PASS PROTOCOL

TITLE:	An Observational, Cross-Sectional Survey to Assess PML Risk Awareness and Understanding From Patients' Perspective and Effectiveness of the Tysabri (Natalizumab) Patient Alert Card in the UK
PROTOCOL VERSION IDENTIFIER:	GB-TYS-12163, Version 2.0
DATE OF LAST VERSION OF PROTOCOL:	05 May 2022 (1.0)
EU PAS REGISTER NUMBER:	ENCEPP/DSPP/46280 (2022)
ACTIVE SUBSTANCE:	Natalizumab
MEDICINAL PRODUCT:	Tysabri
PRODUCT REFERENCE:	Not applicable
PROCEDURE NUMBER:	Not applicable
MARKETING AUTHORISATION HOLDER:	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
JOINT PASS:	No
RESEARCH QUESTIONS:	What proportion of Tysabri-treated patients are aware of the risk of PML? What proportion of Tysabri-treated patients have received the PAC and understood the key safety messages communicated on the PAC?
OBJECTIVES:	To estimate the proportion of patients who are aware of the risk of PML. To estimate the proportion of patients who have received the PAC and who understood the key safety messages communicated on the PAC.
COUNTRIES OF THE STUDY:	National registry from the UK (UK MS Register) will be used.
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2. LIST OF ABBREVIATIONS

ANOVA	analysis of variance
CCI [redacted]	[redacted]
CI	confidence interval
EDSS	Expanded Disability Status Scale
EU	European Union
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practice
HCP	healthcare professional
ICC	intraclass correlation coefficient
ICH	International Council for Harmonisation
IV	intravenous
MAH	marketing authorisation holder
CCI [redacted]	[redacted]
MRI	magnetic resonance imaging
MS	multiple sclerosis
NHS	National Health Service
NIHR	National Institute of Health Research
NRES	National Research Ethics Service
PAC	Patient Alert Card
PML	progressive multifocal leukoencephalopathy
Q4	fourth quarter
RRMS	relapsing-remitting multiple sclerosis
SAP	statistical analysis plan
SC	subcutaneous
SQL	Structured Query Language
UK	United Kingdom
WebEDSS	web-based expanded disability status score

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Protocol Title:	An Observational, Cross-Sectional Survey to Assess PML Risk Awareness and Understanding From Patients' Perspective and Effectiveness of the Tysabri (Natalizumab) Patient Alert Card in the UK
Version Number:	2.0
Date of Protocol:	01 December 2022
Name and Affiliation of Main Author:	Rod Middleton Associate Professor, Disease Registers & Data Research UK MS Register, Swansea University
Rationale and Background:	PML is an important identified risk for Tysabri. As part of Biogen's additional risk minimisation measures, patients treated with Tysabri should receive a PAC. The PAC focuses on providing targeted information on risk of PML (beyond the information available through the Package Leaflet) to educate both patients and their carers on the need for vigilance regarding this risk by providing information on early signs and symptoms and latency and reinforcing the importance of seeking HCP advice in a timely manner. [redacted], it was noted that the effectiveness of the PAC as a risk minimisation tool has not been measured [redacted]. This study is designed to assess the effectiveness of the PAC in educating patients and their partners or caregivers on the risks of PML, early signs and symptoms of PML, latency, and vigilance regarding its development.
Research Questions:	This study's research questions are to assess the following: • What proportion of Tysabri-treated patients are aware of the risk of PML? • What proportion of Tysabri-treated patients have received the PAC and understood the key safety messages communicated on the PAC?
Objectives:	• To estimate the proportion of patients who are aware of the risk of PML. • To estimate the proportion of patients who have received the PAC and who understood the key safety messages communicated on the PAC.

Study Design:	Observational, cross-sectional, prospective study of the identified Tysabri population from the UK MS Register.
Population:	All UK MS Register patients with RRMS who are currently receiving Tysabri or have stopped Tysabri in the past 6 months will be eligible to participate in the survey.
Variables:	Background information to be collected from the UK MS Register for analysis is presented in Table 3. Information to be collected from the PAC questionnaire is presented Section 15.
Data Sources:	All information will be collected via the UK MS Register using the Tysabri (natalizumab) PAC questionnaire.
Study Size:	It is estimated that 400 patients will complete the survey.
Data Analysis:	Descriptive analyses of data will be performed by the UK MS Register to characterise the study population (Tysabri [IV or SC]-treated patients with RRMS). Summary statistics such as mean and standard deviation for continuous variables and a frequency table for categorical variables will be provided. Data analyses will generally be descriptive and will be detailed in the SAP. Patient understanding of the PAC and awareness of the symptoms of PML will be determined for patients treated with Tysabri IV and Tysabri SC. The proportions of patients who have provided correct responses to 5 key questionnaire questions on basic knowledge of PML symptoms and risk factors will be assessed. The average number of correct responses to basic knowledge of PML will be stratified based on HCP- and patient-related PAC metrics (refer to Section 9.7) to determine the effectiveness of the PAC in conveying risk of PML to patients.
Milestones:	Start of data collection: 15 April 2023 End of data collection: 15 June 2023 Final report of study results: Q4 2023

5. AMENDMENTS AND UPDATES

Protocol GB-TYS-12163, Version 2.0 was approved before the start of data collection.

