%)	23 (69,7%)	9 (27,3%)	1 (3,0%)	0 (0,0%)	21 (67,7%)	7 (22,6%)	3 (9,7%)	0 (0,0%)	0 (0,0%)
Precocious puberty	11 (32,4%)	12 (35,3%)	7 (20,6%)	4 (11,8%)	27 (79,4%)	4 (11,8%)	2 (5,9%)	1 (2,9%)	22 (75,9%)	6 (20,7%)	1 (3,4%)	0 (0,0%)	0 (0,0%)
Hypertension	12 (35,3%)	11 (32,4%)	9 (26,5%)	2 (5,9%)	30 (88,2%)	1 (2,9%)	2 (5,9%)	1 (2,9%)	30 (90,9%)	0 (0,0%)	2 (6,1%)	0 (0,0%)	1 (3,0%)
NF2													
Tumors													
Vestibular schwannoma	0 (0,0%)	0 (0,0%)	4 (18,2%)	18 (81,8%)	11 (50,0%)	9 (40,9%)	2 (9,1%)	0 (0,0%)	8 (36,4%)	11 (50,0%)	2 (9,1%)	1 (4,5%)	0 (0,0%)
Meningioma	0 (0,0%)	1 (4,5%)	1 (4,5%)	20 (90,9%)	1 (4,8%)	4 (19,0%)	11 (52,4%)	5 (23,8%)	0 (0,0%)	5 (25,0%)	5 (25,0%)	5 (25,0%)	5 (25,0%)
Ependymoma	0 (0,0%)	0 (0,0%)	10 (45,5%)	12 (54,5%)	1 (4,8%)	7 (33,3%)	9 (42,9%)	4 (19,0%)	1 (5,0%)	3 (15,0%)	6 (30,0%)	7 (35,0%)	3 (15,0%)
Schwannoma in other location	0 (0,0%)	1 (4,5%)	8 (36,4%)	13 (59,1%)	3 (14,3%)	6 (28,6%)	8 (38,1%)	4 (19,0%)	0 (0,0%)	7 (35,0%)	4 (20,0%)	6 (30,0%)	3 (15,0%)
Neuropathies													
Polyneuropathy	0 (0,0%)	2 (9,1%)	8 (36,4%)	12 (54,5%)	4 (18,2%)	9 (40,9%)	4 (18,2%)	5 (22,7%)	4 (20,0%)	5 (25,0%)	1 (5,0%)	5 (25,0%)	5 (25,0%)
Mononeuropathy	0 (0,0%)	5 (22,7%)	8 (36,4%)	9 (40,9%)	1 (4,8%)	3 (14,3%)	5 (23,8%)	12 (57,1%)	1 (5,0%)	2 (10,0%)	1 (5,0%)	5 (25,0%)	11 (55,0%)
Excluded													

Manifestation	Need for new treatment				Available treatments				Evidence for treatments				
Score	1	2	3	4	1	2	3	4	1	2	3	4	5
Visual complications by cataract	4 (18,2%)	11 (50,0%)	6 (27,3%)	1 (4,5%)	3 (14,3%)	0 (0,0%)	1 (4,8%)	17 (81,0%)	2 (10,0%)	1 (5,0%)	0 (0,0%)	2 (10,0%)	15 (75,0%)
Visual complications by retinal hamartoma	4 (18,2%)	8 (36,4%)	7 (31,8%)	3 (13,6%)	0 (0,0%)	2 (9,5%)	2 (9,5%)	17 (81,0%)	0 (0,0%)	1 (5,0%)	1 (5,0%)	4 (20,0%)	14 (70,0%)
Visual complications by orbital meningioma	1 (4,5%)	5 (22,7%)	8 (36,4%)	8 (36,4%)	0 (0,0%)	2 (9,5%)	2 (9,5%)	17 (81,0%)	0 (0,0%)	1 (5,0%)	2 (10,0%)	4 (20,0%)	13 (65,0%)
Cutaneous or subcutaneous schwannoma	2 (9,1%)	13 (59,1%)	5 (22,7%)	2 (9,1%)	3 (13,6%)	2 (9,1%)	2 (9,1%)	15 (68,2%)	1 (5,0%)	2 (10,0%)	3 (15,0%)	4 (20,0%)	10 (50,0%)
Schwannomatosis													
Chronic pain caused by schwannoma	0 (0,0%)	0 (0,0%)	2 (11,8%)	15 (88,2%)	3 (17,6%)	10 (58,8%)	3 (17,6%)	1 (5,9%)	0 (0,0%)	6 (37,5%)	6 (37,5%)	2 (12,5%)	2 (12,5%)
Impaired/loss of function by schwannoma	1 (5,9%)	0 (0,0%)	8 (47,1%)	8 (47,1%)	0 (0,0%)	5 (29,4%)	3 (17,6%)	9 (52,9%)	0 (0,0%)	2 (12,5%)	2 (12,5%)	5 (31,3%)	7 (43,8%)
Numbness or tingling caused by schwannoma	1 (5,9%)	6 (35,3%)	6 (35,3%)	4 (23,5%)	0 (0,0%)	3 (17,6%)	4 (23,5%)	10 (58,8%)	0 (0,0%)	1 (6,7%)	3 (20,0%)	3 (20,0%)	8 (53,3%)
Excluded													
Meningioma	1 (5,9%)	3 (17,6%)	4 (23,5%)	9 (52,9%)	1 (6,3%)	0 (0,0%)	5 (31,3%)	10 (62,5%)	0 (0,0%)	1 (6,3%)	4 (25,0%)	2 (12,5%)	9 (56,3%)
Vestibular schwannoma	1 (5,9%)	1 (5,9%)	7 (41,2%)	8 (47,1%)	7 (43,8%)	2 (12,5%)	1 (6,3%)	6 (37,5%)	2 (12,5%)	5 (31,3%)	2 12,5%)	2 (12,5%)	5 (31,3%)

