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Lessons learned from drug trials in neurofibromatosis: A systematic review

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ABSTRACT

Neurofibromatosis (NF) is the umbrella term for neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis (SWN). EU-PEARL aims to create a framework for platform trials in NF. The aim of this systematic review is to create an overview of recent clinical drug trials in NF, to identify learning points to guide development of the framework. We searched Embase, Medline and Cochrane register of trials on October 1, 2020 for publications of clinical drug trials in NF patients. We excluded publications published before 2010, systematic reviews, secondary analyses and studies with <10 patients. Data was extracted on manifestations studied, study design, phase, number of participating centres and population size. Full-text review resulted in 42 articles: 31 for NF1, 11 for NF2, none for SWN. Most NF1 trials focused on plexiform neurofibromas (32%). Trials in NF2 solely studied vestibular schwannomas. In NF1, single-arm trials (58%) were most common, and the majority was phase II (74%). For NF2 most trials were single-arm (55%) and exclusively phase II. For both diseases, trials were predominantly single-country and included five centres or less. Study population sizes were small, with the majority including ≤50 patients (74%). In conclusion, NF research is dominated by studies on a limited number out of the wide range of manifestations. We need more trials for cutaneous manifestations and high-grade gliomas in NF1, manifestations other than vestibular schwannoma in NF2 and trials for SWN. Drug development in NF may profit from innovative trials on multiple interventions and increased international collaboration.

1. Introduction

Neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis (SWN) are autosomal dominant hereditary disorders that are frequently grouped under the umbrella term neurofibromatosis (NF). All three diseases predispose to benign and malignant tumour formation. Disease manifestations are mainly located in both the peripheral and central nervous system, but NF1 displays a wide range of disease manifestations in (almost) all organ systems (Evans et al., 2010; Blakeley and Plotkin, 2016; Korf, 2013). In addition, NF is characterized by a wide variability in expression of manifestation types and severity, resulting in some patients having little to no symptoms, and others being severely affected (Korf, 2013; Shen et al., 1996).

In rare hereditary diseases with strong phenotype variability like NF, it can be difficult to perform drug trials. Small patient populations are a bottleneck for classical single-center clinical trials, resulting in high

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operational costs, low statistical efficiency and an overall lengthy time to drug approval (Griggs et al., 2009). Diseases such as NF therefore may profit from a different kind of trial to improve research efficiency. A platform trial, also known as a basket or umbrella trial, is a clinical trial with a single master protocol which offers flexible features such as dropping or adding new treatments during the trial, and declaring one or more treatments superior (Saville and Berry, 2016). Ideally, platform trials will involve fewer patients, fewer patient failures, less time, and provide greater probability of success in finding beneficial treatments than traditional clinical trials (Saville and Berry, 2016; Berry et al., 2015).

EU-PEARL (EU Patient-Centric Clinical Trial Platforms) is a European collaborative project that aims to create a framework for the future conduct of platform trials in four main disease areas, including NF (EU-PEARL, 2020). Being in the early stages of developing platform trials in NF, we were in need of information on the current scene of trials in NF so far, to identify gaps and recommendations in past NF research. The aim of this systematic review is to create an overview of clinical drug trials performed in NF over the last ten years and use this information to identify learning points which can be used to guide the development of future platform trials.

2. Methods

2.1. Search strategy

Following a PICOS format we defined our search strategy, without specifying a specific outcome. We were interested in NF patients (population) treated with a drug therapy (intervention and comparator), researched in either a clinical trial or an observational study (study type). This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and recommendations (Moher et al., 2009). The initial literature search was performed on February 4, 2020. However, due to a delay in the writing of this review, we chose to run the search again to include recent articles that were published in the elapsed time. We performed the final literature search on October 1, 2020, searching the databases Embase, Medline and Cochrane register of trials using a string of terms designed by our librarian specifically for this review. For the full search strings per database we refer to appendix I.

2.2. Selection criteria

Two authors (BD and RO) independently performed the screening process and full text reviews. Any conflicting findings were reviewed and discussed until consensus was reached. We included publications that reported results of 1) studies performed in NF patients, or studies that described NF patients as a subgroup of the study population, 2) drug trials, which could be either observational or clinical trials. Articles published earlier than January 1st, 2010 were excluded. We also excluded systematic reviews, secondary analyses of studies already included into our systematic review, studies reporting $n < 10$ patients, and studies that did not report results for NF patients separately. For conference abstracts, we excluded records that were updated in a later publication, which could be either a more recent conference abstract or a full publication. Only publications in English were considered.

