Pediatric Neurology 134 (2022) 1–6

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

A Systematic Review of Recent and Ongoing Clinical Trials in Patients With the Neurofibromatoses

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ARTICLE INFO

Article history:
Received 29 October 2021
Accepted 3 June 2022
Available online 10 June 2022

Keywords:
Neurofibromatosis
Schwannomatosis
Clinical trials
Pediatric tumors

ABSTRACT

Introduction: The neurofibromatoses comprise three different genetic conditions causing considerable morbidity and mortality: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis (SWN). This review summarizes recent and ongoing clinical trials involving patients with neurofibromatoses to better understand the current state of clinical trial research centered around these conditions and inform areas of need.

Methods: A search was conducted using the Cochrane Central Register of Controlled Trials and clinicaltrials.gov databases. Inclusion and exclusion criteria were designed to identify clinical trials focused on patients with NF1, NF2, or SWN completed in or after 2010 and in process as of December 31, 2021. Information was collected using standardized guidelines.

Results: A total of 134 clinical trials were included, with 75 (56%) completed and 59 (44%) in process. For completed trials, 74% (n = 56) involved patients with NF1, and of those based on specific tumors (n = 26, 46%), the majority focused on plexiform neurofibromas (PNs) (n = 12, 46%). For ongoing trials, 79% (n = 47) involve patients with NF1, and of those based on specific tumors (n = 29, 61%), the majority are focused on PNs (n = 13, 45%).

Conclusion: Both recent and ongoing clinical trials have primarily focused on patients with NF1 and the treatment of PNs. This research has led to the first FDA-approved drug for NF1-PN and has changed management of these tumors, allowing for systemic therapy rather than reliance on only a surgical modality. Trials evaluating comorbid psychiatric conditions and quality of life among patients with any of the neurofibromatoses appear less common. These areas may warrant focus in future studies to improve clinical management.

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Introduction

Neurofibromatoses is an umbrella term for a group of genetic disorders that primarily affect the central and peripheral nervous system. It consists of three syndromes: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis (SWN).[1] Each entity is related to a causative gene or set of genes and associated with a constellation of clinical manifestations.[1] Although reported incidences vary, NF1 is estimated to occur in approximately 1 out of every 3000 individuals, NF2 in 1 out of every 25,000 individuals, and SWN in 1 out of every 70,000 individuals.[2-4] Each condition is associated with characteristic clinical manifestations that facilitate the diagnosis and assist in management or prognosis.

Conflicts of interest: A.C.H. has served as a consultant for AstraZeneca and Springworks Therapeutics. A.E.A. has served as a consultant for SpringWorks Therapeutics and EM Partners. The remaining authors declare that there are no conflicts of interests regarding the publication of this article.

Author contributions: S.A. and E.N.B. conceptualized, designed, and performed the literature search. S.A. performed the data analysis. S.A. and E.N.B. drafted the initial manuscript. A.C.H. and A.E.A. provided guidance and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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https://doi.org/10.1016/j.pediatrneurol.2022.06.003
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Typical findings seen in NF1 include pigmentary lesions (café-au-lait macules, cutaneous neurofibroma), bone lesions (tibial dysplasia, scoliosis), peripheral nerve tumors (plexiform neurofibroma [PN], malignant peripheral nerve sheath tumor, spinal neurofibroma), brain tumors (glioma), and cognitive or behavioral problems (learning and attention deficits).[5] NF2, on the other hand, is associated with vestibular and nonvestibular schwannomas, neurofibromas, ependymomas, and meningiomas.[6] SWN is characterized by nonvestibular, nonintradermal schwannomas.[6] Both adults and children often have devastating complications as a result of their condition, leading to significant morbidity and mortality.[7-10] Given new developments in our understanding of these conditions in recent years, including emerging details of the genetic pathogenesis, clinical trials evaluating different therapies are being developed and implemented.[1] However, no recent review exists that comprehensively summarizes recent clinical trial findings and trials in progress for this group of diseases. This study seeks to address this gap by presenting a systematic overview of recent and ongoing clinical trials for patients with the neurofibromatoses in order to better understand the current state of clinical trial research centered around NF1, NF2, and SWN to inform areas of need for future studies.