ANNEX V. Average scores of second Delphi questionnaire of NF experts and results from consensus meeting

Table A2. *Results from the second Delphi questionnaire for experts and the consensus meeting. Average scores for need for treatment and availability of treatments could range between 1 and 4, for evidence of treatments they could range between 1 and 5. A higher average score implies a higher need for treatment, higher lack of available treatments and higher lack of evidence for treatments. A lower ranking implies a higher priority for inclusion into clinical trials. SD = standard deviation, NF1 = neurofibromatosis type I, NF2 = neurofibromatosis type II*

Manifestations	*Average score need for treatment (SD)*	*Average score availability of treatments (SD)*	*Average score evidence for treatments (SD)*	*Average ranking HP consensus meeting*	*SD average ranking consensus meeting*	*% of participants scoring feasibility as "easy"*
Neurofibromatosis type 1						
Peripheral benign nerve sheath tumors				2,33	1,61	92%
Subcutaneous neurofibroma	3,76 (0,43)	3,03 (0,90)	3,70 (1,09)			
Plexiform neurofibroma	3,82 (0,52)	2,06 (0,81)	1,56 (0,56)			
Orbital plexiform neurofibroma	3,62 (0,49)	2,21 (0,82)	2,39 (1,02)			
Atypical neurofibroma	3,71 (0,58)	3,06 (0,92)	3,29 (1,24)			
Spinal nerve root neurofibroma	3,76 (0,65)	2,82 (0,87)	3,06 (1,29)			
Sarcoma (Oncology)				2,67	1,67	75%
MPNST	3,97 (0,17)	2,41 (0,99)	2,68 (1,25)			
Sarcoma other than MPNST and GIST	3,38 (0,85)	2,41 (1,05)	2,85 (1,49)			
Cutaneous manifestations				3,33	2,15	83%
Cutaneous neurofibroma	3,76 (0,43)	3,03 (0,90)	3,70 (1,09)			
Developmental / Neuropsychological abnormalities				4,08	1,38	42%
Cognitive impairment	3,68 (0,47)	3,18 (0,77)	3,48 (1,43)			
Autism spectrum disorder	3,44 (0,82)	3,16 (0,99)	3,63 (1,45)			
ADHD	3,03 (1,06)	1,76 (0,94)	1,83 (1,15)			
Emotional and behavioral problems	3,12 (0,77)	2,58 (1,00)	2,87 (1,50)			
Problems with speech and language development	2,97 (0,87)	3,50 (0,76)	3,93 (1,33)			
Motor/Coordination problems	3,00 (0,89)	3,41 (0,78)	3,97 (1,30)			

Manifestations	Average score need for treatment (SD)	Average score availability of treatments (SD)	Average score evidence for treatments (SD)	Average ranking HP consensus meeting	SD average ranking consensus meeting	% of participants scoring feasibility as "easy"
High grade glioma				4,83	2,21	42%
High grade glioma	3,85 (0,36)	2,35 (1,10)	2,62 (1,47)			
Low grade glioma				4,83	1,47	58%
Low grade brain glioma	3,32 (0,77)	1,85 (0,78)	1,81 (1,00)			
Optical pathway glioma	3,62 (0,55)	1,44 (0,66)	1,55 (0,67)			
Spinal cord low grade glioma	3,24 (0,92)	2,62 (1,07)	3,00 (1,54)			
Bone manifestations				6,42	1,38	17%
Long bone dysplasia	3,00 (0,95)	3,36 (0,82)	4,20 (1,06)			
Sphenoid bone dysplasia	2,59 (0,92)	3,71 (0,63)	4,50 (0,94)			
Tibial bowing, pseudoarthrosis	3,29 (0,80)	3,26 (0,83)	4,03 (1,08)			
Osteoporosis	2,76 (0,85)	1,85 (0,96)	2,16 (1,19)			
Scoliosis	3,03 (0,97)	3,41 (0,96)	4,10 (1,35)			
Vascular manifestations				7,5	0,67	8%
Cerebrovascular - Moya moya, hemorrhage, infarction	3,21 (0,95)	3,36 (1,08)	4,07 (1,39)			
Renal artery stenosis	3,03 (1,03)	3,44 (0,93)	4,13 (1,38)			
Other malignant tumors				-	-	
Breast cancer	3,21 (0,84)	1,65 (0,88)	1,90 (1,32)			
GIST	3,09 (0,87)	2,30 (1,02)	2,74 (1,40)			
Phaeochromocytoma	2,82 (1,03)	2,91 (1,16)	3,44 (1,42)			
Other malignancies	2,88 (1,12)	1,97 (1,06)	2,44 (1,58)			
Other manifestations				-	-	
Pruritus	2,82 (0,67)	2,18 (1,01)	3,11 (1,05)			
Pain	3,56 (0,82)	1,85 (0,86)	2,13 (1,16)			
Excluded				-	-	
Mental health problems	2,85 (0,89)	1,59 (0,82)	1,75 (1,02)			
Neurofibromatous neuropathy	2,97 (0,80)	3,15 (0,93)	3,43 (1,45)			
Migraine	2,38 (0,92)	1,44 (0,75)	1,55 (0,90)			
Epilepsy	2,15 (0,93)	1,24 (0,55)	1,30 (0,64)			

