Understanding caregiver-reported outcomes in clinical trials for children with intellectual disability: a scoping review

Yousif Al-Baldawi

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School of Epidemiology and Public Health (SEPH)
Faculty of Medicine
University of Ottawa

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List of tables and figures

Abbreviations

COA: Clinical Outcome Assessment

ClinRO: Clinician-Reported Outcome

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

GND: Genetic Neurodevelopmental Disorder

ID: Intellectual Disability

ISOQOL: International Society for Quality of Life Research

ObsRO: Observer-Reported Outcome

OMI: Outcome Measurement Instrument

PerfO: Performance Outcome

PRO: Patient-Reported Outcome

ScR: Scoping Review

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Abstract

Objective: To examine how caregiver-reported outcomes are incorporated in clinical trials involving children and adolescents with intellectual disability (ID), including alignment with regulatory guidance about observer- versus proxy-reporting.

Methods: We conducted a scoping review, using a systematic search strategy and screening citations in duplicate to identify interventional trials in children and adolescents with ID, published 2019-2024, that included caregiver-reported outcomes. We extracted trial characteristics and outcome measurement instruments (OMIs) from eligible reports, analyzing OMIs used as primary endpoints.

Results: From 8,167 citations, we identified 88 trials, 38 of which included a caregiver-reported primary outcome; 20 unique OMIs were primary endpoints. Caregiver characteristics, training, and OMI psychometric properties were infrequently reported. OMIs were not easily classifiable as observer- versus proxy-reported based on instructions and item wording.

Conclusions: Clearer reporting of caregiver-reported OMIs in pediatric ID trials, including instrument characteristics and measurement details, is needed to improve interpretability and alignment with guidance.

(150/150 words)

1.0 – Introduction

1.1 – Background

1.1.1 – The role of outcomes in clinical trials

Clinical trials are fundamental to the advancement of medicine, providing the evidence needed to determine whether therapeutic interventions are effective and safe.[1] Trials evaluate interventions against outcomes, which can be defined as measures of the health status of a patient that are used to assess the effects of healthcare interventions.[2,3] The selection of appropriate outcomes is critical to ensuring that trial results translate into meaningful improvements in patient care, inform clinical decision-making, and meet regulatory standards for drug approval. [4,5] To accomplish this, policy decision-makers recommend that trialists select *patient-centred outcomes,* defined as outcomes that reflect how a patient survives, feels, or functions.[3,6] The US Food and Drug Administration (FDA) refers to these patient-centred outcomes as "clinical outcome assessments" (COAs) and distinguishes them from biomarkers or surrogate outcomes.[7]

The FDA has further categorized COAs into four types: Patient-reported outcomes (PROs), Clinician-reported outcomes (ClinROs), Observer-reported outcomes (ObsROs), and Performance outcomes (PerfOs).[3,8] The boundaries between these COA types are not always distinct, with Farmer and colleagues arguing that some assessments can be considered a 'hybrid' between more than one COA type.[9] For example, some measures of child adaptive functioning are based on a combination of caregiver observations (ObsRO) and clinician judgement (ClinRO).[9] This complexity in categorization becomes particularly important when evaluating the validity and appropriateness of outcome measures in clinical trials, especially in populations where standard PROs may not be feasible.

1.1.2 – The importance of patient-reported outcomes

PROs are particularly important as they provide a direct report of the status of a patient's health condition from that patient's own perspective, without amendment or interpretation of the patient's response by a clinician or anyone else.[3] PROs provide valuable insights into a patient's well-being, symptoms, and the impact of a disease and its treatment on their daily life, and are therefore recognized as essential tools in patient-centred healthcare, contributing to a more holistic understanding of treatment benefits and harms.[3,10–12] The direct nature of PROs makes them the gold standard for capturing subjective experiences such as pain, fatigue, quality of life, and treatment satisfaction.[13,14] PRO measures are typically developed using a multidisciplinary approach, often involving patients and clinicians during item generation and validation to ensure relevance and content validity; however, the outcomes themselves are intended to reflect patients' unmediated reports of their own health status.[6,13] In certain situations, PROs may not be feasible to incorporate in a clinical trial due to the patient's inability to report for themselves.[3] This is often the case with young children, people with intellectual disabilities (ID), or those with dementia. [3]

1.1.3 – Intellectual disability: Definition, prevalence, and implications for outcome measurement

Intellectual disability (also referred to as intellectual developmental disorder) is defined as a condition marked by significant limitations in intellectual functioning and adaptive behaviour, typically indicated by an IQ below 70. [15] Intellectual functioning includes reasoning, problem solving, planning, abstract thinking, judgment, and learning from experience, while adaptive functioning encompasses conceptual, social, and practical skills necessary for everyday life.[16] A global meta-analysis of population-based studies published in 2011 indicated that the prevalence of ID was significantly higher among children and adolescents, estimated at 18.30 per

1,000 population, compared to the overall global estimate of approximately 10.37 per 1,000.[17] Furthermore, studies consistently indicate that ID is more prevalent in males than females across both adult and pediatric populations.[16,17] ID frequently co-occurs with other conditions, including autism spectrum disorder, epilepsy, and various mental health disorders.[16–18]

Children and adolescents with ID frequently cannot reliably self-report on many health-related constructs, particularly younger children or those with more severe cognitive impairments.[19] However, there is broad consensus in the literature that self-report should be prioritized wherever feasible, and ongoing efforts have focused on improving the accessibility of self-report for individuals with ID.[20–22] Adapted tools incorporating simplified language, visual supports, and alternative response formats have shown promise in enabling participation for some individuals.[23,24] While mild ID may not be recognized until school age when academic difficulties emerge, more severe ID is typically identified earlier in childhood and is associated with greater challenges in communication and self-report.[15] The feasibility of self-report varies across individuals as some children and adolescents with mild-to-moderate ID, particularly those with sufficient verbal comprehension and basic decision-making skills, may be able to meaningfully self-report, whereas for individuals with more severe impairments, the cognitive and communicative demands of many instruments may exceed their capabilities.[25,26] In addition, children under approximately five years of age may be unable to reliably self-report regardless of cognitive ability.[27] This creates a fundamental challenge for clinical trials where a population that could strongly benefit from therapeutic interventions is often unable to directly communicate their experience of treatment effects, necessitating reliance on caregiver-reported outcomes.[28]

In instances where patients cannot self-report, outcomes are typically reported by a caregiver. The term “caregiver” throughout this thesis refers to an individual such as a parent or

other family member who provides daily care to an individual, as distinguished from a healthcare provider acting in their professional capacity. [3] In this context, caregiver reporting is not intended to replace self-report where it is feasible, but rather to serve as an alternative when direct patient report is not possible. The reliance on caregiver reporting in clinical trials for children and adolescents with ID introduces important methodological considerations regarding the nature of the information being collected and its validity as a reflection of the patient's experience.

1.1.4 – Observer-reported versus proxy-reported outcomes

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), in their roles as regulators of clinical trials for new interventions, have provided guidance on the use of caregiver-reported outcomes in clinical trials.[3,29] Specifically, in the FDA framework for COAs, some caregiver-reported outcomes would be considered ObsROs but other caregiver-reported outcomes would be considered "proxy-reported outcomes" and do not meet the FDA criteria to be considered a COA. This distinction is fundamental to understanding regulatory expectations for outcome measurement in trials involving vulnerable populations. Specifically, ObsROs are assessments of observable signs, events, or behaviours related to a patient's health condition as reported by individuals who observe the patient in daily life, for example, a parent or caregiver. [3] In contrast, the FDA defines proxy-reported outcomes to reflect the situation where someone other than the patient reports on an outcome *as if they were the patient*. [3] To illustrate this distinction, an ObsRO may include questionnaire items where a caregiver reports on behaviours in a child that have been associated with pain (e.g., crying, certain facial expressions), whereas a proxy-reported outcome may include questionnaire items where a caregiver reports their perception of whether a child is *feeling* pain.[30] The former

captures observable phenomena, while the latter requires the caregiver to infer internal states that are inherently subjective and arguably known only to the patient.

The EMA guidance similarly notes that while proxy and patient ratings are often concordant for physical domains, they tend to diverge for psychosocial aspects of health-related quality of life.[30] The EMA states that proxy reporting "should be avoided" in general and used only "where it is clear that the patient themselves cannot contribute… and may be the only effective means of obtaining information that might otherwise be lost."[29]

While regulatory bodies largely frame this distinction between ObsROs and proxy-reported outcomes around the validity of the data source, Pickard and Knight offer a conceptual framework that classifies measures based on the viewpoint the rater is asked to adopt, focusing specifically on measures of health-related quality of life.[31] They distinguish between a “proxy-patient perspective” and a “proxy-proxy perspective”.[31] The proxy-patient perspective relies on substituted judgment where the caregiver is asked to project themselves into the body and mind of the patient to answer as they believe the patient would.[31] This approach aligns closely with the FDA and EMA definitions of proxy reporting because the goal is to bridge the difference between the patient experience and the proxy report, referred to as the “inter-rater gap”.[31]

In contrast, the proxy-proxy perspective explicitly elicits the caregiver's own view of the patient's health-related quality of life. Rather than attempting to simulate the internal voice of the child, this perspective allows the caregiver to provide an assessment that may validly diverge from what the patient might say by offering complementary or reinforcing information.[31] Pickard and Knight describe the unique informational value of this perspective as the “intra-proxy gap”,

which represents the difference between the caregiver's estimation of the patient view and the caregiver's own independent view.[31]

An additional perspective on proxy reporting from a quality of life measurement perspective was offered by the International Society for Quality of Life Research (ISOQOL) in its guidance for implementing PROs assessment in clinical practice.[32] The authors noted that proxy reporters can provide useful information about observable PROs but cautioned about caregivers' ability to distinguish a patient's experience from their own feelings. [32] More recently, ISOQOL published consensus-based considerations for the use of adult proxy reporting, summarizing existing recommendations from different sources, including those outlines above, and recommending that researchers and clinicians follow a structured checklist to justify proxy use, specify proxy selection criteria, and detail the intended reporting perspective (proxy-patient vs. proxy-proxy). [33] Furthermore, specific to rare disease clinical trials, a Task Force from the ISPOR organization (ISPOR focuses on health economics and outcomes research) emphasized that in contexts where patient self-report is not feasible, as is the case in many rare disease trials, researchers should prioritize ObsROs focused on observable behaviours rather than internal states to minimize bias.[34]

Definitions and recommendations related to proxy-reporting based on the above discussion are summarized in Table 1. When these guidance documents and discussion papers are considered together, three key dimensions emerge as relevant for understanding caregiver-reported outcomes in clinical trials for children and adolescents with ID in the context of proxy reporting: (1) the perspective sought, that is, whether the caregiver is asked to represent their own viewpoint or what they perceive as the child trial participant's viewpoint; (2) clinician

involvement, that is, whether a clinician is involved in guiding or interpreting the caregiver report; and (3) the type of information captured, that is, whether the outcome measurement assesses only observable behaviours or involves at least some reporting on the child's internal state.

Table 1. Comparative definitions and key recommendations related to proxy- and observer-reporting by caregivers

Source	Definition and Key Recommendations
Food and Drug Administration (FDA)[3]	Defines a proxy report as a report by someone other than the patient on behalf of the patient's experiences, *as if* they were the patient. *Key recommendations:* Concepts known only to the patient (e.g., symptoms like pain intensity) should ideally be self-reported. If self-report is not possible, the FDA recommends using ObsROs, i.e., assessments of observable signs or behaviours, rather than proxy reports of internal states.
European Medicines Agency (EMA)[29]	Defines a proxy as a person who reports an outcome *as if* they were the patient themselves. *Key recommendations:* Proxy reporting should generally be avoided and utilized only when the patient cannot contribute and when it is the only effective means of obtaining data. The EMA notes that while physical domains often show concordance, proxy and patient ratings tend to diverge on psychosocial aspects of health.
Pickard & Knight (Conceptual Framework)* [31]	Delineates two distinct perspectives for proxy assessment: 1. Proxy-Patient Perspective: The proxy assesses the patient as they think the patient would rate themselves (substituted judgment). 2. Proxy-Proxy Perspective: The proxy assesses the patient from their own viewpoint (caregiver's perspective). *Key recommendations:* The proxy-proxy perspective acknowledges that a caregiver's view may validly diverge from the patient's view. The authors advise that this perspective may offer complementary information (the "intra-proxy gap") rather than simply being a source of error.
ISOQOL Task Force*[32]	Recognizes that proxy respondents (e.g., parents, caregivers) are necessary for populations requiring assistance, such as young children or those with cognitive limitations. *Key recommendations:* Proxy reporters provide useful information on concrete, observable outcomes but may struggle to distinguish their own feelings from the patient's status. The authors state that agreement is often limited between child self-report and parent proxy report, particularly regarding internal states. They recommend that researchers provide a clear justification for proxy use, use sensitivity analyses to assess the impact of proxy data on results, and explicitly discuss the potential for proxy bias as a limitation when reporting outcomes.
Farmer et al. [9]	Refers to the FDA definition of proxy reporting as responding *as if* one were the patient, specifically regarding internal emotions (e.g., sadness) rather than behaviours (e.g., crying). *Key recommendations:* Cautions those designing treatment trials for neurodevelopmental conditions to avoid proxy reports based on FDA recommendations. Discusses the concept of hybrid outcomes, where a clinician's professional judgment is integrated with the caregiver's report (e.g., via semi-structured interviews) to improve the validity and reliability of assessments.
*These resources primarily focus on the proxy assessment of quality of life; however, they provide valuable insight into the nuances of proxy reporting of outcomes in general.	

1.1.5 – Challenges with proxy reporting: caregiver-patient agreement

The discouragement from regulatory bodies and others described above regarding the use of proxy-reported outcomes in clinical trials stems from concern that caregivers may unintentionally introduce bias into their reports (for example, due to their emotional state, their own perceptions of the patient's condition, or their own expectations of the intervention's effect on the patient) and as a result, caregiver proxy reports may not accurately reflect patient well-being. [12,14] Several other authors have discussed challenges with proxy-reported outcomes for children, adolescents, and adults, reaching similar conclusions.[33,35,36]

For example, the ISOQOL's report on proxy-reporting of quality of life measures as noted above cited evidence of poor agreement between child/adolescent reporters of their own well-being and parent proxy reports.[33] A review of 14 studies of proxy- versus self-reports in individuals with ID, including children, adolescents, and adults, identified that the literature on this topic has yielded mixed results, with variation in agreement between patient and proxy reports across different studies and topics.[35] Variation has also been observed across measures within the same study. For example, among children with cancer, agreement between parent and child reporting was low for measures of symptoms and moderate for a measure of mobility, with parents in general tending to underestimate children's well-being.[37]

Importantly, much of the evidence on caregiver–patient agreement is derived from populations in which patient self-report is possible and is used as the reference standard, limiting the generalizability of these findings to children and adolescents with ID, many of whom are unable to self-report. However, this variation in agreement highlights the complexity of caregiver reporting, with the validity of caregiver-reported outcomes potentially depending on the specific

construct being measured, the characteristics of the patient and caregiver, and the characteristics of the outcome measurement instrument itself.

Adding further complexity, the literature on caregiver-reported outcomes in clinical trials often does not clearly distinguish proxy-reported outcomes from ObsROs, with caregiver reports of patient well-being often referred to as "proxy reports" or simply "caregiver reports", regardless of the nature of the questions.[35,38,39] Such terminology obscures whether outcomes are based on criteria-based observations of observable behaviour (ObsROs) or on caregivers' perceptions, judgments, or feelings about a patient's internal experience (proxy reports). This lack of clarity in terminology creates challenges for both researchers designing trials and regulators or other assessors evaluating their results.

Furthermore, a recent systematic review of guidance for proxy- and self-reporting of child-specific health-related quality of life measures that have been mapped to health utilities for use in health economic evaluations revealed that most quality of life instruments lacked comprehensive definitions and evidence-based guidance for their application, creating significant challenges for researchers in determining the appropriateness of self-reporting versus the necessity of proxy completion based on child age or other criteria.[36] Without clear standards on when and how proxy-reporting can be used, the risk of introducing reporting biases into clinical data remains an important challenge to research validity. [36]

1.1.6 – Outcomes in clinical trials for children and adolescents with ID

These challenges in distinguishing and appropriately categorizing and applying caregiver-reported outcomes are particularly salient in clinical trials involving and adolescent with ID, where caregiver reporting is often necessary, yet the nature of that reporting varies considerably across studies.[40] A scoping review by Müller et al identified a myriad of outcomes

and instruments used in clinical trials involving individuals with genetic neurodevelopmental disorders and ID that were published from 2012-2022. They concluded that variability in outcome selection and reporting complicated the interpretation of the data and called for greater consensus on suitable, valid, and relevant outcomes and outcome measures. Greater harmonization of outcome data would facilitate the development of systematic reviews, support comparisons across studies, and ultimately may lead to more credible treatment guidance and standards of care.[40]

These findings also raise questions about whether current study design, conduct and reporting of primary studies align with regulatory guidance that favors ObsROs over proxy-reported outcomes. Understanding current practice in this area is important for multiple interest-holders. For trialists designing studies, clarity about caregiver reporting, including the distinction between ObsROs and proxy-reported outcomes, can inform instrument selection and ensure regulatory compliance. Regulatory compliance is particularly relevant for trials of new products that require regulatory approval to be made available to patients, including medications, supplements, and medical devices. For regulators, for other policy makers such as health technology assessors who produce guidance about reimbursement of drugs and devices, and for clinicians evaluating trial results, systematic characterization of outcome measures can facilitate assessment of evidence quality and applicability. For patients and caregivers, ensuring that outcome measures are both valid and meaningful can help to ensure that trial results reflect outcomes that matter in daily life.

1.1.7 – Summary of rationale

In summary, caregiver reporting plays a central role in pediatric clinical trials when children and adolescents are unable to self-report, particularly among those with ID. These

reports often serve as the primary source of information about outcomes that speak directly to the child's experience, such as changes in behaviour, symptoms, mood, or day-to-day functioning that are important to patients and families. However, reliance on caregiver-reported outcomes has exposed long-standing ambiguity in how caregiver input is conceptualized and applied across trials. While proxy-reported outcomes are discouraged and ObsROs preferred in many guidance documents, some outcome domains may be difficult or impossible to capture through observation alone. For example, pain intensity or the child's sense of fatigue are inherently internal experiences that young children and some children and adolescents with ID cannot reliably self-report, forcing researchers to rely on proxy reports despite their limitations. At the same time, the inconsistent terminology used across the literature makes it difficult to align studies with regulatory and other guidance.

With the continued implementation of intervention trials involving children and adolescents with ID, there is a need for clarity about outcome measures that accurately reflect treatment benefit, are meaningful to the patients and their caregivers who are the eventual beneficiaries of treatment and are acceptable to decision-makers. Building on prior scoping work by others that broadly catalogued outcomes and instruments across genetic neurodevelopmental disorders and ID[40], this thesis focuses specifically on caregiver-reported outcomes in clinical trials involving children and adolescents with ID to examine in detail how these measures are conceptualized, classified, and used in treatment trials.

1.2 – Study objectives

The overall aim of this thesis project was to understand caregiver-reported outcomes in clinical trials for children and adolescents with ID. The specific aims of this project were:

1. To identify and describe recent clinical trials involving children and adolescents with ID that incorporate caregiver-reported outcomes (e.g., proxy-reported, observer-reported, and 'hybrid' outcomes) and where the treatment being trialed would likely require regulatory approval. For example, we aimed to describe the populations, interventions, trial designs and trial phases that are the focus of these trials; and
2. To describe the ways in which caregiver-reported outcomes are defined and measured in these clinical trials, as primary or secondary endpoints, for example:
    a. specific outcome domains and outcome measurement instruments;
    b. characteristics of caregiver reporters of these outcomes (e.g., relationship to the child patient, sociodemographic characteristics);
    c. classification of outcomes (by the authors and according to established definitions) as observer-reported, proxy-reported, or hybrid; and
    d. any evaluation of the measurement properties of proxy-reported outcome measurement instruments including reliability and validity.

By identifying how caregiver-reported outcomes have been used in recent trials of children and adolescents with ID and evaluating selected outcome measurement instruments across key dimensions, including the perspective sought, clinician involvement, and the type of information captured, this study addresses an important gap toward clarifying the distinction between observer- and proxy-reported outcomes. We also identify the use of instruments that may not align with regulatory expectations and highlight areas where outcome measurement remains poorly defined.

Establishing a descriptive foundation is a necessary first step in informing the future development of guidance aimed at improving the clarity, appropriateness, and interpretability of caregiver-reported outcomes in trials involving children with ID. The findings will support future methodological work, guide trialists in selecting and justifying caregiver-reported measures, and contribute to broader efforts to strengthen the use of meaningful, patient-centred outcomes for children and adolescents who cannot self-report.

1.3 – Thesis structure

This thesis is presented in a monograph format and is organized into four chapters as follows:

- Chapter 1 has provided an overview of the background literature on clinical outcome assessment in clinical trials for children and adolescents with ID, with a focus on patient-centred outcomes and the use of caregiver-reported measures when children and adolescents are unable to self-report. This chapter outlined relevant guidance, methodological challenges associated with proxy- and observer-reported outcomes, and variability in outcome measurement practices. It presented the rationale, objectives, and scope of the thesis.
- Chapter 2 describes the methods used in this research project. This chapter details the design and conduct of the scoping review that we used to address the thesis objectives, including the literature search strategy, study selection, data extraction, and synthesis approach. It also outlines the methods we used in our review of specific caregiver-reported outcome measurement instruments that were identified in the scoping review.

- Chapter 3 presents the results of the scoping review and accompanying instrument-level analysis. This chapter summarizes the characteristics of included trials, the extent and nature of caregiver-reported outcomes used as primary endpoints, and the outcome measurement instruments identified. It also reports findings from the evaluation of instruments with respect to the perspective sought, clinician involvement, and the type of information captured.
- Chapter 4 provides an integrated discussion of the findings. This chapter interprets the results in relation to existing literature and regulatory guidance, discusses methodological and practical implications for outcome selection in pediatric trials, identifies key strengths and limitations of this research, and outlines directions for future research.

2.0 – Materials and methods

To address the objectives of this study, we conducted a scoping review, adhering to guidelines from JBI (formerly the Joana Briggs Institute), and reporting our review according to the PRISMA extension for scoping reviews (checklist, Appendix A.1).[41,42] We registered our protocol in advance on Open Science Framework (https://osf.io/nsyga).

2.1 – The team and knowledge user engagement

This review was led by Y Al-Baldawi under the guidance of a multidisciplinary research team that included thesis supervisors and advisors (BK Potter, M Brouwers, M Smith), and co-investigators (A Thurm, M Offringa, B Skidmore). In alignment with guidance from the JBI Scoping Review Methodology Group[43] and team expertise in patient and public engagement, an Advisory Committee of six knowledge users was established to provide additional perspectives; members included caregivers to individuals with ID who had experience with clinical trials, clinicians, trialists, and individuals with policy or regulatory experience. Finally, an additional investigator with psychometric expertise in child neurodevelopmental disability (A Kaat) joined the team partway through the project to contribute to the review of specific outcome measurement instruments. A core team of researchers involved in this scoping review (Y Al-Baldawi, S Cutler, A Thurm, and BK Potter) met on a regular basis (approximately weekly to bi-weekly) during screening, data extraction, and preparation of results summaries. Additional team members, including advisors, co-investigators, and members of the Advisory Committee, met at key stages of the review to provide contextual insight and feedback on emerging findings.

Engagement with knowledge users throughout the review reflected *consultation* and *co-creation* activities. Consistent with the distinctions described in the literature, consultation

involved information-gathering interactions where knowledge users were invited to provide feedback and insight on various aspects of the review.[44] For example, while the nature and extent of engagement varied across team members, advisors, and stages of the review, knowledge users provided feedback on the eligibility criteria, refining the search strategy, and interpreting the findings. Elements of co-creation occurred when knowledge users contributed directly to decision-making processes, such as informing the data extraction form, shaping the interpretation of synthesized results, and co-developing key messages and recommendations.

The two caregiver advisors drew on their lived and living experience, including participating with their children and adolescents in clinical trials, to ensure that our focus was on aspects of the trials and outcome measures that were most important to them. For example, they contributed to decisions to collect information on caregiver reporter characteristics and instructions to caregiver reporters. They also supported the interpretation of findings, including messages about caregiver training and instructions that considered relevance and feasibility. To support meaningful participation, a caregiver engagement strategy was developed by team member (M Smith) with expertise in patient and citizen engagement in methodological research. Caregiver members of the Advisory Committee were provided flexible options for involvement and tailored onboarding adapted from previous patient engagement initiatives in evidence synthesis projects. Caregiver members were offered compensation for their involvement.

2.2 – Eligibility Criteria

Inclusion criteria: Articles were included in the scoping review if they met the following criteria (exclusion criteria are also embedded in the list below where appropriate):

i) **Population**: Studies involving children and adolescents aged 0-18 years with intellectual disability (ID).

   a. **Age**: Studies including participants both younger and older than 18 years were included if at least half of the participants were 18 years or younger, or if results were presented separately for children and adolescents. When more specific age distribution data were unavailable and the mean age was reported instead of the median age, studies were included if the mean age plus one standard deviation was below 18 years.

   b. **ID**: Studies were included if they specifically focused on children and adolescents with ID, defined as a condition marked by significant limitations in intellectual functioning and adaptive behaviour, typically indicated by an IQ below 70.[15] To operationalize this criterion, the study was included if at least some of the participants had a diagnosed condition that is frequently associated with ID according to the list of diagnoses published as part of the Human Phenotype Ontology,[45] aligned with the methods of a previous publication by Müller et al.[40] For studies involving broader diagnostic categories in which ID may be present only in certain subgroups (e.g., autism spectrum disorder, cerebral palsy, or epilepsy), additional criteria were applied. Studies were included if at least one of the following was met: (1) the reported diagnosis or sub-condition was listed on the HPO as being associated with ID; (2) the authors reported that at least 50% of the pediatric sample had ID or global developmental delay; or (3) the study reported assessments of intellectual functioning, adaptive behaviour, or related constructs (e.g., IQ, adaptive functioning, or quality of life) indicative of ID. When eligibility remained unclear after these steps, additional verification was undertaken using the Online Mendelian Inheritance in Man (OMIM) database.[46] Specifically, the

clinical synopsis for the condition was reviewed for neurologic features indicating ID, developmental delay, or global developmental delay. Studies included through this pathway, as well as other cases of residual uncertainty, were discussed by a small adjudication group consisting of the student, supervisor, and two additional core team members with expertise in pediatric neurodevelopmental disability and outcome measurement (A. Thurm and S. Cutler) to determine whether there was sufficient evidence that the study population included children and adolescents with diagnoses associated with ID.

ii) **Types of evidence:** We included primary peer-reviewed sources reporting on completed randomized and non-randomized interventional clinical trials. We excluded clinical practice guidelines, conference abstracts/proceedings, dissertations, methodological papers, commentaries, validation and feasibility studies, economic evaluations, trial protocols, systematic reviews, and grey literature.

iii) **Study design**: We included clinical interventional trials. We excluded single-case trials (both retrospective and prospective) due the challenge in distinguishing a single-case trial from a case report. We also excluded observational studies (including case reports/series, cross-sectional studies, and cohort studies).

a. **Clinical intervention trials definition**: A research study involving human subjects who are prospectively assigned to one or more interventions, including placebos or other controls as well as uncontrolled trials, to evaluate the effects on patient outcomes. This encompasses both randomized and non-randomized trials.[47]

iv) **Interventions:** We included clinical intervention trials only for those interventions that have received or would require regulatory approval, for example, by Health Canada, the FDA, or

EMA, to focus the review on trials that would likely need to adhere to regulatory guidance for trial design and outcome selection. To operationalize this criterion, we restricted the review to trials of drugs, supplements, or medical devices. We excluded trials of behaviour interventions and surgical trials.

v) **Outcomes:** We included trials in which at least one primary or secondary outcome measure was reported by an informal caregiver (e.g., parent or guardian) for at least some of the participants. Caregiver-reported outcomes included proxy-reported, observer-reported, or hybrid outcomes, as defined in the Introduction.

vi) **Language:** We included reports published in English only for feasibility reasons. We tracked articles excluded based on language to evaluate the potential for bias.

vii) **Date:** We included articles published from 2019 onward to ensure their relevance to current practice around caregiver reporting and to maintain the feasibility of our study with respect to the yield of citations and yield of trial reports included.

2.3 – Information Sources and Search Strategy

Informed by the search for a previous related scoping review with overlapping eligibility criteria,[40] an experienced medical information specialist (B Skidmore) developed and tested the search strategies through an iterative process in consultation with the review team. Another senior information specialist (K Campbell) peer reviewed the MEDLINE strategy prior to execution using the PRESS Checklist.[48] The original strategy by Muller et al[40] was compressed where appropriate, and truncation and adjacency searching were introduced to accommodate different word forms and proximities.

Using the OVID platform, we searched Ovid MEDLINE® ALL, Embase Classic+Embase, and the Cochrane Central Register of Controlled Trials on December 19, 2024.

We applied a combination of controlled vocabulary (e.g., “Developmental Disabilities”, “Intellectual Disability”, “Child”) and keywords (e.g., “developmental defect”, “cognitive delay”, “infant”), adjusting the vocabulary and syntax as necessary across the databases. We limited results to the publication years 2019 to the present, and, where possible, removed animal-only, opinion pieces, conference abstracts and preprints. We downloaded and deduplicated the records using EndNote version 9.3.3 (Clarivate Analytics) and uploaded to Covidence (Veritas Health Innovation Ltd).

We extended our search using the database of articles that met inclusion criteria for the previous related scoping review that had overlapping eligibility criteria.[40] Since that prior scoping review included trials published from 2012-2022, this additional database search identified some published trial reports that met our inclusion criteria except that they were published prior to 2019. We set these reports aside in case the yield of eligible reports published in 2019 or later was insufficiently small but ultimately excluded them. Details regarding the search strategies appear in Appendix A.2.

2.4 – Study Selection: Screening

Screening proceeded in two stages. First, after uploading all retrieved citations into Covidence and performing additional de-duplication of records flagged as duplicates by the Covidence software, two reviewers (Y Al-Baldawi and another team member from among a group of 11 reviewers including S Cutler, BK Potter, G Pratt Tremblay, K Pulsipher, W Muchie, L Meng, E Iverson, M Wood, A Chun, A Hehn and O Remsberg) independently conducted title and abstract screening against the eligibility criteria. During the title and abstract screening stage, any record that lacked an abstract (title only) was assessed for relevance based on the title only and if there was not enough information it advanced to the full-text screening stage. Before fully

launching this first stage of screening, each study screener received training and participated in a pilot screen of 25 citations to ensure that the screening instructions were clear and consistently implemented. Additional pilot screening for some screeners was implemented as needed.

Studies meeting the inclusion criteria in stage one or that required further assessment underwent full-text screening. This second stage of screening was also performed independently by Y Al-Baldawi and a second reviewer from the same group of reviewers who participated in title/abstract screening and included a pilot test involving at least 10 articles per reviewer. At this second stage we determined the final eligibility of articles for inclusion in the scoping review. At both stages of screening, discrepancies were resolved by discussion, involving a third reviewer (BK Potter) where needed. Detailed screening questions and instructions are provided in Appendix A.3.

2.5 – Data extraction

We conducted data extraction using a standardized Excel form developed in collaboration with the team, including the Advisory Committee. The form captured key information from included studies, including study characteristics (e.g., author, year, trial design characteristics, country), participant characteristics, intervention details, and details of outcomes reported by caregivers. A post-hoc decision was made to limit further, more detailed, data extraction about outcomes to those outcomes that were used as primary efficacy endpoints for the trials that were the subjects of the included studies. This adjustment was necessitated by the unexpectedly high yield of data and the highly incomplete and inconsistent reporting of information about secondary outcomes across the included trial reports. Specifically, for each caregiver-reported outcome measure identified within the trial, we extracted the measure's name, its status as a primary or secondary outcome, and any available author descriptions of the outcome domain.

For each caregiver-reported outcome measure that was used as a primary efficacy endpoint in the trial, we extracted more details regarding how these measures were used and analyzed in the trial, whether and which psychometric properties were reported by trial authors, and information about the caregiver reporter, e.g., relationship to the child with ID, sex and gender. We also collected on the author classification or description of the primary outcome measures type (e.g., as a proxy-reported outcome, observer-reported outcome, other label, not labelled). The data items extracted from each included study, along with their definitions, are listed in Appendix A.4.

For the data extraction, each form was piloted for 10 studies and then all the studies were extracted by Y Al-Baldawi or S Cutler and verified by Y Al-Baldawi, S Cutler, BK Potter, and/or A Thurm. Disagreements were resolved by discussion with team members BK Potter and A Thurm. If data was missing, we coded it as "not reported"; if data was confusing, we coded it as "unclear". In line with methodological guidance for reviews, studies rather than individual reports were treated as the unit of interest.[49–52] When multiple linked reports were identified as originating from the same underlying trial, all reports were retained and reviewed to extract relevant information, and linkages among reports were documented. Trial linkage was determined using multiple study characteristics, including trial registration numbers, authorship, study setting, intervention details, and conditions studied, consistent with established guidance. Where multiple reports contributed information for a single trial, outcomes were attributed to the trial rather than to individual reports to avoid double counting.

To examine how caregiver-reported outcome measures aligned with concepts discussed in the literature about proxy reporting, Y Al-Baldawi led the development of a structured classification framework informed by the relevant guidance described in the Introduction (Table

1). This framework was operationalized as a brief REDCap survey (Appendix A.5) designed to capture key conceptual dimensions related to proxy reporting. Using this framework, two team members with expertise in neurodevelopmental outcome measurement and psychometrics (A Kaat and A Thurm) independently provided an initial review of each unique instrument across the following dimensions: (1) whose perspective the instrument primarily sought (the child's or the caregiver's), (2) whether clinician involvement was typically required to interpret responses, and (3) whether item content was limited to observable behaviours or included judgements about the child's internal states. Following these initial reviews, Y Al-Baldawi collated the expert responses and used these to inform a discussion with A Kaat, A Thurm, and BK Potter to further consider the instruments across the three dimensions, clarify interpretations, and reflect on the implications for the use of caregiver-reported outcome measures in clinical trials. Findings from the small group discussion were subsequently shared with the Advisory Committee for discussion and interpretive input to contextualize the review findings.

2.6 – Synthesis and Presentation of Results

Data cleaning was conducted by Y Al-Baldawi. A PRISMA flow diagram was used to illustrate the flow of information through the review process to ensure transparency. Data were synthesized and presented using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). A descriptive synthesis was performed, with findings summarized in tables and narrative summaries. The approach to synthesis and presentation was refined iteratively throughout the review process as needed.

3.0 – Results

3.1 – Results of the search

The database searches yielded 8,176 citations deemed unique after the initial automated de-duplication process, 15 of which were later identified as duplicates missed by the automated process and manually removed. After title and abstract screening, 736 reports proceeded to full-text review. At the full-text stage, 20 reports were excluded because they were not available in English. Of the remaining 716 reports, 139 met the initial eligibility criteria (Figure 1). An additional three unique reports meeting the eligibility criteria were identified from a previously published review.[40]

Subsequently, we applied two post-hoc exclusion decisions to this group of 142 initially eligible reports. First, we excluded reports that were secondary analyses of clinical trials and presented no new data because it was challenging to characterize these as primary trial reports (n=10). Second, we excluded reports of trials where we were unable to find any trial registration in a trial register recognized by the World Health Organization (WHO)[53] because it was difficult to adjudicate these studies as clinical trials as distinct from expanded access studies or analyses of case series that were unclearly reported (n=15). These exclusions reduced the number of eligible reports to 117 (see Appendix B.1 for reports excluded at full-text screening by reason and Appendices B.2 and B.3 for reports excluded post-hoc).

Of the 117 eligible reports, 92 met the final inclusion criterion, specifically that at least one analyzed and reported outcome was caregiver-reported for at least some participants. This inclusion criterion was applied after the others because our review was conducted in collaboration with another team conducting a review with a different focus that relied on a

broader set of outcomes. After linking multiple reports arising from the same trial, the analytic sample comprised 88 unique studies from the 92 reports, (see Appendix B.4 for the list of included reports and studies). Specifically, nine studies were represented by multiple linked reports corresponding to sequential trial phases or long-term extensions (see Appendix B.5 for a description of linked studies and how data from these reports were handled). We extracted general information for all 88 trials. We extracted additional information about primary caregiver-reported outcomes from the 38 trials in which at least one primary outcome was caregiver-reported for at least some participants.

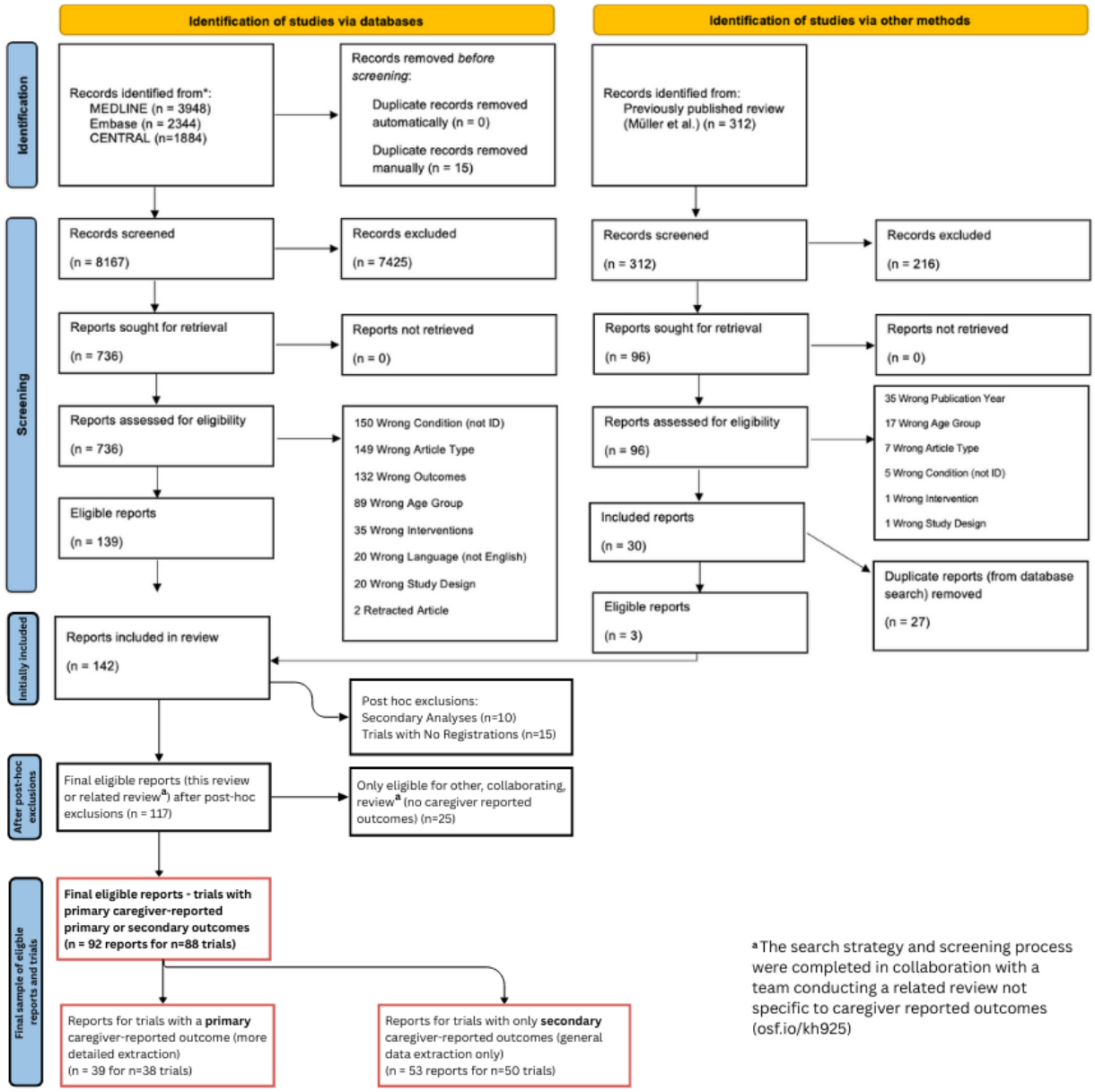

Figure 1. PRISMA flow of records and reports through screening process

*Counts reflect citations unique to each database after staged de-duplication (i.e., Embase citations exclude records already identified in MEDLINE; CENTRAL citations exclude records already identified in MEDLINE or Embase).

3.2 – Trial and participant characteristics

Among the full set of 88 included studies, the vast majority evaluated drugs (77/88, 88%), with smaller proportions assessing supplements (8/88, 9%) or devices (3/88, 3%); no studies evaluated multiple types of interventions (Table 2; and study-level details, Appendix B.6). Studies recruited participants with a wide range of diagnoses, with several studies including more than one eligible condition. The most frequently studied diagnoses were Prader–Willi syndrome (7 studies, 8%), neurofibromatosis type 1 (6 studies, 7%), and Dravet syndrome, Fragile X syndrome, Lennox–Gastaut syndrome, Sanfilippo syndrome (mucopolysaccharidosis type III), and tuberous sclerosis complex (5 studies each, 6%). Eighteen conditions were represented in only one study each. Of the studies reporting funding sources, just over half (41/79, 52%) reported at least some funding from private industry. Participants were most commonly recruited from the United States (54 studies, 61%), followed by Australia (18 studies, 20%), France (15 studies, 17%), the United Kingdom (15 studies, 17%), Spain (14 studies, 16%), and the Netherlands (13 studies, 15%) (Table 2). With respect to age distribution, reporting was incomplete, with age group not reported in 37 of the 88 trials. Among the 51 trials that reported age information, trials most commonly included school-age children (5–11 years; 43/51, 84%), followed by adolescents (12–18 years; 39/51, 76%) and toddlers/preschool-aged children (1–4 years; 31/51, 61%). Infants (<1 year) were rarely included (2/51, 4%).

