Clinical and MRI activity as determinants of sample size for pediatric multiple sclerosis trials

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ABSTRACT

Objective: To estimate sample sizes for pediatric multiple sclerosis (MS) trials using new T2 lesion count, annualized relapse rate (ARR), and time to first relapse (TTFR) endpoints.

Methods: Poisson and negative binomial models were fit to new T2 lesion and relapse count data, and negative binomial time-to-event and exponential models were fit to TTFR data of 42 children with MS enrolled in a national prospective cohort study. Simulations were performed by resampling from the best-fitting model of new T2 lesion count, number of relapses, or TTFR, under various assumptions of the effect size, trial duration, and model parameters.

Results: Assuming a 50% reduction in new T2 lesions over 6 months, 90 patients/arm are required, whereas 165 patients/arm are required for a 40% treatment effect. Sample sizes for 2-year trials using relapse-related endpoints are lower than that for 1-year trials. For 2-year trials and a conservative assumption of overdispersion (θ), sample sizes range from 70 patients/arm (using ARR) to 105 patients/arm (TTFR) for a 50% reduction in relapses, and 230 patients/arm (ARR) to 365 patients/arm (TTFR) for a 30% relapse reduction. Assuming a less conservative θ , 2-year trials using ARR require 45 patients/arm (60 patients/arm for TTFR) for a 50% reduction in relapses and 145 patients/arm (200 patients/arm for TTFR) for a 30% reduction.

Conclusion: Six-month phase II trials using new T2 lesion count as an endpoint are feasible in the pediatric MS population; however, trials powered on ARR or TTFR will need to be 2 years in duration and will require multicentered collaboration. *Neurology*® 2013;81:1215-1221

GLOSSARY

AIC = Akaike information criterion; **ARR** = annualized relapse rate; **DMT** = disease-modifying therapy; **MS** = multiple sclerosis; **NB** = negative binomial; **NBT** = negative binomial time to event; **TTFR** = time to first relapse; **ZINB** = zero-inflated negative binomial; **ZIP** = zero-inflated Poisson.

Therapies to treat pediatric-onset multiple sclerosis (MS)¹⁻⁴ are used off-label, because all approved pharmacologic agents for MS have been studied exclusively in adult patients. With the recent approval of the first oral disease-modifying therapies (DMTs) for MS^{5,6} and several promising new therapies likely to be approved over the next 10 years, pediatric practitioners face the challenge of recommending suitable therapies for pediatric patients with MS despite a lack of evidence on safety and efficacy of these drugs in the pediatric population.⁷ Clinical trials for pediatric-onset MS are being planned, but data on appropriate trial endpoints and required sample sizes to inform trial design are lacking.

Annualized relapse rate (ARR) is a common primary efficacy endpoint in clinical trials of adults with MS, and reduction in new T2 and gadolinium-enhancing lesions are frequently used secondary endpoints in phase III trials.^{5,8-12} Time to first relapse (TTFR) has recently been shown in adults with MS to be a feasible and powerful trial endpoint; using TTFR has the advantage of permitting patients initially randomized to placebo to be switched to active therapy at the time of first relapse.^{13,14}

Supplemental data at
www.neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The aim of this study was to estimate, under various hypothetical scenarios, sample sizes for clinical trials of pediatric-onset MS using accrual of new T2 lesions as an MRI marker of disease activity, and ARR and TTFR as clinical outcomes.

METHODS **Participants and study design.** This cohort has been described previously.^{15,16} Briefly, children younger than 16 years with neurologic deficits and MRI findings consistent with an acute demyelinating syndrome were enrolled within 90 days of symptom onset at 23 Canadian sites into a prospective inception cohort study. Standardized neurologic examinations and brain MRI scans were obtained quarterly during the first year and at a second attack, if it occurred. Clinical assessments were also done annually after the first year. One investigator (B.B.) reviewed all case report forms to confirm that documented relapses met established criteria.¹⁷ The 1.5-tesla MRI protocol included pre- and postcontrast axial T1-weighted, axial proton density and T2-weighted, and sagittal and axial fluid-attenuated inversion recovery images.