Manifestations	Average score need for treatment (SD)	Average score availability of treatments (SD)	Average score evidence for treatments (SD)	Average ranking HP consensus meeting	SD average ranking consensus meeting	% of participants scoring feasibility as "easy"
Fatigue / strength	2,71 (0,91)	3,21 (0,99)	3,58 (1,36)			
Sleep disorder	2,56 (0,99)	2,15 (1,08)	2,40 (1,30)			
Vitamin D deficiency	2,06 (0,95)	1,18 (0,46)	1,34 (0,65)			
Growth hormone deficiency	2,15 (0,99)	1,33 (0,54)	1,42 (0,67)			
Precocious puberty	2,12 (1,01)	1,32 (0,73)	1,28 (0,53)			
Hypertension	2,03 (0,94)	1,24 (0,70)	1,24 (0,83)			
Neurofibromatosis type 2						
Tumor				1	-	
Vestibular schwannoma	3,82 (0,39)	1,59 (0,67)	1,82 (0,80)			
Meningioma	3,86 (0,47)	2,95 (0,80)	3,50 (1,15)			
Ependymoma	3,55 (0,51)	2,76 (0,83)	3,40 (1,10)			
Schwannoma in other location	3,55 (0,60)	2,62 (0,97)	3,25 (1,12)			
Neuropathy				2	-	
Polyneuropathy	3,45 (0,67)	2,45 (1,06)	3,10 (1,55)			
Mononeuropathy	3,18 (0,80)	3,33 (0,91)	4,15 (1,23)			
Excluded				-	-	
Visual complications caused by cataract	2,18 (0,80)	3,52 (1,08)	4,35 (1,35)			
Visual complications caused by retinal hamartoma	2,41 (0,96)	3,71 (0,64)	4,55 (0,83)			
Cutaneous and subcutaneous schwannoma	2,32 (0,78)	3,32 (1,13)	4,00 (1,26)			
Schwannomatosis						
Pain caused by schwannoma	3,88 (0,33)	2,12 (0,78)	3,00 (1,03)	1	-	
Loss of function caused by schwannoma	3,35 (0,79)	3,24 (0,90)	4,06 (1,06)	2	-	
Numbness or tingling caused by schwannoma	2,76 (0,90)	3,41 (0,80)	4,20 (1,01)	3	-	
Excluded				-	-	
Meningioma	3,24 (0,97)	3,50 (0,82)	4,19 (1,05)			
Unilateral vestibular schwannoma	3,29 (0,85)	2,38 (1,41)	3,19 (1,52)			

ANNEX VI. Patient representatives' survey: manifestations of respondents

Table A3. *Characteristics of the respondents of the patient representatives' survey: the number of respondents that have the manifestation, (or the patient they represent has this manifestation) followed by the percentage.*

Manifestations	Yes (%)	No (%)
NF1		
Peripheral benign nerve sheath tumors		
Plexiform neurofibroma	23 (67,6)	11 (32,4)
Subcutaneous neurofibroma	21 (61,8)	13 (38,2)
Neurofibroma near the spinal cord (spine root neurofibroma)	8 (23,5)	26 (76,5)
Sarcomas		
Malignant peripheral nerve sheath tumor	4 (11,8)	30 (88,2)
Sarcoma (other than MPNST)	1 (2,9)	33 (97,1)
Cutaneous manifestations		
Cutaneous neurofibroma	20 (58,8)	14 (41,2)
Developmental / neuropsychological manifestations		
Problems with coordination and/or motor skills	20 (58,8)	14 (41,2)
Emotional and/or behavioral problems	15 (44,1)	19 (55,9)
Cognitive impairment	14 (41,2)	20 (58,8)
Problems with speech and language development	12 (35,3)	22 (64,7)
ADHD	10 (29,4)	24 (70,6)
Autism spectrum disorder	5 (14,7)	29 (85,3)
High grade glioma		
High grade brain glioma	2 (5,9)	32 (94,1)
Low grade glioma		
Low grade brain glioma	9 (26,5)	25 (73,5)
Optical pathway glioma	9 (26,5)	25 (73,5)
Low grade glioma in the spinal cord	1 (2,9)	33 (97,1)
Bone manifestations		
Tibial bowing / pseudoarthrosis	6 (17,6)	28 (82,4)

Manifestations	Yes (%)	No (%)
Scoliosis	11 (32,4)	23 (67,6)
Bone dysplasia of the long bones and/or vertebrae	4 (11,8)	30 (88,2)
Sphenoid bone dysplasia	3 (8,8)	31 (91,2)
Osteoporosis	2 (5,9)	32 (94,1)
Vascular manifestations		
Cerebrovascular manifestations	3 (8,8)	31 (91,2)
Renal artery stenosis	2 (5,9)	32 (94,1)
Other malignancies		
Breast cancer	2 (5,9)	32 (94,1)
Phaeochromocytoma	2 (5,9)	32 (94,1)
Gastrointestinal stromal tumor	1 (2,9)	33 (97,1)
Other manifestations		
Pain	16 (47,1)	18 (52,9)
Pruritus	12 (35,3)	22 (64,7)
NF2		
Tumors		
Vestibular schwannoma	20 (100)	0 (0)
Schwannoma in other location	16 (80)	4 (20)
Meningioma	14 (70)	6 (30)
Ependymoma	6 (30)	14 (70)
Neuropathies		
Peripheral neuropathy	10 (50)	10 (50)
Mononeuropathy	3 (15)	17 (85)
Excluded		
Cutaneous or subcutaneous schwannoma	11 (55)	9 (45)
Visual complication caused by cataract	11 (55)	9 (45)
Visual complications caused by retinal hamartoma	5 (25)	15 (75)
Schwannomatosis		
Pain	7 (77,8)	2 (22,2)
Numbness or tingling due to schwannoma	7 (77,8)	2 (22,2)
Impaired or loss of function due to schwannoma	6 (66,7)	3 (33,3)

