

## Clinical trials in pediatric multiple sclerosis: overcoming the challenges

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To date, none of the formative clinical drug trials in multiple sclerosis (MS) have included children. Just as in other fields in pediatrics, current prescribed therapies are off-label and are based on the results of adult studies. Emerging oral, injectable and intravenous immunotherapies appear to be more efficacious, but simultaneously have more worrisome side effects. In order to optimize therapy for children with MS, these therapies must be evaluated in robust clinical trials with a focus on monitoring for potential toxicities both in the short and long term. Many challenges exist in conducting clinical trials in children, including smaller patient populations. International collaboration and mandated pediatric investigation plans will facilitate the process of conducting these valuable clinical trials, which may lead to a better understanding of MS overall.

**Keywords:** clinical trials • disease-modifying therapies • drug trials  
• pediatric clinical trial ethics • pediatric multiple sclerosis

Despite the increasing awareness of multiple sclerosis (MS) in children in North American and northern European countries, the worldwide prevalence of pediatric MS is low. It is estimated that 2–5% of patients with MS are diagnosed during childhood. The incidence of a first episode of acquired CNS demyelination in children was 0.9/100,000 children per year in Canada [1] and of these children, it is estimated that 25% will have a subsequent diagnosis of MS based on a clinical or MRI relapse [2].

Therapies for MS have been available for the last 20 years, but none of the formative clinical trials included children. There are currently only two clinical drug trials in MS enrolling children: a study evaluating betaferon safety and tolerability in pediatric patients with MS (European centers) and a retrospective cohort study of rebif use in pediatric MS patients (international sites) [10]. There have not been any Phase III clinical drug trials for any of the therapies prescribed for pediatric MS. The first-line therapies (IFN- $\beta$  and glatiramer acetate) are used as first-line disease-modifying therapy (DMT) in children and have been studied in small retrospective and prospective case series demonstrating a similar safety profile to the adult studies [3–10]. In light of the Class IV level of evidence available for pediatric MS therapies, therapeutic strategies have been developed specifically for children [11].

Although pediatric MS patients are offered first-line therapy, almost 50% switch therapy for various reasons (non-compliance, tolerance and breakthrough disease) [12]. This highlights the importance of finding strategies to enhance tolerability and adherence, and evaluating second-line and new emerging MS therapies in the pediatric population.

The future environment for MS therapy involves several oral, injectable and intravenous immunomodulators, undergoing Phase II and III studies. One oral therapy (fingolimod) has recently been approved in the USA, Canada, Europe, Russia and Australia for relapsing-remitting MS in adults. With the increase in

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efficacy, several of the newer medications, including fingolimod, are also demonstrating more worrisome toxicities such as immunosuppression and cardiac side effects.

With the increasing array of new MS therapies, and with the limited data available on the use of available therapies for pediatric MS, there is a clear need for appropriate clinical trials in pediatric MS. The purpose of this paper is to discuss the necessity and challenges of conducting clinical therapeutic trials in the pediatric MS population.

### Disease factors

#### ■ Is MS the same disease in children & adults?

Available data support a shared biological basis for MS in children as in adults. CNS maturation influences clinical presentation and MRI appearance. Children tend to relapse early in the course of disease, with an annualized relapse rate of 1.12–2.76 compared with 0.3–1.78 in adults with MS [13]. Up to 98% of children have a relapsing-remitting course with a progressive course being a red flag for a diagnoses other than MS [14]. Children may present with an initial attack that meets clinical criteria for acute disseminated encephalomyelitis (ADEM; a polyfocal neurological syndrome with encephalopathy and a presumed inflammatory etiology), but subsequent non-ADEM attacks and accrual of silent MRI lesions leads to a diagnosis of MS [15]. This is an important differentiation, as ADEM tends to be a monophasic disease not requiring DMT therapy.

The outcome of MS with childhood onset is similar to adult-onset disease but with a different time course. Pediatric-onset MS patients enter a secondary progressive phase on average 10 years later into the disease course than adults, but at an age 10 years younger than their adult counterparts [16,17]. The MRI appearance of MS in children has many similarities but also a few key distinctions from the MRI features of MS in adults. Children demonstrate a propensity for more infratentorial lesions [18], are more likely to have a transient stage early in the disease where T2 lesions appear to completely resolve ('vanishing T2 lesions') [19] and lesions can be large with a tumefactive appearance. The diagnosis of MS in young children requires greater care to exclude a wider variety of MS mimics, especially ADEM [20]. The recent revision of the McDonald criteria allow for adolescent patients with a typical first demyelinating attack to be diagnosed similarly to adults [21].