Among the subset of 38 trials that included at least one caregiver-reported *primary* outcome, study characteristics were largely similar to those observed across all included studies. Most of these studies evaluated drugs (33/38, 87%). The diagnoses most frequently represented in this subset were Dravet syndrome and Lennox–Gastaut syndrome (4 studies each, 11%), followed by Prader–Willi syndrome (3 studies, 8%), with several other conditions represented in

two or fewer studies. Of the studies reporting funding sources, 21 (66%) reported industry funding. Participants were most commonly recruited from the United States (23 studies, 61%), followed by Australia (10 studies, 26%), France (8 studies, 21%), and Canada (8 studies, 21%) (Table 2). Among the subset of 38 trials that included at least one caregiver-reported primary outcome, age group was not reported in 16 trials. Among the 22 trials that reported age information, most included school-age children (17/22, 77%), adolescents (15/22, 68%), and toddlers/preschool-aged children (14/22, 64%). No trials in this subset included infants.

Reporting of intellectual disability (ID) severity was limited. Among the 38 trials with a caregiver-reported primary outcome, 28 (74%) did not report any explicit information on ID severity. Two trials provided categorical descriptions of severity, indicating predominantly severe to profound impairment. Eight trials (21%) reported intelligence quotient (IQ) data for the study population. Among these, five trials included participants with severe to profound ID (IQ <35), two included participants with moderate ID (IQ 35–49), and one included participants with mild ID (IQ 50–69).

Table 2. Characteristics of trials and participants. All data presented as n (%)

	All trial in the sample (N=88)	**Trials with a caregiver-reported primary outcome (N=38)**
Type of intervention		
Drug	77 (88)	33 (87)
Supplement	8 (9)	3 (8)
Device	3 (3)	2 (5)
Diagnosis of child participants (multi-select)		
Prader-Willi Syndrome	7 (8)	3 (8)
Neurofibromatosis Type 1	6 (7)	0 (0)
Dravet Syndrome	5 (6)	4 (11)
Fragile X Syndrome	5 (6)	2 (5)
Lennox-Gastaut Syndrome	5 (6)	4 (11)
Sanfilippo Syndrome (Mucopolysaccharidosis III)	5 (6)	1 (3)
Tuberous Sclerosis Complex	5 (6)	2 (5)

Autism Spectrum Disorder	4 (5)	2 (5)
Down Syndrome	4 (5)	2 (5)
Duchenne Muscular Dystrophy	4 (5)	1 (3)
Epilepsy	4 (5)	2 (5)
Niemann-Pick (Type C)	4 (5)	1 (3)
Phelan-Mcdermid Syndrome	3 (3)	2 (5)
Alagille Syndrome	2 (2)	1 (3)
CDKL5 Deficiency Disorder	2 (2)	2 (5)
Fetal Alcohol Spectrum Disorder	2 (2)	0 (0)
Glucose Transporter 1 Deficiency Syndrome (Glut1ds)	2 (2)	2 (5)
Rett Syndrome	2 (2)	1 (3)
Other Conditions[a]	18 (20)	8 (21)
Funding source (multi-select)		
Industry	41 (52)	21 (66)
Non-Industry/Academic	40 (51)	12 (38)
*Not reported**	*9*	*6*
Countries from which participants were recruited (multi-select)		
USA	54 (61)	23 (61)
Australia	18 (20)	10 (26)
France	15 (17)	8 (21)
UK	15 (17)	7 (18)
Spain	14 (16)	7 (18)
Netherlands	13 (15)	7 (18)
Germany	12 (14)	5 (13)
Canada	10 (11)	8 (21)
Italy	10 (11)	5 (13)
Poland	9 (10)	7 (18)
Japan	8 (9)	4 (11)
Israel	5 (6)	2 (5)
Sweden	5 (6)	1 (3)
Other Countries[b]	42 (48)	24 (63)
*Not reported**	*3*	*1*
Age group (multi-select)		
Infants (0–<1 year)	2 (4)	0 (0)
Toddlers/Preschool (1–4 years)	31 (61)	14 (64)
School-age (5–11)	43 (84)	17 (77)
Adolescents (12–18)	39 (76)	15 (68)
Not reported	*37*	*16*

[a]Other Conditions (n=1 study each): ADNP Syndrome, Alpha-Mannosidosis, Angelman Syndrome, Classic Galactosemia, Fibrodysplasia Ossificans Progressiva, Focal Cortical Dysplasia Type II, Grin-Related Encephalopathy, Infantile Tremor Syndrome, Inherited Glycosylphosphatidylinositol Deficiencies (IGDs), Lesch-Nyhan Syndrome, Morquio A Syndrome, Osteogenesis Imperfecta, Pantothenate Kinase-Associated Neurodegeneration, Phenylketonuria, Proteus Syndrome, Sialorrhea, Succinic Semialdehyde Dehydrogenase Deficiency (SSADH-D), Williams Syndrome

[b]Country of study - Other Countries (n < 5 studies each): Belgium, China, Japan, UK, Denmark, Switzerland, Turkey, Argentina, Austria, Canada, Czech Republic, Europe, Germany, India, New Zealand, Slovakia, South Korea, Asia, Brazil, Greece, Iran, Ireland, Malaysia, Mexico, Russia, Western Europe
*Studies where information was not reported were excluded from the denominator in calculating the percentage for valid categories

Nearly half of the studies (n=42 of 88) did not specify a trial phase. Of those reporting trial phases, phase II was most common, with 4 trials reported to be phase I/II, 18 phase II, and 1 phase II/III (Table 3). Just under one third of the studies (31%) were single arm trials. Among the 61 studies that included at least one comparison arm, 38% reported an active comparison while 77% included a placebo control (these categories were not mutually exclusive as trials with more than two arms could include both active and placebo comparisons). Participants were randomly assigned to a trial arm in 57 studies (93% of those with at least two arms), and twelve studies (20% of those with at least two arms) described using a cross-over design. Fourteen studies (16% of all studies) were described by the authors as pilot or feasibility trials. Based on the reports deemed eligible in our review, eleven trials (13% of all studies) reported on an extension phase. Details on how extension studies and linked reports were handled are provided in Appendix B.5. For more than half of trials (57%), report authors specifically noted the use of any blinding. Reported sample sizes varied from two to 366 participants, with a median of 36 participants, and trials included follow-up periods ranging from 4 to 208 weeks, with a median duration of 26 weeks (Table 3).

Across the 38 trials that included caregiver-reported primary outcomes, most of the reported study design characteristics were similar to the full set of trials (Table 3, details Appendix B.8). While trial phase was frequently not reported (19/38, 50%), of those reporting phase, phase III trials were most common (12/19, 63%). A majority of this subset of studies included two arms (21/38, 55%). Among studies with comparison arms, placebo comparisons were reported in 24 studies (86%), while active comparisons were reported in 11 studies (39%).

Almost all studies (96%) with more than one arm reported random assignment. Cross-over designs were described in five studies (18%), six studies (16%) were pilot or feasibility studies, and four studies (11%) reported on an extension phase. Any blinding was reported in 23 studies (61%). Among these, 18 studies explicitly reported blinding of participants and/or caregivers, based on trial descriptions stating that “participants,” “caregivers,” or both were blinded. Sample sizes in this subset of 38 studies ranged from 5 to 263 participants, with a median of 62 participants and trial duration ranged from 6 to 156 weeks, with a median of 22 weeks (Table 3).

Table 3. Reported trial designs, methods, and sample size. All data presented as n (%), unless otherwise specified

	All trials in the sample (N=88)	Trials with a caregiver-reported primary outcome (N=38)
Trial phase		
I	4 (9)	0 (0)
I, II	4 (9)	1 (5)
II	18 (39)	5 (26)
II, III	1 (2)	0 (0)
III	18 (39)	12 (63)
IV	1 (2)	1 (5)
Not reported[a]	*42*	*19*
Number of study arms		
1	27 (31)	10 (26)
2	47 (53)	21 (55)
3 or more	14 (16)	7 (18)
Type of comparison arm(s) (multi-select)		
Placebo	47 (77)	24 (86)
Active	23 (38)	11 (39)
*Not applicable (single arm)**	*27*	*10*
Random assignment to study arm		
Yes	57 (93)	27 (96)
No	3 (5)	0 (0)
Unclear	1 (2)	1 (4)
*Not applicable (single arm)**	*27*	*10*
Cross-over design		
Yes	12 (20)	5 (18)
*Not applicable (single arm)**	*27*	*10*
Pilot or feasibility study	14 (16)	6 (16)
Extension study[b]	11 (13)	4 (11)
Any blinding reported (yes)[a]	50 (57)	23 (61)
Sample size (Range; Median [25th, 75th percentiles])	2 - 366; Median = 36 (15, 85)	5-263; Median = 62 (18, 141)
Trial length in weeks (Range; Median [25th, 75th percentiles])	4-208; Median = 26 (14, 52)	6-156; Median = 22 (12, 52)
Extension phase length in weeks[b] (Range; Median [25th, 75th percentiles]	52-350; Median = 156 (64,208)	64-156; Median = 122 (84, 148)

*Trials where information was not reported or relevant were excluded from the denominator in calculating the percentage

[a] Denominator for this variable is all trial reports; we assumed that if blinding was not reported it was not done

[b]Extension study indicates studies that included a long-term extension phase, whether reported within the same publication or in a linked extension report.

3.3 – Outcome measurement instruments

Across the 88 included studies, 181 outcome measurement instruments (OMIs) were caregiver-reported (i.e. reported by a caregiver rather than the child with ID in at least some participants). In counting unique OMIs, we grouped all versions of the same OMI together (e.g., multiple editions published over time, versions produced in different languages) and we grouped different subscales for the same OMI. We also grouped all seizure diaries and all versions of Caregiver Global Impression scales, while recognizing that these OMIs were not standardized (e.g., each seizure diary may contain unique items). From this process, we identified 79 unique OMIs. Table 4 lists OMIs reported in more than one study overall or reported as a primary outcome in any study (a complete list of all OMIs is included in Appendix B.7).

The most frequently cited caregiver-reported OMIs across all included studies in our sample were the Pediatric Quality of Life Inventory (PedsQL) (n=20 studies, 23%), Caregiver Global Impression scales (CaGI) (18 studies, 20%), and Seizure Diaries (17 studies, 19%) (Table 4). Other commonly reported measures included the Aberrant Behavior Checklist (ABC) (10 studies, 11%), the Vineland Adaptive Behavior Scales (10 studies, 11%), and the Child Behavior Checklist (CBCL) (7 studies, 8%). Nearly three quarters of all OMIs (56/79 unique OMIs, 71%) were reported in only one study.

When restricted to the 38 studies in which a caregiver-reported OMI was specified as a *primary* outcome, 44 OMIs were reported as primary endpoints, 20 of which were unique OMIs. Seizure Diaries were the most common caregiver-reported primary OMIs (in n=15 of 38 studies with a caregiver-reported primary outcome, 39%), followed by the Aberrant Behavior Checklist (ABC) (n=5 of 38 studies, 13%), with each other instrument accounting for two or fewer

studies with a primary caregiver-reported outcome (Table 4; additional study details alongside primary outcomes, Appendix B.8). OMIs that were primary outcomes in two studies each included CaGI scales, the Vineland Adaptive Behavior Scales, the CBCL, the Social Responsiveness Scale, and the Dykens hyperphagia questionnaire. Thirteen OMIs were each used as a primary outcome in a single trial.

Among the 38 studies that included caregiver-reported primary outcomes, 13 (34%) included these outcomes as co-primary outcome measures (n=10 studies[54–63]) or as components of composite primary outcomes (n=3 studies[64–66]) (details, Appendix B.9). Two of the 10 studies with co-primary outcomes included more than one primary caregiver-reported outcome: Damen et al. (2021) reported four co-primary outcomes, all of which were caregiver-reported; and Julia-Palacios et al. (2024) reported four caregiver-reported co-primary outcomes among nine total co-primary outcomes.[54,57] In all three trials where a caregiver-reported primary outcome was part of a composite, the other outcome/s in the composite were not reported by caregivers.

Table 4. Unique caregiver-reported outcome measures. All data presented as n (%)

Measure (note: trials may have included all or part of a measure listed, for example, specific subscale/s)	All Studies (n=88)	Primary Outcome (n=38)
Pediatric Quality of Life Inventory (PedsQL)[67]	20 (23)	1 (3)
Caregiver Global Impression (CaGI)[a]	18 (20)	2 (5)
Seizure Diary[b]	17 (19)	15 (39)
Aberrant Behavior Checklist (ABC)[c] [68]	10 (11)	5 (13)
Vineland Adaptive Behavior Scales[d] [69]	10 (11)	2 (5)
Child Behavior Checklist (CBCL)[70]	7 (8)	2 (5)
Social Responsiveness Scale[e] [71]	5 (6)	2 (5)
Repetitive Behavior Scale-Revised (RBS-R) [72]	5 (6)	1 (3)
Sensory Profile[f] [73]	4 (4)	0 (0)
Dykens hyperphagia questionnaire [74]	3 (3)	2 (5)
Anxiety, Depression, and Mood Scales (ADAMS) [75]	3 (3)	1 (3)
Sleep Disturbance Scale for Children [76]	3 (3)	1 (3)
Behavior Assessment System for Children, 3rd Edition (BASC-3)[77]	2 (2)	1 (3)
Hyperphagia Questionnaire for Clinical Trials[78]	2 (2)	1 (3)
Rett Syndrome Behaviour Questionnaire [79]	2 (2)	1 (3)
Behavior Rating Inventory of Executive Function (BRIEF)[80]	2 (2)	0 (0)
Children's Sleep Habits Questionnaire (CSHQ)[81]	2 (2)	0 (0)
Communication and Symbolic Behavior Scales Developmental Profile Infant–Toddler Checklist (CSBS-DP-IT)[82]	2 (2)	0 (0)
Conners 3[83]	2 (2)	0 (0)
EuroQol 5-Dimension Questionnaires[84]	2 (2)	0 (0)
Pain Interference Index [85]	2 (2)	0 (0)
Pediatric Evaluation of Disability Inventory (PEDI)[86]	2 (2)	0 (0)
Quality of Life in Childhood Epilepsy (QOLCE)[87]	2 (2)	0 (0)
Adaptive Behavior Assessment Scale (ABAS)[88]	1 (1)	1 (3)
Oxytocin Questionnaire[89]	1 (1)	1 (3)
PRUCISION: morning and evening ObsRO scratching scores[90]	1 (1)	1 (3)
Parent Report Revised Dimensions of Mastery Questionnaire (DMQ-18)[91]	1 (1)	1 (3)
TNO-AZL Preschool children Quality of Life[92]	1 (1)	1 (3)
Treatment Satisfaction Questionnaire for Medication[93]	1 (1)	1 (3)
Other Measures[g]	50 (57)	0 (0)

[a] Includes caregiver global impressions of change, severity, and symptoms.
[b] Includes many versions of caregiver-completed seizure diaries.
[c] Includes the ABC-Community, ABC-Community for Fragile-X Syndrome, and Simplified Chinese version of the ABC.
[d] Includes the second and third versions of the Vineland Adaptive Behavior Scales.
[e] Includes first and second versions of the Social Responsiveness Scales.
[f] Includes first and second versions of the Sensory Profile
[g] This table lists caregiver-reported outcome measures that are: reported in >1 report AND/OR reported as a primary outcome in at least one report. A complete list of all unique measures can be found in Appendix B.7.

3.4 – Characteristics of Caregiver-Reported Primary Outcomes

Reporting of data collection procedures and psychometric properties for the 44 caregiver-reported outcomes varied among the 38 studies with at least one primary caregiver-reported outcome (Table 5, details Appendix B.10). Unless otherwise specified, results in this section are presented at the outcome level rather than the study level. Regarding reporting consistency, for 11 of 44 primary caregiver-reported outcomes (25%), study authors specified that the same reporter was maintained over time. Details on training of caregivers on reporting were described in the trial report for only seven outcomes (16%) and instructions for caregivers were provided for six outcomes (14%). Of these, three studies documented providing both training details and instructions for their respective outcomes.[58,94,95] For example, one study, with a measure of caregiver-reported scratching behaviour as a primary outcome,[94] reported a combination of initial training of caregivers with instructions for 'daily recording', and subsequent 'retraining' based on compliance checks. Other studies described either training or instructions but not both; for instance, another study where the primary outcome was caregiver-reported hyperphagia behaviour [59] utilized specialized video modules for training caregivers.

Authors discussed psychometric properties for 11 primary caregiver-reported outcomes (25%). In these instances, validity was most frequently cited (9 outcomes), while explicit discussion of reliability was uncommon (2 outcomes), and one outcome referred only to general psychometric properties. Across these 11 outcomes in 11 trials, psychometric justification relied on prior validation or use of the instrument in related populations, with authors typically citing precedent, factor structure, correlations with related constructs, or prior use. No studies reported on responsiveness to change. Caregivers were the sole reporters for 40 outcomes (91%), while four outcomes (9%) allowed for reporting by either the caregiver or the patient (Table 5, details

Appendix B.10). All four of these outcomes were captured using seizure diaries.[96–99] Authors in two instances explicitly classified their tools (PRUCISION scratching scores and the Aberrant Behavior Checklist) as observer-reported outcomes,[94,100] highlighting the caregiver's role in evaluating observable clinical symptoms. No other items were explicitly classified by authors in trial reports as observer-reported or proxy-reported. In describing the caregiver's relationship to the participant, authors most frequently identified reporters as parents (n=25) or used the unspecified term "caregiver" (n=29), while for five outcomes (11%), authors specified "guardians". For only one outcome (2%) in one trial report, the trial report included demographic characteristics of the caregiver reporters, specifically: age, gender, race, ethnicity, education level, employment status, household income, and primary language.[55]

The primary mode of data collection was via questionnaire (n=42) with the exception of two reports utilizing the Vineland Adapted Behavior Scales,[62,64] which were administered via caregiver interview (Table 5, details Appendix B.10). For the subset of questionnaires where the method of completion was described (n=10), seven used only electronic questionnaires and two used only paper questionnaires, with one additional questionnaire being administered using both electronic and paper methods. For the 12 outcomes where a setting of completion was provided, results were evenly split between clinic or hospital settings (n=6) and home (n=6).

Table 5. Trial completeness of reporting for primary caregiver-reported outcomes (n=44 primary or co-primary caregiver-reported trial outcomes for n=38 studies)

Methodological feature	n (% of 44 outcomes)
Consistency of outcome reporter over time	11 (25)
Training for outcome reporter provided or described	7 (16)
Instructions for outcome reporter provided or described	6 (14)
Any psychometric properties of the outcome measure provided	11 (25)
Specific properties mentioned (multi-select, n=11)	
Validity	9 (82)
Reliability	2 (18)
General Psychometric Properties	1 (9)
Outcome reporter	
Caregiver only	40 (91)
Caregiver or Patient	4 (9)
Author classification of measures	
Observer	2 (100)
*Not reported**	*42*
Caregiver reporter's relationship to trial participant (multi-select)	
Unspecified (listed as 'caregiver')	19 (43)
Parent	25 (57)
Guardian	5 (11)
Caregiver demographics	1 (2)
Mode of data collection	
Questionnaire	42 (95)
Interview	2 (5)
Method of questionnaire completion (multi-select)	
Digital questionnaire/form	8 (80)
Paper questionnaire/form	3 (30)
*Not reported**	33
Setting of Completion	
Clinic/Hospital	6 (50)
Home	6 (50)
*Not reported**	32

*Trials where information was not reported were excluded from the denominator in calculating the percentage

3.5 – Primary Outcome Domains

As described, there were 20 unique caregiver-reported OMIs among the 38 trials where caregiver-reported outcomes were primary outcomes. Study authors' descriptions of the outcome domains measured by each OMI are reported in Table 6. Variability in descriptions were noted. For example, among the 15 studies where seizure diaries were a primary caregiver-reported outcome, authors described that these diaries were used to capture seizure frequency, daily seizure frequency, seizure experiences, changes in drop or focal seizure frequency, and paroxysmal events. Similarly, the Aberrant Behavior Checklist was described differently in the 5 trials that reported its use: social withdrawal, irritability, changes in behavioural symptoms, social avoidance, and behavioural problems. In some cases, the differences in the outcome domains reported may reflect the use of specific subscales for the OMI, as noted in Table 6.

Table 6. Unique caregiver-reported primary outcome measures (n=20) and the domain descriptions reported in associated studies (n=38).

Measure	*Measure subset*	*Outcome/Domain descriptions*	**Number of trials (%)**
Seizure Diary	*NA*	Seizure frequency, Daily seizure frequency, Seizure experiences, Change in drop seizure frequency, Frequency of focal seizures, Change in focal seizure frequency, Paroxysmal events	15 (39)
Aberrant Behavior Checklist (ABC)[68]	*NA*	Changes of behavioral symptoms	5 (13)
	Irritability	Irritability, behavioral problems	
	Social withdrawal	Social withdrawal	
	Social avoidance	Social avoidance	
Behavior Assessment System for Children, 3rd Edition (BASC-3)[77]	Activities of daily living (ADLs)	Activities of daily living	1 (3)
	Behavioral Symptoms Index (BSI)	Behavioral outcomes	
Child Behavior Checklist (CBCL)[70]	*NA*	Social and emotional symptoms, Behavioral effects	2 (5)
Dykens hyperphagia questionnaire[78]	*NA*	Changes in eating behavior, Maladaptive and compulsive hyperphagia-related behaviors	2 (5)
Social Responsiveness Scale[71]	*NA*	Social behavior, Social responsiveness	2 (5)
Vineland Adaptive Behavior Scales[69]	*NA*	Independent functioning and adaptive behavior Adaptive behavior	2 (5)
Adaptive Behavior Assessment Scale (ABAS)[88]	*NA*	Functional skills	1 (3)
Anxiety, Depression, and Mood Scales (ADAMS)[75]	*NA*	Anxiety and mood symptoms	1 (3)
Caregiver Global Impression (CaGI) Scales	*NA*	Impression of change	2 (5)
Hyperphagia Questionnaire for Clinical Trials[78]	*NA*	Hyperphagia	1 (3)
Oxytocin Questionnaire[89]	*NA*	Social behavior	1 (3)
PRUCISION: morning and evening ObsRO scratching scores[90]	*NA*	Scratching	1 (3)
Parent Report Revised Dimensions of Mastery	*NA*	Mastery motivation	1 (3)

Questionnaire (DMQ-18)[91]			
PedsQL (Pediatric Quality of Life Inventory)[67]	*NA*	Quality of life	1 (3)
Repetitive Behavior Scale-Revised (RBS-R)[72]	*NA*	Repetitive behavior	1 (3)
Rett Syndrome Behaviour Questionnaire[79]	*NA*	General features of RTT	1 (3)
Sleep Disturbance Scale for Children[76]	*NA*	Sleep disturbance	1 (3)
TNO-AZL Preschool children Quality of Life[92]	*NA*	Quality of life	1 (3)
Treatment Satisfaction Questionnaire for Medication[93]	*NA*	Satisfaction with treatment	1 (3)

Notes: 'NA' indicates that the full measure was administered.
Individual outcome and domain descriptions for each study are delimited by commas within this table.

3.6 – Measure review

We reviewed the 20 unique caregiver-reported OMIs used as primary endpoints in more detail, to examine their characteristics with reference to three dimensions important to considering them as proxy- versus observer-reported measures: the perspective taken (child's or caregiver's), whether the measure relies only on the caregiver's report or also includes clinician interpretation, and whether there are any items on the OMI that require judgement or inference about a child's feelings/internal state. Of the 20 unique instruments identified, 19 were retrieved and included in the expert review. One instrument was not reviewed because the full measure could not be accessed through database searches or via direct contact with the study authors.

Seventeen of the 19 reviewed instruments were classified as standardized measures. Two instruments (seizure diaries and the Caregiver Global Impression (CaGI)) were classified as non-standardized due to variability in format, structure, or content across trials. For these measures, we selected one version to review as an example. First, two experts (A Kaat and A Thurm) independently reviewed the instruments using this framework using a study-specific survey. Both experts reviewed 12 of the 19 OMIs, while seven OMIs were reviewed by one expert only. The results of these assessments were collated and synthesized, and the team met to discuss areas of agreement and disagreement and arrive at final classifications across the three dimensions (Table 7).

Perspective: Based on available instrument instructions, 12 OMIs were classified as explicitly seeking the caregiver's perspective, with one instrument (CaGI) classified as accommodating both caregiver and child perspectives. Specifically, for the CaGI example we reviewed, the instructions explicitly stated that "where appropriate, carer and child decided on

rating together," indicating joint consideration of caregiver and child perspectives. For three instruments, the perspective suggested by the instructions was classified as unclear due to vague, absent, or nonspecific guidance. For four instruments, an instruction-based perspective was not assessed because full instructions were unavailable. Based on item wording, 12 of the 19 OMIs were classified as seeking the caregiver's perspective, typically through phrasing that referred to observations of "your child" or similar wording. For five instruments, the perspective suggested by item wording was classified as unclear due to ambiguous phrasing that could plausibly be interpreted from either a caregiver or child perspective. One instrument (the Treatment Satisfaction Questionnaire for Medication) was classified as seeking the child's perspective based on item wording directed toward the respondent using second-person language. For example, the tool asks, "How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?" This direct phrasing implies the respondent is the primary evaluator of their own treatment experience

Clinician involvement: With respect to clinician involvement in informing or interpreting caregiver assessments, 12 instruments were classified as caregiver-completed without clinician input. For two instruments, clinician involvement was classified as unclear due to limited or absent information regarding administration or interpretation. For four instruments, clinician involvement was not assessed because full instructions were unavailable and therefore recorded as not applicable. Only one instrument (VINELAND-2 Survey Interview Form) clearly included a clinician in contributing to instrument completion and interpretation.

Inclusion of items requiring judgement about a child's internal state: Assessment of whether OMIs included items requiring caregiver judgement or inference about a child's internal

state was challenging. Nine OMIs were classified as including at least some items requiring inference about internal states, such as emotional experiences or subjective well-being. Five instruments were classified as focusing on observable behaviours only. For five instruments, this dimension was classified as unclear due to mixed content or ambiguity in item wording. .

Table 7. Classification of caregiver-reported outcome measures following expert review and team discussion (n=19)

Outcome measurement instrument	Perspective taken		Clinician involvement in informing or interpreting caregiver-assessment?	Any items requiring judgement re: internal state?
	Suggested by instructions	Suggested by item wording		
Aberrant Behavior Checklist (ABC)	Caregiver	Caregiver	No	Unclear
Adaptive Behavior Assessment System (ABAS)	Unclear	Caregiver	Unclear	Unclear
Anxiety, Depression, and Mood Scale (ADAMS)	Caregiver	Unclear	No	Some internal state items
Behavior Assessment System for Children (BASC-3)*	Caregiver	Caregiver	No	Some internal state items
Caregiver Global Impression (CaGI) Scales[a]	Caregiver	Caregiver	No	Some internal state items
Child Behavior Checklist (CBCL)*	Caregiver	Caregiver	No	Unclear
Dimensions of Mastery Questionnaire (DMQ)	NA	Caregiver	NA	Unclear
Dykens Hyperphagia Questionnaire (DHQ)	Caregiver & Child	Caregiver	No	Observable behaviors
Hyperphagia Questionnaire (HQ-CT)	Caregiver	Caregiver	No	Observable behaviors
Pediatric Quality of Life Inventory (PedsQL)*	Caregiver	Caregiver	No	Some internal state items
PRUCISION	Caregiver	Caregiver	Unclear	Observable behaviors
Repetitive Behavior Scale - Revised (RBS-R)	Unclear	Unclear	No	Unclear
Rett Syndrome Behaviour Questionnaire (RSBQ)*	NA	Unclear	NA	Observable behaviors
Seizure Diary[a]	NA	Unclear	NA	Some internal state items[b]
Sleep Disturbance Scale for Children (SDSC)*	Caregiver	Caregiver	No	Observable behaviors
Social Responsiveness Scale (SRS-P)*	Caregiver	Caregiver	No	Some internal state items

TNO-AZL Preschool Quality of Life*	Caregiver	Caregiver	No	Some internal state items
Treatment Satisfaction Questionnaire for Medication	NA	Child	NA	Some internal state items
Vineland Adaptive Behavior Scales (VABS-II)	Unclear	Unclear	Yes	Some internal state items

Indicates that initial review was completed by one expert only
[a] non-standardized measure; only one version was reviewed
[b]the specific seizure diary reviewed contained items asking about child's mood
Note: When full instrument instructions could not be obtained, reviewers did not assess instruction-based perspective or clinician involvement; these fields were recorded as NA.

The discussion among team members resulted in several insights about making judgements across the dimensions, particularly related to determining the presence of items requiring judgement about internal states. First, the use of modifying verbs within questionnaire item wording influenced reviewers' perceptions of the extent to which items required caregivers to make judgements about a child's internal state. For example, "child seems happy" or "child appears upset" could be viewed as being based on a caregiver's direct observations while "child is happy" or "child is upset" are more clearly judgements about internal states. Some questionnaire items had clarifying information embedded within the item itself. For example, for the item "Preoccupied; stares into space" from the Aberrant Behavior Checklist, the phrase "stares into space" seems to clarify that the caregiver should use this observable behaviour as a guide in rating whether "preoccupied" is a problem behaviour for the child. A related observation was that many items did not align clearly with a binary distinction between requiring or not requiring judgment about internal states. Instead, items often fell along a continuum, requiring varying degrees of caregiver judgment or inference. For example, within the Vineland Adaptive Behavior Scales–II (VABS-II) Maladaptive Behavior Index, one item asks whether the individual is "overly anxious or nervous," which was classified by an expert reviewer as

requiring inference about internal states. In contrast, another item asking if the individual "refuses to go to school or work because of fear, feelings of rejection or isolation" was considered more difficult to classify, as it combines an observable behavior (refusal) with inferred internal motivations, requiring a different degree of caregiver judgment. With respect to judgements, reviewers also noted that judgements were sometimes specific to internal states or moods (e.g., "child is sad") but could also be judgements about preferences or motivations (e.g., "prefers to try challenging problems instead of easy ones"). Finally, we identified variability in the clarity of questionnaire instructions for caregivers. Instructions were sometimes vague or incomplete in the reviewed materials and we recognized that additional instructions or training, not covered in the trial reports or copies of the instruments to which we had access, may have been incorporated in individual studies. We also noted that caregivers may not consistently follow or attend to instruction sections appearing within questionnaires, particularly given competing priorities with respect to caregiving. This could result in variation in the caregivers' use of OMIs even with standardized instructions.

Based on our findings, it was often challenging to categorize OMIs definitively as ObsROs or proxy-reported measures using the available classification dimensions. Across instruments, alignment with ObsRO or proxy characteristics varied depending on whether classifications were based on instructions, item wording, clinician involvement, or the type of information captured, and most instruments were not clearly situated as ObsROs or proxy-reported outcomes. Some instruments were more consistently aligned with ObsRO characteristics. For example, PRUCISION: morning and evening scratching scores was explicitly labeled by study authors as an observer-reported outcome and consisted of caregiver-completed ratings of observable behaviours, with few to no requirement for inference about internal states.

Similarly, the Hyperphagia Questionnaire (HQ-CT) and the Sleep Disturbance Scale for Children (SDSC) were characterized by caregiver-only completion, a greater focus on observable behaviours versus internal states, and no explicit clinician involvement, features consistent with ObsROs. In contrast, the Aberrant Behavior Checklist (ABC), while noted as a caregiver-reported tool by the trial authors, included items that required judgment about emotional or internal experiences, resulting in an unclear classification. Only one instrument was more clearly aligned with proxy-reported outcome characteristics: the Treatment Satisfaction Questionnaire for Medication used item wording that sought the child's perspective and required judgment about internal states. However, full instructions for this instrument were unavailable, limiting assessment of instruction-based perspective and clinician involvement. This questionnaire was used in one trial in the sample as part of a composite endpoint alongside two non–caregiver-reported outcomes.[66]

We further discussed these findings with knowledge users as part of the study's Advisory Committee, including researchers, caregivers, clinicians, and individuals with regulatory expertise. A caregiver commented on questionnaire instructions, noting that these are helpful but endorsing that they may not be read in detail if lengthy, particularly given that caregivers are often asked to complete many questionnaires as part of trials and other studies and lengthy instructions add to the time required. Given competing responsibilities, lengthy instructions could discourage people from completing questionnaire. Videos or other ways of communicating may be important to consider if this research leads to recommendations for additional training and instructions. Advisory Committee members also noted that the issues discussed related to training, instructions, and the context of implementation are particularly important to consider for decentralized trials. For example, whether and how guidance or support is available to a

caregiver when completing a questionnaire remotely. Advisory members further noted that subtle differences in wording may not be noted for caregivers completing questionnaires, particularly for non-English speakers. Finally, a clinician reiterated the importance of focusing specifically on the ID population when interpreting these OMI considerations. For example, caregivers' comfort and ability to report on these items on behalf of their child may depend on many factors, some of which could be related to the underlying diagnosis. Most of these OMIs have not been validated in ID populations and words like "seems" and "appears" may not mean the same thing for children and adolescents with complex medical needs and ID.

4.0 – Discussion

4.1 – Summary of findings

This thesis examined how caregiver-reported outcomes are incorporated, defined, and measured in clinical trials involving children and adolescents with intellectual disability (ID), with the aim of clarifying current practices and identifying methodological gaps relevant to trial design and regulatory decision-making. We first mapped the characteristics of recent pediatric trials that incorporated caregiver-reported outcomes and then undertook a detailed examination of how caregiver-reported outcome measurement instruments (OMIs) were used as primary endpoints within those trials, and the characteristics of those OMIs incorporated as primary endpoints.

Across the scoping review, 88 studies involving children and adolescents with ID were identified that included caregiver-reported outcomes, 38 specifying a caregiver-reported outcome as primary and 50 as secondary only. These trials predominantly evaluated pharmacological interventions across a range of ID-associated conditions. With respect to trial design, approximately one third of studies were single-arm designs, with most multi-arm studies incorporated random assignment and placebo controls. Blinding was reported in just over half of studies, and sample sizes and follow-up durations varied widely. Among the subset of 38 studies that included a primary caregiver-reported outcome, design characteristics were broadly similar to those observed across the full set of studies, although descriptively, this subset of studies more commonly reported somewhat larger sample sizes, and placebo-controlled randomized designs relative to the full set of 88 trials. Cross-over designs, pilot or feasibility studies, and extension phases were observed in a minority of studies.

Among 38 studies that specified at least one caregiver-reported outcome as a primary endpoint, we observed substantial heterogeneity in outcomes across studies: among the 88 included studies, there were 181 caregiver-reported OMIS, 78 of which were unique. Among the 38 studies with a primary caregiver-reported outcome, there were 44 primary or co-primary caregiver-reported OMIs, 20 of which were unique. Among studies with a primary caregiver-reported outcome, approximately one third (13 studies) incorporated caregiver-reported outcomes as co-primary outcomes or as components of composite primary endpoints; in 12 of these 13 studies, at least one primary outcome or component of the composite primary outcome was not caregiver-reported.

We observed clear differences between caregiver-reported OMIs that were frequently included across all studies and those most commonly selected as primary outcomes. The Pediatric Quality of Life Inventory (PedsQL) and Caregiver Global Impression (CaGI) scales were the two most frequently reported caregiver-reported OMIs overall, in 23% and 20% of studies, respectively. However, these OMIs were used as primary outcomes in only one (PedsQL) or two (CaGI) of the 38 studies with a primary caregiver-reported OMIs. In contrast, seizure diaries were not only commonly included in the full set of studies (17/88 studies, 19%) but were also the most frequently used primary caregiver-reported outcome, included as a primary outcome in 15 of 38 studies (39%) with a caregiver-reported primary endpoint.

Among the 38 studies where a primary outcome was reported by a caregiver, contextual details about caregiver reporting were frequently sparse. Among the 44 primary or co-primary caregiver-reported outcomes identified in these studies, for only one quarter authors specified that the same caregiver reporter was maintained over time, and for only a small minority (14-16%) authors reported providing caregiver training or standardized instructions for outcome

completion. Similarly, explicit reporting of measurement properties for primary caregiver-reported OMIs was uncommon, with any discussion of psychometric properties provided for only one quarter of outcomes, and very few studies including information about reliability of outcomes (1/44) and none reporting on the responsiveness to change. Information about caregiver characteristics was almost entirely absent, with demographic details reported for only a single outcome across all primary outcomes among 38 studies reviewed.

Our detailed review of the caregiver-reported OMIs used as primary outcomes, including the independent review by individuals with expertise in neuropsychological assessment, the small group discussion, and discussion with the Advisory Committee of researchers, clinicians, caregivers, and individuals with regulatory experience, highlighted additional complexities related to the extent to which caregiver-reported OMIs explicitly define the caregiver's role as an observer versus a proxy reporter. Specifically, this review identified variability in how primary caregiver-reported OMIs articulated the intended respondent and perspective, with many instruments lacking explicit guidance about perspective and including items that were difficult to assess with respect to whether caregivers were expected to report observable behaviours or make inferences about internal states

4.2 – Interpretation in the context of related literature

4.2.1 Diversity in outcome selection and measurement

In our review, 71% of the OMIs were used in only a single study. Similarly, 13 of the 20 unique OMIs included as primary outcomes were included as primary in a single trial. These findings reflect substantial diversity in outcome measurement approaches, which may arise from differing trial objectives, populations of interest, and practical constraints on the number of outcomes that can be included in a single study. These results echo the "outcome maze"

documented by Müller et al. (2024), whose scoping review of trials for population with genetic neurodevelopmental disorders identified 457 different measures, 63% of which were used only once.[40] Our review extends this observation to outcome measurement practices within pediatric ID trials and specifically to caregiver-reported outcomes. Most of the OMIs we identified were previously published generic instruments and not specific to specific ID diagnoses. This heterogeneity in the selection of outcome measures has been described as characteristic of rare disease research, where heterogeneity in clinical presentation, small trial populations, and evolving therapeutic targets complicate agreement on common outcome measures.[101,102] The wide range of outcome measures observed in this review may in part reflect the clinical and etiological heterogeneity of ID diagnoses, given that we identified 37 different diagnoses across the included studies, which can complicate the identification of widely applicable endpoints.[34,102,103]

In response to the wide diversity of outcome measures used across trials, a challenge that is not unique to ID nor rare disease, recent methodological literature has emphasized the development and adoption of Core Outcome Sets (COS) as a strategy to promote greater consistency across trials.[104–106] Initiatives such as the International Consortium for Health Outcomes Measurement (ICHOM) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative aim to establish minimum sets of outcomes that are clinically relevant and aligned with patient- and family-centred priorities for use across all trials within a given health condition.[105,107] Achieving consensus for pediatric populations with ID is particularly challenging given that outcomes must be sensitive to developmental change while remaining sufficiently standardized to support cross-trial comparison.[108,109] Complementary to COS efforts, the Rare Disease Clinical Outcome Assessment Consortium (RD-COAC)[110] takes a domain-

focused approach by prioritizing outcome domains shared across rare diseases and systematically reviewing existing clinical outcome assessments, with an initial emphasis on pediatric populations. This approach may facilitate greater alignment in outcome selection while allowing flexibility for disease-specific contexts. Collectively, these initiatives seek to improve the interpretability and comparability of trial findings, which may otherwise be constrained by the use of multiple instruments to capture similar outcome constructs. This concern is particularly important in ID research, as many commonly used instruments originally developed for general pediatric or clinical populations have not been validated for use in children and adolescents with ID, and psychometric evidence in this population is limited, inconsistent, or absent, potentially undermining confidence in outcome interpretation.[111,112]

As noted, we observed differences in the measures selected as primary versus secondary caregiver-reported outcomes. Seizure diaries were frequently used as primary outcomes, reflecting their role in capturing clinically salient, condition-specific events that are central to treatment evaluation, particularly in epilepsy-related trials, where seizure frequency is widely regarded as a key indicator of treatment response and disease severity.[113,114] In contrast, quality of life instruments, notably the Pediatric Quality of Life Inventory (PedsQL), were more commonly included as secondary outcomes, likely reflecting their utility for contextualizing treatment impact across multidimensional domains of health-related quality of life rather than serving as definitive efficacy endpoints.[67] This distinction may also reflect challenges in measurement associated with quality of life instruments in children and adolescents with ID, including issues of proxy reporting, as seizures are observable phenomena and thus many seizure diary OMIs are more likely to be considered ObsROs. However, seizure diaries are non-standardized questionnaires and in our detailed OMI review the example seizure diary we

reviewed had questions about the child's mood, which made it less clearly and ObsRO. While primary outcomes are designed to meet specific regulatory thresholds for efficacy, secondary endpoints play a crucial role in offering a more holistic representation of clinical meaningfulness that remains vital for clinical decision-making even when not utilized as the primary basis for regulatory submissions.[115]

4.2.2 Suboptimal reporting in publications of trials

Caregiver-reported outcomes raise well-recognized concerns about reporting bias, particularly when outcomes rely on subjective judgments, inference about internal states, or prolonged observation over time. Expectations about treatment benefit, caregiver stress, and contextual factors may all influence how outcomes are perceived and reported, underscoring the importance of transparent reporting practices that allow readers to assess potential sources of bias and variability. Against this backdrop, our findings corroborate and extend previous studies describing suboptimal reporting practices for outcome measures in pediatric trials. Among the 44 caregiver-reported primary OMIs identified in 38 studies, authors discussed psychometric properties for only 11 (25%), indicating challenges with measurement justification and reporting transparency. This pattern is consistent with findings from the Primary Outcomes Reporting in Trials (PORTal) systematic review, which reported that only one-third of pediatric trials published in high-impact journals included information on the psychometric properties of their primary outcomes.[116] A recent systematic review examining outcome measures used in research involving individuals with ID found that many instruments lacked evidence of adequate validity or reliability within these populations,[112] suggesting that reporting such properties may be particularly important to the interpretation of trial results. This reporting standard is foundational to the CONSORT 2010 statement,[117] adherence to which requires a complete definition of all

pre-specified outcomes (Item 6a), and is further reinforced by the CONSORT-PRO extension,[118] which explicitly states that trialists should provide or cite evidence of an instrument's validity and reliability within the target population to ensure the clinical meaningfulness of the findings.

