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ORIGINAL RESEARCH ARTICLE

Adverse Drug Reaction Reporting Using a Mobile Device Application by Persons with Multiple Sclerosis: A Cluster Randomized Controlled Trial

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Abstract

Introduction Patient reporting adds value to pharmacovigilance. Encouraging it to be done through a mobile device application (App) is a method that should be evaluated.

Objective This study aimed to determine whether the use of an App, compared to traditional use through e-mail, telephone, or the national website, increased suspected adverse drug reaction (ADR) reporting by persons with multiple sclerosis receiving a first-line disease-modifying drug.

Methods An open multi-centric, cluster-randomized controlled trial was conducted (VigipSEP study). Clusters were centers allocated (1:1) to the use of the My eReport France® App (experimental arm), and traditional reporting (control arm). Persons with multiple sclerosis initiating or switching to a first-line disease-modifying drug between April 2017 and April 2019 were included. The primary outcome was the mean number of ADR reports per patient for the center-level analysis, and the number of ADR reports per patient for the individual-level analysis using the hierarchical Poisson regression model.

Results Twenty-four centers (12 per arm: six public neurologists from the multiple sclerosis academic expert centers, three public neurologists from general hospitals, and three private practice neurologists) were randomized, including 159 patients. The mean number of ADR reports per patient was significantly higher in centers that used the App: 0.47 vs 0.03 in control centers ($p = 0.002$). At an individual-level analysis, the experimental arm was significantly associated with a relative risk of ADR reports at 18.6 (95% confidence interval 4.1–84.2; $p < 0.001$), compared to the control arm, adjusted for sex and type of disease-modifying drug.

Conclusions The use of a mobile App increased the ADR reporting by persons with multiple sclerosis receiving a first-line disease-modifying drug.

ClinicalTrials.gov identifier NCT03029897, registered in 2017.

Key Points

This study demonstrated a favorable association between a mobile device application used by persons with multiple sclerosis and increasing adverse drug reaction reporting.

Reports with the tested mobile device application were mostly of moderate clinical quality.

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1 Introduction

Spontaneous reporting of suspected adverse drug reactions (ADRs) is key for post-marketing pharmacovigilance. This type of reporting, involving a larger and more varied population of patients with longer periods of exposure, has the potential to be more informative than reporting by selected patients who participate in phase III trials required for drug registration. Spontaneous reporting by physicians and other healthcare professionals (HCPs) is also the backbone of any pharmacovigilance system. Similarly, patient reporting of ADRs is increasingly becoming of interest as it can lead to a broader base of knowledge on drug safety and allows earlier detection of ADRs [1]. In previous studies, the relevance of spontaneous ADR reporting by patients has been well underlined [1–8]. The US Food and Drug Administration and the European Medicines Agency have encouraged patient reporting since 2015 and, in France, French health authorities have allowed online reporting for both HCPs and patients since 2017 with the creation of a dedicated internet portal [9].

Multiple sclerosis is a chronic disease that has had a vast improvement in its therapeutic armamentarium in the last 20 years. Disease-modifying drugs (DMDs), in particular, have significantly impacted the quality of life and the overall global care of persons with multiple sclerosis, irrespective of potential ADRs and their severity [10–15]. Monitoring ADRs during the post-marketing period is fundamental in improving the knowledge of drug safety profiles [16]. However, as for many drugs, ADR reporting by patients for DMDs remains low. According to the French National Pharmacovigilance Database, in 2015, among the 3000 first-line DMDs prescribed for persons with multiple sclerosis in France, only 20 ADRs were reported by patients.

Regarding the delivery, the traditional methods of reporting have been through e-mail, telephone, or a dedicated national website; however, mobile device applications (Apps) are now among the suggested tools that can increase reporting of ADRs. These tools provide new opportunities for collecting patient-reported outcomes in real-life settings [17–19]. Research, however, has been limited on the effectiveness of Apps for ADR reporting by patients. Persons with multiple sclerosis given first-line DMD prescriptions are mostly young adults that fall under a population of digital natives accustomed to the use of smartphones and Apps [20, 21]. The objective of this study was to determine whether the use of an App increased ADR reporting by persons with multiple sclerosis receiving first-line DMD, compared to traditional reporting.

2 Methods

2.1 Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol, known as VigipSEP, was previously published [22]. The study protocol was approved by the Ethics Committee of Nord-Ouest III (France) with approval number 2016–42. All participants were provided with a written informed consent. The protocol was prospectively registered in ClinicalTrials.gov (NCT03029897).