### Clinical issues

#### ■ The evolution of ethical research in pediatrics

Children were automatically excluded from the 1947 Nuremberg code, an international document that outlines the ethical guidelines for conduct of human research,

with emphasis on voluntary consent provided by participants prior to any human experimentation. In order to protect vulnerable populations such as children, the Helsinki Declaration was written and updated in 2000 [22]. In addition, the Council for International Organizations of Medical Sciences [23], a non-profit, international organization established in 1949 by the WHO and UNESCO, is particularly involved in the ethics of medical research involving humans. These guidelines, revised in 2002, specifically mention how to conduct ethical research on groups such as children who have a limited capacity to give voluntary consent (Guideline 14) [102].

The ethics of conducting clinical research in children is complex. As in any human trial, treatment should have a reasonable expectation of benefit and a low risk of harm. Many children and most adolescents are fully capable of providing informed consent. Children who are deemed incapable of providing informed consent, are still able to provide informed assent. Young children have the right to refuse to partake in a clinical study even if their guardian provides consent.

#### ■ Pediatric specific regulations for clinical trials

Several national guidelines have been developed to promote the inclusivity of children in clinical drug trials.

The US FDA Modernization Act was an amendment made to ensure safety of medications approved for children [103]. This act gives pharmaceutical companies an extra 6 months of patent protection or market exclusivity if pediatric trials are conducted. The Best Pharmaceuticals for Children Act extended this incentive if off-patent drugs were studied [104]. Once granted permission to use the drug in the pediatric population, all adverse events must be reported to the FDA during the following year. In 2003, the Pediatric Research Equity Act amended the above acts and made the study of both biologics and drugs mandatory in the pediatric population if the drug is likely to be used in children.

The European Medicines Agency mandated formal Pediatric Investigation Plans in 2007: guidelines for pharmaceutical agencies to submit pediatric-specific protocols for all clinical trials involving diseases that affect children [105]. An initial protocol should be filed soon after a Phase I study has been conducted in adults, with modifications to the protocol as Phase II and III adult trial data emerge. Design of the pediatric investigation plan should encompass children of all ages affected by the disease. The goal of the studies emerging through a Paediatric Investigation Plan would be to allow for augmentation of medication formulation to suit the appropriate age groups, and to provide the ability to collect pediatric specific safety data. In return, pharmaceutical agencies would have a 1-year extension of market protection.

Even with the above incentives and changes to include children in clinical trials, there are still few clinical trials conducted for any medical condition in children [24]. In addition, the proportion of funding from the NIH for pediatric clinical trials has unfortunately remained static since 1992 [25]. A recent initiative by the Standards for Research in Child Health international group has committed to improving the conduct of pediatric research by developing evidence-based standards for designing, conducting and reporting pediatric trials [26].

### Considerations of organ maturity

Childhood and adolescence represents a time of particularly active ongoing changes in development of all organs, including the CNS. Current DMT, as well as the emerging therapies, have the potential to disrupt normal maturational processes. Specific areas of concern in the pediatric age group include potential impact on cognitive development, reproductive health and immunologic maturation. With exposure to immunosuppressive agents at a young age, the risk for secondary malignancies increases over time. This is related to both the duration of exposure as well as to the many years of life ahead for these young children. Pharmacokinetics and pharmacodynamics of medications may also differ in children and adults, which in turn may influence the dosing, titration and side-effect profile of therapies.

### Methodological factors for MS trial design

When considering performing clinical drug trials in children, prior to initiating a Phase III trial, ideally Phase I and II studies should still be conducted to adequately test safety and dosing parameters. However, it is difficult to justify testing therapies in a sequential manner when Phase III studies in adults have already proven a therapy to be effective in MS. This places the clinician in a very difficult position and is the very reason that so many medications are being used off-label in the pediatric population, not only in the field of MS. Up to 75% of drugs used in pediatrics do not have sufficient safety and pharmacokinetic data [24,27,28]. Adverse drug reactions are also more frequent when unlicensed or off-label drugs are prescribed to children [29].