In this scoping review, we also observed that reporting of caregiver sociodemographic characteristics was uncommon, with only one study providing such information. Given that caregivers frequently served as the primary reporters for outcomes in trials involving children and adolescents with ID, this limited reporting constrains the contextual information available to interpret caregiver-reported data. Sociodemographic factors such as caregiver age, education, and socioeconomic context have been shown in prior research to shape perceptions of health and functioning, and may therefore influence how outcomes are interpreted and reported.[108,119,120] While our findings do not permit direct assessment of the impact of these factors on trial outcomes, their omission represents a potential limitation in the transparency and interpretability of caregiver-reported data. This is also relevant because caregiver stress has been shown to influence proxy-reported outcomes, and caregiver perspectives can differ substantially from self-report measures, particularly for less observable domains. [121,122] Furthermore, the ISOQOL minimum standards[123] emphasize that documentation should include the characteristics of those providing the data (including proxies) to ensure the instrument is valid for the target population, while adherence to the CONSORT-PRO extension[118] mandates the explicit identification of the person completing the assessment to facilitate a robust appraisal of potential reporting bias.

Similarly, a small proportion of the included studies described whether caregivers received training or standardized instructions for outcome reporting. Although the absence of reported training does not necessarily indicate that training was not provided, limited reporting in this area raises questions about consistency in outcome assessment across caregivers and time

points. This may be particularly relevant in trials measuring behavioural or functional outcomes, where subtle changes can be difficult to distinguish without clear guidance.[104] The importance of such transparency is underscored by the CONSORT-Outcomes 2022 extension,[124] which explicitly states that authors should include a 'description of the person who assessed the outcome' and the 'qualifications or training' provided to them. Together, limited reporting of caregiver characteristics, training, and instructions reduces transparency and complicates interpretation of caregiver-reported primary outcomes, particularly for less observable domains.[120]

Methodological guidance emphasizes that maintaining a consistent outcome reporter over time is important for minimizing variability unrelated to treatment effects. In our review, however, this practice was infrequently documented: among the 44 primary caregiver-reported outcomes identified, trial authors specified that the same reporter was maintained longitudinally in only 11 instances (25%). ISOQOL recommendations further note that when proxy reporters vary across assessments, such changes should be explicitly documented, as differences in the proxy–patient relationship (e.g., level of contact or familiarity with the child) may influence outcome reporting.[32] ISOQOL guidance also highlights the importance of clearly justifying proxy selection and specifying the intended reporting perspective, given that factors such as the proxy's proximity to daily care and degree of involvement may shape how outcomes are interpreted.[33] Taken together, existing ISOQOL guidance and the findings of this review underscore the importance of improved documentation of reporter identity and longitudinal consistency when caregiver-reported outcomes are used as primary endpoints in pediatric ID trials. The limitations in reporting observed in the included trials suggests a continued need for closer alignment with recommended practices, including the use of standardized terminology to

distinguish observer-, proxy-, and clinician-reported outcomes, so that potential sources of variability are transparent and interpretable.

4.2.3 Trial design features relevant to caregiver-reported outcomes

Beyond reporting practices, trial design features may also influence the extent to which caregiver-reported outcomes are susceptible to bias. In this review, most trials with comparison arms employed random assignment, and 77% of multi-arm trials included placebo controls, design elements that are known to reduce systematic bias related to expectations and subjective reporting.[125] Blinding, which was reported in just over half of the included studies, has been shown to attenuate bias in studies with subjectively assessed outcomes compared with unblinded designs, particularly when caregiver or patient expectations could influence responses.[126–128]

Furthermore, in studies where caregiver-reported outcomes were included as co-primary endpoints alongside non-caregiver-reported measures, the presence of complementary outcome sources may help contextualize caregiver reports and provide a degree of triangulation when interpreting treatment effects, consistent with CONSORT recommendations emphasizing interpretation of patient-reported outcomes in relation to other clinical outcomes.[118] While these design features do not eliminate concerns related to construct validity or reporting consistency, they may partially mitigate the influence of expectancy effects and reporting bias, particularly in well-controlled, blinded studies.

4.2.4 Review and classification of outcome measurement instruments and implications for proxy-reporting

One of the objectives of this project was to classify caregiver-reported OMIs as ObsROs versus proxy-reported measures. We also wanted to understand whether proxy-reported OMIs

were the only feasible option for assessing outcomes in the reviewed trials when they were used. Regulatory guidance from authorities such as the FDA and EMA articulate clear definitions and preferences for ObsROs as they are based on directly observable signs or behaviours and are encouraged when self-report is not feasible, whereas proxy-reported outcomes, in which the caregiver "reports as if the patient," are generally discouraged for subjective internal constructs because they infer the patient's perspective rather than observe it directly.[3,29] Early in this project, we recognized that in many studies, authors themselves did not clearly described OMIs as ObsROs versus proxy reports (only two studies did so).[94,100] We implemented a process involving expert independent review followed by a small group discussion and then a discussion with the Advisory Committee to yield insights about these considerations. We found that it was not straightforward to classify the reviewed OMIs according to the dimensions of interest based on our literature-derived framework: both instructions and item wording often lacked clarity regarding who the respondent should be and whose perspective was being captured, complicating efforts to distinguish ObsROs from proxy-reported outcomes.

In considering recommendations for clearer instructions and caregiver training, a comment from a caregiver member of the Advisory Committee, emphasized that while instructions can improve clarity and consistency, overly detailed or lengthy guidance may increase respondent strain, reduce engagement, or be skipped entirely, particularly in the context of repeated assessments. This underscores the importance of balancing methodological rigor with feasibility and accessibility when designing caregiver-facing materials, a point echoed by the ISOQOL minimum standards for PRO measures.[123] The comment from Advisory Committee members related to the challenges in relying on subtle wording differences, which may not be interpreted equivalently across linguistic or cultural contexts, suggesting that attention to

accessibility and cross-language interpretation is essential when caregiver-reported outcomes are used in diverse populations. Literature on cross-cultural adaptation confirms that achieving semantic and operational equivalence is vital for ensuring that a measure's instructions are understood consistently across different cultural frameworks.[129] Co-development of instructions or training resources with caregivers may help to ensure that guidance is both understandable and appropriately scoped, while alternative formats such as brief videos or interactive tools may support comprehension without substantially increasing strain.

The context of administration is also critical. Comments from the Advisory Committee discussion highlighted issues related to instructions and training in decentralized or remote trials, where caregivers complete outcome measures without in-person support and may lack immediate access to clarification or guidance. As decentralized trial designs become more common,[130] ensuring that caregivers have access to timely support and clear reporting expectations may be particularly important for maintaining data quality. Together, these considerations suggest that improving instructions and training is not solely a matter of adding information, but of designing caregiver-centred, context-sensitive approaches that support accurate and sustainable outcome reporting.

Interpretation of our findings from the expert review and subsequent discussions of the OMIs suggests that many caregiver-reported OMIs occupy an intermediate or mixed position between ObsRO and proxy-reported categories rather than aligning cleanly with either definition. Across instruments, classifications varied depending on whether emphasis was placed on instructions, item wording, clinician involvement, or the degree to which items required judgment about internal states. This variability supports the view that caregiver responses in these studies may often reflect a combination of direct observation, inference, and personal

interpretation, rather than a single, clearly defined reporting perspective.[9] Importantly, these findings do not indicate that proxy reporting was necessarily inappropriate or avoidable for the outcome constructs assessed. Rather, they suggest that caregiver-reported outcomes were often implemented without explicit consideration and reporting of whether the constructs being measured were observable, inferential, or mixed in nature. In this context, proxy reporting may not have been selected because it was the only defensible option, but rather because assumptions about caregiver interpretive capacity and reporting perspective were left implicit.

Taken together, these findings highlight a gap between conceptual and regulatory guidance on observer versus proxy reporting and how caregiver-reported OMIs are applied in pediatric ID trials. Rather than resolving whether proxy-reported measures are the only feasible option, this review underscores the need for clearer specification of reporting perspective, explicit consideration of observability at the item level, and improved documentation of caregiver instructions and expectations. Addressing these issues may better align outcome measurement practices with existing guidance and enhance the interpretability of caregiver-reported outcomes used as primary endpoints in this population.

4.3 – Strengths and limitations

This review has several notable strengths. We systematically mapped caregiver-reported outcomes across studies of children and adolescents with ID, spanning diverse conditions, interventions, and outcome domains to provide a rich dataset that allowed us to examine in depth how caregiver-reported outcomes are used and reported in these studies. We used established scoping review methods developed to ensure research rigour,[131] including a specialist-developed and peer-reviewed search strategy, screening by two team members working independently, and verification of data extracted. The inclusion of a diverse Advisory Committee, including

researchers, people with regulatory expertise, and caregivers of children and adolescents with ID, represents an additional strength. Caregiver involvement in particular helped to ensure that the interpretation of findings and methodological considerations were informed by real-world perspectives on outcome reporting, particularly with respect to feasibility, clarity of instructions, and time impacts of reporting. The involvement of researchers, clinicians, and regulatory experts further strengthened the review's conceptual grounding and relevance to multiple interest-holders.

Several limitations warrant consideration. The review was limited to published reports and is therefore subject to potential publication bias; we speculate that studies that were not completed and/or not published may be characterized by additional or more frequent measurement and reporting challenges than those we reviewed. The review was also restricted to reports published in English for feasibility reasons, and 20 of 736 reports (approximately 3%) were excluded based on language. While this restriction may have introduced some language bias, the small proportion of excluded reports suggests that any impact on the overall findings is likely limited. We were also reliant on author reporting for most of the data we extracted. To mitigate against challenges with reporting that are due to journal requirements for word limits, we consulted supplementary appendices for trials in the review. We also consulted trial registrations if we were uncertain about which outcome measures were considered to be primary based on the trial report. Four team members (Y Al-Baldawi, S Cutler, A Thurm, BK Potter) met regularly throughout the review to review, discuss, and mitigate challenges with data extraction. To define ID-related conditions, we used a list from the Human Phenotype Ontology (HPO),[45] which includes some disorders not universally and exclusively associated with ID (e.g. autism, Cerebral Palsy, and Epilepsy). The requirement that caregiver reporting of outcomes be

explicitly stated for trials to be included in the review may have led to under-identification of some relevant measures. For example, the Vineland Adaptive Behavior Scales were not always explicitly described as caregiver-reported in trial publications, even though standard administration of the instrument relies on caregiver input.[69] We also relied solely on trial author-reported descriptions to classify outcome domains, which likely led to inconsistencies. Finally, we combined non-standardized measures together that measured the same concepts, specifically, the seizure diaries and the caregiver impression of change scales.

4.4 – Implications for future research and policy

The findings of this thesis point to heterogeneity in caregiver-reported outcome measures among treatment trials for children and adolescents with ID, which may limit comparability across studies. Future research may therefore benefit from continued efforts to develop consensus on high-priority outcome domains and greater harmonization of OMIs within and across diagnoses where appropriate, using structured consensus approaches that incorporate the perspectives of clinicians, researchers, and families. These efforts should also prioritize the inclusion of child and adolescent perspectives wherever feasible, including through the development or adaptation of outcome measures that support self-report among individuals with sufficient cognitive and communicative abilities.[21–24] Such initiatives will need to balance standardization with sensitivity to the clinical and etiological heterogeneity that characterizes ID. Our findings also underscore the importance of clear measurement justification and documentation of psychometric properties for caregiver-reported outcomes in treatment trials. Future methodological work could include context-specific validation studies, such as those guided by the COSMIN framework for assessing content validity of patient reported outcome measures,[132] which emphasize evaluating content validity, relevance, and comprehensibility of

outcome measures within the target population and reporting context. Additional evaluation of construct validity is also needed to ensure that caregiver-reported outcomes capture the intended concepts and that observed changes can be meaningfully interpreted. There is also a need to evaluate OMI reliability and responsiveness to change among children and adolescents with ID. Such approaches may help determine whether commonly used caregiver-reported OMIs are fit for use in children and adolescents with ID or require adaptation.

Although regulatory guidance clearly outlines expectations for clinical outcome assessments intended to support efficacy and labeling claims, acceptance of an outcome measure during trial design or early regulatory interactions does not guarantee its acceptability at the time of marketing authorization.[3,133] Recent Patient-Focused Drug Development (PFDD) initiatives aim to mitigate this risk through early sponsor-FDA collaboration on endpoint selection. However, caregiver-reported outcomes that lack clear observability continue to appear in trials, despite guidance prioritizing patient or direct observer reports for primary endpoints.[3,134] This highlights the importance of early and explicit alignment with regulatory expectations when caregiver-reported outcomes are intended to play a central role in evidentiary decision-making.[134]

Our findings draw attention to the role of the caregiver as a proxy reporter. Reporting of caregiver characteristics and reporting procedures was uncommon among the trials reviewed, including those in which caregivers reported primary outcomes. Future research may seek to examine how caregiver factors, such as stress, health literacy, and socioeconomic context, are associated with outcome reporting in pediatric trials, although this will require more systematic collection and reporting of caregiver characteristics by trial authors. Existing reporting guidance, including CONSORT and its extensions (especially CONSORT-PRO, CONSORT-Outcomes,

and CONSORT-Children and Adolescents), as well as ISOQOL recommendations, emphasize the need to clearly document who completed outcome measures, the instructions or training provided, and any changes in reporters over time. However, these elements were infrequently reported in the trials included in this review. Together, these findings suggest that closer adherence to existing reporting standards, and potentially more explicit guidance tailored to caregiver-reported outcomes, may be needed to improve transparency and interpretability, particularly when caregiver-reported measures are used as primary endpoints.

These methodological considerations have implications for the use of caregiver-reported outcomes in regulatory and policy contexts. As regulatory agencies increasingly emphasize patient- and family-focused approaches to drug development, there is a growing need to ensure that caregiver-reported outcome measures are fit for their intended purpose. At the same time, efforts to incorporate patient perspectives directly, where feasible, remain an important priority within patient-focused drug development initiatives. Addressing the research gaps identified in this review may support the development of caregiver-reported OMIs that are psychometrically sound, meaningful to children/adolescents and families, and feasible to implement through accessible training of caregiver reporters. Improvements in outcome harmonization, measurement validation, and reporting transparency may collectively enhance the interpretability and utility of caregiver-reported outcomes in pediatric trials involving children and adolescents with ID.

Finally, future research should consider how caregiver-reported outcomes are implemented within evolving trial contexts. As decentralized and hybrid trial designs become increasingly common, greater attention may be needed to how caregivers receive instructions, access support, and interpret questionnaire items when completing measures remotely.

Methodological guidance on caregiver-reported outcomes may therefore benefit from explicitly addressing modes of instruction delivery, availability of real-time support, and accessibility for caregivers with varying literacy levels, language backgrounds, or time constraints. In parallel, similar considerations should be applied to the design of self-report tools for children and adolescents with ID, to ensure accessibility and feasibility across diverse contexts. Involving caregivers and patient partners in the co-development of instructions and training materials may help ensure that outcome measures are both methodologically robust and feasible for routine use, particularly when caregiver-reported outcomes serve as primary or co-primary endpoints.

4.5 – Final conclusions

In conclusion, clinical trials to evaluate drugs, supplements, or devices among children and adolescents with ID rely on caregiver-reported outcomes to assess meaningful treatment effects when direct self-report is not feasible. This thesis examined how such outcomes are incorporated, defined, and measured in current practice. The scoping review revealed substantial heterogeneity in the caregiver-reported outcome measures included in these trials When caregiver-reported outcomes were used as primary or co-primary endpoints, trial report authors incorporated minimal reporting of psychometric properties, caregiver characteristics, and details about training and administration, complicating the interpretation of trial findings and limiting the opportunity for cross-trial comparison. Our review of selected OMIs that were used as primary outcomes highlighted ambiguity about the intended respondent and the perspective sought. This limited our ability to determine OMI alignment with regulatory standards about proxy reporting, not because proxy reporting was necessarily inappropriate for the constructs assessed, but because key features of reporting perspective, observability, and respondent role were often left implicit. We identified wording features that may affect how OMIs are classified

and that could be further studied and incorporated into measurement guidance. We also discussed the importance of accessible training of caregiver reporters to enhance measurement quality and of reporting caregiver characteristics.

By systematically documenting how caregiver-reported outcomes are used and reported, this thesis contributes to ongoing discussions about outcome, measurement, and reporting in pediatric ID research. The findings may inform future efforts to improve the clarity, interpretability, and consistency of outcome measurement in clinical trials involving children and adolescents with ID, thereby strengthening the evidence base used to inform clinical and regulatory decision-making. Advancing methods that better incorporate the perspectives of children and adolescents with ID, alongside improving the use and reporting of caregiver-reported outcomes, represents an important direction for future research.

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Appendix A: additional details regarding methods

A.1. PRISMA-ScR Checklist – REQUIRES UPDATE AFTER FINAL EDITS

Table 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	i
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	viii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	10
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	11
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	15
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	15
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	19
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	88
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	20
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	21

Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	112
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	23
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	25
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	145
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	145
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	27
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	49
Limitations	20	Discuss the limitations of the scoping review process.	60
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	65
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	vii

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

A.2. Search strategy (MEDLINE)

The following search strategy is for MEDLINE. For the complete search strategy for the other databases, visit: https://osf.io/nsyga
Database: Ovid MEDLINE(R) ALL <1946 to December 18, 2024>
Search Strategy:
---
1 Disabled Children/ (7306)
2 exp Infant/ (1295538)
3 exp Child/ (2242325)
4 Adolescent/ (2294454)
5 (baby or babies or infant? or infantile or infanc* or neonat* or neo-nat* or newborn* or newborn* or preschool* or pre-school* or toddler?).tw,kw,kf. (981455)
6 (adolescen* or child* or juvenil* or kid or kids or minors or pre-adolescen* or preteen* or preteen* or schoolage* or school-age* or schoolchild* or school-child* or teenage* or teen-age* or
teen or teens or tween? or underage* or under-age* or youth?).tw,kw,kf. (2179254)
7 (pediatric* or paediatric* or adolescen* or child* or infant? or youth?).jn,jw. (790635)
8 exp Pediatrics/ (64642)
9 p?ediatric*.tw,kw,kf. (521701)
10 or/1-9 [AGES 0-18, PAEDIATRICS] (5152422)
11 Developmental Disabilities/ (23193)
12 exp Intellectual Disability/ (108856)
13 ((cognit* or developmental* or intellectual* or learning or mental* or psychomotor* or psychomotor*) adj3 (defect* or deficit* or deficien* or disabil* or disabled* or handicap* or incapable or
incapacit* or impair* or retard* or subnormal* or sub-normal*)).mp. (328311)
14 ((cognit* or intellectual* or learning or mental*) adj3 development* disorder*).mp. (860)
15 ((cognit* or intellectual* or learning or mental*) adj3 delay*).mp. (8725)
16 (global development adj3 delay*).mp. (100)
17 ((cat cry or "chromosome 5" or crying cat or "cri-du-chat" or 5p deletion or 5p minus or 5 short
arm deletion) adj3 syndrome?).mp. (849)
18 de lange* syndrome*.mp. (1240)
19 (de lange* syndrome* or cdls or cdls2 or typus degenerativ* amstelodamens*).mp. (1309)
20 (down? syndrome? or "down's syndrome?" or down? disease? or "down's disease?" or
"47,XX,+21" or "47,XY,+21" or mongol* or "trisomy 21" or "trisomy g" or "translocation 15 21
22").mp. (52058)
21 ("trisomy 10p" or "trisomy 12p" or "trisomy 13" or "trisomy 17p" or "trisomy 18p" or "trisomy 5p"
or "trisomy 8p" or "trisomy 9p").mp. (2527)
22 ("tetrasomy 12p" or "tetrasomy 18p").mp. (167)
23 (adrenoleukodystroph* or adreno-leukodystroph* or adreno-leuko-dystroph* or adrenoleukodystroph* or
adrenomyeloneuropath* or adreno-myeloneuropath* or adreno-myelo-neuropath* or
adrenomyelo-neuropath* or bronze schilder* or melanodermic leukodystroph* or melano-dermic
leukodystroph* or melano-dermic leuko-dystroph* or melanodermic leuko-dystroph* or schilderaddison* or siemerling-creutzfeldt* or x-ald or (addison disease adj2 cerebral scleros*)).mp. (2856)
24 ((cerebellar ataxia or cere-bellar ataxia) adj3 (autosomal dominant or autosomal recessive or
brain abnormalit* or pigment* retinopath*)).mp. (562)
25 (coffin-lowry* or (coffin adj2 syndrome?)).mp. (603)
26 ((fragile x or fraxa or fraxe or "fra(x)" or "fragile x-f" or "mar x" or "marker x" or martin-bell) adj3
syndrome?).mp. (7981)
27 ((antopol or danon or glycogen storage or vacuolar) adj3 (disease* or cardiomyopath* or
cardio-myopath*)).mp. (8051)
28 (pseudoglycogenos* or pseudo-glycogenos*).mp. (0)
29 ((guanine phosphoribosyl?transferase or hgprt or hprt or hypoxanthine
phosphoribosyl?transferase or juvenile hyperuric?emia or juvenile hyper-uric?emia or primary
hyperuric?emia or primary hyper-uric?emia) adj3 syndrome?).mp. (53)
30 (choreo?athetos#s self-mutilat* adj3 syndrome?).mp. (0)
31 (lesch-nyhan adj3 (disease? or phenotype? or syndrome?)).mp. (1529)
32 (x-linked adj2 (hyperuric?emia or hyper-uric?emia)).mp. (6)
33 ((copper transport or kinky hair or menkes or steely hair) adj3 (disease? or syndrome?)).mp.
(1521)
34 (congenital adj1 (hypocupr?emia? or hypo-cupr?emia?)).mp. (1)
35 (copper deficien* adj1 (x-linked or xlinked)).mp. (5)

36 (gargolylis* or gargoylis* or mckusick 30990 or MPS 2 or MPS2 or MPS II or MPSII).mp. (1187)
37 (mucopolysaccharidos#s adj2 ("type 2" or "type II")).mp. (555)
38 (mucopolysaccharidos#s 2 or mucopolysaccharidos#s II).mp. (1207)
39 ((hunter or hunter's) adj (disease? or glossitis or syndrome?)).mp. (1162)
40 ((iduronate-2 sulfatase or iduronate sulfatase or sulfoiduronate sulfatase or I2S) adj3 deficien*).mp. (127)
41 ((pdh or pdhc or pyruvate carboxylase or pyruvate decarboxylase or pyruvate dehydrogenase) adj3 deficien*).mp. (899)
42 (lactic acidos#s adj3 ataxia).mp. (20)
43 (abnormal pyruvate adj3 ataxia).mp. (0)
44 ((rett or rett's) adj3 (disorder? or syndrome?)).mp. (4625)
45 (autis* and dement* and ataxia).mp. (49)
46 ((prader or labhart) adj2 willi).mp. (4803)
47 ((royer or royer's) adj3 (disease? or syndrome?)).mp. (3)
48 (rubinstein* adj3 (disease? or syndrome?)).mp. (860)
49 (broad thumb* adj3 (disease? or syndrome?)).mp. (35)
50 ((chromosome 13 or trisomy 13 or 13 trisomy or patau or patau's) adj3 (duplicat* or syndrome?)).mp. (1023)
51 ((wagr or wagro) adj3 (complex$2 or syndrome?)).mp. (246)
52 (wilms and aniridia and (genit* or gonad*)).mp. (215)
53 (11p13 adj3 delet*).mp. (153)
54 11p partial monosom*.mp. (0)
55 ((beuren or williams) adj3 (disorder? or syndrome?)).mp. (3019)
56 ((hypercalc?emia-supravalvar or hyper-calc?emia-supravalvar) adj3 stenos#s).mp. (0)
57 ("7q11.23" adj3 delet*).mp. (198)
58 Learning Disabilities/ (14819)
59 ((academic* or learning or scholastic*) and (development* adj3 (delay* or disorder*))).mp. (6160)
60 (acalculi* or dyscalculi).mp. (261)
61 ((aarskog-scott or achalasia-addisonianism or achalasia-microcephal* or acrocallosal or acrocardiofacial or acro-cardiofacial or acrocardio-facial or acro-cardio-facial or acromegaloid facial appearance or acropectoral or acro-pectoral or adams-oliver or aicardi or aica-ribosiduria or al kaissi or alacrimia-choreoathetosis or alagille or alazami or aldh18a1-related de barsy or alexander or alkuraya-kucinskas or allan-herndon or amed or amelocerebrohypohidrotic or amelocerebrohypohidrotic or ane or angelman or antley-bixler or apert or arboleda-tham or arima or arterial tortuosity or arts or asxl3 deficienc* or ataxia-deafness-retardation or ataxia-microcephalycataract? or atkin-flaitz or "atr-16" or (attenuated adj3 higashi) or au-kline or ayme-gripp or bainbridge-ropers or baller-gerold or bamforth-lazarus or bangstad or bannayan-riley or baraitserwinter or baralle-macken or barber-say or bardet-biedl or bartsocas-papas or bartter or basal cell nevus or basel-vanagaite or basilicata-akhtar or beaulieu-boycott or beck-fahrner or behr or biemond or bjornstad or blepharonasofacial malformation or blepharo-nasofacial malformation or blepharo-naso-facial malformation or blepharonaso-facial malformation or bloom or bohring-opitz or bonnemann-meinecke or borjeson-forssman or bosch-boonstra-schaaf or bosma arhinia or boucher-neuhauser or brachymorphism-onychodysplasia-dysphalangism or brain-lung-thyroid or branchiooculofacial or branchio-oculofacial or branchiooculo-facial or branchio-oculo-facial or branchioskeletogenital or branchio-skeletogenital or branchioskeleto-genital or branchio-skeletogenital or bresek or brooks-wisniewski or brunner) adj3 (disease? or disorder? or syndrome?)).mp. (15190)
62 ((cahmr or camos or (camptodactyly adj2 guadalajara) or cardiac-urogenital or cardiac-urogenital or ehlers-danlos or (cardiocranial adj2 pfeiffer) or (cardio-cranial adj2 pfeiffer) or cardiofaciocutaneous or cardio-facio-cutaneous or cardiofacio-cutaneous or carey-fineman or carpenter or cat eye or (cataract? adj3 deafness adj (ataxia? or hypogonadism)) or (cataract? adj3 (microcephal* or micro-cephal*) adj3 "failure to thrive" adj3 (kyphoscolios* or kypho-scolios*)) or (cataract? adj3 nephropath* adj3 encephalopath*) or catifa or (caudal appendage adj3 deafness) or cebalid or cednik or (cerebellar adj3 facial adj3 dental) or cerebellofaciodental or cerebellofaciodental or cerebello-facio-dental or cerebellofacio-dental or cerebral creatine deficienc* or (cerebral dysgenes* adj3 neuropath* adj3 ichthyos#s adj3 palmoplantar keratoderma*) or cerebrocostomandibular or cerebrocosto-mandibular or cerebro-costo-mandibular or cerebrocosto-mandibular or cerebrofacioarticular or cerebrofacio-articular or cerebro-facioarticular or cerebrooculofacioskeletal or cerebro-oculofacioskeletal or cerebro-oculo-facioskeletal or cerebro-oculo-facio-skeletal or cerebrooculo-facioskeletal or cerebrooculo-facioskeletal or

cerebrooculofacio-skeletal or cerebro-oculofacio-skeletal or cerebrooculonasal or cerebrooculonasal or cerebro-oculo-nasal or cerebrooculo-nasal or chanarin-dorfman or char or charcotmarie-tooth or charge or chediak-higashi or childhood disintegrative or (childhood-onset adj3
((cognitive or motor) adj regression) adj3 extrapyramidal movement) or chime or
(chondrodysplasia* adj3 sex* development*) or chops or christianson or chudley-mccullough or
chylomicron retention or cimdag or cinca or "ck" or clark-baraitser or coach or cockayne or codas
or cohen or cohen-gibson or congenital myasthenic or congenital rubella or congenital varicella or
cooper-jabs or costello or cowchock or cowden or craniofaciofrontodigital or cranio-facio-frontodigital or craniofacio-fronto-digital or cranio-faciofrontodigital or craniofacio-frontodigital or craniofacio-frontodigital or creatine deficienc* or crigler-najjar or (crisponi adj2 cold-induced sweating) or
crome or crouzon or ctcf-related or curry-jones or cyclic vomiting or (cystic fibros#s adj3 gastritis
adj3 megaloblastic an?emia?) or danon or darier-white or de sanctis-cacchione or degcags or dent
or dermotrichic or desanto-shinawi or desbuquois or developmental malformations-deafnessdystonia or diets-jongmans or (distal limb deficienc* adj2 micrognathia?) or donnai-barrow or doors
or down or "down's" or dubowitz or dyggve-melchior-clausen or dysautonomia-like or
dysequilibrium or (dysmorphism adj3 cleft palate adj3 loose skin) or "dysmorphism-short staturedeafness-disorder of sex development" or (ear adj3 patella adj3 short stature) or east or
(ectodermal dysplasia* adj3 blindness) or edinburgh malformation or eec or ehlers-danlos or
elejalde or ellis van creveld or elsahy-waters or emanuel or (epilep* adj3 microcephal* adj3 skeletal
dysplasia*) or (epiphyseal dysplasia* adj2 hearing loss* adj2 dysmorphism)) adj3 (disease? or
disorder? or syndrome?)).mp. (67910)
63 ((faciocardiomelic or facio-cardiomelic or faciocardiorenal or facio-cardiorenal or farber or
feingold or f?etal alcohol or f?etal iodine or f?etal trimethadione or filippi or floating-harbor or
fountain or fraser or free sialic acid storage or fried or frontoocular or fronto-ocular or fryns or
smeets-thiry or gabriele-de vries or galloway-mowat or gapo or (gaucher disease adj3
ophthalmopl?egia* adj3 cardiovascular calcification) or gardner or gemignani or generalized
epilepsy-paroxysmal dyskinesia* or genitopatellar or genito-patellar or german or gillespie or glass
or glut1 deficienc* or gms or goldberg-shprintzen or gombo or gorlin or chaudhry-moss or grange or
greig cephalopolysyndactyly or griscelli or growth hormone insensitivit* or gurrieri or haddad or
hadziselimovic or hallermann-streiff or hall-riggs or hamel cerebro-palato-cardiac or harel-yoon or
harrod or hartnup or ("heart-hand" adj2 "type 2") or helsmoortel-van der or hengel-maroofianschols or hennekam or hiatt-neu-cooper or hirschsprung or histidinuria-renal tubular defect* or
hydrocephalus-costovertebral dysplasia-sprengel anomal* or hooft or hoyeraal-hreidarsson or
hsd10 or hunter-mcalpine or hurler or hutterite cerebro* or hydrocephalus-obesity-hypogonadism
or (hyperinsulinism adj1 hyperammon?emia) or (hyperornithinemia? adj2 homocitrullinuria?) or
hypertelorism-microtia-facial or hypertrichosis-acromegaloid facial or hypoglossia-hypodactyly or
hypomyelination-congenital cataract? or retardation-dysmorphism or (ataxia adj2 delayed
development*) or hypotonia-cystinuria or (hypotonia adj2 developmental delay*) or (ataxia adj3
tooth enamel)) adj3 (disease? or disorder? or syndrome?)).mp. (20159)
64 ((icf or ichthyosis follicularis-alopecia-photophobi* or ifap or imagawa-matsumoto or infantile
choroidocerebral calcification or infantile multisystem neurologic-endocrine-pancreatic or irida or
jaberi-elahi or jacobsen or jawad or jeavons or johanson-blizzard or johnson neuroectodermal or
joubert or juberg-hayward or jung or juvenile polypos#s or peripheral neurodegeneration or kabuki
or kagami-ogata or kahrizi or kallmann or kanzaki or kapur-toriello or kaufman oculocerebrofacial or
kbg or keipert or kennerknecht or keppen-lubinsky or keutel or kifafa seizure or kilquist or kinsship
or kleefstra or klippel or kohlschutter-tonz or koolen-de vries or kufor-rakeb or lambert or lambshaffer or laron or larsen or laurence-moon or laurin-sandrow or leigh or lelis or lennox-gastaut or
leopard or lessel-kreienkamp or liberfarb or li-campeau or lig4 or linear nevus sebaceus or loeysdietz or lopes-macielor or lowe or lowry-maclean or lowry-wood or lujan-fryns or luo-schoch or
luscan-lumish or lysine malabsorption or malan overgrowth or malouf or maple syrup urine or
marden-walker or marinesco-sjogren or nicolaides-baraitser or marshall-smith or martsolf or masa
or matthew-wood or mcdonough or mckusick-kaufman or meckel or mednik or mehmo or meiergorlin or mend or menke-hennekam or menkes or methionine malabsorption* or micro or
(microcephal* adj2 deaf*) or (micro-cephal* adj2 deaf*) or syndromemietens or miller-dieker or
mitochondrial dna depletion or mmep or moebius or momo or mona or morm or morquio or
mowat-wilson or moyamoya or mosaic variegated aneuploidy or moynahan or muenke or (multiple
mitochondrial dysfunction? adj3 "6") or myhre or nabais sa-de vries or nance-horan or narp or
(nephrotic adj2 "type 8") or (nephrogenic diabetes insipidus adj3 intracranial calcification) or
(nephrotic adj2 "type 8") or netherton or ((neuroectodermal or neuro-ectodermal or neuroectodermal or neuro-ecto-dermal) adj (melanolysosomal or melano-lysosomal)) or
neurofaciodigitorenal or neuro-faciodigitorenal or neuro-facio-digitorenal or neuro-facio-digitorenal or neurofacio-digitorenal or neurofacio-digito-renal or neurofaciodigito-renal or

neurofacioskeletal or neuro-facioskeletal or neuro-facio-skeletal or neurofacio-skeletal or
neurofibromatosis-noonan or neuro-fibromatosis-noonan or neurooocular or neuro-ocular or
neurooculocardiogenitourinary or neuro-oculocardiogenitourinary or neuro-oculocardiogenitourinary or neuro-oculo-cardio-
genitourinary or neurooculo-cardiogenitourinary or
neurooculo-cardio-genitourinary or neurooculocardio-genitourinary or niemann-pick or nijmegen
breakage or nizon-isidor or (non-insulinoma adj2 pancreatogenous adj2 (hypoglyc?emi* or
hypoglyc?emi*)) or noonan or norrie or null or occipital horn or (ocular anomal* adj2 axonal
neuropath* adj2 developmental* delay*) or ((oculocerebral or oculo-cerebral) adj2 (hypopigment*
or hypo-pigment*)) or oculocerebrocutaneous or oculo-cerebro-cutaneous or ((oculocerebrofacial
or oculo-cerebro-facial) adj3 (kaufman or lowe)) or oculofaciocardiodental or oculo-facio-cardiodental or oculopalatocerebral or
oculo-palato-cerebral or oculorenocerebellar or oculo-renocerebellar or ohdo or okamoto or okur-chung or oliver or oliver-
mcfarlane or opitz gbbb or opitzkaveggia or orofaciodigital or oro-faciodigital or oro-facio-digital or orofacio-digital or recessive
osteolysis or (osteopathia striata adj2 cranial scleros#s) or (osteopetrosis adj2 related) or (osteopetrosis adj2 related) or
osteoporosis-pseudoglioma or otofaciocervical or oto-faciocervical or otofacio-cervical or otofacio-cervical or
otoonychoperoneal or oto-onycho-peroneal or
((otopalatodigital or oto-palato-digital) adj3 ("type 1" or "type i" or "type 2" or "type ii")) or
(overgrowth adj2 macrocephal* adj2 facial dysmorphism)) adj3 (disease? or disorder? or
syndrome?)).mp. (39735)
65 ((palant cleft palate or pallister or pallister-hall or pallister-killian or papillorenal or papillorenal or partington or patterson
pseudoleprechaunism or patterson pseudo-leprechaunism or
pde4d haploinsufficienc* or pelizaeus-merzbacher or pendred or perlman or peroxisomal fatty
acyl-coa reductase or (peroxisome biogenes#s adj2 ("14b" or "1a" or "2a" or "2b" or "3b" or "4b" or
"5a" or "9b")) or peters plus or pettigrew or pfeiffer or phelan-mcdermid or (piebald trait adj2
neurologic defect*) or pierpont or pilarowski-bjornsson or pitt-hopkins or pituitary stalk interruption
or (plaa-associated adj3 neurodevelopmental*) or poirier-bienvue or (polyendocrine adj1
polyneuropath*) or (poly-endocrine adj1 polyneuropath*) or polyvalvular heart disease or polyvalvular heart disease or pontine
tegmental cap or potocki-lupski or potocki-shaffer or prader-willi
or prader-willi-like or presynaptic congenital myasthenic or prieto or primrose or proteus or
proteus-like or pseudoaminopterin or pseudo-aminopterin or pseudoleprechaunism or pseudoleprechaunism or pseudoprogeria or
pseudo-progeria or pten hamartoma tumo?r) adj3 (disease? or
disorder? or syndrome?)).mp. (8940)
66 ((rabson-mendenhall or radio-tartaglia or radioulnar synostosis-microcephal* or rafiq or
rahman or ramon or ramos-arroyo or raynaud-claes or "recombinant 8" or "recombinant
chromosome 8" or refsum or renpenning or rere-related or richards-rundle or richieri costa or "ring
chromosome 10" or "ring chromosome 13" or "ring chromosome 14" or "ring chromosome 21" or
"ring chromosome 8" or ritscher-schinzel or roberts or roifman or rothmund-thomson or ruvalcaba
or sabinas brittle hair or saethre-chotzen or salla or sanjad-sakati or scarf or schaaf-yang or
schilbach-rott or schimmelpenning-feuerstein or schinzel-giedion or scholte or schuurshoeijmakers or schwartz-jampel or seckel
or seizures-scoliosis-macrocephal* or senior-loken or
severe oculo-renal-cerebellar or shaheen or shashi-pena or (short stature adj3 webbed neck adj3
heart) or shprintzen-goldberg or shwachman-diamond or sifrim-hitz or silver-russell or simha or
simpson-golabi or sjogren-larsson or (skeletal dysplasia* adj3 epilep* adj3 short stature) or
skraban-deardorff or smith-kingsmore or smith-lemli or smith-magenis or snijders blok* or sonoda
or sotos or (spinal muscular atroph* adj3 progressive myoclonic epilep*) or spondylo-ocular or
stankiewicz-isidor or stevenson-carey or (stickler adj2 "type 1") or stimmler or sturge-weber or
subaortic stenosis-short stature or sub-aortic stenosis-short stature or summitt or synaptic
congenital myasthenic or takenouchi-kosaki or tarp or tatton-brown or temple or temtamy or
tenorio or thauvin-robinet or (thoracic dysplasia* adj1 hydrocephalus) or thrombocytopenia-absent
radius or thrombo-cytopenia-absent radius or timothy or tonne-kalscheuer or townes-brocks or
treacher collins or tremor-ataxia or (trichorhinophalangeal adj2 ("type 2" or "type ii")) or turnpennyfry or tyshchenko or urban-
rogers or (usher adj2 "type 1") or usmani-riazuddin or van bogaert or van
den bosch or van esch-o'driscoll or van maldergem or velocardiofacial or velo-cardiofacial or velo-
cardio-facial or velocardio-facial or ververi-brady or vici or viss or vissers-bodmer or (waardenburg
adj2 ("type 3" or "type 2e" or "type 3")) or wagr or waisman or walker-warburg or warburg micro or
warsaw breakage or weaver or weaver-williams or weill-marchesani or weismann-netter or weisskruszka or white-kernohan or
white-sutton or wieacker-wolff or wiedemann-rautenstrauch or
wiedemann-steiner or wilson or wilson-turner or witteveen-kolk or wolcott-rallison or wolfhirschhorn or wolfram or woodhouse-
sakati or woods or wrinkly skin or wyburn-mason or xfe
progeroid or xia-gibbs or yuan-harel or zechi-ceide or zellweger-like or zimmermann or zttk or
zunich or carpenter-waziri or chudley-lowry or clapo or goldenhar or holmes-gang or hutchinsongilford or juberg-marsidi or kid
or nakajo-nishimura or "opitz g" or otomandibular or oto-mandibular

or pitt-hopkins or renier-gabreels or (salt adj2 pepper) or severe canavan or smith-fineman or taysachs or thyrocerebrorenal or thyro-cerebrorenal or thyrocerebro-renal or thyro-cerebro-renal or
unverricht-lundborg or zlotogora) adj3 (disease? or disorder? or syndrome?)).mp. (25492)
67 (("10q22.3q23.3" or "11q22.2q22.3" or "12q14" or "13q12.3" or "14q11.2" or "14q24.1q24.3" or "15q11.2" or "15q13.3" or 15q14 or 15q24 or "16p11.2p12.2" or "16p11.2-p12.2 or 16p13.11" or "16p13.2" or "16q24.3" or 17q11 or 17q12 or "17q21.31" or "17q21.31" or "17q24.2" or "19p13.13" or "19q13.11" or "1p21.3" or 1p36 or "1q21.1" or 1q41q42 or 1q44 or 20p13 or "20q13.33" or "21q22.11q22.12" or "2p15-16.1" or "2p15p16.1" or 2p21 or "2q23.1" or 2q24 or "2q31.1" or 2q32q33 or 2q37 or "3q27.3" or 3q29 or 4q21 or "5q14.3" or 6p22 or 6q25 or "8p23.1" or "8q21.11" or "8q24.3" or "9q31.1q31.3" or "9q33.3q34.11" or 14q12 or xq21 or xp21 or "distal 16p11.2" or "distal 22q11.2" or "distal 7q11.23" or "nf1" or "paternal 20q13.2q13.3" or "proximal 16p11.2") adj2 (microdeletion syndrome? or micro-deletion syndrome?)).mp. (386)
68 (("10q22.3q23.3" or "11p15.4" or 15q11q13 or "16p11.2p12.2" or "16p13.11" or "17p11.2" or "17q11.2" or 17q12 or "17q21.31" or "19p13.3" or "1q21.1" or "20q11.2" or 3q29 or 5q35 or "7q11.23" or xq25 or "22q11.2" or "distal xq28" or "proximal 16p11.2" or "xp11.22p11.23") adj2 (microduplication syndrome? or micro-duplication syndrome?)).mp. (122)
69 ((22q11 or "22q11.2" or "7q11.23" or "8p23.1" or 15q11-q13 or "16p13.3" or 17q12 or "1q21.1" or "22q11.2" or 3q29 or 5p13 or "xp11.23-p11.22" or "xq27.3-q28" or "xp22.13p22.2" or "xq12-q13.3" or xq25 or "xq27.3q28" or "proximal xq28") adj2 duplication syndrome?).mp. (137)
70 (("22q11.2" or 22q13 or "2q33.1" or 6q or "8p inverted" or "8p11.2" or "8p23.1" or "9q subtelomeric" or 10q26 or 11p13 or 13q14 or 13q33-q34 or 14q11-q22 or "15q11.2" or 15q14 or 15q26-qter or "16p12.2-p11.2" or "16p13.2" or "16p13.3" or "17q11.2" or 17q12 or "17q23.1-q23.2" or 18p or 18q or "19p13.13" or "19q13.11" or 1p35 or 1p36 or "1q21.1" or 1q41-q42 or 20q11-q12 or "2p16.1-p15" or 2q37 or 3q29 or 5q12 or 6pter-p24 or 6q25-q25 or "8q21.11" or "9p" or "xp11.3" or xp21 or xq21) adj2 deletion syndrome?).mp. (2392)
71 (("3c" or 3mc or "47,xyy" or "48,xxxy" or "48,xxyy" or "48,xyyy" or "49,xxxxy" or "49,xxxyy" or "49,xyyyy") adj2 syndrome?).mp. (410)
72 ("3-methylglutaconic aciduria" adj2 (type 3 or type 4 or type 7 or type 9 or type v or type ix)).mp. (17)
73 (2q37 adj (monosom* or mono-som*)).mp. (0)
74 ("3-methylglutaconic aciduria" adj3 (cataract? or neurologic* or neutropenia? or deafness or encephalopath* or "leigh-like")).mp. (55)
75 ("3-hydroxy-3-methylglutaric aciduria?" or ("3-methylcrotonyl-coa carboxylase" adj2 deficienc*) or "3-phosphoserine phosphatase deficienc*" or "45,x/46,xy mixed gonadal dysgenesis" or "6-pyruvoyl-tetrahydropterin synthase deficienc*").mp. (253)
76 (abetal or adenylosuccinase deficienc* or adenylosuccinate lyase deficienc* or aicar transformylase deficienc* or imp cyclohydrolase deficienc* or "alg11-cdg" or "alg12-cdg" or "alg1-cdg" or "alg2-cdg" or "alg9-cdg" or alobar holoprosencephal* or "alternating hemipl?egia of childhood" or anauxetic dysplasia* or arachnoid cyst? or argininemia? or argininosuccinic aciduria? or arthrogrypos#s or athyreos#s or aspartylglucosaminuria? or aspartyl-glucosaminuria? or aspartyl-gluco-saminuria? or aspartylgluco-saminuria? or atypical juvenile parkinson* or band heterotopia? or bifid nose? or (bilateral adj3 (polymicrogyria? or poly-microgyria? or poly-microgyria? or polymicro-gyria?)) or congenital bile acid synthesis defect* or biotinidase deficienc* or
"body mass index quantitative trait locus 19" or bmiq19 or (brachydactyly adj3 ("type a1" or cerebellar ataxia or retinitis pigmentosa))).mp. (10455)
77 (acrodysostos#s or ((acrofacial or acro-facial* or acrofronto* or acromelic frontonasal or acromelic fronto-nasal or acropectorovertebral or acro-pectorovertebral or acro-pectoro-vertebral or acropectoro-vertebral) adj3 dysostos#s) or acrogeria?).mp. (458)
78 ((acquired partial or congenital) adj3 (lipodystroph* or lipodystroph*)).mp. (710)
79 ((adenylosuccin* or aicar transformylase or imp cyclohydrolase) adj2 deficienc*).mp. (125)
80 (agenes#s adj5 (cerebral white matter? or corpus callosum* or cerebell* malformation? or (hydrocephal* adj1 cerebell*))).mp. (3732)
81 (alobar holoprosencephal* or alobar holopros-encephal* or alobar holo-pros-encephal* or alobar holo-prosencephal*).mp. (210)
82 ((alopecia* adj3 neurologic* defect* adj3 endocrinopath*) or "amyloidosis of gingiva and conjunctiva" or amyotrophic dystonic paraplegia? or amyotrophic dystonic para-plegia? or anauxetic dysplasia* or (anophthalmia adj2 microphthalmia adj2 esophageal adj3 atresia?) or ((aphalangia adj1 partial) and syndactyly and (metatarsaliv or metatarsal iv)) or argininosuccinic aciduria?).mp. (346)
83 (alpha adj3 ((dystroglycan adj4 muscular dystoph*) or mannosidos#s or methylacetoacetic aciduria? or methyl-acetoacetic aciduria? or acetylgalactosaminidase deficienc* or acetylgalactosaminidase deficienc* or acetyl-galacto-saminidase deficienc* or acetylgalactosaminidase deficienc* or (congenital adj2 muscular dystroph*))).mp. (460)

