

**Official title: Sequential natalizumab – alemtuzumab therapy in patients with relapsing forms of multiple sclerosis (SUPPRESS)**

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**Sequential natalizumab – alemtuzumab therapy in patients with relapsing forms of multiple sclerosis (SUPPRESS)**

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## Protocol Synopsis

### Title of study:

Sequential natalizumab – alemtuzumab therapy Trial (SUPPRESS)

### Study purpose:

The purpose of this study is to determine if a sequential combination therapy of natalizumab and alemtuzumab induces peripheral tolerance and reduces the annualized relapse rate (ARR) in patients with relapsing-remitting multiple sclerosis (RRMS).

### Primary objective:

To determine if treatment with alemtuzumab after natalizumab reduces the ARR in patients with RRMS. The goal of this trial is to establish a disease-free state over a 24 months period in patients who received the natalizumab-alemtuzumab sequential therapy.

### Secondary objectives:

To evaluate the T cell, B cell, and autoreactivity characteristics of immune cells in RRMS patients before and after alemtuzumab treatment.

### Population:

Relapsing MS patients will be recruited from four different sites: UT Southwestern Medical Center (UTSW), Dallas VA Medical Center, Neurology Center of San Antonio, and the Multiple Sclerosis Treatment Center of Dallas.

### Inclusion criteria:

Patients who meet all of the following inclusion criteria will be eligible for enrollment in the study:

1. Age between 18 and 60 years, inclusive.
2. Diagnosis of relapsing forms of MS using revised McDonald Criteria<sup>1</sup>.
3. EDSS 0 - 6.5 (Functional system changes in cerebral (or mental) functions and in bowel and bladder functions not used in determining EDSS for protocol eligibility).
4. Has had a minimum of 12 monthly doses of continuous natalizumab therapy (300 mg/d), either regular or extended dosing.
5. Understands and gives informed consent.

**Exclusion criteria:**

Patients who meet any of the following exclusion criteria will not be eligible for enrollment in the study:

1. Natalizumab failure based on clinician's discretion.
2. Has progressive MS.
3. A diagnosis of PML.
4. Known hypersensitivity to alemtuzumab.
5. Any prior exposure to alemtuzumab.
6. Initiation of new immunosuppressant treatment after the subject becomes protocol-eligible (except for corticosteroids) or enrollment in a concurrent trial with immuno-active pharmacotherapies.
7. Uncontrolled diabetes mellitus defined as HbA1c > 8% and/or requiring intensive management.
8. History of cytopenia consistent with the diagnosis of myelodysplastic syndrome.
9. Clinically significant autoimmune disease other than MS that may affect the CNS, including neuromyelitis optica (NMO), systemic lupus erythematosus (SLE, or Behcet disease.
10. Active hepatitis B or C infection or evidence of cirrhosis.
11. Human immunodeficiency virus (HIV) positivity.
12. Uncontrolled viral, fungal, or bacterial infection.
13. Positive pregnancy test or inability or unwillingness to use effective means of birth control. Effective birth control is defined as:
  - a. Refraining from all acts of vaginal intercourse (abstinence),
  - b. Consistent use of birth control pills,
  - c. Tubal sterilization or male partner who has undergone vasectomy
  - d. Placement of intrauterine device
  - e. Use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.
14. Presence of metallic objects implanted in the body that would preclude the ability of the subject to safely have MRI exams.
15. Psychiatric illness, mental deficiency, or cognitive dysfunction making compliance with treatment or informed consent impossible.

**Investigational drug:**

Alemtuzumab

**Reference therapy:**

None. This is a single arm trial.

**Study design:**

This is an open label, multicenter, efficacy pilot study.

**Key Efficacy Assessments:**

1. The primary endpoint is the annualized relapse rate (ARR) from the time of cessation of natalizumab treatment.
2. A key secondary endpoint is freedom of relapse at 12 months.
3. A key secondary endpoint is the number of new/enlarging T2 lesions on magnetic resonance imaging (MRI).
4. A secondary endpoint is the number of gadolinium (Gd)-enhancing lesions on MRI.
5. An exploratory endpoint is the Expanded Disability Status Scale (EDSS).
6. An exploratory endpoint is retinal nerve fiber layer (RNFL) thickness assessment by optic coherence tomography (OCT).
7. An exploratory outcome will be the assessment of quality of life (QoL) measures by a pre-defined, self-administered testing battery.

**Key Safety Assessments**

1. To minimize the risk of transitioning MS patients from natalizumab to alemtuzumab who already have progressive multifocal leukoencephalopathy (PML), all enrolled patients will undergo a brain MRI within 14 days prior to receiving alemtuzumab.
2. To minimize the risk of herpetic infections while on alemtuzumab, anti-viral prophylaxis for herpetic viral infections should be administered on the first day of each treatment course and continued for a minimum of 2 months following treatment, or until the CD4 lymphocyte count is  $\geq 200$  cells/microliter, whichever occurs later.
3. There may be an exaggerated cytokine response in some patients. Thus, patients will be monitored and management based on the treating physician's best judgement from the final dose of natalizumab to the end of the first course of alemtuzumab treatment.
4. Each relapse will be treated with pulse corticosteroids as per best clinical judgment.



5. Two or more confirmed clinical relapses during the trial would allow rescue therapy as per best clinical judgment.
6. Five or more Gd<sup>+</sup> lesions at the 6 month MRI assessment over the baseline assessment will result in a follow-up scan after 60 days and will count as one relapse. Should a confirmed clinical relapse occur within the 60 day period, it will still count as a single relapse.
7. Sensitivity analyses will be conducted using intent-to-treat (ITT) principles for efficacy to ensure that safety considerations and withdrawals have not altered results.
8. Patients who withdraw from study treatment will be observed as mandated by REMS.

**Data analysis:**

The sample size of 40 patients was chosen to obtain a clinically meaningful result as defined by neurologists.

All outcome measures at 12 months prior to natalizumab treatment, on natalizumab treatment, and on alemtuzumab will be assessed and compared. We will control secondary and exploratory endpoints for multiple comparisons by testing sequentially the proportion of relapse-free patients, EDSS change, and T2-hyperintense lesion volume change.

We will analyze the proportion of patients who are relapse-free with a proportional hazards model. We will analyze changes from baseline in EDSS at the pre-defined time points with a mixed model for repeated measures. We will make treatment comparisons of all available 3 month assessments with a non-parametric test for repeated measures. We will analyze changes in T2-hyperintense lesion volume, and RNFL thickness with a ranked ANCOVA model. We will analyze proportions of patients with new or enlarged T2-hyperintense or Gd<sup>+</sup> lesions with logic regression.

## 1 Background

Multiple sclerosis is an inflammatory disorder of the central nervous system (CNS). A pathological hallmark of this disorder is the infiltration of immune-competent leukocytes into the brain and spinal cord. Natalizumab is a humanized recombinant monoclonal antibody that binds to the alpha ( $\alpha$ )4 chain of the integrin very late activation antigen (VLA)-4. Natalizumab is currently considered the most effective approved therapy in reducing clinical and paraclinical MS disease activity. Our group has made several novel observations with regard to the pharmacodynamic properties of natalizumab: (1) Compared to controls, natalizumab-treated MS patients had significantly fewer white blood cells, CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, CD19<sup>+</sup> B cells, and CD138<sup>+</sup> plasma cells in cerebrospinal fluid (CSF); (2) CD4<sup>+</sup>:CD8<sup>+</sup> ratios in the CSF of MS patients treated with natalizumab were reversed, and not statistically different from those in HIV-infected controls; (3) elevated serum anti-Human Herpesvirus (HHV)-6 IgG, and HHV-6A DNA were detected in the CSF of a subset of patients on natalizumab therapy. In summary, these data indicate that natalizumab therapy substantially alters the composition of immune-competent cells in the CSF of patients with MS.

Since its first approval for patients with MS in November 2004, more than 200 patients treated with natalizumab have been diagnosed with PML, a CNS infection with the polyomavirus JC. PML is typically observed in the setting of prolonged and severe immunosuppression, most commonly in patients infected with HIV. Natalizumab is currently administered monthly as monotherapy to approximately 100,000 patients with MS, and treatment is recommended to continue indefinitely without treatment interruptions.

### 1.1 Biological rationale for proposed trial

Natalizumab is a humanized recombinant monoclonal antibody against alpha4-integrin that was first approved in November 2004 for patients with relapsing forms of multiple sclerosis (MS) based on the results of two phase III trials (1, 2). Natalizumab blocks the egress of leukocytes from the peripheral blood into the CNS. In the short term, the therapeutic benefits are likely due to its effect on lymphocytes as shown by our laboratory and other investigators (3-6). Long-term, the number of myeloid cells that serve as antigen presenting cells (APC) in perivascular spaces is likely also substantially reduced (7). Despite its tremendous efficacy, there are two observations that have limited the use of natalizumab in patients with MS.

### 1.1.1 Opportunistic infections

Approximately 1:250 patients with MS under natalizumab will develop progressive multifocal leukoencephalitis (PML), and infection with the human polyomavirus JC. This potential side effect has substantially limited the use of an effective therapy. An algorithm was recently developed to estimate PML incidence in MS patients considering or receiving natalizumab based on duration of natalizumab treatment (1-24 or 25-48 months), prior immunosuppressant use (yes or no), and anti-JCV antibody status (positive or negative) (8). Based upon the two established risk factors for PML, PML risk was lowest in patients treated with natalizumab for 1-24 months without prior immunosuppressant use, (0.19 cases per 1000 patients), and greatest in those with both risk factors, natalizumab treatment for 25-48 months and prior immunosuppressant use (4.3 cases per 1000). When anti-JCV antibody status was included as a third risk factor, PML risk was lowest in patients who were anti-JCV antibody negative (0.11 per 1000), and highest in patients with all three factors, (11 per 1000). The most recent data indicate that MS patients on natalizumab with all three risk factors appear have a risk of 1:44 to develop PML (9, 10).

### 1.1.2 Disease-reactivation after cessation of natalizumab therapy

While natalizumab is a tremendously effective therapy, disease activity returns 3 to 6 months after treatment discontinuation in a predictable manner. The best data in this regard were generated by O'Connor et al, who analyzed clinical relapses in 1,866 patients, and gadolinium (Gd)-enhancing lesions in 341 patients from the AFFIRM, SENTINEL, and GLANCE studies of natalizumab, and their respective safety extension studies (11). Annualized relapse rates and Gd lesions both increased shortly after natalizumab interruption and peaked between 4 and 7 months. A consistent return of disease activity was observed regardless of overall natalizumab exposure, whether or not patients received alternative MS therapies, and in patients with highly active MS disease.

The return of disease activity may be explained by its biological activities. Leukocytes are sequestered out of the CNS into the peripheral blood, where they assume a more inflammatory phenotype. Krumbholz et al. demonstrated that natalizumab therapy increased CD19<sup>+</sup> mature B cells in peripheral blood 2-3-fold more than that of other lymphocytes and monocytes compared to pre-treatment levels (12). The increase of immature CD19<sup>+</sup>CD10<sup>+</sup> pre-B cells in peripheral blood was 7.4-fold. This pattern remained stable during treatment for up to 16 months. Kivisakk et al showed that the frequency of CD4<sup>+</sup> T cells producing interferon gamma (IFN $\gamma$ ), tumor necrosis factor, and interleukin (IL)-17 upon anti-CD3 stimulation increased 6 months after initiation of natalizumab treatment and remained elevated throughout

the follow-up (13). The frequency of CD4<sup>+</sup> T cells expressing CD25, HLA-DR, and CCR6 *ex vivo* was increased at one or more time points during treatment. Our lab showed in a cohort of 23 patients that return of clinical disease activity in patients who stopped taking natalizumab correlated with the re-constitution of CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells in the cerebrospinal fluid (5).

## **1.2 Alemtuzumab in RRMS**

Alemtuzumab is a humanized monoclonal therapeutic antibody that rapidly depletes CD52<sup>+</sup> cells. Alemtuzumab is effective in ameliorating MS disease activity. In the CARE-MS I phase III trial, a 55 % relapse rate reduction with alemtuzumab (12 mg/d) over interferon-beta (IFN $\beta$ ) was observed for alemtuzumab treated patients after 24 months (14). Significantly more (78 %) alemtuzumab treated patients remained relapse-free at month 24 compared with 59 % of IFN $\beta$ 1a-treated patients, which equates to a 55 % risk reduction. In the CARE-MS II phase III trial a 49 % reduction in relapse rate was observed in patients treated with alemtuzumab (12 mg/d) compared with those treated with IFN $\beta$ -1a over the two years (15). Significantly more alemtuzumab treated patients remained relapse-free at month 24 compared with IFN $\beta$ -1a treated patients. While these data provide a rationale for the use of alemtuzumab in patients with MS, many experts considered the efficacy of this agent in the two phase III studies as perhaps somewhat disappointing. Again, its biological effects may explain this incomplete treatment effect of alemtuzumab. Mainly, there is currently no evidence that alemtuzumab has any biological effect in the CNS. Thus, the number and function of autoimmune-prone lymphocytes and pre-inflammatory myeloid cells that reside in the brain and spinal cord is not reduced.

### **1.2.1 Immune-reconstitution after alemtuzumab therapy in MS**

MS is considered an autoimmune disorder of the CNS. However, an autoantigen has not been identified. Thus, the creation of peripheral tolerance will best be inferred by the disease status.

Recent data from an Immune Tolerance Network (ITN) trial that tested autologous hematopoietic stem cell transplant (HSCT) in patients with very aggressive MS (HALT trial) showed that the reconstitution of the T cell receptor repertoire predicts treatment responses:

- Patients who failed treatment had a significantly less diverse TCR (CD4<sup>+</sup> and CD8<sup>+</sup>) at 2 months post-transplant than “others”
- Treatment effectively reduced dominant baseline CD4<sup>+</sup> TCR clones, did not reduce dominant CD8 TCR clones
- Patients who recovered CD8<sup>+</sup> T cells at year 1 had a less diverse CD8<sup>+</sup> TCR repertoire
- The reconstituted CD8<sup>+</sup> T cell repertoire was dominated by large clonal expansions

- There was up to a 100% “renewal” (ablated→new) of the CD4<sup>+</sup> T cell repertoire; there was less renewal within the CD8<sup>+</sup> T cell repertoire
- Treatment resulted in a “new” Top 100 CD4<sup>+</sup> TCR repertoire at 2 months post-transplant

Immune-reconstitution after alemtuzumab therapy is very similar to that after autologous HSCT. This is perhaps not surprising, as in both treatment paradigms there is almost a complete re-constitution of the lymphocyte compartment that is driven by autologous CD34<sup>+</sup> bone marrow cells. As stated above, alemtuzumab targets CD52, which is a 12-amino-acid glycosylated GPI-bound membrane protein (16, 17). CD52 is expressed on a number of cells derived from the lympho-monocytic cell lineage, including T and B cells, natural killer (NK) cells, dendritic cells and most monocytes and macrophages. By contrast, neutrophils and precursors cells of the hematopoietic lineage do not express CD52 (18-20). The exact biological function of CD52 is not fully understood; CD52 binding may induce T cell activation, and CD52 may be a stimulatory co-factor required for regulatory T cells (Treg) (18, 19). Alemtuzumab depletes CD52<sup>+</sup> cells through ADCC and likely also through activation of the complement cascade (20-23). Cellular depletion is initiated rapidly resulting in almost complete disappearance of CD52<sup>+</sup> cells from the circulation shortly after alemtuzumab administration. Experimentally, complement-mediated cell lysis of leukemic B cells occurs within 1-4 hours after addition of alemtuzumab *in vitro* (24). Lympho-monocytic cells in the periphery are eventually repopulated from pools of stem cells and certain progenitor cells that do not constitutively express CD52. Monocytes and B cells reach pre-alemtuzumab levels in the peripheral blood approximately three to six months after treatment, with B cell levels exceeding baseline levels by 124-165% (21, 22, 25, 26). T cells repopulate considerably slower; CD8<sup>+</sup> T cells reach baseline levels only after a median of 30 months, and CD4<sup>+</sup> T cells after a median of 61 months (21). The lower limits of normal for CD4<sup>+</sup> and CD8<sup>+</sup> T cells are reached earlier with medians of 12 and 11 months, respectively (27). It is particularly noteworthy that Tregs repopulate distinctly before CD4<sup>+</sup> and CD8<sup>+</sup> T cells, resulting in their specific enrichment in the peripheral blood (21, 26).

### **1.3 A potentiation of efficacy through sequential natalizumab – alemtuzumab therapy**

Natalizumab treatment sequesters leukocytes out of the CNS into the peripheral blood. Immediate sequential alemtuzumab therapy will deplete these cells more completely than alemtuzumab monotherapy, and prevent reactivation of disease activity previously treated with natalizumab. Thus, we hypothesize that sequential natalizumab – alemtuzumab therapy will prevent disease activation after cessation of natalizumab, and will provide sustained disease

remission in many patients. The goal of this trial is to establish a disease-free state over a 24 months period in patients who received the natalizumab-alemtuzumab sequential therapy.

## 2 Study purpose

The purpose of this study is to determine if a sequential combination therapy of natalizumab and alemtuzumab induces peripheral tolerance and reduces the AAR in patients with RRMS.

## 3 Study objectives

### 3.1 Primary objective

To determine if treatment with alemtuzumab after natalizumab maintains or reduces the ARR in patients with RRMS. The goal of this trial is to establish a disease-free state over a 24 months period in patients who received the natalizumab-alemtuzumab sequential therapy.

### 3.2 Secondary objectives

To evaluate the T cell, B cell, and autoreactivity characteristics of immune cells in RRMS patients before and after alemtuzumab treatment.

## 4 Study Design

This is a one arm, open-label, multicenter, efficacy pilot study of sequential natalizumab-alemtuzumab treatment in RRMS patients.

### 4.1 Study endpoints

The primary endpoint is the annualized relapse rate (ARR) from the time of cessation of natalizumab treatment.

Key secondary endpoints are freedom from relapse at 12 months and the number of new/enlarging T2 lesions on MRI.

Other secondary endpoints are: Number of Gd-enhancing lesions on MRI.

Other Exploratory endpoints:

1. EDSS.
2. RNFL thickness assessment by OCT.
3. Assessment of quality of life (QoL) measures by a pre-defined, self-administered testing battery.

## 5 Population

The target population for this study are RRMS patients nearing the end of their natalizumab treatment regimen. Participants will be recruited from four different sites: UT Southwestern Medical Center (UTSW), Dallas VA Medical Center, the Multiple Sclerosis Treatment Center of Dallas, and the Neurology Center of San Antonio. Recruitment will occur on a competitive basis.

### 5.1 Inclusion/exclusion criteria

#### 5.1.1 Inclusion criteria

Patients who meet all of the following inclusion criteria will be eligible for enrollment in the study:

1. Age between 18 and 60 years, inclusive.
2. Diagnosis of relapsing forms of MS using revised McDonald Criteria<sup>1</sup>.
3. EDSS 0 - 6.5 (note: functional system changes in cerebral (or mental) functions and in bowel and bladder functions not used in determining EDSS for protocol eligibility).
4. Has had a minimum of 12 monthly doses of continuous natalizumab therapy (300 mg/d), either regular or extended dosing.
5. Understands English, and gives informed consent.