6. MILESTONES

Table 1: Milestones for Protocol GB-TYS-12163

Milestone	Planned Date
Start of data collection	15 April 2023
End of data collection	15 June 2023
Registration in EU PAS Register	ENCEPP/DSPP/46280 (2022)
Final report of study results	Q4 2023

7. RATIONALE AND BACKGROUND

Tysabri (natalizumab) is a recombinant anti-α4 integrin antibody marketed in more than 80 countries for the treatment of RRMS.

In the UK, Tysabri was first licensed in 2006 and is indicated as single disease-modifying therapy in adults with highly active RRMS for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least 1 disease-modifying therapy OR
- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI

PML is an important identified risk for Tysabri. As part of Biogen's additional risk minimisation measures, patients treated with Tysabri should receive a PAC. The PAC focuses on providing targeted information on risk of PML (beyond the information available through the Package Leaflet) to educate both patients and their carers on the need for vigilance regarding this risk by providing information on early signs and symptoms and latency and reinforcing the importance of seeking HCP advice in a timely manner.

CCI [redacted], it was noted that the effectiveness of the PAC as a risk minimisation tool has not been measured CCI [redacted].

This study is designed to assess the effectiveness of the PAC in educating patients and their partners or caregivers on the risks of PML, early signs and symptoms of PML, latency, and vigilance regarding its development.

8. RESEARCH QUESTIONS AND OBJECTIVES

8.1. Research Questions

This study's research questions are to assess the following:

- What proportion of Tysabri-treated patients are aware of the risk of PML?
- What proportion of Tysabri-treated patients have received the PAC and understood the key safety messages communicated on the PAC?

8.2. Objectives

The primary objectives of the study are to assess the following in patients treated with Tysabri (natalizumab) in the UK:

- To estimate the proportion of patients who are aware of the risk of PML.
- To estimate the proportion of patients who have received the PAC and who understood the key safety messages communicated on the PAC.

9. RESEARCH METHODS

9.1. Study Design

This is an observational, cross-sectional, prospective study in patients with RRMS who are currently receiving Tysabri (natalizumab) IV or SC or have stopped Tysabri IV or SC in the past 6 months and are already enrolled in the UK MS Register, to assess PML risk awareness and understanding from patients' perspective and effectiveness of the Tysabri PAC. Patients participating in this study will be asked to complete a self-administered online questionnaire (specific to this study) once. This will be in addition to the UK MS Register standard questionnaire.

The PAC questionnaire will be made available to as many Tysabri-treated patients as possible from 15 April 2023 to 15 June 2023.

9.1.1. Pretesting of the PAC Questionnaire

A close to complete version of the proposed questionnaire and the rationale for this survey will be presented to the UK MS Register's "Brain Stormers" patients with MS group. Feedback on messaging surrounding the dissemination of the questionnaire and of the survey itself will be provided. Once appropriate modifications have been made (for example, making language within the questionnaire more comprehensible to the target audience in line with recommendations from the "Brain Stormers" group), the questionnaire can be disseminated to a test group of patients within the UK MS Register for additional feedback.

9.1.2. Administration of the PAC Questionnaire

There are 2 main study areas within the UK MS Register that overlap.

1. The clinical study where data are collected directly from a number of National Health Service sites from consented patients.
2. The portal study where patient-reported outcome data are captured directly from patients with MS.

Patients can declare all active medications on a specific questionnaire. In this instance, the proposed study will include those patients who have indicated that they currently receive Tysabri or have stopped Tysabri in the past 6 months.

Once patient Tysabri status has been established, all identified patients will be emailed a link to the PAC survey. As of 10 October 2022, there are 1108 patients who are on Tysabri in the UK MS Register, and a further 3 patients who reported having stopped taking Tysabri in the previous 6 months. The survey will be open for 2 months, and patients will be emailed at least weekly to encourage them to take part in the survey. The survey itself will be embedded within the UK MS Register portal, as well as the direct link within the email, and will be available as a clickable link within each patient's "To Do" list on their "Hub" pages once they have logged in. Surveys in this state will remain accessible until they are completed by the patients or until the survey closes.

Patients who complete the PAC questionnaire will not be included in subsequent email reminders.