84 ((ataxia adj2 deaf* adj2 optic atroph*) or (ataxia adj1 deaf* adj2 cardiomyopath*) or (ataxia adj2 posterior column adj2 retinitis pigmentosa)).mp. (27)
85 athyreos#s.mp. (157)
86 (((autism or autistic) adj5 auts2 deficienc*) or ((autism or autistic) adj2 (arthrogryposis adj1 epilep*))).mp. (0)
87 (axenfeld-rieger and partially absent eye muscle? and distinctive face? and hydrocephal* and skeletal abnormalit*).mp. (2)
88 (autosomal dominant adj3 (alzheimer* or cerebellar ataxia or charcot-marie-tooth or deafness or onychodystroph* or frontal lobe epileps* or robinow or (hnf1b adj5 kidney?) or primary microcephal* or striatal degeneration?)).mp. (1463)
89 (autosomal recessive adj3 ((ataxia adj3 pex10 deficienc*) or (ataxia adj3 ubiquinone deficienc*) or (ataxia adj2 beauce) or (axonal neuropath* adj2 neuromyotonia?) or (axonal neuropath* adj2 neuro-myotonia?) or centronuclear myopath* or centro-nuclear myopath* or cerebellar ataxia or cerebelloparenchymal or cerebello-parenchymal or chorioretinopathymicrocephal* or (spastic paraplegia and kennedy) or ("cutis laxa" and "type 1") or ("cutis laxa" and "type 2") or ("cutis laxa" and "type 2a") or ("cutis laxa" and "type iia") or ("cutis laxa" and "type iiia") or ("cutis laxa" and "type iiib") or distal osteolys#s or dopa-responsive dystonia? or faciodigitogenital or facio-digitogenital or facio-digito-genital or (hydrocephalus adj1 nonsyndromic) or (hydrocephalus adj1 non-syndromic) or hyperinsulinism or hypomyelinating leukodystroph* or hypo-myelinating leukodystroph* or (ichthyos#s adj1 congenital) or (macrocephal* adj1 megalencephal*) or (microcephal* adj2 chorioretinopath*) or (muscular dsytroph* adj5 "18") or (muscular dsytroph* adj5 "27") or omodysplasia* or osteopetros#s or periventricular heterotopia? with microcephal* or peri-ventricular heterotopia? with microcephal* or (primary adj3 microcephal*) or robinow or (neutropenia? adj2 severe congenital) or spastic ataxia or spastic paraplegia type or spondylocostal dysostos#s)).mp. (1725)
90 (beta adj3 (ketothiolase deficienc* or mannosidos#s or mercaptolactate cysteine disulfiduria? or protein-associated neurodegeneration? or protein-associated neuro-degeneration? or ureidopropionase deficienc* or (cystathionine and synthase deficienc*))).mp. (628)
91 (band adj3 (heterotopia? or hetero-topia? or (calcification adj3 gyration* adj3 (polymicrogyria? or poly-microgyria? or poly-micro-gyria? or polymicro-gyria?)))).mp. (420)
92 (basal ganglia calcification* and idiopathic and (childhood adj3 onset)).mp. (7)
93 (blepharophimos#s and ptos#s and syndactyly and short stature).mp. (1)
94 ("brain small vessel disease 1" or (branched-chain adj3 ketoacid dehydrogenase kinase deficienc*) or BCKDK deficienc* or (bullous dystroph* adj3 hereditary macular type) or "c syndrome").mp. (79)
95 (((camptodactyly adj3 tall stature) and hearing loss*) or (camptodactyly adj3 fibrous tissue hyperplasia? adj3 skeletal dysplasia*) or carbamoyl phosphate synthetase i deficienc* or CPS1 deficienc* or carnosinase deficienc* or carnosin?emia? or cephalin lipidos#s).mp. (101)
96 (cerebellar ataxia adj3 (brain abnormalit* or mitochondrial myopath* or motor neuropath* or rnu12 mutation?)).mp. (7)
97 ((cerebral pals adj2 "spastic quadriplegic 2") or cerebral visual impairment? or cerebrotendinous xanthomatos* or ceroid lipofuscinos* or childhood absence epilep* or chondrodysplasia* punctata 2 or chondro-dysplasia* punctata 2 or ((chondrodysplasia* or chondro-dysplasia*) and platyspondyly and distinctive brachydactyly and hydrocephal* and (microphthalmia? or micro-phthalmia?))).mp. (4950)
98 (chronic bilirubin encephalopath* or ((citrullin?emia adj1 (classic congenital adrenal hyperplasia* adj3 hydroxylase deficienc*)) or (classic or "type i")) or "ck syndrome?" or (classic adj3 (galactos?emia? or homocystinuria? or homo-cystinuria? or phenylketonuria?)) or ("classic glucose transporter" adj1 type 1 deficienc*)).mp. (298748)
99 ((cleft lip? or cleft palate?) adj3 ((abnormal thumb* adj1 microcephal*) or (abnormal thumb* adj1 micro-cephal*) or ectodermal dysplasia* or ecto-dermal dysplasia* or (cardiac defect* adj2 genital anomal* adj2 ectrodactyly) or (short stature adj2 vertebral anomal*))).mp. (204)
100 ((cleft palate? adj1 isolated) or (cntnap2-related adj3 (developmental or epileptic) adj encephalopath*) or coenzyme q10 deficienc* or co-enzyme q10 deficienc*).mp. (964)
101 ("cog1-cdg" or "cog2-cdg" or "cog5-cdg" or "cog8-cdg").mp. (14)
102 (combined adj (immunodeficienc* adj3 (megaloblastic an?emia? or megalo-blastic an?emia? or facioocculoskeletal anomal* or facio-oculoskeletal anomal* or facio-oculo-skeletal anomal* or facioocculo-skeletal anomal*))).mp. (4)
103 ((combined oxidative phosphorylation defect adj2 ("type 23" or "type 27")) or (combined oxidative phosphorylation adj3 (deficiency 18 or deficiency 24 or deficiency 35 or deficiency 36))).mp. (7)
104 (coenzyme q10 deficienc* or co-enzyme q10 deficienc* or "cone-rod dystrophy 1").mp. (280)

105 (congenital adj ((cataract? adj2 facial dysmorphism adj2 neuropath*) or (cataract? adj2 facial dysmorphism adj2 neuro-path*) or "disorder of glycosylation" or (hemidysplasia* adj2 ichthyosiform erythroderma adj2 limb defect?) or (hemi-dysplasia* adj2 ichthyosiform erythroderma adj2 limb defect?) or hydrocephalus or hydro-cephalus or hypothyroidism or hypothyroidism or (muscular dystroph* adj2 cerebellar involvement) or (muscular dystroph* adj2 fukuyama) or (progressive bone marrow failure adj3 skeletal dysplasia*))).mp. (8208)
106 (cono-spondylar dysplasia* or (cortical dysgenes#s adj3 pontocerebellar hypoplasia? adj3 tubb3 mutation?) or (cortical dysplasia* adj3 brain malformation*)).mp. (17)
107 (((craniodiaphyseal or cranio-diaphyseal or (craniofacial dyssynostos* adj1 short stature) or (cranio-facial dyssynostos* adj1 short stature) or craniofrontonasal or cranio-frontonasal) adj dysplasia*) or craniopharyngioma* or cranio-pharyngioma*).mp. (7031)
108 (craniosynostos#s adj3 ((anal anomal* adj2 porokeratos#s) or (dandy-walker malformation? adj2 hydrocephalus) or (hydrocephalus adj2 arnold-chiari malformation* adj2 radioulnar synostos*))).mp. (9)
109 ((cutaneous mastocytos* and conductive hearing loss and microtia?) or cystathioninuria? or cystinos* or cysteine peptiduria? or "d-2-hydroxyglutaric aciduria 1" or (delayed speech and facial asymmetr* and strabismus and ear lobe creases) or "desbuquois dysplasia 1" or "desbuquois dysplasia 2" or desmosterolos*).mp. (1976)
110 ("deafness and myopia" or (deaf* adj1 conductive adj3 (malform* adj2 external ear)) or (deaf* adj1 congenital* adj3 total albinism) or (deaf* adj3 dystonia? adj3 cerebral hypomyelination*) or (deaf* adj1 sensorineural* adj3 pituitary dwarfism) or (deaf* adj3 enamel hypoplasia adj3 nail defect*) or (deaf* adj3 epiphyseal dysplasia* adj3 short stature) or (deaf* adj3 genital anomal* adj3 metacarpal adj3 metatarsal adj3 synostos*)).mp. (29)
111 (dermatoleukodystroph* or dermato-leukodystroph* or dermato-leuko-dystroph* or dermatoleuko-dystroph*).mp. (1)
112 (developmental* adj3 delay* adj5 (sox5 deficienc* or med13l deficienc*)).mp. (0)
113 (((dextrocardia* or dextro-cardia*) adj3 unusual facies) and (microphthalmia* or microphthalmia*)).mp. (0)
114 ((diabetes insipidus adj1 nephrogenic adj2 "2") or "diamond-blackfan an?emia 1" or ((dglyceric or dibasic amino or dicarboxylicamino or di-carboxylicamino) adj aciduria?) or ((dihydropteridine reductase or di-hydropteridine reductase or dihydropyrimidine dehydrogenase or di-hydropyrimidine de-hydrogenase) adj3 deficienc*) or dihydropyrimidinuria? or dihydropyrimidinuria?).mp. (599)
115 ((distal monosomy adj (10p or 10q or 12q or "19p13.3" or 1q or 6p or 7q36 or 9p)) or ((distal trisomy adj 15q) or 17q or 5q)).mp. (5762)
116 ("dk1-cdg" or double outlet right ventricle* or "dpagt1-cdg" or "dpm3-cdg" or ((duchenne or becker) adj muscular dystroph*) or (dysmyelination adj1 jaundice) or dysosteoscleros* or dysspondyloenchondromatos* or "dystonia 16" or "dystonia 30" or (dystonia adj1 juvenile onset) or (dystonia adj3 dopa-responsive adj3 sepiapterin reductase deficienc*) or (dystonia adj3 parkinsonism adj3 (hypermanganes?emia? or hyper-manganes?emia?))).mp. (15730)
117 ((duplication adj2 pituitary gland?) or ((dwarfism adj1 (low-birth-weight or LBW)) and (unresponsive* adj3 growth hormone?))).mp. (12)
118 ((early infantile or early childhood) adj3 epileptic encephalopath*).mp. (454)
119 (early onset adj (progressive diffuse brain atrophy-microcephaly-muscle weakness-optic atroph* or progressive encephalopathy-spastic ataxia-distal spinal muscular atroph* or seizuresdistal limb anomal*-facial dysmorphism-global developmental* delay# or spastic ataxia-myoclonic epilepsy-neuropath* or x-linked optic atroph*)).mp. (0)
120 (ectodermal dysplasia* adj1 ectrodactyly adj3 (cleft lip palate syndrome 1 or cleft lip palate syndrome 3)).mp. (9)
121 (((encephalocraniocutaneous or encephalo-craniocutaneous or encephalo-craniocutaneous or encephalocranio-cutaneous) adj1 lipomatos*) or (encephalomalacia? adj1 multilocular)).mp. (183)
122 ((encephalopath* adj3 (ethylmalonic* or sul#?ite oxidase deficienc*)) or ((encephalopath* and (progressive and early-onset and brain atroph* and thin corpus callosum)) or (progressive and amyotrophy and optic atroph*) or (neonatal and severe and mecp2 mutation*) or (intracranial calcification* and growth hormone deficienc* and microcephal* and retinal degeneration*) or (acute and infection-induced and herpes-specific)) or enlarged parietal foramina).mp. (211)
123 ((epileptic encephalopath* adj3 (nonspecific or non-specific) adj3 early-onset) or (epileptic encephalopath* adj3 rnf13-related adj3 early-onset) or (epilep* encephalopath* adj3 undetermined early-onset) or (epilep* adj1 idiopathic adj3 ("susceptibility to 12" or "susceptibility to 18")) or (epilep* adj3 juvenile myoclonic) or (epilep* adj3 myoclonic adj3 infanc*) or (epilep* adj3 myoclonic adj3 astatic) or (epilep* adj3 myoclonic adj3 atonic) or (epilep* adj1 nocturnal adj2 frontal lobe adj ("type 1" or "1" or "type 5" or "5")) or (epilep* adj1 progressive myoclonic adj2 ("1" or "1a" or "3" or "8" or "11")) or (polyhydramnios adj3 megalencephal* adj3 symptomatic epilep*) or

(epilep* adj1 pyridoxine-dependent) or (epilep* adj1 rolandic) or (epilep* adj1 telangiectasia?) or ((early or infantile) adj epilep* encephalopath*) or (kcnq2-related adj1 epilep* encephalopath*)).mp. (3820)
124 (((ermine phenotype? or (erythrokeratodermia* or erythro-keratodermia*)) adj1 variabilis) or ethylmalonic encephalopath* or (extrasystoles and multiform ventricular and short stature* and (hyperpigment* or hyper-pigment*) and microcephal*)).mp. (289)
125 (facial dysmorphism and developmental* delay* and behavio?r* abnormalit* and ("10p11.21p12.31 microdeletion*" or wac point mutation*)).mp. (0)
126 ((facial dysmorphism and macrocephaly and myopia and dandy-walker malformation*) or (facial dysmorphism and shawl scrotum and joint laxit*)).mp. (1)
127 ((facioscapulohumeral or facio-scapulohumeral or facio-scapulo-humeral or facioscapulohumeral) adj2 (muscular dystrophy adj2 "1")).mp. (75)
128 (familial adj3 (acute necroti#ing encephalopath* or (adenomatous polypos* adj3 "5q22.2 microdeletion") or congenital mirror movement* or (exudative adj (vitreoretinopath* or vitreoretinopath*)) or (focal epileps* adj2 variable foci) or glucocorticoid deficienc* or infantile bilateral striatal necros* or infantile myoclonic epileps* or lambdoid synostos* or multiple nevi flammei or sporadic hemipl?egic migrain* or sporadic hemi-pl?egic migrain* or paroxysmal ataxia* or (primary hypomagnes?emia adj2 normocalciuria* adj2 normocalc?emia*) or (primary hypo-magnes?emia adj2 normo-calciuria* adj2 normo-calc?emia*) or (scaphocephaly syndrome adj1 mcgillivray type) or thyroid dyshormonogenes*)).mp. (875)
129 (familial adj3 ((hyperinsulin?emi* or hyper-insulin?emi*) adj1 (hypoglyc?emi* or hypoglyc?emi*)) adj2 ("1" or "3" or "4" or "6")).mp. (23)
130 (fanconi an?emi* or farber lipogranulomatos* or (fatal infantile lactic acidos* adj2 methylmalonic aciduria*) or fatty acyl-coa reductase 1 deficienc* or (fbln1-related developmental* delay* and central nervous system anomal* and syndactyly*) or "fg syndrome 4" or ("fg syndrome" adj2 "type 1") or (fibrodysplasia ossificans adj2 progressiv*) or (congenital fibros* adj2 extraocular muscle*) or fibular hemimelia* or fibular hemi-melia*).mp. (7619)
131 (focal adj2 ((cortical dysplasia* adj2 taylor*) or dermal hypoplasia* or dermal hypo-plasia* or (segmental glomeruloscleros* adj2 neurodevelopmental syndrome?) or (segmental glomeruloscleros* adj2 neuro-developmental syndrome?))).mp. (721)
132 ((folate malabsorption adj1 hereditary) or ((formiminoglutamic or formimino-glutamic) adj1 aciduria) or (foxg1 syndrome adj3 14q12 microdeletion) or ((frontometaphyseal or frontometaphyseal) adj1 dysplasia*) or ((frontonasal or fronto-nasal) adj1 dysplasia*) or (fructose intolerance adj1 hereditary) or fryns macrocephal* or fucosidos* or (gaze palsy adj3 (familial or horizontal) adj2 progressive scolios*) or HGPPS or (generali#ed epileps* adj3 febrile seizure? adj3 type 10) or (geroderma adj osteodysplastic*) or giant axonal neuropath* or glutathione synthetase or glutathionuria or glycine encephalopath*).mp. (2416)
133 ((formiminotransferase or formimino-transferase or "fructose-1,6-bisphosphatase" or fumarase or galactokinase or galactose epimerase or glutamate-cysteine ligase or glutathione synthetase or glycerol kinase or (glycogen storage disease adj3 liver phosphorylase kinase) or guanidinoacetate methyltransferase or ((homocystinuria adj3 cystathionine beta-synthase) or (homocystinuria adj3 methylene tetrahydrofolate reductase)) or hypoxanthine guanine phosphoribosyltransferase) adj3 deficienc*).mp. (1039)
134 (glycogen storage disease adj3 (acid maltase deficienc* or aldolase a deficienc* or glycogen debranching enzyme deficienc* or lamp-2 deficienc* or liver phosphorylase kinase deficienc* or phosphoglycerate kinase 1 deficienc* or xii)).mp. (38)
135 (glycosylphosphatidylinositol biosynthes#s adj2 ("defect 11" or "defect 15" or "defect 16")).mp. (2)
136 ((gm1 gangliosidos* adj2 ("type 1" or "type i" or "type 3" or "type iii")) or (gmppb-related adj2 limb-girdle muscular dystroph* r19) or (gonadal dysgenes* adj2 xy type)).mp. (93)
137 (growth delay* adj3 (insulin-like growth factor i resistance or insulin-like growth factor type 1 deficienc*)).mp. (0)
138 (growth retardation and deafness and femoral epiphyseal dysplasia* and (lacrimal duct? adj2 obstruct*)).mp. (0)
139 ("h syndrome" or (((hemifacial or hemi-facial) adj2 (microsomia or micro-somia)) or ((hemihyperplasia* or hemi-hyperplasia*) adj1 isolated) or hemimegalencephal* or hemimegalencephal* or (hemolytic an?emia adj3 (nonspherocytic or non-spherocytic) adj3 (glucose phosphate adj (isomerasedeficienc* or isomerase-deficienc*))))).mp. (1867)
140 (hereditary adj ((bullous dystrophy adj1 macular type) or (cryohydrocytos adj2 reduced stomatin) or hyperekplexia? or hyper-ekplexia? or methemoglobin?emia? or methemoglobin?emia? or (sensory adj3 autonomic adj3 neuropath* adj3 tecpr2 mutation?) or (sensory adj3 autonomic adj3 neuropath* adj3 ("type 4" or "type 5")))).mp. (153)

141 ((hermansky-pudlak adj2 "syndrome 2") or (hidrotic ectodermal dysplasia* adj2 halal) or histidin?emia or (histidinuria adj4 renal tubular defect*)).mp. (236)
142 (holoprosencephal* adj ("1" or ("13" adj1 x-linked) or "2" or "3" or "5" or (recurrent infection* adj3 monocytos*))).mp. (28)
143 (homocarnosinos* or homo-carnosinos* or ((homocystinuria* or homo-cystinuria*) adj3 megaloblastic an?emia adj3 cbl e type) or ((homocystinuria* or homo-cystinuria*) adj3 megaloblastic an?emia adj3 cblg complementation type)).mp. (18)
144 ((hydrocephal* adj3 stenos* adj3 "aqueduct of sylvius") or (hydrocephal* adj1 congenital* adj2 "2") or (hydrocephal* adj3 skeletal anomal* adj3 mental disturbance*) or hydroxykynureninuria* or hydroxy-kynureninuria* or hydroxylysinuria* or hydro-xylysinuria* or hydroxyprolin?emia* or hydroxy-prolin?emia* or (hypercalc?emia* adj1 infantile adj2 "1") or (hypercalc?emia? adj1 infantile adj2 "1")).mp. (89)
145 (((hypercalc?emia or hyper-calc?emia) adj2 "infantile 1") or hyperphenylalanin?emia or hyper-phenylalanin?emia or ((hyperthyroidism or hyper-thyroidism) adj2 (nonautoimmune or nonautoimmune))).mp. (1600)
146 (((hyperinsulinism or hyper-insulinism) adj3 (hnf1a or hnf4a) adj deficienc*) or (hyperleucine adj1 isoleucin?emia?) or hyperlysin?emia? or hyper-lysin?emia? or (hyperlysinuria? adj2 hyperammon?emia?) or (hypermanganese?mia? adj2 "dystonia 2") or (hyper-manganese?mia? adj2 "dystonia 2") or (hypermethionin?emia? adj3 s-adenosylhomocysteine hydrolase deficienc*) or (hyper-methionin?emia? adj3 s-adenosylhomocysteine hydrolase deficienc*) or hyperphenylalanin?emia? or hyper-phenylalanin?emia? or (hyperprolin?emia? adj1 ("type 1" or "type 2" or "type i" or "type ii")) or (hyper-prolin?emia? adj1 ("type 1" or "type 2" or "type i" or "type ii")) or hypertrichos* cubiti or hyper-trichos* cubiti or (hypertelorism adj3 "tetralogy of fallot") or (hyper-telorism adj3 "tetralogy of fallot") or (hypertrichotic adj2 osteochondrodysplasia*) or (hyper-trichotic adj2 osteo-chondrodysplasia*) or (hyper-trichotic adj2 osteo-chondro-dysplasia*) or hypertryptophan?emia* or hyper-tryptophan?emia*).mp. (1745)
147 (((hyperuric?emia or hyper-uric?emia) adj1 infantile adj3 abnormal behavio?r* adj3 normal hypoxanthineguanine phosphoribosyltransferase) or hypochondroplasia* or hypo-chondroplasia* or ((hypoglyc?emi* or hypo-glyc?emi*) adj2 infan* adj3 leucine-sensitive) or ((hypogonadotropic hypogonadism or hypo-gonadotropic hypo-gonadism) adj ("2" or "10")) or ((hypomagnes?emia 4 or hypo-magnes?emia 4) adj2 renal) or ((hypomelanos* or hypo-melanos*) adj2 ito)).mp. (639)
148 (((hypomyelination or hypo-myelination) adj3 (brainstem? or brain stem?) adj3 spinal cord?) and (leg? adj1 spastic*)).mp. (11)
149 (hypothyroidism adj3 deficient transcription factor? adj3 pituitary adj (development or function)).mp. (0)
150 (((ichthyosiform erythroderma adj3 cornea*) and deaf*) or (ichthyos* adj2 male hypogonadism) or ((ichthyos* adj3 split hair?) and amino aciduria)).mp. (3)
151 (iminoglycinuria* or "immunodeficiency 23" or "immunodeficiency 47" or "immunodeficiency 49").mp. (52)
152 (immunodeficienc* adj3 (purine nucleoside phosphorylase deficienc* or (developmental* delay* adj3 (hypohomocystein?emi* or hypo-homocystein?emi*)) or (centromeric instabilit* adj3 facial anomal*))).mp. (121)
153 ((immunoskeletal dysplasia* adj2 (neurodevelopmental abnormalit* or neuro-developmental abnormalit*)) or (inclusion body myopath* adj3 paget disease adj3 bone adj3 frontotemporal dementia*) or incontinentia pigment* or (infantile adj3 cerebellar adj3 retinal degenerat*) or (insensitivit* adj2 pain adj3 congenital adj3 anhidros*)).mp. (1666)
154 (epilep* adj3 ((early-onset adj2 vitamin b6-dependent) or (early-onset adj2 encephalopath*) or (familial focal adj2 variable foci) or familial infantile myoclonic* or familial temporal lobe? or speech disorder? or (idiopathic adj1 generali#ed) or juvenile myoclonic or (kcnq2 adj3 encephalopath*) or (macrocephal* adj3 encephalopath*) or (muscular atroph* adj3 progressive myoclonic) or (myoclonic adj3 infancy) or myoclonic-astatic or myoclonic-atonic or nocturnal frontal lobe? or paroxysmal dyskinesia? or "progressive myoclonic 1a" or "progressive myoclonic 3" or "progressive myoclonic 11" or "progressive myoclonic 8" or (microcephal* adj2 dysplasia*) or (polyhydramnios adj2 megalencephal*) or (poly-hydramnios adj2 megalencephal*) or (progressive myoclonic adj2 "type 1") or (progressive myoclonic adj2 "type 3") or pyridoxine-dependent or rolandic or (skeletal dysplasia* adj2 short stature*) or (syngap* adj5 encephalopath*) or telangiectasia? or (infantile adj2 encephalopath*) or (early childhood adj2 encephalopath*))).mp. (6148)
155 ("l1 syndrome*" or "l-2-hydroxyglutaric aciduria" or "lactic aciduria adj3 d-lactic acid").mp. (248)
156 (isolated adj3 (brachycephal* or focal cortical dysplasia* or glycerol kinase deficienc* or hemihyperplasia* or hemi-hyperplasia* or (lissencephal* adj1 type 1) or oxycephal* or permanent neonatal diabetes or plagiocephal* or spina bifida)).mp. (158)

157 ((laryngeal abductor? adj3 paralys*) or lathosterolos* or lead poisoning).mp. (13441)
158 (leber adj2 (congenital amauros* or (optic atroph* adj3 dystonia*))).mp. (1353)
159 ((lentiginos* adj2 centrofacial neurodysraphic) or (lentiginos* adj2 centro-facial neurodysraphic) or (lentiginos* adj2 centro-facial neuro-dysraphic) or (lentiginos* adj2 centrofacial neuro-dysraphic) or (lenz-majewski adj2 hyperostotic dwarfism) or (lenz-majewski adj2 hyperostotic dwarfism) or leprechaunism).mp. (266)
160 (leukocyte? adj1 adhesion deficienc*).mp. (795)
161 (leukodystroph* adj1 hypomyelinating adj2 ("11" or "12" or "14" or "16" or "17" or "22" or "4" or "5" or "9")).mp. (28)
162 (leukodystroph* adj1 hypomyelinating adj2 (rars-related adj2 autosomal recessive)).mp. (0)
163 (leukodystroph* adj1 hypomyelinating adj2 (vps11-related adj2 autosomal recessive)).mp. (0)
164 (leukodystroph* adj3 (acquired microcephal* or early childhood)).mp. (5)
165 (leukodystroph* adj3 ((bilateral adj2 multicystic) or (bi-lateral adj2 multi-cystic)) adj3 muscle? adj3 eye? adj3 brain?).mp. (0)
166 (leukodystroph* adj3 nkx6-2-related adj3 autosomal recessive adj3 (hypomyelinat* or hypomyelinat*)).mp. (0)
167 ((leukoencephalopath* or leuko-encephalopath*) adj3 (anterior temporal lobe cyst* or ((brainstem? or brain stem?) adj2 spinal cord? adj2 high lactate) or metaphyseal chondrodysplasia? or meta-physeal chondrodysplasia* or spondyloepimetaphyseal dysplasia* or spondylo-epi-metaphyseal dysplasia* or spondylometaphyseal dysplasia*or spondylo-meta-physeal dysplasia*)).mp. (6)
168 ((leukoencephalopath* or leuko-encephalopath*) adj3 (nonprogressive or non-progressive) adj predominantly posterior cavitating adj3 peripheral adj (neuropath* or neuro-path*)).mp. (0)
169 (((leukoencephalopath* or leuko-encephalopath*) adj3 progressive) and pycr2-related and microcephal*).mp. (0)
170 (lissencephal* adj2 ("1" or "3" or "4" or "5" or "8" or "10")).mp. (165)
171 (lissencephal* adj3 (lis1 mutation* or norman-roberts)).mp. (8)
172 (listerios* or (lobar adj2 holoprosencephal*) or (long chain 3-hydroxyacyl-coa dehydrogenase adj3 deficienc*) or (lysinuric protein adj3 intoleran*)).mp. (10317)
173 ((macrocephal* or macro-cephal*) adj3 (autis* or epilep* encephalopath* or developmental* delay* or spastic parapl?egia-dysmorphism or spastic para-pl?egia-dysmorphism)).mp. (274)
174 ((macrothrombocytop?enia* or macro-thrombocytop?enia*) and lymphed?ema* and developmental* delay* and facial dysmorphism and camptodactyly).mp. (0)
175 ((malonyl adj2 coa decarboxylase deficienc*) or "man1b1-cdg" or (mannosidos* adj2 beta a adj2 lysosomal)).mp. (42)
176 (maternal* adj3 (phenylketonuria* or phenyl-ketonuria* or ((uniparental or uni-parental) adj disomy adj2 chromosome 4) or ((uniparental or uni-parental) adj disomy adj2 chromosome 6) or ((uniparental or uni-parental) adj disomy adj2 chromosome x))).mp. (376)
177 megalencephal*.mp. (1189)
178 ((mercaptolactate adj2 cysteine disulfiduria*) or MCDU or ((mesangial scleros* adj2 diffuse renal) and ocular abnormalit*) or (mesoaxial hexadactyly and cardiac malformation*) or (mesoaxial hexadactyly and cardiac malformation*) or (mesomelic dysplasia* adj2 (nievergelt or savarirayan)) or (metabolic encephalomyopath* and rhabdomyolys* and cardiac arrhythmia* and (neurodegenerat* or neuro-degenerat*)) or ((metachromatic or meta-chromatic) adj2 leukodystroph*) or ((metaphyseal or meta-physeal) adj2 acroscyphodysplasia*) or (methemoglobinemia and (deficienc* adj3 methemoglobin reductase)) or (methionine adenosyltransferase adj ("i" or "iii") adj3 deficienc*) or (methylcobalamin deficienc* adj2 cble)).mp. (1883)
179 (methylmalonic* acidemia* adj3 ((homocystein?emia* adj2 cblx) or homocystinuria* or homo-cystinuria*)).mp. (102)
180 (methylmalonic aciduria* adj3 ((homocystinuria* adj2 cblc) or (homo-cystinuria* adj2 cblc) or (homocystinuria* adj2 cbld) or (homo-cystinuria* adj2 cbld))).mp. (48)
181 (mevalonic aciduria* or "mgat2-cdg" or ((microbrachycephal* or micro-brachycephal*) adj3 ptosis adj3 cleft lip?)).mp. (128)
182 ((microcephal* or micro-cephal*) adj3 ((brachydactyly adj2 kyphoscolios*) or cardiomyopath* or (cerebellar hypoplasia* adj3 cardiac conduction defect*) or cervical spine fusion anomal* or (cleft palate adj3 abnormal retinal pigment*) or (congenital cataract* adj3 psoriasiform dermatitis) or (cortical malformation* adj3 short stature adj3 rttn deficienc*) or (developmental* delay* adj3 brittle hair) or (developmental* delay* adj3 seizure*) or (epilep* adj3 diabet*) or ((mandibulofacial or mandibulo-facial) adj2 dysostos*) or (seizure* adj3 spasticit* adj3 brain calcification*) or (short stature adj3 impaired glucose metabolism) or (short stature adj3 limb abnormalit*) or (short stature adj3 polymicrogyria*))).mp. (216)
183 ((microcephal* or micro-cephal*) adj3 (dwarfism adj1 (alazami or dauber or montreal or

osteodysplastic or osteo-dysplastic or rttn deficienc* or toriello))).mp. (7)
184 ((microcephal* or micro-cephal*) and (glomerulonephritis or glomerulo-nephritis) and marfanoid habitus).mp. (1)
185 (((microcephal* or micro-cephal*) adj3 ((microcornea* or micro-cornea*) adj2 seemanova)) or lymphed?ema-adj2 chorioretinopath*).mp. (0)
186 (microform holoprosencephal* or microhydranencephal* or micro-hydranencephal* or microlissencephal* or micro-lissencephal*).mp. (68)
187 ((microphthalmia* or micro-phthalmia*) adj3 (limb anomal* or linear skin defect* or "coloboma 9" or (coloboma adj3 skeletal dysplasia*) or lenz or syndromic)).mp. (207)
188 (((microtriplication or micro-triplication) adj1 "11q24.1") or ((midface hypoplasia* or mid-face hypoplasia? or mid-face hypo-plasia*) and (hearing adj1 impair*) and elliptocytos* and nephrocalcinos*) or ((midline interhemispheric variant? or mid-line interhemispheric variant? or midline inter-hemispheric variant? or mid-line inter-hemispheric variant?) adj3 (holoprosencephal* or holo-prosencephal*)) or (migraine adj1 familial adj2 (hemipl?egic or hemi-pl?egic) adj2 "2") or (mirror movement? adj2 "1")).mp. (38)
189 (mitochondrial complex adj2 ("i" or "iii" or "iv" or "v") adj deficienc* adj3 (nuclear type adj2 ("1" or "3" or "4" or "8" or "16" or "17"))).mp. (4)
190 (mitochondrial adj3 (progressive external ophthalmopl?egia* or (myopathy adj3 sideroblastic an?emi*) or (neurogastrointestinal adj3 encephalomyopath*) or (neuro-gastrointestinal adj3 encephalomyopath*))).mp. (354)
191 ((molybdenum cofactor deficienc* adj2 complementation group a) or (molybdenum cofactor deficienc* adj2 complementation group a) or monilethrix or (monocarboxylate transporter 1 adj3 deficienc*) or (mono-carboxylate transporter 1 adj3 deficienc*) or mucopolysaccharidos* or mulibrey nanism or multiple sulfatase deficienc* or ((multicentric or multi-centric) and osteolys* and nodulos* and arthropath*) or (multiple benign circumferential skin creas* adj limb?)).mp. (9303)
192 (monosom* adj2 (13q14 or 13q34 or 18p or 18q or "22q13.3" or 5p or 9p or "9q22.3")).mp. (240)
193 (mosaic trisom* adj2 ("1" or "14" or "8" or "9")).mp. (188)
194 "mpdu1-cdg".mp. (3)
195 (mucolipidos#s adj2 ("iii" or "iv")).mp. (445)
196 ((multiple congenital anomal* adj3 hypotonia adj3 (seizure adj3 "1")) or (mycophenolate mofetil adj (embryopath* or embryo-path*))).mp. (4)
197 (multiple epiphyseal dysplasia* adj3 al-gazali).mp. (0)
198 (muscular dystroph* adj3 ((congenital adj3 megaconial) or (congenital adj3 merosin adj3 deficien*) or (limb-girdle adj3 autosomal recessive) or (congenital adj3 dystroglycanopath*) or (dystroglycanopath* adj3 limb-girdle))).mp. (388)
199 (myh7-related adj3 late-onset adj3 (scapuloperoneal or scapulo-peroneal) adj3 muscular dystroph*).mp. (0)
200 (myopath* adj3 (diabetes or "centronuclear 2" or (congenital adj3 bailey-bloch) or (lactic acidos* adj3 sideroblastic an?emi*) or (mitochondrial adj3 ataxia*))).mp. (188)
201 ((myotonia* adj1 permanens) or (myotoni* adj2 dystroph* adj2 "1") or "n syndrome" or (native america* adj2 myopath*) or (nephrogenic diabetes adj2 (intracranial calcification or intra-cranial calcification) adj3 facial dysmorphism)).mp. (2133)
202 ((nephronophthis* adj2 ("18" or "nephropathy 1")) or nephrosialidos*).mp. (17)
203 ((neurodegenerati* or neuro-degenerati*) and ((cerebral folate transport adj3 deficienc*) or "brain iron accumulation 2a" or "brain iron accumulation 5" or (childhood-onset adj3 brain atroph*))).mp. (26)
204 ((neurodegenerati* or neuro-degenerati*) adj3 pantothenate adj3 kinase-associated).mp. (753)
205 (((neurodevelopmental* or neuro-developmental*) adj3 jaw? adj3 eye? adj3 digital) or ((neurodevelopmental* or neuro-developmental*) adj3 (craniofacial or cranio-facial) adj3 renal adj3 cardiac adj3 abnormal*) or ((neurodevelopmental* delay* or neuro-developmental* delay*) adj3 seizure? adj3 ophthalmic adj3 osteop?enia adj3 cerebellar atroph*) or ((neurodevelopmental* or neuro-developmental*) adj3 (craniofacial or cranio-facial) adj3 cardiac defect? adj3 skeletal anomal*)).mp. (1)
206 (neuroferritinopath* or neuro-ferritinopath* or neuronal ceroid lipofuscinos*).mp. (3102)
207 ((neurofibromatos* or neuro-fibromatos*) adj2 ("type 1" or "type i")).mp. (8151)
208 (neuraminidase deficienc* or ((neurocutaneous or neuro-cutaneous) adj melanocytos*) or (neurologic adj3 (infantile adj2 (multisystem? or multi-system?)) adj3 osseous fragilit*) or (neurologic adj3 endocrine adj3 pancreatic adj3 infantile-onset) or ((neuromuscular or neuromuscular) adj3 (ocular or auditory) adj3 anomal*)).mp. (214)