Standard protocol approvals, registrations, and patient consents. All participants and their families provided informed consent, and assent was obtained from younger children.

Method of MS diagnosis. Participants meeting 2010 McDonald criteria for MS diagnosis¹⁸ were included. We excluded 1) children who met diagnostic criteria for neuromyelitis optica,¹⁹ 2) children who presented with polyfocal neurologic deficits and encephalopathy, thereby meeting criteria for acute disseminated encephalomyelitis,¹⁷ and 3) participants for whom the clinical, MRI, or laboratory findings suggested an alternative diagnosis.^{20,21} As detailed in our prior work,²² MS diagnosis was based on demonstration of clinical or MRI evidence of new disease by either a confirmed second clinical attack occurring more than 28 days after the incident demyelinating event,²³ or confirmation of MRI lesion dissemination in time.¹⁸

Clinical and MRI outcome definitions. Endpoints modeled include number of new T2 lesions, ARR, and TTFR. For the evaluation of new T2 lesions, all MRI scans were scored by one investigator (L.H.V.) with 5 years of experience in MRI reading. Scans were analyzed on OsiriX (version 3.9.2) and GE Centricity Picture Archiving and Communication System (version 3.2.0.2; GE Healthcare, Waukesha, WI) workstations, using parallel monitors for comparison of images across multiple time points. The number of newly emerging T2 lesions with respect to the previous scan was counted on each scan. Enlarging lesions were not scored as new T2 lesion counts. A lesion was defined as a T2-weighted or fluid-attenuated inversion recovery hyperintensity at least 3 mm in diameter in the axial, sagittal, or coronal plane. Adjacent lesions were scored as discrete when separated by at least 1 mm of normal-appearing white or gray matter. Given our objective to estimate sample sizes for a phase II trial of 6 months' duration, simulations were based on the participant-wise number of new T2 lesions accrued over the 6-month interval from time of MS diagnosis.

Regarding the clinical endpoints of TTFR and ARR, simulations were based on hypothetical phase III trials of either 1 or 2 years' duration from time of MS diagnosis. A relapse was defined as an episode of objective neurologic dysfunction lasting a minimum of 24 hours and occurring more than 28 days from any previous neurologic symptoms.²³ TTFR was defined as the

time from MS diagnosis, based on either a second clinical attack²³ or MRI lesion dissemination in time¹⁸—whichever occurred first, to the time of the subsequent attack. The follow-up time was censored at the date of last follow-up or initiation of DMT.

For ARR, the duration over which the number of relapses was counted was the time from MS diagnosis to either the time of last follow-up visit or DMT initiation—whichever resulted in the minimum duration. If either the time of DMT initiation or last follow-up visit occurred after 12 months (for a 1-year trial) and after 24 months (for a 2-year trial), then relapses were counted over 12 months or 24 months after MS diagnosis. ARR was calculated by dividing the total number of relapses by the total person-years of observation.

Statistical methods. The distribution of MRI lesion counts^{24,25} and clinical relapse counts²⁶ are better fitted by an overdispersed distribution such as the negative binomial (NB) model than by the Poisson distribution. Zero-inflated models also give a good fit to lesion count data.²⁷ Zero-inflated distributions are used to model count data with many zero counts; they are 2-component mixture models that combine a “point mass” function at zero with a count distribution (in this case, a Poisson or an NB distribution). Furthermore, a new parametric model (the NB time-to-event [NBT] model) has been developed that fits the distribution of time to relapse better than the conventional exponential distribution.¹³

Therefore, 4 parametric statistical models were evaluated for their fit to the distribution of number of new T2 lesions counted over 6 months in children with MS: i) the basic Poisson model, ii) the basic NB model, iii) the zero-inflated Poisson (ZIP) model, and iv) the zero-inflated NB (ZINB) model.

Furthermore, the Poisson and NB models were evaluated for their fit to the raw relapse counts. Because the exponential model is the distribution of time to first event when events are distributed according to a Poisson model, and the NBT model has been shown to be the distribution of time to first events when events are distributed according to an NB model,¹³ the exponential and NBT models were assessed to fit the TTFR data.