Methods

A systematic review was conducted using two publicly available databases to identify relevant clinical trials for patients with the neurofibromatoses: the Cochrane Controlled Registered Trials and clinicaltrials.gov. The searched terms used to identify relevant clinical trials included the following: (*neurofibromato** OR *NF1* OR *NF2* OR *Von Recklinghausen disease* OR *morbus Von Recklinghausen* OR *multiple inherited schwannomas, meningiomas, and ependymomas* OR *MISME syndrome* OR *schwannomatosis*). This queried for keywords in posted titles and abstracts relevant to clinical trials or subsequent publications arising from respective clinical trials. The search was conducted on June 25, 2021, and updated through December 31, 2021. Additional information regarding the initial search can be found in the Supplement 1. Initial screening excluded postings in a language other than English or clinical trials completed prior to 2010. For ongoing clinical trials, postings that had not been updated in the last 2 years were also excluded. Duplicates were removed. Publications not pertinent to a corresponding clinical trial were not included. Remaining clinical trials and their associated publications were further assessed for eligibility and excluded if no trial registration number could be identified or if one of the neurofibromatoses was determined to not be a primary focus of the study. Two authors (S.A. and E.N.B.) performed the search independently and resolved any conflicting findings. All authors reviewed the final clinical trials and came to a consensus on the studies included. Data collected included study design, primary condition under investigation, intervention being assessed, sample size of patient population, available patient demographics, main study objectives, country of primary institution or sponsor, and completion or estimated completion date. This review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11]

Results

The initial query identified 482 clinical trials: 248 from the Cochrane Controlled Registered Trials and 234 from clinicaltrials.gov prior to screening. After removing duplicates and studies completed prior to 2010, 389 clinical trials were identified. Following the application of additional inclusion and exclusion criteria, 202 clinical trials were further screened for eligibility. A total of 134 clinical trials were included in this review, with 75 (56%) considered completed (Supplement 2) and 59 (44%) ongoing (Supplement 3). This workflow is displayed in Fig 1.

Completed trials

From the number of completed clinical trials, 56 (75%) were associated with NF1 and 15 (20%) with NF2. One (1%) trial was associated with both NF1 and NF2, and 3 (4%) trials included patients with any of the neurofibromatoses. Regarding the study design for completed trials, 40 (53%) trials were open label, 4 (5%) were crossover, and 9 (12%) were placebo controlled. Comprehensive information about trial design, sample size, primary objectives, and outcomes of completed trials can be found in Supplement 2. The details of completed trials regarding the population and phase distribution, intervention in question, and country of primary institution or sponsor are shown in Table 1. Twenty-six (46%) NF1 trials and 13 (86%) NF2 trials were focused on evaluating outcomes based on associated tumors. The distribution of associated tumor types for completed NF1 and NF2 trials is shown in Table 2. There were no trials related to SWN focused on evaluating outcomes based on associated tumors.

Ongoing trials

From the number of ongoing clinical trials, 47 (80%) are associated with NF1, 8 (14%) with NF2, and 1 (2%) with SWN. Three trials include patients with any of the neurofibromatoses. Regarding the study design for ongoing trials, 32 (54%) trials are open label, 3 (5%) were crossover, and 8 (14%) were placebo controlled. Comprehensive information about trial design, sample size, primary objectives, and outcomes of ongoing trials can be found in Supplement 3. The details of ongoing trials regarding the population and phase distribution, intervention in question, and country of primary institution or sponsor can be found in Table 1. Twenty-nine (62%) NF1 trials and 7 (87%) NF2 trials are focused on evaluating outcomes based on associated tumors. The trial related to SWN evaluates pain relief with drug therapy. The distribution of associated tumor types for ongoing NF1 and NF2 trials can be found in Table 2.

