UNIVERSITY OF THESSALY

SCHOOL OF MEDICINE

MASTER'S DEGREE PROGRAMME

" Biomedical Research Methodology, Biostatistics and
Clinical Bioinformatics"

DIPLOMA DISSERTATION

**OBSERVATIONAL STUDY PROTOCOL FOR INF FOR TREATING
MULTIPLE SCLEROSIS**

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ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

"Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική
και Κλινική Βιοπληροφορική"

ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

**ΠΡΩΤΟΚΟΛΛΟ ΜΕΛΕΤΗΣ ΠΑΡΑΤΗΡΗΣΗΣ ΓΙΑ ΙΝΤΕΡΦΕΡΟΝΗ
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**ΤΡΙΜΕΛΗΣ ΕΞΕΤΑΣΤΙΚΗ ΕΠΙΤΡΟΠΗ**

**ΓΕΩΡΓΙΟΣ ΧΑΤΖΗΓΕΩΡΓΙΟΥ**       ΚΑΘΗΓΗΤΗΣ, ΕΠΙΒΛΕΠΩΝ

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# ΠΡΟΛΟΓΟΣ

Η παρούσα Διπλωματική Εργασία, εκπονήθηκε στα πλαίσια του Μεταπτυχιακού Προγράμματος «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική» του Τμήματος Ιατρικής του Πανεπιστημίου Θεσσαλίας.

Το αντικείμενο αφορά σε πρωτόκολλο κλινικής μελέτης σχετικά με την αποτελεσματικότητα και την ανεκτικότητα της Ιντερφερόνης β-1a σε ασθενείς με υποτροπιάζουσα-διαλείπουσα πολλαπλή σκλήρυνση. Πρόκειται για μια προοπτική μελέτη παρατήρησης που περιλαμβάνει 250 ασθενείς με υποτροπιάζουσα-διαλείπουσα πολλαπλή σκλήρυνση που υποβάλλονται σε θεραπεία με υποδόρια IFN β-1a 44 μg ή 22 μg για 12 μήνες.

Η μορφή της διπλωματικής εργασίας ακολουθεί την οδηγία *Guideline for Good Clinical Practice E6 (R1)* του International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) και υποβάλλεται στην Αγγλική γλώσσα.

Στο σημείο αυτό θα ήθελα να ευχαριστήσω τον επιβλέποντα της διπλωματικής μου εργασίας, καθηγητή Νευρολογίας κ. Γεώργιο Χατζηγεωργίου, για την ανάθεση του θέματος, και τις χρήσιμες υποδείξεις κατά την εκπόνησή της, όπως επίσης και τους καθηγητές μου κ.κ. Ηλία Ζιντζαρά και Χρήστο Χατζηχρηστοδούλου, μέλη της τριμελούς εξεταστικής επιτροπής, για τις πολύτιμες γνώσεις που μου προσέφεραν κατά τη διάρκεια των μεταπτυχιακών μου σπουδών.

# TIMS Study: An Observational Study of the efficacy and tolerability of Subcutaneous Interferon β-1a in Patients With Relapsing-Remitting Multiple Sclerosis

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# LIST OF ABBREVIATIONS

AE          Adverse event

ARR         Annualized relapse rate

CI          Confidence interval

CNS         Central nervous system

CRF         Case Report/Record Form

DMT         Disease-modifying therapy

EDSS        Expanded disability status scale

EMA         European Medicines Agency

GCP         Good Clinical Practice

ICF         Informed consent form

ICH         International Conference on Harmonization of Technical

            Requirements for Registration of Pharmaceuticals for Human Use

IEC         Independent ethics committee

IFN         Interferon

i.m.        intra-muscular

i.v.        intra-venous

IRB         Institutional review board

ISR         Injection site reactions

MS          Multiple sclerosis

REB         Research Ethics Board

RRMS        Relapsing Remitting Multiple Sclerosis

SAE         Serious adverse event

s.c         subcutaneous

UADE        Unexpected Adverse Device Effect

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# Brief Title

Tolerability of Interferon-beta 1-A (Rebif)® Therapy in patients with Relapsing Remitting MS (TIMS).