Goodness of fit of the different models was evaluated using the Bayesian information criterion and the Akaike information criterion (AIC), and comparisons between the models were performed using the Vuong and likelihood ratio tests. Model parameters were estimated using STATA routines (STATA version 12; StataCorp, College Station, TX).

Sample sizes were estimated for hypothetical trials in which the primary outcome is the number of new T2 lesions over a 6-month period, and ARR or TTFR over 12- and 24-month periods. Details about the simulation methodology are reported in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

Briefly, when using new T2 lesion count as the primary outcome, sample size estimates were generated by resampling from the distribution best fitting the raw new T2 lesion count data, and by assuming treatment benefit ranging between a 40% and 70% reduction in new T2 lesions (in the experimental arm compared with the reference arm).

When using ARR as the primary endpoint, simulations were run sampling from the distribution best fitting the raw relapse count data and assuming different treatment effects. Simulations for TTFR as the primary outcome were run sampling from the NBT or exponential model (depending on the assumptions on the distribution of relapse counts) with parameters derived from the distributions fitting the number of relapses. Accrual time was set to 2 years, assuming a uniform distribution of accrual time. Sample sizes were estimated for treatment effects ranging from a reduction in ARR of 20% to 50%. Sample sizes were also

estimated for hypothetical cohorts in which the ARR is 25% or 50% lower than the ARR observed in the present cohort, to correct for a possible selection bias caused by the inclusion of active patients shortly after diagnosis and before treatment initiation (appendix e-1).

RESULTS Demographic and clinical characteristics. As detailed in our recent work,²² 62 participants met 2010 McDonald criteria based on baseline MRI features or MRI evidence of new lesions over time.¹⁸ Of the 62 children, 42 were eligible for the present study (figure 1). Demographic and clinical features of the included participants are presented in table 1. The mean time from incident demyelinating attack to initiation of DMT was 16.3 months (SD 12.5; range 2.5–51.6). New T2 lesions and clinical relapses accrued after DMT initiation were not included in the patient-wise lesion and relapse counts.

Sample size estimates using new T2 lesion counts. The mean number of new T2 lesions counted over 6 months was 9.0 (SD = 9.3). The distribution of lesion counts was highly asymmetrical (figure e-1). The best fit to the data were observed for the NB model and for its zero-inflated extension (figure e-1,

green line = NB, blue line = ZINB), as compared with the Poisson and ZIP models (red line = Poisson, and violet line = ZIP). The Vuong test indicated that the fit was not significantly improved by changing from the NB to the ZINB model ($p = 0.35$) while, using the likelihood ratio test, there was significant difference in favor of the NB model compared with Poisson ($p < 0.001$). The NB model gave the best fit to the distribution of new T2 lesions also according to the lowest AIC (226.5), whereas AIC values were 227.7 for the ZINB model, 450.2 for the Poisson, and 352 for the ZIP.

Sample sizes for trials using the number of new T2 lesions counted over 6 months were therefore estimated assuming an NB distribution for lesion counts (table 2). The NB model had the following parameters: $\mu = 9.0$ (mean value of the new T2 lesion count) and $\vartheta = 0.7$ (overdispersion). The sample size requirement, calculated for a power of 90% and a significance level of 5% and assuming a 50% reduction in new T2 lesions, was 90 patients for each treatment arm, whereas if the minimum detectable treatment effect was assumed to be 40%, the sample size needed was 165 patients per arm.

Figure 1 Study profile

Four children (mean duration of clinical follow-up: 6.5 years) had a clinical and MRI course more indicative of monophasic acute demyelinating syndrome (ADS) than multiple sclerosis: 2 presented with transverse myelitis (TM), one with TM and optic neuritis (ON), and one with polyfocal neurologic deficits; 3 have had no clinical relapses to date, whereas the child who presented with TM and ON had a recurrent episode of ON 48 days later. All 4 children had brain T2 lesions at onset; one had no serial brain T2 lesions, and 3 had new T2 lesions within 3 months of onset but no further new lesions on serial MRI. *Ten children met clinical criteria for acute disseminated encephalomyelitis (ADEM)¹⁷ at the time of incident attack and have demonstrated no clinical or MRI evidence of relapsing disease to date. **Attacks are separated by at least 28 days and localize to distinct regions of the CNS.²³ ***Have not had a second clinical attack to date, but fulfill the 2010 McDonald criteria for dissemination in time.¹⁸ NMO = neuromyelitis optica; SV-cPACNS = small-vessel childhood primary angiitis of the CNS.