2.3. Data extraction

Data was directly abstracted from publication texts, tables and figures by the first author (BD). Information extracted includes study design and phase (if applicable), number of participating centres, the manifestation that was targeted in the study, number of study population, and number of dropouts and dropout reasons. Analysing all used endpoints in trials would fall outside the scope of this systematic review, so we decided to only extract the primary endpoints of each study. To group the wide variability of manifestations in NF, we adopted the approach from a previous study (Dhaenens et al., 2021), resulting in ten manifestation groups for NF1, and two for NF2 (Appendix 2). Manifestations that were studied in the included articles of this systematic review were grouped according to those defined groups.

2.4. Quality and bias assessment

We performed an assessment of the risk of bias in the results of the included full-text articles. In addition to the overall risk of bias, we investigated which domains are the most common causes of bias in drug trials in NF. Two independent researchers (BD and GH of the Sophia Children's Hospital) applied the ROBINS-I tool for non-randomised trials (Sterne et al., 2016) and the RoB 2 tool for randomised trials (Sterne et al., 2019). The ROBINS-I tool investigates risk of bias for the following domains: 1) confounding, 2) selection of participants, 3) deviations from intended interventions, 4) missing outcome data, 5) measurements of the outcome and 6) selection of the reported result. The risk of bias judgement can be low, moderate, serious and critical risk of bias, both for each domain-level risk of bias and the overall risk of bias. The RoB 2 tool investigates the same domains as the ROBINS-I tool, except that the domains 1) and 2) are replaced by the domain risk of bias due to the randomisation process. The risk of bias judgement can be low risk, some concerns and high risk of bias, both for each domain-level judgement about the risk of bias and the overall risk of bias.

3. Results

The database search identified 3478 records (see Fig. 1 for the results of the screening and full-text eligibility process). After removing duplicates and adding four additional records through searching reference lists, 2363 records remained for title and abstract screening. After screening, 121 records were deemed eligible for full-text review. Seventy-two publications were subsequently excluded. In the end, 49 records were included into this systematic review, consisting of 42 full articles and 7 conference abstracts.

Of the full-text articles, 31 described trials in NF1, 11 in NF2, but none in SWN. Among the conference abstracts, we identified five trials in NF1, two in NF2, but none in SWN. Most records were identified in the years 2014 and 2016 (Appendix 3). Multiple conference abstracts published in 2018 have not yet been updated by a later conference abstract or article.

3.1. Targeted manifestations

Most trials within the NF1 population focused on the manifestation group benign peripheral nerve sheath tumours (10/31 published articles (32%)), followed by the groups neurodevelopmental manifestations (eight articles, 26%) and low grade glioma (LGG) (seven articles, 23%) (Fig. 2). Malignant peripheral nerve sheath tumours (MPNST) were featured in four trials, and for bone and cutaneous manifestations only one trial was performed. There were no trials performed for high-grade brain glioma and vascular manifestations in NF1 patients. All studies within the NF2 population focused on the tumour manifestations, and solely on the vestibular schwannomas.

The majority of trials targeted one specific manifestation within their respective manifestation group: trials within the benign peripheral nerve sheath tumour group exclusively targeted plexiform neurofibromas, and trials for LGG prioritized low grade brain gliomas (5/7 trials) over optic pathway gliomas. As an exception, trials in the group of neurodevelopmental manifestations included a wide scope of targeted manifestations. Studies on malignant peripheral nerve sheath tumours/sarcomas (MPNST/Sarcomas) were only published from 2017 and onwards, while the studies on benign peripheral nerve sheath tumours, LGG, neurodevelopmental disorders and NF2 tumour manifestations were quite evenly distributed among the 10 year scope of this systematic

