**Protocol acronym: INPSYSEP**
**RCB ID: 2025-A01541-48**
**CHU NUMBER: 25-0187**

NON-INTERVENTIONAL RESEARCH (NIR)

**TITLE: INFLUENCE OF THERAPEUTIC FAILURE ON THE PSYCHOSOCIAL EXPERIENCE OF PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS (INPSYSEP)**

**STUDY SPONSOR:**


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This protocol contains confidential information and must only be used for the conduct of the study. The protocol must not be passed on to persons not involved in this study, nor used for any other purpose, without prior written agreement of the coordinating investigator.

| Version tracking | | | | |
|---|---|---|---|---|
| ☒ | Initial version | V01 | Date of version V01: | 25/08/2025 |
| ☐ | Amended version | V… | Date of version V …: | ../../.... |
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| ☐ | Favourable opinion from the CPP | | Authorisation date: | ../../.... |

## History of protocol updates

| Version | Date | Reason for update |
|---|---|---|
| 01 | 25/08/2025 | Applying for a promotion at CHU CAEN NORMANDIE |
| XX | ../../.... | Responses sent to the CPP (admissibility) |
| 01 | 25/08/2025 | Approved by the CPP on 05/12/2025 |

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## GENERAL INFORMATION

Regulatory information:

| ACRONYM | |
|---|---|
| Title | INFLUENCE OF THERAPEUTIC FAILURE ON THE PSYCHOSOCIAL EXPERIENCE OF PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS (INPSYSEP) |
| RCB ID number | 2025-A01541-48 |
| CHU number | 25-0187 |
| Number and date of version of approved protocol | V01 du 25/08/2025 |

Signature of protocol

| CHU CAEN NORMANDIE | NOM | DATE | SIGNATURE |
|---|---|---|---|
| Directeur Général ou son représentant | **Mme Aurélie VILLERS** | **27/08/2025** | Fabien Chaillot<br><br>P/o responsable des affaires réglementaires |
| Investigateur coordonnateur | **Dr Pierre Branger** | **27/08/2025** | |

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▲ *Remember to collect the CVs, dated, signed and bearing the registration number with the Order of Physicians or RPPS, as well as BPC training date, to make a submission to the CPP*

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Abbreviations:

| Abbreviation | Meaning |
|---|---|
| BMI | Body Mass Index |
| CRA | Clinical Research Associate |
| CRC-SEP | Centre de Ressources et de Compétences Sclérose En Plaques (French MS expert centre) |
| CHU | Centre Hospitalier Universitaire (University Hospital) |
| CPP | Comité de Protection des Personnes (French Independent Ethics Committee) |
| DMT | Disease Modifying Treatment |
| e-CRF | electronic Case Report Form |
| EDI | European Deprivation Index |
| EDMUS | European Database for Multiple Sclerosis |
| EDSS | Expanded Disability Status Scale |
| GDPR | General Data Protection Regulation |
| HADS | Hospital Anxiety and Depression Scale |
| ICECAP-A | ICEpop CAPability measure for Adults |
| iPCQ | iMTA Productivity Cost Questionnaire |
| MCID | Minimal Clinically Important Difference |
| MR | Méthodologie de Référence (Reference Methodology) |
| MS | Multiple Sclerosis |
| NIR | Non-Interventional Research |
| OFSEP | Observatoire Français de la Sclérose en Plaques (French Multiple Sclerosis Observatory) |
| PREM | Patient Reported Experience Measurement |
| PROM | Patient Reported Outcome Measurement |
| QoL | Quality of Life |
| RRMS | Relapsing-Remitting Multiple Sclerosis |
| SES | Socioeconomic Status |
| Th-F | Therapeutic Failure |

## SYNOPSIS

| **Title of study** | INFLUENCE OF THERAPEUTIC FAILURE ON THE PSYCHOSOCIAL EXPERIENCE OF PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS |
|---|---|
| Protocol | INPSYSEP |
| Sponsor | CHU CAEN NORMANDIE |
| RCB ID NUMBER | 2025-A01541-48 |
| Type of research | Non-Interventional Research (NIR) |
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| Population concerned | Patients with MS |
| Objectives of the study | Main objective:<br>• To compare changes in QoL at 2 years in RRMS patients treated for at least 6 months and less than 3 years, according to the occurrence or non-occurrence of Th-F.<br><br>Secondary objective(s):<br>• To compare, according to the occurrence or non-occurrence of a Th-F, the 2-year change in the QoL, in well-being, in distress and activity levels (PROM), of RRMS patients treated for at least 6 months and less than 3 years, in accordance with the care experience (PREM) and SES.<br>• To assess the impact of Th-F at the time of the event (TE) between inclusion T0 and T1 (2-year follow-up) on PROMs and PREMs, compared with values at T0 (group of patients with Th-F only).<br>• To assess the impact of PROMs and PREMs at inclusion (T0) and their relation to SSE at the risk of developing Th-F. |