ANNEX VII. Patient representatives' survey results

Table A4. *All results from the patient representatives' survey. Average scores could range between 1 and 4, a higher average score implies a higher need for treatment, higher burden and more severity. A lower ranking implies a higher priority for inclusion into clinical trials. SD = standard deviation*

Manifestations	Average score need for new treatment (SD)	Average score severity (SD)	Average score physical burden (SD)	Average score psychosocial burden (SD)	Average score economic burden (SD)	Average ranking patient representatives
Neurofibromatosis type 1						
Peripheral benign nerve sheath tumors						4,38
Subcutaneous neurofibroma	3,65 (0,60)	3,09 (0,71)	3,18 (0,80)	3,35 (0,73)	2,97 (0,80)	
Plexiform neurofibroma	4,00 (0,00)	3,85 (0,36)	3,91 (0,29)	3,88 (0,33)	3,47 (0,71)	
Atypical neurofibroma	3,74 (0,51)	3,29 (0,72)	3,41 (0,74)	3,41 (0,82)	3,15 (0,74)	
Spinal nerve root neurofibroma	3,91 (0,29)	3,79 (0,41)	3,74 (0,67)	3,68 (0,68)	3,44 (0,70)	
Sarcoma (Oncology)						3,35
MPNST	3,94 (0,24)	3,97 (0,17)	3,94 (0,24)	3,97 (0,17)	3,82 (0,39)	
Sarcoma other than MPNST and GIST	3,91 (0,29)	3,91 (0,29)	3,85 (0,36)	3,94 (0,34)	3,82 (0,39)	
Cutaneous manifestations						4,56
Cutaneous neurofibroma	3,74 (0,51)	3,47 (0,75)	3,38 (0,65)	3,79 (0,41)	3,12 (0,81)	
Developmental / Neuropsychological abnormalities						6,18
Cognitive impairment	3,06 (0,85)	2,71 (0,80)	-	3,00 (0,60)	3,29 (0,72)	
Autism spectrum disorder	2,76 (0,85)	2,56 (1,08)	-	2,82 (1,14)	3,00 (1,02)	
ADHD	2,88 (0,69)	2,62 (0,89)	-	2,91 (0,83)	2,85 (0,86)	
Emotional and behavioral problems	3,12 (0,77)	2,85 (0,70)	-	3,00 (0,65)	2,94 (0,78)	
Problems with speech and language development	2,85 (0,96)	2,65 (0,73)	-	2,74 (0,83)	2,82 (0,87)	
Motor/Coordination problems	3,12 (1,01)	2,82 (0,80)	-	2,79 (0,84)	2,82 (0,94)	
High grade glioma						3,18
High grade glioma	3,91 (0,29)	3,97 (0,17)	3,94 (0,24)	3,94 (0,24)	3,82 (0,39)	
Low grade glioma						5,32
Low grade brain glioma	3,65 (0,54)	3,24 (0,74)	3,15 (0,74)	3,15 (0,86)	3,24 (0,70)	

Manifestations	Average score need for new treatment (SD)	Average score severity (SD)	Average score physical burden (SD)	Average score psychosocial burden (SD)	Average score economic burden (SD)	Average ranking patient representatives
Optical pathway glioma	3,79 (0,41)	3,53 (0,56)	3,59 (0,56)	3,38 (0,74)	3,44 (0,66)	
Spinal cord low grade glioma	3,74 (0,51)	3,47 (0,56)	3,59 (0,50)	3,44 (0,66)	3,44 (0,66)	
Bone manifestations						6,97
Long bone dysplasia	3,38 (0,82)	3,32 (0,81)	3,62 (0,60)	3,65 (0,54)	3,35 (0,77)	
Sphenoid bone dysplasia	3,26 (0,90)	3,21 (0,81)	3,50 (0,71)	3,65 (0,49)	3,24 (0,85)	
Tibial bowing, pseudoarthrosis	3,47 (0,79)	3,59 (0,66)	3,76 (0,50)	3,82 (0,39)	3,47 (0,66)	
Osteoporosis	3,09 (0,83)	2,88 (0,88)	3,24 (0,78)	3,12 (0,81)	3,03 (0,90)	
Scoliosis	3,35 (0,81)	3,38 (0,70)	3,62 (0,60)	3,56 (0,66)	3,38 (0,70)	
Vascular manifestations						7,29
Cerebrovascular - Moya moya, hemorrhage, infarction	3,71 (0,58)	3,59 (0,61)	3,68 (0,47)	3,65 (0,60)	3,62 (0,49)	
Renal artery stenosis	3,26 (0,86)	3,06 (0,85)	3,24 (0,78)	3,21 (0,73)	3,18 (0,80)	
Other malignant tumors						-
Breast cancer	3,50 (0,71)	3,53 (0,66)	3,41 (0,70)	3,59 (0,74)	3,71 (0,58)	
GIST	3,53 (0,61)	3,47 (0,66)	3,47 (0,71)	3,59 (0,66)	3,65 (0,54)	
Phaeochromocytoma	3,44 (0,79)	3,44 (0,86)	3,26 (0,86)	3,50 (0,79)	3,56 (0,70)	
Other malignancies	3,44 (0,75)	3,50 (0,79)	3,41 (0,82)	3,53 (0,75)	3,56 (0,66)	
Other manifestations						-
Pruritus	3,06 (0,74)	2,76 (0,85)	3,00 (0,82)	3,00 (0,74)	2,59 (0,74)	
Pain	3,68 (0,64)	3,38 (0,65)	3,53 (0,66)	3,47 (0,66)	3,24 (0,82)	
Neurofibromatosis type 2						
Tumor						1,05
Vestibular schwannoma	3,95 (0,22)	3,85 (0,37)	3,75 (0,55)	3,65 (0,59)	3,65 (0,75)	
Meningioma	3,65 (0,59)	3,45 (0,83)	2,85 (1,23)	2,85 (1,14)	2,90 (1,02)	
Ependymoma	3,75 (0,55)	3,35 (0,93)	2,80 (1,11)	2,90 (1,17)	3,10 (1,02)	
Schwannoma in other location	3,65 (0,49)	3,40 (0,68)	3,20 (0,83)	2,70 (1,17)	2,95 (1,00)	
Neuropathy						1.95
Polyneuropathy	3,50 (0,61)	3,20 (0,70)	3,40 (0,75)	3,30 (0,80)	3,10 (1,02)	
Mononeuropathy	3,35 (0,67)	2,95 (0,76)	3,30 (0,73)	3,20 (0,77)	2,90 (1,02)	