A definite barrier to clinical trials in the general pediatric population is the number of patients available for enrollment. This highlights the importance of developing multicentered international clinical and research networks. The International Pediatric MS Study Group, a group of clinicians and researchers from over 40 countries was formed to address these key issues. In order to power a study adequately, with at least an 80% probability to detect a true difference between treated and untreated groups, or between two comparative therapies, most clinical trials require hundreds of participants.

### ■ Inclusion criteria

The design of pediatric MS therapeutic trials must first clearly define the inclusion criteria. Only children and adolescents with a definite diagnosis of MS, based on the most recent diagnostic criteria, should be included in future clinical trials. Criteria for diagnosing MS have been revised in 2010 in order to make a more timely diagnosis while retaining high specificity [21]. After an initial acquired demyelinating event suggestive of a first episode of MS (e.g., optic neuritis, multifocal neurological symptoms), both dissemination in time and space must be demonstrated as per the 2010 McDonald criteria. To meet the dissemination in space criteria after a typical inflammatory demyelinating event, MRI must demonstrate at least one lesion in two of the following locations: periventricular, juxtacortical, infratentorial, or spinal cord with the caveat that the symptomatic lesion cannot contribute toward the total lesion count. Dissemination in time can be demonstrated by acquisition of new T2 lesions on serial imaging, or if both gadolinium-enhancing and -non-enhancing lesions are present simultaneously on baseline imaging. These criteria are applicable to children over 11 years of age but are less sensitive in younger children and children who present with a first episode of ADEM [30], and therefore one must be judicious when considering enrollment of these children into an MS clinical trial. Currently, children with a diagnosis of ADEM, without further clinical relapses or MRI lesions confirming the diagnosis of MS, should be excluded from enrollment.

Recruitment for trials will also need to consider the level of disease activity required for inclusion, which may be reflected clinically by relapse rate or imaging findings. Other variables such as age, time from first attack, number of attacks in the preceding time prior to study, and level of disability would also be important factors to consider during enrollment.

Placebo-controlled trials have been conducted for all currently approved DMT in adults [31–37]. Adult randomized controlled trials clearly demonstrate the benefit of treatment in preventing both clinical relapses and accumulation of MRI lesions [38] and several agents have demonstrated a positive impact of disability accrual. In pediatric MS studies, it is difficult to justify placebo-controlled trials while still maintaining clinical equipoise. The role for placebo-controlled trials in pediatric MS is challenged by the fact that such trials will inevitably follow trials in adults in which the therapeutic agent has been shown to be effective. Temple and Ellenberg argue that placebo-controlled trials can still be conducted, even if effective therapy is available, as long as participating patients are fully informed of the available therapies and will not undergo harm by participating [39]. In a consensus statement, the International Pediatric

MS Study Group stated that placebo-controlled trials would be acceptable to clinicians caring for pediatric MS patients provided that the trial was short, and that rescue strategies were provided for children with high relapse rates during the trial [40]. Recommendations include that pediatric MS patients should be enrolled in robust, well-designed clinical trials of medications that have shown efficacy in adult MS Phase III trials (or if Phase II adult trials have demonstrated enough safety data and a positive risk/benefit ratio, or if the medication has been utilized in children with other diseases with available safety data). In addition to, and as an extension of clinical trials, a prospective, standardized registry designed to evaluate long-term safety, fertility and developmental data has been advocated.

Alternative trial designs have been suggested to minimize the number of patients enrolled but to still adequately power a study (Table 1). Historical placebo groups should not be used as controls to minimize study participants as such populations often differ in many respects from patients in clinical trials. This is particularly true for a disease such as MS where there is tremendous disease heterogeneity. Parallel designs with 2–3 study arms, either placebo controlled, or with multiple intervention groups provide the opportunity to evaluate more than one agent concurrently but actually require larger populations to demonstrate superiority of any one agent or even to demonstrate non-inferiority of two or more agents.