| | |
|---|---|
| Inclusion criteria | • Patient aged 18 or over.<br>• Patient with RRMS according to McDonald 2024 criteria.<br>• Uninterrupted use of a moderately effective treatment, or highly effective treatment only if it is the first DMT, for at least 6 months.<br>• Collection of non-objection.<br>• Patient affiliated to the social security system. |
| Exclusion criteria | • Patient with progressive MS.<br>• Patient treated continuously with the same DMT for 3 years or more.<br>• Patient who received a second line DMT or an immunosuppressant before taking a first line DMT.<br>• Patients who have received mitoxantrone as the first treatment<br>• Pregnant or breast-feeding woman at the time of inclusion.<br>• Severe cognitive and/or psychological disorders which, according to the investigator (with or without a neuropsychological assessment), prevent the participant from completing the self-questionnaires independently and accurately. |
| Assessment criteria | Primary:<br>• To compare changes in health-related quality of life (MusiQoL scale) at 2 years (T1) in regard to whether or not Th-F had occurred.<br><br>Secondary:<br>• To compare changes in health-related quality of life (QoL) at 2 years (T1) in regard to whether or not Th-F had occurred, and in interaction with patients' experience, quality of care (PREM) and socioeconomic status.<br>We hypothesise that the deterioration in QoL between inclusion (T0) and the end of the observation period (T1 = T0 +2 years) will be greater in patients suffering from Th-F than in patients without Th-F (who constitute the control group, between-subjects model), especially as patients have reported a poor quality of care (PREM) and a low socioeconomic level at T0.<br>• To compare changes at 2 years (T1) in other PROM measures: symptoms of anxiety and depression (HADS scale), well-being (ICAP scale) and level of activity (iPCQ scale) as a function of the occurrence or non-occurrence of Th-F, and in interaction with patients' experience, quality of care (PREM-MusiCare scale) and SES.<br>• To assess the impact of Th-F at the time of the event (TE) on PROMs and PREMs, compared with the values at T0 (for the group of patients with Th-F). |
| Act(s) or visit(s) added by search | At inclusion (T0), TE and T1: Completion of 5 questionnaires (MusiQoL, HADS, ICECAP-A, iPCQ, MusiCare).<br><br>The questionnaires will be completed either as an online survey (a link to the survey on the LimeSurvey platform will be available via an invitation sent to the patient by email) or on a paper copy handed over during a routine visit or sent by post to participants' homes. Questionnaires take an estimated 1h to complete. |
| Number of patients | Based on published works and our experience, we have set a participation rate of 50% to 70% and a 2-year Th-F rate of 15% to 20%. For a total number of patients that could be included of around 300, we hope to recruit between 150 |

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| | and 210 patients in the study, including 23 to 30 patients with a Th-F at 2 years of around 15% and 32 to 42 patients with a Th-F at 2 years of 20%. With these numbers, considering a power of 80% and a type 1 error of 5% (two-tailed Student t-test), it will be possible to highlight an effect size (standardised difference) of around 0.6, corresponding to an effect size value between moderate and high, corresponding to a threshold generally accepted as the minimal clinically important difference for quality of life. |
| Number of centres | 5 centres:<br>• CRC-SEP<br>• CHU Rouen Normandie<br>• CHU Amiens<br>• Groupement des Hôpitaux de l'Institut Catholique de Lille<br>• CHU de Lille |
| Provisional agenda | - Duration of inclusion: 12 months<br>- Duration of monitoring period: 30 months maximum |

## SCIENTIFIC JUSTIFICATION FOR STUDY AND GENERAL DESCRIPTION OF RESEARCH

**Rationale (context and assumptions)**
Multiple sclerosis (MS), an inflammatory, neurodegenerative disease of the central nervous system, affects around 120,000 patients in France and is the leading cause of non-traumatic disability in young adults. It affects patients' health-related quality of life (QoL) and has a significant economic impact on patients and society as a whole. Early initiation of disease-modifying therapy (DMT) is recommended in relapsing-remitting MS (RRMS)[1]. Nevertheless, according to a recent French cohort, 30% of patients initially treated with a first-line FT will switch to a highly effective compound within 5 years[2] due to its ineffectiveness. Therapeutic failure (Th-F) is therefore a frequent occurrence, but its psychological, social and economic consequences are poorly understood. These elements are generally the subject of measurements reported by patients, and several studies have highlighted the importance of taking them into account in the management of these patients[3].

Here, we will study two categories of these measures in a Th-F situation. On the one hand, we will examine patient-reported outcome measurements (PROMs). Patients' psychological distress and their QoL are two important examples of psychosocial impacts in patients with MS, compared to the general population. The impact on activity levels is also well known[4], but the specific effect of Th-F has not yet been studied. On the other hand, we will also study patients' experiences of their care pathway and their opinion on the quality of care (patient-reported experience measurement [PREM]). Some PREMs refer to care coordination, satisfaction with the relationship with carers or doctors' empathy levels. To date, data on the experience of MS patients regarding their care pathway remains limited and non-existent during Th-F[5].

Finally, the influence of socioeconomic status (SES) on PROMs and PREMs is worth considering. In the general population, we know that patients' experience of care can be influenced by their socioeconomic status[6]. Compared with research on other diseases (notably cardiovascular diseases and cancers), there is relatively little work on the association between socioeconomic status and MS[7] and none has focused on the topic of Th-F.

We therefore hypothesise that a quality of care perceived favourably by MS patients may moderate the negative impact of Th-F on their QoL, anxiety/depression and activity levels (as recently described in oncology[8]), and a more recent measure of abilities assessing well-being defined in a broad sense, as a function of their SES.