#### 5.1.2 Exclusion criteria

Patients who meet any of the following exclusion criteria will not be eligible for enrollment in the study:

1. Natalizumab failure based on clinician's discretion.
2. Any prior exposure to alemtuzumab.
3. Progressive MS.
4. A diagnosis of PML.
5. Known hypersensitivity to alemtuzumab.
6. Initiation of new immunosuppressant treatment after the subject becomes protocol-eligible (except for corticosteroids) or enrollment in a concurrent trial with immuno-active pharmacotherapies.
7. Uncontrolled diabetes mellitus defined as HbA1c > 8% and/or requiring intensive management.
8. History of cytopenia consistent with the diagnosis of myelodysplastic syndrome.
9. Clinically significant autoimmune disease other than MS that may affect the

CNS, including neuromyelitis optica (NMO), systemic lupus erythematosus (SLE), or Behcet disease.

10. Active hepatitis B or C infection or evidence of cirrhosis.
11. HIV positivity.
12. Uncontrolled viral, fungal, or bacterial infection.
13. Positive pregnancy test or inability or unwillingness to use effective means of birth control. Effective birth control is defined as:
  - a. Refraining from all acts of vaginal intercourse (abstinence),
  - b. Consistent use of birth control pills,
  - c. Tubal sterilization or male partner who has undergone vasectomy
  - d. Placement of intrauterine device
  - e. Use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.
14. Presence of metallic objects implanted in the body that would preclude the ability of the subject to safely have MRI exams.
15. Psychiatric illness, mental deficiency, or cognitive dysfunction making compliance with treatment or informed consent impossible.

## 5.2 Consent

The informed consent form is a method of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before participating in the study, taking study drug, and/or undergoing any study-specific procedures.

The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect a participants' participation in the trial.

A copy of the informed consent form will be given to a prospective participant for review. The attending physician, in the presence of a witness, will review the consent form and answer questions. The participant will be informed that their participation is voluntary and that they may withdraw from the study at any time, for any reason.



### **5.3 Privacy and confidentiality**

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers, rather than names, will be used to collect, store, and report participant information.

### **5.4 Deviations**

Any protocol deviations that impact patient safety will be reported within 7 days to the principal investigator and the IRB. Deviations from the inclusion and exclusion criteria will be minimized via eligibility criteria checks prior to initiation of alemtuzumab therapy.

### **5.5 Premature patient withdrawal**

Patients may be withdrawn from the study for any of the following reasons:

- Withdrawal of the informed consent
- Lost to follow-up
- Withdrawal at the investigator's discretion

Patients should be withdrawn at any time if the investigator concludes that it would be in the patients' best interest for any reason. Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety. If premature patient withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on a CRF. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. In the case of death, a patient will be considered withdrawn. Patients who are prematurely withdrawn from the study will not be replaced.

## 6. Treatment

### 6.1 Patient numbering

Patients will be assigned a unique study number upon signing the informed consent form (PID#1). The PID#1 is used during screening. The numbering will be designated based on the recruitment site and will follow the convention: ccc-pppp, where ccc represents center and pppp participant. The PID#1 is numeric for the center and alphanumeric for the participant. Patients will retain their PID#1 regardless of whether they enter the treatment arm of the trial or subsequently withdrawal. PID#2 will be assigned at randomization and has the form ccc-ppppp. PID#2 is numeric for the center and 5 digit numeric field for the participant. Assignment of PID#1 will be performed by the study data management system provided that an informed consent was signed and that screening evaluations can commence. Assignment of PID#2 will be performed by the study data management system at the time of study initiation.

### 6.2 Investigational drug

Alemtuzumab (Lemtrada<sup>®</sup>) will be administered at a dose of 12 mg/d by intravenous (i.v.) infusion every day for five consecutive days within 14 days of the last dose of natalizumab. After 12 months, patients will be treated with a second course of alemtuzumab and they will be followed open-label for another 12 months per standard of care. Outside the scope of this study, the intention is to follow all study participants in participating centers long-term, and to record disease activity and treatment response.

### 6.3 Treatment arms

There is only one treatment arm in the trial, alemtuzumab treatment.

### 6.4 Treating the patient

All study participants will use commercial drug. All products will be labeled appropriately.

**Year One:** Alemtuzumab 12 mg (1.2 ml) in 100 ml of sterile 0.9% sodium chloride (or 5% dextrose in water) IV Infusion via pump over a minimum of four hours daily for five days to be given within eight hours after dilution. Gently invert the bag to mix the solution.

**Year Two:** Alemtuzumab 12 mg (1.2 ml) in 100 ml of sterile 0.9% sodium chloride (or 5% dextrose in water) IV Infusion via pump over a minimum of four hours daily for three days to be given within eight hours after dilution. Gently invert the bag to mix the solution.

#### **6.4.1 Baseline lab studies before starting alemtuzumab infusion**

The following labs will be completed within 30 days of infusion:

- Complete blood counts (CBC) with differential
- Comprehensive metabolic panel (CMP), or only serum creatinine
- CD4<sup>+</sup> T cell counts (optional)
- Complete urinalysis with cell count
- Thyroid function test (TSH)
- Free T4 (optional)
- Other optional labs for endemic areas or patients-specific include human immunodeficiency virus (HIV), hepatitis B (HBcAb and HBsAg), hepatitis C virus antibody, Varicella Zoster virus (VZV), TB Quantiferon Gold, and human papilloma virus (HPV) screening.

If all hepatitis B and C studies are negative, alemtuzumab can be administered. If laboratory assessments are completed more than 30 days before infusion, the only blood work that needs to be re-drawn is the CBC with differential, serum creatinine, TSH, and urinalysis with cell count. Perform baseline and yearly skin examinations to monitor for melanoma and annual HPV screening is recommended for female patients.

#### **6.4.2 Prior to alemtuzumab infusion**

##### **6.4.2.1 Forms to complete** (see Appendix 1)

- Lemtrada® Services Form - to enroll patients in central laboratory program
- Lemtrada® REMS Patient Enrollment Form
- Lemtrada® Prescription Ordering Form
- EMSI Request for Services Form- for traveling phlebotomist

##### **6.4.2.2 Laboratory assessments and procedures**

- CBC with differential
- CMP
- TSH

- MRI Brain W & W/O contrast (baseline)
- VZV antibodies (as needed with first infusion only)
- Urinalysis
- Tuberculosis testing (as indicated)
- A dermatology referral to screen for any suspicious lesions is recommended in the alemtuzumab package insert, but not absolutely required.
- Appointment for gynecology exam and pap smear for women to rule out active HPV infection is recommended in the alemtuzumab package insert, but not absolutely required.
- CD4<sup>+</sup> T cell counts (optional)
- Hepatitis screening blood tests

#### **6.4.2.3 Preparing the participant**

- Educate patients regarding the mild-to-moderate infusion-associated reactions that can occur commonly with alemtuzumab
- Remind patients to bring all their routine medications, including inhalers, antihypertensive, anti-diabetes, etc.
- Solumedrol 1000 mg in 100 ml of sterile 0.9% sodium chloride IV infusion via pump over 60 minutes daily for three days, starting immediately prior to the initial alemtuzumab infusion.
- Solumedrol 250 mg in 100 ml of sterile 0.9% sodium chloride IV infusion via pump over 30 minutes on day 4 and 5.

#### **6.4.2.3.1 Prescriptions**

- Acyclovir 200 mg 1 tab BID #60
- Hydroxyzine 25 mg, 1-2 tab every 6 hours as needed for itching/rash
- Zolpidem 5 mg, 1-2 tab every night as needed for sleep (due to steroid)
- Medrol® Dose Pack (1) – take as directed; if patient develops a diffuse rash after the alemtuzumab infusion

#### **6.4.2.4 Day before infusion**

- Patients will be encouraged hydrate with several liters of water.

- Ascertain that the patients have transportation to and from the clinic arranged for everyday of the alemtuzumab infusions.
- Patients will be instructed to take cetirizine 10 mg & ranitidine 150 mg (start taking 3-5 days prior to infusion). These medications should be continued after the infusion for 30 days.
- Instruct the patient to rest. Specifically, patients should pack a travel bag for the time of the infusion (food, snacks, water bottle, entertainment, blanket/sweatshirt) – it is a 4-6 hours infusion plus 2 hours mandatory post-infusion monitoring
- Have patient avoid these foods while on treatment:
  - Sushi
  - Raw Meat
  - Wash all fruits and vegetables well
  - Unpasteurized milk or foods
  - Ready to eat foods that have been unrefrigerated more than a 1 day

#### **6.4.3 Dispensing study drug**

Study drug will be dispensed by the pharmacy at each study site. At each study visit, study medication will be administered by medical/research staff.

##### **6.4.3.1 Days of infusion**

- Patients will be instructed to bring their packed bags (please see above), and to wear layered, comfortable clothes.
- Patients will be instructed to take cetirizine 10 mg & ranitidine 150 mg and to start acyclovir 200mg before arrival (or replacement medications as needed).
- Patients will be asked to arrive early to the infusion clinic.
- Patients will frequently be encouraged to stay hydrated before, during, and after their alemtuzumab treatments.
- Patients will also be asked to adhere to a low-sodium diet to prevent corticosteroid-induced hypertension and peripheral edema.
- In addition, patients will be requested to avoid high sugar foods to prevent corticosteroid-induced hyperglycemia.

- Prophylactic use of insomnia medication will be offered (please see above).
- Patient will be monitored for at least 2 hours post-infusion every day of treatment.

#### **6.4.3.2 Preparation for nurse on days of infusion**

- A pregnancy test will be performed in all female patients.
- 1 gram of methylprednisolone will be infused IV over 60 minutes during the initial three days of treatment. If the dosage is split three days and then two days (such as M/T/W then next M/T), then infuse 125-250 mg methylprednisolone I IV on day four and five.
- Five days of alemtuzumab needs to be infused within a 30 day period the 12 months of treatment.
- Check blood pressure, pulse, and body temperature every hour during the infusions, and 2 hours after the infusions.
- Administer IV or oral diphenhydramine 25-50mg every 8 hours as needed for persistent rash / hives / itching. Administer acetaminophen 500-1000 mg every 4-6 hours as needed for fever / headaches / flulike symptoms.
- Cover alemtuzumab with bag to protect from light exposure.
- Alemtuzumab is to be infused over four hours at a rate of 25ml/hour.
- Do not shake vial prior to use.
- Do not freeze alemtuzumab. Do not use alemtuzumab if vial has been frozen.

#### **6.4.3.3 Monitoring parameters**

- Monitor vital signs prior to infusion and every hour for at least 6 hours
- For signs/symptoms of a hypersensitivity reactions (urticarial, dizziness, fever, rash, rigors, pruritus, flushing, hypotension, chest pain, dyspnea), slow or stop medication infusion, maintain IV access, notify physician. Follow reaction protocols.

#### **6.4.4 Post-Infusion**

- Observe and monitor patient for reactions 2 hours post-infusion.

- During the two hours of observation, use extra hydration of 100 ml bag (sterile sodium chloride or 5% dextrose in water) to keep IV open and infuse all the alemtuzumab out of the tubing.
- Send patient home with over the counter prescriptions for additional anti-histamine and anti-pyretic in case of rash, headache or fever after leaving the clinic.
- Infusion-associated reactions during the first alemtuzumab treatment cycle typically are not allergic or anaphylactic in etiology. Thus, patients can be re-challenged once the initial reaction subsides, often with additional pre-medications. To temporarily stop or slow down the infusion rate will often resolve or minimize these adverse reactions.

#### 6.4.5 Reaction treatments

- If patient experiences bronchospasm: Administer B-adrenergic agonist inhaler
- If anaphylactic reaction occurs:
  - Administer epinephrine 0.3 mg IV or IM or Epi-Pen; epinephrine 1:1000 (1 ml): Give 0.2-0.5 ml SQ, start with lower dose and may repeat in 3-5 minutes
  - Diphenhydramine 50 mg (1 ml) - administer 50 mg in 100 ml 0.9% sodium chloride IV infusion via pump over 10-15 minutes
  - Sodium chloride 0.9% 500 ml infuse IV at a rate of 50 ml/hour
- If bradycardia or hypotension occurs:
  - Stop infusion, or reduce infusion rate
  - Normal saline bolus of 500 ml IV
- For severe bradycardia: Atropine 0.5 mg IV push, and may repeat up to a total dose of 3 mg. Epinephrine 2-10 µg/kg/minute can be used if atropine not effective
- If fever occurs: Administer acetaminophen 500-1000 mg PO PRN up to a total daily dose of 3 g per 24 hours.
- If hypertension occurs: Administer clonidine 0.1 mg PO, if BP is persistently > 180/110 mmHG. Administer an additional 0.1 mg if no success with the first dose.

#### **6.4.6 Monthly/quarterly labs and procedures (all covered by Genzyme)**

- CBC with differential
- CD4 counts (optional)
- Serum creatinine level
- Complete urinalysis
- TSH (every 3 months)
- Patient to F/U with physician 3 months, 6 months, and every 6 months thereafter (alemtuzumab patient status form to be filled out every 6 months) MS 1:1 will remind you every 6 months.

#### **6.4.7 Annual labs and procedures**

- Complete blood count with differential
- Comprehensive metabolic panel, or serum creatinine
- TSH
- Complete urinalysis
- A dermatology assessment is recommended in the alemtuzumab package insert, but not absolutely required.
- Appointment with primary MD
- Appointment for gynecological examination and PAP smear for female patients is recommended in the alemtuzumab package insert, but not absolutely required.

#### **6.4.8 Treatment of MS Relapses**

Each relapse will be treated with pulse corticosteroids as per best clinical judgment.

Two or more confirmed clinical relapses during the trial would allow natalizumab re-initiation as rescue therapy or other therapies as per best clinical judgment. Five or more Gd<sup>+</sup> lesions at the 6 month MRI assessment over the baseline assessment will result in a follow-up scan after 60 days and will count as one relapse. Should a confirmed clinical relapse occur within the 60 day period, it will still count as a single relapse.

#### **6.4.9 Other concomitant treatment**

All the concomitant medications used by participants will be recorded at each study visit on the relevant CRFs. The concomitant medications will be analyzed in regard to the use of corticosteroids, MS modifying therapies, and anti-inflammatory medications.

#### **6.4.10 Unexpected adverse event**

An adverse event is considered unexpected when the nature (specificity) or severity of the event is not consistent with applicable product information, such as safety information provided in the



package insert, the investigational plan, the investigator's brochure, the protocol, or the informed consent document.

#### **6.4.11 Grading of adverse event**

Toxicity grades are assigned by the study site to indicate the severity of adverse events occurring in study participants. The principal investigator (PI) has adopted the use of the National Cancer Institute's manual *Common Terminology Criteria for Adverse Events v3.0* (CTCAE; published June 10, 2003) for application in adverse event reporting. The purpose of using the CTCAE system is to provide a standard language to describe toxicities, to facilitate tabulation and analysis of the data, and to facilitate the assessment of the clinical significance of all adverse events. The CTCAE provides the following grades and descriptions in the CTCAE manual (v3.0). Adverse events should be recorded and graded 1 to 5 according to the CTCAE grades provided below:

Grade 1 = Mild adverse event

Grade 2 = Moderate adverse event

Grade 3 = Severe and undesirable adverse event

Grade 4 = Life-threatening or disabling adverse event

Grade 5 = Death

Note: In contrast to the CTCAE guidelines provided the National Cancer Institute's *Common Terminology Criteria for Adverse Events v3.0* (published June 10, 2003) all adverse events are to be reported and graded whether or not they are related to disease progression or treatment.

#### **6.4.12 Relationship to study treatment**

The relationship or attribution between an adverse event and an investigational product is determined by the site investigator and recorded on the appropriate case report form and/or SAE reporting form. The Common Terminology Criteria for Adverse Events (CTCAE) provides the following descriptors and definitions (one category classified as unrelated [Code 1] and 4 categories classified as related [Codes 2-5]) for assigning an attribution to each adverse event (for most recent update of terminology see [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)).

The investigator's determination of drug-relatedness (attribution) for each adverse event should be recorded in the source documentation.

#### **6.4.13 Serious adverse event reporting**

The following process for reporting a serious adverse event will ensure appropriate compliance with the ICH guidelines (<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>).

Serious adverse event identification and determination of reporting timeline:

When an investigator identifies a serious adverse event (as defined above), he or she must notify the principal investigator, the IRB, and Genzyme pharmacovigilance. In addition to telephone reporting, these events must be entered on the Serious Adverse Event Form (MedWatch).

#### **6.4.14 Study drug discontinuation**

At the initial clinic visit, study patients will be made aware of potential side effects of alemtuzumab. At each patient visit, patients will be inquired about any of these side effects. Should it be felt by the patient and the examining physician that these side effects warrant discontinuation of study drug, the offending therapeutic intervention will be terminated.

#### **6.4.15 Pregnancy (SAE reporting requirements)**

Any pregnancy that occurs during a clinical study with an investigational drug must be reported as an SAE for tracking purposes only. All pregnancies that are identified during this study need to be followed to conclusion and the outcome reported. Female participants should immediately inform the investigator of pregnancies and future treatment options should be discussed.

The site investigator should report all pregnancies within 24 hours (as described above in SAE Reporting) using the SAE form. The site investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy, and a follow-up SAE reporting form should be submitted detailing the outcome.

#### **6.4.16 Study completion and post-study treatment**

Outside the scope of this study, the intention is to follow all study participants in participating centers long-term, and to record disease activity and treatment response.

#### **6.4.17 Role of key site personnel**

The treating physician and other designated qualified personnel will see the participant. The physician will perform all neurological and non-neurological assessments, and will have access to laboratory results.

#### **6.4.18 Statement of compliance**

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements.

Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate ethics review committee or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are implemented.

## 7 Visit schedule and assessments

### 7.1 Study outline

Visit	1	2	3	4	5	6	7	8	9
Month	Screening -1	Baseline -15	0 - 0.5	3	6	9	12	18	24
Inclusion/exclusion	x	x							
Demographic information	x								
Informed consent	x								
Medical history	x								
Concomitant meds	x	x		x	x	x	x	x	x
Physical exam	x			x		x			x
Vitals	x			x	x	x	x	x	x
EDSS	x				x		x		x
Alemtuzumab treatment (5 consecutive days, 12 mg/d)			x				x		
Columbia Suicide Severity Rating Scale	x			x	x	x	x	x	x
QoL	x				x		x		x
Neurological examination	x			x	x	x	x		x
Blood draw for mechanistic studies	x			x	x	x	x		x
Laboratory assessments for safety monitoring*	x	x							
Pregnancy test		x							
OCT	x				x		x		x
Visual acuity	x				x		x		x
MRI	x				x		x		x
Adverse events	x	x		x	x	x	x	x	x

*\*Laboratory assessments for safety monitoring will be drawn monthly for until 48 months after the last dose of alemtuzumab as per REM. These laboratory assessments include a CBC with differential, a serum creatinine, and urine analyses with cell count. A thyroid function test such as a TSH will be obtained at baseline, and every 3 months thereafter.*

## 7.2 Screening

This research study will be explained in lay language to each potential research participant. The participant will sign an informed consent form before undergoing any screening study procedures. If the inclusion criteria are met at the screening visit, the participants will be enrolled in study. Each participant will be assigned a unique study ID.