9.1.3. Primary Endpoints

Table 2: Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
To estimate the proportion of patients who are aware of the risk of PML.	The proportions of patients who have provided correct responses to 5 key questionnaire questions on basic knowledge of PML (further details are provided in Section 9.7.1).
To estimate the proportion of patients who have received the PAC and who understood the key safety messages communicated on the PAC.	• The proportion of patients who have received the PAC. • The association between HCP- and patient-related PAC metrics and average number of correct responses to 5 key questionnaire questions on basic knowledge of PML (further details of both endpoints are provided in Section 9.7.1).

9.2. Setting

9.2.1. Selection Criteria

All UK MS Register patients with RRMS who are currently receiving Tysabri or have stopped Tysabri in the 6 months prior to the date of participating in the survey will be eligible to participate in the survey.

9.2.1.1. Inclusion Criteria

Patients who meet all the inclusion criteria are eligible to participate in the survey.

1. Patient aged 18 years or older.
2. Patient can read and understand English.

9.2.2. Study Location

National registry from the UK (UK MS Register) will be used.

9.2.3. Overall Study Duration and Follow-Up

The survey will be available for patients over a 2-month period. Patient participation in the study will be 1 day. Once started, questions remain open for 24 hours. An individual study patient will be included only once in the study.

9.2.4. Description of Source Population

All UK MS Register patients with RRMS who are currently receiving Tysabri or have stopped Tysabri in the past 6 months will be eligible to participate in the survey.

9.3. Variables

Background information of patients enrolling in the survey to be collected, when available, from the UK MS Register is presented in Table 3.

Table 3: Data Elements

Category	Subcategory
Patient characteristics	Age (at survey completion) Gender Educational level Occupation Geographical location Cognition scores (if available) Number of relapses 1 year prior to survey enrolment Tysabri treatment history: treatment duration and route of administration Age at MS onset MS duration Years since MS symptom onset MS severity level (EDSS score[1]) Prior MS therapy Prior IS therapy (if available) Comorbidities Concomitant medications (including both MS and non-MS medications)

[1] EDSS score assessed through WebEDSS. WebEDSS is a web-based tool that lets patients with MS self-assess their disability within 0.5 of a clinical EDSS score (depending on MS Type and has been shown to be most effective in RRMS) [Leddy 2013].

Information to be collected from the PAC questionnaire is presented in Section 15.

Background information of patients who complete the survey will be linked to the UK MS Register.

9.4. Data Sources

All information will be collected via the UK MS Register using the Tysabri (natalizumab) PAC Questionnaire (Section 15).

The UK MS Register was launched in 2011 by the team at Population Data Science in Swansea University Medical School and is primarily funded by the UK MS Society. The

fundamental concept is to capture more real-world data about living with MS in the UK. The UK MS Register does this in 2 ways:

1. Patients with MS recording information about their MS directly through the UK MS Register website (https://ukmsregister.org/) via simple questionnaires.
2. A collaboration with a number of hospitals across the UK to link consented website patients' medical records with their questionnaire responses.

The UK MS Register has been approved by the South West Central Bristol Research Ethics Committee (currently: 21/SW/0085).

Requirements for the Register are that patients must be at least 18 years of age and have a confirmed diagnosis of MS via a UK neurologist.

Procedure of Enrolment: The Register was designed such that patients with MS will be able to both consent within the NHS and sign up online wherever they were in the UK. Patients sign up for the clinical element of the UK MS Register via informed consent (either written or electronic), as the UK MS Register is an NIHR portfolio study. For the online component, patients are required to sign up to the terms of service, with those who have also clinically consent invited to enter their clinical Register Study ID.

Follow-Up: The UK MS Register is an ongoing observational study; patients may join, leave, and rejoin as they wish, and as such there is no defined follow-up period for the Register as a whole. Similarly, while comprehensive ongoing follow-up data are requested from clinical sites, some do not have the resources to send data beyond the required minimum dataset.

As of October 2022, there are 24,000 patients enrolled via the web portal and 16,500 consented clinically. The overlap between the 2 domains is 5400 patients. This means that a portion of those from each domain overlaps and that the web/clinical records are linkable.

This provides a rich bank of data and great potential for research. There are more than 30 publications based on UK MS Register data; ones from the UK MS Register team can be seen at https://ukmsregister.org/Research/Publications

9.5. Study Size

There are 1108 RRMS patients using Tysabri in the UK MS Register as of 10 October 2022, with a typical response rate around 20% to 70% to the survey and after an evaluation for the primary endpoints, the final study size is set to 400 patients who complete the survey based on the percentage of correct responses for each of the 5 key questionnaire questions to assess patient's basic knowledge of PML.