**Inter-regional context - the FHU PRECISE specifies the following**: Few studies have explored the links between PREMs, PROMs and Th-F in MS. In an original and innovative way, these questions are at the heart of the inter-regional hospital-university federation, FHU PRECISE (PREcision health in Complex Immune-mediated inflammatory diseases), accredited by Aviesan (Alliance nationale pour les sciences de la vie et de la santé) on January 1st, 2021. Its aim is to improve support for patients suffering from complex immunodeficiency diseases by bringing them the latest innovations in care, research and teaching. Our project is part of Work Package 4 (leaders: Gilles Defer - Delphine Grynberg), which has taken an innovative transdisciplinary approach to understanding the impact of psycho-socioeconomic factors on the development and experiences of patients with complex dysimmune diseases, through collaboration between medical researchers, MS specialists in this case and researchers in epidemiology and human and social sciences. It is fully in line with current recommendations for investigating PROMs in clinical trials[9]. At the same time, the evaluation of the quality of care (PREM) and of the SES is an innovative complementary approach.

**Key words:** Patient-reported-outcome, Patient-reported-experience, quality of life, socioeconomic status, therapeutic failure, multiple sclerosis.

## RESEARCH OBJECTIVES

1. Primary objective:

To compare changes in QoL at 2 years in RRMS patients treated for at least 6 months and less than 3 years, according to the occurrence or non-occurrence of Th-F.

Secondary objectives:

a) To compare, according to the occurrence or non-occurrence of a Th-F, the 2-year change in the QoL, in well-being, in distress and activity levels (PREM), of RRMS patients treated for at least 6 months and less than 3 years, relating to the care experience (PREM) and SES.

b) To assess the impact of Th-F at the time of the event (TE) between inclusion T0 and T1 (2-year follow-up) on PROMs and PREMs, compared with values at T0 (group of patients with Th-F only).

c) To assess the impact of PROMs and PREMs at inclusion (T0) and their relation to SES at the risk of developing Th-F.

## EVALUATION CRITERIA

1. Main assessment criterion:

We hypothesise that the deterioration in quality of life (MusiQoL scale) between inclusion (T0) and the end of the observation period (T1) will be greater in patients with Th-F than in patients without Th-F (who constitute the control group, between-subjects model).

The criterion will be a comparison of changes in health-related quality of life (QoL)[10] at 2 years (T1) depending on the occurrence or non-occurrence of Th-F.

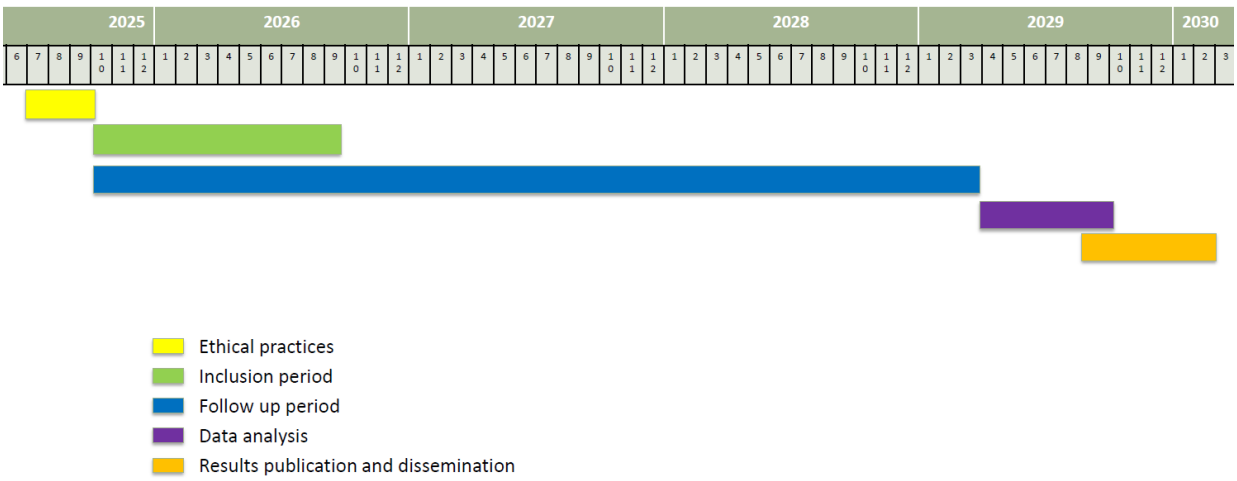
Secondary assessment criteria:

- To compare changes in health-related quality of life (QoL)[10] at 2 years (T1) depending on the occurrence or non-occurrence of Th-F, and in interaction with patients' experience and quality of care (PREM) and socioeconomic status. The difference is likely to be greater the more patients report poor quality of care (PREM) and low socioeconomic status.
- To compare changes at 2 years (T1) in other PROMs: symptoms of anxiety and depression (HADS scale[11]), well-being (ICAP scale[12]) and level of activity (IPCQ scale[13]) as a function of the occurrence or non-occurrence of Th-F, and in interaction with patients' experience and quality of care (PREM musical scale[14]), and their SSE[15].
- To assess the impact of Th-F at the time of the event (TE) on PROMs and PREMs, compared with the values at T0 (for the group of patients with Th-F only).