## 7.3 Patient demographics and baseline characteristics

Each selected study site has a large population representing diverse age, backgrounds, and ethnicity. This study will enroll all patients that meet the inclusion criteria.

## 7.4 Treatment exposure and compliance

The participant will receive treatment at study visits 3 and 7

Because study drug is administered IV in the presence of research team members, participant will be 100% compliant.

## 7.5 Efficacy

Efficacy will be assessed by clinical evaluation and MRI scanning. Clinical evaluation includes neurological examination, and EDSS assessment. Brain MRI will assess T1 lesion load, T2 number and lesion load, number of Gd<sup>+</sup> lesions.

### 7.5.1 Definition of a relapse

A clinical relapse is defined as new neurologic symptoms, lasting at least 24 hours, is associated with an increase in the EDSS by  $\geq 0.5$  points, and consistent with new demyelination. Two relapses must be separated by at least 30 days. Due diligence to rule out pseudoexacerbations will be up to the PI in each individual case.

### 7.5.2 EDSS

A standard EDSS will be performed at certain study visits (screening or baseline, 6 months, 12 months, and any relapse visits). This will include both a composite score and subsection score, recorded on a CRF. The EDSS is a scale providing a disability score (0 to 10) based on neurological examination and information about how the patient is able to perform tasks such as long walking. The EDSS may be conducted by a different doctor than the one the patient typically sees for treatment of MS. In order to make sure that this EDSS doctor is as objective as possible, the patient should not explain to this doctor how he/she is feeling that particular day, what symptoms may be bothersome at that time, or what treatment the patient is currently receiving for MS (see Appendix 2).

### 7.5.3 MRI

All imaging data at UT Southwestern will be acquired on single 1.5 or 3 Tesla MRI unit within the Advanced Imaging Research Center (AIRC), located in the Bill and Rita Clements Advanced Medical Imaging Building within UT Southwestern Medical Center campus. Study participants at the Dallas VA, the Multiple Sclerosis Treatment Center of Dallas, and the Neurology Center of San Antonio will be scanned on similar scanners at their sites, using compatible software sequences. All imaging data will be analyzed at the AIRC. The AIRC, in partnership with other North Texas institutions, aims to further research in magnetic resonance imaging and translation of discoveries into clinical practice.

#### 7.5.4 Standard MRI protocol performed at all sites

Standardized MRI studies of the brain will be performed at weeks 0 and 96. Clinical imaging studies of the brain and/or spinal cord performed during or immediately following the onset of a clinical exacerbation will be performed at the discretion of the site PI with scan costs covered under the medical standard of care. A clinical MRI of the cervical spinal cord with and without contrast will be recommended to study participants at week 0 and week 96 as medical standard of care. The MS specialist with neuro-imaging expertise will be responsible for ensuring that a uniform protocol (“Dummy scans”) is implemented at specified sites for the collection of uniform, multi-center data for post processing. In addition, this specialist will evaluate all MRI studies of the CNS for interval change (i.e. new and enlarging T2 lesion(s), gadolinium enhancement) during follow-up imaging studies and imaging studies acquired during clinical events. At Year 2, changes in T2-lesion volumes, and brain atrophy (SIENA) will be determined.

Standard imaging protocol:

1. Scout/Localizers

Routine T1-weighted axial, coronal, and sagittal scout images will be acquired to assess the field of view and head positioning.

2. 3D T2-Weighted Images

A 3D T2-weighted imaging sequence will be performed to allow for a proper assessment of infratentorial lesions.

- 1.0 x 1.0 x 1.0 mm<sup>3</sup>, TE/TR/TI=229/2500/1600, flip angle 90 degrees, 250 x 250 x 180 FOV, NEX=1, 164 slices, 4:33 duration

3. 3D Pre-Contrast T1-Weighted Volumetric Gradient Echo Images

A 3D pre-contrast T1-weighted volumetric gradient echo sequence will be performed (anticipated acquisition time: 4-5 minutes) for future volumetric

analyses. The sequence will generate approximately 180 slices with a  $1\text{mm}^3$  voxel size using the corresponding field of view and matrix.

-  $1.0 \times 1.0 \times 1.0 \text{ mm}^3$ , TE/TR/TI=3.7/8.1/864, flip angle 12 degrees, 256 x 220 x 170 FOV, NEX=1, 170 slices, 4:11 duration

4. Following Series 3, Gadavist (0.1mmol/kg at a rate of 2cc/second) will be administered.

5. 3D Fluid Attenuated Inversion Recovery (FLAIR) Images

A 3D FLAIR sequence will be performed that will enable full appreciation of the brain surface. The acquisition will be performed in sagittal or axial plane. The anticipated acquisition time is 5 minutes.

-  $1.1 \times 1.1 \times 1.1 \text{ mm}^3$ , TE/TR/TI=350/4800/1600, flip angle 90 degrees, 250 x 250 x 180 FOV, NEX=1, 163 slices, 5:02 duration

6. Post-Contrast 3D T1-Weighted Volumetric Gradient Echo Images

A post-contrast 3D T1-weighted volumetric gradient echo image will be performed following Series 5 which will allow for at least 5 minutes to elapse prior to the acquisition of the post-contrast images to assess for blood brain barrier breakdown. The expected acquisition time is 4-5 minutes.

### 7.5.5 OCT

The OCT tests measure peripapillary RNFL thickness using the Spectralis OCT device (Heidelberg Engineering), the Cirrus OCT device (Carl Zeiss Meditec) or comparable devices. All scans will be performed by the same experienced operator. An internal fixation target will be used because it provides the highest reproducibility.

All participants will undergo testing using the RNFL image acquisition protocols on either Spectralis OCT (RNFL Circle Scan), the Cirrus OCT (200 x 200 ONH Scan), or a comparable device on each eye. In addition, ganglion cell layer (GCL), and inner plexiform layer (IPL) will be assessed by measuring their combined thickness in a  $4.8 \times 4.0 \text{ mm}$  oval with a longer horizontal axis. Each patient will be longitudinally assessed on the same machine. The database name should be de-identified with the study assigned identifier. The default printing protocol will be used to print out the RNFL report on both eyes.

RNFL protocols on the Spectralis OCT, the Cirrus OCT, or comparable devices generate a thickness map with mean thickness, thickness of the four quadrants (superior, nasal, inferior, and temporal).

There are potential risks associated with OCT. All of the proposed procedures are validated, safe, and standard assessments that are utilized in the clinical practice of neurology or ophthalmology. In a limited number of participants, testing may require dilation of the eyes prior to assessment using standard ophthalmic solution if the data capture is not possible without dilating their eyes. This may cause minimal discomfort to the participant. Vision may become more sensitive to sunlight, the drops may cause a slight stinging sensation upon administration, and vision may be blurry for up to four hours after initial dilation.

#### **7.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)**

The C-SSRS is used extensively across primary care, clinical practice, surveillance, research, and institutional settings. It is a suicidal ideation rating scale to evaluate suicidality in ages 12 and up. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." This will be administered by research staff. See Appendix 3.

#### **7.5.7 Professional Quality of Life Scale (ProQOL)**

This is a self-administered assessment of quality of life. It measures the pleasure one derives from being able to do their work well, feelings of hopelessness and difficulties in dealing with work or in doing their job effectively, and work-related, secondary exposure to extremely stressful events. See Appendix 4.

### 7.5.8 Blood Draw for Mechanistic Studies

Blood will be collected at each time point to assess the immune-modulating effects of the trial. Blood will be collected at the study sites, in Cyto-Chex BCT tubes for flow Cytometry, ACD tubes for isolation of PBMC's and SST tube to collect serum. and shipped to the PI's laboratory at UT Southwestern by FedEx express overnight. Samples collected at UT Southwestern will be picked up in the clinic.

## 8 Data Analysis

The sample size of 40 patients was chosen to obtain a result that would be seen as meaningful by neurologists. Disease activity is expected to be extremely low on natalizumab and subsequently on alemtuzumab. Thus, it will be impossible to power a superiority or non-inferiority study.

All outcome measures will be assessed in the 12 months prior to natalizumab, on natalizumab, and on alemtuzumab. We will control secondary endpoints for multiple comparisons by testing sequentially the proportion of relapse-free patients, EDSS change, and T2-hyperintense lesion volume change.

The analysis of the acquired standardized imaging data will include a qualitative assessment of structural features suggestive of progressive multi-focal leukoencephalopathy (PML), T2-weighted lesion volumes, T1-weighted lesion volumes, a determination of new or enlarging T2 foci, the presence of acute blood brain barrier compromise and number of identified contrast enhanced lesions, and an assessment of brain volumetric changes by SIENA between the baseline and year 2 MRI study.

We will analyse the proportion of patients who are relapse-free with a proportional hazards model. We will analyse changes from baseline in EDSS at the pre-defined time points with a mixed model for repeated measures. We will make treatment comparisons of all available 3 month assessments with a non-parametric test for repeated measures. We will analyze changes in T2-hyperintense lesion volume, and RNFL thickness with a ranked ANCOVA model. We will analyse proportions of patients with new or enlarging T2-hyperintense lesions or Gd+ lesions, and those who were free from disease activity, with logistic regression.

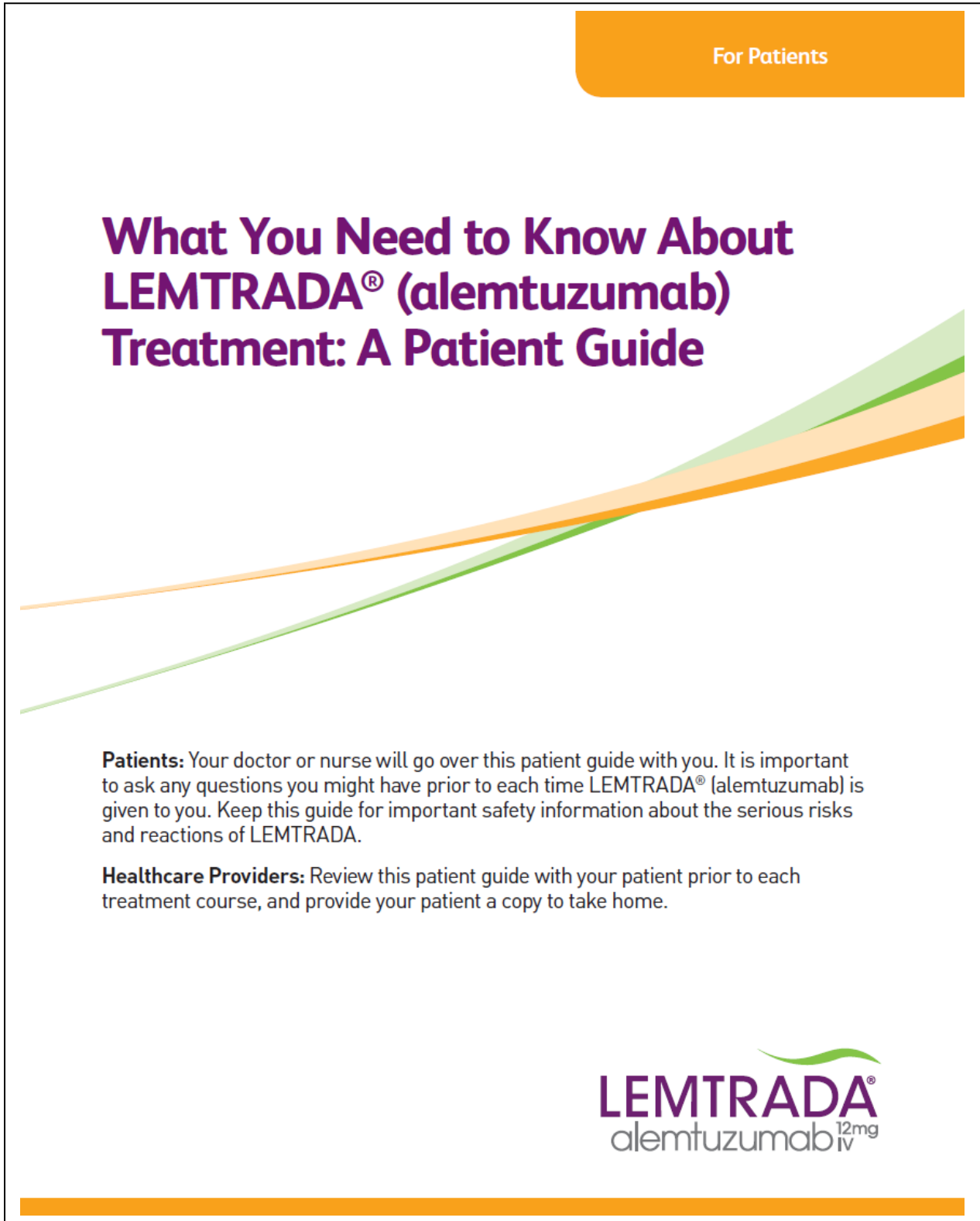


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Appendix 1. Lemtrada REMS Program Prescriber Enrollment



The image shows the cover of a patient guide for LEMTRADA (alemtuzumab) treatment. The cover is white with a purple and orange color scheme. At the top right, there is an orange rounded rectangle containing the text "For Patients". The main title is in purple: "What You Need to Know About LEMTRADA® (alemtuzumab) Treatment: A Patient Guide". Below the title is a decorative graphic consisting of three overlapping, upward-sloping lines in shades of green and orange. At the bottom right, the LEMTRADA logo is displayed in purple, with "alemtuzumab 12mg iv" in a smaller font below it. A thick orange horizontal bar is at the very bottom of the cover.

**For Patients**

## What You Need to Know About LEMTRADA® (alemtuzumab) Treatment: A Patient Guide

**Patients:** Your doctor or nurse will go over this patient guide with you. It is important to ask any questions you might have prior to each time LEMTRADA® (alemtuzumab) is given to you. Keep this guide for important safety information about the serious risks and reactions of LEMTRADA.

**Healthcare Providers:** Review this patient guide with your patient prior to each treatment course, and provide your patient a copy to take home.

**LEMTRADA®**  
alemtuzumab<sup>12mg</sup> iv

## What Is LEMTRADA?

LEMTRADA is a prescription medicine approved to treat adult patients with relapsing forms of multiple sclerosis. Because of serious risks with LEMTRADA, it is generally reserved for patients that have not been helped enough by 2 or more MS treatments. You and your healthcare provider have determined that LEMTRADA is an appropriate treatment for you.

LEMTRADA is only available at your doctor's office, clinic, or hospital. It is not a medicine you will give yourself at home because of the serious risks of LEMTRADA.

## What Is the Most Serious Risk Information About LEMTRADA Treatment?

LEMTRADA may cause serious side effects, including infusion reactions, autoimmune conditions, and malignancy.

- > Most patients treated with LEMTRADA will experience side effects at the time of the infusion or within 24 hours after the infusion (**infusion reactions**). Common infusion reactions include nausea, hives, itching, difficulty sleeping, chills, flushing, fatigue, shortness of breath, congestion of the lungs, upset stomach, dizziness, and pain.
- > Patients receiving LEMTRADA are at risk of **autoimmune conditions**. Your body's immune system contains particular cells that help fight infections. Autoimmune side effects are illnesses that occur when these cells of the immune system fight against your own body.
- > Receiving LEMTRADA may increase your chance of getting some kinds of cancers (**malignancies**), including thyroid cancer, skin cancer (melanoma), and blood cancers called lymphoproliferative disorders and lymphoma. Call your healthcare provider if you have the following symptoms that may be a sign of thyroid cancer:
  - new lump
  - swelling in your neck
  - pain in the front of your neck
  - hoarseness or other voice changes that do not go away
  - trouble swallowing or breathing
  - cough that is not caused by a cold

You should have your skin checked before you start receiving LEMTRADA, and each year while you are receiving treatment, to monitor for symptoms of skin cancer.

## What Are the Signs and Symptoms of Infusion Reactions and Autoimmune Conditions After LEMTRADA Treatment, and What Should I Do?

### INFUSION REACTIONS

Most patients treated with LEMTRADA will experience side effects at the time of the infusion, some of which may be serious or life-threatening. Serious infusion reactions may happen while you receive LEMTRADA, or up to 24 hours or longer after you receive LEMTRADA.

Tell your healthcare provider right away if you have any of the following symptoms of a serious infusion reaction during the infusion or after you have left the healthcare facility:

- > swelling in your mouth or throat
- > trouble breathing
- > weakness
- > fast, slow, or irregular heart beat
- > chest pain
- > rash

In order to try to reduce these effects, your doctor will give you medication (corticosteroids) prior to the first 3 infusions of a treatment course. You may also be given other treatments before or after the infusion to try to reduce your chances of these reactions or to treat them after they happen. In addition, you will be observed during the infusion and for at least 2 hours after the infusion has been completed, or longer if your healthcare provider decides you need to stay longer. In case of serious reactions, it is possible that the infusion may be stopped.

  
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## DELAYED SIDE EFFECTS

As mentioned previously, patients receiving LEMTRADA are at risk of certain autoimmune conditions. The autoimmune conditions include:

- > Immune thrombocytopenia (ITP, or low platelets)
- > Other blood disorders (including neutropenia, hemolytic anemia, and pancytopenia)
- > Certain types of kidney diseases
- > Thyroid disorders

**All of these conditions can be treated when identified early, but delaying treatment increases the risk of complications. This is why it is so important to recognize and immediately report any signs or symptoms of these conditions to your doctor.**

**In the following pages, you will learn more about each of these side effects, including the signs and symptoms that you may experience and what to do if they happen.**

### Immune Thrombocytopenia (ITP, or low platelets)

ITP is a condition which results in a decrease in the number of platelets in the blood. ITP has been observed in approximately 2% of patients treated with LEMTRADA in MS clinical trials. Platelets are necessary for normal blood clotting. ITP can cause severe bleeding. If detected early, ITP is usually treatable, but if left untreated it may lead to serious health problems and possibly death.

A blood test will help your doctor watch for changes in your platelet count in order to catch this side effect early. Therefore, your doctor will have your blood tested before starting LEMTRADA and on a monthly basis after your first infusion. The monthly testing must continue for 4 years after your last infusion, or longer if you have signs or symptoms of ITP.

Importantly, ITP may also be detected by certain signs or symptoms that you need to be aware of.

#### What are the signs and symptoms of ITP?

- > Small, scattered spots on your skin that are red, pink, or purple
- > Easy bruising
- > Bleeding from a cut that is harder to stop
- > Heavier, longer, or more frequent menstrual periods than normal. Bleeding between your menstrual periods could also be a sign of ITP
- > Bleeding from your gums or nose that is new or takes longer than usual to stop

**Call your doctor immediately if you have any of these signs or symptoms. If you cannot reach your doctor, seek immediate medical attention.**

These pictures show examples of spots and bruises caused by ITP.



This is an example of a leg with scattered spots under the skin that are red, pink, or purple. They might look like pinpricks.

It is important to note that the spots could occur anywhere on your body, not just on your leg.



This is an example of arms with easy or excessive bruising.

It is important to note bruises could occur anywhere on your body, not just on your arms.



This is an example of spots due to bleeding under the tongue.

It is important to note that this could occur anywhere in your mouth—under the tongue, on the roof of your mouth, on your inner cheeks, on your tongue, or on your gums.

Note: These pictures are only a guide in order to show examples of bruises or rashes.