2.2 Study Design

VigipSEP was an open, multi-centric, cluster-randomized controlled trial. Twenty-four investigator centers in France were centrally (1:1) randomized to the experimental arm or to the control arm. Randomization was stratified based on the structure type and performed by blocks of size two using the ALEA function (Microsoft Excel, 2013). Centers were informed of the randomization on the day of the trial initiation visit. Patients were recruited by public neurologists in multiple sclerosis academic expert centers and general hospitals, and by private practice neurologists.

2.3 Participants and Disease-Modifying Drugs

Persons with relapsing–remitting multiple sclerosis were included if they were (1) adults aged ≥ 18 years, (2) with benefits from the French social security, and (3) undergoing the initiation or change in treatment (switch) to a first-line DMD in France. All first-line DMDs marketed in France were included in the study: interferon-β, peginterferon-β, glatiramer acetate, teriflunomide, and dimethyl fumarate. Participants had to have access to a smartphone, tablet, or other computer device that could host the App and a satisfactory level of understanding and writing in French.

2.4 Intervention

My eReport France®, a free mobile App developed by the eVeDrug® company, was used (https://www.evedrug.eu/myereport.php). The form contained questions (with mandatory questions*) about the reporter type* (patient or HCP), the patient (initials*/age*/weight/size/sex*/medical history), the suspected drug(s) [name and holder*/route of administration*/date of start*], causality according to the patient, and ADR(s) [description*, seriousness, date of onset*/evolution/photo], and is compatible with the

ICH-E2B format (European standards on electronic transmission of individual case safety reports), which is the current standard for the electronic transfer of ADR reports.

It was chosen as it was the only available App in France to report suspected ADRs to the French authorities in E2B language, in accordance with European regulations. Data hosting was provided by a certified health data host. My eReport France® was available on Google Play and the App store for Android and iOS devices, respectively.

In the experimental arm, a patient was introduced to the App by their treating neurologist. A video tutorial created by the investigator's team of the VigipSEP study was presented to the patient. Each patient received a participant card containing QR codes (Android and iOS) to download the App. The participant card also provided contact details, phone numbers, and the e-mail of the study coordinators for technical support. A patient was only then able to report ADRs via the App. Reports were electronically sent directly to the Regional Center of Pharmacovigilance, based on the region of a patient [23].

In the control arm, patients were encouraged to report an ADR according to the usual reporting procedures: by phone or e-mail to their corresponding Regional Center of Pharmacovigilance, or using the national online report form (https://signalement.social-sante.gouv.fr/). All patients were provided with information by their treating neurologist and given further information in the letter of consent (Fig. 2 of the Electronic Supplementary Material [ESM]).

In both arms, patients were encouraged to describe all ADRs to their physician during the study period. A physician who was informed of an ADR by a patient could voluntarily report it via the traditional reporting tools.

Reports from both arms were then assessed by a clinical pharmacologist in one of the Regional Centers of Pharmacovigilance as per the usual procedure [23]. The causality assessment (relatedness with the French imputability method [24]) was conducted and recorded by the clinical pharmacologist in the French National Pharmacovigilance Database.

2.5 Outcome Measures

The primary outcome was the mean number of ADR reports per patient for the center-level analysis (primary analysis) and the number of reports per patient for the individual-level analysis (secondary analysis). Adverse drug reaction reports were collected in both arms for 6 months after the inclusion of each patient. A report contained one or more ADRs and recurrent ADRs were considered as one reaction type.

The secondary outcome was the listed or unlisted characteristic of an ADR. This outcome was considered as an indicator of knowledge for the safety profile of a drug. An ADR in the Preferred Term from the Medical Dictionary for Regulatory Affairs (MedDRA®) was qualified as an unlisted characteristic if it did not match with a Preferred Term in the Summary of Product Characteristics (SmPC) of a given drug. The referential in the SmPC was found in paragraph 4.8 of the current SmPC of each DMD in the European Medicines Agency site, or if unavailable in the national database of drugs [25–29]. For the ADR coding, we retained the coding in the primary Preferred Term from the Low Level Term coded by the clinical pharmacologist that assessed the ADR, and clinical pharmacologists were used to following the guidance of MedDRA® [30].