In a published study that also assessed patient's basic knowledge of natalizumab-associated PML [Rath 2017], the percentage of patients who correctly answered 1 of the 3 PML basic knowledge questions ranged from 57% to 76% (see Section 9.7.1). Although patients will take the survey online instead of within a specific hospital, patients from the same hospital are expected to share similar characteristics, and their responses can be correlated. Therefore, a total of 3 ICCs among responses from

patients are considered: 0 (no correlation), 0.15, and 0.3. With around 40 hospitals in the registry, assuming an average of 10 patients from each hospital, Table 4 shows the 95% CIs of the correct response rates to questions on PML risk for various combinations of sample sizes and ICCs. Assuming the allowable deviation from the true correct response rate is 10%, if 400 patients complete the survey, the 2-sided 95% CI will be 65.5% to 74.5%, assuming a correct response rate of 70% and no correlation among responses from the same hospital (ICC = 0). The 95% CI range will become wider (61.4%, 78.6%) if the correlation increases to 0.3.

Table 4: CIs of the Correct Response Rates to Questions on PML Risk Within Combinations of Sample Size and Intraclass Correlation Coefficients

Sample Size	Intraclass Correlation Coefficient[1]	Correct Response Rate[2] (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
300	0	55	49.4	60.6
300	0	60	54.5	65.5
300	0	65	59.6	70.4
300	0	70	64.8	75.2
300	0	75	70.1	79.9
300	0	80	75.5	84.5
300	0.15	55	46.4	63.6
300	0.15	60	51.5	68.5
300	0.15	65	56.7	73.3
300	0.15	70	62.1	77.9
300	0.15	75	67.5	82.5
300	0.15	80	73.1	86.9
300	0.3	55	44.2	65.8
300	0.3	60	49.3	70.7
300	0.3	65	54.6	75.4
300	0.3	70	60.0	80.0
300	0.3	75	65.6	84.4
300	0 3	80	71 3	88 7
400	0	55	50.1	59.9
400	0	60	55.2	64.8
400	0	65	60.3	69.7
400	0	70	65.5	74.5

Sample Size	Intraclass Correlation Coefficient[1]	Correct Response Rate[2] (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
400	0	75	70.8	79.2
400	0	80	76.1	83.9
400	0.15	55	47.5	62.5
400	0.15	60	52.6	67.4
400	0.15	65	57.8	72.2
400	0.15	70	63.1	76.9
400	0.15	75	68.5	81.5
400	0.15	80	74.0	86.0
400	0.3	55	45.6	64.4
400	0.3	60	50.8	69.2
400	0.3	65	56.0	74.0
400	0.3	70	61.4	78.6
400	0.3	75	66.8	83.2
400	0.3	80	72.5	87.5
500	0	55	50.6	59.4
500	0	60	55.7	64.3
500	0	65	60.8	69.2
500	0	70	66.0	74.0
500	0	75	71.2	78.8
500	0	80	76.5	83.5
500	0.15	55	48.3	61.7
500	0.15	60	53.4	66.6
500	0.15	65	58.6	71.4
500	0.15	70	63.8	76.2
500	0.15	75	69.2	80.8
500	0.15	80	74.6	85.4
500	0.3	55	46.6	63.4
500	0.3	60	51.7	68.3
500	0.3	65	57.0	73.0
500	0.3	70	62.3	77.7

Sample Size	Intraclass Correlation Coefficient[1]	Correct Response Rate[2] (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
500	0.3	75	67.7	82.3
500	0.3	80	73.3	86.7

Note: Table calculations assume an average of 10 patients in each hospital.

[1] The design effects corresponding to intraclass correlation coefficients of 0.15 and 0.3 are 2.35 and 3.7, respectively.

[2] This column represents the correct response rate to each of the 5 key questions on PML risk.

9.6. Data Management

Data management will be conducted by the UK MS Register. Data will be managed as per all other UK MS Register projects. Only anonymised data will be deployed to the analysis platform. Patients to be contacted will be selected, and then anonymised data will be checked by 2 other UK MS Register analysts. All data will be kept and stored at ISO27001 levels. Procedures for data collection, retrieval, and analysis are outlined in the SAP.

9.7. Data Analysis

Descriptive analyses of data will be performed by the UK MS Register to characterise the study population (Tysabri [IV or SC]-treated patients with RRMS). Summary statistics such as mean and standard deviation for continuous variables and a frequency table for categorical variables will be provided. Data analyses will generally be descriptive and will be detailed in the SAP.

9.7.1. Analysis of Endpoints

The proportions of patients who have provided correct responses to 5 key questionnaire questions on basic knowledge of PML

Basic knowledge of PML is determined by the following 5 critical factors (criteria adapted from [Rath 2017]):

1. Whether patients can correctly identify that Tysabri can lead to PML, a rare brain infection (Question 4 of questionnaire);
2. Whether patients can correctly identify the symptoms of PML (Question 9 of questionnaire);
3. Whether patients' carers, including partners, caregivers, friends, or families, are aware of PML symptoms that the patient might not notice (Question 10 of questionnaire);
4. Whether patients can correctly identify that PML can occur up to 6 months after stopping Tysabri (Question 13 of questionnaire); and
5. Whether patients can correctly identify that management of PML requires immediately stopping Tysabri (Question 6 of questionnaire).