Images ©2015 Genzyme Corporation.

### What if I develop ITP?

It is best to identify and treat ITP as early as possible. That is why it is so important that you continue to have your monthly blood test and check for symptoms, which could detect a problem before you have symptoms. It is also important that you, your family members, and/or caregivers are watching for any of the signs or symptoms described in this guide. Delaying treatment of ITP raises the chance of more serious problems.

If detected early, ITP is usually treatable. If you develop ITP, you and your doctor will decide which treatment is best for you.

**If you notice any of the signs or symptoms as described above, call your healthcare provider right away to report the symptoms. If you cannot reach your healthcare provider, seek immediate medical attention.**

### Other blood disorders (including neutropenia, hemolytic anemia, and pancytopenia)

LEMTRADA may cause a decrease in some types of blood cells. Symptoms may include weakness, dark urine, chest pain, yellowing of the skin or whites of your eyes (jaundice), or fast heartbeat. Your healthcare provider will do blood tests to check for low blood counts.

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alemtuzumab<sup>12mg</sup>  
iv

## **Kidney disorders (such as anti-glomerular basement membrane disease)**

LEMTRADA may cause a condition known as anti-glomerular basement membrane disease, or anti-GBM disease. Kidney disorders, including anti-GBM disease, have been observed in 0.3% (3 per 1000) patients treated with LEMTRADA in MS clinical trials. Anti-GBM disease is an autoimmune side effect that can result in severe damage to the kidneys. Anti-GBM disease can also damage the lungs, although this was not seen in clinical trials with LEMTRADA. If untreated it can cause kidney failure requiring chronic dialysis or transplant, and may lead to death. Most of the time, doctors can treat kidney problems. It is best to begin treatment as early as possible.

A blood test and a urine test will help your doctor watch for signs of kidney disease to help catch this potential side effect early. Your doctor will have your blood and urine tested in the month before you start treatment with LEMTRADA, and on a monthly basis after your initial infusion. Your doctor will test your urine monthly, so if you are a woman, it is important to avoid urine testing during your menstrual period as this may give a false result. This testing will continue for 4 years after your last infusion, or longer if you have signs or symptoms of a kidney disorder.

Importantly, anti-GBM disease can also be detected by certain signs and symptoms that you need to be aware of.

### **What are the signs and symptoms of kidney problems or anti-GBM disease?**

- > Blood in the urine (red or tea-colored urine)
- > Swelling in your legs or feet
- > Coughing up blood

### **What if I develop kidney problems?**

It is best to begin treatment as early as possible. It is important that you are familiar with the signs and symptoms of kidney problems and anti-GBM disease, and complete your regular laboratory tests (blood and urine tests). Kidney problems will almost always need treatment.

**If you notice any of the signs or symptoms as described above, call your doctor right away to report the symptoms. If you cannot reach your doctor, seek immediate medical attention.**



## Thyroid disorders

The thyroid is a gland found in the lower part of the neck. This gland produces hormones that are important throughout your body. In some people, the immune system may mistakenly attack the cells of the thyroid gland (autoimmune thyroid condition), which affects its ability to make and control the level of hormones.

LEMTRADA may cause development of thyroid disorders including:

- > Overactive thyroid gland, or hyperthyroidism, when the thyroid produces too much hormone
- > Underactive thyroid gland, or hypothyroidism, when the thyroid does not produce enough hormone

An estimated 34% of patients experienced autoimmune thyroid disorders following treatment with LEMTRADA, in MS clinical trials.

Your blood will be checked in the month before you start treatment with LEMTRADA, and every 3 months after your initial infusion, until 4 years after your last LEMTRADA infusion, or longer if you show signs or symptoms of a thyroid disorder. This blood test will help your doctor detect thyroid disorders early.

### What are the signs and symptoms of a thyroid disorder?

Overactive thyroid, or hyperthyroidism	Underactive thyroid, or hypothyroidism
<ul style="list-style-type: none"><li>&gt; Excessive sweating</li><li>&gt; Unexplained weight loss</li><li>&gt; Eye swelling</li><li>&gt; Nervousness</li><li>&gt; Fast heartbeat</li></ul>	<ul style="list-style-type: none"><li>&gt; Unexplained weight gain</li><li>&gt; Feeling cold</li><li>&gt; Worsening tiredness</li><li>&gt; Newly occurring constipation</li></ul>




### What if I develop a thyroid disorder?


Tell your doctor if you experience these symptoms. Most of the time, thyroid disorders are manageable with treatment. Depending on the type of thyroid disorder, your doctor will decide which treatment is best for you. It will be important to follow your doctor's recommendations to be sure to benefit the most from your treatment. In some cases, you may have to take medication for the rest of your life for your thyroid disorder. In some situations, your thyroid may need to be removed.


If you develop a thyroid disorder, it is very important that you are properly treated for it, especially if you become pregnant after using LEMTRADA. Having an untreated thyroid disorder could harm your unborn baby, or harm your baby after birth.

### IMPORTANT!

Since all of these autoimmune conditions could occur long after you received a course of treatment with LEMTRADA, it is very important that you continue to have your monthly blood and urine tests (even if you are feeling well).

 **You must continue to watch for signs and symptoms**

 **Do this for 4 years after your last LEMTRADA infusion**

 **Early detection and prompt treatment may give you the best opportunity for improvement**

Carry your LEMTRADA Patient Safety Information Card with you at all times and show it to any healthcare professionals who are providing you with treatment (including for non-MS conditions) or in the event of a medical emergency.

These are **NOT** all the possible side effects of LEMTRADA. Refer to the LEMTRADA Medication Guide that you were given or talk to your doctor or nurse for medical advice about other side effects.

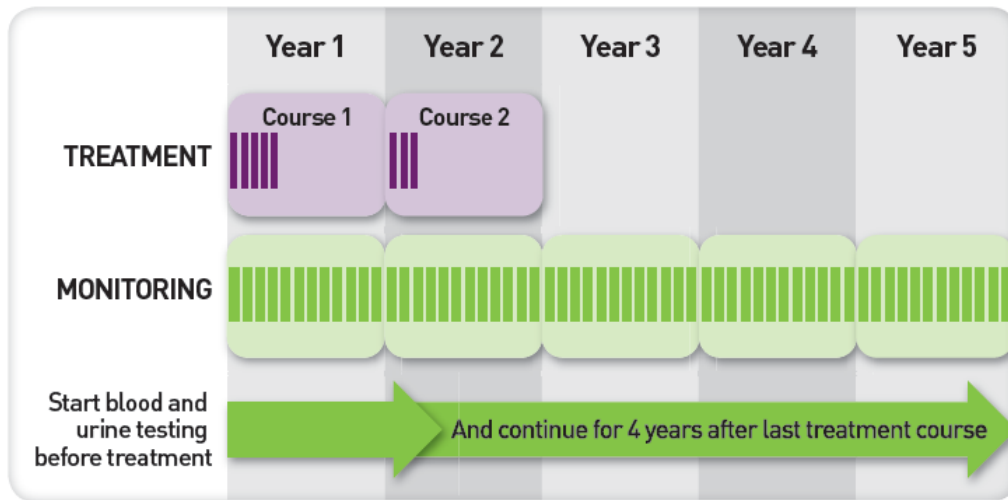
## How Can I Detect the Delayed Side Effects from LEMTRADA?

To check for the development of autoimmune conditions (previously described), you will have to be monitored monthly by having your blood and urine tested. Your doctor will order blood and urine tests in the month before you start LEMTRADA treatment, and these tests will continue each month for 4 years after your last LEMTRADA infusion. Monitoring may need to continue for longer if you have signs or symptoms of autoimmune conditions. Your doctor will check the results of these tests to see if you have developed any side effects.

It is very important that you continue to have these tests for 4 years after your last LEMTRADA infusion, even if you are feeling well (no symptoms or side effects). Side effects may occur many months to years after your LEMTRADA infusion and may be (in rare cases) life-threatening, so it is very important that you continue to be checked and that you watch out for symptoms. This will help allow a problem to be detected and treatment to begin right away.

This means that you commit to the monthly blood and urine laboratory tests, continuing for 4 years after your last infusion with LEMTRADA. You and your doctor will work together as a team to make sure you get these tests done, and to plan them around your normal activities. If you are a woman, it is also important to avoid urine testing during your menstrual period, as this may give a false result.

To help you better understand the duration of the effects of LEMTRADA treatment and the length of required follow-up, please refer to the diagram below.



The following table shows you which laboratory tests are done, when, and for how long.

Test	When?	For how long?
Blood tests	Before treatment starts and every month after treatment	For 4 years after your last LEMTRADA infusion
Urine tests	Before treatment starts and every month after treatment	For 4 years after your last LEMTRADA infusion

### How Is LEMTRADA Given?

You will receive LEMTRADA through an intravenous line in your vein (infusion). LEMTRADA is given in two treatment courses. Generally, you will receive LEMTRADA for 5 days for the first treatment course and then for 3 days approximately 1 year later (second treatment course).

The infusion takes place in a healthcare facility or infusion center. It takes about 4 hours to receive a full dose each day, but can take longer if you have side effects (infusion reactions), in which case the infusion may need to be slowed down or stopped. In order to try to reduce some of these reactions, your doctor will give you medication (corticosteroids) prior to the first 3 infusions of a treatment course. You may also be given other treatments before, during, or after the infusion to try to avoid these reactions or to treat them once they happen. In addition, you will be observed during the infusion and for at least 2 hours after the infusion has been completed or longer if your healthcare provider decides you need to stay longer. In case of serious reactions, it is possible that the infusion may be stopped.

### Where Can I Get More Information on LEMTRADA?

There is a LEMTRADA Medication Guide that your doctor or nurse will give you at the beginning of your treatment course. You can also find additional information at [www.LemtradaREMS.com](http://www.LemtradaREMS.com) or call the LEMTRADA REMS Program at 1-855-676-6326.

### How Can I Reach My Doctors?

To make it easier to contact your doctor(s) or your healthcare team, please fill in their telephone numbers and addresses in the chart below.

Doctor/Healthcare Team	Telephone Number	Address



For Prescribers to Complete



## LEMTRADA REMS PRESCRIBER ENROLLMENT FORM

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478 or submit online at [www.LemtradaREMS.com](http://www.LemtradaREMS.com)

LEMTRADA® (alemtuzumab) is available only through the LEMTRADA REMS Program, a restricted distribution program. Only prescribers, pharmacies, healthcare facilities, and patients enrolled in the Program are able to prescribe, dispense, administer, and receive LEMTRADA.

### Instructions:

1. Review the LEMTRADA REMS Education Program for Prescribers, including the Prescribing Information
2. Successfully complete the LEMTRADA REMS Knowledge Assessment
3. Complete and submit this LEMTRADA REMS Prescriber Enrollment Form
4. Send your patient to a healthcare facility that is enrolled in the LEMTRADA REMS Program

Please complete all required fields on this form and fax it to 1-855-557-2478. You will receive enrollment confirmation via your preferred method of communication (email or fax) within 2 business days.

\*Indicates a mandatory field.

### LEMTRADA PRESCRIBER INFORMATION (PLEASE PRINT)

Name (Last, First)/Degree\*

Name of Institution or Healthcare Facility\*

Street Address\*

City\*

State\*

ZIP Code\*

Office Phone Number\*

Fax Number\*

Email Address

Mobile Phone Number

National Provider Identification (NPI) Number\*

If you are dispensing LEMTRADA from your clinic, a LEMTRADA REMS Healthcare Facility Enrollment Form must also be completed and submitted.

### PRESCRIBER AGREEMENT

By completing this form, I attest that:

- > I understand that LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
- > I understand that LEMTRADA is only available through the LEMTRADA REMS Program and that I must comply with the program requirements in order to prescribe LEMTRADA.
- > I have completed the *LEMTRADA REMS Education Program for Prescribers*, including a review of the LEMTRADA Prescribing Information, and successfully completed the LEMTRADA REMS Knowledge Assessment.
- > I understand that by completing the training program and signing this LEMTRADA REMS Prescriber Enrollment Form, I will be enrolled in the LEMTRADA REMS Program and can prescribe LEMTRADA.
- > I understand that I am responsible for reviewing *What You Need to Know About LEMTRADA Treatment: A Patient Guide* with each patient, and counseling each patient on an ongoing basis about the serious risks associated with the use of LEMTRADA and how to mitigate these risks through periodic monitoring.
- > I understand that I must enroll all patients being treated with LEMTRADA into the LEMTRADA REMS Program prior to initiating the patient on treatment with LEMTRADA. I am responsible for completing a LEMTRADA REMS Patient Enrollment Form with the patient (or patient's legal representative), obtaining the patient's (or patient's legal representative's) signature on the form, and submitting the signed form to the LEMTRADA REMS Program. A completed copy should be provided to the patient and another copy should be stored in the patient's records.
- > I will provide enrolled patients with a LEMTRADA Patient Safety Information Card and instruct patients to carry this card with them at all times in case of an emergency.
- > I understand that I must submit a LEMTRADA REMS Prescription Ordering Form for each LEMTRADA prescription. I understand that I am responsible for completing baseline lab monitoring within 30 days prior to infusion of LEMTRADA.



**PRESCRIBER AGREEMENT (CONTINUED)**

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>&gt; I understand that I must submit a LEMTRADA REMS Patient Authorization and Baseline Lab Form indicating completion of each patient’s baseline labs within 30 days prior to the patient’s infusion date.</li> <li>&gt; I understand the risks of autoimmune conditions and malignancies associated with the use of LEMTRADA, and the need for periodic monitoring in order to identify and mitigate these risks:                         <ul style="list-style-type: none"> <li>- Complete blood counts with differential obtained within 30 days prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion.</li> <li>- Serum creatinine levels obtained within 30 days prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion.</li> <li>- Urinalysis with urine cell counts obtained within 30 days prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion.</li> <li>- Thyroid function tests, such as thyroid stimulating hormone (TSH) level, obtained within 30 days prior to initiation of treatment and every 3 months thereafter until 48 months after the last infusion.</li> <li>- Baseline and yearly skin examinations.</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>&gt; I will report any adverse events of autoimmune conditions, infusion reactions, or malignancies to Genzyme.</li> <li>&gt; I will complete the LEMTRADA REMS Patient Status Form 6 months after the patient’s first infusion and every 6 months thereafter, until 48 months after the completion of the patient’s last infusion.</li> <li>&gt; I understand that I will notify Genzyme if a patient is no longer under my care.</li> <li>&gt; I understand that if I fail to comply with the requirements of the LEMTRADA REMS Program, I may no longer be able to participate in the Program.</li> <li>&gt; I understand Genzyme and its agents may contact me via phone, mail, fax, or email to support administration of the LEMTRADA REMS Program.</li> </ul> |
|--|---|

**WEBSITE CONSENT**

I understand that the LEMTRADA REMS Program will publish my name, business address, and phone number (“Contact Information”) on its website in a directory of physicians certified to prescribe and administer LEMTRADA and consent to the foregoing. I understand that I am waiving the right to inspect my Contact Information prior to its inclusion on the website, and I agree to hold harmless and release the LEMTRADA REMS Program and Genzyme Corporation and its affiliates from any and all actions, claims, or demands arising out of or in connection with the use of my Contact Information on the website. I understand that I can request the removal of my Contact Information from the LEMTRADA REMS Program website at any time by contacting the LEMTRADA REMS Program at 1-855-676-6326.

Yes  No

**SIGNATURE**

\_\_\_\_\_  
 Prescriber Signature\* Date\*

\_\_\_\_\_  
 Print Name\*

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478 or enroll online at [www.LemtradaREMS.com](http://www.LemtradaREMS.com)

If you have any questions regarding the LEMTRADA REMS Program, call 1-855-676-6326

For Prescribers to Complete



**LEMTRADA REMS PATIENT STATUS FORM**

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478 or submit online at [www.LemtradaREMS.com](http://www.LemtradaREMS.com)

This form must be completed every 6 months for each LEMTRADA® (alemtuzumab) patient under your care. Please complete this form 6 months after your patient's first infusion with LEMTRADA, and every 6 months thereafter, until 48 months after the patient's last infusion.

\*Indicates a mandatory field.

**PRESCRIBER INFORMATION (PLEASE PRINT)**

Name (Last, First)*		Office Phone Number*
Address*		
City*	State*	ZIP Code*

**PATIENT INFORMATION (PLEASE PRINT)**

Name (Last, First)*	
Patient LEMTRADA REMS Program Identification Number*	
Date of Birth (MM/DD/YYYY)*	Date of Last LEMTRADA Infusion (MM/DD/YYYY)*

Is the above-named patient still under your care? (Check one)  Yes  No

**IF NO, please indicate the name of the healthcare provider now responsible for this patient's care**

Healthcare Provider Name
Healthcare Provider Phone Number
Patient's Current Healthcare Provider Is Unknown <input type="checkbox"/>

**IF YES, please complete the following information**

The patient has completed the periodic monitoring within the last 6 months.  Yes  No

Since submitting last LEMTRADA REMS Patient Status Form, has the patient been diagnosed with any of the following?

a. Autoimmune conditions  Yes  No

b. Infusion reactions  Yes  No

c. Malignancies  Yes  No

This adverse event has already been reported to Genzyme (specify date of report):

**Report all adverse events to Genzyme Medical Information at 1-800-745-4447 (option 2) or the FDA at 1-800-FDA-1088 (1-800-332-1088) or [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch)**

In signing this form, I acknowledge that I have reviewed *What You Need to Know About LEMTRADA Treatment: A Patient Guide* with this patient and counseled the patient about the serious risks associated with the use of LEMTRADA, and how to mitigate these risks through periodic monitoring.

**PRESCRIBER'S SIGNATURE**

Prescriber Signature*	Date*
-----------------------	-------

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478 or submit online at [www.LemtradaREMS.com](http://www.LemtradaREMS.com)

If you have any questions regarding the LEMTRADA REMS Program, call 1-855-676-6326

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For Prescribers to Complete



**LEMTRADA REMS PATIENT AUTHORIZATION AND BASELINE LAB FORM**

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478 or submit online at [www.LemtradaREMS.com](http://www.LemtradaREMS.com)

This form must be completed within 30 days prior to the first infusion date of each LEMTRADA® (alemtuzumab) patient's treatment course.

\*Indicates a mandatory field.

**PRESCRIBER INFORMATION (PLEASE PRINT)**

Name (Last, First)*		Office Phone Number*	
Address*			
City*		State*	ZIP Code*
Prescriber LEMTRADA REMS Program Identification Number*			

**PATIENT INFORMATION (PLEASE PRINT)**

Name (Last, First)*
Patient LEMTRADA REMS Program Identification Number*
Date of Birth (MM/DD/YYYY)*

**AUTHORIZATION AND BASELINE LABS**

Do you authorize LEMTRADA treatment for the above-referenced patient?\*  Yes  No

Do you attest that required baseline laboratory testing has been completed prior to LEMTRADA treatment and within 30 days of the patient's first infusion?\*  Yes  No

**PRESCRIPTION INFORMATION**

Check one\*  Initial course (1 vial [12 mg/day]) X 5 consecutive days Total number of vials: \_\_\_\_\_

Subsequent course (1 vial [12 mg/day]) X 3 consecutive days Total number of vials: \_\_\_\_\_

**SIGNATURE**

Prescriber Signature*	Date*
-----------------------	-------

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478 or submit online at [www.LemtradaREMS.com](http://www.LemtradaREMS.com)

If you have any questions regarding the LEMTRADA REMS Program, call 1-855-676-6326

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[Date]

[Patient\_First\_Name] [Patient\_Last\_Name]  
[Patient\_Primary\_Address\_2]  
[Patient\_Primary\_Address\_1]  
[Patient\_Primary\_City], «Patient\_State» «Patient\_ZIP»

Dear [Patient\_First\_Name] [Patient\_Last\_Name]:

When enrolling in the LEMTRADA REMS Program, you and your doctor agreed that you will participate in monthly laboratory monitoring for 4 years after your last infusion to monitor for possible side effects.