The third outcome was the clinical quality of each suspected ADR, manually scored with the clinical documentation assessment tool ClinDoc by an independently blinded pharmacologist [31]. Clinical quality score was divided into four categories: excellent (≥ 75%) and well (61–75%), moderately (45–60%), or poorly (≤ 45%) documented reports. The fourth outcome was the number of physician reports during the same period.

2.6 Data Collection Procedures

All ADRs reports related to a first-line DMD were extracted from the French National Pharmacovigilance Database from the first inclusion up to the sixth month after the last inclusion. Data (sex/age/month of birth/first-line DMD prescribed/ADR(s)/date of onset of ADR) were reconciliated between the VigipSEP database and the extraction of the French National Pharmacovigilance Database to identify reports by the VigipSEP participants (Fig. 1 of the ESM).

2.7 Statistical Analysis Method

2.7.1 Sample Size Calculation

Patient ADR reporting was hypothesized to increase ten times with the use of the My eReport France® App compared with the traditional methods. This hypothesis was based on a prior study in which a patient social media community adopted the MedWatcher® App [32]. The statistical unit for the primary analysis was the cluster. The mean number of ADR reports per patient were pooled by a center, and the comparison was performed at the cluster (center) level.

The estimation of the number of clusters required was a comparison of the two means with one for the control arm of 20 ADRs per 3000 persons with multiple sclerosis = 0.67% (based on the French National Pharmacovigilance Database in 2015); and one for the experimental arm of 6.7%. The power was 90% according to a bilateral test with a 5% error risk and an estimated standard deviation of 0.04 [22]. It was estimated that ten clusters in each arm were needed to test the hypothesis. Twelve clusters per arm were targeted to be included to counter the tendency of over-reporting due to informing physicians of the study (Hawthorne effect).

A total of 24 multiple sclerosis outpatient-clinic departments were asked to recruit 180 patients (90 per arm) with the following expected distribution: ten patients per public neurologist from a multiple sclerosis academic expert center, five patients per public neurologist from a general hospital, and five patients per neurologist from a private practice. No interim analysis was planned.

The primary outcome was computed as follows: for center 1, m1 = n1 reports/N1 patients, where *n1* is the number of ADRs reports in the center and *N1* is the number of patients included in the cluster. The method of aggregation in each group followed the formula Σmi/N, where *i* represents the i cluster and *N* is the number of clusters in the group.

2.7.2 Statistical Analyses

The plan of the statistical analyses was previously published [22]. The mean number of ADRs per patient at the cluster level was compared between arms using the Student's *t* test with the number of enrolled patients in each center as a weighting factor. A post-hoc sensitivity analysis with the weighted Wilcoxon rank test was performed. In addition, a hierarchical model (level 1: clusters; level 2: individuals nested within clusters) was computed with an analysis at the level of the patient, taking into account the intra-cluster correlations using a multivariate generalized linear model with Poisson distribution. This model included the number of ADRs per patient as the dependent variable and the arm of randomization, sex, and type of DMD as the independent variables. This pre-planned analysis took into account potential confounders at the individual level. A post-hoc unadjusted generalized linear model with Poisson distribution, including no other covariates, was realized. Other outcomes were only descriptive. The clinical quality score was described by median (inter-quartile range) and by arm. All statistical analyses were conducted with SAS version 9.4 software (SAS Institute, NC, Cary, USA) and a *p*-value below 0.05 denoted a statistical significance.

2.7.3 Data Availability

Anonymized data can be made available to investigators upon request to the corresponding author.

3 Results

Twenty-four centers were randomized on 18 April, 2017 (Fig. 1). In both the experimental and control arms, 12 centers were included: neurologists from six multiple sclerosis academic expert centers, public neurologists from three general hospitals, and three neurologists with a private practice. The first patient was included on 24 April, 2017. The last patient completed the 6-month follow-up on 24 April, 2019. There were 159 patients included in total (91 in the experimental arm, 68 in the control arm). Baseline patients' demographic and clinical characteristics are described in Table 1. The median age of patients was 38 years (range 19–78 years). Characteristics were similar between patients in both arms, except for the DMD. For 97 patients among 159, the first-line DMD was the first drug prescribed (51 in the experimental arm vs 46 in the control arm). During the study, two patients, both in in the control arm, had a drug prescription change and were switched from glatiramer to teriflunomide.

Among the patients in the experimental arm (91 patients), there were 64 ADRs in 43 reports (1.49 reactions by report, range 1–12), and among the control arm, three ADRs in two reports (range 1–2), all ADRs were recorded in the French National Pharmacovigilance Database (Fig. 1 and Table 1 of the ESM). All suspected ADR events were assessed as possibly related to the first-line DMD by both the patient and the clinical pharmacologist.