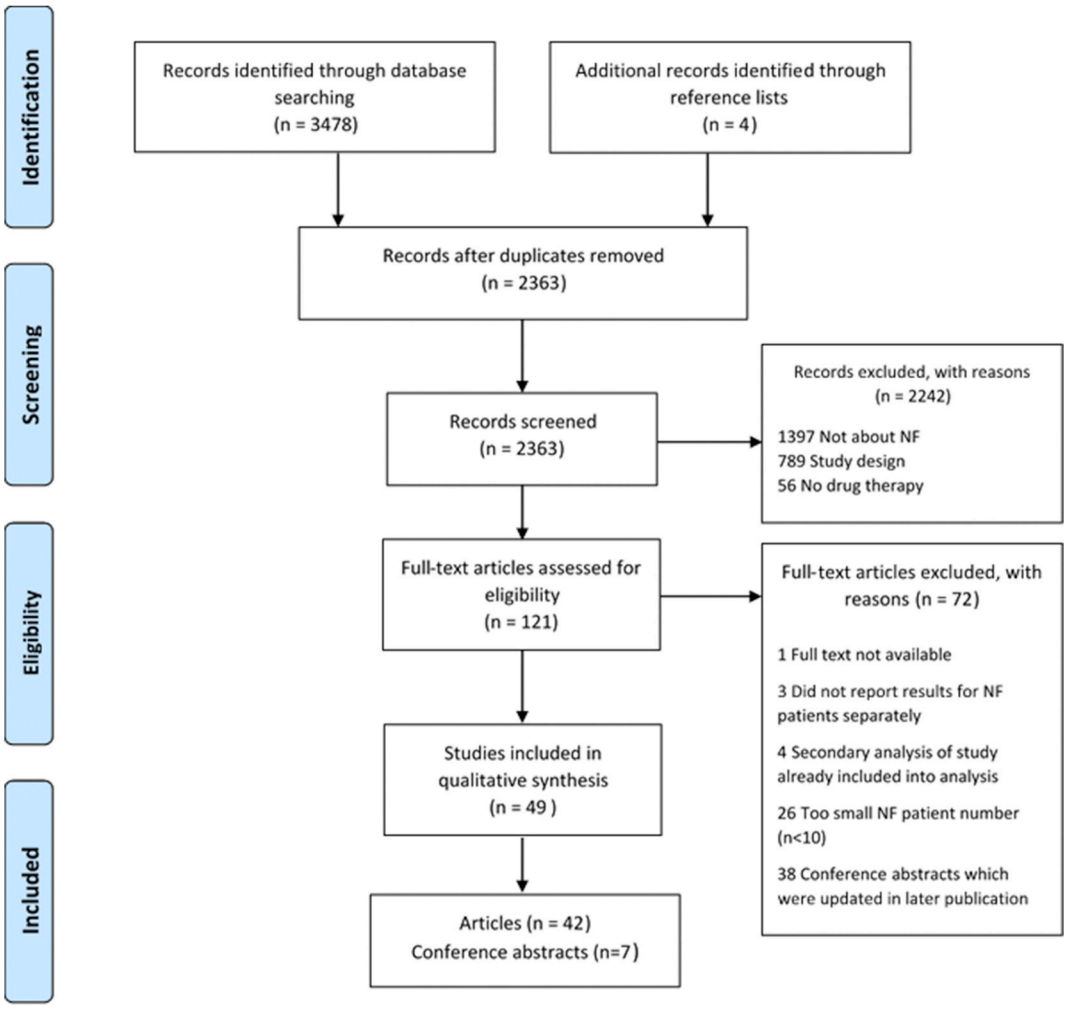

Fig. 1. A flowchart of the search results according to the PRISMA-guidelines.

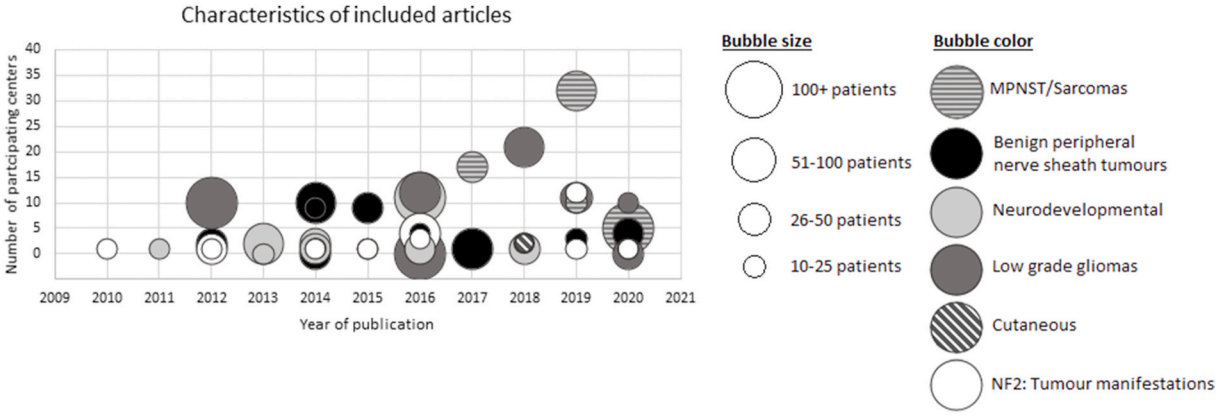

Fig. 2. Bubble graph representing characteristics of the included full-text articles: the number of participating centres, year of publication and number of patients included. The colour/fill of the bubbles represents the type of manifestation that was targeted in the article. MPNST = malignant peripheral nerve sheath tumour, NF2 = Neurofibromatosis type 2.

review.