209 (((neuropath* or neuro-path*) adj3 hereditary sensory adj3 (autonomic adj2 type v)) or neutral lipid storage myopath* or (neutrop?enia* adj3 (severe congenital adj2 "3") adj3 autosomal recessive) or (obesity adj3 (hyperphagia* or hyper-phagia*) adj3 developmental* delay*)).mp. (49)
210 ((oculodentodigital or oculo-dento-digital) adj2 dysplasia*).mp. (214)
211 (("ondontochondrodysplasia 2" or "ondonto-chondro-dysplasia 2") adj3 (hearing adj2 loss* adj3 diabet*)).mp. (0)
212 (optic atroph* adj2 ("2" or "10" or "11")).mp. (123)
213 ((osteoglosphonic adj2 dysplasia*) or (ornithine adj2 transcarbamylase adj2 deficienc*) or (osteopathia striata adj2 cranial scleros*) or (osteop?enia adj2 sparse hair) or (osteoporosis adj2 macrocephal* adj3 blindness adj2 joint hyperlaxit*) or (osteosclerotic adj2 metaphyseal adj2 dysplasia*)).mp. (986)
214 ((osteopetros* or osteo-petros*) adj3 (renal tubular acidos* or "autosomal recessive 3")).mp. (80)
215 (pancreatic hypoplasia? adj3 diabetes adj3 congenital heart).mp. (2)
216 ((paroxysmal dystonic choreathetos* and episodic ataxia and spasticity) or (paroxysmal adj2 dyskinesia* adj2 exertion-induced)).mp. (3)
217 ((paris-trousseau adj2 (thrombocytop?enia? or thrombo-cytop?enia?)) or (parkinson disease 19a adj2 juvenile-onset)).mp. (7)
218 ((partial deletion adj3 short arm adj3 "chromosome 7") or (partial adj (trisomy adj2 tetrasomy) adj3 short arm adj3 "chromosome 9") or (paternal uniparental disom* adj3 "chromosome x") or (paternal uni-parental disom* adj3 "chromosome x")).mp. (2)
219 (pcna-related adj3 (progressive neurodegenerative or progressive neuro-degenerative) adj3 (photosensitivit* or photo-sensitivit*)).mp. (0)
220 ((pelger-huet adj2 anomal*) or "pentasomy x" or (perioral myoclonia? adj2 absences) or (perioral myoclonia? adj2 absences) or peripheral hypothyroidism or peripheral hypo-thyroidism or (peroxisomal acyl-coa oxidase adj3 deficienc*)).mp. (535)
221 (peripheral demyelinating neuropath* adj3 central dysmyelinati* adj3 waardenburg adj3 hirschsprung).mp. (13)
222 ((periventricular or peri-ventricular) adj3 heterotopia adj3 (microcephal* or micro-cephal*) adj3 autosomal recessive).mp. (2)
223 ((periventricular or peri-ventricular) adj nodular heterotopia adj ("7" or "9")).mp. (3)
224 ("pgm3-cdg" or phenobarbital embryopath* or phenobarbital embryo-path* or phenylketonuria? or phenyl-ketonuria?).mp. (8961)
225 (phosphoglycerate adj2 ((dehydrogenase adj2 deficienc*) or (kinase adj2 deficienc*))).mp. (133)
226 (((phosphoribosylpyrophosphate synthetase or phosphoribosylpyro-phosphate synthetase or PRPP synthetase or PRS) adj2 (superactivit* or super-activit*)) or (phosphoserine adj2 phosphatase adj2 deficienc*)).mp. (58)
227 ((piebald trait? adj3 neurologic defect*) or piebaldism or (pituitary hormone deficienc* adj2 combined) or "pmm2-cdg").mp. (1312)
228 (((polymicrogyria? or poly-microgyria?) adj3 (tubb2b mutation? or bilateral frontoparietal or bi-lateral frontoparietal or bilateral fronto-parietal or bi-lateral fronto-parietal)) or (bilateral perisylvian or bi-lateral perisylvian)).mp. (263)
229 ((pomgnt2-related adj2 limb-girdle muscular dystroph* adj2 r24) or (pomt1-related adj2 limbgirdle muscular dystroph* adj2 r11) or ((pontine tegmental cap or PTC) adj3 dysplasia*)).mp. (41)
230 ((pontocerebellar hypoplasia? or ponto-cerebellar hypoplasia?) adj2 ("type 10" or "type 1a" or "type 7" or "type 11" or "type 14" or "type 15" or "type 2d" or "type 2e" or "type 2f of type 8")).mp. (26)
231 (porencephal* or por-encephal* or (porphyria? adj4 dehydratase deficienc*) or (posterior column ataxia adj3 retinitis pigmentosa)).mp. (1084)
232 ((primary and hyperaldosteronism and seizure? and neurological abnormalit*) or (primary and (hypergonadotropic or hyper-gonadotropic) and (hypogonadism or hypo-gonadism) and partial alopecia) or (primary adj (nonessential or non-essential) adj cutis verticis gyrata)).mp. (12)
233 ((proger* adj3 (short stature adj3 pigmented nevi)) or (facial appearance adj3 hand anomal*)).mp. (10)
234 ((progressive external ophthalmopl?egia* adj3 myopath* adj3 emaciation) or (prolactin deficienc* adj3 obesity adj3 enlarged test*) or (prolidase deficienc* or propionic acid?emia?)).mp. (1118)
235 ((proteasome adj3 (autoinflammator* or auto-inflammator*)) and (digenic or di-genic)).mp. (1)
236 (PRTA or type II RTA or (proximal adj3 (renal tubular acidos* or RTA))).mp. (398)
237 ((pseudohypoparathyroidism or pseudo-hypoparathyroidism or pseudo-hypoparathyroidism) adj3 (type 1a or type 1c or albright hereditary osteodystroph* or albright hereditary

osteo-dystroph*)).mp. (140)
238 (pseudopseudohypoparathyroidism or pseudo-pseudohypoparathyroidism or pseudopseudo-hypoparathyroidism or pseudopseudo-hypoparathyroidism or pseudopseudohypoparathyroidism or pseudo-pseudohypo-parathyroidism or pseudo-pseudo-hypo-parathyroidism or
pseudo PHP or PPHP).mp. (462)
239 (((pura-related and (neonatal hypotonia or neo-natal hypotonia) and seizure? and
encephalopath*) or purine nucleoside phosphorylase) adj3 deficienc*).mp. (219)
240 ((((radioulnar or radio-ulnar) adj synostos*) and amegakaryocytic thrombocytop?enia*) or
RUSAT).mp. (18)
241 (renal adj3 mullerian duct? adj3 (hypoplasia* or hypo-plasia*)).mp. (8)
242 ((retinal adj2 (dystroph* or pigmentosa)) or (rhizomel* adj2 (chondrodysplasia* or chondrodysplasia*) adj2 punctata) or RCDP or rhombencephalosynaps* or rhomb-encephalosynaps* or
rhomb-encephalo-synaps* or rhombencephalo-synaps* or (riboflavin transporter adj2 deficienc*)
or (robin sequence? and distinctive facial appearance? and brachydactyly) or rodrigues
blindness).mp. (4627)
243 (ROHHAD or (rapid-onset and childhood obesity and (hypothalamic dysfunction or hypothalamic dysfunction) and (hypoventilat* or hypo-ventilat*) and autonomic dysregulation)).mp. (98)
244 schizencephal*.mp. (552)
245 (((semilobar or semilobar) adj2 (holoprosencephal* or HPE)) or septo-optic dysplasia* or
((septopreoptic or septo-preoptic or septopre-optic or septo-pre-optic) adj2 (holoprosencephal* or
HPE))).mp. (711)
246 (severe achondroplasia* and developmental* delay* and acanthosis nigricans).mp. (20)
247 (skeletal dysplasia* and ((t-cell? or tcell?) adj2 (immunodeficienc* or immuno-deficienc*))
and developmental* delay*).mp. (1)
248 ((skin creas* adj3 congenital symmetric circumferential*) or CSCSC1 or CSCSC-1 or CSCSC2
or CSCSC-2).mp. (4)
249 ("slc35a2-cdg" or "slc39a8-cdg").mp. (24)
250 ((short stature adj3 (craniofacial anomal* or cranio-facial anomal*)) or (genital hypoplasia* or genital hypo-plasia*) or (short-rib adj3 "thoracic dysplasia 10") or (sialidos* adj2 "type 1") or
sialuria*).mp. (358)
251 (solitary median maxillary central incisor? or SMMCI).mp. (79)
252 ((spastic ataxia adj2 charlevoix-saguenay) or (spastic diplegia adj2 infantile type)).mp. (277)
253 (("spastic paraplegia 11" or "spastic paraplegia 14" or "spastic paraplegia 15" or "spastic
paraplegia 18" or "spastic paraplegia 20" or "spastic paraplegia 26" or "spastic paraplegia 32" or
"spastic paraplegia 35" or "spastic paraplegia 45" or "spastic paraplegia 46" or "spastic paraplegia
47" or "spastic paraplegia 48" or "spastic paraplegia 50" or "spastic paraplegia 51" or "spastic
paraplegia 52" or "spastic paraplegia 54" or "spastic paraplegia 55" or "spastic paraplegia 64" or
"spastic paraplegia 81" or "spastic paraplegia 82" or "spastic paraplegia 9b") adj3 autosomal
recessive).mp. (82)
254 (("spastic paraplegia 3" or "spastic paraplegia 4" or (spastic paraplegia adj1 ("type 4" or "type
10"))) adj3 autosomal dominant).mp. (43)
255 (("spastic paraplegia 16" or "spastic paraplegia 2") adj3 "x-linked").mp. (3)
256 (spastic paraplegia and (psychomotor retardation or psycho-motor retardation or
(kyphoscolios* adj2 lateral tongue atroph*))).mp. (18)
257 (spastic paraplegia adj1 "type 2").mp. (53)
258 (spastic paraplegia adj3 (nephritis or deafness or precocious puberty or developmental*
delay*)).mp. (19)
259 (spastic tetraplegia adj3 thin corpus callosum adj3 (progressive microcephal* or progressive micro-cephal* or progressive postnatal microcephal* or progressive post-natal microcephal*)).mp. (5)
260 (spinocerebellar ataxia adj2 ("13" or "21" or "27" or "29" or "35" or "42" or "47" or axonal
neuropath*)).mp. (194)
261 ((spinocerebellar ataxia or spinocerebellar degeneration?) adj3 (autosomal recessive adj
("10" or "12" or "13" or "15" or "17" or "18" or "2" or "21" or "22" or "23" or "28" or "29" or "30" or
"4"))).mp. (22)
262 (spinocerebellar degeneration? adj3 corneal dystroph*).mp. (2)
263 (split-hand* adj2 foot malformation*).mp. (284)
264 (sponastrime dysplasia* or spondyloenchondrodysplasia* or spondyloenchondro-dysplasia*
or (spondyloepiphyseal dysplasia tarda adj3 kohn)).mp. (83)
265 (spondyloepimetaphyseal dysplasia* adj3 (joint laxit* or faden-alkuraya or genevieve or
sponastrime)).mp. (45)
266 (sporadic f?etal brain disrupt* sequenc* or (steinert adj2 myotonic dystroph*) or (stomatindeficient cryohydrocytos* adj2 neurologic defect*) or (striatonigral degeneration adj2 infantile)).mp.

(87)
267 ("srd5a3-cdg" or "ssr4-cdg" or "stt3a-cdg" or "stt3b-cdg").mp. (33)
268 (succinic semialdehyde dehydrogenase deficienc* or (suprabulbar pares#s adj3 congenital) or (supra-bulbar pares#s adj3 congenital) or syndromic diarrh?ea or (syngap1-related and developmental and epilep* encephalopath*)).mp. (244)
269 ((t-substance adj3 anomal*) or telecanthus or ((tetrameli* or tetra-ameli*) and ectodermal dysplasia* and lacrimal duct abnormalit*) or ((tetrameli* or tetra-ameli*) and deficienc* and ectodermal dysplasia* and deformed ear? and abnormalit*) or (tetrasom* adj (12p or 18p)) or thanatophoric dysplasia* or (thoc6-related and developmental* delay* and microcephal* and facial dysmorphism)).mp. (1159)
270 (thumb? adj3 ((deform* adj3 alop?ecia) or (stiff adj3 brachydactyly adj3 developmental* delay*))).mp. (1)
271 (thyroid? adj3 (ectopia? or (genetic* defect* adj3 hormonogenes*) or (genetic* defect* adj3 hormono-genes*) or hypoplasia* or hypo-plasia*)).mp. (283)
272 ((thyrotropin-releasing adj3 hormon* deficienc*) or (tmem70-related and mitochondrial encephalo* and (cardiomypath* or cardio-myopath*)) or (transcobalamin ii adj3 deficienc*) or (transient adj (neonatal or neo-natal) adj diabetes) or (transketolase adj3 deficienc*) or (trappc11-related adj3 limb-girdle muscular dystroph* adj3 r18)).mp. (421)
273 (trichothiodystroph* or trichothio-dystroph* or (triglyceride deposit adj3 (cardiomyovasculopath* or cardio-myovasculopath* or cardio-myo-vasculopath* or cardiomyovasculopath*)) or TGCV).mp. (573)
274 ((trigonocephal* or tri-gonocephal*) adj3 (short stature adj3 developmental* delay*)).mp. (3)
275 "trisomy xq28".mp. (0)
276 (tryptophanuria* adj3 dwarfism).mp. (1)
277 (tuberous scleros* adj2 (complex or "1" or "2")).mp. (6327)
278 (tyrosin* adj3 (transaminase deficienc* or "type 2" or "type ii" or "type 3" or "type iii")).mp. (566)
279 ((unilateral adj3 polymicrogyria*) or (uni-lateral adj3 polymicrogyria*) or (unilateral adj3 polymicrogyria*) or (uni-lateral adj3 poly-microgyria*) or (urocanase adj3 deficienc*) or (vacterl adj2 hydrocephal*) or (vacterl adj2 hydro-cephal*)).mp. (84)
280 ((ventricular extrasystoles and syncopal episod* and perodactyly and robin sequence?) or (vertebral and cardiac and renal and limb defect?)).mp. (67)
281 ((vitamin b12 or vitamin b 12) adj3 (responsive methylmalonic acid?emia or unresponsive methylmalonic acid?emia)).mp. (19)
282 vitamin k antagonist embryofetopath*.mp. (0)
283 (wac-related and facial dysmorphism and developmental* delay* and behavio?r* abnormalit*).mp. (0)
284 (wars2-related adj3 combined oxidative phosphorylation defect*).mp. (0)
285 (((x-linked or xlinked) adj3 (acrogigantism* or acro-gigantism* or adrenoleukodystroph* or adreno-leukodystroph* or cerebral-cerebellar-coloboma or (charcot-marie-tooth disease adj2 type 2) or (charcot-marie-tooth disease adj2 type 3) or (charcot-marie-tooth disease adj2 type 4) or complicated corpus callosum dysgenes#s or (complicated spastic paraplegia* adj2 type 1) or creatine transporter deficienc* or (dominant chondrodysplasia* adj2 chassaing-lacombe type) or lissencephal* or (multiple congenital anomalies adj2 neurodevelopmental*) or (multiple congenital anomalies adj2 neuro-developmental*) or (neurodegenerative adj2 bertini type) or (neurodegenerative adj2 bertini type) or (neurodegenerative adj2 hamel type) or (neuro-degenerative adj2 hamel type) or (spastic parapl?egia* adj2 type 16) or spondyloepimetaphyseal dysplasia* or spondylo-epimetaphyseal dysplasia*)) or (syndromic recessive adj3 ichthyos*) or (heterotopia* adj2 periventricular)).mp. (2102)
286 (x small ring? or xeroderma pigmentosum or (xq28 adj2 mecp2 adj2 duplication) or (xy type adj2 gonadal dysgenes#s-associated anomal*) or "xylt1-cdg").mp. (6877)
287 or/11-286 [INTELLECTUAL DISABILITIES] (960543)
288 10 and 287 [CHILDREN - INTELLECTUAL DISABILITIES] (319957)
289 exp Animals/ not Humans/ (5290499)
290 288 not 289 [ANIMAL-ONLY REMOVED] (311074)
291 (comment or editorial or letter or news or newspaper article).pt. (2529371)
292 290 not 291 [OPINION PIECES REMOVED] (299646)
293 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt. (720751)
294 "Clinical Trials as Topic"/ (204031)
295 exp "Controlled Clinical Trials as Topic"/ (186735)
296 (randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw,kf. (1340704)

297 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw,kf. (210788)
298 trial.ti. (324893)
299 or/293-298 (1809152)
300 292 and 299 [RCTs] (10486)
301 controlled clinical trial.pt. (95662)
302 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (101363)
303 (control* adj2 trial).tw,kw,kf. (239524)
304 Non-Randomized Controlled Trials as Topic/ (1138)
305 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw,kf. (82502)
306 (nRCT or non-RCT).tw,kw,kf. (619)
307 Controlled Before-After Studies/ (772)
308 (control* adj3 ("before and after" or "before after")).tw,kw,kf. (5714)
309 (pre- adj5 post-).tw,kw,kf. (148867)
310 ((pretest adj5 posttest) or (pre-test adj5 post-test)).tw,kw,kf. (13394)
311 Historically Controlled Study/ (237)
312 ((historical* or external*) adj control*).tw,kw,kf. (11994)
313 (control* adj2 study).tw,kw,kf. (228870)
314 or/301-313 (773976)
315 292 and 314 [nRCTs] (7317)
316 ((single-arm$2 or singlearm$2) adj3 (design? or study or studies or trial?)).tw,kw,kf. (12117)
317 ((open-label* or openlabel*) adj3 (design? or study or studies or trial?)).tw,kw,kf. (40410)
318 or/316-317 (50955)
319 292 and 318 [SINGLE-ARM, OPEN-LABEL STUDIES] (620)
320 300 or 315 or 319 [ALL STUDY DESIGNS OF INTEREST] (14546)
321 preprint.pt. (33778)
322 320 not 321 [PREPRINTS REMOVED] (14537)
323 limit 322 to yr="2019-current" (3985) [DATE LIMIT APPLIED]
****

A.3. Screening questions and detailed instructions

Screen questions and additional instructions

1. **Is this article in English?**
    a. Yes: [Move on to criterion #2]
    b. No: [Exclude – Reason: Wrong language (not English)]

2. **Is this an article reporting on a completed primary research study in human participants?**
    a. Yes: [Move on to criterion #3]
        i. Primary research studies that involve the completed collection or analysis of original data.
    b. No: [Exclude - Reason: Wrong Article Type]
        i. Review articles with the use of data that have already been collected and published by others (i.e., systematic reviews, scoping reviews, and meta-analyses). This type of research analyzes, interprets, or summarizes the existing completed research and may not capture sufficient details about clinical trial methods and/or may not reflect the final published protocol/methods for existing trials.
        ii. Also exclude protocols, conference abstracts and proceedings, dissertations errata/corrections and short summaries/abstracts that are not conference abstracts (e.g., lay summaries). Similarly, these publication types, while they may reflect primary research, are less likely to capture sufficient details.
        iii. Studies that specify that they are done in non-human animals (e.g., mice).
        iv. Retracted Articles: If an article has been officially retracted, exclude it and select "Retracted Article" as the reason in Covidence

3. **Does the study population consist of at least 50% children and adolescents aged 0 to under 18 years, OR are the results separately reported for this age group?**
    a. Yes: [Move on to criterion #4]
        i. Studies involving participants both younger and older than 18 years will be included if at least half of the participants are younger than 18 years (median age is <18 years) OR if the published report presents results separately for children <18 years. Note: if the median age is <18 years, you can assume that at least half of the participants are <18 years.
        ii. For studies that include a mix of children and adults but report only the mean age and standard deviation (SD) of the mean age:
            1. If (Mean + 1 SD) for age is less than 18 (for the overall sample if reported, or in both/all study arms if the study only reports age separately for the intervention and comparison arms), you can assume that the median age is also <18 and in this case, include the study. Important: Please record this study on your personal tracker and note that age eligibility was determined using the “mean + 1 SD” approximation.

2. If (Mean + 1 SD) for age is 18 or higher (overall if reported; or in at least one arm if age only reported separately by study arm), you can Exclude the study, also with a note – please see ii below.

b. No: [Exclude - Reason: Wrong Age Group]
    i. If the population is adults only or more than half adults (18+ years), including studies where the age range is not specified but the authors state that it is a study of "adults".
    ii. If you only have access to the mean and standard deviation (SD) for age and mean + SD is 18 or older (for the overall sample; or if only broken down by arm, in at least one arm) OR if you otherwise have insufficient information regarding age, exclude (wrong age group) and note this in your personal tracker as "insufficient age data".

4. Does the study evaluate interventions that would be likely to require regulatory approval/registration, such as studies of medications/drugs, supplements, or medical devices?

a. Yes: [Move on to criterion #5]
    i. Include studies that evaluate medications/drugs or supplements.
    ii. Medical devices:
        1. Include studies that evaluate a new medical device as a product – i.e., the intervention being studied is the device itself. Example: trial of a new communication device.
        2. Include studies that evaluate an already existing/approved medical device as a product, where it is being used for a new indication or population – i.e., the intervention being studied is the use of this device for this specific group or purpose. Examples: trial of the use of a dynamic harness system or of transcranial direct current stimulation, for a specific purpose/population

b. No: [Exclude – Reason: Wrong Interventions]
    i. Behavioral or educational studies, surgical studies, studies of therapies that do not involve medications/drugs, supplements, or medical devices.
    ii. Medical devices:
        1. Exclude studies where a medical device is mentioned but the trial is focused on a "practice of medicine" question and not on evaluating the device as a product – this means that the device is typically something that is widely available or part of routine care. Examples: trials of physical activity interventions where the physical activity is being done using a device such as a treadmill, trampoline, or ergometer but the device itself is not what's being evaluated.

5. **Does the study focus on children and adolescents with intellectual disability (ID)?**
    a. Yes: [Move on to criterion #6]
        i. Check if Intellectual Disability or synonyms are mentioned (intellectual disability, developmental delay, global developmental delay). If found, then answer Yes (move to criterion # 6)
        ii. Check the INCLUSION conditions on the: DiseaseAssociation_HPOTerms.xlsx,. If diagnoses in full-text are on the list, then answer Yes (move to criterion #6)

    Important note: Use control F (PC) or command F (Mac) to look up each word of the diagnosis on this list (e.g., if the diagnosis is "neuronal ceroid lipofuscinosis", look up each of those words to see if there is a match).

    b. No: [Exclude – Reason: Wrong Condition]
        i. Check the EXCLUSION list ConditionExclusionList_ID.xlsx. If all diagnoses in the full-text are on the exclusion list answer No (Exclude)
        ii. If not included in the INCLUSION LIST or EXCLUSION LIST, you should do the following:

For Autism, Cerebral Palsy, and Epilepsy:	For other conditions:
1. Answer YES if the associated sub-condition is on the HPO list (if not mentioned, move to the next step). 2. Answer YES if there is explicit mention that at least 50% of the children and adolescents have an intellectual disability (ID) or global developmental delay (if not mentioned, move to the next step). . If yes, note down ref ID (#XYZ) on a personal document. 3. Answer YES if there is a measurement of adaptive behaviour, IQ, quality of life, or adaptive functioning. If yes, note down ref ID (#XYZ) on a personal document. Otherwise, answer NO and EXCLUDE (Reason: Wrong Condition).	1. On OMIM (https://omim.org/) search for the condition. 2. Click on Clinical Synopsis 3. Check under "**NEUROLOGIC**" for the following: Intellectual disability, Mental Retardation, Developmental Delay, or Global Developmental Delay. If no mention of the terms above, EXCLUDE (Reason: Wrong Condition).

6. **Is the study design a clinical interventional trial?**
    a. **Yes:** [Move to criterion #7]
        i. Clinical interventional trial report, feasibility study, or pilot study (see definitions below).
        ii. Clinical interventional trials are studies where researchers intervene to investigate a particular intervention (i.e., medication) to determine its safety, effectiveness, and/or efficacy on human participants.
        iii. Clinical interventional trials involve prospectively collected data as changes occur from participants that are followed over time.
        iv. There are several design types for clinical interventional trials, including, but not limited to:
            1. Randomized controlled trial
            2. Adaptive randomized controlled trial
            3. Non-randomized controlled trial
            4. Single-arm clinical trial
            5. Open-label clinical trial
            6. Historically controlled / externally controlled trial
            7. Cross-over trial
            8. Delayed start trial
            9. Single participant studies only if labelled as a clinical research trial (randomized n-of-1/n-of-few trial)
            10. Factorial trial
            11. Master protocol trial (basket trial, platform trial)
            12. Registry-based randomized trial
            13. Controlled before/after studies
            14. Pre-post studies
            15. Pragmatic clinical trial
    b. No: [Exclude – Reason: Wrong Study Design]
        i. Single-participant studies that are not randomized (e.g., case study reporting on experience with a therapy).
        ii. Observational studies, including case reports/series, cross-sectional studies, and cohort studies.
        iii. Designs focused exclusively on validation, feasibility, or methodology without evaluating clinical outcomes.
    c. Maybe: [Move to full text]

Definitions:

Trial report: Summary of results and findings of a clinical interventional trial (i.e., information about the design, methods, data analysis, demographics, results, outcomes, conclusions, etc.).

Feasibility study: A preliminary research study to assess if an intervention is safe and feasible for a specific population (usually before pursuing a large-scale clinical interventional trial to evaluate its safety, effectiveness, and efficacy).

Pilot study: A smaller preliminary study that is conducted in advance of a large-scale clinical interventional trial to assess the trial methods and their feasibility.

Prospective data: Data collected as changes occur, from participants that are followed over time.

Included study designs:

Randomized controlled trial: A clinical trial where two or more interventions (or treatment arms) are being compared to each other. When a trial is randomized, participants are assigned by chance to one of the interventions (or treatment arms).

Adaptive randomized controlled trial: A randomized controlled trial where the chance of assignment to one of the treatment arms is adapted based on results accumulating during the trial.

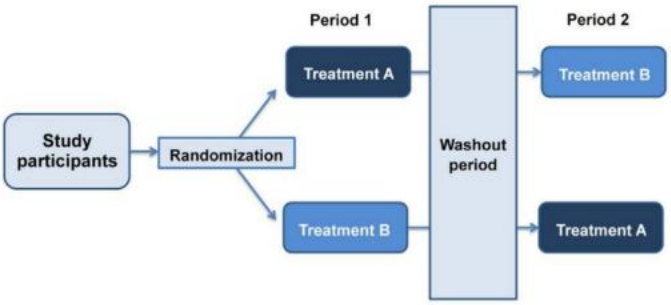
Non-randomized controlled trial: A clinical trial where two or more interventions (or treatment arms) are being compared to each other and participants are not randomly assigned by chance to one of the interventions.

Single-arm clinical trial: A clinical trial with a single treatment arm and no comparator group.

Open-label clinical trial: A clinical trial where participants and researchers are aware of which intervention they are receiving or administering.

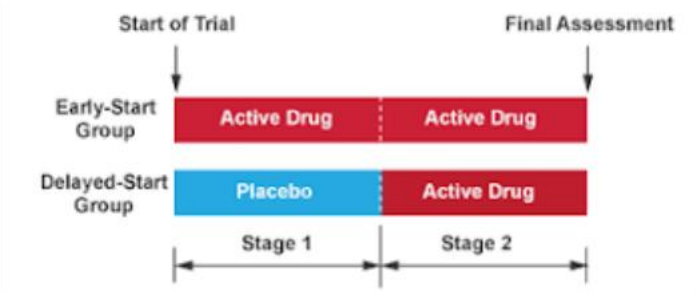
Historically controlled/externally controlled trial: A clinical trial where the treatment group is being compared to an external group that is not apart of the trial (i.e., a historical comparator group from a patient registry).

Cross-over trial: A clinical trial where participants are randomly assigned to receive two or more treatments at different time periods. The simplest model is the AB/BA study (see figure below). Participants assigned to the AB study arm receive treatment A first, followed by a period with no treatment to ensure the effects of treatment A have subsided (called a "washout period"), followed by treatment B, and vice versa in the BA arm. Crossover trials allow the response of a participant to treatment A to be contrasted with the same participant's response to treatment B.



Li et al. PLoS ONE 10(8):e0133023. doi:10.1371/journal.pone.0133023

Delayed start trial: A clinical trial where participants are randomly assigned to receive the same treatment at different times. For example, in stage one in the figure below, the early-start group receives the treatment while the delayed-start group receives a placebo until a specific time point (stage 2) in which both groups eventually receive the same treatment.



On Biostatistics and Clinical Trials: Demonstrating the disease modifying effect through delayed start study design or delayed start analyses. Accessed January 3, 2025. https://onbiostatistics.blogspot.com/2016/01/demonstrating-disease-modifying-effect.html

Randomized n-of-1/n-of-few trial: A clinical trial where there is only one participant. The participant is often randomized to receive a particular treatment in the first stage and then there is a washout period that is followed by a cross-over in which the same participant will receive a different treatment (similar to a cross-over design).

Factorial trial: A clinical trial where two or more interventions are being compared at the same time. The figure below demonstrates a factorial trial in which participants are randomized to receive aspirin versus placebo and also randomized to receive behavioural intervention versus standard care to compare both interventions simultaneously.

		Randomization of B	
		Behavioural intervention (B)	**Standard care (not B)**
Randomization of A	**Aspirin (A)**	A and B	A, not B
	Placebo (not A)	B, not A	Not A, not B

16.5.6 Factorial trials. Accessed January 3, 2025. https://handbook51.cochrane.org/chapter_16/16_5_6_factorial_trials.htm

Basket trial: A master clinical trial protocol where an intervention is tested in various populations that may be defined by a disease stage, specific histology, genetic biomarker, or demographic characteristics. An example is a clinical trial investigating the effect of a drug on participants with several types of cancer that have the same genetic mutation.

Platform trial: An open-ended clinical trial where new interventions can be added, assessed, and removed as time goes on.

Registry-based randomized trial: A clinical trial where treatment and outcome data are collected in an existing patient registry. They study real-life patients in real-life clinical settings and potentially have an important role to play in informing best clinical practice and health policy.

Controlled before/after studies/Pre-post studies: A non-randomized clinical trial where participants are observed before and after receiving an intervention or a comparator (i.e., placebo).

Pragmatic clinical trial: A clinical trial where the intervention of interest is evaluated in a real-world setting similar to where it would be implemented.

Excluded non-interventional (i.e., observational) study designs:

Retrospective studies: Data collected from participants' past (i.e., medical chart review).

Observational study: A type of study where individuals are observed, and health exposures and outcomes are measured without any intervention from researchers.

Cohort studies (retrospective and prospective): Observational studies that follow a group of people over time to assess the effects of certain exposures.

Post-market real-world data studies (unless part of follow-up for a specific clinical trial): Studies using data collected from routine clinical practice to evaluate the safety and effectiveness of treatment.

Case series: Descriptive studies that track patients with a known exposure or treatment to document outcomes.

Case studies: Detailed reports of a single patient or a small group of patients, often used to highlight novel treatments or rare conditions.

Case-control studies: Observational studies that compare patients with a specific condition (cases) to those without the condition (controls) to identify risk factors.

Nested case-control studies: Case-control studies conducted within a defined cohort, where cases and controls are drawn from the same population.

Others: Various other observational study designs that do not involve intervention by the researchers

7. **Are caregiver-reported outcomes included as primary or secondary outcome measures for some trial participants OR are outcome domains of interest to Protocol 2 included?**
    a. **Yes:** [Move to data extraction] Include studies where caregiver-reported outcomes or outcome domains of interest to protocol 2 are primary or secondary outcome measures. This includes:
        i. Mention of caregivers (parents, guardians, and other informal caregivers) reporting for the children and adolescents enrolled in the trials. You may also see terms like proxy-reported outcomes or observer-reported outcomes.
        ii. For protocol 2 look for the following terms or related concepts. Given the complexity of this domain, please err on the side of inclusion.
            1. Expressive communication/expressive language/speech/language use/language
            2. Fine motor/manual dexterity, finger coordination/precise movement/small muscle control
            3. Emotion dysregulation/emotional instability/emotion regulation/depression/volatility/anxiety/maladaptive emotion regulation/maladaptive emotional reactivity/behavior problems/affective/mood/internalizing/externalizing/aggression
            4. Cognitive functioning/cognitive abilities/cognitive processes/cognition/mental functioning/intellectual functioning
            5. Adaptive behavior/adaptive functioning/daily living skills/life skills
    b. **No** [Exclude – Reason: Wrong Outcomes]**:** Caregiver-reported outcomes or outcome domains of interest are not included.
        i. Excluded outcomes: gross motor, ambulation, heart function, height, weight, biomarkers/lab tests.

Answer Flow for Q7

1. If a study clearly states that caregivers were involved in the reporting of outcomes (i.e. parents completed questionnaire XYZ) OR if the study uses terms like proxy-reporting/reported outcomes or observer reporting/reported outcomes – **INCLUDE**, if not mentioned move to the next step.
2. If a study clearly states expressive communication, fine motor, emotion dysregulation, cognitive functioning, or adaptive behavior (functioning) - or any related term in slide 14 - as an outcome domain **– INCLUDE,** if not mentioned move to the next step.

If a study utilizes a measure that is on the short list – **INCLUDE**, otherwise Exclude – Reason: Wrong Outcomes

A.4. Data items

A.4.1. General study details

Extraction item	Instruction/question for extractor	Item on consort-2010	Additional item rationale, definitions, and/or resources
Protocol 1 or 2 or both	Does this article have outcomes of interest to protocol 1, 2, or both?	Na	Protocol 1: ya_research_protocol_jan14.docx Protocol 2: at_subprotocol_jan15.pdf
Title	Copy the title of article	1a*	
Country	Note down all countries where study was conducted (where participants were enrolled)	4b	
Countries - other	Note down the rest of the countries if "other" is selected	4b	
Funding	Select the most appropriate funding source as stated in article. Sometimes referred to as 'sponsor'	25	Industry: financial support provided by private companies or corporations. Non-industry: financial support from entities, such as organizations, educational institutions, charities, associations, or grants
Registration id	If registered, provide the registration number (ex. Nct____, chictr_____, eudract number:, etc.). If not registered or missing, put "not reported".	23	***Note: for 'not registered' we conducted a search on the registries in:*** **https://www.who.int/tools/clinical-trials-registry-platform/network/primary-registries + clinicaltrials.gov** **We searched for the title of the trial (or keywords such as condition and intervention) in the most appropriate registries from the list above:** 3. **We searched in registries relevant to where trial was conducted (e.g. If a trial was conducted in india, we would first search the clinical trials registry - india (ctri))** 4. **Then we searched through the most common registries:** a. **Clinical trials . Gov** b. **Eu clinical trials register (eu-ctr)**
Registration id (2)	Alternative registration (1)	23	

Registration id (3)	Alternative registration (2)	23	
Study design - randomization	Is the trial randomized?	3a	
Study design - number of study arms	How many arms are in the trial?	3a	
Study design - active vs. Placebo	If there is a comparison arm, is it an active or placebo comparison arm?	3a	Active, Placebo, >1 active, >1 placebo, NA/Single arm
Design type	What is the design type?	3a	Parallel: participants are assigned to one of two or more groups, each receiving a different treatment simultaneously. Cross-over: participants receive multiple treatments in a sequence, with a washout period in between to prevent carryover effects. Each participant serves as their own control, which can reduce variability Externally (historical) controlled trial: a clinical trial where the treatment group is being compared to an external group that is not apart of the trial (i.e., a historical comparator group from a patient registry)., Controlled before/after studies/pre-post studies: a trial where participants are assessed before and after receiving an intervention. A nonequivalent control group can be added ("nonequivalent control group: a control group that is not randomly assigned to receive or not receive the intervention. An intact group is selected that is thought to be similar to the intervention group" (handley et al., 2018))
Study design - was the trial blinded?	Was the trial blinded?	3a	The term 'masking' may be used instead of blinding.
Study design - who was blinded?	Who was blinded in this study after assignment to interventions?	11a	The list of individuals who can be blinded include **participants, caregivers, healthcare providers, data collectors, outcome adjudicators, outcome assessors,**

			and data analysts. This list is from the consort 2010 explanation and elaboration document with the addition of caregivers given the context of this review and outcome assessors to help extractors select more precisely. "trial investigators" was added in as a general cateogry for the studies that did not specify who was blinded.
Trial phase (phase 1, 2, 3, 4)	What is the trial phase?	11a	I II Iii Iv
Study design (other)	Specify other study design information (about design type, blinding, phase)	3a	
Trial follow up duration	What is the length of the trial in weeks? (specifically, this trial, excluding linked study lengths)	3a	Here we are extracting the time of follow up in the trial.
Sample size	What is the total sample size at randomization/start of the study?	15	
Intervention(s) - type	What is the intervention?	5	
Condition(s) included	Note down all conditions included in the study (id associated conditions only)	15	
Other notes	Note down any other conditions	Na	

In cases where an article is reporting on a trial and its extension:

- We will report the methods for the initial trial but we will mention that there is also an extension portion
- For the trial duration, we will include the time of the trial and report the duration of any included extension separately.

A.4.2. Outcome characteristics

Extraction Item	Definitions and details	Example extraction or choices
Measure	Note the specific measure used (name)	VABS-III, VABS-II, Vineland-3, Vineland-2, WPPSI-III, WPPSI-IV, WISC-IV, WISC-V, WAIS-III, WAIS-IV, CBCL, other.
Measure - other	If selected other to the previous question, please note the specific measure name	

Entire measure	Was the whole measure administered?	Yes, Yes but also subscores used individually, No
Measure Subset - other	If entire measure was not administered, which subtests were administered?	
Domain of COS of interest - verbatim	Describe the specific measure variables (verbatim from trial report)	
Type of Outcome	Is this assessment a primary, secondary, or unknown endpoint?	Primary, secondary, not reported
Protocol relevance	Does this assessment pertain to P1, P2, or Both?	Protocol 1, Protocol 2, Both

When to add a new row? (if any of the following is encountered while extracting)

General Principle

Create a new row only if the outcome (domain or subscale) was analyzed and reported separately in the trial report. Do not rely solely on trial registrations or protocols to infer outcome structure; extraction decisions must be based on the published trial report (mainly the methods and the results sections).

- If a new domain of interest to either protocol is encountered, ADD a new extraction row.
- If a new measure of interest to either protocol is encountered, ADD a new extraction row.

Multi-domain or multi-component measures rule: If a measurement instrument includes multiple domains or subscales:

- Extract each domain/subscale as a separate row only if the trial analyzes and reports them separately (i.e., provides results for them individually).
- For “Domain of COS of interest – verbatim" , we extracted what the authors said the measure OR subset measured. For e.g., if authors said Measure X was used to assess Domain Y but they reported subsets for Measure X only, we input the Domain Y for this column.
- If the trial analyzes and reports only a total or composite score, extract a single row for that measure, regardless of the descriptive language used (e.g., even if the measure is broadly described as covering multiple constructs).
- Example: If a trial uses the Vineland Adaptive Behavior Scales and reports subscale scores (e.g., "Daily Living," "Communication"), extract each as a separate row, if relevant to either protocol. If the trial only presents a composite score or a general summary, extract one row for the entire measure.

Unclear reporting or partial reporting rule. In cases where reporting is unclear (e.g., the authors list the measure as an outcome but do not specify domains):

- If no total score is reported, but subscales are analyzed and presented, extract separate rows for each subscale that is reported.
- If neither a total score nor subscale scores are presented clearly, extract one row only, using the general construct label provided in the trial (e.g., “adaptive behavior” or “motor function”).

A.4.3. Additional outcome characteristics (for trials where outcome used as primary endpoint)

Extraction Item	Definitions and details	Type (e.g., MC, Multi select, Text)
Reporter consistency	Was the outcome captured by the same reporter, if outcome collected at multiple timepoints?	MC
Reliability, Validity, and responsiveness to change of Instrument (COSMIN Taxonomy)	Was any information given about reliability, validity, and responsiveness?	Multi-select
Comments re: reliability, validity, and responsiveness to change	Note any information provided by authors re: psychometric properties of the tool	Text
Reliability in the Same population?	Was the information provided re: reliability in a population similar to the study sample (age and conditions)?	Multi-select
Validity in the Same population?	Was the information provided re: validity and validity in a population similar to the study sample (age and conditions)?	Multi-select
Responsiveness to change in same population?	Was the information provided re: responsiveness to change in a population similar to the study sample (age and conditions)?	Multi-select
Reporter training?	Were caregivers that reported an outcome formally trained to use the outcome measure?	Multi-select
Reporter instructions?	Were caregivers given any instructions for reporting their children's health outcomes?	MC
Comments re: instructions or training given	Note any information given about the training or specific instructions given to caregivers (verbatim)	Text
Outcome Assessor(s)	Describe who collected/completed the outcome assessment (e.g., nurse, caregiver, child (the patient))	Multi-select
Caregiver Reporter(s) specifics	Which caregiver is reporting on behalf of the child? (select all that apply)	Multi-select
Caregiver reporting classification	Do authors classify reporting as Proxy, Observer, or hybrid?	Multi-select
Caregiver demographics	Are the demographic details of the caregiver (age, gender, sex at birth, and education level) reported in the trial? (select all that apply)	Multi-select
Mode of Completion (Self/Staff)	Was the information self-completed (completed by caregivers alone) or staff-completed (i.e. completed via interview of caregivers)	Multi-select
Mode of Completion (Format)	How was the caregiver-reported outcome completed? (e.g., paper, digital, interview, other)	Multi-select
Setting of Completion	Where was the outcome completed?	Multi-select
Birth Order	Was the birth order of the child (enrolled in study) mentioned?	MC

A.5. REDCAP Survey

Dimension A: The perspective sought

Based on the instrument's instructions, whose perspective is sought (select one)?