The lab tests, which are required every 30 days, are important to identify side effects like autoimmune conditions. Please make sure to continue to schedule and go to your monthly lab appointments.

It is also important that you look for symptoms of these side effects by doing your own symptom self-checks, as described in *What You Need to Know About LEMTRADA Treatment: A Patient Guide* that your doctor gave you before you started your LEMTRADA treatment.

As part of the program, you are receiving these monthly reminders for your lab tests. For your convenience, the program offers options on how you can receive your monthly reminders:

- > By mail
- > By phone
- > By email

If you wish to change the way you receive these reminders, please call the LEMTRADA REMS Program at 1-855-676-6326.

If you have questions about LEMTRADA or your monthly lab monitoring, please call the LEMTRADA REMS Program at 1-855-676-6326, Monday through Friday, 8:30 am to 8:00 pm ET. In addition, please contact the LEMTRADA REMS Program if your contact information has changed.

Sincerely,

LEMTRADA REMS Program

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### LEMTRADA REMS Prescription Ordering Form

Please fax this completed form to 1-855-557-2478

\*Indicates a mandatory field.

#### I: PATIENT INFORMATION (PLEASE PRINT)

Name (Last, First)*		
Date of Birth (MM/DD/YYYY)*	Gender* <input type="checkbox"/> Male <input type="checkbox"/> Female	
Street Address 1*		
Street Address 2*		
City*	State*	ZIP Code*
Phone Number*		

#### THIS SECTION SHOULD BE FILLED OUT BY THE PRESCRIBER

<b>II: INSURANCE INFORMATION</b> Patient does not have insurance. <input checked="" type="checkbox"/>				
Primary Insurance Company*	Phone Number*	Name of Insured*	Policy Number*	Group/Policy Number*
Secondary Insurance Company	Phone Number	Name of Insured	Policy Number	Group/Policy Number

<b>III: PRESCRIBER INFORMATION</b>				
Prescriber Name (Last, First)*	NPI Number*	Name of Institution or Facility*	Tax ID*	
Office Contact*	Street Address*		City*	State* ZIP Code*
Email Address	Phone Number*	Fax Number*		

<b>IV: PRESCRIPTION INFORMATION</b>				
LEMTRADA* (alemtuzumab) 12 mg IV				
Check one*	<input type="checkbox"/> Initial course (1 vial [12 mg/day]) X 5 consecutive days	Total number of vials ordered: _____	Primary diagnosis: ICD-9 CM340	
	<input type="checkbox"/> Subsequent course (1 vial [12 mg/day]) X 3 consecutive days	Total number of vials ordered: _____	ICD-10 G35	

<b>V: INFUSION CENTER INFORMATION*</b>				
Infusion Center Where Patient Is Referred*			Phone Number*	
Street Address*				
City*	State*	ZIP Code*		

\*Note: LEMTRADA can only be infused at REMS Certified infusion sites. Genzyme Corporation will contact you if the infusion center you have indicated is not certified to infuse LEMTRADA.

<b>VI: SIGNATURE</b>		
<b>Note to Prescribers:</b> This form does not authorize the certified pharmacy or infusion center to dispense LEMTRADA. The LEMTRADA REMS Patient Authorization and Baseline Lab Form must be submitted in order to authorize LEMTRADA to be dispensed.		
By signing below, I authorize the LEMTRADA REMS Program and its agents and representatives to forward this prescription on my behalf to a certified pharmacy or infusion center to dispense LEMTRADA to the patient named above.		
<b>X</b>	Print Name*	Date*
Licensed Prescriber Signature* (Signature required; no stamps accepted)		

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478  
 If you have any questions regarding the LEMTRADA REMS Program, call 1-855-676-6326

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For Patients to Complete



### LEMTRADA REMS PATIENT ENROLLMENT FORM

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478

This form must be completed before you can receive LEMTRADA® (alemtuzumab). LEMTRADA is available only through a restricted distribution program called the LEMTRADA REMS Program. Your prescriber will help you complete this form and will give you a copy.

\*Indicates a mandatory field.

#### PATIENT INFORMATION (PLEASE PRINT)

Name (Last, First)*	Date of Birth (MM/DD/YYYY)*		
Street Address*	City*	State*	ZIP Code*
Phone Number*	Gender* <input type="checkbox"/> Male <input type="checkbox"/> Female		
Secondary Contact (Last, First)	Phone Number		

#### PRESCRIBER INFORMATION (PLEASE PRINT)

Prescriber Name (Last, First)*	NPI Number*	Phone Number*
--------------------------------	-------------	---------------

#### PATIENT AGREEMENT

By signing this form, I acknowledge that:

- > I have received, read, and understand *What You Need to Know About LEMTRADA Treatment: A Patient Guide* that my doctor has given to me.
- > My doctor has reviewed with me the benefits and risks of treatment with LEMTRADA.
- > I am aware that LEMTRADA is associated with serious risks, including autoimmune conditions, infusion reactions, and malignancies, and that these complications can be identified through periodic monitoring and awareness of the initial signs and symptoms.
- > I understand the need to have blood and urine tests within 30 days prior to my first LEMTRADA treatment, then each month for 4 years following my last treatment with LEMTRADA.
- > I understand the need to have thyroid testing within 30 days prior to my first LEMTRADA treatment, then every 3 months for 4 years following my last treatment with LEMTRADA.
- > I understand the need to have yearly skin exams prior to my first LEMTRADA treatment, and continuing for 4 years following my last treatment with LEMTRADA.
- > I will tell my doctor if I have any reactions or symptoms after receiving LEMTRADA.
- > I understand that I must tell all of my doctors that I have received LEMTRADA.
- > I understand that in order to receive LEMTRADA, I am required to enroll in the LEMTRADA REMS Program and my information will be stored in a secure and confidential database of all patients who receive LEMTRADA in the United States. After enrolling, my doctor will provide me with a signed copy of the enrollment form.
- > My doctor has counseled and provided me with a LEMTRADA Patient Safety Information Card, which I should carry with me at all times in case of an emergency.
- > I understand that I must tell Genzyme if I change my doctor.
- > I understand that I must tell Genzyme if my contact information changes.
- > I give permission to Genzyme and its agents to use and share my personal health information for the purposes of enrolling me into the LEMTRADA REMS Program, coordinating the dispensing of receiving LEMTRADA, administering the LEMTRADA REMS Program, and releasing my personal health information to the Food and Drug Administration (FDA) as necessary.
- > By completing the information below, I understand Genzyme and its agents will contact me via phone, mail, or email to support administration of the LEMTRADA REMS Program.

I prefer to be contacted:  
 By mail  By phone  
 By email (please provide email address)

#### PATIENT SIGNATURE

_____ Patient/Legal Representative Signature*	_____ Relationship to Patient*
_____ Print Name*	_____ Date*

#### PRESCRIBER SIGNATURE

I acknowledge that I have explained the LEMTRADA REMS Program to this patient.

_____ Prescriber Signature*	_____ Date*
--------------------------------	----------------

Please fax this completed form to the LEMTRADA REMS Program at 1-855-557-2478

If you have any questions regarding the LEMTRADA REMS Program, call 1-855-676-6326

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## Appendix 2. Expanded Disability Status Scale (EDSS)

### neurostatus

#### DEFINITIONS

for a standardised neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

By Stacy S. Wu, MD and Prof. Ludwig Kappos, MD

#### GENERAL GUIDELINES

To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment. Patients must be observed to walk the required distance.

#### NEUROSTATUS (NS)

In the Neurostatus, "signs only" is noted when the examination reveals signs of which the patient is unaware.

#### FUNCTIONAL SYSTEMS (FS)

A score of 1 in a Functional System implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities. However, this general rule does not apply to the Visual, Bowel/Bladder and Cerebral FS.

#### EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS. Signs or symptoms that are not due to multiple sclerosis will not be taken into consideration for assessments, but should be noted.

Slightly modified from J.F. Kurtzke, Neurology 1983;33:1444-52  
© L. Kappos, Department of Neurology, University Hospital,  
CH-4031 Basel, Switzerland; Version 12/05

**1 VISUAL (OPTIC) FUNCTIONS**

**VISUAL ACUITY**

The visual acuity score is based on the line in the Snellen chart at 20 feet (5 meters) for which the patient makes no more than one error (use best available correction). Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during follow-up examinations.

**VISUAL FIELDS**

- 0 normal
- 1 signs only: deficits present only on formal (confrontational) testing
- 2 moderate: patient aware of deficit, but incomplete hemianopsia on examination
- 3 marked: complete homonymous hemianopsia or equivalent

**SCOTOMA**

- 0 none
- 1 small: detectable only on formal (confrontational) testing
- 2 large: spontaneously reported by patient

**\* DISC PALLOR**

- 0 not present
- 1 present

**NOTE**

When determining the EDSS step, the Visual FS score is converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1

\*optional

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1 disc pallor and/or mild scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
- 2 worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
- 3 worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
- 4 worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1); grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less
- 5 worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less
- 6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

**2 BRAINSTEM FUNCTIONS**

**EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT**

- 0 none
- 1 **signs only:** subtle and barely clinically detectable EOM weakness, patient does not complain of blurry vision, diplopia or discomfort
- 2 **mild:** subtle and barely clinically detectable EOM weakness of which patient is aware; or obvious incomplete paralysis of any eye movement of which patient is not aware
- 3 **moderate:** obvious incomplete paralysis of any eye movement of which patient is aware; or complete loss of movement in one direction of gaze in either eye
- 4 **marked:** complete loss of movement in more than one direction of gaze in either eye

**NYSTAGMUS**

- 0 none
- 1 **signs only or mild:** gaze evoked nystagmus below the limits of "moderate" (equivalent to a Brainstem FS score of 1)
- 2 **moderate:** sustained nystagmus on horizontal or vertical gaze at 30 degrees, but not in primary position, patient may or may not be aware of the disturbance
- 3 **severe:** sustained nystagmus in primary position or coarse persistent nystagmus in any direction that interferes with visual acuity; complete internuclear ophthalmoplegia with sustained nystagmus of the abducting eye; oscillopsia

**TRIGEMINAL DAMAGE**

- 0 none
- 1 **signs only**
- 2 **mild:** clinically detectable numbness of which patient is aware
- 3 **moderate:** impaired discrimination of sharp/dull in one, two or three trigeminal branches; trigeminal neuralgia (at least one attack in the last 24 hours)
- 4 **marked:** unable to discriminate between sharp/dull or complete loss of sensation in entire distribution of one or both trigeminal nerves

**FACIAL WEAKNESS**

- 0 none
- 1 **signs only**
- 2 **mild:** clinically detectable facial weakness of which patient is aware
- 3 **moderate:** incomplete facial palsy, such as weakness of eye closure that requires patching overnight or weakness of mouth closure that results in drooling
- 4 **marked:** complete unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids

**HEARING LOSS**

- 0 none
- 1 **signs only**
- 2 **mild**
- 3 **moderate:** cannot hear finger rub and/or misses several whispered numbers
- 4 **marked:** misses all or nearly all whispered numbers

**DYSARTHRIA**

- 0 none
- 1 **signs only**
- 2 **mild:** clinically detectable dysarthria of which patient is aware
- 3 **moderate:** obv. dysarthria during ordinary conversation that impairs comprehensibility
- 4 **marked:** incomprehensible speech
- 5 **inability to speak**

**DYSPHAGIA**

- 0 none
- 1 **signs only**
- 2 **mild:** difficulty with thin liquids
- 3 **moderate:** difficulty with liquids and solid food
- 4 **marked:** sustained difficulty with swallowing; requires a pureed diet
- 5 **inability to swallow**

**OTHER BULBAR FUNCTIONS**

- 0 normal
- 1 **signs only**
- 2 **mild disability:** clinically detectable deficit of which patient is usually aware
- 3 **moderate disability**
- 4 **marked disability**

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1 **signs only**
- 2a moderate nystagmus
- 2b other mild disability
- 3a severe nystagmus
- 3b marked extraocular weakness
- 3c moderate disability of other cranial nerves
- 4a marked dysarthria
- 4b other marked disability
- 5 **inability to swallow or speak**

**3 PYRAMIDAL FUNCTIONS**

**REFLEXES**

0 absent	Cutaneous Reflexes
1 diminished	0 = normal
2 normal	1 = weak
3 exaggerated	2 = absent
4 nonsustained clonus (a few beats of clonus)	* Palmomental Reflex
5 sustained clonus	0 = absent
	1 = present
	Plantar Response
	0 = flexor
	1 = neutral or equivocal
	2 = extensor

**LIMB STRENGTH**

The weakest muscle in each group defines the score for that muscle group. Use of functional tests, such as hopping on one foot and walking on heels/toes, are recommended in order to assess BMRC grades 3-5.

**BMRC RATING SCALE**

- 0 no muscle contraction detected
- 1 visible contraction without visible joint movement
- 2 visible movement only on the plane of gravity
- 3 active movement against gravity, but not against resistance
- 4 active movement against resistance, but not full strength
- 5 normal strength

**FUNCTIONAL TESTS**

- \* Pronator Drift (upper extremities) Pronation and downward drift:
  - 0 none
  - 1 mild
  - 2 evident
- \* Position Test (lower extremities – ask patient to lift both legs together, with legs fully extended at the knee) Sinking:
  - 0 none
  - 1 mild
  - 2 evident
  - 3 able to lift only one leg at a time (grade from the horizontal position at the hip joints...)
  - 4 unable to lift one leg at a time

\* Walking on heels/toes

- 0 normal
- 1 impaired
- 2 not possible

\* Hopping on one foot

- 0 normal
- 1 6–10 times
- 2 1–5 times
- 3 not possible

**LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)**

- 0 none
- 1 mild: barely increased muscle tone
- 2 moderate: moderately increased muscle tone that can be overcome and full range of motion is possible
- 3 severe: severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible
- 4 contracted

**GAIT SPASTICITY**

- 0 none
- 1 barely perceptible
- 2 evident: minor interference with function
- 3 permanent shuffling: major interference with function

\*optional

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1 abnormal signs without disability
- 2 minimal disability: patient complains of fatigability or reduced performance in strenuous motor tasks and/or BMRC grade 4 in one or two muscle groups
- 3a mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups or BMRC grade 3 in one or two muscle groups; movements against gravity are possible
- 3b severe monoparesis: BMRC grade 2 or less in one muscle group
- 4a marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs
- 4b moderate tetraparesis: BMRC grade 3 in three or more limbs
- 4c monoplegia: BMRC grade 0 or 1 in one limb
- 5a paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs
- 5b hemiplegia
- 5c marked tetraparesis: BMRC grade 2 or less in three or more limbs
- 6 tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs



**4 CEREBELLAR FUNCTIONS**

**HEAD TREMOR**

- 0 none
- 1 mild
- 2 moderate
- 3 severe

**TRUNCAL ATAXIA**

- 0 none
- 1 signs only
- 2 mild: swaying with eyes closed
- 3 moderate: swaying with eyes open
- 4 severe: unable to sit without assistance

**LIMB ATAXIA**

**(TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)**

- 0 none
- 1 signs only
- 2 mild: tremor or clumsy movements easily seen, minor interference with function
- 3 moderate: tremor or clumsy movements interfere with function in all spheres
- 4 severe: most functions are very difficult

**TANDEM (STRAIGHT LINE) WALKING**

- 0 normal
- 1 impaired
- 2 not possible

**GAIT ATAXIA**

- 0 none
- 1 signs only
- 2 mild: abnormal balance only with tandem walking
- 3 moderate: abnormal balance with ordinary walking
- 4 severe: unable to walk more than a few steps unassisted or requires a walking aid or assistance by another person because of ataxia

**ROMBERG TEST**

- 0 normal
- 1 mild: mild instability with eyes closed
- 2 moderate: not stable with eyes closed
- 3 severe: not stable with eyes open

**OTHER CEREBELLAR TESTS**

- 0 normal
- 1 mild abnormality
- 2 moderate abnormality
- 3 severe abnormality

**NOTE**

The presence of severe gait ataxia alone (without severe truncal ataxia and severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.  
 If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking an "X" after the Cerebellar FS score.

UE = upper extremities  
 LE = lower extremities

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1 abnormal signs without disability
- 2 mild ataxia
- 3a moderate truncal ataxia
- 3b moderate limb ataxia
- 3c moderate or severe gait ataxia
- 4 severe truncal ataxia and severe ataxia in three or four limbs
- 5 unable to perform coordinated movements due to ataxia
- X pyramidal weakness (BMRC grade 3 or worse in limb strength) interferes with cerebellar testing

**5 SENSORY FUNCTIONS**

**SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)**

- 0 normal
- 1 signs only: slightly diminished sensation (temperature, figure-writing) on formal testing of which patient is not aware
- 2 mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
- 3 moderate: impaired discrimination of sharp/dull
- 4 marked: unable to discriminate between sharp/dull and/or unable to feel light touch
- 5 complete loss: anaesthesia

**VIBRATION SENSE (AT THE MOST DISTAL JOINT)**

- 0 normal
- 1 mild: graded tuning fork 5–7 of 8; alternatively, detects more than 10 seconds but less than the examiner
- 2 moderate: graded tuning fork 1–4 of 8; alternatively, detects between 2 and 10 sec.
- 3 marked: complete loss of vibration sense

**POSITION SENSE**

- 0 normal
- 1 mild: 1–2 incorrect responses, only distal joints affected
- 2 moderate: misses many movements of fingers or toes; proximal joints affected
- 3 marked: no perception of movement, atasia

**\* LHERMITTE'S SIGN**

- 0 = negative
  - 1 = positive
- (does not contribute to the Sensory FS score)

**\* PARAESTHESIAE (TINGLING)**

- 0 = none
  - 1 = present
- (does not contribute to the Sensory FS score)

UE = upper extremities  
 LE = lower extremities  
 \*optional

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1 mild vibration or figure-writing or temperature decrease only in one or two limbs
- 2a mild decrease in touch or pain or position sense and/or moderate decrease in vibration in one or two limbs
- 2b mild vibration or figure-writing or temperature decrease alone in three or four limbs
- 3a moderate decrease in touch or pain or position sense and/or essentially lost vibration in one or two limbs
- 3b mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
- 4a marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs
- 4b moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
- 5a loss (essentially) of sensation in one or two limbs
- 5b moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
- 6 sensation essentially lost below the head

**6 BOWEL AND BLADDER FUNCTIONS**

**URINARY HESITANCY AND RETENTION**

- 0 none
- 1 mild: no major impact on lifestyle
- 2 moderate: urinary retention; frequent urinary tract infections
- 3 severe: requires catheterisation
- 4 loss of function: overflow incontinence

**URINARY URGENCY AND INCONTINENCE**

- 0 none
- 1 mild: no major impact on lifestyle
- 2 moderate: rare incontinence occurring no more than once a week; must wear pads
- 3 severe: frequent incontinence occurring from several times a week to more than once a day; must wear urinal or pads
- 4 loss of function: loss of bladder control

**BLADDER CATHETERISATION**

- 0 none
- 1 intermittent self-catheterisation
- 2 constant catheterisation

**BOWEL DYSFUNCTION**

- 0 none
- 1 mild: no incontinence, no major impact on lifestyle, mild constipation
- 2 moderate: must wear pads or alter lifestyle to be near lavatory
- 3 severe: in need of enemata or manual measures to evacuate bowels
- 4 complete loss of function

**\*SEXUAL DYSFUNCTION**

- 0 none
- 1 mild
- 2 moderate
- 3 severe
- 4 loss of function

**NOTE**

When determining the EDSS step, the Bowel and Bladder FS score is converted to a lower score as follows:

Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

\*optional

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1 mild urinary hesitancy, urgency and/or constipation
- 2 moderate urinary hesitancy and/or urgency and/or rare urinary incontinence and/or severe constipation
- 3 frequent urinary incontinence or intermittent self-catheterisation; needs enemata or manual measures to evacuate bowels
- 4 in need of almost constant catheterisation
- 5 loss of bladder or bowel function; external or indwelling catheter
- 6 loss of bowel and bladder function

**7 CEREBRAL FUNCTIONS**

**DEPRESSION AND EUPHORIA**

- 0 none
- 1 present: Patient complains of depression or is considered depressed or euphoric by the investigator or significant other.