3.1 Primary Outcome

3.1.1 Center-Level Analysis (Primary Analysis)

There was a higher mean number of reports per patients in the experimental arm (0.47 vs 0.03; $p = 0.002$) (Fig. 2). The post-hoc sensitivity analysis with non-parametric testing obtained similar results (experimental arm, median [IQR]: 0.36 [0.20–1.00] vs the control arm: 0.00 [0.00–0.00]; $p < 0.0001$).

3.1.2 Individual-Level Analysis (Secondary Analysis)

The relative risk for the App effect as compared with the control was 18.6 (95% confidence interval 4.1–84.2), adjusting for the female sex and DMD. In the post-hoc unadjusted generalized linear model analysis, the effect of app remained significant (relative risk = 16.07 95% confidence interval 3.81–67.74, $p = 0.0002$).

3.2 Secondary Outcomes

3.2.1 Listed/Unlisted Character of Adverse Drug Reactions

Sixteen ADRs (24%) were unlisted in the SmPC of a given DMD (Table 2). Among them, two ADRs were reported by more than one patient (two patients in both cases); which were "back pain" related to teriflunomide, and "extreme fatigue" related to glatiramer acetate.

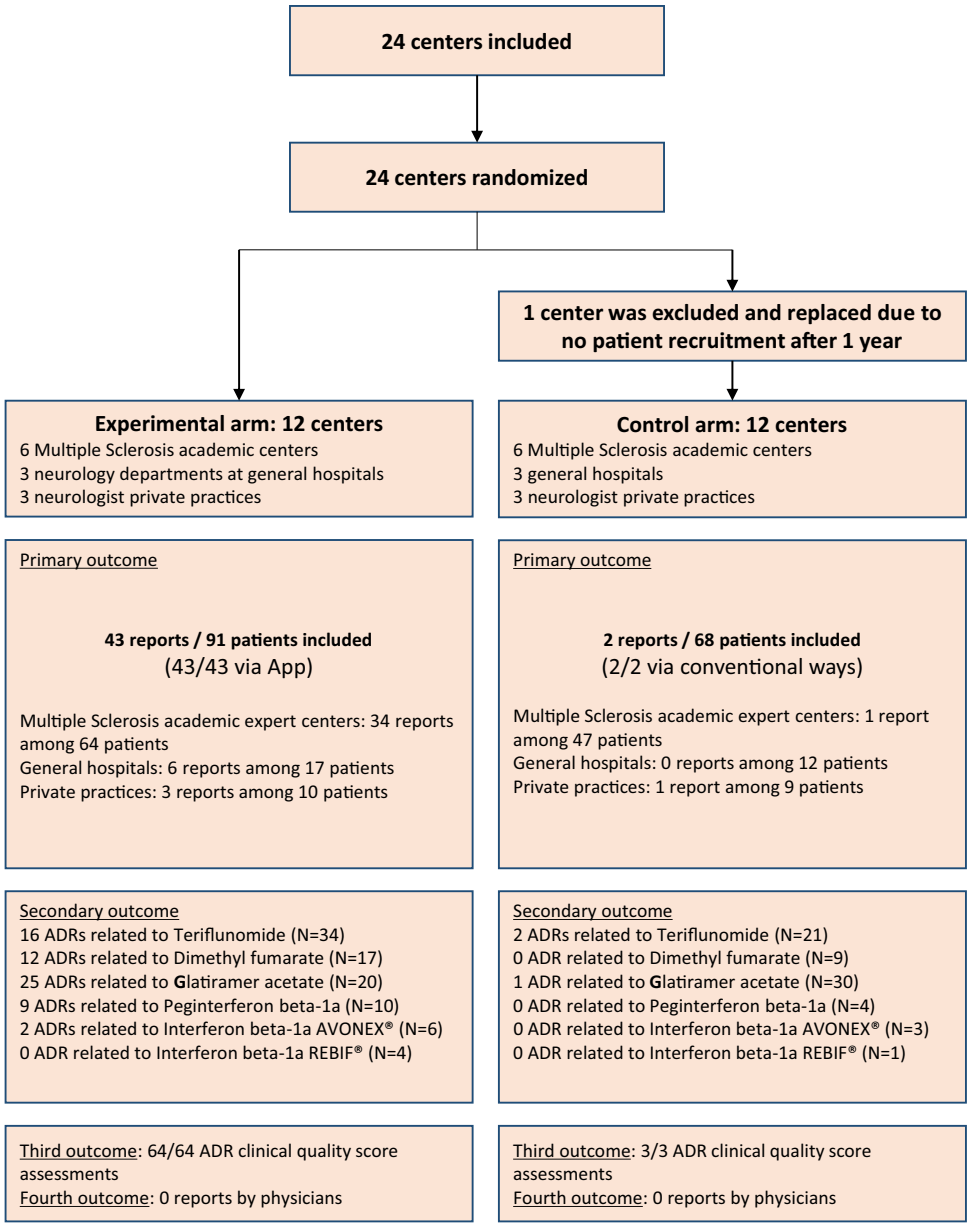

Fig. 1 Flowchart of the VigipSEP study to assess adverse drug reaction (ADR) reporting using a mobile device application (App) by persons with multiple sclerosis

Table 1 Demographic and clinical characteristics of the population at baseline from the VigipSEP study

	Experimental arm ($N=91$)	Control arm ($N=68$)	p value
Age, median (IQR)	38 (30–48)	38 (30–45)	0.60
BMI, median (IQR)	24.8 (21.8–28.4)	23.8 (22.0–27.5)	0.59
EDSS score, median (IQR)	1 (0.0–2.5)	1 (0.0–2.0)	0.88
Female, *n* (%)	74 (81)	47 (69)	0.07
Disease-modifying drug, *n* (%)			
Glatiramer acetate (Copaxone®)	20 (22)	30 (44)	0.02
Teriflunomide (Aubagio®)	34 (37)	21 (31)	
Dimethyl fumarate (Tecifidera®)	17 (19)	9 (13)	
Interferon (interferon β-1a [Avonex®], interferon β-1a [Rebif®], peginterferon β [Plegridy®])	20 (22)	8 (12)	

BMI body mass index, *EDSS* Expanded Disability Status Scale (neurologic impairment score in multiple sclerosis), *IQR* interquartile range