This is a prospective, cohort observational study of 250 patients with relapsing-remitting MS treated with subcutaneous IFN β-1a 44 μg or 22 μg 3 times weekly for 12 months or until early discontinuation.

## 1. INTRODUCTION/BACKGROUND

Multiple Sclerosis (MS) is a chronic, demyelinating disease of the central nervous system (CNS) characterized by inflammation, demyelination and axonal/neuronal destruction, that may lead in the end to severe disability. MS affects currently about 2.5 million patients worldwide. Approximately 85% of patients have relapsing-remitting MS (RRMS), characterized by recurrent, acute episodes (relapses) of neurological symptoms. After 6-10 years, 30-40% of patients with RRMS might gradually worsen and progress to secondary progressive MS

Ttreatment with disease-modifying therapy (DMT) can reduce the frequency of disease exacerbations and may delay disability progression. Subcutaneous (sc) interferon (IFN) β-1a (Rebif®; Merck Serono SA, Geneva, Switzerland) has been shown to be effective in improving all three key measures of efficacy (relapse rate, disability progression, and magnetic resonance imaging measures of disease) in relapsing forms of MS when administered at dosages of 44 or 22 μg three times weekly (1-3). Rebif safetely profile is generally well established and the drug is used in clinical practice for over 1 0 years with over 15 million doses sold since its approval by the U.S. Food and Drug Administration (FDA) in 2002 (4). One of the most common and less studied side effects are injection site reactions (ISR), and injection site pain that may lead to poor adherence to treatment in some patients.

Several dermatological adverse events have been reported in the literature for MS patients treated with IFN β such as severe necrotising cutaneous lesions and severe dermatomyositis (5). Most of these events are related to the injection-site reaction and are

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usually mild-tomoderate local inflammatory reactions. Other events including panniculitis (6-7), skin necrosis or ulceration have also been reported. Women seem to be at a greater risk of skin reactions due to their higher incidence of autoimmune disease.

## 1.1 Investigational agent

Interferon-beta 1-A (Rebif)®

## 1.2 Trial conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

## 1.3 Population

Patients with RRMS that take s/c Interferon-beta 1-A (Rebif)®.

## 2. STUDY OBJECTIVES AND PURPOSE

The purpose of this prospective, observational study in patients with relapsing remitting MS, is to assess the tolerability and efficacy of s/c IFN β-1a; in particular to assess the proportion of patients developing injection site reactions (ISR) after a time period of 12 months.

## 3. STUDY DESIGN

### 3.1 Study Endpoints

**Primary Study endpoints**
The proportion of patients with moderate to severe injection site reactions based on pain, bruising and/or transient (<24 hours) erythema; inflammation alone and with necrosis at injection site; even when plastic surgery required for necrosis.

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**Secondary Study endpoints**

- Annual relapse rate

- Change in EDSS score

- Time to first relapse

- Incidence of side effects associated with Rebif therapy

## 3.2 Type of Study

The study is an observational prospective study. During the screening period demographic data, medical history (including history of MS) and details of concommitant medications/procedures and medical conditions (safety assessment) were collected. Patients underwent neurological examination, a urine pregnancy test (where appropriate) and review of inclusion/exclusion criteria. Patients could withdraw from the study at any time.

## 3.3 Treatments of interest

Patients eligible for participation in this study will, as part of their routine medical care, receive either IFN β-1a 44 μg or 22 μg 3 times weekly. The decision on the prescribed dose of IFN β-1a, as well as the decision to discontinue treatment, depended on the treating physician and reflected the current standard of care in a real-life setting. Patients will be followed in the study for 12months. Injection site reactions will be monitored after 6 and 12 months of Rebif treatment.Moreover ARR, change in EDSS score, time to first relapse and incidence of side effects associated with therapy will be monitored at baseline and after 12 months of therapy.