- The caregiver's perspective: caregivers are asked to respond based on their own impressions of the child.
- The child's perspective: caregivers are asked to respond as if they were the child or instrument is meant to be completed by the patient rather than a caregiver.
- Both perspectives: the instructions accommodate both the caregiver's and child's perspective.
- Unclear: no explicit direction is provided regarding perspective.

Additional reviewer comments on instrument instructions

Based on the wording of the instrument's items, whose perspective is sought (select one)?

- The caregiver's perspective only: all items worded to seek the caregiver's perspective.
- The child's perspective (alone or in addition to the caregiver's perspective): at least some items are worded to ask the caregiver to respond as if they were the child or as if the child is answering.
- Unclear: while no questions are definitively the child's perspective, at least some questions are worded ambiguously regarding perspective.

Please list items (or item/question numbers) from the child's perspective

Please list the items (or item/question numbers) that are unclear with respect to perspective

Additional reviewer comments on instrument items

Dimension B: Clinician involvement

Based on the instrument’s instructions, is a clinician involved in guiding or interpreting the caregiver’s responses during the instrument’s completion (select one)?

- Clinician involved: the instrument requires or involved in guiding or interpreting the caregiver's explicitly allows clinician input or responses during the instrument's completion
- Caregiver-only: the instrument is intended to be completed solely by the caregiver, with no clinician input or interpretation.
- Unclear: no explicit instructions regarding clinician judgement.

Additional reviewer comments on clinician involvement

Dimension C: Type of information captured

Based on the wording of the instrument's items, are the questions focused on observable behaviours, internal states, or is this unclear (select one)?

- Observable behaviours: all items are based solely the questions focused on behaviours or events that can be directly observed by a caregiver.
- Internal states: at least some items require judgement or inference on the part of the caregiver about the child's internal experiences.
- Unclear: while no questions are definitively about the child's internal experiences, at least some questions are worded ambiguously regarding internal experiences.

Please list items (or item/question numbers) that require judgement or inference about the child's internal state

Please list items (or item/question numbers) that are unclear with respect to type of information captured

Additional reviewer comments on type of information captured

Appendix B: additional results

B.1. Excluded at full-text by exclusion reasons

Study	Exclusion reason	DOI
Chen 2022	Retracted Article	https://doi.org/10.1155/2022/5316992
Gao 2022	Retracted Article	https://dx.doi.org/10.1155/2022/5245200
Aitken 2023	Wrong Age Group	https://dx.doi.org/10.1093/bjd/ljad243
Aledo-Serrano 2023	Wrong Age Group	https://dx.doi.org/10.1007/s13311-023-01395-z
Amin 2021	Wrong Age Group	https://dx.doi.org/10.1016/j.eclinm.2020.100715
Attarian 2021	Wrong Age Group	https://dx.doi.org/10.1186/s13023-021-02040-8
Baderkhan 2021	Wrong Age Group	https://dx.doi.org/10.1016/j.ejvs.2020.10.020
Berry-Kravis 2020	Wrong Age Group	https://dx.doi.org/10.1016/j.pediatrneurol.2020.04.019
Bird 2021	Wrong Age Group	https://dx.doi.org/10.1212/WNL.0000000000011409
Blickwedel 2019	Wrong Age Group	https://doi.org/10.3109/13668250.2019.1587594
Bremova-Ertl 2022	Wrong Age Group	https://dx.doi.org/10.1007/s00415-021-10717-0
Brunetti-Pierri 2022	Wrong Age Group	https://dx.doi.org/10.1056/EVIDoa2200052
Bruno 2019	Wrong Age Group	https://dx.doi.org/10.1177/0269881119858304
Callisto 2020	Wrong Age Group	https://dx.doi.org/10.1002/jcph.1611
Cao 2022	Wrong Age Group	https://dx.doi.org/10.1177/03000605221139723
Chen 2020	Wrong Age Group	https://dx.doi.org/10.1016/j.ymgme.2019.11.007
Chen 2020	Wrong Age Group	https://dx.doi.org/10.1111/bjd.18949
Chen 2022	Wrong Age Group	https://dx.doi.org/10.1016/j.wjam.2022.05.001
Cheng 2023	Wrong Age Group	https://dx.doi.org/10.1080/19490976.2023.2284247
Cle 2023	Wrong Age Group	https://dx.doi.org/10.3324/haematol.2022.281808
Consoli 2019	Wrong Age Group	https://dx.doi.org/10.1038/s41398-019-0597-0
Costa 2022	Wrong Age Group	https://dx.doi.org/10.1016/S1474-44222100369-0
Craig 2023	Wrong Age Group	https://dx.doi.org/10.1016/S0140-67362300350-1
Daneshyar 2022	Wrong Age Group	https://dx.doi.org/10.22088/cjim.13.3.617
DeFreitas 2019	Wrong Age Group	https://dx.doi.org/10.3389/fneur.2019.00024
DeGiglio 2019	Wrong Age Group	https://dx.doi.org/10.1212/WNL.0000000000007970
DeGiorgis 2024	Wrong Age Group	https://dx.doi.org/10.1002/mds.29822
Diaz-Manera 2021	Wrong Age Group	https://dx.doi.org/10.1016/S1474-44222100241-6
Driscoll 2021	Wrong Age Group	https://dx.doi.org/10.1002/epi4.12492
Esteves 2020	Wrong Age Group	https://dx.doi.org/10.1002/hon.2789
Fabio 2020	Wrong Age Group	https://dx.doi.org/10.3390/brainsci10050276
Farrukh 2020	Wrong Age Group	
Fisher 2021	Wrong Age Group	https://dx.doi.org/10.1038/s41591-020-01193-6
Foo 2019	Wrong Age Group	https://dx.doi.org/10.1016/j.yebeh.2019.106505
Furie 2019	Wrong Age Group	https://dx.doi.org/10.1172/JCI124466
Gast 2023	Wrong Age Group	https://doi.org/10.1111/jar.13041
Gatzoulis 2019	Wrong Age Group	https://dx.doi.org/10.1161/CIRCULATIONAHA.118.033575

Gatzoulis 2019	Wrong Age Group	https://dx.doi.org/10.1161/CIRCULATIONAHA.118.033575
Germain 2019	Wrong Age Group	https://dx.doi.org/10.1038/s41436-019-0451-z
Giugliani 2021	Wrong Age Group	https://dx.doi.org/10.1016/j.ymthe.2021.03.019
Goodall 2024	Wrong Age Group	https://dx.doi.org/10.1016/S2213-26002400186-3
Guffon 2022	Wrong Age Group	https://dx.doi.org/10.1002/jimd.12467
Gul 2020	Wrong Age Group	https://dx.doi.org/10.12659/MSM.919166
Han 2023	Wrong Age Group	https://dx.doi.org/10.1177/13623613231169547
Harrison 2023	Wrong Age Group	https://dx.doi.org/10.1016/j.jhepr.2022.100563
Hazegh 2024	Wrong Age Group	https://doi.org/10.48307/IAHSJ.2023.407118.1011
Hessl 2019	Wrong Age Group	https://dx.doi.org/10.1371/journal.pone.0209984
Higashida 2019	Wrong Age Group	https://dx.doi.org/10.3390/diseases7010024
Horrigan 2020	Wrong Age Group	https://dx.doi.org/10.1016/j.pediatrneurol.2020.08.001
Iannone 2021	Wrong Age Group	https://dx.doi.org/10.3389/fneur.2021.673135
Imel 2019	Wrong Age Group	https://dx.doi.org/10.1002/jbmr.3715
Jolly 2020	Wrong Age Group	https://dx.doi.org/10.1159/000505001
Kahraman 2021	Wrong Age Group	https://dx.doi.org/10.1177/1120672120977824
Kanazawa 2023	Wrong Age Group	https://dx.doi.org/10.1186/s12969-023-00817-8
Kerr 2022	Wrong Age Group	https://dx.doi.org/10.1111/epi.17411
Kishnani 2023	Wrong Age Group	https://dx.doi.org/10.1001/jamaneurol.2023.0552
Klein 2021	Wrong Age Group	https://dx.doi.org/10.1056/NEJMoa2027892
Klopstock 2019	Wrong Age Group	https://dx.doi.org/10.1016/S1474-44221930142-5
Klopstock 2021	Wrong Age Group	https://dx.doi.org/10.1002/mds.28392
Kvanta 2024	Wrong Age Group	https://dx.doi.org/10.1038/s41467-024-51575-4
Latreche 2024	Wrong Age Group	https://dx.doi.org/10.1016/j.psychres.2024.115835
Lazareva 2024	Wrong Age Group	https://dx.doi.org/10.1016/j.orcp.2024.07.001
Lee 2023	Wrong Age Group	https://doi.org/10.1016/j.amjcard.2023.06.018
Levy 2024	Wrong Age Group	https://dx.doi.org/10.1016/j.xhgg.2024.100393
LorcaLarrosa 2019	Wrong Age Group	https://dx.doi.org/10.1111/jir.12593
Maguire 2019	Wrong Age Group	https://dx.doi.org/10.1016/j.ophtha.2019.06.017
Maguire 2021	Wrong Age Group	https://dx.doi.org/10.1016/j.ophtha.2021.03.031
Marathe 2023	Wrong Age Group	https://doi.org/10.1007/s13555-023-00923-1
Martakis 2023	Wrong Age Group	https://dx.doi.org/10.1212/WNL.0000000000201660
McKinney 2024	Wrong Age Group	https://dx.doi.org/10.1089/cap.2024.0103
Merritt 2020	Wrong Age Group	https://doi.org/10.1177/0269881120922967
Miller 2022	Wrong Age Group	https://dx.doi.org/10.1210/clinem/dgac105
Miller 2023	Wrong Age Group	https://dx.doi.org/10.1210/clinem/dgad014
Nguyen 2021	Wrong Age Group	https://dx.doi.org/10.1210/clinem/dgab499
Nguyen 2022	Wrong Age Group	https://dx.doi.org/10.1002/jbm4.10597
Ni 2024	Wrong Age Group	https://dx.doi.org/10.1007/s10803-024-06477-1
Oldrati 2024	Wrong Age Group	https://dx.doi.org/10.1016/j.nicl.2024.103582
Parhizkar 2024	Wrong Age Group	https://dx.doi.org/10.1186/s12879-024-09211-5
Perez 2021	Wrong Age Group	https://dx.doi.org/10.1111/dom.14366
Pignolo 2022	Wrong Age Group	https://dx.doi.org/10.1002/jbmr.4655

Polymeropoulos 2021	Wrong Age Group	https://dx.doi.org/10.1038/s41436-021-01282-y
Punia 2024	Wrong Age Group	https://dx.doi.org/10.1007/s00415-024-12399-w
Ramerman 2019	Wrong Age Group	https://dx.doi.org/10.1111/jir.12584
Sarin 2024	Wrong Age Group	https://dx.doi.org/10.1126/sciadv.adk4946
Srivastava 2022	Wrong Age Group	https://dx.doi.org/10.1093/hmg/ddac111
Taylor 2019	Wrong Age Group	https://dx.doi.org/10.1212/WNL.0000000000006950
Tiraboschi 2023	Wrong Age Group	https://dx.doi.org/10.1007/s10928-023-09874-8
Vossler 2020	Wrong Age Group	https://dx.doi.org/10.1136/jnnp-2020-323524
Wagner 2024	Wrong Age Group	https://dx.doi.org/10.1111/cts.13832
Warren 2022	Wrong Age Group	https://dx.doi.org/10.1002/ana.26368
Wong 2024	Wrong Age Group	https://dx.doi.org/10.1177/13623613231225899
Abreu, 2021	Wrong Article Type	
Acheson 2023	Wrong Article Type	https://dx.doi.org/10.1080/0075417X.2023.2246077
Adams, 2019	Wrong Article Type	
Adang 2022	Wrong Article Type	https://dx.doi.org/10.1016/j.ymgme.2022.06.003
Aguayo 2023	Wrong Article Type	https://dx.doi.org/10.1038/s43016-023-00703-2
Ahadi, 2020	Wrong Article Type	
Ali 2019	Wrong Article Type	https://dx.doi.org/10.1111/dmcn.14087
Alsayouf 2024	Wrong Article Type	https://dx.doi.org/10.3390/children11020163
Ameri 2019	Wrong Article Type	https://dx.doi.org/10.1111/bjd.18144
Anonymous 2020	Wrong Article Type	
Anonymous 2024	Wrong Article Type	https://dx.doi.org/10.1200/JCO-24-02561
Anonymous 2024	Wrong Article Type	https://dx.doi.org/10.1111/dmcn.16157
Anonymous 2024	Wrong Article Type	https://dx.doi.org/10.1371/journal.pone.0315226
Arya 2020	Wrong Article Type	https://doi.org/10.4103/apc.APC920
Auvin 2019	Wrong Article Type	https://dx.doi.org/10.1111/j.1527-3458.2008.00046.x
Auvin 2021	Wrong Article Type	https://doi.org/10.1016/j.ejpn.2021.03.002
Auvin 2023	Wrong Article Type	https://dx.doi.org/10.1111/epi.17618
Baderkhan, 2021	Wrong Article Type	
Barranco 2022	Wrong Article Type	https://dx.doi.org/10.1038/s41575-021-00558-7
Basmaison, 2019	Wrong Article Type	
Bast 2022	Wrong Article Type	https://dx.doi.org/10.1002/epi4.12628
Baumann, 2021	Wrong Article Type	
Bekkers, 2021	Wrong Article Type	
Berry-Kravis, 2020	Wrong Article Type	
Bharucha-Goebel 2024	Wrong Article Type	https://dx.doi.org/10.1056/NEJMoa2307952
Bird, 2021	Wrong Article Type	
Bruno, 2019	Wrong Article Type	
Callisto, 2020	Wrong Article Type	
Cappuccio, 2021	Wrong Article Type	
Carey-Smith 2024	Wrong Article Type	https://dx.doi.org/10.3324/haematol.2023.284271
Casas-Alba 2021	Wrong Article Type	https://dx.doi.org/10.1002/ajmg.a.61939
Casas-Alba, 2021	Wrong Article Type	

Chiriboga 2023	Wrong Article Type	https://doi.org/10.1007/s40120-023-00444-1
Clemens, 2020	Wrong Article Type	
Cockerell 2023	Wrong Article Type	https://dx.doi.org/10.1186/s13023-023-02982-1
Dahlgren 2021	Wrong Article Type	https://dx.doi.org/10.3389/fendo.2021.737893
Dahlgren, 2021	Wrong Article Type	
Dai, 2021	Wrong Article Type	
Darwish 2024	Wrong Article Type	https://dx.doi.org/10.1038/s41372-024-02056-5
Dawson, 2020	Wrong Article Type	
De 2019	Wrong Article Type	
de 2021	Wrong Article Type	
Deshpande, 2021	Wrong Article Type	
Devinsky 2019	Wrong Article Type	https://dx.doi.org/10.1111/epi.14628
Di, 2019	Wrong Article Type	
Diaz, 2021	Wrong Article Type	
Diaz-Manera, 2021	Wrong Article Type	
Dittrich, 2019	Wrong Article Type	
Efron, 2021	Wrong Article Type	
Eshraghi, 2019	Wrong Article Type	
Finkel, 2021	Wrong Article Type	
Fisher, 2021	Wrong Article Type	
Foland-Ross, 2019	Wrong Article Type	
Frank, 2020	Wrong Article Type	
Fujioka 2020	Wrong Article Type	https://dx.doi.org/10.1097/MD.0000000000019763
Fujioka, 2020	Wrong Article Type	
Fukunaga, 2020	Wrong Article Type	
Gamalero 2024	Wrong Article Type	https://dx.doi.org/10.55563/clinexprheumatol/oak19l
GanapathySankar 2020	Wrong Article Type	https://dx.doi.org/10.31838/ijpr/2020.sp2.470
Gil-Nagel 2021	Wrong Article Type	https://dx.doi.org/10.1016/j.yebeh.2021.108212
Giugliani, 2021	Wrong Article Type	
Groeneweg, 2019	Wrong Article Type	
Grohs, 2020	Wrong Article Type	
Grootjen, 2021	Wrong Article Type	
Gul, 2020	Wrong Article Type	
Hausman-Kedem, 2020	Wrong Article Type	
Haws 2021	Wrong Article Type	https://dx.doi.org/10.1016/j.conctc.2021.100780
Hessl, 2019	Wrong Article Type	
Hikita, 2020	Wrong Article Type	
Horikawa, 2020	Wrong Article Type	
Horrigan, 2020	Wrong Article Type	
Hoschler, 2020	Wrong Article Type	
Hughes 2023	Wrong Article Type	https://dx.doi.org/10.1056/NEJMc2308286

iDali, 2020	Wrong Article Type	
Ismail, 2020	Wrong Article Type	
Jacobs, 2020	Wrong Article Type	
Joshi 2024	Wrong Article Type	https://dx.doi.org/10.1177/15357597231225097
Jung 2023	Wrong Article Type	https://dx.doi.org/10.1186/s13063-023-07392-z
Kassai, 2019	Wrong Article Type	
Kishnani 2023	Wrong Article Type	https://dx.doi.org/10.1016/j.gim.2022.10.010
KizilcanCetin 2022	Wrong Article Type	https://dx.doi.org/10.4274/jcrpe.galenos.2022.2022-12-13
Klein, 2021	Wrong Article Type	
Klopstock, 2019	Wrong Article Type	
Klotz, 2021	Wrong Article Type	
Knupp 2023	Wrong Article Type	https://dx.doi.org/10.1111/epi.17431
Komaki, 2020	Wrong Article Type	
Kong, 2021	Wrong Article Type	
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Maguire, 2021	Wrong Article Type	
McDonald, 2021	Wrong Article Type	
Mendell, 2020	Wrong Article Type	
Mercuri 2022	Wrong Article Type	https://dx.doi.org/10.1016/S1474-4422%2821%2900367-7
Mercuri 2023	Wrong Article Type	https://dx.doi.org/10.1007/s00415-023-11687-1
Muenzer 2024	Wrong Article Type	https://dx.doi.org/10.1002/jimd.12790
Nasomyont, 2020	Wrong Article Type	
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Olmos 2020	Wrong Article Type	https://dx.doi.org/10.1186/s12879-020-05132-1
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Pekeles 2024	Wrong Article Type	https://dx.doi.org/10.1016/j.eclinm.2024.102740
Perry 2019	Wrong Article Type	https://dx.doi.org/10.1177/1535759719835671
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Pobric 2019	Wrong Article Type	
Polymeropoulos, 2021	Wrong Article Type	
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Scheffer 2021	Wrong Article Type	https://dx.doi.org/10.1111/epi.17036
Schroder, 2019	Wrong Article Type	
Sharawat 2020	Wrong Article Type	https://dx.doi.org/10.4103/aian.AIAN_204_19
Sharawat, 2020	Wrong Article Type	
Shovlin 2022	Wrong Article Type	https://dx.doi.org/10.3389/fnins.2022.868008

Sikic 2024	Wrong Article Type	https://dx.doi.org/10.1002/jmd2.12439
Smith 2020	Wrong Article Type	https://dx.doi.org/10.1371/journal.pmed.1003222
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Souza 2021	Wrong Article Type	https://dx.doi.org/10.1183/13993003.01407-2020
Ssemata, 2020	Wrong Article Type	
Sullivan 2020	Wrong Article Type	https://dx.doi.org/10.1111/epi.16722
Suo, 2021	Wrong Article Type	
Taylor, 2019	Wrong Article Type	
Teng 2022	Wrong Article Type	https://dx.doi.org/10.1016/j.jaad.2022.07.028
Thiele 2019	Wrong Article Type	https://dx.doi.org/10.1111/epi.14670
Thiele 2022	Wrong Article Type	https://dx.doi.org/10.1111/epi.17150
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Unknown Authors 2020	Wrong Article Type	
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vanTilburg 2024	Wrong Article Type	https://dx.doi.org/10.1186/s12885-024-11820-x
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Weiner 2022	Wrong Article Type	https://dx.doi.org/10.1002/ppul.25894
Wijburg 2021	Wrong Article Type	https://dx.doi.org/10.1016/j.ymgme.2021.07.001
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Yu 2021	Wrong Article Type	https://dx.doi.org/10.1002/lary.29290
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Anderson 2021	Wrong Condition not ID	https://dx.doi.org/10.1016/j.yebeh.2021.108325
Anto 2019	Wrong Condition not ID	https://dx.doi.org/10.3889/oamjms.2019.299
Argente 2024	Wrong Condition not ID	https://dx.doi.org/10.1016/S2213-85872400273-0
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Azevedo 2023	Wrong Condition not ID	https://dx.doi.org/10.1016/j.yebeh.2023.109512

Azizi 2020	Wrong Condition not ID	https://dx.doi.org/10.32598/bcn.11.4.1211.1
Balevic 2022	Wrong Condition not ID	https://dx.doi.org/10.1136/lupus-2022-000811
Bashiri 2024	Wrong Condition not ID	https://dx.doi.org/10.3390/children11101187
Basmaison 2019	Wrong Condition not ID	https://dx.doi.org/10.1016/j.ando.2019.02.001
Baumann 2021	Wrong Condition not ID	https://dx.doi.org/10.1016/j.clinre.2021.101751
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Belostotsky 2024	Wrong Condition not ID	https://dx.doi.org/10.1177/20543581241234723
Berger 2023	Wrong Condition not ID	https://dx.doi.org/10.3390/jcm12237494
Boone 2020	Wrong Condition not ID	https://dx.doi.org/10.1542/peds.2020-0715
Bourikas 2025	Wrong Condition not ID	https://dx.doi.org/10.1016/j.eplepsyres.2024.107482
Braniecki 2024	Wrong Condition not ID	https://dx.doi.org/10.3389/fneur.2024.1263373
Bravo 2021	Wrong Condition not ID	https://doi.org/10.1111/jpc.15344
Brito 2021	Wrong Condition not ID	https://dx.doi.org/10.1016/j.jped.2019.10.012
Brogan 2019	Wrong Condition not ID	https://dx.doi.org/10.1002/art.41004
Cappadona 2023	Wrong Condition not ID	https://dx.doi.org/10.3390/children10081336
Cappagli 2019	Wrong Condition not ID	https://dx.doi.org/10.1038/s41598-019-39981-x
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Chen 2024	Wrong Condition not ID	https://dx.doi.org/10.3389/fimmu.2024.1336599
Chiriboga 2024	Wrong Condition not ID	https://dx.doi.org/10.1007/s00415-024-12318-z
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Daniels 2023	Wrong Condition not ID	https://dx.doi.org/10.1186/s13229-023-00546-5
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Dauber 2024	Wrong Condition not ID	https://dx.doi.org/10.1016/j.eclinm.2024.102591
Dawson 2020	Wrong Condition not ID	https://dx.doi.org/10.1016/j.jpeds.2020.03.011
denHollander 2024	Wrong Condition not ID	https://dx.doi.org/10.1016/j.ymgme.2024.108347
DiLorenzo 2024	Wrong Condition not ID	https://dx.doi.org/10.1002/jpn3.12306
Doaei 2021	Wrong Condition not ID	https://dx.doi.org/10.5114/pedm.2020.101806
Drabinska 2019	Wrong Condition not ID	https://dx.doi.org/10.1016/j.bone.2019.03.001
Easterlin 2021	Wrong Condition not ID	https://dx.doi.org/10.1038/s41372-021-00931-z
Egberts 2022	Wrong Condition not ID	https://dx.doi.org/10.1055/a-1716-1856
Elson 2019	Wrong Condition not ID	https://dx.doi.org/10.1371/journal.pntd.0007822
Esposito 2022	Wrong Condition not ID	https://dx.doi.org/10.3389/fendo.2022.923448
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Fayoux 2024	Wrong Condition not ID	https://dx.doi.org/10.1111/dmcn.15841
Feng 2022	Wrong Condition not ID	https://dx.doi.org/10.3389/fped.2022.990724
Ferrero 2024	Wrong Condition not ID	https://dx.doi.org/10.1007/s40272-024-00625-x
Foland-Ross 2019	Wrong Condition not ID	https://dx.doi.org/10.1016/j.psyneuen.2018.09.039
Gallini 2024	Wrong Condition not ID	https://dx.doi.org/10.1001/jamanetworkopen.2024.35347
Gao 2024	Wrong Condition not ID	https://dx.doi.org/10.1055/a-2407-9446

Garner 2024	Wrong Condition not ID	https://doi.org/10.1210/clinem/dgad717
Gaudet 2022	Wrong Condition not ID	https://doi.org/10.1016/j.jacl.2022.07.005
Grohs 2020	Wrong Condition not ID	https://dx.doi.org/10.3389/fnhum.2020.608131
Handisides 2019	Wrong Condition not ID	https://dx.doi.org/10.1016/j.jpeds.2018.08.061
Heinen 2021	Wrong Condition not ID	https://dx.doi.org/10.3233/PRM-210040
Hoschler 2020	Wrong Condition not ID	https://dx.doi.org/10.1016/j.vaccine.2020.02.024
Hunt 2021	Wrong Condition not ID	https://dx.doi.org/10.1001/jamanetworkopen.2021.39604
Jacobs 2020	Wrong Condition not ID	https://dx.doi.org/10.1016/S2352-46422030104-8
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Juujarvi 2019	Wrong Condition not ID	https://dx.doi.org/10.1111/apa.14614
Kean 2022	Wrong Condition not ID	https://dx.doi.org/10.1002/ptr.7372
Keller 2024	Wrong Condition not ID	https://dx.doi.org/10.1038/s41467-024-47057-2
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Khanam 2022	Wrong Condition not ID	https://dx.doi.org/10.3329/bjms.v21i4.60282
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Kim 2024	Wrong Condition not ID	https://dx.doi.org/10.4097/kja.23747
Kiritsi 2024	Wrong Condition not ID	https://dx.doi.org/10.1016/j.eclinm.2024.102900
Klotz 2021	Wrong Condition not ID	https://dx.doi.org/10.1007/s40263-021-00867-0
Knupp 2022	Wrong Condition not ID	https://dx.doi.org/10.1177/08830738211073400
Ko 2021	Wrong Condition not ID	https://dx.doi.org/10.3389/fped.2021.713792
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Lazzaro 2021	Wrong Condition not ID	https://dx.doi.org/10.1016/bs.pbr.2021.01.015
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Minor 2023	Wrong Condition not ID	https://dx.doi.org/10.1016/j.clnesp.2023.04.004
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Mobini 2022	Wrong Condition not ID	https://dx.doi.org/10.3390/jcm11010247
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Morales-Quezada 2019	Wrong Condition not ID	https://dx.doi.org/10.1016/j.yebeh.2019.106570
Mufti 2025	Wrong Condition not ID	https://dx.doi.org/10.1016/j.jnrt.2024.100169
Natalucci 2020	Wrong Condition not ID	https://dx.doi.org/10.1001/jama.2020.19395
Newfield 2023	Wrong Condition not ID	https://dx.doi.org/10.1210/clinem/dgad270

Ng 2020	Wrong Condition not ID	https://dx.doi.org/10.1089/thy.2019.0293
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Raman 2023	Wrong Condition not ID	https://dx.doi.org/10.1001/jamapediatrics.2022.4912
Ramaswami 2019	Wrong Condition not ID	https://dx.doi.org/10.1016/j.ymgme.2019.03.010
Reddihough 2019	Wrong Condition not ID	https://dx.doi.org/10.1001/jama.2019.14685
Reshef 2019	Wrong Condition not ID	https://dx.doi.org/10.1111/pai.13065
Roudi 2020	Wrong Condition not ID	https://dx.doi.org/10.5812/ijp.102118
Samir 2022	Wrong Condition not ID	https://dx.doi.org/10.3233/NPM-200659
Sarafoglou 2024	Wrong Condition not ID	https://dx.doi.org/10.1056/NEJMoa2404655
Schiller 2023	Wrong Condition not ID	https://dx.doi.org/10.1093/brain/awac380
Schroder 2019	Wrong Condition not ID	https://dx.doi.org/10.1007/s10803-019-04046-5
Schulz 2024	Wrong Condition not ID	https://dx.doi.org/10.1016/S1474-44222300384-8
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Singh 2019	Wrong Condition not ID	https://dx.doi.org/10.1111/pan.13582
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Sofyani 2020	Wrong Condition not ID	https://dx.doi.org/10.3889/oamjms.2020.3285
Ssemata 2020	Wrong Condition not ID	https://dx.doi.org/10.1038/s41390-020-0957-8
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Sun 2023	Wrong Condition not ID	https://dx.doi.org/10.23812/j.biol.regul.homeost.agents.20233706.287
Suo 2021	Wrong Condition not ID	https://dx.doi.org/10.1007/s13760-021-01613-5
Tauzin 2021	Wrong Condition not ID	https://dx.doi.org/10.1016/j.jpeds.2020.12.001
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Thompson 2020	Wrong Condition not ID	https://dx.doi.org/10.1016/j.yebeh.2020.107299
Trzcinska 2021	Wrong Condition not ID	https://dx.doi.org/10.3390/ijerph19010065
Vaisbich 2022	Wrong Condition not ID	https://dx.doi.org/10.1002/jmd2.12260
Wang 2023	Wrong Condition not ID	https://doi.org/10.1002/aur.3018
Ward 2021	Wrong Condition not ID	https://dx.doi.org/10.1210/clinem/dgab458

Wawrzynski 2024	Wrong Condition not ID	https://dx.doi.org/10.1038/s41433-023-02859-4
Weinstein 2024	Wrong Condition not ID	https://dx.doi.org/10.1186/s13023-024-03274-y
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Wu 2022	Wrong Condition not ID	https://dx.doi.org/10.1056/NEJMoa2119660
Xu 2022	Wrong Condition not ID	https://dx.doi.org/10.1186/s40001-022-00890-x
Yoshinaga 2023	Wrong Condition not ID	https://dx.doi.org/10.3805/eands.15.1
Yuan 2022	Wrong Condition not ID	https://dx.doi.org/10.3389/fendo.2022.864908
Zemestani 2022	Wrong Condition not ID	https://dx.doi.org/10.1002/aur.2803
Zeng 2024	Wrong Condition not ID	https://dx.doi.org/10.1007/s00415-024-12416-y
Zha 2022	Wrong Condition not ID	https://dx.doi.org/10.1097/MD.0000000000031495
Zhang 2023	Wrong Condition not ID	https://dx.doi.org/10.1186/s12969-023-00881-0
Zhu 2022	Wrong Condition not ID	https://dx.doi.org/10.3389/fphar.2022.903488
Zhuxiao 2023	Wrong Condition not ID	https://dx.doi.org/10.1016/j.eclinm.2023.101844
Adams 2019	Wrong Interventions	https://dx.doi.org/10.1177/1740774519855715
Arnold 2019	Wrong Interventions	https://dx.doi.org/10.2147/OPTH.S219031
AtalanEfkere 2024	Wrong Interventions	https://dx.doi.org/10.1080/08990220.2023.2183829
Bekkers 2021	Wrong Interventions	https://dx.doi.org/10.1111/dmcn.14924
Bentenuto 2020	Wrong Interventions	https://dx.doi.org/10.3390/brainsci10050289
Chan 2022	Wrong Interventions	https://dx.doi.org/10.1038/s41598-022-18286-6
DeKorte 2020	Wrong Interventions	https://dx.doi.org/10.1177/1362361320935006
deMoraes 2020	Wrong Interventions	https://dx.doi.org/10.1002/aur.2208
deWeger 2019	Wrong Interventions	https://dx.doi.org/10.1111/aos.13944
deWeger 2020	Wrong Interventions	https://dx.doi.org/10.1111/aos.14186
deWeger 2021	Wrong Interventions	https://dx.doi.org/10.1038/s41598-021-96308-5
Fauroux 2024	Wrong Interventions	https://dx.doi.org/10.1016/j.lanepe.2024.101035
Garcia-Galant 2023	Wrong Interventions	https://dx.doi.org/10.1007/s00431-023-05072-3
Ghafoor 2021	Wrong Interventions	
Gundogmus 2024	Wrong Interventions	https://dx.doi.org/10.5014/ajot.2024.050706
Huschner 2023	Wrong Interventions	https://dx.doi.org/10.1038/s41467-023-42855-6
Ismail 2020	Wrong Interventions	https://dx.doi.org/10.3389/fped.2020.00426
Jang 2019	Wrong Interventions	https://dx.doi.org/10.3343/alm.2019.39.3.299
Khorana 2020	Wrong Interventions	https://dx.doi.org/10.35755/jmedassocthai.2020.06.11026
Kotulska 2021	Wrong Interventions	https://dx.doi.org/10.1002/ana.25956
Kurt-Aydin 2024	Wrong Interventions	https://dx.doi.org/10.1002/mus.28084
Lai 2024	Wrong Interventions	https://dx.doi.org/10.1080/10400435.2023.2267626
Li 2019	Wrong Interventions	https://dx.doi.org/10.1007/s12031-018-1239-3
Luyt 2019	Wrong Interventions	https://dx.doi.org/10.3310/hta23040
Luyt 2020	Wrong Interventions	https://dx.doi.org/10.1136/archdischild-2019-318231
Megerian 2022	Wrong Interventions	https://dx.doi.org/10.1038/s41746-022-00598-6
Nabil 2023	Wrong Interventions	https://dx.doi.org/10.4103/ija.ija_471_23
Ozsoy 2023	Wrong Interventions	https://dx.doi.org/10.1007/s13760-023-02370-3
Preetha 2024	Wrong Interventions	https://doi.org/10.37506/akrs4x83
Regani 2023	Wrong Interventions	https://dx.doi.org/10.4103/IJO.IJO_2992_22

Vineet 2019	Wrong Interventions	https://doi.org/10.443/JDOH/Vineet07
Witters, 2021	Wrong Interventions	
Xu 2021	Wrong Interventions	https://dx.doi.org/10.1016/j.eplepsyres.2021.106621
Yang 2024	Wrong Interventions	https://dx.doi.org/10.1111/cns.14917
Zhou 2021	Wrong Interventions	https://dx.doi.org/10.3389/fped.2021.664801
Kokoreva 2023	Wrong Language not English	https://dx.doi.org/10.14341/probl13141
Azizi, 2020	Wrong Language not English	
DiazHurtado 2024	Wrong Language not English	https://dx.doi.org/10.20882/adicciones.1912
Dun 2019	Wrong Language not English	https://dx.doi.org/10.3760/cma.j.issn.0578-1310.2019.11.007
Fateeva 2023	Wrong Language not English	https://dx.doi.org/10.17116/jnevro202312312268
Fischetto, 2020	Wrong Language not English	
Fukunaga 2020	Wrong Language not English	https://dx.doi.org/10.15036/arerugi.69.192
Ganapathy 2020	Wrong Language not English	
Jiang 2023	Wrong Language not English	https://dx.doi.org/10.3760/cma.j.cn112140-20230131-00067
Lai, 2020	Wrong Language not English	
Nesterova 2022	Wrong Language not English	https://dx.doi.org/10.15690/pf.v19i5.2466
Sa 2024	Wrong Language not English	https://dx.doi.org/10.7499/j.issn.1008-8830.2308013
Sofyani, 2020	Wrong Language not English	
Tang 2023	Wrong Language not English	https://dx.doi.org/10.3760/cma.j.cn101070-20230530-00425
Tian 2023	Wrong Language not English	https://dx.doi.org/10.3969/j.issn.1001-5256.2023.09.017
Yeraliyeva 2020	Wrong Language not English	https://dx.doi.org/10.20953/1817-7646-2020-6-27-34
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Yuan 2021	Wrong Language not English	https://dx.doi.org/10.7499/j.issn.1008-8830.2106042
Zavadenko 2019	Wrong Language not English	https://dx.doi.org/10.17116/jnevro201911910130
Zavadenko 2020	Wrong Language not English	https://dx.doi.org/10.17116/jnevro202012009128
Abreu 2021	Wrong Outcomes	https://dx.doi.org/10.1172/jci.insight.145188
Agarwal 2022	Wrong Outcomes	https://dx.doi.org/10.1016/j.ejpn.2022.05.006
Ahadi 2020	Wrong Outcomes	https://dx.doi.org/10.4103/jrpp.JRPP_20_53
Ahmet 2024	Wrong Outcomes	https://dx.doi.org/10.1210/clinem/dgae521
Akhtar 2024	Wrong Outcomes	https://dx.doi.org/10.2147/MDER.S484354
AlAaraj 2019	Wrong Outcomes	https://dx.doi.org/10.23750/abm.v90i8-S.8503
Alfadhel 2021	Wrong Outcomes	https://dx.doi.org/10.1186/s13023-021-02032-8
Antonarakis 2020	Wrong Outcomes	https://dx.doi.org/10.1016/j.nmd.2019.11.009
Archna 2022	Wrong Outcomes	https://dx.doi.org/10.1016/j.seizure.2022.10.015

Arzimanoglou 2021	Wrong Outcomes	https://dx.doi.org/10.1016/j.yebeh.2021.108275
Auvin 2019	Wrong Outcomes	https://dx.doi.org/10.1002/epi4.12314
Bagherian 2019	Wrong Outcomes	
Bajestani 2021	Wrong Outcomes	
Bakhtiary 2021	Wrong Outcomes	https://dx.doi.org/10.22037/ijcn.v15i4.30591
Barbero 2021	Wrong Outcomes	https://doi.org/10.1177/1055665620964141
Best 2019	Wrong Outcomes	https://dx.doi.org/10.1016/j.jpeds.2018.10.042
Bianchi 2022	Wrong Outcomes	https://dx.doi.org/10.1002/jbm4.10685
Boal 2020	Wrong Outcomes	https://dx.doi.org/10.1158/1078-0432.CCR-20-1696
Bourke 2021	Wrong Outcomes	https://dx.doi.org/10.1212/CPJ.0000000000001023
BuxbaumGrice 2024	Wrong Outcomes	https://dx.doi.org/10.1038/s41398-024-03005-8
Cappuccio 2021	Wrong Outcomes	https://dx.doi.org/10.1002/ajmg.a.62019
Clemens 2020	Wrong Outcomes	https://dx.doi.org/10.1001/jamaneurol.2020.1264
Clemens 2022	Wrong Outcomes	https://doi.org/10.3233/JND-220811
Crow 2024	Wrong Outcomes	https://dx.doi.org/10.1111/dmcn.16199
Cunha 2024	Wrong Outcomes	https://dx.doi.org/10.1155/2024/5522139
Daly 2019	Wrong Outcomes	https://dx.doi.org/10.3390/nu11030520
Daly 2019	Wrong Outcomes	https://dx.doi.org/10.1186/s13023-019-1011-y
Daly 2021	Wrong Outcomes	https://dx.doi.org/10.3390/nu13062075
Dang 2024	Wrong Outcomes	https://dx.doi.org/10.1212/WNL.0000000000208112
Deshpande 2021	Wrong Outcomes	https://dx.doi.org/10.1111/scd.12597
Deswal 2022	Wrong Outcomes	https://dx.doi.org/10.4103/aian.aian_481_22
Devinsky 2021	Wrong Outcomes	https://dx.doi.org/10.1002/acn3.51306
Diaz 2021	Wrong Outcomes	https://dx.doi.org/10.1038/s41436-021-01156-3
Diaz 2021	Wrong Outcomes	https://dx.doi.org/10.1002/jimd.12343
Diene 2022	Wrong Outcomes	https://dx.doi.org/10.1210/clinem/dgac549
Dittrich 2019	Wrong Outcomes	https://dx.doi.org/10.1186/s13023-019-1066-9
Efron 2021	Wrong Outcomes	https://dx.doi.org/10.1111/bcp.14399
Eid 2022	Wrong Outcomes	https://doi.org/10.12968/ijtr.2020.0162
Elsadek 2021	Wrong Outcomes	https://dx.doi.org/10.1016/j.jocn.2021.10.021
Eshraghi 2019	Wrong Outcomes	https://dx.doi.org/10.1515/jpem-2018-0503
Finanger 2019	Wrong Outcomes	https://dx.doi.org/10.3233/JND-180341
Finkel 2021	Wrong Outcomes	https://dx.doi.org/10.1016/j.nmd.2021.02.001
Flanigan 2022	Wrong Outcomes	https://dx.doi.org/10.1016/j.omtm.2022.08.009
Frank 2020	Wrong Outcomes	https://dx.doi.org/10.1212/WNL.0000000000009233
Fumagalli 2022	Wrong Outcomes	https://dx.doi.org/10.1016/S0140-67362102017-1
Galetaki 2024	Wrong Outcomes	https://dx.doi.org/10.1159/000542102
Groeneweg 2019	Wrong Outcomes	https://dx.doi.org/10.1016/S2213-85871930155-X
Guglieri 2022	Wrong Outcomes	https://dx.doi.org/10.1001/jamaneurol.2022.2480
Hafner 2019	Wrong Outcomes	https://dx.doi.org/10.1001/jamanetworkopen.2019.14171
Hamod 2022	Wrong Outcomes	https://dx.doi.org/10.1155/2022/7344928
Haqq 2022	Wrong Outcomes	https://dx.doi.org/10.1016/S2213-8587%2822%2900277-7
Harper 2024	Wrong Outcomes	https://dx.doi.org/10.1038/s41598-024-70783-y