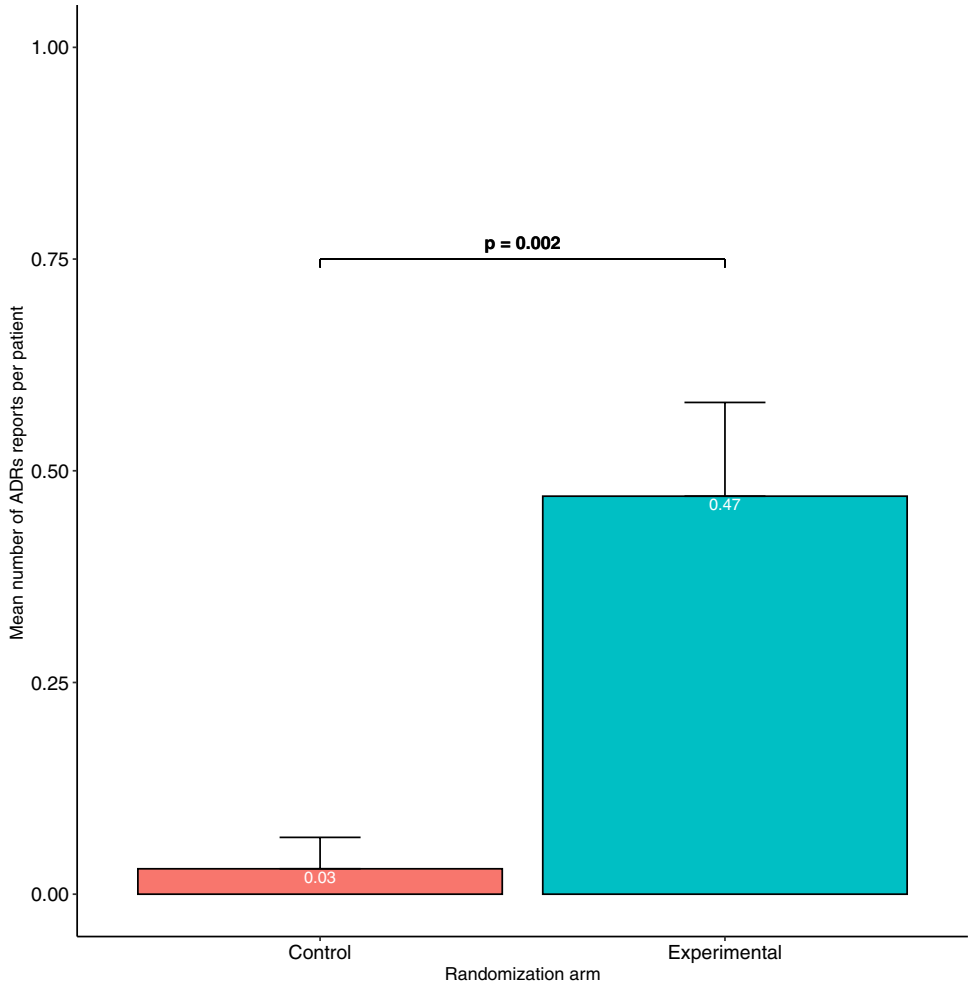

Fig. 2 Mean number of adverse drug reaction (ADR) reports per patient between the experimental and control arms in the VigipSEP study. *App* mobile device application

3.2.2 Clinical Quality of Adverse Drug Reactions

Among 64 ADRs in the experimental arm (clinical quality score, median 57% [50–64]), 23 (36%) were well documented, 40 (62%) were moderately documented, and 1 (2%) was poorly documented. Among three ADRs in the control arm (clinical quality score, median 79% [71–79]), two were excellently documented and one was well documented.

3.2.3 Physician Reporting

No ADRs were reported by neurologists or other HCPs in charge of the patients.

4 Discussion

This study is the first randomized controlled trial that demonstrated a favorable impact and effectiveness of an App to increase reporting of ADRs by persons with multiple sclerosis receiving a first-line DMD. One ADR out of four was unlisted. Reported ADRs were mostly of moderate clinical quality.

Apps were suggested to increase ADR reporting by patients and improve the emergence of new safety information for pharmacovigilance [21]. In a previous observational study by Montastruc et al. the use of an App improved and facilitated notifications by patients, where patient reports were significantly more frequent with an App (6.7%) than through traditional methods (3.4%). The study was non-randomized, and there was a relatively low number of ADRs reported through the App [33]. With an adapted methodology, our study demonstrated the positive effect of using such tools for patient ADR reporting.

Our results underlined the relevance of using eHealth tools, by involving patients in the ADR reporting process through the use of an App [34]. However, our results for the clinical quality of ADRs reported via a tested App, mostly of moderate quality, encourage improvement of the system. For example, the App did not include the reporting of decisions made by patients and/or the physicians to discontinue their medication, as a result of the ADRs [35]. Through better