## RESEARCH METHODOLOGY

Experimental design:

This is a prospective multicentre study involving the MS expert centres of the CHUs of Caen, Rouen, Amiens and Lille, as well as the Neurology Department of the Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL). The Normandie and Hauts-de-France MS networks (Normandie-SEP and PARC-SEP) will provide support for patients' follow-up. Université de Lille will be involved in centralising the response to the questionnaires. Université de Lausanne will be involved in interpreting the results.




## SELECTION AND EXCLUSION OF RESEARCH PARTICIPANTS

1. Criteria for inclusion of research participants:

- 1) Patient aged 18 or over.
- 2) Patient with RRMS according to McDonald 2024 criteria.
- 3) Uninterrupted use of a moderately effective treatment, or highly effective treatment only if it is the first DMT, for at least 6 months.
- 4) Collection of non-objection.
- 5) Patient affiliated to the social security system.

Criteria for non-inclusion of research participants:

- 1) Patient with progressive MS.
- 2) Patient treated continuously with the same DMT for 3 years or more.
- 3) Patient who received a second line DMT or an immunosuppressant before taking a first line DMT (see Appendix 1).
- 4)Patients who have received mitoxantrone as the first treatment
- 5) Pregnant or breast-feeding woman at the time of inclusion.
- 6) Severe cognitive and/or psychological disorders which, according to the investigator (with or without a neuropsychological assessment), prevent the participant from completing the self-questionnaires independently and accurately.

## PRACTICAL CONDUCT OF THE STUDY

1- Selection of participants

Patients will be identified on the basis of regional clinico-radiological cohorts (EDMUS software) and local database in the investigating centres, all of which participate in the Observatoire Français de la Sclérose en Plaques (OFSEP). EDMUS (European Database for Multiple Sclerosis) is a specific software package with a standardised language, which has been fully integrated into the daily practice of MS expert centres for many years.

Once the patients have been pre-selected from the regional and local cohorts (EDMUS database and local database of the investigating centres), the inclusion and non-inclusion criteria will be checked by the patient's neurologist.

During a routine consultation or a dedicated teleconsultation, the neurologist or the investigating Clinical Research Associate (CRA) will propose that the patient take part in the study. If agreed, a letter of information will be given to each patient (in person or by email in the case of teleconsultation). If the patient so wishes, a reflection period will be granted. In this case, patients will be contacted by telephone by the CRA regarding any questions they may have about the protocol. If the patient agrees to take part, the non-objection will be recorded in the patient's medical file.

2- Inclusion

Patients will then be able to complete the study questionnaires either on paper (sent and returned to the care centre in a pre-stamped envelope given to the patient) or in the form of an online survey (a link to the survey will be available via an invitation sent to the patient by email, using the secure Lime Survey system on the platform of Prof Delphine Grynberg's Research Unit). Questionnaires take an estimated 1h to complete.

If the questionnaires are completed in paper format, they will be returned by the patient to the care centre to check that they have been completed correctly and that anonymity has been preserved. They will then be scanned and sent to a member of Prof Delphine Grynberg's Research Unit for input.)

In both cases, the confidentiality of the data will be respected thanks to an identification code made up of information known by the patient (e.g. year of birth, first letter of the investigating centre) which will make it possible to match the patient's clinical data (from the pseudonymised EDMUS database) with their answers to the questionnaires (from the "questionnaires" database via Limesurvey). The correspondence table between the study identification code and the identity of the participants will be kept in the care centre. An investigator file will be kept in a locked cabinet in the department, accessible only to investigators. This file contains a list of correspondences between nominative data and the patient anonymisation code. Data protection and secure storage will be implemented in accordance with the recommendations of the General Data Protection Regulation (GDPR) under the supervision of the Clinical Research and Innovation Delegation of CHU Caen.

3- Follow-up

Participants will be asked to complete these questionnaires again, either on computer or on paper (sent either during a routine consultation or by post with a pre-stamped return envelope) in the time of event (TE) (=Th-F) and at the end of the study (T1).

If TE < 18 months after T0 inclusion, then T1=T0+24 months (patient participation of 24 months).