3.2. Study design and phase

The majority of included NF1 articles reported the results of single arm trials (18/31 articles, 58%)(Fig. 3). A total of eight Randomised Controlled Trials (RCTs) were identified, of which six were performed for neurodevelopmental manifestations (75% of the performed RCTs). The remaining five articles were observational trials. The trials on benign peripheral nerve sheath tumours and LGG consisted almost exclusively out of single arm trials: 8/10 trials (80%) and 6/7 trials (86%), respectively. Of all 31 NF1 publications, 23 were phase II studies (74%), but no phase III or phase IV studies were identified. The majority of studies in NF2 were single arm trials (55%), and all were phase II. The

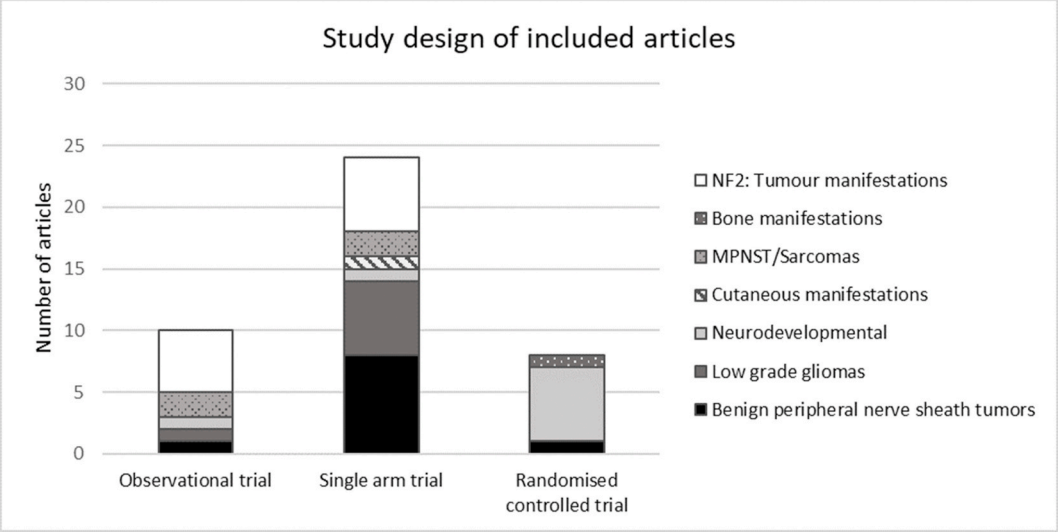

Fig. 3. Bar chart showing the study designs used in the included articles. The colour or fill of the bars represent the type of manifestation that was targeted in the article.

other studies were observational studies; there was no RCT performed.

3.3. Collaboration between countries and number of participating centres

For NF1, 25 studies were single-country studies (81%), and six resulted from an international collaboration (19%)(Table 1). Trials for benign peripheral nerve sheath tumours were single-country only. The number of participating centres varied greatly among studies. Seven out of 31 studies were single-center studies (23%), while only six trials had eleven or more participating centres (19%). Studies for LGG were large multi-center trials most often, with three out of six trials involving 11 centres or more (50%). All included NF2 studies were single-country. Eight studies were single-center, with only three studies involving two centres or more.

3.4. Primary endpoints

Endpoints used in NF1 varied widely amongst studies (Appendix 5). The most common primary endpoint was a description of tumour response, related to the high number of trials that studied tumour manifestations: out of 21 trials in tumour manifestations, 17 used tumour response on MRI as primary endpoint (81%). Studies in the field of neurodevelopmental manifestations showed the greatest variability in endpoints used (eight different primary endpoints for eight studies), partly due to the difference in targeted manifestations. Only three out of 31 NF1 trials used a patient-reported outcome measure (PROM) as a primary endpoint (10%). In NF2 trials almost all studies used tumour response on MRI as primary endpoint (82%) and seven studies used hearing response (73%). In addition, there was one study that also used a PROM on tinnitus, vertigo and headache symptoms as primary endpoint, and one study that used a quality of life questionnaire.

3.5. Population characteristics

Most of the trials in this systematic review only included patients that were diagnosed with NF (32 out of 41 trials (78%))(Appendix 4). Inclusion of a combination of NF and non-NF patients was only seen in trials for MPNST/Sarcomas and LGG. For MPNST, all trials included both NF1 and non-NF1 patients. Within the LGG manifestation group, 5/7 trials provided a subgroup analysis for NF1 patients, and 2/7 studies focused exclusively on NF1 patients.