Table 1 Clinical and demographic characteristics of children with MS

	Diagnosed with MS (n = 42)
Length of clinical observation from incident attack, y, mean $\pm$ SD (range)	5.9 $\pm$ 1.2 (3.6–8.0)
Age at incident attack, y, mean $\pm$ SD (range)	13.3 $\pm$ 2.1 (7–15.9)
Sex, n (%) female	30 (71)
Time from first attack to MS diagnosis, mo, mean $\pm$ SD (range)	3.4 $\pm$ 3.6 (0–15.4)
Time from MS diagnosis to first relapse, mo, median (range)	7.4 (0.07–85.9)
Proportion with second clinical attack, n (%)	37 (88)
Clinical phenotype at incident demyelinating attack, n (%)	
Optic neuritis	12 (29)
Transverse myelitis ^a	2 (5)
Monofocal, other ^b	10 (24)
Polyfocal	18 (43)

Abbreviation: MS = multiple sclerosis.

For patients diagnosed with MS based on 2010 McDonald criteria for MRI dissemination in time,¹⁸ first relapse refers to the first attack after the incident demyelinating event, whereas for those children diagnosed with MS based on the occurrence of a second clinical attack (i.e., clinically definite MS),²³ the first relapse corresponds to the third attack after the incident demyelinating event.

^aCriteria for transverse myelitis diagnosis: acute motor/sensory spinal cord deficits, bilateral symmetrical or asymmetrical, defined spinal sensory level, progression to maximal deficit 4 hours to 21 days, and neuroimaging exclusion of spinal compression, as well as one of CSF pleocytosis, increased immunoglobulin G index, or gadolinium enhancement of the spinal cord.³²

^bRefers to monofocal neurologic deficits other than optic neuritis or transverse myelitis.

Sample size estimates using ARR and TTFR. The mean duration of follow-up (i.e., time from MS diagnosis to initiation of DMT or last follow-up visit) was 31.2 months (median = 20.4; range = 0.48–86.4). The relapse-free survival of the cohort after confirmation of MS diagnosis is represented in figure 2. At 1 year after MS diagnosis, 42.9% (standard error = 7.6%) of children had a clinical relapse, whereas at 2 years the proportion of relapsing children was 59.6% (standard error = 7.6%). The ARR was 0.76 over 1 year and 0.69 over 2 years of follow-up.

The best fit to the distribution of relapse counts was given by the NB model, but the model fit was not statistically significantly superior to the fit by

the Poisson model. In fact, using the likelihood ratio test to compare the Poisson and NB model fit, no statistically significant differences were detected between the 2 models fitting relapses counted over 1 year ($p = 0.19$) or over 2 years ($p = 0.21$). The mean value (parameter μ) of the Poisson and NB models that best fit the relapse data were $\mu = 0.76$ for trials lasting 1 year (ARR = 0.76) and $\mu = 1.38$ for trials lasting 2 years (ARR over 2 years was 0.69). The overdispersion parameter (ϑ) estimated for the NB distribution of relapses over 1 year was $\vartheta = 2$, and $\vartheta = 4$ for relapses counted over 2 years. Therefore, to estimate sample sizes using ARR as a primary endpoint, we performed simulations based on both the NB and Poisson distributions. Simulations based on the NB distribution had the following parameters: $\mu = 0.76$ or $\mu = 1.38$ and $\vartheta = 2$ (the more conservative assumption). Simulations based on the Poisson model had the same mean values as that for the NB models, but $\vartheta = \infty$ (a less conservative assumption). To estimate sample sizes using TTFR as a primary endpoint, we performed simulations based on an NBT model with the same parameters reported above for the NB model, and also based on an exponential model with the same parameters as the Poisson model.