Manifestations	*Average score need for new treatment (SD)*	*Average score severity (SD)*	*Average score physical burden (SD)*	*Average score psychosocial burden (SD)*	*Average score economic burden (SD)*	*Average ranking patient representatives*
Schwannomatosis						
Pain caused by schwannoma	3,89 (0,33)	3,67 (0,50)	3,56 (0,73)	3,67 (0,50)	3,22 (0,67)	1,22
Loss of function caused by schwannoma	3,56 (0,73)	3,11 (0,60)	2,78 (0,67)	3,00 (1,00)	2,89 (0,93)	2,11
Numbness or tingling caused by schwannoma	3,33 (0,71)	2,33 (0,71)	2,44 (0,73)	2,67 (0,87)	2,56 (1,13)	2,67

ANNEX VIII. Patient representatives' survey results: distribution of scores and percentages

Table A5. *Distribution of the scores as appointed to the different manifestations by patient representatives. A higher score implies higher need for treatment, more severity, and higher burden. Items where more than 75% of the respondents chose the highest scores are marked green. NF1 = Neurofibromatosis type I, NF2 = Neurofibromatosis type II, SWN = Schwannomatosis*

Manifestation	Need for new treatment				Severity				Physical burden				Psychosocial burden				Economic burden			
Score	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
NF1																				
Peripheral benign nerve sheath tumors																				
Subcutaneous neurofibroma	0 (0,0%)	2 (5,9%)	8 (23,5%)	24 (70,6%)	0 (0,0%)	7 (20,6%)	17 (50,0%)	10 (29,4%)	2 (5,9%)	2 (5,9%)	18 (52,9%)	12 (35,3%)	1 (2,9%)	2 (5,9%)	15 (44,1%)	16 (47,1%)	1 (2,9%)	8 (23,5%)	16 (47,1%)	9 (26,5%)
Plexiform neurofibroma	0 (0,0%)	0 (0,0%)	0 (0,0%)	34 (100,0%)	0 (0,0%)	0 (0,0%)	5 (14,7%)	29 (85,3%)	0 (0,0%)	0 (0,0%)	3 (8,8%)	31 (91,2%)	0 (0,0%)	0 (0,0%)	4 (11,8%)	30 (88,2%)	0 (0,0%)	4 (11,8%)	10 (29,4%)	20 (58,8%)
Orbital plexiform neurofibroma	0 (0,0%)	1 (2,9%)	7 (20,6%)	26 (76,5%)	0 (0,0%)	5 (14,7%)	14 (41,2%)	15 (44,1%)	1 (2,9%)	2 (5,9%)	13 (38,2%)	18 (52,9%)	1 (2,9%)	4 (11,8%)	9 (26,5%)	20 (58,8%)	1 (2,9%)	4 (11,8%)	18 (52,9%)	11 (32,4%)
Atypical neurofibroma	0 (0,0%)	0 (0,0%)	3 (8,8%)	31 (91,2%)	0 (0,0%)	0 (0,0%)	7 (20,6%)	27 (79,4%)	1 (2,9%)	1 (2,9%)	4 (11,8%)	28 (82,4%)	1 (2,9%)	1 (2,9%)	6 (17,6%)	26 (76,5%)	1 (2,9%)	1 (2,9%)	14 (41,2%)	18 (52,9%)
Spine root neurofibroma	0 (0,0%)	2 (5,9%)	8 (23,5%)	24 (70,6%)	0 (0,0%)	7 (20,6%)	17 (50,0%)	10 (29,4%)	2 (5,9%)	2 (5,9%)	18 (52,9%)	12 (35,3%)	1 (2,9%)	2 (5,9%)	15 (44,1%)	16 (47,1%)	1 (2,9%)	8 (23,5%)	16 (47,1%)	9 (26,5%)
Sarcomas																				
MPNST	0 (0,0%)	0 (0,0%)	2 (5,9%)	32 (94,1%)	0 (0,0%)	0 (0,0%)	1 (2,9%)	33 (97,1%)	0 (0,0%)	0 (0,0%)	2 (5,9%)	32 (94,1%)	0 (0,0%)	0 (0,0%)	1 (2,9%)	33 (97,1%)	0 (0,0%)	0 (0,0%)	6 (17,6%)	28 (82,4%)
Sarcoma other than MPNST	0 (0,0%)	0 (0,0%)	3 (8,8%)	31 (91,2%)	0 (0,0%)	0 (0,0%)	3 (8,8%)	31 (91,2%)	0 (0,0%)	0 (0,0%)	5 (14,7%)	29 (85,3%)	0 (0,0%)	1 (2,9%)	0 (0,0%)	33 (97,1%)	0 (0,0%)	0 (0,0%)	6 (17,6%)	28 (82,4%)
Cutaneous manifestations																				
Cutaneous neurofibroma	0 (0,0%)	1 (2,9%)	7 (20,6%)	26 (76,5%)	1 (2,9%)	2 (5,9%)	11 (32,4%)	20 (58,8%)	0 (0,0%)	3 (8,8%)	15 (44,1%)	16 (47,1%)	0 (0,0%)	0 (0,0%)	7 (20,6%)	27 (79,4%)	0 (0,0%)	9 (26,5%)	12 (35,3%)	13 (38,2%)
Developmental / neuropsychological manifestations																				
Cognitive impairment	1 (2,9%)	8 (23,5%)	13 (38,2%)	12 (35,3%)	1 (2,9%)	14 (41,2%)	13 (38,2%)	6 (17,6%)					0 (0,0%)	6 (17,6%)	22 (64,7%)	6 (17,6%)	0 (0,0%)	5 (14,7%)	14 (41,2%)	15 (44,1%)
Autism spectrum disorder	2 (5,9%)	11 (32,4%)	14 (41,2%)	7 (20,6%)	7 (20,6%)	9 (26,5%)	10 (29,4%)	8 (23,5%)					6 (17,6%)	7 (20,6%)	8 (23,5%)	13 (38,2%)	5 (14,7%)	2 (5,9%)	15 (44,1%)	12 (35,3%)