If a placebo-controlled trial is conducted, ways to minimize numbers of children exposed to placebo include having unbalanced arms (fewer patients randomized to placebo), and dose–response studies where the lowest dose is low enough that it is not expected to have a treatment effect thereby almost considered a placebo arm. A randomized partial crossover design may also be useful where only the placebo arm crosses over to the treatment arm. This would allow investigators to look at deferred treatment effects and enhance recruitment by guaranteeing that all participants will be exposed to the investigational drug (Table 1).

### MS outcome measures

Primary outcome measures are typically selected as metrics that are likely to be impacted based on the *a priori* established mechanisms of drug action. As such, in adult MS trials of disease-modifying agents, relapse rate, time to relapse and clinical disability are typically evaluated.

Relapse rate has been noted to be higher in the first few years of disease in pediatric MS patients as compared with adult onset patients, with an average of 1–3 attacks per year [13]. Thus, it can be anticipated that relapse rate reduction will serve as a valuable primary end point for pediatric trials involving therapies targeted at the inflammatory aspect of MS.

There are several ways that relapses can be measured: by grouping patients into categories based on an absolute number of relapses, by measuring the change in relapse rate pre- and post-treatment initiation, by measuring the annual relapse rate, or by measuring the time to first relapse [41].

A statistical model has been developed to evaluate the feasibility and sample size requirement for ‘time to first relapse’ as the primary outcome event [42]. This model takes into account the distribution of relapses in patients with MS. Time to first relapse is the same end point used in previous adult studies of clinically isolated syndromes where the primary outcome measure is the subsequent diagnosis of MS (e.g., the first relapse) but is now being considered as an outcome metric in patients with established MS. This type of outcome has many benefits applicable to pediatric patients with MS including minimizing the time on placebo (especially considering that children have a high annualized relapse rate [13]), allowing all participants to be on treatment once the outcome has been met, and possibly even reducing sample size [42]. This metric would depend on the time to biological activity of the therapies being studied.

MRI features are powerful outcomes, especially given that increasing disease activity is often visible on MRI prior to clinical relapse. MRI parameters (number of new T2 or enhancing lesions, cumulative lesion count, lesion size or atrophy) are currently the best biomarkers available for evaluating disease activity in short-term trials. Currently, MRI markers are used as primary outcome measures in Phase I and II studies [43–48]. Phase III trials utilize relapses (relapse rate or time to relapse) as primary end points [37,49].

Outcome measures should ideally also be meaningful to the patient and family. A systematic review of outcome measures selected for pediatric clinical trials revealed that very few studies involved patients and their families when deciding which outcomes to measure [50]. This review suggested that a structured process (such as the Delphi method [106]) is in place, comprised of statisticians, clinical researchers, experts in the field and stakeholders (including children and their guardians), when deciding on appropriate outcomes. While patient and family-endorsed outcome metrics are clearly paramount, such metrics may not be suited as primary outcomes in a trial where outcomes must be met within the short time frame of most clinical trials. Patient- or family-endorsed outcomes may be ideal for longer term studies and certainly should be evaluated as secondary outcomes in all trials.

Clinical metrics such as mood, pain, fatigue and cognition are very meaningful to the patient, but very difficult to quantitate as an individual or composite end points. Additional measures include the quality of family

Alternative trial design	Description	Advantages	Disadvantages
Unbalanced arms	Fewer patients are randomized to placebo	More patients exposed to a treatment	–
Time to event	Outcome measure is time to first relapse [41] rather than number of relapses, number of MRI lesions	Patients exposed to placebo can be offered therapy at time of outcome (first relapse) Fewer patients required	Inability to evaluate secondary outcome measures at set time points
Deferred treatment/partial crossover	Rerandomization of patients initially randomized to placebo to treatment arms after a prespecified time period	Ability to look at early versus late treatment effects Time on placebo would be minimal Smaller sample size	Must still have time after initial randomization to determine safety prior to rerandomization
Sequential design	Phase II–III study; if drug appears safe, randomization occurs with full study enrollment	May minimize sample size	Time invested in study will be longer
Deferred randomization (enrichment design)	Only randomizing patients who would be expected to be responsive to therapy	Smaller sample size	Need a well-documented untreated patient population to be able to determine which patients are most appropriate
Dose response studies	Exposing different treatment arms to different doses of the same drug	Ability to analyze minimal effective dose, thereby possibly reducing side effect profile	May require larger sample size as effect size may be minimal between groups

and peer relationships, activities of daily living, school performance and extracurricular activities. Quality of life scales may capture such issues in a standardized manner and can be considered as secondary outcome measures. Pediatric-specific quality of life tools have been utilized in clinical trials in pediatric epilepsy [51]. Parameters such as mood and fatigue may be evaluated appropriately as primary end points in symptomatic therapy clinical trials.