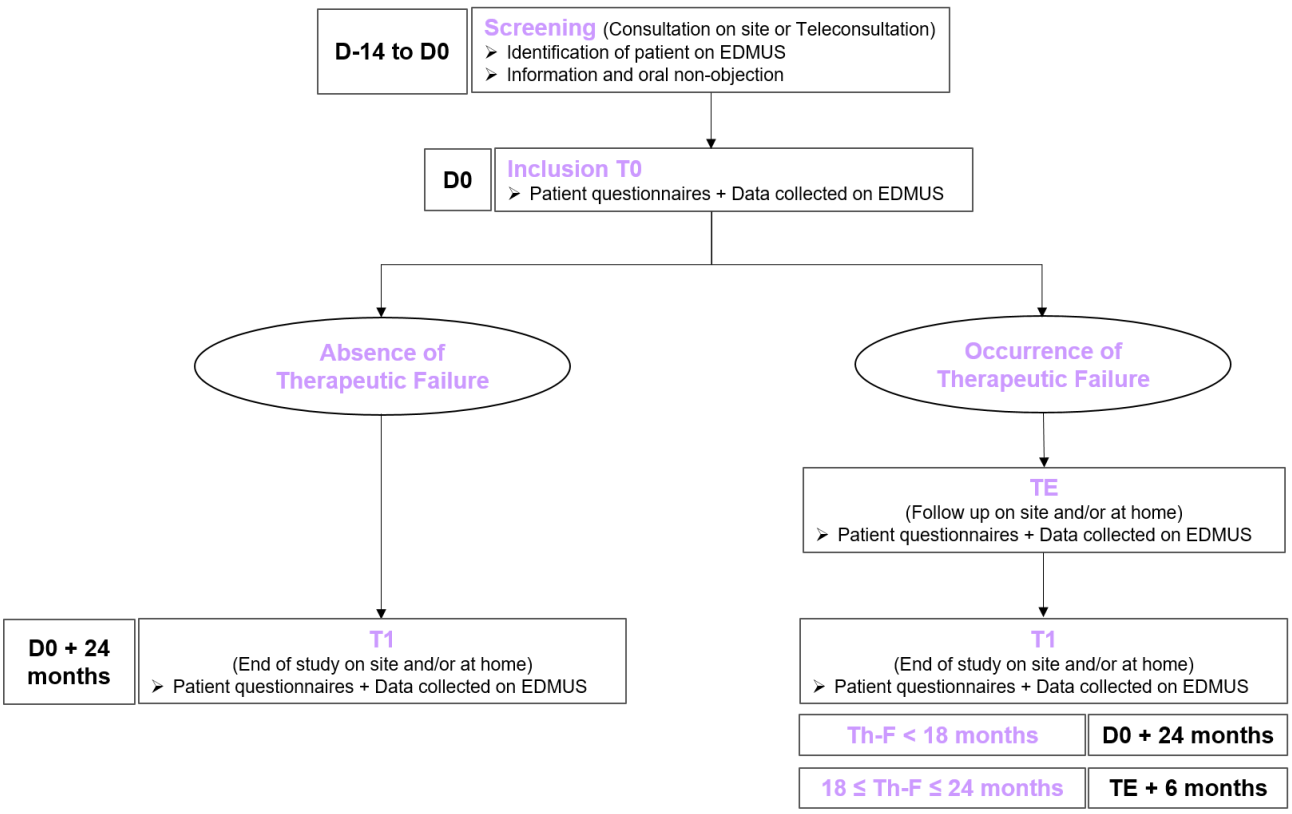
If 18 months ≤ TE ≤ 24 months after T0 inclusion, then T1=TE+6 months (patient participation between 24 and 30 months).

**Definition of therapeutic failure (Th-F)**: Change or discontinuation of the DMT decided by the treating neurologist, linked to a progression of the disease characterised by inflammatory activity (clinical and/or radiological) and/or progression of the disease unrelated to inflammatory activity.

The following events will not be considered:

- Change or discontinuation of the DMT due to an adverse event, discomfort and/or compliance difficulties and/or failure to comply with clinical and biological monitoring,
- Discontinuation due to pregnancy after inclusion,
- Discontinuation due to an unrelated intercurrent medical condition (e.g. cancer).

Questionnaires in paper form will be received in the original investigating centre for verification of completion. They will then be scanned and transmitted securely for centralisation to: Delphine Grynberg, SCALab Laboratory, Université de Lille (Pont de Bois site) - Rue du Barreau, BP 60149, 59653 Villeneuve d'Ascq Cedex, France.



Calendar of summary:

| Ratings | Selection (D-14 to D0) | T0 (D0) | TE (Th-F) | T1* (End of study) |
|---|---|---|---|---|
| Enlightened information | X | | | |
| Collection of non-objection | X | | | |
| Eligibility criteria verification | X | | | |
| Questionnaires completion | | X | X | X |
| Demographic and clinical data (EDMUS) | | X | X | X |

* If TE < 18 months after T0 inclusion, then T1=T0+24 months. If 18 months ≤ TE ≤ 24 months after T0 inclusion, then T1=TE+6 months.

## DESCRIPTION OF THE DATA TO BE COLLECTED

Clinical data is collected at routine follow-up visits, retrospectively at the first visit and prospectively thereafter. The mandatory clinical data set includes demographic and socioeconomic characteristics, relapses and disability, as well as disease-modifying therapies (start and stop dates with reasons for stopping).

**Demographic and clinical data: data from the EDMUS database**

- Age, gender, education level (number of years), marital status, household composition, employed or not, full-time/part-time employment, disability/early retirement.
- At inclusion: duration of disease, number of relapses in the year and in the two years preceding the start of treatment, EDSS, comorbidities (number of significant pathologies), smoking, overweight (BMI), measurement of fatigue with the EMIF MS questionnaire during other self-assessments (short questionnaire of 21 questions).
- During follow-up care (as part of the normal course of treatment): EDSS, number of clinical attacks, MRI data as reported in the EDMUS software.

**PROM data: data from the "questionnaires" database via Limesurvey**

- Quality of life: The International Multiple Sclerosis Quality of Life Questionnaire (MusiQoL) is a multidimensional, self-administered questionnaire that has been developed internationally (including a French version). It comprises 31 questions describing nine dimensions (daily activities, psychological well-being, relationships with friends, symptoms, relationships with family, relationships with the healthcare system, emotional and sexual life, adaptation, and rejection). The study of internal structural validity, external validity, reproducibility and acceptability indicates that the tool meets generally accepted standards. The simultaneous participation of several countries in the development process provides a common assessment tool, which is useful for international research projects.
- Psychological distress: Anxiety and depression symptoms will be assessed using the Hospital Anxiety and Depression Scale (HADS) validated in French. It contains 14 items divided into two dimensions (anxiety and depression). This questionnaire has already been used with MS patients and has shown good psychometric indicators.
- Measure of well-being: ICECAP-A (ICEpop CAPability measure for Adults) is a measure of the capability of the general adult population (18+) intended for use in economic evaluation

and focused on well-being in the broad sense, rather than health. ICECAP-A comprises five attributes (attachment, stability, fulfilment, pleasure, autonomy). Qualitative and quantitative studies on the validity of ICECAP-A have been carried out and a French translation of ICECAP-A has been developed for the general population.