**DECREASE IN MENTATION**

- 0 none
- 1 signs only: not apparent to patient and/or significant other
- 2 mild: Patient and/or significant other report mild changes in mentation. Examples include: impaired ability to follow a rapid course of association and in surveying complex matters; impaired judgement in certain demanding situations; capable of handling routine daily activities, but unable to tolerate additional stressors; intermittently symptomatic even to normal levels of stress; reduced performance; tendency toward negligence due to obliviousness or fatigue.
- 3 moderate: definite abnormalities on brief mental status testing, but still oriented to person, place and time
- 4 marked: not oriented in one or two spheres (person, place or time), marked effect on lifestyle
- 5 dementia, confusion and/or complete disorientation

**+ FATIGUE**

- 0 none
- 1 mild: does not usually interfere with daily activities
- 2 moderate: interferes, but does not limit daily activities for more than 50 %
- 3 severe: significant limitation in daily activities (> 50% reduction)

+ Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

**NOTE**

The presence of depression and/or euphoria alone results in a Cerebral FS score of 1a, but does not affect the EDSS step. However, a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step.

**FUNCTIONAL SYSTEM SCORE**

- 0 normal
- 1a mood alteration (depression and/or euphoria) alone (does not affect EDSS step)
- 1b mild fatigue; signs only decrease in mentation
- 2 mild decrease in mentation; moderate or severe fatigue
- 3 moderate decrease in mentation
- 4 marked decrease in mentation
- 5 dementia

## 8 AMBULATION

### DEFINITIONS

Observe the patient walking unassisted for a minimum distance of 500 meters, if possible. If the patient walks with assistance, observe the patient walking with the assistive device for a minimum distance of 130 meters, if possible.

If a patient walks without assistance and the walking range determines the EDSS step, please note that the definitions mark the lower limit for each step. For example, if a patient is able to walk 280 meters without aid or rest, the EDSS step is still 5.0. An EDSS step of 4.5 is defined by an unassisted walking distance of  $\geq 300$  meters (but  $< 500$  meters).

The definitions of EDSS steps 6.0 and 6.5 include both a description of the type of assistance required when walking and the walking range. In general, the type of assistance required (unilateral vs. bilateral) overrules the walking range when determining the EDSS step.

### HOWEVER, THE FOLLOWING EXCEPTIONS APPLY:

1. If a patient is able to walk considerably longer than 100 meters ( $> 120$  meters) with two sticks, crutches or braces, the EDSS step is 6.0.
2. If a patient needs two sticks, crutches or braces to walk between 10 and 120 meters, the EDSS step is 6.5.
3. If a patient is able to walk more than 50 meters with one stick, crutch or brace, the EDSS step is 6.0.
4. If a patient cannot walk more than 50 meters with one stick, crutch or brace, the EDSS step is 6.5.

### NOTE

1. Assistance by another person (as opposed to one stick, crutch or brace) is equivalent to bilateral assistance.
2. The use of an ankle foot orthotic device, without any other type of assistive device, is not considered unilateral assistance.

When determining the EDSS step, the Visual FS and Bowel and Bladder FS scores are converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1
Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

Please enter both the actual and converted scores.

**9 KURTZKE'S EXPANDED DISABILITY STATUS SCALE**

**DEFINITIONS**

- EDSS steps below 4 refer to patients who are fully ambulatory (able to walk ≥ 500 meters). The precise step is defined by the Functional System (FS) scores.
- EDSS steps between 4.0 and 5.0 are defined by both the FS scores and the walking range. In general, the more severe parameter determines the EDSS step.
- EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.
- From steps 0 to 4.0, the EDSS should not change by 1.0 step, unless there is a similar change in a FS score by 1 grade.
- The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS.

**NOTE**

A Cerebral FS score of 1a due to depression and/or euphoria alone does not affect the EDSS step. However, a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step.

**EXPANDED DISABILITY STATUS SCALE**

- 0 normal neurological exam (all FS grade 0)
- 1.0 no disability, minimal signs in one FS (one FS grade 1)
- 1.5 no disability, minimal signs in more than one FS (more than one FS grade 1)
- 2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)
- 2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)
- 3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
- 3.5 fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)
- 4.0 ambulatory without aid or rest for ≥ 500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
- 4.5 ambulatory without aid or rest for ≥ 300 meters; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
- 5.0 ambulatory without aid or rest for ≥ 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
- 5.5 ambulatory without aid or rest ≥ 100 meters
- 6.0 unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting
- 6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
- 7.0 unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
- 7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
- 8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
- 8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
- 9.0 helpless bed patient; can communicate and eat
- 9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow
- 10.0 death due to MS

# neuroSTATUS

Standardised Neurological Examination and Assessment of Kurtzke's *Functional Systems*<sup>1</sup> and *Expanded Disability Status Scale*<sup>1</sup>

## SOURCE DOCUMENT

SUBJECT NO/SUBJECT INITIALS

COUNTRY/CENTRE NO

NAME OF EDSS RATER

DATE OF EXAMINATION

<sup>1</sup> slightly modified from J. F. Kurtzke, *Neurology* 1983;33,1444-52  
© L. Kappos, Department of Neurology, University Hospitals,  
CH-4031 Basel, Version 10/2002

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## neurostatus

## GENERAL GUIDELINES

*To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment.*

*Patients must be observed to walk the required distance.*

### **NEUROSTATUS (NS)**

In the Neurostatus «signs only» is noted when the examination reveals signs of which the patient is unaware.

### **FUNCTIONAL SYSTEMS (FS)**

A score of 1 in the Functional Systems implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities (with the exceptions of optic, vegetative and cerebral functions).

### **EXPANDED DISABILITY STATUS SCALE (EDSS)**

EDSS should not be lower than the highest score of the FS.

Symptoms which are not MS-related will not be taken into consideration for assessments, but should be noted.



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**NEUROSTATUS**

Definitions

**Visual acuity**

The visual acuity score is based upon the line on the Snellen chart at 20 feet (5 m) for which the patient makes no more than one error (use best available correction).

Alternatively best corrected near vision can be assessed but this should be noted and consistently done during follow up.

**Fields**

- 0 = normal
- 1 = signs only, deficits present only on formal testing
- 2 = moderate, patient aware of deficit, but incomplete hemianopsia on examination
- 3 = marked, complete homonymous hemianopsia or equivalent

**Scotoma**

- 0 = none
- 1 = small, detectable only on formal (confrontational) testing
- 2 = large, spontaneously reported by patient

**Disc pallor**

- 0 = not present
- 1 = present

**VISUAL (OPTIC) FUNCTIONS**

OPTIC FUNCTIONS	OD	OS
Visual acuity (corrected)		
Visual fields		
Scotoma		
Disc pallor		

**FUNCTIONAL SYSTEM SCORE**

0 = normal
1 = disc pallor and/or mild scotoma and/or visual acuity of worse eye (corrected) less than 30/30 (1.0) but better than 20/30 (0.67)
2 = worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
3 = worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
4 = worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.1–0.2); grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less
5 = worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less
6 = grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

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**neuroSTATUS**

**BRAINSTEM FUNCTIONS**

Definitions

**Assessment of impairment/disability**

0 = normal

1 = signs only: clinically detectable numbness, facial weakness, or cranial nerve deficit of which patient is not aware

2 = mild: clinically detectable numbness, facial weakness, dysarthria or cranial nerve deficits of which patient is aware

3 = moderate: diplopia with incomplete paralysis of any eye movement, impaired discrimination of sharp/dull in 1 or 2 trigeminal branches, trigeminal neuralgia (at least one attack in the last 24 hours), weakness of eye closure, cannot hear finger rub and/or misses several whispered numbers, obvious dysarthria during ordinary conversation impairing comprehensibility

4 = severe (marked): complete loss of movement of either eye in one direction, impaired discrimination of sharp/dull or complete loss of sensation in the entire distribution of one or both trigeminal nerves, unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids, sustained difficulty with swallowing, incomprehensible voice

**Nystagmus**

0 = normal

1 = signs only

2 = gaze evoked nystagmus below limits of "moderate" (usual equivalent is grade one in FS score)

3 = moderate, sustained nystagmus on 30° horizontal or vertical gaze, but not in primary position, patient may or may not realize disturbance (usual equivalent is grade 2 in FS score)

4 = severe, sustained nystagmus in primary position or coarse persistent nystagmus in any direction interfering with visual acuity, complete internuclear ophthalmoplegia with sustained nystagmus of abducting eye, oscillopsia

CRANIAL NERVE EXAMINATION	
EOM (extra ocular movements) impaired	
Nystagmus	
Trigeminal damage	
Facial weakness	
Hearing loss	
Dysarthria	
Dysphagia	
Other bulbar signs	

FUNCTIONAL SYSTEM SCORE	
0 = normal	
1 = signs only	
2a = moderate nystagmus or/and 2b = other mild disability	
3a = severe nystagmus or/and 3b = marked extraocular weakness or/and 3c = moderate disability of other cranial nerves	
4a = marked dysarthria or/and 4b = other marked disability	
5 = inability to swallow or speak	

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**neuroSTATUS**

Definitions \* = optional

**REFLEXES**

0 = absent, 1 = weak, 2 = normal, 3 = exaggerated, 4 = cloniform, 5 = inexhaustible (indicate difference between R & L by < or >)

**Plantar response**

0 = flexor, 1 = neutral, 2 = extensor

**Cutaneous reflexes**

0 = normal, 1 = weak, 2 = absent

**\*Palmomental reflex**

0 = absent, 1 = present

**LIMB STRENGTH**

The weakest muscle in each group defines the score for that group. Use of functional tests like jumping with one foot, walking on toes or heels are recommended in order to assess grades 3-5 BMRC.

**BMRC Rating scale**

0 = no activity, 1 = visible contraction without visible joint movement, 2 = visible movements with elimination of gravity, 3 = movements against gravity possible but impaired, 4 = movements against resistance possible but impaired, 5 = normal strength

**FUNCTIONAL TESTS**

\*Position test UE (upper extremities)

Sinking, 0 = none, 1 = mild, 2 = evident

**\*Position test LE (lower extremities)**

Sinking, 0 = none, 1 = mild, 2 = evident

1 = only separate lifting possible (grades from horizontal position in hip joints...°)

2 = even separate lifting not possible

**\*Walking on heels/tiptoes**

0 = normal, 1 = impaired, 2 = not possible

**\*Monopedal hopping**

0 = normal, 1 = 6–10 times, 2 = 1–5 times, 3 = not possible

**LIMB SPASTICITY**

0 = normal, 1 = mild, barely increased muscular tone after rapid flexion of an extremity, 2 = moderate, 3 = severe, barely surmountable increased spastic tonus after rapid flexion of an extremity, 4 = contracted

**Gait spasticity**

0 = normal, 1 = barely perceptible, 2 = evident, minor interference with function, 3 = permanent shuffling, major interference with function

**PYRAMIDAL FUNCTIONS**

REFLEXES	R	><	L
Biceps			
Triceps			
Radial			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
*Palmomental reflex			

LIMB STRENGTH			
Shoulder			
Elbow flexors			
Elbow extensors			
Hand/finger flexors			
Hand/finger extensors			
Hip flexion			
Knee flexors			
Knee extensors			
Foot/toe flexors			
Foot/toe extensors			
* Position test UE, pronation			
* Position test UE, sinking			
* Position test LE, sinking			
only lifting of single leg possible		°	°
* Walking on heels			
* Walking on tiptoes			
* Hopping on one foot			

SPASTICITY			
Arm			
Leg			
Gait			

FUNCTIONAL SYSTEM SCORE	
0 = normal	
1 = abnormal signs without disability	
2 = minimal disability, patient complains about fatiguability in motor tasks and/or BMRC grade 4 in one or two muscle groups	
3a = mild to moderate paraparesis or hemiparesis (usually BMRC grade 4 in more than two muscle groups or BMRC grade 3 in one or two) movements against gravity are possible	
3b = severe monoparesis, refers to BMRC grade 2 or less in one muscle group	
4a = marked paraparesis or hemiparesis (usually BMRC grade 2 in 2 limbs)	
4b = moderate tetraparesis (refers to BMRC grade 3 in 3 or more limbs)	
4c = monoplegia (BMRC grade 0 or 1 in one limb)	
5a = paraplegia, BMRC grade 0 or 1 in all muscle groups of the lower limbs	
5b = hemiplegia	
5c = marked tetraparesis (BMRC grade 2 or less in 3 or more limbs)	
6 = Tetraplegia (grade 0 or 1 in all muscle groups of upper and lower limbs)	

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**neuroSTATUS**

**CEREBELLAR FUNCTIONS**

**Definitions**

- UE = upper extremities
- LE = lower extremities
- EO = eyes open
- EC = eyes closed

**Head tremor, rebound**

- 0 = normal
- 1 = mild abnormality
- 2 = moderate abnormality
- 3 = severe abnormality

**Truncal ataxia**

- 0 = none
- 1 = signs only
- 2 = mild, swaying with EC
- 3 = moderate, swaying with EO
- 4 = severe, unable to sit without assistance

**Limb ataxia**

- 0 = none
- 1 = signs only
- 2 = mild, tremor or clumsy movements seen easily, minor interference with function
- 3 = moderate, tremor or clumsy movements interfere with function in all spheres
- 4 = severe, most functions are very difficult

**Gait ataxia**

- 0 = none
- 1 = signs only
- 2 = mild, abnormal balance only on heel or toe walking, or walking along a line
- 3 = moderate, abnormal balance on ordinary walking or while seated
- 4 = severe, unable to walk more than a few steps or requires support by another person or walking aid because of ataxia

**Romberg test**

- 0 = normal
- 1 = mild, mild insecurity with EC
- 2 = moderate, not stable with EC
- 3 = severe, not stable with EO

**Straight line walking**

- 0 = without problems
- 1 = impaired
- 2 = not possible

**Note**

The presence of severe gait ataxia alone results in a grade of 3 in the cerebellar FS. If weakness interferes with the testing of ataxia, score the patient's actual performance, but also indicate the possible role of weakness by marking the box marked 'X'.

**CEREBELLAR EXAMINATION**

Head tremor		
Truncal ataxia, EO		
Truncal ataxia, EC		
	<b>R</b>	<b>L</b>
Tremor/dysmetria UE		
Tremor/dysmetria LE		
Rapid alternate movements impaired UE		
Rapid alternate movements impaired LE		
Gait ataxia, EO		
Straight line walking, EO		
Other, e.g. rebound		
Romberg test		

**FUNCTIONAL SYSTEM SCORE**

0 = normal
1 = abnormal signs without disability
2 = mild ataxia
3a = moderate truncal ataxia
3b = moderate limb ataxia
4 = severe ataxia in all limbs or trunk
5 = unable to perform coordinated movements due to ataxia
X = weakness (grade 3 or more on pyramidal) interferes with testing

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**NEUROSTATUS**

**SENSORY FUNCTIONS**

**Definitions**

UE = upper extremities  
 LE = lower extremities

\* = optional

**Superficial sensation – Touch/pain**

0 = normal  
 1 = signs only, patient is not aware of deficit, but slightly reduced sensation of feeling (temperature, figure writing)  
 2 = mild, patient is aware of impaired light touch or pain, but able to discriminate sharp/dull  
 3 = moderate, impaired discrimination of sharp/dull  
 4 = severe, no discrimination of sharp/dull and/or unable to feel light touch  
 5 = complete loss, anaesthesia

**Vibration sense**

0 = normal  
 1 = mild, graded tuning fork 5–7 of 8 (alternatively) detects more than 10 sec. but less than examiner  
 2 = moderate, graded tuning fork 1–4 of 8 (alternatively) detects more than 2 sec. but less than 11 sec.  
 3 = marked, complete loss of vibration sense

**Position sense**

0 = normal  
 1 = mild, 1–2 incorrect responses on testing, only distal joints affected  
 2 = moderate, misses many movements of fingers or toes, proximal joints affected  
 3 = marked, no perception of movement/astasia

**\*Lhermitte**

0 = negative  
 1 = positive

**\*Paraesthesia (tingling)**

(do not influence FS-score)  
 0 = none  
 1 = present

SENSORY EXAMINATION	R	L
Superficial sensation (touch/pain) UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		
Position sense UE		
Position sense LE		
*Lhermitte		
*Paraesthesiae UE		
*Paraesthesiae trunk		
*Paraesthesiae LE		

**FUNCTIONAL SYSTEM SCORE**

0 = normal
1 = mild vibration or figure-writing decrease only in 1 or 2 limbs
2a = mild decrease in touch or pain or position sense and/or moderate decrease in vibration in 1 or 2 limbs 2b = mild vibration or figure-writing decrease alone in 3 or 4 limbs
3a = moderate decrease in touch or pain or position sense and/or essentially lost vibration in 1 or 2 limbs 3b = mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs
4a = marked decrease in touch or pain or loss of proprioception, alone or combined in 1 or 2 limbs 4b = moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
5a = loss (essentially) of sensation in 1 or 2 limbs 5b = moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 = sensation essentially lost below the head

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**neuroSTATUS**

**BOWEL/BLADDER FUNCTIONS**

Definitions

\* = optional

**BLADDER**

**Hesitancy/retention**

- 0 = none
- 1 = mild, no major impact on lifestyle
- 2 = moderate, urine retention, frequent UTI
- 3 = severe, requires catheterisation
- 4 = loss of function, overflow incontinence

**Urgency/incontinence**

- 0 = none
- 1 = mild, no major impact on lifestyle
- 2 = moderate, rare incontinence, no more than once a week, must wear pads
- 3 = severe, frequent incontinence, several times a week up to more than once daily, must wear urinal or pads
- 4 = loss of function, loss of bladder control

**Catheterisation**

- 0 = none
- 1 = intermittent self catheterisation
- 2 = constant

**Bowel**

- 0 = none
- 1 = mild, no incontinence, no major impact on lifestyle, constipation
- 2 = moderate, must wear pads or alter lifestyle to be near lavatory
- 3 = severe, in need of intermittent enemata
- 4 = complete loss of function

**\*Sexual dysfunction**

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe
- 4 = loss

BLADDER AND BOWEL FUNCTIONS	
Hesitancy/retention	
Urgency/incontinence	
Catheterisation	
Bowel dysfunction	
*Sexual dysfunction	

FUNCTIONAL SYSTEM SCORE	
0	normal
1	mild urinary hesitancy, urgency and/or constipation
2	moderate urinary hesitancy and/or urgency and/or rare incontinence and/or severe constipation
3	frequent urinary incontinence or intermittent self catheterisation; needs constantly enemata or manual measures to evacuate bowel
4	in need of almost constant catheterisation
5	loss of bladder or bowel function, external or indwelling catheter
6	loss of bowel and bladder function

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**neuroSTATUS**

**CEREBRAL FUNCTIONS**

**Definitions**

The presence of depression and/or euphoria alone results in a score of 1 on the cerebral FS, but does not affect the EDSS score.