Most NF1 studies were small, including 10 to 25 patients (32%) or 26 to 50 patients (36%). The majority of these small studies were seen in the benign peripheral nerve sheath tumour group (4/10 studies (40%)), and consisted of small single arm trials or single-center experiences. A minority of studies included 100 patients or more (13%). The majority of studies that included more than 50 patients were performed in the LGG manifestation group (4 out of 6 studies). The studies with larger patient populations were generally multi-center studies (80%) and half of them were international collaborations. In NF2, population numbers were small, with 9 studies including 10 to 25 patients (82%) and two studies including 30 patients or more.

In most trials of this systematic review, children were the target population (Appendix 4). Fourteen studies were performed in children only (defined as <18 years old), and eight reported on trials performed in children and young adults (mainly defined as <21 years old), representing 71% of all NF1 trials. Five studies included patients of all ages, while only 4 focused on adult patients only. The median age of the included patient population was therefore generally low, with a median age of 20 or lower in 21 studies (68%) (Table 1). One study in NF2 focused on adults only, while the remaining ten included both children and adults into the study. The patient population was generally older than the NF1 population, with the majority of patient populations having a median age of 21–30 years old (73% of studies).

3.6. Drop-out rates

One-third of the trials in NF1 reported drop-out rates of 20% or less. Overall, studies on neurodevelopmental manifestations reported the least amount of drop-outs, with 5 out of 8 studies reporting 20% drop-outs or less (63%). Studies on benign peripheral nerve sheath tumours generally performed worse with only 2 out of 9 clinical trials reporting 20% dropouts or less. Dropout rates in NF2 were low: five studies reported 0–10% of the included patient population as dropout (45%), and three studies reported 11–20% (27%). The other 3 studies were retrospective observational studies so dropout rates were not applicable. The reasons of the drop-outs were very diverse. The most common reasons were progressive disease (32%), toxicity (20%) and patient withdrawal (19%).

3.7. Conference abstracts

The majority of conference abstracts in NF1 were about plexiform neurofibromas (Appendix 6). There was one conference abstract on

Table 1
Summary of the results from the data extraction. NA = not applicable, NF1 = neurofibromatosis type 1, NF2 = neurofibromatosis type 2, SWN = Schwannomatosis, MPNST = malignant peripheral nerve sheath tumour, RCT = randomised controlled trial. *Studies with either NA, or those that did not specify this item in their article were not used in de calculation of the median, range and/or percentage.

NF1/NF2/SWN and manifestation group	References	Study design (% within manifestation group)	Phase (% within manifestation group)*	Single-country/ Multi-country (% within manifestation group)	Median number of participating centres (range)	Median number of population (range)*	Range of patient ages in years (median age range)*	Median dropouts (% included population) (range)*
NF1								
MPNST/ Sarcomas	Meister et al. (2020), van Noesel et al. (2019), Widemann et al. (2019), Higham et al. (2017)	2*x* Single arm trial (50%)2*x* Observational (50%)	2x Phase II (100%)	2*x* Single-country (50%)2*x* Multi-country (50%)	14 (5 - 32)	50 (25–159)	Newborn – 66 (12,7 - 33)	23%
Benign peripheral nerve sheath tumours	Gross et al. (2020), Espírito Sano et al. (2020), Zehou et al. (2019), Jakacki et al. (2017), Weiss et al. (2015), Dombi et al. (2016), Widemann et al. (2014a), Widemann et al. (2014b), Weiss et al. (2014), Robertson et al. (2012)	8*x* Single arm trial (80%)1*x* Observational (10%)1*x* RCT (10%)	1*x* Phase I (11%)8*x* Phase II (89%)	10x Single-country (100%)	4 (1 - 10); ;	33 (12–86)	1,6–52 (8,2 - 16); ; ;	36% (0–100)
Cutaneous manifestations	Slopis et al. (2018)	Single arm trial	Phase II	Single-country	2	22	Not specified	23%
Neurodevelop-mental manifestations	Stivaros et al. (2018), Payne et al. (2016), Bearden et al. (2016), Lion-François et al. (2014), Lidzba et al. (2014), van der Vaart et al. (2013), Mainberger et al. (2013), Acosta et al. (2011)	1*x* Single arm trial (13%)1*x* Observational (13%)6*x* RCT (75%)	1*x* Phase I (14%)6*x* Phase II (86%)	6*x* Single-country (75%)2*x* Multi-country (25%)	1 (1 - 11); ; ;	42 (22–146)	7,1–44 (9,3 - 25,7); ; ;	10% (0–27)
Low grade gliomas	Vairy et al. (2020), Ullrich et al. (2020), Fangusaro et al. (2019), Falzon et al. (2018), Lassaletta et al. (2016), Ater et al. (2016), Fisher et al. (2012)	6*x* Single arm trial (86%)1*x* Observational (14%)	1*x* Phase I (17%)5*x* Phase II (83%)	5*x* Single-country (71%)2*x* Multi-country (29%)	10 (1 - 21)	54 (23–264)	0,4–21 (2,7 - 10,2)	32% (7 - 48)
Bone manifestations	Das et al. (2014)	RCT	Phase II	Single-country	1	20	2–7 (mean age 4,1 years)	0
NF2								
Tumour manifestations	Fujii et al. (2020), Plotkin et al. (2019), Sverak et al. (2019), Blakeley et al. (2016), Morris et al. (2016), Goutagny et al. (2015), Alanin et al. (2015), Karajannis et al. (2014), Karajannis et al. (2012), Plotkin et al. (2012), Plotkin et al. (2010)	6*x* Single arm trial (55%)5*x* Observational (45%)	6x Phase II (100%)	11x Single-country (100%)	1 (1 - 12); ; ;	14 (10–61)	10–79 (23 - 34);	10% (0–20)