Manifestation	Need for new treatment				Severity				Physical burden				Psychosocial burden				Economic burden			
Score	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
ADHD	0 (0,0%)	10 (29,4%)	18 (52,9%)	6 (17,6%)	3 (8,8%)	13 (38,2%)	12 (35,3%)	6 (17,6%)					2 (5,9%)	7 (20,6%)	17 (50,0%)	8 (23,5%)	3 (8,8%)	6 (17,6%)	18 (52,9%)	7 (20,6%)
Emotional and behavioural problems	0 (0,0%)	8 (23,5%)	14 (41,2%)	12 (35,3%)	1 (2,9%)	8 (23,5%)	20 (58,8%)	5 (14,7%)					0 (0,0%)	7 (20,6%)	20 (58,8%)	7 (20,6%)	1 (2,9%)	8 (23,5%)	17 (50,0%)	8 (23,5%)
Speech and language development problems	3 (8,8%)	9 (26,5%)	12 (35,3%)	10 (29,4%)	2 (5,9%)	11 (32,4%)	18 (52,9%)	3 (8,8%)					2 (5,9%)	11 (32,4%)	15 (44,1%)	6 (17,6%)	2 (5,9%)	10 (29,4%)	14 (41,2%)	8 (23,5%)
Motor/Coordination problems	3 (8,8%)	6 (17,6%)	9 (26,5%)	16 (47,1%)	2 (5,9%)	8 (23,5%)	18 (52,9%)	6 (17,6%)					2 (5,9%)	10 (29,4%)	15 (44,1%)	7 (20,6%)	2 (5,9%)	12 (35,3%)	10 (29,4%)	10 (29,4%)
High grade glioma																				
High grade glioma	0 (0,0%)	0 (0,0%)	3 (8,8%)	31 (91,2%)	0 (0,0%)	0 (0,0%)	1 (2,9%)	33 (97,1%)	0 (0,0%)	0 (0,0%)	2 (5,9%)	32 (94,1%)	0 (0,0%)	0 (0,0%)	2 (5,9%)	32 (94,1%)	0 (0,0%)	0 (0,0%)	6 (17,6%)	28 (82,4%)
Low grade glioma																				
Low grade glioma	0 (0,0%)	1 (2,9%)	10 (29,4%)	23 (67,6%)	0 (0,0%)	6 (17,6%)	14 (41,2%)	14 (41,2%)	0 (0,0%)	7 (20,6%)	15 (44,1%)	12 (35,3%)	0 (0,0%)	10 (29,4%)	9 (26,5%)	15 (44,1%)	0 (0,0%)	5 (14,7%)	16 (47,1%)	13 (38,2%)
Optic pathway glioma	0 (0,0%)	0 (0,0%)	7 (20,6%)	27 (79,4%)	0 (0,0%)	1 (2,9%)	14 (41,2%)	19 (55,9%)	0 (0,0%)	1 (2,9%)	12 (35,3%)	21 (61,8%)	0 (0,0%)	5 (14,7%)	11 (32,4%)	18 (52,9%)	0 (0,0%)	3 (8,8%)	13 (38,2%)	18 (52,9%)
Spinal cord glioma	0 (0,0%)	1 (2,9%)	7 (20,6%)	26 (76,5%)	0 (0,0%)	1 (2,9%)	16 (47,1%)	17 (50,0%)	0 (0,0%)	0 (0,0%)	14 (41,2%)	20 (58,8%)	0 (0,0%)	3 (8,8%)	13 (38,2%)	18 (52,9%)	0 (0,0%)	3 (8,8%)	13 (38,2%)	18 (52,9%)
Bone manifestations																				
Long bone dysplasia	1 (2,9%)	4 (11,8%)	10 (29,4%)	19 (55,9%)	0 (0,0%)	7 (20,6%)	9 (26,5%)	18 (52,9%)	0 (0,0%)	2 (5,9%)	9 (26,5%)	23 (67,6%)	0 (0,0%)	1 (2,9%)	10 (29,4%)	23 (67,6%)	0 (0,0%)	6 (17,6%)	10 (29,4%)	18 (52,9%)
Sphenoid bone dysplasia	2 (5,9%)	4 (11,8%)	11 (32,4%)	17 (50,0%)	1 (2,9%)	5 (14,7%)	14 (41,2%)	14 (41,2%)	1 (2,9%)	1 (2,9%)	12 (35,3%)	20 (58,8%)	0 (0,0%)	0 (0,0%)	12 (35,3%)	22 (64,7%)	1 (2,9%)	6 (17,6%)	11 (32,4%)	16 (47,1%)
Tibial bowing, pseudoarthrosis	1 (2,9%)	3 (8,8%)	9 (26,5%)	21 (61,8%)	0 (0,0%)	3 (8,8%)	8 (23,5%)	23 (67,6%)	0 (0,0%)	1 (2,9%)	6 (17,6%)	27 (79,4%)	0 (0,0%)	0 (0,0%)	6 (17,6%)	28 (82,4%)	0 (0,0%)	3 (8,8%)	12 (35,3%)	19 (55,9%)
Osteoporosis	1 (2,9%)	7 (20,6%)	14 (41,2%)	12 (35,3%)	2 (5,9%)	9 (26,5%)	14 (41,2%)	9 (26,5%)	0 (0,0%)	7 (20,6%)	12 (35,3%)	15 (44,1%)	1 (2,9%)	6 (17,6%)	15 (44,1%)	12 (35,3%)	1 (2,9%)	10 (29,4%)	10 (29,4%)	13 (38,2%)
Scoliosis	1 (2,9%)	4 (11,8%)	11 (32,4%)	18 (52,9%)	0 (0,0%)	4 (11,8%)	13 (38,2%)	17 (50,0%)	0 (0,0%)	2 (5,9%)	9 (26,5%)	23 (67,6%)	0 (0,0%)	3 (8,8%)	9 (26,5%)	22 (64,7%)	0 (0,0%)	4 (11,8%)	13 (38,2%)	17 (50,0%)
Vascular manifestations																				