**Depression/euphoria**

0 = none

1 = present

Patient complains of depression or is considered depressed or euphoric by the investigator or «significant other».

**Decrease in mentation**

0 = none

1 = signs only, not apparent to patient and/or «significant other»

2 = mild, difficulties apparent to patient and/or «significant other» such as impaired ability to follow a rapid course of association and of surveying complex matters, impaired judgement in certain demanding situations, able to handle the daily routine, but no tolerance for additional stressors, intermittently symptomatic to even normal levels of stress, reduced performance, tendency toward negligence due to obliviousness or fatigue.

However, not apparent while taking the history or performing the routine neurological examination.

3 = moderate, definite abnormalities on formal mental status testing, but still oriented to time, place and person

4 = marked, not oriented in 1 or 2 spheres of time, place or person, marked effect on lifestyle

5 = dementia, confusion and/or complete disorientation

**Fatigue\***

0 = none

1 = mild, not interfering with daily activities

2 = moderate, interfering but not limiting daily activities for more than 50 %

3 = severe, significantly limiting daily activities

(> 50% reduction)

\*Because difficult to evaluate objectively, in some studies fatigue does not contribute to this Functional System or the EDSS Score. Please adhere to the study's specific instructions.

**MENTAL STATUS EXAMINATION**

Depression

Euphoria

Decrease in mentation

Fatigue

**FUNCTIONAL SYSTEM SCORE**

0 = normal

1 = mood alteration only  
 (does not affect EDSS score)/mild fatigue

2 = mild decrease in mentation/  
 moderate or severe fatigue

3 = moderate decrease in mentation

4 = marked decrease in mentation

5 = dementia

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**NEUROSTATUS**

**AMBULATION**

**Definitions**

Actual walking distance without assistance obligatory up to 500 m (if possible). Actual walking distance with assistance obligatory up to 150 m (if possible).

In the definitions of EDSS grades 6.0 and 6.5 both a description of assistance required and of the walking range are included. In general, the distinction of bilateral versus unilateral assistance required to walk overrules the walking range.

However, the following exceptions are suggested,

If a patient is able to walk considerably longer than 100 m (> 120) with two sticks, crutches or braces he is in grade 6.0.

If a patient is able to walk more than 10 m and up to 100 m with two sticks, crutches or braces he is in grade 6.5.

If a patient needs assistance by another person (as opposed to one stick, crutch or brace) and/or is not able to walk more than 50 m with one stick, crutch or brace he is in grade 6.5.

**AMBULATION**

**Walking range as reported (without help or sticks)**

	meters
in	min

**Able to walk without rest or assistance**

<input type="checkbox"/>	≥ 100 meters, but < 200 meters
<input type="checkbox"/>	≥ 200 meters, but < 300 meters
<input type="checkbox"/>	≥ 300 meters, but < 500 meters
<input type="checkbox"/>	≥ 500 meters but not unrestricted
<input type="checkbox"/>	Unrestricted

**Actual distance (obligatory up to 500 m if possible)**

	meters
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**Unable to walk 100 m without constant assistance**

Unilateral assistance		meters
	Cane/crutch	
	Other	
Bilateral assistance		meters
	Canes/crutches	
	Other	
Other person		

**SYNOPSIS OF FS SCORES**

<input type="checkbox"/>	Visual <sup>1,3</sup>
<input type="checkbox"/>	Brainstem
<input type="checkbox"/>	Pyramidal
<input type="checkbox"/>	Cerebellar
<input type="checkbox"/>	Sensory
<input type="checkbox"/>	Bladder/Bowel <sup>2,3</sup>
<input type="checkbox"/>	Mental

<sup>1</sup> For calculation of the EDSS the score of the visual FS is to be converted as follows, 6 = 4; 5 = 3; 4 = 3; 3 = 2; 2 = 2; 1 = 1.

<sup>2</sup> Scores of the bowel/bladder FS are converted as follows: 6=5, 5=4, 4=3, 3=3, 2=2, 1=1.

<sup>3</sup> Please enter both the actual and the converted score.



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**neurostatus**

**KURTZKE EXPANDED DISABILITY SCALE (EDSS)**

EDSS steps below 4 refer to patients who are fully ambulatory (able to walk >500 m), and the precise step is defined by the functional systems (FS) score(s). EDSS steps between 4.0 and 5.0 are defined by both FS-scores and walking range. In general, the worst of both should determine the score. Steps 5.5-8.0 are exclusively defined by ability to ambulate or use wheelchair.

Up to 4.0 EDSS should not change by 1.0 step unless there is a change in same direction of at least one step in at least one FS. EDSS should not be lower than each of FS (excepted visual and bowel/bladder FS).

<p>0 normal neurological exam (all grade 0 in FS)</p> <p>1.0 no disability, minimal signs in one FS1 (i.e. grade 1)</p> <p>1.5 no disability, minimal signs in more than one FS 1 (more than one grade 1)</p> <p>2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)</p> <p>2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)</p> <p>3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory</p> <p>3.5 fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)</p> <p>4.0 ambulatory without aid or rest for &gt; 500 m; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps</p> <p>4.5 ambulatory without aid or rest for &gt; 300 m; up and about much of the day; characterised by relatively severe disability usually consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps</p>	<p>5.0 ambulatory without aid or rest for &gt; 200 m (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.5)</p> <p>5.5 ambulatory without aid or rest &gt; 100 m</p> <p>6.0 unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting</p> <p>6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting</p> <p>7.0 unable to walk 5 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 h a day</p> <p>7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transfer and in wheeling self</p> <p>8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms</p> <p>8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions</p> <p>9.0 helpless bed patient; can communicate and eat</p> <p>9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow</p> <p>10.0 death due to MS</p>
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Actual EDSS
Signature

<sup>1</sup> Mental function's grade 1 does not contribute to EDSS-step definitions

**neurostatus**

SCORING DEFINITIONS AND SCORING SHEET ARE INCLUDED IN CONVENIENT POCKET-SIZE IN THE DVD PACKAGE AND CAN BE ORDERED SEPARATELY (SCORING SHEETS IN PADS OF 40).

STUDY NAME EXAMPLE STUDY

PERSONAL INFORMATION

Patient

Date of Birth (04-Jun-1980)  -  -

Centre Nr/Country

Name of EDSS rater

Date of Examination  -  - 20

SYNOPSIS OF FS SCORES

1. Visual <sup>1</sup>	<input type="text"/>	5. Sensory	<input type="text"/>
2. Brainstem	<input type="text"/>	6. Bowel/Bladder <sup>1</sup>	<input type="text"/>
3. Pyramidal	<input type="text"/>	7. Cerebral	<input type="text"/>
4. Cerebellar	<input type="text"/>		

<sup>1</sup> converted FS Score

EDSS Step

Signature

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS	Scotoma	<input type="text"/>	<input type="text"/>
Visual acuity (corrected)	<input type="text"/>	<input type="text"/>	* Disc pallor	<input type="text"/>	<input type="text"/>
Visual fields	<input type="text"/>	<input type="text"/>	FUNCTIONAL SYSTEM SCORE	<input type="text"/>	

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION			
Extraocular movements (EOM) impairment	<input type="text"/>	Hearing loss	<input type="text"/>
Nystagmus	<input type="text"/>	Dysarthria	<input type="text"/>
Trigeminal damage	<input type="text"/>	Dysphagia	<input type="text"/>
Facial weakness	<input type="text"/>	Other bulbar functions	<input type="text"/>
		FUNCTIONAL SYSTEM SCORE	<input type="text"/>

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L		
Biceps	<input type="text"/>	<input type="text"/>	<input type="text"/>	Knee flexors	<input type="text"/>
Triceps	<input type="text"/>	<input type="text"/>	<input type="text"/>	Knee extensors	<input type="text"/>
Brachioradialis	<input type="text"/>	<input type="text"/>	<input type="text"/>	Plantar flexion (feet/toes)	<input type="text"/>
Knee	<input type="text"/>	<input type="text"/>	<input type="text"/>	Dorsiflexion (feet/toes)	<input type="text"/>
Ankle	<input type="text"/>	<input type="text"/>	<input type="text"/>	* Position test UE, pronation	<input type="text"/>
Plantar response	<input type="text"/>	<input type="text"/>	<input type="text"/>	* Position test UE, downward drift	<input type="text"/>
Cutaneous reflexes	<input type="text"/>	<input type="text"/>	<input type="text"/>	* Position test LE, sinking	<input type="text"/>
* Palmomental reflex	<input type="text"/>	<input type="text"/>	<input type="text"/>	Able to lift only one leg at a time (grade in °)	<input type="text"/>
				* Walking on heels	<input type="text"/>
LIMB STRENGTH		R	L	* Walking on toes	<input type="text"/>
Deltoids	<input type="text"/>	<input type="text"/>	<input type="text"/>	* Hopping on one foot	<input type="text"/>
Biceps	<input type="text"/>	<input type="text"/>	<input type="text"/>	SPASTICITY	
Triceps	<input type="text"/>	<input type="text"/>	<input type="text"/>	Arms	<input type="text"/>
Wrist/finger flexors	<input type="text"/>	<input type="text"/>	<input type="text"/>	Legs	<input type="text"/>
Wrist/finger extensors	<input type="text"/>	<input type="text"/>	<input type="text"/>	Gait	<input type="text"/>
Hip flexors	<input type="text"/>	<input type="text"/>	<input type="text"/>	FUNCTIONAL SYSTEM SCORE	<input type="text"/>

\* optional

**4. CEREBELLAR FUNCTIONS**

**CEREBELLAR EXAMINATION**

Head tremor	<input type="checkbox"/>	Rapid alternating movements UE impairment	<input type="checkbox"/>	<input type="checkbox"/>
Truncal ataxia	<input type="checkbox"/>	Rapid alternating movements LE impairment	<input type="checkbox"/>	<input type="checkbox"/>
	R L	Tandem walking	<input type="checkbox"/>	<input type="checkbox"/>
Tremor/dysmetria UE	<input type="checkbox"/>	Gait ataxia	<input type="checkbox"/>	<input type="checkbox"/>
Tremor/dysmetria LE	<input type="checkbox"/>	Romberg test	<input type="checkbox"/>	<input type="checkbox"/>
		Other, e. g. rebound	<input type="checkbox"/>	<input type="checkbox"/>
		<b>FUNCTIONAL SYSTEM SCORE</b>	<input type="checkbox"/>	

**5. SENSORY FUNCTIONS**

**SENSORY EXAMINATION**

	R	L	Position sense UE	<input type="checkbox"/>	<input type="checkbox"/>
Superficial sensation UE	<input type="checkbox"/>	<input type="checkbox"/>	Position sense LE	<input type="checkbox"/>	<input type="checkbox"/>
Superficial sensation trunk	<input type="checkbox"/>	<input type="checkbox"/>	* Lhermitte's sign	<input type="checkbox"/>	<input type="checkbox"/>
Superficial sensation LE	<input type="checkbox"/>	<input type="checkbox"/>	* Paraesthesiae UE	<input type="checkbox"/>	<input type="checkbox"/>
Vibration sense UE	<input type="checkbox"/>	<input type="checkbox"/>	* Paraesthesiae trunk	<input type="checkbox"/>	<input type="checkbox"/>
Vibration sense LE	<input type="checkbox"/>	<input type="checkbox"/>	* Paraesthesiae LE	<input type="checkbox"/>	<input type="checkbox"/>
			<b>FUNCTIONAL SYSTEM SCORE</b>	<input type="checkbox"/>	

**6. BOWEL/ BLADDER FUNCTIONS**

Urinary hesitancy/retention	<input type="checkbox"/>	Bowel dysfunction	<input type="checkbox"/>
Urinary urgency/incontinence	<input type="checkbox"/>	* Sexual dysfunction	<input type="checkbox"/>
Bladder catheterisation	<input type="checkbox"/>	<b>FUNCTIONAL SYSTEM SCORE</b>	<input type="checkbox"/>

**7. CEREBRAL FUNCTIONS**

**MENTAL STATUS EXAMINATION**

Depression	<input type="checkbox"/>	Decrease in mentation	<input type="checkbox"/>
Euphoria	<input type="checkbox"/>	* Fatigue	<input type="checkbox"/>
		<b>FUNCTIONAL SYSTEM SCORE</b>	<input type="checkbox"/>

**8. AMBULATION**

**Walking range as reported (without help or sticks)**

meters	<input type="checkbox"/>
in min	<input type="checkbox"/>

**Distance able to walk without rest or assistance**

≥ 100 meters, but < 200 meters	<input type="checkbox"/>
≥ 200 meters, but < 300 meters	<input type="checkbox"/>
≥ 300 meters, but < 500 meters	<input type="checkbox"/>
≥ 500 meters but not unrestricted	<input type="checkbox"/>
Unrestricted	<input type="checkbox"/>

**Actual distance (obligatory up to 500 m if possible)**

meters	<input type="checkbox"/>
--------	--------------------------

**Requires constant assistance to walk 100 meters**

Unilateral assistance (in meters)	<input type="checkbox"/>
Cane/crutch	<input type="checkbox"/>
Other	<input type="checkbox"/>
Bilateral assistance (in meters)	<input type="checkbox"/>
Canes/crutches	<input type="checkbox"/>
Other	<input type="checkbox"/>
Assistance by another person (in meters)	<input type="checkbox"/>

\* optional

\* Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale  
 Slightly modified from J.F. Kurtzke, Neurology 1983;33,1444-52  
 © L. Kappos, Department of Neurology, University Hospital, CH-4031 Basel, Switzerland; Version 12/05

Appendix 3. Components of the CSSRS will be performed at months 0, 3, 6, 9, 12, 18 and 24

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)*

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<b>SUICIDAL IDEATION</b>	
<p><i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i></p>	Since Last Visit
<p><b>1. Wish to be Dead</b>                      Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.  <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>	Yes    No <input type="checkbox"/> <input type="checkbox"/>
<p><b>2. Non-Specific Active Suicidal Thoughts</b>                      General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.  <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>	Yes    No <input type="checkbox"/> <input type="checkbox"/>
<p><b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b>                      Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."  <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>	Yes    No <input type="checkbox"/> <input type="checkbox"/>
<p><b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b>                      Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them."  <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>	Yes    No <input type="checkbox"/> <input type="checkbox"/>
<p><b>5. Active Suicidal Ideation with Specific Plan and Intent</b>                      Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.  <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>	Yes    No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>	
<p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</i></p> <p><b>Most Severe Ideation:</b> _____</p> <p style="text-align: center; margin-left: 150px;"> <span style="margin-right: 100px;">Type # (1-5)</span> <span>Description of Ideation</span> </p>	Most Severe
<p><b>Frequency</b>  <i>How many times have you had these thoughts?</i>                      (1) Less than once a week    (2) Once a week    (3) 2-5 times in week    (4) Daily or almost daily    (5) Many times each day</p>	_____
<p><b>Duration</b>  <i>When you have the thoughts, how long do they last?</i>                      (1) Fleeting - few seconds or minutes    (4) 4-8 hours/most of day                      (2) Less than 1 hour/some of the time    (5) More than 8 hours/persistent or continuous                      (3) 1-4 hours/a lot of time</p>	_____
<p><b>Controllability</b>  <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i>                      (1) Easily able to get attention, revenge or a reaction from others    (4) Can control thoughts with a lot of difficulty                      (2) Can control thoughts with little difficulty    (5) Unable to control thoughts                      (3) Can control thoughts with some difficulty    (0) Does not attempt to control thoughts</p>	_____
<p><b>Deterrents</b>  <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i>                      (1) Deterrents definitely stopped you from attempting suicide    (4) Deterrents most likely did not stop you                      (2) Deterrents probably stopped you    (5) Deterrents definitely did not stop you                      (3) Uncertain that deterrents stopped you    (0) Does not apply</p>	_____
<p><b>Reasons for Ideation</b>  <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i>                      (1) Completely to get attention, revenge or a reaction from others    (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)                      (2) Mostly to get attention, revenge or a reaction from others    (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)                      (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain    (0) Does not apply</p>	_____

Version 1/14/09

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>		Since Last Visit
<p><b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <b>any</b> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. <i>Have you made a suicide attempt?</i> <i>Have you done anything to harm yourself?</i> <i>Have you done anything dangerous where you could have died?</i> <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or did you think it was possible you could have died from _____?</i> <i>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</i> (Self-Injurious Behavior without suicidal intent) If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	
<p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p> <p><b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. <i>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>	
<p><b>Aborted Attempt:</b> When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. <i>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>	
<p><b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <i>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</i> If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	
<p><b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	
<p><b>Completed Suicide:</b></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	
<p><b>Answer for Actual Attempts Only</b></p>	<p>Most Lethal Attempt Date:</p>	
<p><b>Actual Lethality/Medical Damage:</b> 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death</p>	<p>Enter Code _____</p>	
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b> Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>	<p>Enter Code _____</p>	

**COLUMBIA-SUICIDE SEVERITY RATING SCALE**

*Screen Version - Recent*

<b>SUICIDE IDEATION DEFINITIONS AND PROMPTS</b>	<b>Past month</b>	
<b>Ask questions that are bolded and <u>underlined</u>.</b>	<b>YES</b>	<b>NO</b>
<b>Ask Questions 1 and 2</b>		
<p><b>1) Wish to be Dead:</b></p> <p>Person endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.</p> <p><b><u>Have you wished you were dead or wished you could go to sleep and not wake up?</u></b></p>		
<p><b>2) Suicidal Thoughts:</b></p> <p>General non-specific thoughts of wanting to end one’s life/commit suicide, “<i>I’ve thought about killing myself</i>” without general thoughts of ways to kill oneself/associated methods, intent, or plan.</p> <p><b><u>Have you actually had any thoughts of killing yourself?</u></b></p>		
<p><b>If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.</b></p>		

