Author's response to reviews

Title: Drug adherence and multidisciplinary care in patients with multiple sclerosis: Protocol of a prospective, web-based, patient-centred, nation-wide, Dutch cohort study in glatiramer acetate treated patients (CAIR study)

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Author's response to reviews: see over
Cover letter: Answers to the Reviewer’s report (MS: 1131627746439980)

We thank the reviewer for the valuable comments. We have dealt with the points as follows.

Major Compulsory Revisions

1. APPENDIX A lists the questions that the study aims to answer.

2. The database of the study is compliant with EU-regulations on data storage and activation for medical purposes. There are 2 separated databases: one with personal identifiers (name, address, ID-number) and one with medical records (answers to the questions, ID-number). Only after login the two databases are connected to each other (encrypted key). Hence for analytical purposes only the medical records are submitted to the investigators, not the personal records.

3. After data has been analyzed the coordinating investigator (PJJ) writes a concept study report. This is sent to all investigators for comments. The final report then is the basis for a manuscript that will be submitted to a peer-reviewed international scientific journal for publication. Oral or poster communications will be given on international and national symposia. Participating patients will receive a summary of the study report (findings, conclusions), written in a wording that is understandable to lay persons, as soon as the report has been finalized. A section on reporting of the results has been added to the protocol.

Minor Essential Revisions

1. Major parts of the manuscript have been rewritten. Changes are listed below. Then the text was critically reviewed by a native speaker, Mr. Thomas Harrison, for GB English.

List of changes

Title
The title has been changed:


Authors
“Jos Vliegen” has been changed into “Joseph Vliegen”
“Dorothea Siepman” has been changed into “Theodora Siepman”

Abstract
Background.

First paragraph.

The 3rd sentence “Disease-modifying drugs (DMDs) reduce number and severity of relapses and disability progression” has been changed into “Disease-modifying drugs (DMDs) reduce relapses and disability progression.”

The 7th sentence “In GA-treated patients the 6-month discontinuation rate is between 9% and 27% ...” has been changed into “The 6-month discontinuation rate is up to 27% ...”.

Second paragraph.

1st sentence “Treatment adherence is influenced by factors relating to socio-economic situation, health care and caregivers, disease, treatment and patient characteristics.” has been changed into “Treatment adherence is influenced by the socio-economic situation, health care and caregivers, disease, treatment and patient characteristics.”

2nd sentence “Only few studies dealt with adherence-related factors in GA-treated patients.” has been changed into “Only a few studies have dealt with adherence-related factors in DMD-treated patients.”

4th sentence “Patient education and optimal support are thought to improve adherence in general.” has been changed into “Patient education and optimal support improve adherence in general.”

5th sentence “Detailed knowledge on those disciplines or duration of care, given to GA-treated patients, that significantly relate to adherence could lead to adherence-improving measures.” has been changed into “Knowledge of the aspects of care that significantly relate to adherence could lead to adherence-improving measures.”

6th sentence “Moreover, identification of patients at risk of inadequate adherence could lead to more effective care and more efficient allocation of resources.” has been changed into “Moreover, identification of patients at risk of inadequate adherence could lead to more efficient care.”

Third paragraph.

2nd sentence “More extensive knowledge on factors prognostic of adherence and on care aspects associated with adequate adherence would improve the chances of these drugs to become effective treatments.” has been changed into “Detailed knowledge on factors prognostic of adherence and on care aspects that are associated with adequate adherence will improve the chances of these drugs becoming effective treatments.”

3rd sentence “We set ourselves to investigate in RRMS patients the relations between GA adherence and received care, as well as factors associated with adherence.” has been changed into “We investigated in RRMS patients the relationship between drug adherence and multidisciplinary care, as well as factors associated with adherence.”

The sentence “Given the differences in the frequency of administration and in the side effects between the DMDs we decided to study patients treated with the same DMD (GA).” has been added.
Methods/design
Second paragraph.