cutaneous neurofibroma. The two conference abstracts for NF2 were in the tumour manifestation group and targeted meningiomas. Most were single arm trials, and there were no reports on phase III or IV studies. Six out of seven abstracts dated from 2018 and later. Only one abstract published in 2011 was older and was not updated in later conference abstract or a full article.

3.8. Quality assessment

Fig. 4a and b presents the risk of bias per domain, and the final overall bias risk. Five out of eight RCTs were classified as low risk of bias, three studies were assigned moderate to high risk of bias. This bias originated from the domains bias due to missing outcome data (25% of RCTs), bias in selection of the reported result (13%), and bias arising from the randomisation process (25%)(Fig. 4a).

Due to possible bias by confounding (resulting from their non-randomised design), the observational and single arm studies are always classified as moderate risk of bias or higher (Fig. 4b). Six studies were judged as having "serious risk of bias" (18%). This was related to bias in measurement of the outcome (3%) and bias in the selection of the reported result (18%). Besides the bias due to confounding, moderate risk of bias judgement was most commonly seen in the domains bias due to missing outcome data (26%) and bias due to selection of the reported result (38%). All studies that were marked as serious risk of bias were observational studies. A detailed result from the bias assessment can be found in appendix 7 and 8.

4. Discussion

Our systematic review highlights the dominance of NF1 in NF trials,

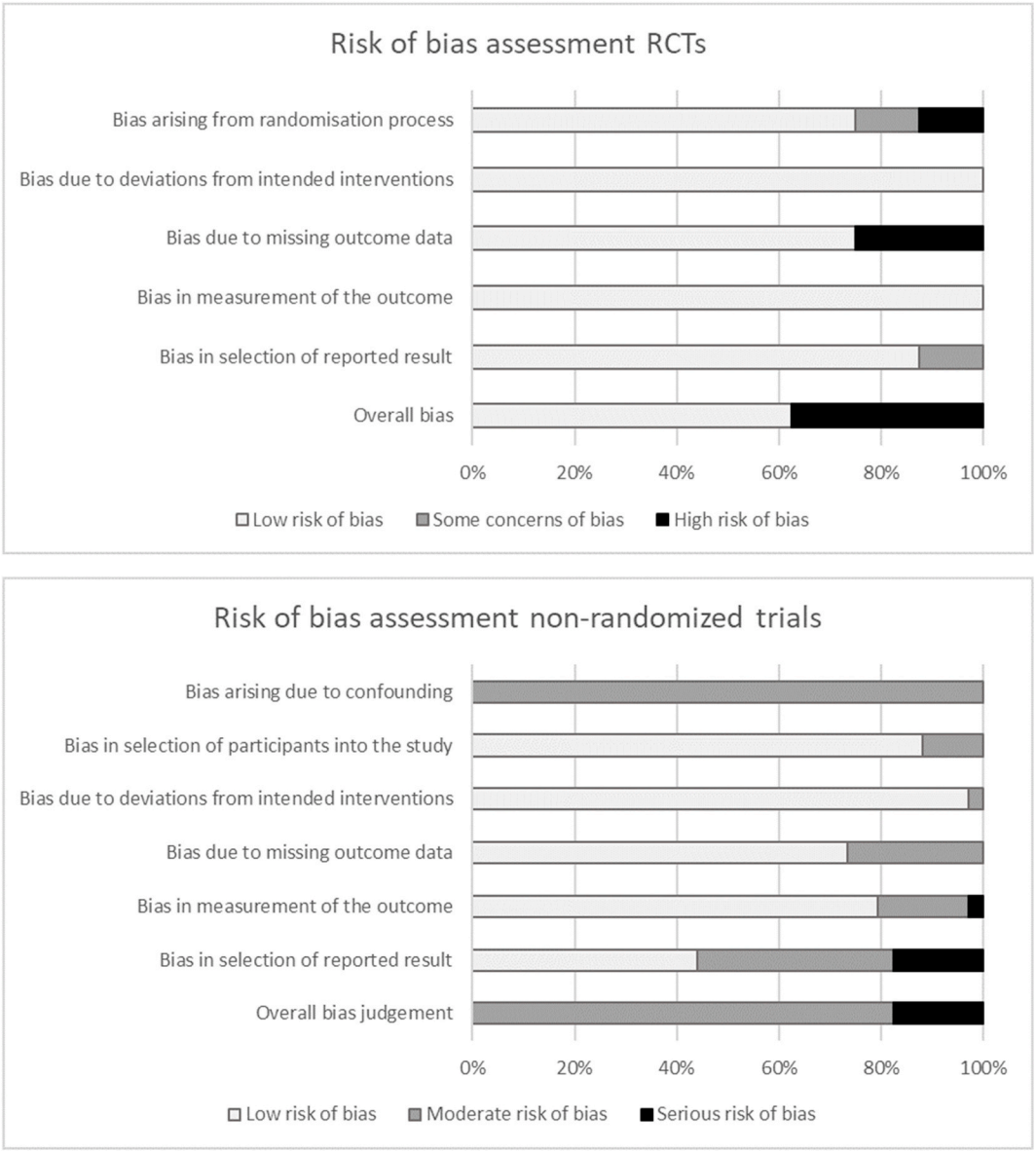

Fig. 4. a) Bar chart representing the results from the bias assessment of the randomised controlled trials (RCTs), depicting the percentage of studies that scored low risk, some concerns and high risk of bias on the different domains and the overall risk of bias. b) Bar chart representing the results from the bias assessment of the non-randomised controlled trials, depicting the percentage of studies that scored low risk, some concerns and high risk of bias on the different domains and the overall risk of bias.