<b>SUICIDE IDEATION DEFINITIONS AND PROMPTS</b>	<b>Past month</b>	
<b>Ask questions that are bolded and <u>underlined</u>.</b>	<b>YES</b>	<b>NO</b>
<p><b>3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act):</b></p> <p>Person endorses thoughts of suicide and has thought of a least one method during the assessment period. This is different than a specific plan with time, place or method details worked out. <i>"I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it...and I would never go through with it."</i></p> <p><b><u>Have you been thinking about how you might do this?</u></b></p>		
<p><b>4) Suicidal Intent (without Specific Plan):</b></p> <p>Active suicidal thoughts of killing oneself and patient reports having <u>some intent to act on such thoughts</u>, as opposed to <i>"I have the thoughts but I definitely will not do anything about them."</i></p> <p><b><u>Have you had these thoughts and had some intention of acting on them?</u></b></p>		
<p><b>5) Suicide Intent with Specific Plan:</b></p> <p>Thoughts of killing oneself with details of plan fully or partially worked out and person has some intent to carry it out.</p> <p><b><u>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</u></b></p>		
<p><b>6) Suicide Behavior Question:</b></p>	<b>YES</b>	<b>NO</b>



<p><b><u>Have you ever done anything, started to do anything, or prepared to do anything to end your life?</u></b></p> <p>Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.</p> <p><b>If YES, ask: <u>How long ago did you do any of these?</u></b></p> <p><input type="checkbox"/> Over a year ago    <input type="checkbox"/> Between three months and a year ago    <input type="checkbox"/> Within the last three months</p>		
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**COLUMBIA-SUICIDE SEVERITY RATING SCALE**

*Screening Version – Since Last Visit*

SUICIDE IDEATION DEFINITIONS AND PROMPTS	Since Last Visit	
Ask questions that are bold and <u>underlined</u>	YES	NO
<b>Ask Questions 1 and 2</b>		
<p><b>1) Wish to be Dead:</b>                      Person endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.   <u><i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></u></p>		
<p><b>2) Suicidal Thoughts:</b>                      General non-specific thoughts of wanting to end one’s life/die by suicide, “<i>I’ve thought about killing myself</i>” without general thoughts of ways to kill oneself/associated methods, intent, or plan.   <u><i>Have you actually had any thoughts of killing yourself?</i></u></p>		
<b>If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6</b>		
<p><b>3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act):</b>                       Person endorses thoughts of suicide and has thought of a least one method during the assessment period. This is different than a specific plan with time, place or method details worked out. “<i>I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it....and I would never go through with it.</i>”   <u><i>Have you been thinking about how you might do this?</i></u></p>		

<b>SUICIDE IDEATION DEFINITIONS AND PROMPTS</b>	<b>Since Last Visit</b>	
	<b>YES</b>	<b>NO</b>
<p><b>4) Suicidal Intent (without Specific Plan):</b></p> <p>Active suicidal thoughts of killing oneself and patient reports having <u>some intent to act on such thoughts</u>, as opposed to “<i>I have the thoughts but I definitely will not do anything about them.</i>”</p> <p><b><u>Have you had these thoughts and had some intention of acting on them?</u></b></p>		
<p><b>5) Suicide Intent with Specific Plan:</b></p> <p>Thoughts of killing oneself with details of plan fully or partially worked out and person has some intent to carry it out.</p> <p><b><u>Have you started to work out or worked out the details of how to kill yourself and do you intend to carry out this plan?</u></b></p>		
<p><b>6) Suicide Behavior</b></p> <p><b><u>Have you done anything, started to do anything, or prepared to do anything to end your life?</u></b></p> <p>Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn’t swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn’t jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.</p>		

## COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Posner, Brent, Lucas, Gould, Stanley, Brown, Fisher, Zelazny, Burke, Oquendo, & Mann

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### RISK ASSESSMENT

**Instructions:** Check all risk and protective factors that apply. To be completed following the patient interview, review of medical record(s) and/or consultation with family members and/or other professionals.

Past 3 Months	Suicidal and Self-Injurious Behavior	Lifetime	Clinical Status (Recent)	
<input type="checkbox"/>	Actual suicide attempt <input type="checkbox"/> Lifetime	<input type="checkbox"/>	<input type="checkbox"/>	Hopelessness
<input type="checkbox"/>	Interrupted attempt <input type="checkbox"/> Lifetime	<input type="checkbox"/>	<input type="checkbox"/>	Major depressive episode
<input type="checkbox"/>	Aborted or Self-Interrupted attempt <input type="checkbox"/> Lifetime	<input type="checkbox"/>	<input type="checkbox"/>	Mixed affective episode (e.g. Bipolar)
<input type="checkbox"/>	Other preparatory acts to kill self <input type="checkbox"/> Lifetime	<input type="checkbox"/>	<input type="checkbox"/>	Command hallucinations to hurt self
<input type="checkbox"/>	Self-injurious behavior <i>without</i> suicidal intent	<input type="checkbox"/>	<input type="checkbox"/>	Highly impulsive behavior
<b>Suicidal Ideation</b>			<input type="checkbox"/>	Substance abuse or dependence
<b>Check Most Severe in Past Month</b>			<input type="checkbox"/>	Agitation or severe anxiety
<input type="checkbox"/>	Wish to be dead		<input type="checkbox"/>	Perceived burden on family or others
<input type="checkbox"/>	Suicidal thoughts with method (but without specific plan or intent to act)		<input type="checkbox"/>	Chronic physical pain or other acute medical problem (HIV/AIDS, COPD, cancer, etc.)

<input type="checkbox"/>	Suicidal intent (without specific plan)	<input type="checkbox"/>	Homicidal ideation
<input type="checkbox"/>	Suicidal intent with specific plan	<input type="checkbox"/>	Aggressive behavior towards others
<b>Activating Events (Recent)</b>		<input type="checkbox"/>	Method for suicide available (gun, pills, etc.)
<input type="checkbox"/>	Recent loss(es) or other significant negative event(s) (legal, financial, relationship, etc.)	<input type="checkbox"/>	Refuses or feels unable to agree to safety plan
Describe:		<input type="checkbox"/>	Sexual abuse (lifetime)
		<input type="checkbox"/>	Family history of suicide (lifetime)
<input type="checkbox"/>	Pending incarceration or homelessness	<b>Protective Factors (Recent)</b>	
<input type="checkbox"/>	Current or pending isolation or feeling alone	<input type="checkbox"/>	Identifies reasons for living
<b>Treatment History</b>		<input type="checkbox"/>	Responsibility to family or others; living with family
<input type="checkbox"/>	Previous psychiatric diagnoses and treatments	<input type="checkbox"/>	Supportive social network or family
<input type="checkbox"/>	Hopeless or dissatisfied with treatment	<input type="checkbox"/>	Fear of death or dying due to pain and suffering
<input type="checkbox"/>	Non-compliant with treatment	<input type="checkbox"/>	Belief that suicide is immoral; high spirituality
<input type="checkbox"/>	Not receiving treatment	<input type="checkbox"/>	Engaged in work or school
<b>Other Risk Factors</b>		<b>Other Protective Factors</b>	
<input type="checkbox"/>		<input type="checkbox"/>	
<input type="checkbox"/>		<input type="checkbox"/>	
<input type="checkbox"/>		<input type="checkbox"/>	
<b>Describe any suicidal, self-injurious or aggressive behavior (include dates)</b>			

**COLUMBIA-SUICIDE SEVERITY RATING SCALE**

*Psychiatric Inpatient Setting – Discharge Screener*

<b>Ask questions that are bold and <u>underlined</u></b>	<b>Discharge</b>	
<b>Ask Questions 1 and 2</b>	<b>YES</b>	<b>NO</b>
<p><b>3) Wish to be Dead:</b></p> <p>Person endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.</p> <p><b><u>While you were here in the hospital, have you wished you were dead or wished you could go to sleep and not wake up?</u></b></p>		
<p><b>4) Suicidal Thoughts:</b></p> <p>General non-specific thoughts of wanting to end one’s life/die by suicide, “<i>I’ve thought about killing myself</i>” without general thoughts of ways to kill oneself/associated methods, intent, or plan.</p> <p><b><u>While you were here in the hospital, have you actually had thoughts about killing yourself?</u></b></p>		
<b>If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6</b>		
<p><b>3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act):</b></p> <p>Person endorses thoughts of suicide and has thought of a least one method during the assessment period. This is different than a specific plan with time, place or method details worked out. “<i>I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it....and I would never go through with it.</i>”</p> <p><b><u>Have you been thinking about how you might kill yourself?</u></b></p>		

<b>Ask questions that are bold and <u>underlined</u></b>	<b>Discharge</b>	
<b>Ask Questions 1 and 2</b>	<b>YES</b>	<b>NO</b>
<p><b>4) Suicidal Intent (without Specific Plan):</b></p> <p>Active suicidal thoughts of killing oneself and patient reports having <u>some intent to act on such thoughts</u>, as opposed to “<i>I have the thoughts but I definitely will not do anything about them.</i>”</p> <p><b><u>Have you had these thoughts and had some intention of acting on them or do you have some intention of acting on them after you leave the hospital?</u></b></p>		
<p><b>5) Suicide Intent with Specific Plan:</b></p> <p>Thoughts of killing oneself with details of plan fully or partially worked out and person has some intent to carry it out.</p> <p><b><u>Have you started to work out or worked out the details of how to kill yourself either for while you were here in the hospital or for after you leave the hospital? Do you intend to carry out this plan?</u></b></p>		
<p><b>6) Suicide Behavior</b></p> <p><b><u>While you were here in the hospital, have you done anything, started to do anything, or prepared to do anything to end your life?</u></b></p> <p>Examples: Took pills, cut yourself, tried to hang yourself, took out pills but didn’t swallow any because you changed your mind or someone took them from you, collected pills, secured a means of obtaining a gun, gave away valuables, wrote a will or suicide note, etc.</p>		

**COLUMBIA-SUICIDE SEVERITY RATING SCALE**

*Daily/Shift Screen*

<b>Ask questions that are bold and <u>underlined</u></b>	<b>Since Last Asked</b>	
<b>Ask Question 2*</b>	<b>YES</b>	<b>NO</b>
<p><b>5) Suicidal Thoughts:</b></p> <p style="text-align: center;"><i><u>Since you were last asked, have you actually had thoughts about killing yourself?</u></i></p>		
<b>If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6</b>		
<p><b>3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act):</b></p> <p style="text-align: center;"><i><u>Have you been thinking about how you might do this?</u></i></p>		
<p><b>4) Suicidal Intent (without Specific Plan):</b></p> <p style="text-align: center;"><i><u>Have you had these thoughts and had some intention of acting on them?</u></i></p>		
<p><b>5) Suicide Intent with Specific Plan:</b></p> <p style="text-align: center;"><i><u>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</u></i></p>		



<b>Ask questions that are bold and <u>underlined</u></b>	<b>Since Last Asked</b>	
<b>Ask Question 2*</b>	<b>YES</b>	<b>NO</b>
<p><b>6) Suicide Behavior</b></p> <p><i><u>Have you done anything, started to do anything, or prepared to do anything to end your life?</u></i></p> <p>Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.</p> <p><i><u>If YES, what did you do?</u></i></p> <p>-----</p> <p>-----</p> <p>-----</p>		

**\* Note – for frequent assessment purposes, Question 1 has been omitted**

**COLUMBIA-SUICIDE SEVERITY RATING SCALE**

*Screener/Recent – Self-Report*

	In The Past Month	
	YES	NO
Answer Questions 1 and 2		
<b>1) Have you wished you were dead or wished you could go to sleep and not wake up?</b>		
<b>2) Have you actually had any thoughts about killing yourself?</b>		
If <b>YES</b> to 2, answer questions 3, 4, 5, and 6. If <b>NO</b> to 2, go directly to question 6		
<b>3) Have you thought about how you might do this?</b>		
<b>4) Have you had any intention of acting on these thoughts of killing yourself, as opposed to you have the thoughts but you definitely would not act on them?</b>		
<b>5) Have you started to work out or worked out the details of how to kill yourself?</b>  <i>Do you intend to carry out this plan?</i>		
	In the Past 3 Months	
<b>6) Have you done anything, started to do anything, or prepared to do anything to end your life?</b>		

	In The Past Month
<p>Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.</p> <p><i>In your entire lifetime, how many times have you done any of these things?</i></p>	

**COLUMBIA-SUICIDE SEVERITY RATING SCALE**

*Screener/Since Last Contact – Self-Report*

	Since Last Contact	
	YES	NO
Answer Questions 1 and 2		
<b>3) Have you wished you were dead or wished you could go to sleep and not wake up?</b>		
<b>4) Have you actually had any thoughts about killing yourself?</b>		_____
If <b>YES</b> to 2, answer questions 3, 4, 5, and 6. If <b>NO</b> to 2, go directly to question 6		
<b>3) Have you thought about how you might do this?</b>		
<b>4) Have you had any intention of acting on these thoughts of killing yourself, as opposed to you have the thoughts but you definitely would not act on them?</b>		

	Since Last Contact	
<p><b>5) Have you started to work out or worked out the details of how to kill yourself?</b></p> <p><i>Do you intend to carry out this plan?</i></p>		
<p><b>6) Have you done anything, started to do anything, or prepared to do anything to end your life?</b></p> <p>Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.</p> <p><i>If YES, How many times have you done any of these things?</i></p>		←

Appendix 4. Professional Quality of Life Scale (ProQOL)

## Professional Quality of Life Scale (ProQOL)

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*Compassion Satisfaction and Compassion Fatigue  
(ProQOL) Version 5 (2009)*

When you [help] people you have direct contact with their lives. As you may have found, your compassion for those you [help] can affect you in positive and negative ways. Below are some questions about your experiences, both positive and negative, as a [helper]. Consider each of the following questions about you and your current work situation. Select the number that honestly reflects how frequently you experienced these things in the last 30 days.

<b>1=Never</b>	<b>2=Rarely</b>	<b>3=Sometimes</b>	<b>4=Often</b>	<b>5=Very Often</b>
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- \_\_\_\_\_ 1. I am happy.
- \_\_\_\_\_ 2. I am preoccupied with more than one person I [help].
- \_\_\_\_\_ 3. I get satisfaction from being able to [help] people.
- \_\_\_\_\_ 4. I feel connected to others.
- \_\_\_\_\_ 5. I jump or am startled by unexpected sounds.
- \_\_\_\_\_ 6. I feel invigorated after working with those I [help].
- \_\_\_\_\_ 7. I find it difficult to separate my personal life from my life as a [helper].
- \_\_\_\_\_ 8. I am not as productive at work because I am losing sleep over traumatic experiences of a person I [help].
- \_\_\_\_\_ 9. I think that I might have been affected by the traumatic stress of those I [help].
- \_\_\_\_\_ 10. I feel trapped by my job as a [helper].
- \_\_\_\_\_ 11. Because of my [helping], I have felt "on edge" about various things.
- \_\_\_\_\_ 12. I like my work as a [helper].
- \_\_\_\_\_ 13. I feel depressed because of the traumatic experiences of the people I [help].
- \_\_\_\_\_ 14. I feel as though I am experiencing the trauma of someone I have [helped].
- \_\_\_\_\_ 15. I have beliefs that sustain me.
- \_\_\_\_\_ 16. I am pleased with how I am able to keep up with [helping] techniques and protocols.
- \_\_\_\_\_ 17. I am the person I always wanted to be.
- \_\_\_\_\_ 18. My work makes me feel satisfied.
- \_\_\_\_\_ 19. I feel worn out because of my work as a [helper].
- \_\_\_\_\_ 20. I have happy thoughts and feelings about those I [help] and how I could help them.
- \_\_\_\_\_ 21. I feel overwhelmed because my case [work] load seems endless.
- \_\_\_\_\_ 22. I believe I can make a difference through my work.
- \_\_\_\_\_ 23. I avoid certain activities or situations because they remind me of frightening experiences of the people I [help].
- \_\_\_\_\_ 24. I am proud of what I can do to [help].
- \_\_\_\_\_ 25. As a result of my [helping], I have intrusive, frightening thoughts.
- \_\_\_\_\_ 26. I feel "bogged down" by the system.
- \_\_\_\_\_ 27. I have thoughts that I am a "success" as a [helper].
- \_\_\_\_\_ 28. I can't recall important parts of my work with trauma victims.
- \_\_\_\_\_ 29. I am a very caring person.
- \_\_\_\_\_ 30. I am happy that I chose to do this work.

**PROFESSIONAL QUALITY OF LIFE SCALE (PROQOL)**

COMPASSION SATISFACTION AND COMPASSION FATIGUE  
 (PROQOL) VERSION 5 (2009)

When you [help] people you have direct contact with their lives. As you may have found, your compassion for those you [help] can affect you in positive and negative ways. Below are some questions about your experiences, both positive and negative, as a [helper]. Consider each of the following questions about you and your current work situation. Select the number that honestly reflects how frequently you experienced these things in the last 30 days.

**1=Never                      2=Rarely                      3=Sometimes                      4=Often                      5=Very Often**

- \_\_\_\_\_ 1. I am happy.
- \_\_\_\_\_ 2. I am preoccupied with more than one person I [help].
- \_\_\_\_\_ 3. I get satisfaction from being able to [help] people.
- \_\_\_\_\_ 4. I feel connected to others.
- \_\_\_\_\_ 5. I jump or am startled by unexpected sounds.
- \_\_\_\_\_ 6. I feel invigorated after working with those I [help].
- \_\_\_\_\_ 7. I find it difficult to separate my personal life from my life as a [helper].
- \_\_\_\_\_ 8. I am not as productive at work because I am losing sleep over traumatic experiences of a person I [help].
- \_\_\_\_\_ 9. I think that I might have been affected by the traumatic stress of those I [help].
- \_\_\_\_\_ 10. I feel trapped by my job as a [helper].
- \_\_\_\_\_ 11. Because of my [helping], I have felt "on edge" about various things.
- \_\_\_\_\_ 12. I like my work as a [helper].
- \_\_\_\_\_ 13. I feel depressed because of the traumatic experiences of the people I [help].
- \_\_\_\_\_ 14. I feel as though I am experiencing the trauma of someone I have [helped].
- \_\_\_\_\_ 15. I have beliefs that sustain me.
- \_\_\_\_\_ 16. I am pleased with how I am able to keep up with [helping] techniques and protocols.
- \_\_\_\_\_ 17. I am the person I always wanted to be.
- \_\_\_\_\_ 18. My work makes me feel satisfied.
- \_\_\_\_\_ 19. I feel worn out because of my work as a [helper].
- \_\_\_\_\_ 20. I have happy thoughts and feelings about those I [help] and how I could help them.
- \_\_\_\_\_ 21. I feel overwhelmed because my case [work] load seems endless.
- \_\_\_\_\_ 22. I believe I can make a difference through my work.
- \_\_\_\_\_ 23. I avoid certain activities or situations because they remind me of frightening experiences of the people I [help].
- \_\_\_\_\_ 24. I am proud of what I can do to [help].
- \_\_\_\_\_ 25. As a result of my [helping], I have intrusive, frightening thoughts.
- \_\_\_\_\_ 26. I feel "bogged down" by the system.
- \_\_\_\_\_ 27. I have thoughts that I am a "success" as a [helper].
- \_\_\_\_\_ 28. I can't recall important parts of my work with trauma victims.
- \_\_\_\_\_ 29. I am a very caring person.
- \_\_\_\_\_ 30. I am happy that I chose to do this work.

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