The number and proportion of patients with correct responses to each of the 5 key questionnaire questions will be summarized. The number and proportion of patients will also be summarized by the total number of questions they answer correctly out of the above 5 questions on basic knowledge of PML.

The proportion of patients who have received the PAC

The proportion of patients who have received the PAC will be determined by the responses to the following factor:

1. Whether the patient was given a PAC (Question 15 of the Questionnaire).

The number and proportion of patients will be summarized by whether they have received the PAC or not.

The association between HCP- and patient-related PAC metrics and average number of correct responses to 5 key questionnaire questions on basic knowledge of PML

To ascertain whether patients understood key safety messages communicated on the PAC, to determine whether patients follow the instructions on the PAC, and to better understand the role of the HCP's contribution in communicating the risk of PML to patients, PAC metrics will be stratified into patient-related metrics and HCP-related metrics.

Patient-related metrics include the following 4 factors:

1. Whether the patient still carries the PAC (Question 20 of questionnaire);
2. Whether the patient read the PAC (Question 21 of questionnaire);
3. How well the patient understands the PAC (Question 22 of questionnaire); and
4. Whether the patient's partner, caregiver, friend, or family member is aware of the PAC (Question 23 of questionnaire).

HCP-related metrics include the following 3 factors:

1. Whether the patient was given a PAC by an HCP (Question 15 of questionnaire);
2. Whether the HCP explained the PAC to the patient (Question 18 of questionnaire); and
3. How often the patient was given the PAC by the HCP (Question 19 of questionnaire).

The number and proportion of patients for each response in each of the above metrics will be reported.

To assess the effectiveness of the PAC, the average number of correct responses to the 5 key questionnaire questions on basic PML knowledge will be compared across the HCP- and patient-related PAC metrics. In addition, the total number of correct responses to the 5 key questionnaire questions on basic PML knowledge will also be compared across the patient- and HCP-related PAC metrics.

To provide an example for how an HCP-related metric will be used to assess patient's basic knowledge of PML, the association between receipt of the PAC and the average number of correct responses will be assessed by comparing the average number of correct responses among those who receive the PAC versus patients who report not receiving the PAC using a 2-sample t-test. The total number of correct responses will be compared by the receipt status of the PAC using a Chi-squared test.

Patient characteristics will also be evaluated for each PAC metric. The 2-sample t-test or the ANOVA test will be used to test the equivalence of means for the continuous characteristics, and the Mann-Whitney U-test or the Kruskal-Wallis test will be used to test the equivalence of medians. The Chi-squared test or Fisher's exact test will be used to test the equivalence of the proportions for the categorical characteristics. Then, a multiple linear regression may be performed to evaluate the effectiveness of the PAC, adjusting for the patient characteristics that are significantly different for patients when stratified by PAC metrics.

9.7.2. Exploratory Analysis

There are 2 parts in the survey. The first part includes questions related to PML risk (which is relevant to the first objective: to estimate the proportion of patients who are aware of the risk of PML) and the second part includes questions related to the PAC (which is relevant to the second objective: to estimate the proportion of patients who have received the PAC and who understood the key safety messages communicated on the PAC). Patients must complete the first part in order to move on to the second part of the survey. Based on survey completeness, patients will be categorised as follows:

- Responders
  - Complete responders: Patients who complete both parts of survey and
  - Partial responders: Patients who only complete the first part of the survey.
- Nonresponders: Patients who do not take the survey or do not complete the first part of the survey.

Patient characteristics will be summarised for both responders (including complete and partial responders) and nonresponders to evaluate the heterogeneity and representativeness of the population.

PML risk awareness and the effectiveness of the PAC may also be evaluated for subgroups based on the route of Tysabri (i.e., the Tysabri SC subgroup and the Tysabri IV subgroup) if a sufficient number of patients can be recruited.

9.8. Quality Control

9.8.1. Quality Assurance

Data captured on the questionnaire platform is subject to validation controls. Only patients satisfying the identified criteria are able to access the questionnaire in the first instance. Fields within the questionnaire are set to have "required" parameters, so no

blank data can be entered. Questions that have free text are removed as much as possible to reduce difficulties in analysis and to promote easy entry via radio buttons for patients with MS. All data entry using radio buttons/pick lists, etc. are codified, i.e., No = 0, Yes = 1.

Data captured from forms are directly inserted into a Microsoft SQL server database, and queries against the data are carried out there. All connections to the database are monitored and logged, with analysts only being given read access to questionnaire data.