Sample size estimates assuming 90% power are reported in table 3, and are interpolated for all treatment effect sizes ranging from 20% to 50% reduction in relative relapse rate. For hypothetical trials of 1-year duration and a 30% treatment effect, the required sample size when using ARR as the primary outcome ranged between 260 and 350 patients per arm, according to less or more conservative assumptions about the overdispersion parameter. This number was lower (145–230 per arm) when the follow-up was extended to 2 years. Sample sizes were generally higher when TTFR was the primary endpoint; specifically, for trials of 1-year duration (treatment effect = 30%), the sample size ranged from 365 to 410 per arm, and for trials of 2 years' duration, the number of patients needed was in the range of 200 to 240.

Sample size estimates were also determined for clinical trials using ARR and TTFR as primary endpoints in which the hypothetical cohort has a mean ARR of 25% (table e-1) or 50% (table e-2) lower than that of our cohort. Whereas the sample sizes required for trials in which the mean ARR is 25% lower are similar to those estimates obtained from our data, the required sample sizes when the ARR is 50% lower than that of the present cohort are substantially higher.

DISCUSSION We modeled the distributions of new T2 lesions and relapse rates for children with MS to estimate sample sizes required for clinical trials in

Table 2 Number of patients per arm for a controlled trial with the number of new T2 lesions counted over 6 months

Treatment effect ^a	Study duration, mo	Sample size per arm
40	6	165
50	6	90
60	6	55
70	6	35

$\mu = 9$, $\vartheta = 0.7$.

^aProportional reduction in T2 lesion count.

Figure 2 Relapse-free survival after multiple sclerosis diagnosis

which the number of new T2 lesions, ARR, or TTFR serves as the primary endpoint. We are uniquely poised to calculate sample sizes required for pediatric MS clinical trials given the prospective nature of our incident cohort and the standard clinical and MRI evaluations from which the parametric models of lesion accrual and relapse rate were generated. Studies that inform on trial design and sample size in the context of pediatric MS are imperative, considering that pharmaceutical companies are currently planning the first pediatric trials. The estimated sample size for a trial assuming a 50% relative reduction in new T2 lesion accrual counted over 6 months is 90 patients per arm, suggesting that short-duration phase II trials using MRI endpoints are achievable in the context of pediatric MS. Conversely, longer trials (i.e., 2 years) are recommended when using ARR and TTFR as study outcomes, given that the estimated sample sizes when assuming a moderate relative relapse rate reduction are considerably smaller for 2-year trials than for those of 1-year duration.

New T2 lesion counts and relapse rates in our cohort were modeled with an NB distribution. This model has been shown to be an appropriate model in the context of MS.^{24–26} For MRI lesion counts, we extended the NB model to zero-inflated distributions—a model that has recently been evaluated for white-matter²⁷ and cortical²⁸ MRI lesions. We have confirmed that the NB and ZINB distributions better fit the T2 lesion count data than the Poisson and ZIP in a pediatric MS population, and therefore, we generated sample size estimates by resampling the NB distribution.

We calculated sample size requirements for trials using TTFR, a recently described primary efficacy endpoint.^{13,14} Even if TTFR generally requires a larger number of patients per arm than does ARR, as our and recently published adult data show,¹⁴ TTFR may

be an appropriate endpoint for pediatric phase III trials when active therapies are compared with placebo. Use of TTFR mitigates the ethical concern of having children on placebo for the duration of the trial by permitting participants initially randomized to placebo to switch to active treatment at the time of relapse.

The sample size estimates we generated for trials using ARR and TTFR are smaller than those recently estimated based on placebo data from an adult cohort,¹⁴ likely because of the higher relapse rate in children compared with adults. While the ARR estimated over 2 years in our pediatric cohort was 0.69, the 2-year ARRs of adults in the placebo arms of the FREEDOMS and CLARITY trials were 0.40 and 0.33, respectively.^{5,29} A similar trend was also observed in a study that compared relapse rates between adult-onset (ARR = 0.4) and pediatric-onset (ARR = 1.13) patients.³⁰ Given the higher relapse rate in pediatric-onset MS, it is reasonable to assume that a larger treatment effect would be expected in children than adults; if true, the sample sizes required would be lower than the present estimates.