Measures of cognition have the potential to be powerful end points, particularly relevant to the pediatric population when cognitive maturation is impeded by the disease. Clinical studies have demonstrated significant cognitive impairment in almost a third of children with MS [52,53]. This parameter appears to be an independent variable as it is not correlated with the number of relapses, disability status, fatigue or mood but does appear to be correlated with age of disease onset and disease duration.

Measures of disability include the Expanded Disability Status Scale (EDSS) developed in 1983 [54]. This scale has many limitations including inter-rater variability earlier in the scale, and emphasis on physical disability with very little focus on other facets of MS progression after a score of three. The EDSS is likely to be of low sensitivity in pediatric trials given that few children acquire measurable physical disability in the first 10 years of disease [16]. Thus, studies conducted even over a 2-year period will not be able to identify changes in this clinical end point.

The Multiple Sclerosis Functional Composite (MSFC) scale integrates ambulation, arm/hand function and cognitive function [55]. Advantages of this scale include the

ability to examine different functional domains reflecting the clinical variation in patients. It appears to be a promising measure for clinical trials but a suggestion has been made to transform each component of the scale into events with binary outputs, with each event having an *a priori* designated clinically meaningful amount of change. Then the overall change in the MSFC composite score would also be clinically meaningful [56]. As mentioned, this scale has not been utilized for adult clinical trials thus far, and the individual components would have to be modified to reflect meaningful changes for a child. An ideal composite disability scale for a child would include measures of cognition, fatigue, and more sensitive measures of early physical disability.

The timed 25-foot walk, a component of the MFSC, has been considered to be a good independent outcome measure for adult studies. Nearly all children with MS should be able to complete this task without difficulty, and thus the test is unlikely to distinguish children responding or non-responding to a given therapy

Evaluation of data gained from the PRISMS study in adult MS evaluating the effect of IFN- $\beta$ 1a on active MRI lesions [33] demonstrated the concordance of a 'true end point' (EDSS progression) to surrogate end points (MRI active lesions and clinical relapses) and found that when MRI active lesions and clinical relapses were considered together they accounted for 100% of the treatment effect on EDSS deterioration at 2 years [38]. Thus, just as in adults, relapse rate in combination with MRI metrics, may be the best

current option for outcome measure in pediatric MS clinical trials.

Perhaps, with knowledge from future studies, other MRI measurements such as atrophy and diffusion tensor imaging will play a role as a surrogate for long-term disease progression. However, long-term metrics will not be measured by the standard 2- to 3-year clinical trial and will require Phase IV longitudinal studies. Other short-term end points should also be considered such as hospitalization rates and school attendance in addition to overall quality-of-life measures, neurodevelopment, growth, cognition and fatigue [57].

### Future perspective

Clinical drug investigation needs to be as rigorous in children with MS as in adults in order to use medications safely and effectively. Understanding disease

mechanisms and effects of therapy in children may lend to a better understanding of MS overall. In the interim, pediatric MS long-term drug monitoring registries must be urgently created in order to obtain valuable information on the short- and long-term safety of the currently utilized DMTs.

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### Executive summary

- There are currently no randomized prospective clinical drug trials for pediatric multiple sclerosis patients.
- All new multiple sclerosis clinical trials require a pediatric investigation plan to be in place.
- Emerging immunotherapies, although more efficacious, may have effects on cognitive development, fertility, and immunologic maturation and require close follow up in children.
- International collaboration is required to enroll a sufficient number of patients into well-designed, robust clinical drug trials.
- Alternative trial designs may allow more children to participate in treatment arms, avoiding children remaining on placebo.
- Outcome measures require some modification to suit the pediatric population but MRI metrics and relapse rate are still the most appropriate measures.
- Registries evaluating the safety of currently used disease modifying therapies in the pediatric population are urgently required.

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