- Activity levels: The self-administered iMTA Productivity Cost Questionnaire (or iPCQ) will be used to measure the impact of the disease on market and household activities. This recently validated questionnaire, available in French, comprises 18 items.

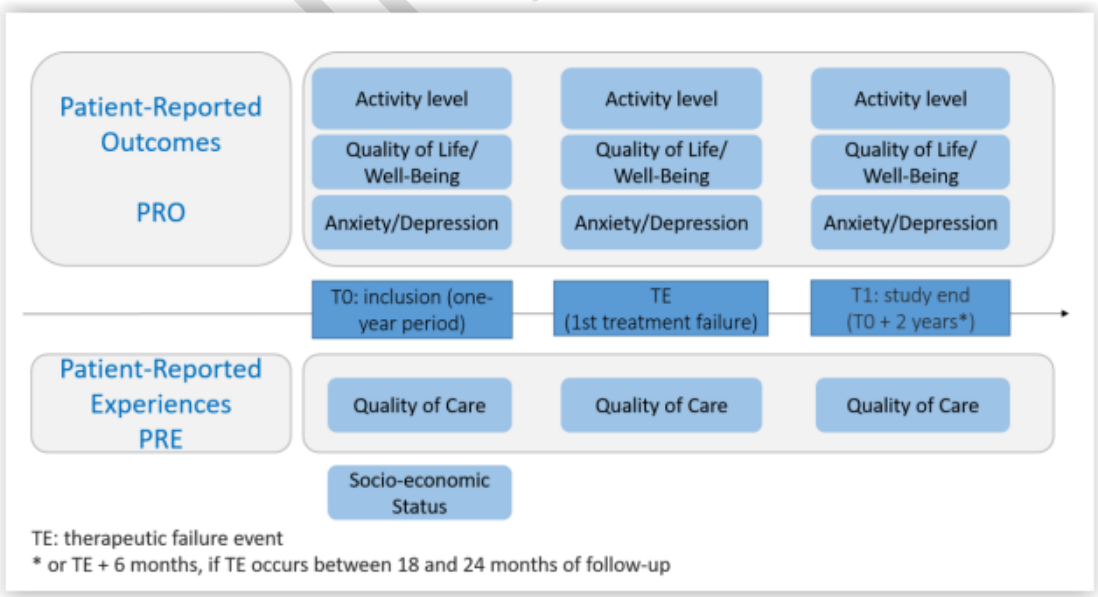
**PREM data: data from the "questionnaires" database via Limesurvey**

- Quality of care: MusiCare is the only French-language questionnaire specific to MS for assessing the quality of care as perceived by MS patients and their careers. It was developed in two standard phases: (i) item generation, based on interviews with patients and carers; and (ii) validation, consisting of measures of validity, reliability, external validity, reproducibility and responsiveness. The validation process produced a 35-item questionnaire with satisfactory internal consistency and stability in 5 different areas describing information, quality and coordination of care and medical empathy (information on the disease; information on treatments/medical investigations; relations with care teams; access to care; reception in care facilities). The external validity test revealed the expected associations between MusiCare scores and socio-demographic and clinical data. The questionnaire showed good reproducibility.

**Socioeconomic status:**

- This item will be assessed using individual measures of socioeconomic position (highest degree of education, occupation).

As shown in the figure below, each patient will complete the questionnaire at inclusion (T0) and two years later, at the end of the study (T1). Patients in therapeutic failure will complete the questionnaires as soon as possible after confirmation of Th-F and no later than 4 weeks after the occurrence of this event (TE). If the event occurs during the last 6 months of the 2-year follow-up period after patient inclusion, the T1 end-of-study visit will be conducted 6 months after the TE visit. As a result, these patients can be monitored for a maximum of 30 months.



## STATISTICAL METHODOLOGY

Based on published works and our experience, we have set a participation rate of 50% to 70% and a 2-year Th-F rate of 15% to 20%. For a total number of patients that could be of around 300, we hope to recruit between 150 and 210 patients to the study, including 23 to 30 patients with a Th-F at 2 years of around 15% and 32 to 42 patients with a Th-F at 2 years of 20%. With these numbers, considering a power of 80% and a type 1 error of 5% (two-tailed Student t-test), it will be possible to highlight an effect size (standardised difference) of around 0.6, corresponding to an effect size value between moderate and high, corresponding to a threshold generally accepted as the minimal clinically important difference for quality of life.