## 3.4 Study discontinuation

Reasons for the termination of the study include ethical concerns, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, and/or reaching a positive or negative statistical end point earlier than expected. Other causes of study discontinuation might be commercial such as lack of financial resources. The discontinuation of a clinical trial can be decided by either the investigator, the study

sponsor, or by mutual agreement.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1 Inclusion criteria

Patients diagnosed with RRMS according to the 2005 McDonald criteria (8) were eligible for enrollment in the study if they were aged over 18 years old and did not receive any disease-modifying MS therapy before.

## 4.2 Exclusion criteria

Patients were excluded from the study if they had one of the following criteria:

- primary progressive or secondary progressive MS

- previously administered IFN β, glatiramer acetate, any other immunomodulatory or immunosuppressive agents, or any other MS therapy in the past

- Initiation of treatment in pregnancy.

- Subjects with a history of hypersensitivity to interferon-ß, or skin allergies.

## 4.3 Subject withdrawal

Subjects have the right to withdraw from the study anytime. If a subject decides to withdraw from the study, all of the following research activities involving the subject's participation will be discontinued:

- Interacting or intervening with the subject in order to obtain data about him or her

- Obtaining additional identifiable private information about the subject by collecting or receiving such information from any source and

- Obtaining additional identifiable private information about the subject by observing or recording private behavior without interacting or intervening with the subject

In addition, patients might be withdrawn by the investigator if the investigator feels that the patient is not gaining any clinical benefit or because of unacceptable toxicity. Patients who are withdrawn or are removed from the study will be required to have an off-study clinic visit at the time of discontinuation, a 30-day follow-up safety visit.

**4.4 Study duration**

The study will be considered to be completed once the last patient enrolled will have been followed for 12 months.

**4.5 Procedures for monitoring subject compliance**

Regular contact through phone calls or sms messages with the patients for reminding them their treatment dosing schedule. Different contents can be sent to subjects. For the younger, the words can be lively and relaxing, and a joke or health tip can be added, while for the older a simple and kind message is appropriate .

Providing rewards or compensation in several forms is also an effective measure including oral incentives, advising appropriate holiday, and covering transportation fee.

Investigators and participants should increase open communication and trust each other.

*Follow-Up Plan*

Follow-up plan should depend on the specific situation of participants such as avoiding holidays or any inconvenient day.

# 5. ASSESSMENT OF EFFICACY

**Efficacy parameters**

The primary endpoint efficacy variable is ISR whereas secondary endpoint efficacy variables are ARR, change in EDSS score and time to first relapse.

# 6. ASSESSMENT OF SAFETY

**6.1 Adverse event definitions**

*Adverse effect.* Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

*Associated with the investigational device or, if applicable, other study treatment or*

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*diagnostic product(s)*.  There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

*Disability*.  A substantial disruption of a person's ability to conduct normal life functions.

*Life-threatening adverse effect*.  Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect <u>as it occurred</u> (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

*Serious adverse effect*.  An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:
- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

<u>*Unexpected adverse effect.*</u>  Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

**Unanticipated adverse effect:** Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

**6.2 Eliciting adverse effect information**

The subjects of the clinical study will be routinely and regurarly questioned about adverse effects at study visits.

**6.3 Recording and assessment of adverse effects**

All observed adverse effects (serious or non-serious) and abnormal test findings, regardless of the group, if applicable, or suspected causal relationship to the investigational device or,

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if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories.  For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational product or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings that are associated with the investigational product or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

## 6.4 Reporting of adverse effects to the EMA

The investigator-sponsor will submit a completed  EMA form to the EMA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an *unanticipated adverse device effect (UADE).*  A copy of this completed form will be provided to all participating sub-investigators.

The completed Form will be submitted to the EMA as soon as possible and, in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

## 6.5 Reporting adverse effects to the responsible IRB

For any adverse event determined to be a UADE, the sponsor-investigator will submit the completed EMA form and cover letter to the IRB as soon as possible and no later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available.