1st sentence “Primary objective is to investigate whether GA adherence is associated with specific disciplines or durations of received care” has been changed into “The primary objective is to investigate whether GA adherence is associated with specific disciplines of care or quantity of care.”

2nd sentence “Secondary objective is to investigate whether adherence to GA treatment is associated with aspects of socio-economic situation, health care and caregivers, disease (e.g. disease activity), treatment (e.g. adverse events) or patient characteristics (e.g. self-efficacy, health-related quality of life [HR-QoL], mood).” has been changed into “The secondary objective is to investigate whether GA adherence is associated with specific aspects of the socio-economic situation, health care and caregivers, disease, treatment or patient characteristics.”

Third paragraph.

1st sentence “All data are acquired on internet via the study website www.cairstudie.nl.” has been changed into “All data are acquired online via a study website.”

2nd sentence “All RRMS patients in the Netherlands who start GA treatment are eligible and are informed on the study by neurologists and nurses. Information is also available on websites from national MS patient organisations.” has been changed into “All RRMS patients in the Netherlands starting GA treatment are eligible. Patients are informed by neurologists, nurses, and websites from national MS patient organisations.”

4th sentence “All data, except on disability, are obtained by patient self-report ...” has been changed into “All data, except on disability, are obtained by patient self-reports ...”

5th sentence “Number of missed doses and number of patients having discontinued GA treatment are measures of adherence.” has been changed into “The number of missed doses and the number of patients having discontinued GA treatment at 6 and 12 months are measures of adherence.”

6th sentence “Per care discipline number of sessions and total care duration are measures of received care.” has been changed into “Per care discipline the number of sessions and the total duration of care are measures of received care.”

7th sentence “The full spectrum of MS-relevant non-experimental care that is available in the Netherlands is assessed.” has been changed into “The full spectrum of non-experimental care that is available in the Netherlands is assessed.”

8th sentence “Care includes ‘physical’ contacts, e.g. in out-patient clinics, contacts by telephone, e-mail or internet, health-promoting activities or community care activities.” has been changed into “Care includes ‘physical’ contacts, contacts by telephone or internet, health-promoting activities and community care activities.”

Fourth paragraph.

1st sentence “The Dutch Adherence Questionnaire-90 (DAQ-90) is a 90-item questionnaire based on the World Health Organisation (WHO) 2003 report on adherence and designed to
comprehensively assess five domains ...” has been changed into “The Dutch Adherence Questionnaire-90 (DAQ-90) is a 90-item questionnaire based on the World Health Organisation (WHO) 2003 report on adherence and comprehensively assesses five domains ...”

2nd sentence “Self-efficacy is assessed by the MS Self-Efficacy Scale (MSSES).” and 3rd sentence “HR-QoL and mood are assessed by the Multiple Sclerosis Quality of Life-54 questionnaire (MSQoL-54).” have been changed and combined into “In addition, self-efficacy is assessed by the MS Self-Efficacy Scale (MSSES), and mood and HR-QoL by the Multiple Sclerosis Quality of Life-54 questionnaire (MSQoL-54).”

Discussion

2nd sentence “On-line data acquisition by patients, neurologists and nurses does not require study visits to the hospital and can easily be integrated into daily life and daily practice.” has been changed into “Online data acquisition by patients does not require study visits to the hospital and can easily be integrated into daily life.”

Background

Multiple sclerosis

2nd sentence “Most patients start with a relapsing-remitting (RR) phase during which incomplete remissions cause ...” has been changed into “Most patients start with a relapsing-remitting (RR) phase during which incomplete remissions often cause ...”

3rd sentence “Glatiramer acetate (GA), interferon-beta (INFb)-1a and INFb-1b are first-line disease-modifying drugs (DMDs) for RRMS [1]” has been changed into “Glatiramer acetate (GA), interferon-beta (INFb)-1a and INFb-1b are first-line disease-modifying drugs (DMDs) for RRMS treatment [1], reducing relapses and disability progression [1]”

4th sentence “Phase 3 randomized controlled trials (RCTs) showed these drugs to be efficacious in reducing relapse rate and disability progression [1].” has been deleted.