Table 2 Characteristics of adverse drug reactions (ADRs) reported as listed or unlisted, according to the Summary of Product Characteristics (SmPC) of a disease-modifying drug (DMD)

DMD	System organ class in MedDRA®	Preferred Term in MedDRA® reported in the French National Pharmacovigilance Database	Number of ADRs in the experimental arm	Number of ADRs in the control arm
Teriflunomide (Aubagio®)	Musculoskeletal and connective tissue disorders	**Back pain**	**2**	
		Myalgia	*1*	
		Arthralgia	*1*	
		Musculoskeletal pain	*1*	
		Muscle spasm	**1**	
	Gastrointestinal disorders	**Tooth disorder**	**1**	
		Constipation	**1**	
		Diarrhea	*1*	
		Vomiting	*1*	
		Nausea		*1*
		Intestinal pain		**1**
	General disorders and administration-site conditions	*Headache*	*4*	
	Skin and subcutaneous tissue disorders	*Alopecia*	*1*	
		Erythema	**1**	
Dimethyl fumarate (Tecifidera®)	Gastrointestinal disorders	*Nausea*	*1*	
		Abdominal pain upper	*1*	
	General disorders and administration-site conditions	*Feeling hot*	*1*	
		Dizziness	**1**	
	Nervous system disorders	*Burning sensation*	*1*	
	Skin and subcutaneous tissue disorders	*Pruritus generalized*	*1*	
		Generalized erythema	*2*	
		Erythema	*1*	
	Vascular disorders	*Hot flush*	*2*	
		Flushing	*1*	
Glatiramer acetate (Copaxone®)	Gastrointestinal disorders	*Nausea*	*3*	
		Vomiting	*1*	
		Gastrointestinal disorder	*1*	
		Abdominal pain upper	*1*	
		Intestinal time transit decrease	*1*	
	General disorders and administration-site conditions	**Fatigue extreme**	**2**	
		Fatigue	*1*	
		Injection-site reaction	*2*	
		Injection-site pain	*2*	*1*
		Injection-site induration	*1*	
		Injection-site plaque	*1*	
		Feeling hot	**1**	
		Headache	*2*	
		Dizziness	**1**	
	Musculoskeletal and connective tissue disorders	**Muscle spasms**	**1**	
	Nervous system disorders	**Paresthesia**	**1**	
	Skin and subcutaneous tissue disorders	*Pruritus*	*1*	
		Dry skin	**1**	
		Nodule skin	*1*	