Manifestation	Need for new treatment				Severity				Physical burden				Psychosocial burden				Economic burden			
Score	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Cerebrovascular (Moya moya, aneurysm etc.)	0 (0,0%)	2 (5,9%)	6 (17,6%)	26 (76,5%)	0 (0,0%)	2 (5,9%)	10 (29,4%)	22 (64,7%)	0 (0,0%)	0 (0,0%)	11 (32,4%)	23 (67,6%)	0 (0,0%)	2 (5,9%)	8 (23,5%)	24 (70,6%)	0 (0,0%)	0 (0,0%)	13 (38,2%)	21 (61,8%)
Renal artery stenosis	1 (2,9%)	6 (17,6%)	10 (29,4%)	17 (50,0%)	1 (2,9%)	8 (23,5%)	13 (38,2%)	12 (35,3%)	1 (2,9%)	4 (11,8%)	15 (44,1%)	14 (41,2%)	0 (0,0%)	6 (17,6%)	15 (44,1%)	13 (38,2%)	0 (0,0%)	8 (23,5%)	12 (35,3%)	14 (41,2%)
Other malignancies																				
Breast cancer	1 (2,9%)	1 (2,9%)	12 (35,3%)	20 (58,8%)	0 (0,0%)	3 (8,8%)	10 (29,4%)	21 (61,8%)	0 (0,0%)	4 (11,8%)	12 (35,3%)	18 (52,9%)	0 (0,0%)	5 (14,7%)	4 (11,8%)	25 (73,5%)	0 (0,0%)	2 (5,9%)	6 (17,6%)	26 (76,5%)
GIST	0 (0,0%)	2 (5,9%)	12 (35,3%)	20 (58,8%)	0 (0,0%)	3 (8,8%)	12 (35,3%)	19 (55,9%)	0 (0,0%)	4 (11,8%)	10 (29,4%)	20 (58,8%)	0 (0,0%)	3 (8,8%)	8 (23,5%)	23 (67,6%)	0 (0,0%)	1 (2,9%)	10 (29,4%)	23 (67,6%)
Phaeochromocytoma	1 (2,9%)	3 (8,8%)	10 (29,4%)	20 (58,8%)	2 (5,9%)	2 (5,9%)	9 (26,5%)	21 (61,8%)	1 (2,9%)	6 (17,6%)	10 (29,4%)	17 (50,0%)	0 (0,0%)	6 (17,6%)	5 (14,7%)	23 (67,6%)	0 (0,0%)	4 (11,8%)	7 (20,6%)	23 (67,6%)
Other malignancies	0 (0,0%)	5 (14,7%)	9 (26,5%)	20 (58,8%)	1 (2,9%)	3 (8,8%)	8 (23,5%)	22 (64,7%)	1 (2,9%)	4 (11,8%)	9 (26,5%)	20 (58,8%)	0 (0,0%)	5 (14,7%)	6 (17,6%)	23 (67,6%)	0 (0,0%)	3 (8,8%)	9 (26,5%)	22 (64,7%)
Other manifestations																				
Pruritus	1 (2,9%)	5 (14,7%)	19 (55,9%)	9 (26,5%)	2 (5,9%)	11 (32,4%)	14 (41,2%)	7 (20,6%)	0 (0,0%)	11 (32,4%)	12 (35,3%)	11 (32,4%)	0 (0,0%)	9 (26,5%)	16 (47,1%)	9 (26,5%)	1 (2,9%)	16 (47,1%)	13 (38,2%)	4 (11,8%)
Pain	0 (0,0%)	3 (8,8%)	5 (14,7%)	26 (76,5%)	0 (0,0%)	3 (8,8%)	15 (44,1%)	16 (47,1%)	0 (0,0%)	3 (8,8%)	10 (29,4%)	21 (61,8%)	0 (0,0%)	3 (8,8%)	12 (35,3%)	19 (55,9%)	1 (2,9%)	5 (14,7%)	13 (38,2%)	15 (44,1%)
NF2																				
Tumors																				
Vestibular schwannoma	0 (0,0%)	0 (0,0%)	1 (5,0%)	19 (95,0%)	0 (0,0%)	0 (0,0%)	3 (15,0%)	17 (85,0%)	0 (0,0%)	1 (5,0%)	3 (15,0%)	16 (80,0%)	0 (0,0%)	1 (5,0%)	5 (25,0%)	14 (70,0%)	1 (5,0%)	0 (0,0%)	4 (20,0%)	15 (75,0%)
Meningioma	0 (0,0%)	1 (5,0%)	5 (25,0%)	14 (70,0%)	1 (5,0%)	1 (5,0%)	6 (30,0%)	12 (60,0%)	5 (25,0%)	1 (5,0%)	6 (30,0%)	8 (40,0%)	3 (15,0%)	5 (25,0%)	4 (20,0%)	8 (40,0%)	2 (10,0%)	5 (25,0%)	6 (30,0%)	7 (35,0%)
Ependymoma	0 (0,0%)	1 (5,0%)	3 (15,0%)	16 (80,0%)	2 (10,0%)	0 (0,0%)	7 (35,0%)	11 (55,0%)	4 (20,0%)	2 (10,0%)	8 (40,0%)	6 (30,0%)	4 (20,0%)	2 (10,0%)	6 (30,0%)	8 (40,0%)	3 (15,0%)	0 (0,0%)	9 (45,0%)	8 (40,0%)
Schwannoma in other location	0 (0,0%)	0 (0,0%)	7 (35,0%)	13 (65,0%)	0 (0,0%)	2 (10,0%)	8 (40,0%)	10 (50,0%)	1 (5,0%)	2 (10,0%)	9 (45,0%)	8 (40,0%)	4 (20,0%)	5 (25,0%)	4 (20,0%)	7 (35,0%)	2 (10,0%)	4 (20,0%)	7 (35,0%)	7 (35,0%)
Neuropathies																				
Polyneuropathy	0 (0,0%)	1 (5,0%)	8 (40,0%)	11 (55,0%)	0 (0,0%)	3 (15,0%)	10 (50,0%)	7 (35,0%)	0 (0,0%)	3 (15,0%)	6 (30,0%)	11 (55,0%)	0 (0,0%)	4 (20,0%)	6 (30,0%)	10 (50,0%)	2 (10,0%)	3 (15,0%)	6 (30,0%)	9 (45,0%)