Discussion

This review provides a summary of recently completed and ongoing trials related to the neurofibromatoses and identifies potential areas of study that could be further explored. Particularly, we observed that most trials have placed emphasis on evaluating pharmacologic agents and outcomes for PNs in patients with NF1, while the assessment of other interventions as well as trials focused on NF1-associated cutaneous neurofibroma, glioma, and malignant peripheral nerve sheath tumor appear understudied. Additionally, there were limited studies on NF2-associated tumors and no completed trials focusing on SWN-associated tumors. Overall, for both completed and ongoing trials, more than 40 were phase 2, investigating side effects and potential efficacy, with less than 10 phase 3 or phase 4 trials combined. This highlights the potential challenges in studying rare tumors as it may be difficult to obtain a sample size large enough for phase 3 or phase 4 clinical trials. Moreover, fewer pharmaceutical companies may be willing to focus on rare tumors due to smaller capital gains, thereby limiting the number of clinical trials for these conditions. Of 75 completed trials reviewed, 15 had some support (drug, partial funding) as noted in the trial registries and publications. Of 59 ongoing trials reviewed, nine have some support and 14 were run by pharmaceutical companies as noted in the registries (Supplements 2 and 3). It is also worth noting that overall, a relatively small number of total

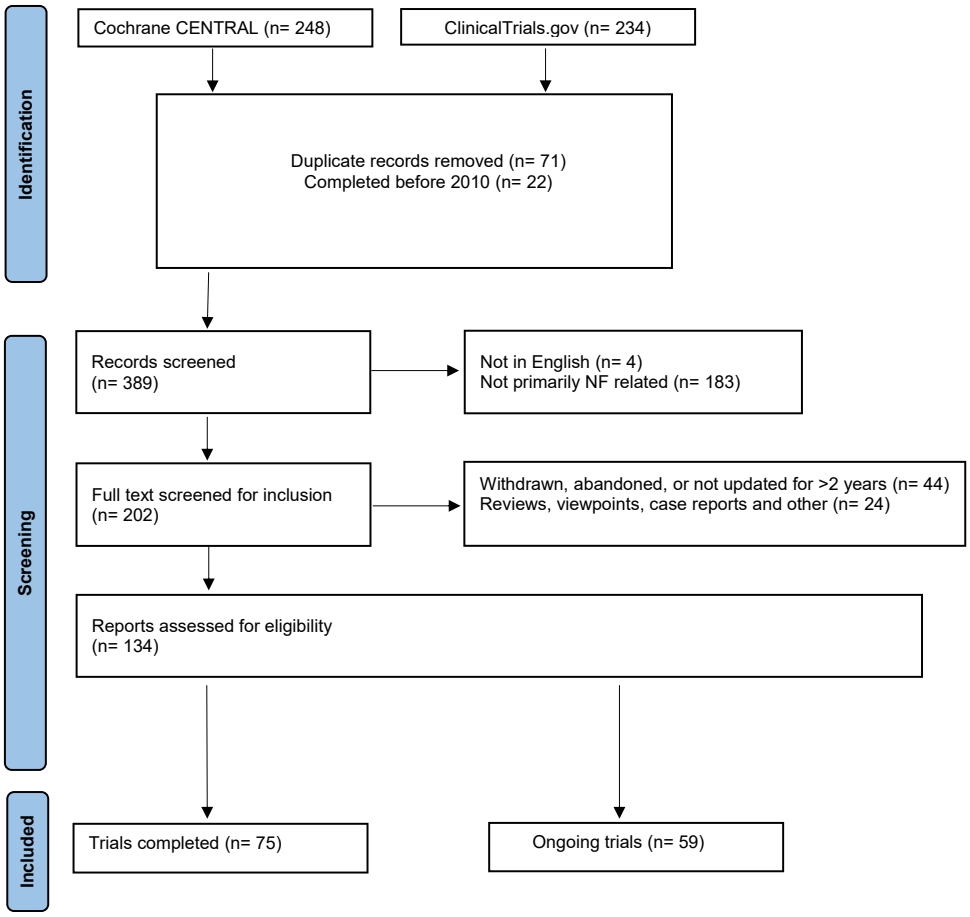


FIGURE. PRISMA flow chart demonstration selection of clinical trials. NF, neurofibromatosis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The color version of this figure is available in the online edition.