Henzi 2023	Wrong Outcomes	https://dx.doi.org/10.1016/S1474-4422%2823%2900285-5
Henzi 2024	Wrong Outcomes	https://dx.doi.org/10.1007/s00431-024-05670-9
Hitzler 2021	Wrong Outcomes	https://dx.doi.org/10.1182/blood.2021012206
Hoffman 2019	Wrong Outcomes	https://dx.doi.org/10.1212/WNL.0000000000008168
Horikawa 2020	Wrong Outcomes	https://dx.doi.org/10.1507/endocrj.EJ19-0371
Horikawa 2022	Wrong Outcomes	https://dx.doi.org/10.1159/000524600
Huang 2024	Wrong Outcomes	https://dx.doi.org/10.1007/s12519-024-00824-z
IDali 2020	Wrong Outcomes	https://dx.doi.org/10.1016/j.ymgme.2020.07.002
Imbard 2022	Wrong Outcomes	https://dx.doi.org/10.1186/s13023-022-02567-4
Kassai 2019	Wrong Outcomes	https://dx.doi.org/10.1186/s12887-019-1544-1
Katz 2022	Wrong Outcomes	https://dx.doi.org/10.1136/thoraxjnl-2021-218196
Keary 2023	Wrong Outcomes	https://dx.doi.org/10.1016/j.ejpn.2023.07.008
Khan 2019	Wrong Outcomes	https://dx.doi.org/10.3233/JND-180351
Koeberl 2024	Wrong Outcomes	https://dx.doi.org/10.1038/s41586-024-07266-7
Komaki 2020	Wrong Outcomes	https://dx.doi.org/10.1002/acn3.50978
Komaki 2020	Wrong Outcomes	https://dx.doi.org/10.1002/acn3.51235
Kong 2021	Wrong Outcomes	https://dx.doi.org/10.1007/s12602-021-09800-9
Kroll 2020	Wrong Outcomes	https://dx.doi.org/10.3324/haematol.2019.224774
Lai 2020	Wrong Outcomes	https://dx.doi.org/10.1111/epi.16638
Lauer 2023	Wrong Outcomes	https://dx.doi.org/10.1038/s41467-023-37262-w
Lewis 2023	Wrong Outcomes	https://dx.doi.org/10.1186/s13023-023-02756-9
Li 2020	Wrong Outcomes	https://dx.doi.org/10.1002/jcph.1632
Li 2024	Wrong Outcomes	https://dx.doi.org/10.1038/s41598-024-59320-z
Lund 2019	Wrong Outcomes	https://dx.doi.org/10.1038/s41598-019-50595-1
Luo 2023	Wrong Outcomes	https://dx.doi.org/10.3389/fped.2023.1187078
Mah 2022	Wrong Outcomes	https://dx.doi.org/10.1001/jamanetworkopen.2021.44178
Martinez-Monseny 2019	Wrong Outcomes	https://dx.doi.org/10.1002/ana.25457
Mazaheri 2020	Wrong Outcomes	https://dx.doi.org/10.1007/s11255-019-02351-7
McDonald 2021	Wrong Outcomes	https://dx.doi.org/10.3233/JND-210643
McDonald 2022	Wrong Outcomes	https://dx.doi.org/10.1016/S0140-67362200012-5
Mendell 2020	Wrong Outcomes	https://dx.doi.org/10.1001/jamaneurol.2020.1484
Mendell 2024	Wrong Outcomes	https://dx.doi.org/10.1002/mus.27955
Mendell 2024	Wrong Outcomes	https://dx.doi.org/10.1038/s41591-024-03304-z
Mercuri 2024	Wrong Outcomes	https://dx.doi.org/10.1016/S1474-44222400036-X
Muntau 2024	Wrong Outcomes	https://dx.doi.org/10.1016/S0140-67362401556-3
Muntoni 2019	Wrong Outcomes	https://dx.doi.org/10.1002/cpdd.642
Nasomyont 2020	Wrong Outcomes	https://dx.doi.org/10.1007/s00198-020-05549-z
Okuyama 2019	Wrong Outcomes	https://dx.doi.org/10.1016/j.ymthe.2018.12.005
PegancNuncic 2024	Wrong Outcomes	https://dx.doi.org/10.3389/fped.2024.1362918
Pinto 2024	Wrong Outcomes	https://dx.doi.org/10.1016/j.ymgme.2024.108607
Pollard 2022	Wrong Outcomes	https://dx.doi.org/10.1182/bloodadvances.2021006490
Previtali 2020	Wrong Outcomes	https://dx.doi.org/10.1016/j.phrs.2020.104999

Protic 2024	Wrong Outcomes	https://dx.doi.org/10.1177/20503121241282401
Qi 2019	Wrong Outcomes	https://dx.doi.org/10.1007/s40262-018-0721-y
Raman 2019	Wrong Outcomes	https://dx.doi.org/10.1161/JAHA.119.013501
Reddy 2022	Wrong Outcomes	https://dx.doi.org/10.1016/j.ejpn.2022.04.004
Reynolds 2021	Wrong Outcomes	https://dx.doi.org/10.1016/j.ymgmr.2021.100772
Rio 2024	Wrong Outcomes	https://dx.doi.org/10.1016/S0140-6736%2824%2901880-4
Rodriguez-Cruz 2019	Wrong Outcomes	https://dx.doi.org/10.1016/j.clnu.2018.10.017
Rossi 2024	Wrong Outcomes	https://dx.doi.org/10.1016/j.medj.2024.10.021
Schiava 2024	Wrong Outcomes	https://dx.doi.org/10.1212/WNL.0000000000209206
Servais 2022	Wrong Outcomes	https://dx.doi.org/10.1089/nat.2021.0043
Rodriguez 2022	Wrong Outcomes	
Unknown authors 2020	Wrong Outcomes	
Tiele 2019	Wrong Outcomes	https://dx.doi.org/10.1088/1752-7163/ab4097
Trueba-Timmermans 2024	Wrong Outcomes	https://dx.doi.org/10.1093/ejendo/lvae088
Trueba-Timmermans 2024	Wrong Outcomes	https://doi.org/10.1093/ejendo/lvae088
Tsabari 2021	Wrong Outcomes	https://dx.doi.org/10.1016/j.nmd.2021.05.005
Tsuji 2020	Wrong Outcomes	https://dx.doi.org/10.1038/s41598-020-61311-9
Tzifi 2022	Wrong Outcomes	https://dx.doi.org/10.1515/jpem-2021-0458
Ullrich 2020	Wrong Outcomes	https://dx.doi.org/10.1093/neuonc/noaa071
VanMontfort 2021	Wrong Outcomes	https://dx.doi.org/10.1159/000519963
vanWegberg 2021	Wrong Outcomes	https://dx.doi.org/10.1016/j.ymgme.2021.02.008
Vermeulen-Serpa 2024	Wrong Outcomes	https://dx.doi.org/10.3390/nu16193299
Villaldama-Soriano 2022	Wrong Outcomes	https://dx.doi.org/10.1111/ene.15184
Vita 2021	Wrong Outcomes	https://dx.doi.org/10.3390/brainsci11010115
Vossler 2024	Wrong Outcomes	https://dx.doi.org/10.1111/epi.18193
Wagdy 2024	Wrong Outcomes	https://doi.org/10.56984/8ZG020A29H
Wagner 2020	Wrong Outcomes	https://dx.doi.org/10.1016/j.nmd.2020.05.002
Wagner 2021	Wrong Outcomes	https://dx.doi.org/10.2217/bmm-2021-0222
Wagner 2021	Wrong Outcomes	https://dx.doi.org/10.1002/mus.27347
Wang 2024	Wrong Outcomes	https://dx.doi.org/10.1016/j.scib.2024.04.072
Wasfy 2020	Wrong Outcomes	https://dx.doi.org/10.1080/11101849.2020.1727669
Wheless 2019	Wrong Outcomes	https://dx.doi.org/10.1177/2329048X19835047
Wu 2022	Wrong Outcomes	https://dx.doi.org/10.1111/epi.17199
Xiong 2023	Wrong Outcomes	https://dx.doi.org/10.1371/journal.pone.0288863
Yamamoto 2024	Wrong Outcomes	https://dx.doi.org/10.1016/j.pediatrneurol.2023.11.014
YanninHernandez-delaCruz 2024	Wrong Outcomes	https://dx.doi.org/10.1016/j.braindev.2024.02.001
Zacharin 2021	Wrong Outcomes	https://dx.doi.org/10.1210/clinem/dgab302
Zhao 2023	Wrong Outcomes	https://dx.doi.org/10.1002/jnr.25187
Bozaci 2023	Wrong Study Design	https://dx.doi.org/10.1016/j.ymgmr.2023.100979
Zubarioglu 2023	Wrong Study Design	https://dx.doi.org/10.1111/jpc.16231

Grootjen 2022	Wrong Study Design	https://dx.doi.org/10.3390/jcm11092496
Yan 2022	Wrong Study Design	https://dx.doi.org/10.3389/fimmu.2022.1054422
Adams 2022	Wrong Study Design	https://dx.doi.org/10.1186/s12887-022-03628-0
Iwan 2021	Wrong Study Design	https://dx.doi.org/10.12688/f1000research.54556.2
Grootjen 2021	Wrong Study Design	https://dx.doi.org/10.1530/EJE-21-0211
Hikita 2020	Wrong Study Design	https://dx.doi.org/10.1177/2333794X20969281
Hausman-Kedem 2020	Wrong Study Design	https://dx.doi.org/10.1016/j.eplepsyres.2020.106325
Di 2019	Wrong Study Design	https://dx.doi.org/10.1089/hum.2019.049
Biag 2019	Wrong Study Design	https://dx.doi.org/10.1002/mgg3.956
Haller 2019	Wrong Study Design	https://dx.doi.org/10.1002/jmd2.12043
He 2024	Wrong Study Design	https://dx.doi.org/10.4314/tjpr.v23i8.12
Yi 2023	Wrong Study Design	https://dx.doi.org/10.3389/fphar.2023.1189058
Fischetto 2020	Wrong Study Design	https://dx.doi.org/10.1002/mgg3.1371
Ortolano 2024	Wrong Study Design	https://doi.org/10.3390/children11091136
Xie 2022	Wrong Study Design	https://doi.org/10.3389/fneur.2022.951850
denHollander 2023	Wrong Study Design	https://dx.doi.org/10.1002/jimd.12643
Strong 2024	Wrong Study Design	https://dx.doi.org/10.1186/s11689-024-09536-x
Witters 2021	Wrong Study Design	https://dx.doi.org/10.1186/s13023-020-01609-z

B.2. Post-hoc exclusion reason 1: secondary research

Study	Title	DOI
Forsythe 2023	Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet-Biedl syndrome: phase 3 trial results	https://dx.doi.org/10.1186/s13023-022-02602-4
Franz 2021	Adjunctive everolimus therapy for tuberous sclerosis complex-associated refractory seizures: Results from the postextension phase of EXIST-3	https://dx.doi.org/10.1111/epi.17099
Han 2019	A placebo-controlled trial of folic acid and betaine in identical twins with Angelman syndrome.	https://dx.doi.org/10.1186/s13023-019-1216-0
Juarez-Martinez 2022	Bumetanide Effects on Resting-State EEG in Tuberous Sclerosis Complex in Relation to Clinical Outcome: An Open-Label Study	https://dx.doi.org/10.3389/fnins.2022.879451
Kim 2022	Effects of Cannabidiol on Adaptive Behavior and Quality of Life in Pediatric Patients With Treatment-Resistant Epilepsy	https://dx.doi.org/10.3988/jcn.2022.18.5.547
McDonald 2024	Caregiver Global Impression Observations from EMBARK: A Phase 3 Study Evaluating Delandistrogene Moxeparvovec in Ambulatory Patients with Duchenne Muscular Dystrophy	https://dx.doi.org/10.1007/s40120-024-00685-8
Mizuguchi 2019	Everolimus for epilepsy and autism spectrum disorder in tuberous sclerosis complex: EXIST-3 substudy in Japan.	https://dx.doi.org/10.1016/j.braindev.2018.07.003
Neul 2024	Trofinetide Treatment Demonstrates a Benefit Over Placebo for the Ability to Communicate in Rett Syndrome	https://dx.doi.org/10.1016/j.pediatrneurol.2023.11.005
Walsh 2021	Impact of MEK Inhibitor Therapy on Neurocognitive Functioning in NF1	https://dx.doi.org/10.1212/NXG.0000000000000616
Yee 2023	A post hoc analysis of Projected Retained Ability Scores (PRAS) for the longitudinal assessment of cognitive functioning in patients with neuronopathic mucopolysaccharidosis II receiving intrathecal idursulfase-IT	https://dx.doi.org/10.1186/s13023-023-02957-2

B.3. Post-hoc exclusion reason 2: no trial registration

Study	Title	DOI
Bishop 2023	Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome	https://dx.doi.org/10.1016/j.yebeh.2022.108994
D'Onofrio 2020	Slow Titration of Cannabidiol Add-On in Drug-Resistant Epilepsies Can Improve Safety With Maintained Efficacy in an Open-Label Study	https://dx.doi.org/10.3389/fneur.2020.00829
D'Urso 2022	Cerebellar transcranial direct current stimulation in children with autism spectrum disorder: A pilot study on efficacy, feasibility, safety, and unexpected outcomes in tic disorder and epilepsy	https://dx.doi.org/10.3390/jcm11010143
El-Sharkawy 2024	The beneficial effect of probiotics as an adjuvant treatment in childhood drug resistant epilepsy: A prospective pilot study	https://dx.doi.org/10.1177/03946320241291276
Fernell 2021	Bumetanide for autism: Open-label trial in six children	https://dx.doi.org/10.1111/apa.15723
FeyziDehkharghani 2024	The effectiveness of transcranial direct current stimulation (tDCS) on information processing speed in children with intellectual disability	https://dx.doi.org/10.1016/j.ridd.2024.104863
Herlopian 2020	Cannabidiol in treatment of refractory epileptic spasms: An open-label study	https://dx.doi.org/10.1016/j.yebeh.2020.106988
Hurley 2022	Efficacy and safety of cannabidivarin treatment of epilepsy in girls with Rett syndrome: A phase 1 clinical trial	https://dx.doi.org/10.1111/epi.17247
Jozwiak 2019	Preventive Antiepileptic Treatment in Tuberous Sclerosis Complex: A Long-Term, Prospective Trial	https://dx.doi.org/10.1016/j.pediatrneurol.2019.07.008
Kang 2022	Effects of 1Hz repetitive transcranial magnetic stimulation on autism with intellectual disability: A pilot study.	https://dx.doi.org/10.1016/j.compbiomed.2021.105167
Pietrafusa 2019	Purified Cannabidiol for Treatment of Refractory Epilepsies in Pediatric Patients with Developmental and Epileptic Encephalopathy	https://dx.doi.org/10.1007/s40272-019-00341-x
Sadowski 2022	Antiepileptic Effect and Safety Profile of Rapamycin in Pediatric Patients With Tuberous Sclerosis Complex	https://dx.doi.org/10.3389/fneur.2022.704978
San-Juan 2022	Safety and efficacy of cathodal transcranial direct current stimulation in patients with Lennox Gastaut Syndrome: An open-label, prospective, single-center, single-blinded, pilot study	https://dx.doi.org/10.1016/j.seizure.2022.06.009
Scala 2021	Epigallocatechin-3-Gallate Plus Omega-3 Restores the Mitochondrial Complex I and F_0F_1-ATP Synthase Activities in PBMCs of Young Children with Down Syndrome: A Pilot Study of Safety and Efficacy.	https://dx.doi.org/10.3390/antiox10030469
Wood 2019	Use of electropalatography in the treatment of speech disorders in children with Down syndrome: a randomized controlled trial	https://dx.doi.org/10.1111/1460-6984.12407

B.4. Included study reports

Article Number	Study	Title	DOI
#234	Abuatiq 2024[55]	Exploring the Efficacy of a Dynamic Harness System on Gross Motor Development and Motivation for Infants With Down Syndrome: A Pilot Study	https://dx.doi.org/10.1097/PEP.0000000000001130
#312	Amat-Bou 2020[135]	Effects of Bifidobacterium animalis Subsp. lactis (BPL1) Supplementation in Children and Adolescents with Prader–Willi Syndrome: A Randomized Crossover Trial	https://dx.doi.org/10.3390/nu12103123
#336	Arzimanoglou 2019[136]	Evaluation of long-term safety, tolerability, and behavioral outcomes with adjunctive rufinamide in pediatric patients (>=1 to <4 years old) with Lennox-Gastaut syndrome: Final results from randomized study 303	https://dx.doi.org/10.1016/j.ejpn.2018.09.010
#196	Azevedo 2021[137]	Transcranial Direct Current Stimulation for Prader-Willi Syndrome	10.1097/YCT.0000000000000722
#228	Bailey 2024[65]	Results of the ACTION-Galactosemia Kids Study to Evaluate the Effects of Govorestat in Pediatric Patients with Classic Galactosemia	https://dx.doi.org/10.1002/jcph.6170
#352	Bebin 2024[138]	Early Treatment with Vigabatrin Does Not Decrease Focal Seizures or Improve Cognition in Tuberous Sclerosis Complex: The PREVeNT Trial	https://dx.doi.org/10.1002/ana.26778
#271	Berry-Kravis 2022[100]	A randomized, controlled trial of ZYN002 cannabidiol transdermal gel in children and adolescents with fragile X syndrome (CONNECT-FX)	https://dx.doi.org/10.1186/s11689-022-09466-6
#246	Berry-Kravis 2023[139]	Effects of AFQ056 on language learning in fragile X syndrome	https://dx.doi.org/10.1172/JCI171723
#286	Berweck 2021[61]	Placebo-Controlled Clinical Trial of IncobotulinumtoxinA for Sialorrhea in Children	https://dx.doi.org/10.1212/WNL.0000000000012573
#347	Bhattacharya 2020[140]	Safety and Efficacy of Elosulface Alfa in Australian Patients with Morquio A Syndrome: A Phase 3b Study	https://dx.doi.org/10.1590/2326-4594-JIEMS-2020-0001
#316	Boroda 2020[141]	A randomized controlled trial of transcranial direct-current stimulation and cognitive training in children with fetal alcohol spectrum disorder	https://dx.doi.org/10.1016/j.brs.2020.04.015
#350	Bremova-Ertl 2024[142]	Trial of N-Acetyl-l-Leucine in Niemann–Pick Disease Type C	https://dx.doi.org/10.1056/NEJMoa2310151
#287	Budimirovic 2021[143]	Gaboxadol in Fragile X Syndrome: A 12-Week Randomized, Double-Blind, Parallel-Group, Phase 2a Study	https://dx.doi.org/10.3389/fphar.2021.757825

#218	Carson 2021[144]	Nutritional Formulation for Patients with Angelman Syndrome: A Randomized, Double-Blind, Placebo-Controlled Study of Exogenous Ketones	https://dx.doi.org/10.1093/jn/nxab284
#358	Cha 2023[145]	Safety and Efficacy of Allogeneic Umbilical Cord Blood Therapy for Global Development Delay and Intellectual Disability	https://dx.doi.org/10.1089/scd.2022.0252
#314	Chang 2020[146]	Pilot trial on the efficacy and safety of pantethine in children with pantothenate kinase-associated neurodegeneration: a single-arm, open-label study	https://dx.doi.org/10.1186/s13023-020-01530-5
#272	Cieuta-Walti 2022[147]	Safety and preliminary efficacy on cognitive performance and adaptive functionality of epigallocatechin gallate (EGCG) in children with Down syndrome. A randomized phase Ib clinical trial (PERSEUS study)	https://dx.doi.org/10.1016/j.gim.2022.06.011
#249	Combs 2023[148]	The combination of atomoxetine and oxybutynin for the treatment of obstructive sleep apnea in children with Down syndrome	https://dx.doi.org/10.5664/jcsm.10764
#194	Damen 2021[54]	Oxytocin in young children with Prader-Willi syndrome: Results of a randomized, double-blind, placebo-controlled, crossover trial investigating 3 months of oxytocin	https://dx.doi.org/10.1111/cen.14387
#369	Davidson 2021[149]	Effect of a multicomponent nutritional supplement on functional outcomes for Duchenne muscular dystrophy: A randomized controlled trial	https://dx.doi.org/10.1016/j.clnu.2021.06.008
#371	Devinsky 2021[150]	Effect of fenfluramine on convulsive seizures in CDKL5 deficiency disorder	https://dx.doi.org/10.1111/epi.16923
#325	Farmer 2019[62]	Long-term neuropsychological outcomes from an open-label phase 1/2a trial of 2-hydoxypropyl-β-cyclodextrins (VTS-270) in Niemann-Pick Disease, Type C1	https://dx.doi.org/10.1007/s40263-019-00642-2
#210	Fastman 2021[151]	A randomized controlled trial of intranasal oxytocin in Phelan-McDermid syndrome	https://dx.doi.org/10.1186/s13229-021-00459-1
#298	Finkel 2021[152]	A Randomized, Double-Blind, Placebo-Controlled, Global Phase 3 Study of Edasalonexent in Pediatric Patients with Duchenne Muscular Dystrophy: Results of the PolarisDMD Trial	https://dx.doi.org/10.3233/JND-210689
#367	Franz 2021[153]	Adjunctive everolimus therapy for tuberous sclerosis complex--associated refractory seizures: Results from the postextension phase of EXIST-3	https://dx.doi.org/10.1111/epi.17099
#300	Ghosh 2021[154]	High dose genistein in Sanfilippo syndrome: A randomised controlled trial	https://dx.doi.org/10.1002/jimd.12407
#219	Glaze 2019[155]	Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome	https://dx.doi.org/10.1212/WNL.0000000000007316
#213	Goeldner 2022[64]	A randomized, double-blind, placebo controlled phase II trial to explore the effects of a GABAA-α5 NAM (basmisanil) on intellectual disability associated with Down syndrome	10.1186/S11689-022-09418-0

#291	Gonzales 2021[156]	Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study	https://dx.doi.org/10.1016/S0140-6736(21)01256-3
#201	Gross 2020[157]	Selumetinib in Children with Inoperable Plexiform Neurofibromas	https://dx.doi.org/10.1056/NEJMoa1912735
#258	Gross 2023[158]	Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas	https://dx.doi.org/10.1093/neuonc/noad086
#260	Guffon 2023[159]	Long-term safety and efficacy of velmanase alfa treatment in children under 6 years of age with alpha-mannosidosis: A phase 2, open label, multicenter study	https://dx.doi.org/10.1002/jimd.12602
#278	Guglieri 2022[66]	Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy A Randomized Clinical Trial	https://dx.doi.org/10.1001/jama.2022.4315
#273	Hahn 2022[160]	A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox– Gastaut syndrome (ELEKTRA)	https://dx.doi.org/10.1111/epi.17367
#385	Hainque 2019[99]	Long-term follow-up in an open-label trial of triheptanoin in GLUT1 deficiency syndrome: a sustained dramatic effect	https://dx.doi.org/10.1136/jnnp-2018-320283
#274	Harmatz 2022[161]	Chemically modified recombinant human sulfamidase (SOBI003) in mucopolysaccharidosis IIIA patients: Results from an open, non-controlled, multicenter study	https://dx.doi.org/10.1016/j.ymgme.2022.06.008
#208	Heussler 2019[162]	A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome	https://dx.doi.org/10.1186/s11689-019-9277-x
#200	Hollander 2021[163]	Intranasal oxytocin versus placebo for hyperphagia and repetitive behaviors in children with Prader-Willi Syndrome: A randomized controlled pilot trial	https://dx.doi.org/10.1016/j.jpsychires.2020.11.006
#301	Infante 2021[164]	Reiterative infusions of MSCs improve pediatric osteogenesis imperfecta eliciting a pro-osteogenic paracrine response: TERCELOI clinical trial	https://dx.doi.org/10.1002/ctm2.265
#242	Julia-Palacios 2024[57]	L-serine treatment in patients with GRIN-related encephalopathy: a phase 2A, non-randomized study	https://dx.doi.org/10.1093/brain/awae041
#282	Kato 2022[96]	Sirolimus for epileptic seizures associated with focal cortical dysplasia type II	https://dx.doi.org/10.1002/acn3.51505
#330	Keppler-Noreuil 2019[165]	Pharmacodynamic Study of Miransertib in Individuals with Proteus Syndrome	https://dx.doi.org/10.1016/j.ajhg.2019.01.015

#356	Kesavan 2023[166]	A Randomized, Controlled, Noninferiority Trial Comparing Vitamin B12 Monotherapy Versus Combination Multinutrient Therapy with Vitamin B12 for Efficacy in Treatment of Infantile Tremor Syndrome	https://dx.doi.org/10.1007/s12098-022-04327-5
#232	Kim 2024[167]	Safety and effcacy of selumetinib in pediatric and adult patients with neurofbromatosis type 1 and plexiform neurofbroma	https://dx.doi.org/10.1093/neuonc/noae121
#340	Kimonis 2019[168]	A randomized pilot efficacy and safety trial of diazoxide choline controlled-release in patients with Prader-Willi syndrome	https://dx.doi.org/10.1371/journal.pone.0221615
#270	Knight 2022[169]	Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial	https://dx.doi.org/10.1016/S1474-4422(22)00077-1
#276	Knupp 2022[170]	Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial	https://dx.doi.org/10.1001/jamaneurol.2022.0829
#263	Kolevzon 2022[171]	An open-label study evaluating the safety, behavioral, and electrophysiological outcomes of low-dose ketamine in children with ADNP syndrome	https://dx.doi.org/10.1016/j.xhgg.2022.100138
#364	Kolevzon 2022[172]	Clinical trial of insulin-like growth factor-1 in Phelan-McDermid syndrome	https://dx.doi.org/10.1186/s13229-022-00493-7
#383	Lagae 2019[173]	Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial	https://dx.doi.org/10.1016/S0140-6736%2819%2932500-0
#267	Li 2022[60]	Effectiveness of Recombinant Human Growth Hormone Therapy for Children With Phelan-McDermid Syndrome: An Open-Label, Cross-Over, Preliminary Study	https://dx.doi.org/10.3389/fpsyt.2022.763565
#346	London 2024[63]	High-Dose Propranolol for Severe and Chronic Aggression in Autism Spectrum Disorder	https://dx.doi.org/10.1097/JCP.0000000000001895
#199	Mengel 2021[174]	Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment	https://dx.doi.org/10.1002/jimd.12428
#307	Metternich 2021[175]	Cognitive and behavioral effects of cannabidiol in patients with treatment-resistant epilepsy	https://dx.doi.org/10.1016/j.yebeh.2020.107558
#380	Miller 2020[98]	Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome A Randomized Clinical Trial	https://dx.doi.org/10.1001/jamaneurol.2020.0073
#239	Miller 2024[176]	Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study	https://dx.doi.org/10.1002/oby.23928
#241	Mobini 2024[56]	Effects of Trehalose Administration in Patients with Mucopolysaccharidosis Type III	https://dx.doi.org/10.21740/09298673306662304061025555

#226	Moertel 2024[177]	ReNeu: A Pivotal, Phase IIb Trial of Mirdametinib in Adults and Children With Symptomatic Neurofibromatosis Type 1-Associated Plexiform Neurofibroma	https://dx.doi.org/10.1200/JCO.24.01034
#290	Muntau 2021[178]	Long-term efficacy and safety of sapropterin in patients who initiated sapropterin at <4 years of age with phenylketonuria: results of the 3-year extension of the SPARK open-label, multicentre, randomised phase IIIb trial	https://dx.doi.org/10.1186/s13023-021-01968-1
#381	Nabbout 2020[179]	Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens	https://dx.doi.org/10.1001/jamaneurol.2019.4113
#250	Neul 2023[58]	Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study	https://dx.doi.org/10.1038/s41591-023-02398-1
#351	Olson 2024[180]	Long-term treatment with ganaxolone for seizures associated with cyclin-dependent kinase-like 5 deficiency disorder: Two-year open-label extension follow-up	https://dx.doi.org/10.1111/epi.17826
#229	Ottenhoff 2024[181]	Lamotrigine for cognitive deficits associated with neurofibromatosis type 1: A phase II randomized placebo controlled trial	https://dx.doi.org/10.1111/dmcn.16094
#244	Ou 2024[182]	Efficacy of Sulforaphane in Treatment of Children with Autism Spectrum Disorder: A Randomized Double-Blind Placebo-Controlled Multi-center Trial	https://dx.doi.org/10.1007/s10803-022-05784-9
#238	Ovchinsky 2024[94]	Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT): a phase 3, double-blind, randomised, placebo-controlled trial	https://dx.doi.org/10.1016/S2468-1253(24)00074-8
#222	Overwater 2019[183]	A randomized controlled trial with everolimus for IQ and autism in tuberous sclerosis complex	https://dx.doi.org/10.1212/WNL.0000000000007749
#295	Patel 2021[184]	Long-term safety and efficacy of add-on cannabidiol in patientswith Lennox–Gastaut syndrome: Results of a long-term open-label extension trial	https://dx.doi.org/10.1111/epi.17000
#235	Percy 2024[185]	Trofinetide for the treatment of Rett syndrome: Long-term safety and efficacy results of the 32-month, open-label LILAC-2 study	https://dx.doi.org/10.1016/j.medj.2024.06.007
#236	Percy 2024[186]	Trofinetide for the treatment of Rett syndrome: Results from the open-label extension LILAC study	https://dx.doi.org/10.1016/j.medj.2024.05.018
#359	Pignolo 2023[187]	Reduction of New Heterotopic Ossification (HO) in the Open-Label, Phase 3 MOVE Trial of Palovarotene for Fibrodysplasia Ossificans Progressiva (FOP)	https://dx.doi.org/10.1002/jbmr.4762
#237	Polgreen 2024[188]	Anakinra in Sanfilippo syndrome: a phase 1/2 trial	https://dx.doi.org/10.1038/s41591-024-03079-3
#344	Potter 2019[189]	A Randomized Controlled Trial of Sertraline in Young Children With Autism Spectrum Disorder	https://dx.doi.org/10.3389/fpsyt.2019.00810
#362	Rangarajan 2022[190]	Efficacy of pulse intravenous methylprednisolone in epileptic encephalopathy: a randomised controlled trial	https://dx.doi.org/10.1136/jnnp-2022-329027

#259	Roof 2023[59]	Intranasal Carbetocin Reduces Hyperphagia, Anxiousness,and Distress in Prader-Willi Syndrome: CARE-PWS Phase 3 Trial	https://dx.doi.org/10.1210/clinem/dgad015
#320	Rutter 2020[191]	Recombinant human insulin-like growth factor-1 therapy for 6 months improves growth but not motor function in boys with Duchenne muscular dystrophy	https://dx.doi.org/10.1002/mus.26846
#335	Sands 2019[192]	Long-Term Safety, Tolerability, and Efcacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US	https://dx.doi.org/10.1007/s40263-018-0589-2
#294	Scheffer 2021[193]	Safety and Tolerability of Transdermal Cannabidiol Gel in Children With Developmental and Epileptic Encephalopathies A Nonrandomized Controlled Trial	https://dx.doi.org/10.1001/jamanetworkopen.2021.23930
#251	Schoeler 2023[95]	Classic ketogenic diet versus further antiseizure medicine in infants with drug-resistant epilepsy (KIWE): a UK, multicentre, open-label, randomised clinical trial	https://dx.doi.org/10.1016/S1474-4422(23)00370-8
#289	Schreiber 2021[194]	A Randomized Controlled Trial of SGS742, a GABA-B Receptor Antagonist, for SSADH Deficiency	https://dx.doi.org/10.1177/08830738211012804
#255	Sharma 2023[195]	Long-term administration of intravenous Trappsol® Cyclo™ (HP-β-CD) results in clinical benefits and stabilization or slowing of disease progression in patients with Niemann-Pick disease type C1: Results of an international 48-week Phase I/II trial	https://dx.doi.org/10.1016/j.ymgmr.2023.100988
#277	Striano 2022[196]	A randomized, double-blind trial of triheptanoin for drug-resistant epilepsy in glucose transporter 1 deficiency syndrome	https://dx.doi.org/10.1111/epi.17263
#254	Suenobu 2023[197]	Selumetinib in Japanese pediatric patients with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas: An open-label, phase I study	https://dx.doi.org/10.1093/noajnl/vdad054
#355	Sullivan 2023[198]	Fenfluramine in the treatment of Dravet syndrome: Results of a third randomized, placebo-controlled clinical trial	https://dx.doi.org/10.1111/epi.17737
#348	Suzuki 2024[199]	Effect of levodopa on pathological gait in Dravet syndrome: A randomized crossover trial using three-dimensional gait analysis	https://dx.doi.org/10.1111/epi.17888
#373	Tanigawa 2021[200]	High-dose pyridoxine treatment for inherited glycosylphosphatidylinositol deficiency	https://dx.doi.org/10.1016/j.braindev.2021.02.007
#304	Thiele 2021[97]	Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized Clinical Trial.	https://dx.doi.org/10.1001/jamaneurol.2020.4607
#225	Thom 2024[201]	A Prospective Open-Label Trial of Buspirone for the Treatment of Anxiety in Williams Syndrome	https://dx.doi.org/10.1089/cap.2024.0124
#209	Thurman 2020[202]	Controlled trial of lovastatin combined with an open-label treatment of a parentimplemented language intervention in youth with fragile X syndrome	https://dx.doi.org/10.1186/s11689-020-09315-4
#223	vanAndel 2020[203]	Effects of bumetanide on neurodevelopmental impairments in patients with tuberous sclerosis complex: an open-label pilot study	https://dx.doi.org/10.1186/s13229-020-00335-4

#297	Vasiljevski 2021[204]	L-carnitine supplementation for muscle weakness and fatigue in children with neurofibromatosis type 1: A Phase 2a clinical trial	https://dx.doi.org/10.1002/ajmg.a.62392
#224	Wijburg 2019[205]	Intrathecal heparan-N-sulfatase in patients with Sanfilippo syndrome type A: A phase IIb randomized trial	https://dx.doi.org/10.1016/j.ymgme.2018.10.006
#319	Wozniak 2020[206]	Four-year follow-up of a randomized controlled trial of choline for neurodevelopment in fetal alcohol spectrum disorder	https://dx.doi.org/10.1186/s11689-020-09312-7

B.5. Linked studies

Cluster	Article #	New #	Study	Study Title	Description of linkages	Duplicate decisions
1	#270	#C1	Knight 2022	Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial	#270 is a phase 3 report and #351 is an extension report	Main
1	#351		Olson 2024	Long-term treatment with ganaxolone for seizures associated with cyclin-dependent kinase-like 5 deficiency disorder: Two-year open-label extension follow-up		Collapse with main
2	#219	*NA*	Glaze 2019	Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome	#219 is a phase 2 report, #250 is a phase 3 report, #236 is an extension report, and #235 is a longer extension report.	Unique
2	#250	#C2	Neul 2023	Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study		Main
2	#236		Percy 2024	Trofinetide for the treatment of Rett syndrome: Results from the open-label extension LILAC study		Collapse with main
2	#235		Percy 2024	Trofinetide for the treatment of Rett syndrome: Long-term safety and efficacy results of the 32-month, open-label LILAC-2 study		Collapse with main
3	#254	*NA*	Suenobu 2023	Selumetinib in Japanese pediatric patients with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas: An open-label, phase I study	#254 is phase 1 report in a specific geographic cohort (Japanese patients), #201 is a phase 2 report, and #258 is an extension report (with the phase 1/2 data included)	Unique
3	#201	#C3	Gross 2020	Selumetinib in Children with Inoperable Plexiform Neurofibromas		Main
3	#258		Gross 2023	Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas		Collapse with main
4	#383	*NA*	Lagae 2019	Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial	Reports #355 and #383 arose from the same phase 3 development program and were treated as linked studies representing non-overlapping enrollment cohorts. Report #381 was also considered linked, as it evaluated similar outcomes within a narrower, pharmacologically defined subgroup.	Unique
4	#355	*NA*	Sullivan 2023	Fenfluramine in the treatment of Dravet syndrome: Results of a third randomized, placebo-controlled clinical trial		Unique
4	#381	*NA*	Nabbout 2020	Fenfluramine for Treatment-Resistant Seizures in Patients with Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial		Unique
5	#239	*NA*	Miller 2024	Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study	#239 is a long-term open-label extension study of the randomized, double-blind, placebo-controlled parent trial reported in Miller 2023,	Unique
5	*NA*	*NA*	*Miller 2023*[207]*	*Diazoxide Choline Extended-Release Tablet in People With Prader-Willi Syndrome: A Double-Blind, Placebo-Controlled Trial*		*NA*

					which did not meet the inclusion criteria.	
6	#290	*NA*	Muntau 2021	Long-term efficacy and safety of sapropterin in patients who initiated sapropterin at <4 years of age with phenylketonuria: results of the 3-year extension of the SPARK open-label, multicentre, randomised phase IIIb trial	#290 reports the 3-year extension of the SPARK phase IIIb trial, with the parent randomized study reported in Muntau 2017, published outside the prespecified search date range	Unique
6	*NA*	*NA*	*Muntau 2017[208]**	*Efficacy, safety and population pharmacokinetics of sapropterin in PKU patients <4 years: results from the SPARK open-label, multicentre, randomized phase IIIb trial*		*NA*
7	#295	*NA*	Patel 2021	Long-term safety and efficacy of add-on cannabidiol in patients with Lennox–Gastaut syndrome: Results of a long-term open-label extension trial	#295 is a long-term open-label extension of the pivotal randomized controlled trial reported in Devinsky 2018, which was published outside the prespecified search date range.	Unique
7	*NA*	*NA*	*Devinsky 2018[209]**	*Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome*		*NA*
8	#319	*NA*	Wozniak 2020	Four-year follow-up of a randomized controlled trial of choline for neurodevelopment in fetal alcohol spectrum disorder	#319 reports four-year follow-up data from a randomized controlled trial originally reported in Wozniak 2015, published outside the prespecified search date range.	Unique
8	*NA*	*NA*	*Wozniak 2015[210]**	*Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial*		*NA*
9	#367	*NA*	Franz 2021	Adjunctive everolimus therapy for tuberous sclerosis complex--associated refractory seizures: Results from the postextension phase of EXIST--3	#367 represents post-extension follow-up of the EXIST-3 phase 3 trial, originally reported in French 2016, which was published outside the prespecified search date range.	Unique
9	*NA*	*NA*	*French 2016[211]**	*Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study*		*NA*
10	#385	*NA*	Hainque 2019	Long-term follow-up in an open-label trial of triheptanoin in GLUT1 deficiency syndrome: a sustained dramatic effect	#385 is a long-term follow-up report of an open-label trial originating from the parent study reported in Mochel 2015, published outside the prespecified search date range.	Unique
10	*NA*	*NA*	*Mochel 2016[212]**	*Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency*		*NA*

NA: not applicable.
Asterisk (*) indicates that the parent study did not meet the inclusion criteria.