We chose to model new T2 lesions rather than gadolinium-enhancing lesions as a trial endpoint. The disadvantage of using gadolinium-enhancing lesions as a surrogate marker of disease activity is dependence on the frequency of imaging. Trials in which the endpoint is reduction in contrast-enhancing lesions require monthly MRI scans to obtain robust enhancing lesion counts. Additionally, because gadolinium administration is not well-tolerated in children, monthly contrast-enhanced MRI would pose a practical challenge. Furthermore, estimates of treatment effect when measured by relative reduction in contrast-enhancing lesions and new T2 lesions are virtually the same (slope = 0.96),³¹ suggesting that either endpoint is suitable for monitoring MRI activity in clinical trials. Taken together, new T2 lesion count is a more suitable MRI trial endpoint than enhancing lesions in the pediatric context.

Corticosteroid therapy was provided to 87% of children enrolled in our study at the time of acute attack. As such, patients were approximately 60 days from corticosteroid exposure when imaged at the 3-month time point and 180 days from exposure at 6 months. We cannot exclude an inhibitory effect of initial corticosteroid treatment on early lesion formation, and acknowledge that the number of new lesions detected at 3 months may conceptually have been higher had children not received treatment at the time of acute attack. We think it unlikely that corticosteroid therapy at onset affected lesion formation between 3 and 6 months.

A limitation of this study is the small number of participants. Despite this, we obtained robust sample size estimates because only the distribution mean and overdispersion parameters were obtained from the

Table 3 Sample size per arm for a clinical trial lasting 1 or 2 years, with 90% power and ARR or TTFR as the primary outcome, assuming different variances

ARR in the control arm	Study duration, y	Treatment effect (relative relapse rate reduction)	ARR sample size per arm	TTFR sample size per arm ^a
$\mu = 0.76$, $\vartheta = 2$; NB distribution	1	20	840	1,010
		25	520	620
		30	350	410
		35	240	280
		40	180	200
		45	135	150
		50	105	120
$\mu = 1.38$, $\vartheta = 2$; NB distribution	2	20	570	950
		25	345	560
		30	230	365
		35	160	260
		40	115	180
		45	90	135
		50	70	105
$\mu = 0.76$, $\vartheta = \infty$; Poisson distribution	1	20	630	560
		25	400	350
		30	260	240
		35	185	165
		40	140	120
		45	105	90
		50	85	70
$\mu = 1.38$, $\vartheta = \infty$; Poisson distribution	2	20	340	520
		25	210	315
		30	145	200
		35	105	140
		40	75	105
		45	60	80
		50	45	60

Abbreviations: ARR = annualized relapse rate; NB = negative binomial; TTFR = time to first relapse.

^aTTFR is defined as the time from multiple sclerosis diagnosis, which is based on either a second clinical attack²³ or MRI lesion dissemination in time¹⁸—whichever occurred first, to the time of the subsequent attack.

raw relapse and new T2 lesion counts, whereas the sample size estimates were generated from multiple simulations performed by resampling the distributions. Furthermore, the limited number of patients highlights that pediatric-onset MS is rare, and international multicenter involvement will be imperative to adequately power clinical trials in the pediatric population.

The sample size estimates generated in this work are based on the accrual of relapses and new T2 lesions in

children with MS during the period before initiation of DMT. Thus, we provide evidence-based data from a natural history cohort to guide planning and design of clinical trials in pediatric MS. Our work suggests that MRI-monitored trials are feasible in pediatric MS, and highlights the potential of using both clinical and MRI endpoints in pediatric clinical trials to comprehensively evaluate therapeutic efficacy.

AUTHOR CONTRIBUTIONS

D.L. Arnold, A. Bar-Or, A.D. Sadovnick, R.A. Marrie, and B. Banwell are principal investigators of the Canadian Pediatric Demyelinating Disease Study, and obtained operating grant funding. L.H. Verhey, D.L. Arnold, B. Banwell, and M.P. Sormani were responsible for the study concept and design. L.H. Verhey, A. Signori, B. Banwell, and M.P. Sormani had access to all components of the data and were responsible for interpretation of the data. A. Signori and M.P. Sormani performed the statistical analyses. L.H. Verhey was responsible for data collection and drafted and revised the manuscript, and A. Signori and M.P. Sormani provided content additions and revisions. D.L. Arnold, R.A. Marrie, and B. Banwell provided content revisions.