5th sentence “They are injected subcutaneously (GA every day; INFb-1a thrice a week; ...” has been changed into “They are injected subcutaneously (GA every day; INFb-1a thrice weekly; ...”.

7th sentence “Phase 4 studies indicate that both INFb [2] and GA treatment [unpublished data] are associated with an increase in HR-QoL.” has been changed into “Phase 4 studies show that both INFb-1a [2] and GA treatment [3] are associated with an increase in HR-QoL.”

9th sentence “In all, year-long treatment and adequate adherence improve a patient’s chance of clinical stability.” has been deleted.

Adherence

First paragraph.

1st sentence “In general, adherence to pharmacotherapy is inadequate in 30% to 50% of patients,
irrespective of disease, prognosis or treatment setting [4,5].” has been changed into “Adherence to pharmacotherapy is inadequate in 30% to 50% of patients, irrespective of disease, prognosis or treatment settings [5,6].”

3rd sentence “Inadequate adherence relates to 10% of all hospital admissions and 23% of all nursing home admissions in the U.S.A., leading to costs of $100 million per year [7].” has been deleted.

Second paragraph.

6th sentence “In MS patients with two or more DMD dispensings mean medication possession ratio (MPR) was as low as 68% for 24 months [10]” has been changed into “In MS patients with two or more DMD dispensings the mean medication possession ratio (MPR) was as low as 68% for a 24 month period [11]”

Third paragraph.

1st sentence “Studies indicate that after 4 months up to 11% of DMD treated RRMS patients have discontinued treatment [11], and after 6 months figures vary from 9% to 27% [12].” Has been changed into “After 4 months up to 11% of DMD-treated RRMS patients have discontinued treatment [12], and after 6 months figures vary from 9% to 27% [13].”

2nd sentence “However, in a report from MS-specialised academic centres discontinuation rate was only 1.7% after 6 months and 8% after 2 years [13].” has been changed into “However, in MS-specialised academic centres discontinuation rate was only 1.7% after 6 months and 8% after 2 years [14], suggesting that adherence may relate to certain qualitative or quantitative aspects of care.”

3rd sentence “These data suggest that adherence to DMDs may significantly relate to certain aspects of care.” has been deleted.

4th sentence “Academic MS-centres provide multidisciplinary care, coordinated by MS-nurses.” and 5th sentence “In contrast, MS care may be limited in hospitals without special interest in MS.” have been combined into “Academic MS-centres provide multidisciplinary care, coordinated by MS-nurses, whereas care may be more limited in hospitals without a special interest in MS.”

Fourth paragraph.

1st sentence “Retrospective analysis of data on GA use in the Netherlands in the period 2003 - 2005 showed a discontinuation of 23.9% ...” has been changed into “Retrospective analysis of data on GA use in the Netherlands in the period 2003 - 2005 showed a discontinuation rate of 23.9% ...”

Factors relating to adherence

First paragraph

1st sentence “Adherence is influenced by a multitude of factors, whereby factors relating to missing of doses may be different from those relating to discontinuation [8].” has been changed into “Factors relating to the missing of doses may be different from those relating to discontinuation [9].”
2nd sentence “The WHO 2003 report on adherence groups evidence-based factors in five domains [5]: factors related to 1) socioeconomic situation, 2) health care and caregivers, 3) disease, 4) treatment, and 5) patient.” has been changed into “The WHO 2003 report on adherence puts evidence-based factors into five domains [6]: factors related to 1) the socio-economic situation, 2) health care and caregivers, 3) disease, 4) treatment, and 5) the patient.”

3rd sentence “Only few studies dealt with adherence-related factors in DMD treatment in MS [8].” has been changed into “Only a few studies dealt with adherence-related factors in DMD treatment in RRMS [9].”