## 7. STATISTICAL PLAN

### 7.1 Sample size determination

The study is planned to include 125 patients on the Rebif 44mg dosage and 125 patients on the 22mg dosage.

The assumed incidence rates for the parallel cohort were estimated from the observed incidence rates by Pelletier et al., 2005 who found that 66.7 % of the patients in the 44mg group and 48.5% of the patients in the 22mg group developed ISR.

20% difference in ISR between the two groups was considered as clinically important. Therefore, the required sample size to detect a statistically significant difference of 20% in response at P-value, P=0.05, with a Power 90% is 125 patients in each group.

### 7.2 Statistical methods

Data for the main variables will be presented using descriptive statistics by using mean, median, SD, quartiles, percentages with 95% confidence intervals and extreme values for continuous variables, and counts and percentages for categorical variables. The proportion of patients with ISR s were not normally distributed between the different patient subgroups; therefore, nonparametric tests were used to test the differences between the different sc IFN β-1a doses (Mann–Whitney$U$-test)  The level of significance will be set at p<0.05.

### Interim analyses

A descriptive summary of the data of this study will be performed on a periodic basis (at least 3monthly) in addition to the regular periodic safety updates that are required by the local health authorities

### 7.3 Procedure for accounting for any missing, unused and spurious data

Multiple imputation will be used to replace missing values . Multiple imputation is a method that makes maximum useof available data and maximises statistical power while requiring less strict theoretical assumptions than to a complete case analysis, or single imputation of mean values.

This is now one of the methods most commonly used for analysing clinical trials data and considered more accurate than the last observation carried forward method (10)

### 7.4 Procedures for reporting any deviations from the original statistical plan

Any deviations from the original statistical plan will be described and justified in the final report.

## 8. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator and Aristotle University of Thessaloniki will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documentation.

## 9. ETHICAL CONSIDERATIONS

### 9.1 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient.

In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding.

If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before collecting any data described in this study protocol. The process of obtaining informed consent should be documented in the patient source documents.

### 9.2 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC or equivalent board reviewing specifically non-interventional

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study protocol, before the start of the study. Prior to study start, the treating physician is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures that are found in this protocol.

## 9.3 Early termination of the study

The study can be terminated at any time for any reason after agreement with health authorities. The treating physician might be informed of the procedures that need to be followed in order to make sure that adequate consideration is given to the protection of the patient's interests. The participating physician will be responsible for informing the IRB/IEC of the early termination of the study.

## 10. DATA HANDLING AND RECORD KEEPING

A Case Report Form (CRF) will be completed for each subject that is enrolled into the clinical study. Trained site staff will enter protocol defined data in the CRF. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical data entered on the CRF are complete and accurate.

In any case, the physician must maintain source documents for each patient in the study,consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any tests performed.

All information entered in the CRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must arrange for the retention of the subject identification codes for a sufficient period of time to permit any medical follow-up which may be warranted.

## 11. LIMITATIONS

This is an observational, non-randomized study, therefore different biases may occur. Systematic differences between the 2 patient cohorts may exist, influenced by clinical decisions of the treating physicians that will assign patients to different drug dosage based mostly on disease severity but also disease duration, presence of comorbidities, and other factors. These differences can potentially introduce channeling bias and confound the association between treatment and the risk of the safety outcome.

## 12. PUBLICATION POLICY

The protocol and the key results will be posted in a publicly accessible database such as clinicaltrials.gov. Moreoever, at least upon study completion and finalization of the study report the results of this study will be either submitted for publication in a peer-reviewed journal or presented in a conference and/or posted in a publicly accessible database of study results.

## 13. FINANCING AND INSURANCE

The clinical study is funded by the Aristotle University of Thessaloniki. The insurance of the subjects that participate will be covered by their health insurance. Any extra costs needed will be covered by the Aristotle University of Thessaloniki.

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## 15. SUPPLEMENT

# Flow Chart