9.8.2. Retention of Study Data

All data captured by the UK MS Register will be stored within the UK MS Register SQL Server database. Data will be stored in the form inserted automatically by the questionnaire engine and will not be written by analysts/developers. All logs will be stored on database that can be accessed only by authenticated users of the UK MS Register active directory. “Live data” from the start of the MS Register project is always available and will be for the duration of the MS Register project, which is currently funded until August 2027. Data will be kept available for at least 5 years beyond the end of the project.

If users choose to leave the study, all identifiable parameters are removed but submitted data remain as part of analysis/previous analyses. Patients are made aware that elements of their data persist.

Study data are available (to approved users) on a live basis on a highly available, redundant cluster of database and application servers. Study data are also backed up to “tape” on a 24-hour basis, with transaction log shipping every hour for deltas of changes. “Tapes” are changed every 24 hours on a monthly rolling basis, where backup media are swapped out every month to ensure fault tolerance.

9.9. Limitations of the Research Methods

Patients on the UK MS Register are likely to be slightly more affluent and better educated and to have easier access to technology, given the nature of an electronic only register. This is, however, in keeping with other MS registers across the world.

Patients who cannot read/understand English are not eligible to participate in the survey, as the PAC is available only in English.

Patients on the UK MS Register’s online portal are likely to be more engaged with research than the general clinical population, and the majority of these patients are well enough to complete surveys.

Tysabri is indicated as single disease-modifying therapy in adults with highly active RRMS. MS patients in the portal population tend to have more progressive MS than the clinical population diagnosed with RRMS. However, because RRMS patients in the portal are the focus of the current study, these patients are representative of the clinical population with RRMS. The disability (EDSS) and mean age are similar between portal and clinical populations.

Baseline characteristics will be evaluated for each HCP- and patient-related PAC metric and will be adjusted for the characteristics that are significantly different, if necessary, to address the confounding bias. However, due to the existence of unmeasured confounders, residual confounding bias will remain a concern.

9.10. Other Aspects

9.10.1. Study Funding

This is a collaboration between Biogen and the UK MS Register. The UK MS Register is the sponsor of this study. Biogen is the MAH of Tysabri and is providing funding to support the conduct of the study. All financial details are provided in the separate contracts between the UK MS Register, Investigator, and Biogen.

9.10.2. Publications

There is a plan to publish the study data. Details on the publication of study data are included in the clinical study agreement for this study. Publication and authorship will be based on International Committee of Medical Journal Editors criteria.

10. PROTECTION OF HUMAN PARTICIPANTS

Investigators must comply with this protocol and applicable ICH, GCP, and GVP guidelines, and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH, GCP, and GVP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

10.1. Ethics Committee

The UK MS Register has NRES ethical approval: currently 21/SW/0085 from South West Central Bristol Research Ethics Committee.

10.2. Participant Information and Consent

All patients on the portal have already provided their consent, and a separate consent for this survey is not required.

10.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect patient safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

10.4. Participant Data Protection

Prior to any data collection under this protocol, patients must also provide all authorisations required by local law.

10.5. Internal Safety Review

This is not applicable, as adverse event data are not collected in this study.

10.6. Compensation for Injury

Data storage within the UK MS Register is subject to current laws within the UK (General Data Protection Regulation/Data Protection Act 2018, Freedom of Information). All data will be stored and used in accordance with UK MS Register ethics and standard procedures. There will be no compensation for injury.

10.7. Conflict of Interest

The UK MS Register is primarily funded by the MS Society. Other commissioned studies have been carried out by the following:

- Novartis
- Merck KGaA
- Sanofi/Genzyme

These have been funded to maintain/enhance the current UK MS Register infrastructure and licensing. No member of the UK MS Register team or the Principal Investigator has received any benefits or personal remuneration from these studies.

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

This study will assess effectiveness of the PAC and patient's awareness of PML risk when treated with Tysabri and does not collect adverse event data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report will be sent by the MAH to regulators within 12 months of the end of data collection.

12.1. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study and sent a copy of the study synopsis in accordance with necessary timelines.

12.2. Registration of Study and Disclosure of Study Results

The UK MS Register, in collaboration with Biogen, will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

13. REFERENCES

Leddy S, Hadavi S, McCarren A, et al. Validating a novel web-based method to capture disease progression outcomes in multiple sclerosis. J Neurol. 2013;260(10):2505-10. Epub 20130627.

Rath L, Vijiaratnam N, Skibina O. Assessing understanding of individual risk and symptoms of progressive multifocal leukoencephalopathy in patients prescribed natalizumab for multiple sclerosis. Intern Med J. 2017;47(2):194-199.