Second paragraph

1st sentence “…attitude towards self-injecting, previous immunomodulation, reason for switching, other chronic disease, disability, cognition, disease duration, …” has been changed into “…the attitude towards self-injecting, previous immunomodulation, the reason for switching, concurrent chronic disease, …”

2nd sentence “Scoring each item for presence (1) or absence (0) and addition of scores yields the Discontinuation Risk Score (DRS), ranging from 0 to 16.” has been changed into “Scoring each item for presence (1) or absence (0) the adding up of the scores yields the Discontinuation Risk Score (DRS), ranging from 0 to 16.”

Study rationale

First paragraph.


2nd sentence “Care that may improve one or both levels of adherence pertains to factors in all five WHO domains [5].” has been deleted.

Second paragraph.

2nd sentence “Knowledge on which disciplines or duration of care are associated with adherence could positively influence the care given to patients starting a DMD.” has been changed into “Knowledge on which qualitative or quantitative aspects of care are associated with adherence could guide the care given to patients starting a DMD.”

3rd sentence “Moreover, determination of factors prognostic of adherence would enable identification of patients at risk of missing doses or discontinuation.” has been changed into “Moreover, the determination of factors prognostic of adherence would enable identification of patients at risk of inadequate adherence.”

4th sentence “As a result, adherence-promoting care could become more effective”
and allocation of resources more efficient." has been changed into “As a result, adherence-promoting care could become more effective and efficient. “

Third paragraph.

1st sentence “Recently new drugs with different working mechanisms have been proven efficacious in RRMS and are expected to become available from 2011 on.” has been changed into “At present new DMDs for RRMS are becoming available.”

2nd sentence “More detailed knowledge on adherence in RRMS patients, on factors prognostic of adherence, and on adherence-improving care would undoubtedly help to convert new efficacious drugs into effective treatments.” has been changed into “More knowledge on which aspects of multidisciplinary care are related to adherence, and the factors prognostic of inadequate adherence could increase the chances that the new efficacious drugs become effective treatments.”

Fourth paragraph

1st sentence “So, we conceived the idea to investigate relations between adherence and received care in RRMS patients starting DMD treatment.” has been changed into “We conceived the idea to investigate adherence and multidisciplinary care in RRMS patients starting DMD treatment.”

3rd sentence “... we decided to study patients ... “ was changed into “...we choose to study patients ...”

Methods/Design

Objectives

The text of this section has been rewritten.

Old: “Primary objective is to investigate whether adherence to GA treatment is associated with specific disciplines or duration of care. Secondary objectives are to investigate: 1) whether adherence to GA treatment is associated with specific characteristics of socio-economic situation, health care or caregivers, disease (e.g. disease activity), treatment (e.g. adverse events), or patient (e.g. self-efficacy, HR-QoL, mood). 2) the predictive value of the DRS with respect to adherence.”

New: “Appendix A lists the questions of the study. Primary objective is to investigate whether GA adherence is associated with specific disciplines of care or quantities of specific care. Secondary objective is to investigate whether GA adherence is associated with specific characteristics of socio-economic situation, health care or caregivers, disease, treatment, or the patient. Tertiary objective is to assess the predictive value of the DRS with respect to GA adherence.”

Study design

The caption “Study design” has been changed into “Study design and treatment”.

The text “GA is prescribed by neurologists as per regular care and dispensed as a commercial drug by...”
general pharmacies (Copaxone ®). GA is administered by the patient according to the instructions in the package leaflet. “ has been added to this section.

### Treatment

The caption “Treatment” and the corresponding text have been deleted.

### Outcomes

The text of this section has been rewritten.

**Old:**

Primary outcomes are correlations between percentages of missed doses and percentage of patients who discontinued GA treatment, and numbers of care sessions per discipline. Secondary outcomes are correlations between percentages of missed doses and percentages of patients who discontinued GA treatment, and presence of degree of socio-economic, health care, caregivers, disease, treatment or patient characteristics.

**New:**

Primary outcomes:

a) relations between numbers of missed doses and numbers of care sessions per discipline.
b) relations between number of patients who discontinued treatment and numbers of care sessions per discipline.