participants across clinical trials were seen as compared to other fields relevant to pediatrics possibly due to similar reasons noted including prevalence of condition and limited funding (Supplements 2 and 3). Interestingly, a general lack of phase 0 trials assessing pharmacokinetic or pharmacodynamic parameters was observed. The concept for phase 0 trials was introduced less than twenty years ago and still remains relatively limited in drug development, potentially reflecting their absence seen here.[12] In order to facilitate the identification and evaluation of candidate drug therapies, the Neurofibromatosis Preclinical Consortium and the research collaborative Synodos were created in 2008 and 2014, respectively.[13,14] These initiatives aim to help researchers gather and analyze preclinical data to inform future studies. Although these may not necessarily result in phase 0 clinical trials, the research from these efforts is essential to develop the rationale for future trials. Another unique, but perhaps unsurprising, finding was the distribution in country of origin for primary institutions or sponsors, with over two-thirds of completed trials and around three-fourths of ongoing trials coming from the United States. Others have previously noted the importance of creating and maintaining clinical trials with a global health focus in order to better understand the burden shaped by different contexts or settings.[15] This will require building capacity and infrastructure systems in low- and middle-income countries. At the same time, ensuring national and international coordination and collaboration to design and produce clinical trials of high quality in low-income settings around the globe is necessary. Valuable lessons in accomplishing this can be borrowed from the COVID-19 pandemic research community and their example in leading increased international collaborations and collective data sharing for a common goal.[16]

Clinical trials evaluating cognitive and behavioral abnormalities in NF1 represented less than one-fifth of all trials despite being the most common manifestation for pediatric patients with NF1.[17] Another potentially overlooked area of study was the evaluation of interventions aimed at improving quality of life (QoL). Nonmalignant manifestations of tumor predisposition syndromes are difficult to assess and treat compared to malignant manifestations as non-life-threatening factors may attract less attention, and their outcome might not be as dependent on drug responses as is the case when assessing tumor size among patients with cancer.[18] Incorporating QoL measures as secondary outcomes has been successful in NF1 trials and could be an important area of focus in all clinical trials for these conditions.[18] Pain and itching in NF1 are difficult to treat and affect QoL in a significant number of patients.[19,20] Treatment with antihistamines provides only partial relief for itch, and the pain is usually resistant to over-the-counter medications and surgical removal of neurofibromas.[19,21] However, there are no clinical trials focusing on improving pain and itch in NF1 patients. Understanding the underlying signaling mechanisms of pain and itch in these patients is fundamental to developing effective therapies in the clinical setting. Interestingly, previous studies have noted that QoL in patients with NF1 decreases with more marked visible signs of disease although not necessarily reflective of general health, thus highlighting the importance of cosmesis in a patient's life.[22,23] Additional clinical trials focusing on

TABLE 1.
Summary of Completed and Ongoing Trials

Population	Completed (N = 75)		Ongoing (N = 59)	
	N	(%)	N	(%)
Pediatric	17	22	13	22
Adult	20	27	15	25
Pediatric & adult	38	51	31	53
Phases				
Phase 0	1	1	0	0
Phase 1	10	13	6	10
Phase 2	23	31	22	37
Phase 3	2	3	3	5
Phase 4	1	1	0	0
Mixed phase	2	3	7	12
N/A[*]	16	21	13	22
Observational	20	27	8	14
Intervention				
Pharmacologic	37	49	38	64
Cognitive & behavioral	8	11	6	10
N/A	17	23	7	12
Other[†]	13	17	8	14
Pharmaceutical companies[‡]	15	20	23	39
Country[§]				
North America[‖]	50	67	39	87
Europe	20	27	3	7
Asia	3	4	2	4
South America	1	1	0	0
Australia	1	1	1	2