Table 2 (continued)

DMD	System organ class in MedDRA®	Preferred Term in MedDRA® reported in the French National Pharmacovigilance Database	Number of ADRs in the experimental arm	Number of ADRs in the control arm
Peginterferon beta-1a (Plegridy®)	Gastrointestinal disorders	**Gastroesophageal reflux disease**	**1**	
	Musculoskeletal and connective tissue disorders	*Myalgia*	*2*	
	General disorders and administration-site conditions	*Injection-site erythema*	*1*	
		Injection-site reaction	*1*	
		Influenza-like illness	*2*	
		Pyrexia	*1*	
		Headache	*1*	
Interferon beta-1a (Avonex®)	Musculoskeletal and connective tissue disorders	*Pain in extremity*	*1*	
	General disorders and administration-site conditions	*Headache*	*1*	

Bold: unlisted characteristic of the DMD in the SmPC, italics: listed characteristic of the DMDM in the SmPC

MedDRA® Medical Dictionary for Regulatory Affairs

knowledge and understanding of discontinuation, labeling a patient information leaflet could provide advice by HCPs on potential management or the need to discuss the discontinuation of medication [36]. In this study, satisfaction for a DMD was not recorded and may have affected adherence. The reporting of DMD satisfaction could be considered alongside ADR reporting, to enhance the understanding of patients' perspectives [37–39]. This measure could be integrated in the App by a validated outcome, for example, by the Treatment Satisfaction Questionnaire for Medication (TSQM) [40].

The Apps in Europe for ADRs reporting include VigiBIP® (designed by the pharmacovigilance network in France, which has already been tested [33], but with the need of technical support to extend it nationally) and My eReport France® in France (2015), the Yellow card App® in the UK (2015), Lareb App® in the Netherlands (2016), Halmed App® in Croatia (2016), and the international App WebRADR® in the context of the Web-Recognizing Adverse Drug Reactions (Web-RADR) project [36]. The Web-RADR application recently proposed a simplified reporting form that promises a sufficient quality of reports, which might be a suggestion for the French competent authority to recommend.

In the VigipSEP study, patients reported one quarter of unlisted ADRs. The two drugs that were the most concerned by unlisted ADRs were a recent drug (teriflunomide) and an older drug (glatiramer), the oldest one should have been with a more completed safety profile. Similarly, in a recent Italian study, 411 ADRs were collected from patients with relapsing–remitting multiple sclerosis by a systematic report, of which 16% of ADRs were unlisted [16]. These results may confirm that information provided from clinical trials during and after their experimental development, and information from HCPs during the premarketing period, are insufficient to describe the profile of ADRs. Moreover, spontaneous patient ADR reporting complements HCP reporting not only by providing a similar relevance of clinical information but also by including additional information about the impact ADRs have on daily life [4, 6, 36, 41–43].

Regarding pharmacovigilance, patient reports contributed to a signal detection either in case-by-case reviews or in using disproportionality analyses to detect signals. Watson et al. reported an assessment process by a multidisciplinary team from the Uppsala Monitoring Centre and the Netherlands Pharmacovigilance Centre Lareb to identify signals from case series comprising a majority of patient reports in the VigiBase (the World Health Organization global database of individual case safety reports) [44]. For example, a signal of a new unlabeled ADR of color vision distortion with pregabaline was identified thanks to six patient reports out of a total ten. In the VigipSEP study trial, among the 91 first-line DMDs introduced in the experimental arm, there were unlisted ADR reports of "back pain" related to teriflunomide by two patients. One of these cases was reported with four other national cases to alert neurologists and contributed to a potential safety signal [45]. Emergence of signals may thus be anticipated with the extension of the VigipSEP reporting process in France in wider target groups, such thousands of patients per year concerned with the introduction of a DMD.