B.6. Additional details for included trial reports, sorted by whether a primary outcome was caregiver reported and then alphabetically by last name of first author

Study	*Article ID*	*Country*	*Funding*	*Registration ID*	*Randomization*	*Number of study arms*	*Comparator Arm*	*Pilot*	*Design Type*	*Blinding used*	*Trial Phase*	*Extension phase*	*Follow-up duration*	*Sample Size*	*Intervention*	*Condition(s) included*	*Infant (0–<1 yr)*	*Young Children (1–4 yr)*	*School-age (5–11 yr)*	*Adolescent (12–18 yr)*
*Abuatiq 2024**	#234	USA	NR	NCT05307523	Yes	2	Placebo	Yes	Cross-over	No	NR	No	9	17	Device	Down Syndrome	No	Yes	No	No
*Arzimanoglou 2019**	*#336*	Canada, USA, France, Greece, Italy, Poland	Industry	NCT01405053	Yes	2	Active	No	Parallel	No	III	No	106	37	Drug	Lennox-Gastaut Syndrome	No	Yes	No	No
*Azevedo 2021**	#196	Brazil	NR	NCT03324906	No	1	No comparison arm	No	NA/Single arm	No	NR	No	6	12	Device	Prader-Willi Syndrome	No	No	Yes	Yes
*Bailey 2024**	#228	USA	Industry	NCT04902781	Yes	2	Placebo	No	Parallel	Yes	NR	No	78	47	Drug	Classic Galactosemia	NR	NR	NR	NR
*Berry-Kravis 2022**	#271	USA, Australia, New Zealand	Industry	NCT03614663	Yes	2	Active	No	Parallel	Yes	III	No	12	212	Drug	Intellectual disability	NR	NR	NR	NR
*Berweck 2021**	#286	USA, Germany, Poland	Industry	NCT02270736, 2013-004532-30	Yes	2	Active	No	Parallel	Yes	III	No	72	220	Drug	Intellectual disability	NR	NR	NR	NR
*Damen 2021**	#194	Netherlands	NR	2017-003423-30	Yes	2	Placebo	No	Cross-over	Yes	NR	No	30	26	Drug	Prader-Willi Syndrome	No	No	Yes	No
*Farmer 2019**	#325	USA	NR	NCT01747135	No	1	No comparison arm	No	NA/Single arm	No	NR	No	156	14	Drug	Niemann-Pick (Type C)	No	Yes	Yes	Yes
*Fastman 2021**	#210	USA	Non-Industry	NCT02710084	Yes	2	Placebo	No	Parallel	Yes	NR	No	24	18	Drug	Phelan-McDermid Syndrome	No	No	Yes	Yes
*Goeldner 2022**	#213	USA, Spain, France	Industry	NCT02024789	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	II	No	24	173	Drug	Down Syndrome	No	No	No	Yes

*Guglieri 2022**	#278	Canada, Germany, UK, USA, Italy	Industry, Non-Industry	NCT01603407	Yes	2	Placebo	No	Parallel	Yes	NR	No	156	196	Drug	Duchenne Muscular Dystrophy	NR	NR	NR	NR
*Hahn 2022**	#273	Canada, USA, China, Spain	Industry	NCT03650452	Yes	2	Placebo	No	Parallel	Yes	II	No	32	141	Drug	Lennox-Gastaut Syndrome, Dravet syndrome	NR	NR	NR	NR
*Hainque 2019**	#385	France	Industry	NCT02014883	No	1	No comparison arm	No	NA/Single arm	No	NR	Yes	182	5	Drug	Glucose transporter 1 deficiency syndrome (Glut1DS)	NR	NR	NR	NR
*Heussler 2019**	#208	Australia	Industry	ACTRN12617000150347	No	1	No comparison arm	No	NA/Single arm	No	I, II	No	12	20	Drug	Fragile X Syndrome	NR	NR	NR	NR
*Julia-Palacios 2024**	#242	Spain	Non-Industry	NCT04646447	No	1	No comparison arm	No	NA/Single arm	No	II	No	64	23	Drug	GRIN-related encephalopathy	NR	NR	NR	NR
*Kato 2022**	#282	Japan	Non-Industry	jRCTs031190157	No	1	No comparison arm	No	NA/Single arm	No	NR	No	12	75	Drug	focal cortical dysplasia type ii	NR	NR	NR	NR
*Kesavan 2023**	#356	India	Non-Industry	CTRI/2018/05/013841	Yes	2	Active	No	Parallel	No	NR	No	16	72	Supplement	Infantile Tremor Syndrome	Yes	Yes	No	No
*Knight 2022**	#C1	USA, UK, France, Australia, Israel, Italy, Poland, Russia	Industry	NCT03572933	Yes	2	Placebo	No	Parallel	Yes	III	No	17	101	Drug	CDKL5 deficiency disorder	No	Yes	Yes	No
*Knupp 2022**	#276	Canada, USA, Netherlands, France, Germany, Spain, Japan, Austral	Industry	NCT03355209	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	III	No	14	263	Drug	Lennox-Gastaut Syndrome	No	Yes	Yes	Yes

		ia, Belgium, Denmark, Italy, Mexico, Poland, Sweden																		
*Lagae 2019**	#383	Canada, USA, Australia, Europe	Industry	NCT02682927, NCT02826863	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	III	No	20	119	Drug	Dravet syndrome	No	Yes	Yes	Yes
*Li 2022**	#267	China	Non-Industry	NCT05105685	Unclear	2	Placebo	Yes	Cross-over	Unclear	NR	No	30	6	Drug	Phelan-McDermid Syndrome	No	Yes	Yes	No
*London 2024**	#346	USA	Non-Industry	NCT04047355	Yes	2	Placebo	Yes	Cross-over	Yes	NR	No	12	6	Drug	ASD	No	No	No	Yes
*Miller 2020**	#380	USA, Netherlands, Spain, Australia, Poland, Israel	Industry	NCT02224703	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	NR	No	20	199	Drug	Dravet syndrome	No	Yes	Yes	Yes
*Mobini 2024**	#241	Iran	Non-Industry	IRCT20130829014521N16	No	1	No comparison arm	Yes	NA/Single arm	No	NR	No	12	5	Drug	mucopolysaccharidosis Type III	No	No	Yes	No
*Nabbout 2020**	#381	Canada, USA, UK, Netherlands, France, Germany, Spain	Industry	NCT02926898	Yes	2	Placebo	No	Parallel	Yes	III	No	15	87	Drug	mucopolysaccharidosis Type III	No	Yes	Yes	Yes
*Neul 2023**	#C2	NR	Industry	NCT04181723, NCT04279314	Yes	2	Placebo	No	Parallel	Yes	III	No	12	187	Drug	Rett Syndrome	NR	NR	NR	NR
*Ou 2024**	#244	China	Non-Industry	NCT02879110	Yes	2	Placebo	No	Parallel	Yes	NR	No	12	135	Drug	Autism Spectrum Disorder	No	Yes	Yes	Yes
*Ovchinsky 2024**	#238	USA, UK, Netherlands, Germa	Industry	NCT04674761, EudraCT (2020-	Yes	2	Placebo	No	Parallel	Yes	III	No	24	52	Drug	Alagille syndrome	NR	NR	NR	NR

		ny, France, Belgium, Italy, Malaysia, Poland, Turkey		004011-28)															
*Rangarajan 2022**	#362	India	NR	CTRI/2019/02/017807	Yes	2	Placebo	No	Parallel	Yes	NR	No	28	80	Drug	epileptic encephalopathy	NR	NR	NR	NR
*Roof 2023**	#259	Canada, USA, Australia	Industry	NCT03649477	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	III	No	64	130	Drug	Prader-Willi Syndrome	NR	NR	NR	NR
*Sands 2019**	#335	USA	NR	NCT03676049	No	1	No comparison arm	No	NA/Single arm	No	NR	No	104	26	Drug	Lennox-Gastaut Syndrome, Dravet syndrome, CDKL5 epileptic encephalopathy	No	Yes	Yes	Yes
*Schoeler 2023**	#251	UK	Non-Industry	EudraCT (2013–002195–40)	Yes	2	Active	No	Parallel	No	IV	No	52	136	Drug	drug-resistant epilepsy	NR	NR	NR	NR
*Schreiber 2021**	#289	USA	Non-Industry	NCT02019667	Yes	2	Placebo	No	Cross-over	Yes	II	No	71	19	Drug	succinic semialdehyde dehydrogenase deficiency (SSADH-D)	No	No	Yes	Yes
*Striano 2022**	#277	USA, Australia, Asia, Europe	Industry	NCT01993186, EudraCT 2013-003771-35, UX007G-CL201	Yes	2	Placebo	No	Parallel	Yes	II	No	52	36	Supplement	Glucose transporter 1 deficiency syndrome (Glut1DS)	No	Yes	Yes	Yes
*Sullivan 2023**	#355	Canada, USA, Japan, Australia, Western Europe	Industry	NCT02826863, NCT02682927	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	III	No	14	143	Drug	Dravet Syndrome	NR	NR	NR	NR

*Tanigawa 2021**	#373	Japan	Non-Industry	UMIN000024185	No	1	No comparison arm	Yes	NA/Single arm	No	NR	No	52	9	Supplement	Inherited glycosylphosphatidylinositol deficiencies (IGDs)	NR	NR	NR	NR
*Thiele 2021**	#304	USA, Spain, Netherlands, UK, Australia, Poland	Industry	NCT02544763	Yes	Multi-arm (>2)	Placebo, >1 active	No	Parallel	Yes	III	No	16	224	Drug	Tuberous Sclerosis Complex	No	Yes	Yes	Yes
*vanAndel 2020**	#223	Netherlands	Industry	EudraCT 2016-002408-13	No	1	No comparison arm	Yes	NA/Single arm	No	NR	No	17	15	Drug	Tuberous Sclerosis Complex	No	No	Yes	Yes
Amat-Bou 2020	#312	Spain	Non-Industry	NCT03548480	Yes	2	Placebo	No	Cross-over	Yes	NR	No	36	39	Supplement	Prader-Willi Syndrome	NR	NR	NR	NR
Bebin 2024	#352	USA	Non-Industry	NCT02844571	Yes	2	Active	No	Parallel	Yes	II	No	130	72	Drug	Tuberous Sclerosis Complex	NR	NR	NR	NR
Berry-Kravis 2023	#246	USA	Non-Industry	NCT02920892	Yes	2	Active	No	Parallel	Yes	II	No	70	99	Drug	Fragile X Syndrome	NR	NR	NR	NR
Bhattacharya 2020	#347	Australia	Industry	NCT01966029	No	1	No comparison arm	No	NA/Single arm	No	III	No	49	13	Drug	Morquio A Syndrome	No	Yes	Yes	Yes
Boroda 2020	#316	USA	Non-Industry	NCT03361293	Yes	2	Placebo	No	Parallel	Yes	NR	No	6	44	Device	fetal alcohol spectrum disorder	NR	NR	NR	NR
Bremova-Ertl 2024	#350	USA, UK, Germany, Netherlands,	Industry	NCT05163288, 2021-005356-10	Yes	2	Placebo	No	Cross-over	Yes	III	No	26	60	Drug	Niemann-Pick (Type C)	NR	NR	NR	NR
Budimirovic 2021	#287	USA, Israel	Industry	NCT03697161	Yes	Multi-arm (>2)	>1 active	No	Parallel	Yes	II	No	12	23	Drug	Fragile X Syndrome	NR	NR	NR	NR

Carson 2021	#218	USA	Non-Industry	NCT03644693	Yes	2	Placebo	No	Cross-over	Yes	NR	No	16	19	Supplement	Angelman Syndrome	No	No	Yes	No
Cha 2023	#358	South Korea	Non-Industry	NCT01769716	No	1	No comparison arm	Yes	NA/Single arm	No	NR	No	52	13	Drug	**Lesch-Nyhan syndrome, ASD**	NR	NR	NR	NR
Chang 2020	#314	China	Non-Industry	ChiCTR1900021076	No	1	No comparison arm	Yes	NA/Single arm	No	NR	No	24	15	Drug	Pantothenate Kinase-Associated Neurodegeneration	No	Yes	Yes	Yes
Cieuta-Walti 2022	#272	Spain, France	NR	NCT03624556	Yes	2	Placebo	Yes	Parallel	Yes	I	No	36	73	Drug	Down Syndrome	No	No	Yes	Yes
Combs 2023	#249	USA	Non-Industry	NCT04115878	Yes	2	Active	No	Cross-over	Yes	NR	No	10	15	Drug	Down Syndrome	NR	NR	NR	NR
Davidson 2021	#369	Australia	Non-Industry	ACTRN12610000462088	Yes	2	Placebo	No	Cross-over	Yes	NR	No	76	36	Supplement	Duchenne Muscular Dystrophy	NR	NR	NR	NR
Devinsky 2021	#371	USA	Industry	NCT03861871	No	1	No comparison arm	No	NA/Single arm	No	NR	No	23	6	Drug	CDKL5 deficiency disorder	No	Yes	Yes	Yes
Finkel 2021	#298	Canada, USA, UK, Germany, Ireland, Sweden, Israel, Australia	Non-Industry	NCT03703882	Yes	2	Placebo	No	Parallel	Yes	III	No	52	131	Drug	Duchenne Muscular Dystrophy	NR	NR	NR	NR
Franz 2021	#367	USA, Japan, France, Other (specify)	Industry	NCT01713946	Yes	Multi-arm (>2)	Placebo, Active	No	Parallel	Yes	NR	Yes	162	244	Drug	Tuberous Sclerosis Complex	No	Yes	Yes	Yes
Ghosh 2021	#300	NR	Non-Industry	EudraCT: 2013-001479-18	Yes	2	Placebo	No	Parallel	Yes	NR	Yes	104	21	Drug	MPS III	No	Yes	Yes	Yes

Glaze 2019	#219	USA, Australia	Industry	NCT02715115	Yes	Multi-arm (>2)	Placebo, >1 active	No	Parallel	Yes	II	No	10	82	Drug	Rett Syndrome	NR	NR	NR	NR
Gonzales 2021	#291	USA, France, Switzerland, Belgium	Industry	NCT02160782	Yes	2	Placebo	No	Parallel	Yes	II	No	204	31	Drug	Alagille syndrome	No	Yes	Yes	No
Gross 2020	#C3	USA	Non-Industry	NCT01362803	No	1	No comparison arm	No	NA/Single arm	No	II	No	52	50	Drug	neurofibromatosis type 1	No	Yes	Yes	Yes
Guffon 2023	#260	France, Germany, Austria, Italy, Denmark	NR	NCT02998879	No	1	No comparison arm	No	NA/Single arm	No	II	No	104	6	Drug	Alpha-mannosidosis	NR	NR	NR	NR
Harmatz 2022	#274	USA, Turkey	Industry	NCT03423186, NCT03811028	No	Multi-arm (>2)	>1 active	No	Parallel	No	I, II	No	24	6	Drug	MPS IIIA	No	Yes	No	No
Hollander 2021	#200	USA	Non-Industry	NCT03197662	Yes	2	Placebo	Yes	Parallel	Yes	NR	No	8	23	Drug	Prader-Willi Syndrome	No	No	Yes	Yes
Infante 2021	#301	Spain	Non-Industry	NCT02172885, 2012-002553-38	No	1	No comparison arm	No	NA/Single arm	No	I	No	78	2	Drug	Osteogenesis imperfecta	NR	NR	NR	NR
Keppler-Noreuil 2019	#330	USA	Non-Industry	NCT02476955, NCT01473095	No	1	No comparison arm	No	NA/Single arm	No	I	No	52	6	Drug	Proteus syndrome	No	No	No	Yes
Kim 2024	#232	South Korea	Industry	KCT0003700	No	1	No comparison arm	No	NA/Single arm	No	II	No	104	60	Drug	neurofibromatosis type 1	No	Yes	Yes	Yes
Kimonis 2019	#340	USA	Industry	NCT02034071	Yes	2	Placebo	Yes	Parallel	Yes	II	No	14	13	Drug	Prader-Willi Syndrome	NR	NR	NR	NR
Kolevzon 2022	#263	USA, Sweden	NR	NCT04388774	No	1	No comparison arm	Yes	NA/Single arm	No	NR	No	4	10	Drug	ADNP Syndrome	No	No	Yes	Yes
Kolevzon 2022	#364	USA	Non-Industry	NCT01525901	Yes	2	Placebo	No	Cross-over	Yes	NR	No	12	10	Drug	Phelan-McDermid Syndrome	No	No	Yes	No
Mengel 2021	#199	USA, UK, France, Germa	Non-Industry	NCT02612129	Yes	2	Placebo	No	Parallel	Yes	II, III	No	52	50	Drug	Niemann-Pick (Type C)	No	Yes	Yes	Yes

		ny, Spain, Denmark, Italy, Poland, Switzerland																	
Metternich 2021	#307	Germany	Non-Industry	https://drks.de/search/en/trial/DRKS00013177	No	1	No comparison arm	No	NA/Single arm	No	NR	No	13	39	Drug	Treatment-resistant Epilepsy	Yes	Yes	Yes	Yes
Miller 2024	#239	USA, UK	Industry	NCT03440814, NCT03714373	Yes	2	Placebo	No	Parallel	No	III	Yes	52	127	Drug	Prader-Willi Syndrome	No	Yes	Yes	Yes
Moertel 2024	#226	USA	Industry	NCT03962543	No	1	No comparison arm	No	NA/Single arm	No	II	No	96	56	Drug	neurofibromatosis type 1	No	Yes	Yes	Yes
Muntau 2021	#290	Netherlands, UK, Germany, Austria, Belgium, Czech Republic, Italy, Slovakia, Turkey	Industry	NCT01376908	Yes	2	Active	No	Parallel	No	III	Yes	156	51	Drug	Phenylketonuria	NR	NR	NR	NR
Ottenhoff 2024	#229	Netherlands	Non-Industry	NCT02256124	Yes	2	Placebo	No	Parallel	Yes	II	No	26	31	Drug	neurofibromatosis type 1	NR	NR	NR	NR
Overwater 2019	#222	Netherlands	Industry, Non-Industry	NCT01730209	Yes	2	Placebo	No	Parallel	Yes	NR	No	52	32	Drug	Tuberous Sclerosis Complex, Autism Spectrum Disorder	NR	NR	NR	NR
Patel 2021	#295	USA, UK, Netherlands, Spain, France, Poland	Industry	NCT02224573	No	1	No comparison arm	No	NA/Single arm	No	NR	Yes	155	366	Drug	Lennox-Gastaut Syndrome	No	Yes	Yes	Yes

Pignolo 2023	#359	Canada, USA, UK, France, Spain, Japan, Argentina, Australia, Italy, Sweden	Industry	NCT03312634	No	2	Active	No	Parallel	No	III	No	208	99	Drug	Fibrodysplasia Ossificans Progressiva	No	Yes	Yes	Yes
Polgreen 2024	#237	USA	Non-Industry	NCT04018755	No	1	No comparison arm	No	NA/Single arm	No	I, II	No	36	24	Drug	Sanfilippo syndrome	No	No	Yes	Yes
Potter 2019	#344	USA	Non-Industry	NCT02385799	Yes	2	Placebo	No	Parallel	Yes	NR	No	26	58	Drug	Autism Spectrum Disorder	NR	NR	NR	NR
Rutter 2020	#320	USA	Non-Industry	NCT01207908	Yes	2	Placebo	Yes	Parallel	Yes	NR	No	26	44	Drug	Duchenne Muscular Dystrophy	NR	NR	NR	NR
Scheffer 2021	#294	Australia, New Zealand	Industry	ACTRN12618000516280	No	Multi-arm (>2)	>1 active	No	Parallel	No	NR	No	26	48	Drug	drug-resistant epilepsy	NR	NR	NR	NR
Sharma 2023	#255	USA, UK, Sweden, Israel	Industry	NCT02912793	Yes	Multi-arm (>2)	>1 active	No	Parallel	Yes	I, II	No	48	12	Drug	Niemann-Pick (Type C)	No	Yes	Yes	Yes
Suenobu 2023	#254	Japan	Industry	NCT04495127	No	1	No comparison arm	Yes	NA/Single arm	No	I	No	50	12	Drug	neurofibromatosis type 1	No	No	Yes	Yes
Suzuki 2024	#348	Japan	Non-Industry	jRCTs041190116	Yes	2	Placebo	No	Cross-over	No	NR	No	16	9	Drug	Dravet Syndrome	No	No	Yes	Yes
Thom 2024	#225	NR	Non-Industry	NCT04807517	No	1	No comparison arm	No	NA/Single arm	No	NR	No	16	20	Drug	Williams Syndrome	No	No	Yes	Yes
Thurman 2020	#209	USA	Non-Industry	NCT02642653	Yes	2	Placebo	No	Parallel	Yes	NR	No	20	30	Drug	Fragile X Syndrome	No	No	Yes	Yes
Vasiljevski 2021	#297	Australia	Non-Industry	ACTRN number 12618002021257	No	1	No comparison arm	No	NA/Single arm	No	II	No	12	6	Supplement	neurofibromatosis type 1	No	No	Yes	Yes

Wijburg 2019	#224	USA, France, Germany, Netherlands, Spain, UK, Argentina, Italy	Industry	NCT02060526, 2013-003450-24 (EudraCT Number)	Yes	Multi-arm (>2)	>1 active	No	Parallel	Yes	II	No	48	21	Drug	Sanfilippo syndrome type A	No	Yes	No	No
Wozniak 2020	#319	USA	Non-Industry	NCT01149538	Yes	2	Placebo	No	Parallel	Yes	NR	Yes	208	31	Supplement	Fetal Alcohol Spectrum Disorder	NR	NR	NR	NR

B.7. Full list of Included measures (all studies vs. primary outcomes)

Measure	All Studies (n=88)	Primary Outcome (n=38)
Pediatric Quality of Life Inventory (PedsQL)	20 (23%)	1 (3%)
Carers' Global Impression (CGI) Scales	18 (20%)	2 (5%)
Seizure Diary	17 (19%)	15 (39%)
Aberrant Behavior Checklist (ABC)	10 (11%)	5 (13%)
Vineland Adaptive Behavior Scales	10 (11%)	2 (5%)
Child Behavior Checklist (CBCL) / Caregiver-Teacher Report Form	7 (8%)	2 (5%)
Social Responsiveness Scale (SRS)	5 (6%)	2 (5%)
Repetitive Behavior Scale-Revised (RBS-R)	5 (6%)	1 (3%)
Sensory Profile Measure	4 (5%)	0 (0%)
Dykens hyperphagia questionnaire	3 (3%)	2 (5%)
Anxiety, Depression, and Mood Scales (ADAMS)	3 (3%)	1 (3%)
Sleep Disturbance Scale for Children (SDSC)	3 (3%)	1 (3%)
Behavior Assessment System for Children (BASC-3)	2 (2%)	1 (3%)
Hyperphagia Questionnaire for Clinical Trials	2 (2%)	1 (3%)
Rett Syndrome Behaviour Questionnaire	2 (2%)	1 (3%)
Behavior Rating Inventory of Executive Function (BRIEF)	2 (2%)	0 (0%)
Children's Sleep Habits Questionnaire (CSHQ)	2 (2%)	0 (0%)
Conners 3	2 (2%)	0 (0%)
EuroQol 5-Dimension Questionnaires	2 (2%)	0 (0%)
Pain Interference Index	2 (2%)	0 (0%)
Pediatric Evaluation of Disability Inventory (PEDI)	2 (2%)	0 (0%)
Quality of Life in Childhood Epilepsy (QOLCE)	2 (2%)	0 (0%)

Measure	All Studies (n=88)	Primary Outcome (n=38)
Adaptive Behavior Assessment Scale (ABAS)	1 (1%)	1 (3%)
Caregiver-Teacher Report Form	1 (1%)	1 (3%)
Oxytocin Questionnaire	1 (1%)	1 (3%)
PRUCISION: morning and evening ObsRO scratching scores	1 (1%)	1 (3%)
Parent Report Revised Dimensions of Mastery Questionnaire (DMQ-18)	1 (1%)	1 (3%)
TNO-AZL Preschool children Quality of Life	1 (1%)	1 (3%)
Treatment Satisfaction Questionnaire for Medication	1 (1%)	1 (3%)
Attention-deficit/hyperactivity problems questionnaire (Dutch 'Aandachtsvragenlijst')	1 (1%)	0 (0%)
Autism Behavior Checklist	1 (1%)	0 (0%)
Bayley Scales	1 (1%)	0 (0%)
Beck Depression Inventory (BDI-II)	1 (1%)	0 (0%)
Callier-Azusa Scale (CAS)	1 (1%)	0 (0%)
Changes in seizure presentation caregiver questionnaire (author prepared)	1 (1%)	0 (0%)
Child Adolescent Symptoms Inventory	1 (1%)	0 (0%)
Child Health Questionnaire–Parent Form [CHQ-PF50]	1 (1%)	0 (0%)
Child Sleep Health Questionnaire	1 (1%)	0 (0%)
Communication and Symbolic Behavior Scales Developmental Profile Infant–Toddler Checklist (CSBS-DP-IT)	1 (1%)	0 (0%)
Disordered movement 7-d log	1 (1%)	0 (0%)
Dutch Children's Communication Checklist [CCC-2-NL]	1 (1%)	0 (0%)
Epilepsy and Learning Disabilities Quality of Life	1 (1%)	0 (0%)
FOP-Physical Function Questionnaire	1 (1%)	0 (0%)

Measure	All Studies (n=88)	Primary Outcome (n=38)
Food and behavior diary	1 (1%)	0 (0%)
Gillette Functional Assessment Questionnaire	1 (1%)	0 (0%)
Impact of Pediatric Illness (IPI) scale	1 (1%)	0 (0%)
Infant Toddler Quality of Life Questionnaire	1 (1%)	0 (0%)
Itch Reported Outcome Observer	1 (1%)	0 (0%)
Macarthur-Bates Communication Developmental Inventory	1 (1%)	0 (0%)
Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part 2)	1 (1%)	0 (0%)
Non-communicating Children's Pain Checklist - Revised	1 (1%)	0 (0%)
Numeric Rating Scale-11 (NRS-11)	1 (1%)	0 (0%)
OSA-18 score	1 (1%)	0 (0%)
Observer memory questionnaire - parent form (OMQ-PF)	1 (1%)	0 (0%)
PROMIS: Fatigue Parent Proxy Custom Short Form	1 (1%)	0 (0%)
PROMIS: Mobility and Upper Extremity Short Form	1 (1%)	0 (0%)
PROMIS: Physical Function Measure	1 (1%)	0 (0%)
PWS Anxiousness and Distress Behaviors Questionnaire (PADQ)	1 (1%)	0 (0%)
PWS Profile (PWSP) Questionnaire	1 (1%)	0 (0%)
Pediatric Anxiety Rating Scale (PARS-R)	1 (1%)	0 (0%)
Pediatric Outcomes Data Collection tool (PODCI)	1 (1%)	0 (0%)
Pittsburgh Sleep Quality Index	1 (1%)	0 (0%)
Preschool Anxiety Scale - Revised	1 (1%)	0 (0%)
Sanfilippo Behavior Rating Score	1 (1%)	0 (0%)
Screen for Childhood Anxiety-Related Emotional Disorders (SCARED)	1 (1%)	0 (0%)

Measure	All Studies (n=88)	Primary Outcome (n=38)
Sensory Processing Measure - Preschool	1 (1%)	0 (0%)
Standardised developmental milestones parent/guardian report form (Author-prepared)	1 (1%)	0 (0%)
Standardized behavior diaries	1 (1%)	0 (0%)
Systematic Assessment for Treatment Emergent Effects-Specific Inquiry (SAFTEE-SI)	1 (1%)	0 (0%)
TAND Checklist	1 (1%)	0 (0%)
Visual Analog Scale for hyperactivity/hyperarousal/aggression	1 (1%)	0 (0%)
Visual Analog Scale for language/communication	1 (1%)	0 (0%)
Visual Analog Scale for obsessive-compulsive behavior/anxiety	1 (1%)	0 (0%)
Visual Analog Scale for social impairment	1 (1%)	0 (0%)
Visual Analog Scale for spoken language impairment	1 (1%)	0 (0%)
Visual Analogue Scale - Tantrum/Mood	1 (1%)	0 (0%)
Visual Analogue Scale - anxiety	1 (1%)	0 (0%)
Visual Analogue Scale - hyperactivity	1 (1%)	0 (0%)
developmental behavior checklist version 2 (DBC2) Parent edition	1 (1%)	0 (0%)

B.8. Additional design characteristics for the 44 primary caregiver reported outcomes among 38 trials that used caregiver reported outcomes as a primary outcome

Study	*Article #*	***Primary Outcome Measure/s***	***Design***	***Randomized***	***Study arms***	***Blinded***	***Care-givers Blinded***	*Control Arm(s)*	***Trial Phase***	***Pilot***	***Extension Phase***	***ID Severity***
Abuatiq 2024	**#234**	The parent report Revised Dimensions of Mastery Questionnaire (DMQ-18)	Cross-over	Yes	2	**No**	**NA**	Placebo	NR	Yes	No	NR
Arzimanoglou 2019	**#336**	CBCL	Parallel	Yes	2	**No**	**NA**	Active	III	No	No	NR
Azevedo 2021	**#196**	Dykens Hyperphagia Questionnaire (DHQ)	NA/Single arm	No	1	**No**	**NA**	NA	NR	No	No	IQ Reported (45-72)
Bailey 2024	**#228**	Behavioral Assessment Scales for Children 3 Parent-Reported Scales (BASC-3 PRS)	Parallel	Yes	2	**Yes**	**No**	Placebo	NR	No	No	NR
Berry-Kravis 2022	**#271**	Aberrant Behavior Checklist–Community Edition FXS (ABC-CFXS)	Parallel	Yes	2	**Yes**	**No**	Placebo	III	No	No	NR
Berweck 2021	**#286**	carers' Global Impression of Change Scale (GICS)	Parallel	Yes	2	**Yes**	**Unclear**	Active	III	No	No	NR
Damen 2021	**#194**	Dykens hyperphagia questionnaire	Cross-over	Yes	2	**Yes**	**Yes**	Placebo	NR	No	No	NR
		Oxytocin Questionnaire										
		Repetitive Behavior Scale-Revised (RBS-R)										

		Social Responsiveness Scale (SRS-P)										
Farmer 2019	**#325**	VINELAND-2	NA/Single arm	No	1	**No**	**NA**	NA	NR	No	No	IQ Reported (>10-90)
Fastman 2021	**#210**	ABC	Parallel	Yes	2	**Yes**	**No**	Placebo	NR	No	No	NR
Goeldner 2022	**#213**	VABS-II	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	Placebo	II	No	No	IQ Reported (32-93)
Guglieri 2022	**#278**	Treatment Satisfaction Questionnaire for Medication	Parallel	Yes	2	**Yes**	**No**	Placebo	NR	No	No	NR
Hahn 2022	**#273**	Seizure diary	Parallel	Yes	2	**Yes**	**Unclear**	Placebo	II	No	No	NR
Hainque 2019	**#385**	paroxysmal event diary	NA/Single arm	No	1	**No**	**NA**	NA	NR	No	Yes	IQ Reported (63-72)
Heussler 2019	**#208**	Anxiety, Depression, and Mood Scales (ADAMS)	NA/Single arm	No	1	**No**	**NA**	NA	I, II	No	No	No
Julia-Palacios 2024	**#242**	Caregiver-Teacher Report Form	NA/Single arm	No	1	**No**	**NA**	NA	II	No	No	Classification Reported(Severe-profound ID (61%); Moderate ID (17%); Mild ID (17%))
Julia-Palacios 2024	**#242**	Pediatric Quality of Life Inventory Version 4.0 (PedsQL - V4.0)										
Julia-Palacios 2024	**#242**	Sleep Disturbance Scale for Children										
Julia-Palacios 2024	**#242**	CBCL										
Kato 2022	**#282**	Seizure diary	NA/Single arm	No	1	**No**	**NA**	NA	NR	No	No	NR
Kesavan 2023	**#356**	Likert Caregiver impression of change	Parallel	Yes	2	**No**	**NA**	Active	NR	No	No	NR
Knight 2022	**#C1**	Seizure diary	Parallel	Yes	2	**Yes**	**Yes**	Placebo	III	No	No	NR
Knupp 2022	**#276**	Seizure Diary	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	*Placebo*	III	No	No	NR

Lagae 2019	**#383**	Seizure diary	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	*Placebo*	III	No	No	NR
Li 2022	**#267**	Simplified Chinese version of the Aberrant Behavior Checklist (SC-ABC)	Cross-over	Yes	2	**No**	**NA**	Placebo	NR	Yes	No	NR
London 2024	**#346**	Aberrant Behavior Checklist—Community (ABC-C)	Cross-over	Yes	2	**Yes**	**Unclear**	Placebo	NR	Yes	No	Nonverbal IQ Reported (32-110)
Miller 2020	**#380**	Seizure Diary	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	*Placebo*	NR	No	No	NR
Mobini 2024	**#241**	TNO-AZL Preschool children Quality of Life	NA/Single arm	No	1	**No**	**NA**	NA	NR	Yes	No	NR
Nabbout 2020	**#381**	Seizure diary	Parallel	Yes	2	**Yes**	**No**	Placebo	III	No	No	NR
Neul 2023	**#250**	Rett Syndrome Behaviour Questionnaire (RSBQ)	Parallel	Yes	2	**Yes**	**Yes**	Placebo	III	No	No	NR
Ou 2024	**#244**	Social Responsiveness Scale-First Version (SRS)	Parallel	Yes	2	**Yes**	**Yes**	Placebo	NR	No	No	IQ Reported (20-155)
Ovchinsky 2024	**#238**	PRUCISION: morning and evening ObsRO scratching scores	Parallel	Yes	2	**Yes**	**No**	Placebo	III	No	No	NR
Rangarajan 2022	**#362**	Seizure diary	Parallel	Yes	2	**Yes**	**No**	Placebo	NR	No	No	NR
Roof 2023	**#259**	Hyperphagia Questionnaire for Clinical Trials [HQ-CT]	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	*Placebo*	III	No	No	NR
Sands 2019	**#335**	Seizure diary	NA/Single arm	No	1	**No**	**NA**	NA	NR	No	No	NR
Schoeler 2023	**#251**	Seizure diary	Parallel	Yes	2	**No**	**NA**	Active	IV	No	No	NR
Schreiber 2021	**#289**	Adaptive Behavior	Cross-over	Yes	2	**Yes**	**Yes**	Placebo	II	No	No	IQ Reported (31-97)

		Assessment Scale (ABAS)										
Striano 2022	**#277**	Seizure diary	Parallel	Yes	2	**Yes**	**Unclear**	Placebo	II	No	No	NR
Sullivan 2023	**#355**	Seizure diary	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	*Placebo*	III	No	No	NR
Tanigawa 2021	**#373**	Seizure diary	NA/Single arm	No	1	**No**	**NA**	NA	NR	Yes	No	Classification reported (All patients presented with severe to profound developmental delay)
Thiele 2021	**#304**	Caregiver diary	Parallel	Yes	Multi-arm (>2)	**Yes**	**Yes**	*Placebo*	III	No	No	NR
vanAndel 2020	**#223**	ABC	NA/Single arm	No	1	**No**	**NA**	NA	NR	Yes	No	IQ Reported (<40 – 107)

Notes: NA indicates not applicable; NR indicates not reported.

B.9. Coprimary and Composite outcome measures

List of all primary outcome measures in trial reports where a caregiver-reported primary outcome was either co-primary or part of a composite

Study (Article #)	Primary Outcome Measures	Caregiver Reported
Trials where a primary caregiver-reported outcome measure was co-primary		
Abuatiq 2024 (#234)	Gross Motor Function Measure-88 (GMFM-88)	No
	Right ankle-mounted accelerometer (Actigraph GT3X+)	No
	The parent report Revised Dimensions of Mastery Questionnaire (DMQ-18)	Yes
Berweck 2021 (#286)	The change in unstimulated salivary flow rate (uSFR)	No
	Carers' Global Impression of Change Scale (GICS)	Yes
Damen 2021 (#194)	Dykens hyperphagia questionnaire	Yes
	Oxytocin Questionnaire	Yes
	Repetitive Behavior Scale-Revised (RBS-R)	Yes
	Social Responsiveness Scale (SRS-P)	Yes
Farmer 2019 (#325)	Mullen Scales of Early Learning (MSEL)	No
	Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III)	No
	Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)	No
	Wechsler Abbreviated Scales of Intelligence	No
	VINELAND-2	Yes
Julia-Palacios 2024 (#242)	Bayley-III	No
	Gross Motor Function Measure-88 (GMFM-88)	No
	VINELAND-2	No
	Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V)	No
	Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)	No
	Child Behavior Checklist (CBCL)	Yes
	Caregiver-Teacher Report Form	Yes
	Pediatric Quality of Life Inventory Version 4.0 (PedsQL - V4.0)	Yes
	Sleep Disturbance Scale for Children	Yes
Li 2022 (#267)	Adverse events	No
	Chinese version of the Gesell Development Scale (GDS)	No
	Level of Serum IGF-1 and IGFBP-3	No
	Simplified Chinese version of the Aberrant Behavior Checklist	Yes

	(SC-ABC)	
London 2024 (#346)	Clinical Global Impression Improvement Scale (CGI-I)	No
	Aberrant Behavior Checklist—Community (ABC-C)	Yes
Mobini 2024 (#241)	Serum biomarkers (GAGs, liver aminotransferase levels, antioxidant status	No
	TNO-AZL Preschool children Quality of Life	Yes
Neul 2023 (#C2)	Clinical Global Impression–Improvement (CGI-I) scale	No
	Rett Syndrome Behaviour Questionnaire (RSBQ)	Yes
Roof 2023 (#259)	Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)	No
	Hyperphagia Questionnaire for Clinical Trials [HQ-CT]	Yes
Trials where a primary caregiver-reported outcome measure was part of a composite		
Bailey 2024 (#228)	Oral and Written Language Skills test (OWLS-II)	No
	Behavioral Assessment Scales for Children 3 Parent-Reported Scales (BASC-3 PRS)	Yes
Goeldner 2022 (#213)	Clinical Global Impression-Improvement (CGI-I)	No
	Repeatable Battery for the Assessment of Neuropsychological Scale (RBANS)	No
	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)	Yes
Guglieri 2022 (#278)	Forced vital capacity (in liters)	No
	Rise from the floor velocity (in rise/seconds)	No
	Treatment Satisfaction Questionnaire for Medication	Yes

B.10 – Psychometric information for the 44 caregiver reported primary outcomes among 38 trials that used caregiver reported outcomes as a primary outcome

Study	*Article #*	*Measure*	*Reporter consistency*	*Psychometrics*	*Reporter training*	*Reporter instructions*	*Outcome Assessor*	*Caregiver Reporter specifics*	*Reporting classification*	*Caregiver demographics*	*Mode of Completion*	*Method of Completion*
Abuatiq 2024	**#234**	the parent report Revised Dimensions of Mastery Questionnaire (DMQ-18)	Yes	Reliability, Validity	No	No	Caregiver	Parent	ProxyRO	Age, gender, education level, other	Self-completed by caregiver	NR
Arzimanoglou 2019	**#336**	CBCL	NR	Validity	No	No	Caregiver	Parent, Guardian	NR	NR	Self-completed by caregiver	NR
Azevedo 2021	**#196**	Dykens Hyperphagia Questionnaire (DHQ)	NR	General Psychometric Properties	No	No	Caregiver	Parent, Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
Bailey 2024	**#228**	Behavioral Assessment Scales for Children 3 Parent-Reported Scales (BASC-3 PRS)	NR	NR	No	Yes	Caregiver	Parent	NR	NR	Self-completed by caregiver	Paper, digital
Berry-Kravis 2022	**#271**	Aberrant Behavior Checklist–Community Edition FXS (ABC-CFXS)	NR	NR	No	No	Caregiver	Caregiver (unspecified)	ObsRO	NR	Self-completed by caregiver	NR
Berweck 2021	**#286**	carers' Global Impression of Change Scale (GICS)	NR	NR	No	No	Caregiver	Caregiver (unspecified), Parent	NR	NR	Self-completed by caregiver	NR

Damen 2021	**#194**	Dykens hyperphagia questionnaire	NR	NR	No	No	Caregiver	Parent	NR	NR	Self-completed by caregiver	NR
Damen 2021	**#194**	Oxytocin Questionnaire										
Damen 2021	**#194**	Repetitive Behavior Scale-Revised (RBS-R)										
Damen 2021	**#194**	Social Responsiveness Scale (SRS-P)										
Farmer 2019	**#325**	VINELAND-2	NR	NR	No	No	Caregiver	Caregiver (unspecified)	NR	NR	staff-administered	in person
Fastman 2021	**#210**	ABC	NR	Validity	No	No	Caregiver	Parent	NR	NR	Self-completed by caregiver	NR
Goeldner 2022	**#213**	VABS-II	NR	Reliability, Responsiveness to Change	No	No	Caregiver	Caregiver (unspecified)	NR	NR	staff-administered	NR
Guglieri 2022	**#278**	Treatment Satisfaction Questionnaire for Medication	Yes	NR	No	No	Caregiver	Parent, Guardian	NR	NR	Self-completed by caregiver	NR
Hahn 2022	**#273**	Seizure diary	NR	NR	No	No	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	Paper
Hainque 2019	**#385**	paroxysmal event diary	NR	NR	No	No	Caregiver, Patient	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR

Heussler 2019	**#208**	Anxiety, Depression, and Mood Scales (ADAMS)	NR	Validity	No	Yes	Caregiver	Parent, Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
Julia-Palacios 2024	**#242**	Caregiver-Teacher Report Form	Yes	NR	No	No	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
Julia-Palacios 2024	**#242**	Pediatric Quality of Life Inventory Version 4.0 (PedsQL - V4.0)										
Julia-Palacios 2024	**#242**	Sleep Disturbance Scale for Children										
Julia-Palacios 2024	**#242**	CBCL										
Kato 2022	**#282**	Seizure diary	NR	NR	No	No	Caregiver, Patient	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
Kesavan 2023	**#356**	Likert Caregiver impression of change	NR	Validity	No	No	Caregiver	Parent, Guardian	NR	NR	Self-completed by caregiver	NR
Knight 2022	**#C1**	Seizure diary	NR	NR	No	No	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	digital
Knupp 2022	**#276**	Seizure Diary	Yes	NR	Yes	No	Caregiver	Caregiver (unspecified), Parent	NR	NR	Self-completed by caregiver	digital
Lagae 2019	**#383**	Seizure diary	NR	NR	No	No	Caregiver	Caregiver (unspec	NR	NR	Self-completed	digital

								ified), Parent			by caregiver	
Li 2022	**#267**	Simplified Chinese version of the Aberrant Behavior Checklist (SC-ABC)	NR	Validity	No	No	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
London 2024	**#346**	Aberrant Behavior Checklist—Community (ABC-C)	NR	NR	No	No	Caregiver	Parent	NR	NR	Self-completed by caregiver	NR
Miller 2020	**#380**	Seizure Diary	Yes	NR	No	Yes	Caregiver, Patient	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	digital
Mobini 2024	**#241**	TNO-AZL Preschool children Quality of Life	NR	NR	No	No	Caregiver	Caregiver (unspecified), Parent	NR	NR	Self-completed by caregiver	NR
Nabbout 2020	**#381**	Seizure diary	Yes	NR	No	No	Caregiver	Caregiver (unspecified), Parent	NR	NR	Self-completed by caregiver	NR
Neul 2023	**#250**	Rett Syndrome Behaviour Questionnaire (RSBQ)	Yes	Validity	Yes	Yes	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
Ou 2024	**#244**	Social Responsiveness Scale-First Version (SRS)	NR	NR	No	No	Caregiver	Parent	NR	NR	Self-completed by caregiver	NR
Ovchinsky 2024	**#238**	PRUCISION: morning and evening ObsRO	NR	Validity	Yes	Yes	Caregiver	Caregiver (unspecified)	ObsRO	NR	Self-completed by	digital

		scratching scores									caregiver	
Rangarajan 2022	**#362**	Seizure diary	NR	NR	Yes	No	Caregiver	Caregiver (unspecified), Parent	NR	NR	Self-completed by caregiver	NR
Roof 2023	**#259**	Hyperphagia Questionnaire for Clinical Trials [HQ-CT]	NR	Validity	Yes	Yes	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR
Sands 2019	**#335**	Seizure diary	NR	NR	No	No	Caregiver	Caregiver (unspecified), Parent	NR	NR	Self-completed by caregiver	NR
Schoeler 2023	**#251**	Seizure diary	NR	NR	Yes	Yes	Caregiver	Parent, Guardian	NR	NR	Self-completed by caregiver	NR
Schreiber 2021	**#289**	Adaptive Behavior Assessment Scale (ABAS)	NR	NR	No	No	Caregiver	Parent, Guardian	NR	NR	Self-completed by caregiver	NR
Striano 2022	**#277**	Seizure diary	NR	NR	No	No	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	Paper
Sullivan 2023	**#355**	Seizure diary	NR	NR	No	No	Caregiver	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	digital
Tanigawa 2021	**#373**	Seizure diary	NR	NR	No	No	Caregiver	Parent	NR	NR	Self-completed by caregiver	NR

Thiele 2021	**#304**	Caregiver diary	Yes	NR	Yes	No	Caregiver, Patient	Caregiver (unspecified)	NR	NR	Self-completed by caregiver	digital
vanAndel 2020	**#223**	ABC	NR	NR	No	No	Caregiver	Parent, Caregiver (unspecified)	NR	NR	Self-completed by caregiver	NR