Abbreviation:
FDA = Food and Drug Administration
[*] Clinical trial did not have a study phase as defined by the FDA or the study phase could not be determined.
[†] Other forms of interventions for completed trials include genetic testing, standardized outcome measures, and patient registry. Other forms of interventions for ongoing trials include pain management, diagnostic imaging, and genetic testing.
[‡] Includes trials that are run by pharmaceutical companies or have collaboration with pharmaceutical companies.
[§] Country distribution percentages are calculated after subtracting trials that are primarily run by pharmaceutical companies.
[‖] All trials originating from North America were run in institutions in the United States.

cutaneous neurofibromas or other cutaneous manifestations in patients with NF1 may help improve QoL and increase emotional well-being.[24] Importantly, clinical trials focusing on QoL, including functional outcome measures like pain, appear to be from more recent years, possibly suggesting a new emphasis and a projected increase in the proportion of these types of trials in the future. There is also a high prevalence of psychiatric conditions, particularly autism spectrum disorder and attention-deficit hyperactivity disorder, in patients with NF1.[25] However, only 5 completed or ongoing trials had a focus on studying attention-deficit hyperactivity disorder or autism spectrum disorder. Musculoskeletal abnormalities are also relatively common in patients with NF1, occurring in up to 30% of patients,[26] but we show that only 8 completed or ongoing trials had an emphasis on evaluating outcomes for patients with musculoskeletal abnormalities in NF1.

When reviewing clinical trials enrolling patients with NF2, the majority evaluated outcomes specific to vestibular schwannoma, with less than one-third including multiple tumor types. This may serve as another potential area that can be further explored given that meningiomas are the second most common tumor in NF2, and incidence can reach up to 80% by age 70.[3,27] Finally, we found a paucity of clinical trials evaluating outcomes in patients with SWN overall. Schwannomas commonly affect peripheral and spinal nerves, causing chronic pain associated with anxiety and depression.[28,29] Gabapentin, opioids, and nonsteroidal anti-inflammatory drugs have been used for pain management in patients with SWN, but with limited benefit. SMARCB1 and LZTR1 mutations are implicated in the pathogenesis of SWN; however, there are no systemic treatments for SWN as of this writing. These mutations are potential targets for future therapies, and histone deacetylase inhibitors are currently under development for SWN treatment.[30] As new information is revealed regarding the cellular and molecular underpinnings behind the neurofibromatoses, further understanding behind these diseases is likely to appear and may result in revisions to the diagnostic criteria for these conditions. Recently, the diagnostic criteria for NF1 have been updated to include identification of a pathogenic germline variant in *NF1*.[31] How this will affect clinical trial accruement remains to be seen, although it may allow for a greater inclusion of patients with more clinically limited involvement of NF1. For example, a patient with only a plexiform neurofibroma and no other clinical criteria would previously not have been eligible for a therapeutic PN trial if they did not also have a family history of NF1. However, with the updated criteria, if this patient has a germline pathogenic variant in *NF1*, he/she would now be eligible.

Clinical trials are essential to advance medical knowledge and help improve treatments. Among the clinical trials focusing on manifestations in NF1, PN has been the most studied. While numerous trials failed to show benefits to several drugs tested, selumetinib, a mitogen/extracellular signal regulated kinase inhibitor, was approved by the Food and Drug Administration (FDA) for the treatment of symptomatic and inoperable NF1-PN for pediatric patients older than age 2 years in April 2020.[32] This is the first FDA-approved drug for NF1-PN and further shows the importance of clinical trials in directing clinical practice as this provided an option for NF1-PN treatment other than surgery for

TABLE 2.
Tumor Type Distribution of Completed and Ongoing Trials for NF1 and NF2 That Focused on Associated Tumors