Secondary outcomes:

a) relations between numbers of missed doses and presence of specific characteristics of the patient, socio-economic situation, health care, caregivers, disease, or treatment.
b) relations between number of patients who discontinued treatment, and presence of specific characteristics of the patient, socio-economic situation, health care, caregivers, disease, or treatment.

Tertiary outcomes:

a) predictive value of Discontinuation Risk Score with respect to missed doses,
b) predictive value of Discontinuation Risk Score with respect to number of patients who discontinued treatment.

### Patient recruitment

The text of the first paragraph has been rewritten.

**Old:**

As the CAIR study is a nation-wide cohort study it is crucial to inform virtually all patients in the Netherlands who start GA treatment. Patients are informed in different and complementary ways: by neurologists, MS-nurses, specialised nurses who teach patients to self-inject, and websites of patient organisations. In the latter two situations patients are advised to visit the CAIR study website (www.cairstudie.nl) and to contact their neurologist or MS-nurse, the study helpdesk by telephone or e-mail, or the coordinating investigator (PJJ) by e-mail, for further information.

**New:**

Patients are informed by neurologists, MS-nurses, or specialised nurses who teach patients to self-inject, and the websites of patient organisations. Patients are also advised to visit the study website (www.cairstudie.nl). For further information they may contact the study helpdesk by telephone or e-mail, or the coordinating investigator (PJJ) by e-mail.

- **First phase**
The text of this section has been rewritten.

Old: “In 2009 15 neurologists with special interest in MS care and respective MS-nurses were recruited as investigators. Practices were fairly distributed over the country. Since July 2009 they inform patients who start GA treatment on the possibility to participate in the study. Objectives and overall requirements are discussed with the patient. Importantly, the information on the CAIR study is preceded by and independent from the decision to start GA. Patients may visit the study website www.cairstudie.nl for additional information, contact the study helpdesk by telephone or by e-mail, or contact the coordinating investigator by e-mail. When a patient decides to participate, neurologist or MS-nurse gives notice to the helpdesk and the patient’s participation is activated.”

New: “In 2009 15 neurological practices with a special interest in MS care and MS-nurses were recruited as investigators. Practices were fairly distributed over the whole country. Since July 2009 they inform patients starting GA treatment of the possibility of participation in the study. Objectives and overall requirements are discussed with the patient. The study information is preceded by and independent from the decision to start GA. When a patient decides to participate, the neurologist or the MS-nurse notifies the helpdesk and participation is then activated.

- Second phase

The text of this section has been rewritten.

Old: “In the Netherlands it is common practice that every MS patient who is prescribed an injectable DMD is given the opportunity to be visited by a specialised nurse for information on the drug and instructions on the injection procedure. Since February 2010 these nurses briefly inform patients on the existence of the CAIR study. Patients who are interested in receiving further information are handed out a postage paid cart to send to the study helpdesk.

On receipt of the card the helpdesk contacts the patient by phone and gives information. Patients who, after being informed, are willing to participate either sign the informed consent form at their neurologist’s or MS-nurses’ office or, in case the neurologist is not yet familiar with the study, confirm the text of the informed consent by clicking on a specific web page on the study website www.cairstudie.nl. In the latter case the coordinating investigator contacts the neurologist by telephone to introduce the study, followed by an e-mail to which the study protocol, study synopsis and informed consent text are attached in pdf format. Within two weeks a second contact is established, by telephone or e-mail, and the neurologist informs the coordinating investigator on his/her decision to participate or not. If the neurologist participates he/she and the MS-nurses are contacted by the helpdesk and the site is activated.

A negative decision by the neurologist does not interfere with the patient’s participation, as the study is patient-centred and the primary research question may be answered by only patient-derived data.”