and the absence of trials performed for SWN. In NF1, clinical trial publications mainly focused on plexiform neurofibromas, neurodevelopmental disorders and LGG. NF2 trials were solely focused on vestibular schwannomas. Single-arm trials were the most common, all limited to phase I and II trials. RCTs were performed in a quarter of NF1 trials and mainly performed in neurodevelopmental manifestations. Most trials were single-country (NF2 in particular) and included 5 participating centres or less. Primary endpoints were mainly functional; PROMs were only used in 10% of all trials as primary endpoint. The majority of NF1 trials included only children and young adults into their study population. Included patient populations were small, with high drop-out rates of more than 20% in two-thirds of NF1 trials. Risk of bias was mainly due to missing outcome data, bias arising from the (lack of a) randomisation process, and bias in selection of the reported result.

Our study shows an evident neglect of the disease Schwannomatosis among clinical trials. This may be expected due to its low prevalence (1 in 69.000 (Evans et al., 2018)), however clinical drug trials in SWN are still urgently needed. Schwannomatosis patients commonly present with chronic pain that can severely affect quality of life, masses due to growing schwannomas, and depression and anxiety are common comorbidities as a result from chronic pain (Evans et al., 2018; Schraepen et al., 2020). The fact that, at the time of writing this systematic review, a randomised, double-blind, placebo controlled clinical trial is being conducted on the effect of Tanezumab on moderate to severe pain in SWN patients (https://clinicaltrials.gov/ct2/show/NCT04163419), is a first important step in the right direction. Another research gap is the absence of trials on manifestations in NF2 other than vestibular schwannoma. Recently, a platform-basket screening study was launched to test multiple experimental therapies in NF2 patients with multiple associated tumours, including ependymomas and meningiomas (https://clinicaltrials.gov/ct2/show/NCT04374305).

As shown in this systematic review, cutaneous manifestations have received less to no priority in clinical trials, in contrast to the relative high manifestation's prevalence. Qualitative studies in NF1 patients

have shown that cutaneous manifestations are often considered as one of the worst aspects of the condition, and that they often cause emotional distress (Crawford et al., 2015; Rietman et al., 2018), highlighting the priority of finding new therapies in the future. There is a noticeable increase in (planned) trials for oral and/or topical drug treatments and laser/photodynamic therapy for cutaneous manifestations, but more adequately designed trials are needed to find suitable treatment options for patients with high burden due to cutaneous manifestations.