The MusiQoL scale values obtained for the control group (group without Th-F) and the group with Th-F are summarised in the following table:

| Group | MusiQoL scale (T0) | MusiQoL scale (T1) |
|---|---|---|
| Th-F | $x_1$ | $y_1$ |
| Without Th-F (Control) | $x_2$ | $y_0$ |

To meet the main objective, the following will be assessed:

- the absolute difference at T1 (y1-y0)
- the difference between the changes (y1-x1) - (y0-x0) = c1 - c0

The Student t-test will be performed after verification of the homoscedasticity hypothesis. The effect-size (Cohen's d) will be calculated by the difference divided by the combined (pooled) standard deviation. This can be interpreted conventionally: a d around 0.2 is described as a "weak" effect, 0.5 as "medium" and 0.8 as "strong". The statistical analysis will be done globally but also in relation to a group without Th-F-bis constructed from propensity score matching (PSM) between Th-F patients and patients without Th-F. The propensity score will be estimated using multivariate logistic regression based on various factors collected at admission; these can be very different due to the disparity in numbers between the two groups with or without Th-F formed at the end of the study

Several special cases that may affect the study will be considered:
- if the method of filling out the questionnaires (paper or electronic) leads to a difference, it will be considered in the analysis
- patients who have multiple therapeutic failures should be a very small number; these will remain in the study and their profile will be analysed to highlight possible differences with patients who had only one therapeutic failure.
- for patients who, for any reason other than therapeutic failure, need to modify or discontinue or stop treatment, two cases will occur:
  - first, this event occurs before the therapeutic failure, they will be excluded from the study and replaced,
  - second, if the event occurs after a therapeutic failure, these patients will remain in the study and will be analysed in intention to treat but not in per protocol analysis.

### Secondary objectives

The first secondary objective will be studied using an appropriate function, the variation of the PRO measurement using time up to Th-F as the interaction terms. Depending on the PRO indicator studied, the regression will be either a linear regression, an ordered logistical regression or a Poisson regression. All the PRO measurements and associated models used in this study are presented in the following table (Table 1). Variation in patient-reported outcomes will be the primary outcome. These models allow us to measure the association between patient-reported outcomes, socioeconomic status and variation in PROs. In these models, the time elapsed until Th-F could be considered as an interaction term. The inclusion of such an interaction term would allow us to test the hypothesis that the time between the Th-F and the end of the study has an influence on the evaluation of PROs.

$\Delta PRO0,1=(\mathbb{I}e,[t1\text{-}te],PRO0,PRE0,SSE,Z0, Z1$, interaction terms)
With $t0$:inclusion $t1$:end of follow-up ($t1=t0+2$) $te\ time\ to\ therapeutic\ failure\ Th\text{-}F$
$\mathbb{I}e$ Th-F indicator Yes=1; 0 either([$t1$- $te$] = 0 if $\mathbb{I}e$=0)
$PROt$:Patient reported outcome at t
$PREt$: patient reported experiment at t
$\Delta PROt,'$: variation between PRO at t & t'
$\mathcal{SES}$:: socioeconomic status
$Zt$: other variables (demographic, clinical)

The probability of having a Th-F during follow-up will be studied using logistic regression (Th-F=1 if Th-F during follow-up, 0 otherwise). In the model, the explanatory variables will be PRO and PRE at inclusion, and socioeconomic status.
Assessment of the impact of Th-F at time of event (TE) between inclusion of T0 and T1 (2-year follow-up) on PROMs and PREMs, compared to values at T0 (group of patients with Th-F only) will follow a procedure similar to that proposed for the main objective but for one group only on the difference before/after. Note that for the MusiCare scale, the analysis will be done according to the following 5 areas: Information on disease, Information on medical treatments/ investigations, Relations with care teams, Access to care, Reception in care facilities. Each item is rated from 1 (strongly agree) to 5 (do not know).

In all analyses, the influence of missing values will be studied. If the missing data is not completely random, multiple imputation will be carried out in accordance with international guidelines on missing data. All models will be calculated using standard statistical software (SAS 9.4 and STATA).

| **PRO** | **Variable type** | **Regression method** |
|---|---|---|
| Quality of life (MusiQoL) | one global index score between 0 and 100 | Linear regression<br>ordered logistic regression |
| Psychological distress (HADS) | two scores (anxiety and depression) between 0 and 21 | Linear regression<br>ordered logistic regression |
| Well-being/capabilities (ICECAP-A) | one score between 0 and 1 | Linear regression<br>ordered logistic regression |
| Activity level (iPCQ) | Percentage of people becoming inactive, number of days of inactivity, productivity losses (market and domestic activity) - positive or zero value | Multinomial logistic regression<br>Poison regression<br>Generalized linear model (GLM) |
| Quality of care (MusiCare) | one global index score between 0 and 100 | Linear regression<br>ordered logistic regression |

## VIGILANCE

During the course of the trial, the investigator must:

- report adverse drug reactions to the Regional Pharmacovigilance Centre (CRPV)
- report any adverse reactions linked to a medical device or to the procedure for fitting a medical device to the local materials vigilance correspondent
- notify the establishment's quality department in the event of an adverse reaction related to care.

## PARTICIPATION IN THE STUDY

- Duration of participation for a participant: 30 months maximum
- Details of the tests to be carried out: participants will be asked to complete 5 questionnaires at 3 points in the study (T0, TE, T1). These questionnaires will be completed during a routine consultation or sent home by post with a return envelope or on a dedicated electronic platform (LimeSurvey).
- Period of exclusion from any further trials: No exclusion period
- Possibility to take part in other trials at the same time: no
- Compensation payments. Participants will not be compensated
- Locations where the study will be carried out: Participants will be included and monitored in each centre
  5 participating centres : CRC-SEP, CHU Rouen Normandie, CHU Amiens, CHU Lille, GHICL.