New: “Since February 2010 nurses who teach patients to self-inject briefly inform patients of the study. Patients interested in receiving further information are handed a postage paid cart addressed to the study helpdesk. On receipt of the card the helpdesk contacts the patient by phone and gives information. Patients who, after being informed, are willing to participate either sign the informed consent form at their neurologist’s or MS-nurses’ office or, in case the neurologist is not yet involved in the study, confirm the text of the informed consent by clicking on a specific page on the study website. In the latter case the coordinating investigator contacts the neurologist by telephone or e-mail to introduce the study, and provides the study protocol, study synopsis and informed consent text. Within two weeks a second contact is established and the neurologist informs the coordinating investigator on
his/her decision to participate or not. If the neurologist participates he/she and the MS-nurses are contacted by the helpdesk and the site is activated. A negative decision by the neurologist does not interfere with the patient’s participation, as the study is patient-centred and the primary research question may be answered by patient-derived data only.”

Eligibility criteria

1st and 2nd sentences
The text “In line with the observational design of the study the eligibility criteria for patients to participate are minimal. Inclusion criteria: 1) indication for GA treatment, as formulated by the regulatory authorities in the Netherlands,... “ has been changed into “Eligibility criteria are minimal. Inclusion criteria: 1) indication for GA treatment, ...”

3rd sentence “Exclusion criteria: 1) contra-indications to GA as defined in the Summary of Product Characteristics (SPC) text, 2) hypersensitivity to GA or mannitol, 3) worsening of symptoms suggestive of relapse, 4) pregnancy or lactation, 5) time interval between first GA injection and baseline assessment more than 4 weeks.” has been changed into “Exclusion criteria: 1) contra-indications to GA as defined in the Summary of Product Characteristics text, 2) hypersensitivity to GA or mannitol, 3) worsening of symptoms suggestive of relapse, 4) pregnancy or lactation, 5) the time interval between the first GA injection and baseline assessment is more than 4 weeks.”

Ethics

The text of this section has been changed.

Old: “The protocol has been reviewed by the Independent Review Board (IRB), an approved ethical committee residing in Amsterdam, the Netherlands. The IRB concluded that, because of the observational design of the study, a detailed assessment by an ethical committee was not required. Thus, the study did not qualify for being tested according to the Dutch Medical Research Involving Human Subjects Act of 1999 [18].”

New: “The protocol has been submitted to the Independent Review Board (IRB), an approved ethical committee residing in Amsterdam, the Netherlands. The IRB concluded that, because of the observational design of the study, a review by an ethical committee was not required, as the study did not qualify for being tested according to the Dutch Medical Research Involving Human Subjects Act of 1999 [19].”

Online assessments and measures

1st – 6th sentences have been rewritten.

Old: “Data are acquired via the study website www.cairstudie.nl. Patients log in with a personal code provided by the help desk and choose their username and password. On-line they go through various web pages containing the case record forms (CRFs) with study related questions and questionnaires. These electronic CRFs (eCRFs) are specifically designed for the CAIR study and are comparable to data sheets in paper CRFs.
Questions relate to missing doses, GA discontinuation, adverse events, medication and relapses. Questionnaires pertain to self-efficacy, HR-QoL, mood, and adherence-related factors.”

New: “Data is acquired via the study website. Patients log in with a code provided by the help desk and choose a username and password. Online they go through various web pages containing the case record forms (CRFs) with questions and questionnaires. These electronic CRFs (eCRFs) are similar to paper questionnaires and data sheets. Questions relate to missing doses, GA discontinuation, adverse events, medication and relapses. Questionnaires pertain to self-efficacy, mood, other adherence-related factors and HR-QoL.”

Fourth paragraph.

3rd sentence has been changed.

Old: “Within this time frame eCRFs may be filled in on moments that are suitable to the participant (patient, neurologist or MS-nurse).”

New: “Within this time frame eCRFs may be filled in at moments that are suitable to the participant.”