14. ANNEX 1: ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

Study title: An Observational, Cross-Sectional Survey to Assess PML Risk Awareness and Understanding From Patients' Perspective and Effectiveness of the Tysabri (Natalizumab) Patient Alert Card in the UK

EU PAS Register® number: ENCEPP/DSPP/46280 (2022)
Study reference number (if applicable): Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

This is a short study, so there is no need to generate interim or progress reports.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

This is a descriptive study with no defined hypotheses.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.2, 9.1.3, & 9.7
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.1.3 & 9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

This study will not collect adverse event data.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1, 9.2.4, & 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.3
	4.2.2 Age and sex	☒	☐	☐	9.2.1.1
	4.2.3 Country of origin	☒	☐	☐	9.2.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1 & 9.4

Comments:

Age limit is specified in Section 9.2.1.1 but not sex. This study will include both male and female patients.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a cross-sectional, observational survey, and therefore there is no specific exposure to measure.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.3 & 9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.3 & 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7
7.3 Does the protocol address information bias (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3 & 9.7
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3 & 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.7
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.3 & 9.4

Comments:

This is a cross-sectional, observational survey, and therefore there is no specific exposure to measure. The purpose of this study is not to measure drug exposure as we are specifically interested in the Tysabri PAC and its effectiveness in conveying the risk of PML to patients.

The study will not collect outcomes (i.e., adverse events) to be coded according to ICD, MedDRA, or other coding system. Although there is an internal coding system for covariates and other characteristics in the UK MS Register, this information is not described in the protocol.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.1

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.4

Comments:

There is no specific ethics review for this study protocol; however, the UK MS Register has NRES ethics approval.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12, 9.10.2

Comments:

Name of the main author of the protocol: Rod Middleton

Date: 09 DEC 2022

Signature:

15. ANNEX 2: TYSABRI (NATALIZUMAB) PATIENT ALERT CARD QUESTIONNAIRE

Survey Questions (in English only).

The purpose of this study is to learn more about patients' understanding of the safety information related to Tysabri (natalizumab). We will be asking questions related to your current understanding of the Tysabri (natalizumab) Patient Alert Card; therefore, please do not look at the Tysabri Patient Alert Card or other materials unless asked to do so.

NOTE for reviewer: For questions with pre-determined correct responses, an asterisk (*) indicates which responses are correct.

Tysabri Treatment

We will first ask about your treatment history with Tysabri (natalizumab).

1. Are you currently receiving Tysabri or have you stopped in the past 6 months?
    a. Yes (continue)
    b. No (stop)
2. Are you currently receiving (or have you stopped in the past 6 months):
    a. Tysabri IV (intravenous infusion) or
    b. Tysabri SC (subcutaneous; 2 injections under the skin)?
3. How many years have you been on Tysabri? This is the whole treatment duration since your very first Tysabri administration.
    a. 0 to less than 2 years
    b. About 2 years
    c. More than 2 to less than 6 years
    d. 6 or more years

Risk Assessment

The next set of questions is to assess your knowledge of the side effects that patients could experience when receiving Tysabri.

4. Progressive multifocal leukoencephalopathy (PML), a rare brain infection, has occurred in patients who have been given Tysabri.
    a. True*
    b. False
    c. Don't know

5. PML can lead to severe disability or death.

    a. True*
    b. False
    c. Don't Know

6. Management of PML requires immediately stopping Tysabri.

    a. True*
    b. False
    c. Don't Know

7. If you experience severe, persistent infection such as a persistent fever you should:

    a. It is important that you speak to your doctor as soon as possible*
    b. Wait and see
    c. Ignore these symptoms

8. If you experience any side effects while receiving Tysabri, you should: (select all that apply)

    a. It is important that you speak to your doctor as soon as possible*
    b. Report these side effects directly via the national reporting system*
    c. Wait and see
    d. Ignore them

9. Which of the following are symptoms of progressive multifocal leukoencephalopathy (PML)? (Select "Yes", "No", or "I don't know" for each possible symptom listed below.)

Possible Symptom	Yes, this is a symptom of PML	No, this is not a symptom of PML	I do not know if this is a symptom of PML
Symptoms like MS relapse	□*	□	□
Changes in mental ability and concentration	□*	□	□
Chest pain	□	□*	□
Behavioural changes	□*	□	□
Weakness on one side of the body	□*	□	□
Vision problems	□*	□	□
Breathlessness	□	□*	□
New neurological problems that are unusual for you	□*	□	□
Cough	□	□*	□

10. Do you know if your partner, caregiver, friend, or family member is aware of signs and symptoms of PML that you might not notice?

    a. Yes (continue to Question 11)
    b. No (skip to Question 12)
    c. I do not have a partner, caregiver, friend, or family member (skip to Question 12)

11. Do you know if your partner, caregiver, friend, or family member is aware of the possible signs and symptoms of PML? (Select symptoms that are usually associated with PML)

Symptoms	Partner, caregiver, friend, or family member is aware this is a possible symptom of PML
Changes in mood or behaviour*	□
Memory lapses*	□
Breathlessness	□
Speech and communication difficulties*	□
Palpitations	□