Another gap for NF trials is the absence of trials for NF1 patients with high-grade gliomas. This may be due to its very low incidence, lack of early detection methods, and a current short life expectancy from diagnosis, complicating trials for this manifestation (Uusitalo et al., 2016; Huttner et al., 2010; Marchese and Chang, 1990; Sposto et al., 1989; Wen and Kesari, 2008; Verburg et al., 2017). This contrasts, however, to the high priority as assigned by patients to this manifestation (Dhaenens et al., 2021).

The small patient numbers in trials, and the lack of (multi-country) multi-center studies identify the need for multi-center efforts in NF1, NF2 and SWN. Platform trials may fill this gap, by testing multiple interventions simultaneously and requiring fewer participants. Almost all trials on LGG and MPNST/Sarcomas included in this review included both NF patients and non-NF patients into their study population. This hampers the disease-specific evaluations of new drug treatments in NF, since treatment effects may differ significantly from the non-NF population (Watson et al., 2017; Falzon et al., 2018). Given the different genetic pathology of the manifestations, finding NF-specific treatments is essential, and should not be ignored due to the low feasibility of performing NF-only trials.

By performing the search and data-extraction in a systematic fashion, we aimed to provide a complete and unbiased review of drug research in NF. A limitation of this study is that we only included trials that were performed during the last ten years. This may have resulted in a skewed image of studies performed in NF (e.g. what manifestations have been studied), but we felt that a review of the past decade would provide a realistic view on the current scene of trial development in NF. Another limitation in our search is that we only included published articles and conference abstracts, and did not search for published trial protocols. Given the fact that institutions will be more likely to report a positive trial result, as opposed to negative or null findings, this can lead to publication bias. Another limitation is that we might have missed a relevant trial that was not specifically focused on NF patients only, since NF patients might have been included in the study population of a trial without being specifically mentioned in the text.

The results from our systematic review reveal gaps in NF research of the last decade and highlight possible implications for research in the future. Some manifestations are targeted more frequently than others, resulting in manifestations being under-represented in NF clinical trials. Next we identified the need for more RCTs and phase III and IV trials. An internationally organized NF research network could reform and improve NF research through collaboration between both NF centres and countries, facilitating data sharing and enlarging patient populations in trials for this rare condition. There is an obvious lack of trials in adult NF1 patients. With respect to trial endpoints, PROMs are rarely used as outcome measures and should be used much more frequently to assess treatment effects in clinical trials in NF, given the impact of these conditions on patients' quality of life (Wolters et al., 2013). While the REiNS group has provided advice on the domains pain and physical functioning (Wolters et al., 2016), there is no consensus on the use of PROMs in other domains as of yet. Drop-outs in NF research seem quite high when comparing it to research in other fields (Wood et al., 2004), and were mainly related to progressive disease, toxicity and patient withdrawal. Trials should aim to reduce these sources of drop-outs as much as possible. Patient withdrawal could especially be reduced by adequately addressing the patient burden of participating in a trial. Advances in discovering and testing new drug treatments for all NF manifestations in clinical trials are likely to require research efforts across multiple countries and NF centres. Through the EU-PEARL project, we encourage the creation of further collaborative, multi-center, and international efforts to ensure that all NF manifestations that urgently need new treatments are adequately represented in future research.

In conclusion, we in particular identify the need for more research on underrepresented manifestations like cutaneous manifestations and high-grade gliomas in NF1, tumour manifestations other than vestibular schwannoma in NF2, and schwannomatosis. We also see a need for more trials for adult NF1 patients. Innovative trial designs such as platform trials with more efficient use of participants and the possibility of testing multiple interventions simultaneously could be a solution for these research gaps.

Author statement

Britt A. E. Dhaenens: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Rosalie E. Ferner: Conceptualization, Writing - Review & Editing D. Gareth Evans: Conceptualization, Writing - Review & Editing Guenter Heimann: Conceptualization, Writing - Review & Editing, Visualization Cornelia Potratz: Conceptualization, Writing - Review & Editing Edwin van de Ketterij: Writing - Review & Editing Angela M. Kaindl: Writing - Review & Editing Geesje Hissink: Investigation, Writing - Review & Editing Charlotte Carton: Writing - Review & Editing Annette Bakker: Conceptualization, Writing - Review & Editing, Supervision Marco Nievo: Conceptualization, Writing - Review & Editing, Supervision Eric Legius: Conceptualization, Writing - Review & Editing Rianne Oostenbrink: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision.

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Declaration of competing interest

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Appendix A. Supplementary data

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