Adherence

The text of this section has been revised as follows:

Old: “Number of missed doses per patient and number of patients having discontinued GA treatment are measures of adherence. Number of care sessions per discipline and duration of care per discipline are measures of received care. Number of missed doses in the preceding 14 days, and discontinuation of GA, date of discontinuation and date of restart, whatever applicable, are recorded by patients on-line via the study website at 3, 6, 9 and 12 months. In addition, number of missed doses are documented at 6 random time points unknown to patients, neurologists and MS-nurses. Neurologist or MS-nurse also record date of discontinuation or date of restart.”

New: “The number of missed doses in the preceding 14 days, and discontinuation of GA, the date of discontinuation and the date of restart, which ever is applicable, are recorded by patients at 3, 6, 9 and 12 months. In addition, the number of missed doses are documented at 6 random time points unknown to patients, neurologists and MS-nurses. Neurologist or MS-nurse also record the date of discontinuation or the date of restart.”

Received care

The following changes have been made.

1st sentence “As this is a real-life observational study, care is given as per regular practice.” has been deleted.
Disciplines will vary per patient, depending on need, indication and feasibility.

Therefore, we assess the full spectrum of MS-relevant non-experimental care disciplines that are available in the Netherlands: 1) neurologist, ... has been changed into “Care given by the following disciplines is assessed 1) neurologist, ...”

Care includes ‘physical’ contacts, e.g. in out-patient clinics, contacts by telephone, email or internet, ...

Care received in the preceding 14 days ...

Self-efficacy

Self-efficacy is the subjective belief that one can overcome challenges that one is faced with, and has been found to be a determinant of GA adherence in patients with RRMS [15].

In order to incorporate the subjective experiences of individuals with MS, a 'patient-focused' methodology was adopted to develop the MSSES [19].

The scale has shown sensitivity to detecting change following a therapeutic intervention.

The scale has shown sensitivity to detecting change following a therapeutic intervention.

Mood and health-related quality of life

Mood is assessed by the questions 25 and 28 from the Multiple Sclerosis Quality of Life-54 questionnaire (MSQoL-54) [21]. Health-related quality of life (HR-QoL) is an overall measure of effectiveness from a patient’s perspective.

HR-QoL is an overall measure of well being and is becoming increasingly important in the evaluation of therapies in chronic disorders. HR-QoL is assessed by the Multiple Sclerosis Quality of Life-54 questionnaire (MSQoL-54) [20].
It consists of ... additional questions exploring items relevant to patients with MS [21]."

5th sentence “The MSQoL-54 contains 52 items distributed into 12 scales, and two single items.” has been deleted.

Last sentence “Mood is assessed by two questions, the numbers 25 and 28, from the MSQoL-54 [20].” has been deleted.

- **Adherence-related factors**

1st and 2nd sentences have been changed and combined:

Old: “The Dutch Adherence Questionnaire-90 (DAQ-90) assesses adherence-related factors. The DAQ-90 is a 90-item questionnaire designed to assess all factors identified by the WHO 2003 report [5] as evidence-based determinants of adherence”

New: “The Dutch Adherence Questionnaire-90 (DAQ-90) is a 90-item questionnaire designed to assess all factors identified by the WHO 2003 report [6] as evidence-based determinants of adherence (See Appendix B).”

3rd sentence has been changed:

Old: “The DAQ-90 consists of 5 sections corresponding to the five domains of adherence-related factors in the WHO 2003 report [5]: 1) general (socio-economic factors), 2) health care (factors relating to health care and caregivers), 3) disease (disease-related factors, 4) treatment (treatment-related factors, and 5) 16 patient (patient-related factors).”

New: “The DAQ-90 consists of 5 sections corresponding to the five domains of adherence-related factors in the WHO 2003 report [6].”

The caption “- Discontinuation risk” has been changed into “Discontinuation Risk Score”.

- **Discontinuation Risk Score**

The text of this section has been rewritten:

Old: “At baseline the 16 items constituting the DRS are scored 0 (absent) or 1 (present) by the specialised nurses as per regular care, during the injection instruction visits. Addition of item scores yields the DRS.”