Careful interpretation of mobile health data requires an appropriate use of statistical methods and analyses [17]. As expected for a system that encourages patients to submit an ADR report, our results indicate that a high proportion of the reports were symptoms as opposed to medical diagnoses. Increases in symptom reports for a type of medication will tend to decrease the proportions of potentially more important medical diagnosis reports when compared with other medications in a safety database, which could have the overall effect of decreasing the likelihood of detecting important safety signals. This could create additional noise, interfering with the signal detection. However, this risk is avoidable using a disproportionality analysis by including or excluding patient reports from a database. Direct patient reporting also may be considered as an independent system. In any case, further qualitative evaluation is essential when determining whether a real ADR is being signaled.

No ADR reports were given by neurologists or any other HCPs in this study. This result was consistent with the 94% underreporting of ADRs by HCPs in real-world practice [46].

There were limitations to this study. A multicenter cluster-randomized trial design was chosen to ease the implementation of the study within the 24 centers. Neither the number of subjects included in each arm nor their baseline characteristics could be controlled. More patients were included in the experimental arm (91 vs 68 in the control arm). This may have been because of a lower motivation from neurologists to include patients or from patients to adhere to the study in the control arm. Additionally, the distribution of DMDs (Table 1) significantly differed between the control and experimental arms ($p = 0.02$). Differing prescribing habits by varying HCPs in the centers may have contributed to this observation. The lower frequency of glatiramer acetate and the higher frequency of interferon in the experimental arm compared with the control arm may have also contributed to our observed results. Nevertheless, a hierarchical analysis was conducted to control the differences between the arms at a subject level, in a pre-planned sensitivity analysis [22] and these results were consistent with the primary analysis.

Despite involving several centers in France, our results may not be directly replicable in other countries with similar ADR reporting mechanisms, owing to the international diversity of pharmacovigilance systems. Furthermore, the study only involved persons with multiple sclerosis, which is a chronic condition with an evolving therapeutic regimen. Further studies using the App would need to be conducted by patients with other chronic conditions and diseases to match our findings [37].

The patients in the interventional arm were educated and supported to using the App, whereas the education provided was not mirrored in the control group. It was difficult to separate the effect of the App to the effect of awareness of reporting. We should have handed the patients in the control group with a participant card on where to turn for technical support if they did not manage to report through the online reporting form. Additionally, the user experience and design of the App were not considered in this study. The user experience of the App used for ADR reporting may be another independent factor to consider on the impact of the App's usability. In real-life settings, education should be implemented in the strategy to encourage patients use of the App. Neurologists, as well as nurses, may play a role in teaching patients about the use of an App to report ADRs. A new randomized controlled trial study will be conducted to introduce education on the App for patients, through a network of multiple sclerosis specialized nurses (VigipSEP2 trial, NCT04116424), and will be the core of the experimental arm.

5 Conclusions

This study demonstrated a favorable association between an App used by persons with multiple sclerosis and ADR reporting. Apps provide new opportunities for collecting real-world data in the field of pharmacovigilance, not only for persons with multiple sclerosis but more broadly to all patients with chronic conditions. To improve the clinical quality of reporting, a revised App could be designed to include patient education and treatment satisfaction from the patient's perspective.

The results of this study may influence clinical practices of ADR reporting in the future. Physicians and HCPs caring for persons with multiple sclerosis are encouraged to inform their patients of existing ADR-reporting Apps, particularly when introducing new DMDs.

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Declarations

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Ethics Approval The study protocol was approved by the Ethics Committee of Nord-Ouest III (France) with approval number 2016–42.

Consent to Participate All participants provided a written informed consent.

Consent for Publication Not applicable.

Availability of Data and Material Anonymized data can be made available to investigators upon request to the corresponding author.

Code Availability Not applicable.

Authors' Contributions All authors read and approved the final version. Gilles Defer designed and conceptualized the study, participated as a neurologist for one of the centers of the trial, analyzed the data, and drafted the manuscript for intellectual content. Sophie Fedrizzi interpreted the data and revised the manuscript for intellectual content. Damien Chevanne had a major role in the acquisition of data and revised the manuscript for intellectual content. François Montastruc designed and conceptualized the study and revised the manuscript for intellectual content. Anais R. Briant performed the statistical analysis and revised the manuscript for intellectual content. Jean-Jacques Parienti designed and conceptualized the study, performed the statistical analysis, and revised the manuscript for intellectual content. Laure Peyro-Saint-Paul designed and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content.

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