Manifestation	Need for new treatment				Severity				Physical burden				Psychosocial burden				Economic burden			
Score	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Mononeuropathy	0 (0,0%)	2 (10,0%)	9 (45,0%)	9 (45,0%)	1 (5,0%)	3 (15,0%)	12 (60,0%)	4 (20,0%)	0 (0,0%)	3 (15,0%)	8 (40,0%)	9 (45,0%)	0 (0,0%)	4 (20,0%)	8 (40,0%)	8 (40,0%)	2 (10,0%)	5 (25,0%)	6 (30,0%)	7 (35,0%)
SWN																				
Chronic pain caused by schwannoma	0 (0,0%)	0 (0,0%)	1 (11,1%)	8 (88,9%)	0 (0,0%)	0 (0,0%)	3 (33,3%)	6 (66,7%)	0 (0,0%)	1 (11,1%)	2 (22,2%)	6 (66,7%)	0 (0,0%)	0 (0,0%)	3 (33,3%)	6 (66,7%)	0 (0,0%)	1 (11,1%)	5 (55,6%)	3 (33,3%)
Impaired/loss of function by schwannoma	0 (0,0%)	1 (11,1%)	2 (22,2%)	6 (66,7%)	0 (0,0%)	1 (11,1%)	6 (66,7%)	2 (22,2%)	0 (0,0%)	3 (33,3%)	5 (55,6%)	1 (11,1%)	0 (0,0%)	4 (44,4%)	1 (11,1%)	4 (44,4%)	1 (11,1%)	1 (11,1%)	5 (55,6%)	2 (22,2%)
Numbness or tingling caused by schwannoma	0 (0,0%)	1 (11,1%)	4 (44,4%)	4 (44,4%)	1 (11,1%)	4 (44,4%)	4 (44,4%)	0 (0,0%)	1 (11,1%)	3 (33,3%)	5 (55,6%)	0 (0,0%)	0 (0,0%)	5 (55,6%)	2 (22,2%)	2 (22,2%)	2 (22,2%)	2 (22,2%)	3 (33,3%)	2 (22,2%)