New: “At baseline the 16 items of the DRS are scored for absence (0) or presence (1) by the nurses who teach patients to self-administer. The adding up of item scores yields the DRS.”

- **Adverse events**

1st sentence has been changed:

Old: “Adverse events considered by patients, neurologists or nurses as probably or definitely related to GA treatment are reported on-line at 3, 6, 9 and 12 months, on a separate eCRF.

New: “Adverse events considered by patients, neurologists or nurses as probably or definitely related to GA treatment are reported on-line at 3, 6, 9 and 12 months.”

- **Disease characteristics**

1st sentence has been changed:
Old: “At baseline ... number of relapses in last 12 and 24 months, number of steroid-treated relapses in last 12 and 24 months.”
New: “At baseline ... the number of relapses in the last 12 and 24 months, the number of steroid-treated relapses in the last 12 and 24 months.”

Schedule of assessments

Old: “The schedule of assessments is presented in the flow chart [Appendix].”
New: “The schedule of assessments is presented in the flow chart (Appendix C).”

A new section has been added:

“Reporting of results
A manuscript, based on the study report, will be submitted to a peer-reviewed international scientific journal for publication. Oral or poster communications will be given on international and national symposia. Participating patients will receive a summary of the study report (findings, conclusions), written in a wording that is understandable to lay persons, as soon as the report has been finalized.”

Discussion

Second paragraph.

2nd sentence has been changed:
Old: “Data are obtained by patients’ self-report via the internet.”
New: “Data is obtained by the patient’s online self-reporting.”

3rd paragraph has been rewritten:
Old: “We aim to inform every RRMS patient in the Netherlands who starts GA treatment, according to the cohort-based nation-wide design. To that end neurologists and MS-nurses in 15 MS dedicated hospitals, evenly distributed over the country, actively recruit patients. In addition, the specialised nurses, who give instructions on the GA injection procedure, inform patients on the possibility to participate. … Recruitment is on schedule, with 99 patients being enrolled as per July 2010.”
New: “According to the cohort-based, nation-wide design we aim to inform every RRMS patient in the Netherlands who starts GA treatment. Neurologists and MS-nurses in 15 MS-dedicated hospitals, evenly distributed over the country, actively recruit patients. In addition, the nurses, who teach patients to self-inject inform them of the possibility of participating. … Recruitment is on schedule, with 119 patients being enrolled as per October 2010.”

Last paragraph.

2nd sentence has been changed:
Old: “The nation-wide cohort design makes that results will be applicable to Dutch RRMS patients.”
New: “The nation-wide cohort design makes sure that results will be applicable to Dutch RRMS patients.”
patients.”

Authors’ information

1st sentence has been changed:
Old:  “Peter Joseph Jongen is neurologist and founding director of the MS4 Research Institute, Nijmegen, the Netherlands.”
New:  “Peter Joseph Jongen is a neurologist and the founding director of the MS4 Research Institute, Nijmegen, the Netherlands.”

Funding

2nd sentence has been changed:
Old:  “To this end MS4 Research Institute receives an unrestricted grant from ...”
New:  “To this end the MS4 Research Institute receives an unrestricted grant from ...”

Acknowledgements

Text has been revised:
Old:  “We thank ... ... the study helpdesk, and Elly Beeren and colleague nurses for their invaluable role in informing patients.”
New:  “We thank ... ... the study helpdesk, Elly Beeren and colleague nurses for their invaluable role in informing patients, and Thomas Harrison for critically reading the manuscript.”

References

Reference 3 has been added:

The numbers of the following references have been changed accordingly.

Appendices

Appendix A has been added: LIST OF QUESTIONS OF THE STUDY
Appendix B has been added: DUTCH ADHERENCE QUESTIONNAIRE-90 (DAQ-90)
Appendic C is former ‘Appendix’: FLOW CHART OF ASSESSMENTS

We hope that we have adequately addressed the points raised by reviewer.

Kind regards,
Dr. Peter Joseph Jongen
2010-12-17