ACKNOWLEDGMENT

The authors thank Zografos Caramanos and Rozie Arnaoutelis at the Montreal Neurological Institute (Montreal, Canada) for contributions in the initial phase of the work, the staff of the Pediatric Demyelinating Disease Program at The Hospital for Sick Children (Toronto, Canada), and the children and families for their cooperation and commitment to the research program.

STUDY FUNDING

Supported by the Canadian Multiple Sclerosis Scientific Research Foundation.

DISCLOSURE

L. Verhey has received scholarship support from the Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Master's and Doctoral Canada Graduate Scholarships (201010GSD-249751-175560 and 200802CGM-186751-175560), the Multiple Sclerosis Society of Canada (MSSC) Master's Award, and The Hospital for Sick Children Foundation Research Training Award. A. Signori reports no disclosures. D. Arnold served as one of the lead investigators of the Canadian Pediatric Demyelinating Disease Study, and funds from the study grant (Canadian Multiple Sclerosis Scientific Research Foundation) have supported work done at their institutions. None of the investigators receive personal salary support from the study sponsor. D. Arnold has served as a speaker at meetings or as a consultant for Bayer, Biogen, Elan, GlaxoSmithKline, Roche, and Teva Neuroscience; D. Arnold receives financial remuneration and stock options from NeuroRx Research. A. Bar-Or served as one of the lead investigators of the Canadian Pediatric Demyelinating Disease Study, and funds from the study grant (Canadian Multiple Sclerosis Scientific Research Foundation) have supported work done at their institutions. None of the investigators receive personal salary support from the study sponsor. A. Bar-Or has received consultancy fees from Bayhill Therapeutics, Berlex, Biogen-IDEC, BioMS, DioGenix, Eli-Lilly, Genentech, GlaxoSmithKline, Guthy-Jackson/GGF, Merck Serono, Novartis, Roche, Teva Neuroscience, and Wyeth; A. Bar-Or has funding from the NIH, CIHR, MSSC, Biogen-IDEC, and Teva Neuroscience for research unrelated to this study. A. Sadovnick served as one of the lead investigators of the Canadian Pediatric Demyelinating Disease Study, and funds from the study grant (Canadian Multiple Sclerosis Scientific Research Foundation) have supported work done at their institutions. None of the investigators receive personal salary support from the study sponsor. A. Sadovnick has received speakers honoraria from Biogen, Merck Serono, Teva Neuroscience, and Bayer; A. Sadovnick has grant support from CIHR, MSSC, and the Canadian Multiple Sclerosis Scientific Research Foundation for research unrelated to this study. R. Marrie served as one of the lead investigators of the Canadian Pediatric Demyelinating Disease Study,

and funds from the study grant (Canadian Multiple Sclerosis Scientific Research Foundation) have supported work done at their institutions. None of the investigators receive personal salary support from the study sponsor. R. Marrie has funding from CIHR, MSSC, Manitoba Health Research Council, HSC Foundation, Public Health Agency of Canada, Rx & D Health Research Foundation, Consortium of MS Centers, and Sanofi-Aventis for research unrelated to this study. B. Banwell served as one of the lead investigators of the Canadian Pediatric Demyelinating Disease Study, and funds from the study grant (Canadian Multiple Sclerosis Scientific Research Foundation) have supported work done at their institutions. None of the investigators receive personal salary support from the study sponsor. B. Banwell has received speakers honoraria from Merck Serono, Biogen-IDEC, Bayer Healthcare, and Teva Neuroscience; B. Banwell serves as an advisor on pediatric therapies for Biogen-IDEC, Merck Serono, and Genzyme. M. Sormani has received speakers honoraria and consultation fees from Actelion, Merck Serono, Synthon, Allozyne, Teva Neuroscience, and Biogen-IDEC. Go to Neurology.org for full disclosures.

Received February 28, 2013. Accepted in final form July 5, 2013.

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