Tumor Types	Completed NF1 Trials (N = 26)	Ongoing NF1 Trials (N = 29)	Tumor Types	Completed NF2 Trials (N = 13)	Ongoing NF2 Trials (N = 7)
Plexiform neurofibroma	12	13	Vestibular schwannoma	7	4
Cutaneous neurofibroma	8	8	Meningioma	1	1
Glioma	3	2	Cutaneous schwannoma	1	0
Malignant peripheral nerve sheath tumor	2	5	Vestibular schwannoma & meningioma	2	0
Plexiform neurofibroma & cutaneous neurofibroma	1	0	Vestibular schwannoma & meningioma& ependymoma	2	0
Glioma & plexiform neurofibroma	0	1	Vestibular schwannoma & meningioma & ependymoma & glioma	0	1
			Vestibular schwannoma & meningioma & ependymoma & nonvestibular schwannoma	0	1

Abbreviations:
NF1 = Neurofibromatosis type 1
NF2 = Neurofibromatosis type 2

patients. Yet for other NF1-related tumors, many NF2-related tumors and SWN, and nontumor manifestations of any of these syndromes, there has been little progress in clinical practice in terms of the FDA approval of new systemic therapies. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration has grown and developed as a response to such need, providing recommendations for clinical trials including those involving selumetinib.[33] Recommendations set forth by the REiNS concerning primary outcome measures play a critical role in the design and execution of future studies, thus also having the potential to impact which areas of study might be prioritized by the scientific community. In this way, the REiNS can have an impact among areas that have been understudied in previous years resulting in greater attention, especially as it seeks to increase patient engagement in clinical trial design.[33] Notably, the REiNS includes several working groups with emphasis on different areas, including focusing on developing recommendations for reproducible functional outcomes measures.[34] This highlights the need to incorporate measures other than tumor size, such as hearing, visual acuity, or other changes from impairments due to tumor location. Improvement in the management of neurofibromatoses remains a challenge that warrants future clinical trials—especially for understudied aspects of these diseases. Potential barriers to the design, implementation, and completion of clinical trials for certain areas of investigation across the scope of conditions involving the neurofibromatoses will continue to be important to keep in consideration, including lack of general awareness of their importance among the greater scientific community and limited funding available to investigate all aspects that affect patients with rare diseases.

Limitations

This review contains several potential limitations. First, there were a number of publications that were reported as results of clinical trials, but not found to have a corresponding trial registration/number available. It is possible that, if included, these data may have influenced our findings. However, individual publications can be part of larger clinical trials evaluating multiple outcomes or conditions and may have been included elsewhere. Second, inclusion into clinical trial databases typically result from team members creating a public posting and a trial may have been missed if the research team did not generate such posts. This is less likely given that it is normally recommended or sometimes required to make these postings when subsequent publication of results is expected. Third, the proportion of clinical trials with a pharmaceutical company involvement was reported based on data collected directly from database and published articles associated with trial numbers. However, institutional collaborations with pharmaceutical companies might not be accurately represented since some trials have not been published yet or the trials are still ongoing. Finally, we attempted to include ongoing clinical trials with recent updates, but it is possible that some trials have had slow enrollment for many years and have not posted recent preliminary findings online, potentially influencing our observations.

Conclusion

This review outlines the current progress in clinical trials for patients with the neurofibromatoses and highlights potential areas of focus for future research. In particular, we report that the majority of clinical trials have focused on NF1-PNs in patients with NF1, and continue to do so, while other tumor types within NF1 have been less commonly studied in a clinical trial setting. Clinical trials involving patients with NF2 did not commonly focus on meningioma and cutaneous schwannoma, and there was a paucity of studies for patients with SWN. Additionally, most clinical trials originated in the United States, despite the global burden of disease caused by NF1, NF2, and SWN. Finally, we suggest other areas of future study to include a greater emphasis on the management of psychiatric conditions commonly seen among NF1 patients as well as addressing cosmetic features, pain, and itch which have a strong association with overall QoL. Additionally, it could be beneficial to see future studies evaluating other tumor types, such as meningiomas in NF2, due to their high prevalence, and studies involving patients with SWN as no therapeutic clinical trials for this population were identified. Clinical trials remain a critical component in advancing new interventions to increase QoL and reduce morbidity and mortality among patients with the neurofibromatoses; increasing the number of trials and expanding the areas currently being evaluated may help ensure faster progress toward bettering the life of these patients.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2022.06.003.

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