All research participants must be covered by the social security system.

## RIGHTS OF ACCESS TO DATA AND SOURCE DOCUMENTS

Patient information:
In accordance with the Data Protection Act and Act no. 2002-303 of 4 March 2002, patients may at any time exercise their right to access and correct the data collected. A patient's participation in the research, as well as the procedures for obtaining their non-objection and for providing information about the research, is specified in the patient's medical file. CHU CAEN NORMANDIE will keep patients informed of the overall results of this research at the end of the study.

## DATA PROCESSING AND STORAGE OF DOCUMENTS AND RESEARCH DATA

Insofar as such research is conducted in the context of strict legislative and regulatory requirements in accordance with standardised methodologies, CHU CAEN NORMANDIE undertakes to adopt and comply with Deliberation No. 2018-154 of 3 May 2018 approving a reference methodology relating to the processing of personal data implemented in the context of research in the field of health that does not require the express or written consent of the data subject (MR-003) - Declaration number 2011519 V0.

This automated processing of health data complies with the European Regulation of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

The investigator coordinating the study undertakes to carry out the research in accordance with this reference methodology and to keep the source documents for a period of 15 years: ultrasound examination reports, biological examinations, clinical observations in the patient's medical file, etc.

## REGULATORY CONSIDERATIONS AND INVESTIGATOR OBLIGATIONS

Regulatory considerations:
The medical procedures for this trial comply with the most recent recommendations of the Declaration of Helsinki and Law no. 2012-300 of 5 March 2012 and its implementing decree no. 2016-1537 of 16 November 2016.

The sponsor or their representatives:

- Provide the investigating centres with the instructions and documents they need to conduct the trial (protocol, data collection booklets),
- May organise a set-up session to train investigators and study coordinators (at this session, all sections of the protocol will be reviewed, the completion of case report forms will be explained, as well as study procedures),
- Be available for consultation at all times and maintain contact with the investigating centre's staff by post, telephone and/or fax,
- Examine and evaluate the data in the case report form and look for any errors in data collection.

Investigator obligations:
The investigator undertakes to accept quality assurance audits carried out by the sponsor or inspections carried out by the health authorities.

The investigator also undertakes to provide the sponsor with the following information:

- ClinicalTrials registration number (NCT number): https://clinicaltrials.gov/
- Date of first inclusion in the study
- Annual update (calendar year) of the number of inclusions
- Date of last inclusion in the study
- Date of last follow-up visit for the last patient in the study

## LEGAL AND ETHICAL CONSIDERATIONS

Informing participants:
The patient will be informed of the purpose of the research, the progress and duration of the study, the benefits, potential risks and constraints of the study and the opinion given by the CPP. They may exercise their right to object.

Request for an opinion from the CPP:
"Non-interventional research," as stated in Article L. 1121-1 of the Public Health Code (Law no. 2012-300 of 5 March 2012 and its implementing decree no. 2016-1537 of 16 November 2016) will be subject to the opinion of a CPP.

The CPP must approve the protocol and the enlightened information document.

Substantial changes:
Any changes to the protocol must be submitted to the CPP for authorisation.

Declaration of start/end of trial:
The sponsor will declare the start and end of inclusion in the study to the CPP.

## PUBLICATION RULES

All study data are the exclusive property of the sponsor. Any publication relating to these may only be made after validation by the sponsor and the methodologist, where applicable.

Any person designated as an author must be competent to do so, and investigators are bound by the law to professional secrecy. According to the International Committee of Medical Journal Editors (ICMJE), each author must have participated sufficiently in the work to take responsibility for all or part of the content. The credibility of the authorship of the article is based on 3 essential contributions:

- the design and method and/or analysis and interpretation of results,
- the drafting of the article or critical revisions with significant involvement in the intellectual content,
- the final approval of the published version.

Order of authors (coordinating investigator(s), methodologist, primary investigators of the participating centres):

The order will take into account the participation of the various investigators in the trial (number of patients included and evaluable) and those who make a significant contribution during the course of the trial.

The source of funding will be indicated.

In the case of ancillary studies, their results may only be published with the agreement of the sponsor and the methodologist, and only after publication of the main study, which must be cited.

The coordinating investigator will sign the final clinical trial report, thereby indicating their agreement with the analyses, results and conclusions of the report.

The results will be presented at conferences and published.

These publications and presentations will be discussed with all the investigators taking part in the trial.

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## APPENDICES

## APPENDIX 1 : DISEASE MODIFYING TREATMENTS FOR MULTIPLE SCLEROSIS

| Moderate efficacy DMTs |
|---|
| Dimethyl Fumarate |
| Diroximel Fumarate |
| Glatiramer Acetate |
| Interferon Beta |
| Peginterferon Beta |
| Teriflunomide |

| High efficacy DMTs |
|---|
| Cladribine |
| Fingolimod |
| Mitoxantrone |
| Natalizumab |
| Ocrelizumab |
| Ofatumumab |
| Ponesimod |
| Rituximab* |

* : DMT used without French marketing authorisation but with a strong consensus in the MS experts' community.