12. Do you know what to do if you believe that your MS is getting worse or if you notice any new symptoms?

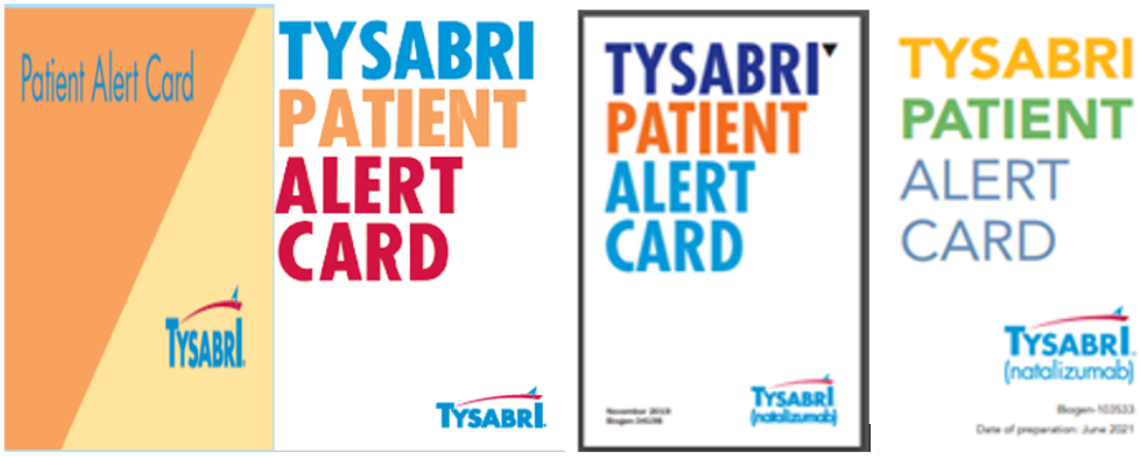
    a. It is important that you speak to your doctor as soon as possible*
    b. Wait and see
    c. Ignore them

13. PML can occur even up to 6 months after stopping Tysabri (natalizumab).

    a. True*
    b. False
    c. Don't know

14. Which of the following risk factors are associated with developing PML? (Select all that apply)

    a. Positive anti-JCV antibody status*
    b. Previous use of an immunosuppressant (drugs that suppress the immune system)*
    c. Smoking
    d. Receiving Tysabri for more than 2 years*
    e. Female gender
    f. Don't Know



February 2010	September 2012	November 2019	June 2021

Patient Alert Card Receipt and Review

Now we are going to ask you some questions about the Patient Alert Card that you may have received from your doctor or healthcare professional (examples of the 4 versions shown above: February 2010, September 2012, November 2019, and June 2021). This small, pocket-sized card contains important safety information about Tysabri (natalizumab). Please feel free to pull out your Patient Alert Card if you have it with you.

15. Have you ever received or been given a Patient Alert Card for Tysabri (natalizumab)? [display 4 visuals]. It is often included in a patient guide on Tysabri.

    a. Yes
    b. No
    c. Don't know

Answer Questions 16-20 only if you have received a Patient Alert Card for Tysabri (natalizumab). Otherwise, if you have not received the Patient Alert Card, then this is the end of the survey. Thank you for your participation.

16. Which version of the Patient Alert Card do you have?

    a. February 2010
    b. September 2012
    c. November 2019
    d. June 2021
    e. None of above
    f. Don't know

17. Who gave you the card?

    a. Your consultant neurologist
    b. Your MS nurse or infusion nurse
    c. Other: _____
    d. Don't know

18. Did this person explain the card to you?

    a. Yes
    b. No
    c. Don't know

19. How often have you received or been given a Patient Alert Card for Tysabri (natalizumab)? (multiple choice, select all that apply)

    a. Around the first time I received Tysabri
    b. Approximately once a year
    c. When I ask for a new card
    d. When I switched formulation from Tysabri IV to Tysabri SC
    e. Other: _____
    f. Don't know

20. Do you still have the Patient Alert Card with you?

    a. Yes
    b. No

Answer Questions 21-23 if you have the Patient Alert Card for Tysabri (natalizumab) with you. Otherwise, if you do not have the Patient Alert Card with you, then this is the end of the survey. Thank you for your participation.

21. Have you read it?

    a. Yes
    b. No

22. I feel like I understand what's on the card.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
☐	☐	☐	☐	☐

23. Is your partner, caregiver, friend, or family member aware of this card?

    a. Yes
    b. No
    c. Don't know
    d. I do not have a partner, caregiver, friend, or family member

Thank you for completing this survey. This concludes this study.

16. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "An Observational, Cross-Sectional Survey to Assess PML Risk Awareness and Understanding From Patients' Perspective and Effectiveness of the Tysabri (Natalizumab) Patient Alert Card in the UK," and agree to conduct the study according to the protocol and the applicable ICH, GCP, and GVP guidelines, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)