International Guillain-Barré Syndrome Outcome Study (IGOS):

Protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome

Bart C. Jacobs1,2, Bianca van den Berg1,+, Christine Verboon1,+, Govindsinh Chavada3, David R. Cornblath4, Kenneth C. Gorson5, Thomas Harbo6, Hans-Peter Hartung7, Richard A.C. Hughes8, Susumu Kusunoki9, Pieter A. van Doorn1, Hugh J. Willison3, the IGOS Consortium*

1Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
2Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
3Department of Neurology, University of Glasgow, Glasgow, Scotland, United Kingdom
4Department of Neurology, Johns Hopkins University, Baltimore, United States of America
5Department of Neurology, St. Elizabeth’s Medical Center, Tufts University School of Medicine, Boston, United States of America
6Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
7Department of Neurology, University of Düsseldorf, Düsseldorf, Germany
8Department of Neurology, Institute of Neurology, University College, London, United Kingdom
9Department of Neurology, Kinki University School of Medicine, Osaka, Japan

B.C. Jacobs: b.jacobs@erasusmc.nl
B. van den Berg: b.vandenberg.2@erasusmc.nl
C. Verboon: j.verboon@erasusmc.nl
G. Chavada: govindsinh.chavada@glasgow.ac.uk

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jns.12209

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D.R. Cornblath: dcornbl@jhmi.edu

K. C. Gorson: kengorson@comcast.net

T. Harbo: thanbo@dadlnet.dk

H.P. Hartung: Hans-Peter.Hartung@uni-duesseldorf.de

R.A.C. Hughes: rhughes11@btinternet.com

S. Kusunoki: kusunoki-tky@umin.ac.jp

P.A. van Doorn: p.a.vandoorn@erasusmc.nl

H.J. Willison: Hugh.Willison@glasgow.ac.uk

*These co-authors contributed equally

*Full list of author information is presented in the Appendix

Corresponding author:

Prof. B.C. Jacobs

Departments of Neurology and Immunology
Erasmus MC University Medical center

P.O. Box 2040, 3000 CA
Rotterdam, The Netherlands

Telephone number 0031 10 7043999

b.jacobs@erasusmc.nl or gbsstudies@erasusmc.nl

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Abstract

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy with a highly variable clinical presentation, course, and outcome. The factors that determine the clinical variation of GBS are poorly understood which complicates the care and treatment of individual patients. The protocol of the ongoing International GBS Outcome Study (IGOS), a prospective, observational, multi-centre cohort study that aims to identify the clinical and biological determinants and predictors of disease onset, subtype, course and outcome of GBS is presented here. Patients fulfilling the diagnostic criteria for GBS, regardless of age, disease severity, variant forms, or treatment, can participate if included within two weeks after onset of weakness. Information about demography, preceding infections, clinical features, diagnostic findings, treatment, course and outcome is collected. In addition, cerebrospinal fluid and serial blood samples for serum and DNA is collected at standard time points. The original aim was to include at least 1000 patients with a follow-up of 1-3 years. Data are collected via a web-based data entry system and stored anonymously. IGOS started in May 2012 and by January 2017 included more than 1400 participants from 143 active centres in 19 countries across 5 continents. The IGOS data/biobank is available for research projects conducted by expertise groups focusing on specific topics including epidemiology, diagnostic criteria, clinimetrics, electrophysiology, antecedent events, antibodies, genetics, prognostic modelling, treatment effects and long-term outcome of GBS. The IGOS will help to standardize the international collection of data and biosamples for future research of GBS.

Keywords: Guillain-Barré syndrome, diagnosis, treatment, prognosis, outcome, biomarkers

ClinicalTrials.gov Identifier: NCT01582763
Introduction

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy clinically characterized by a rapidly progressive symmetrical flaccid weakness of the limbs (van den Berg, et al., 2014; Willison, et al., 2016). The clinical presentation, course and outcome of GBS is variable. Some patients have mild weakness of the lower legs only, while others develop complete tetraplegia and respiratory failure requiring mechanical ventilation (van den Berg, et al., 2014; Willison, et al., 2016). Patients may have variant forms of GBS, including Miller Fisher syndrome (MFS), pure motor, paraparetic or pharyngeal-cervical-brachial forms (van den Berg, et al., 2014; Wakerley, et al., 2014; Willison, et al., 2016). The electrophysiological findings are equally heterogeneous with subgroups of patients showing features of either demyelination or axonal degeneration (Hadden, et al., 1998; Ho, et al., 1995; Uncini and Kuwabara, 2012). The clinical recovery also varies: some patients recover spontaneously with no residual limitations, while others require mechanical ventilation for months and remain wheelchair bound for the rest of their lives or even die despite treatment (van den Berg, et al., 2014; Willison, et al., 2016). Independent of the GBS subtype, severity or predicted outcome, the standard treatment regimen for the past two decades has consisted of intravenous immunoglobulin (IVlg) or plasma exchange (PE) (Hughes, et al., 2007; Hughes, et al., 2014; Raphael, et al., 2012). Despite treatment, outcome of GBS is frequently poor since 2-5% of the patients die and 10-20% of patients remain severely disabled (Fokke, et al., 2014; Hughes, et al., 2007; Willison, et al., 2016). Outcome is even...
worse in low-income countries: in Bangladesh for example 85% of patients receive no treatment, 15% die, and 30% remain severely disabled (Islam, et al., 2010). These findings show the need for more effective, personalized and accessible treatments worldwide.

The factors that determine the heterogeneity of GBS and that could provide a basis to personalize treatment are largely unknown. Previous studies observed an association between the clinical course in patients and the acute phase clinical characteristics or biomarkers such as electrophysiological subtype, preceding infections, anti-ganglioside antibodies, serum levels of IgG and albumin and genetic polymorphisms (Fokkink, et al., 2016; Geleijns, et al., 2006; Kuitwaard, et al., 2009; Kusunoki, et al., 2008; van Koningsveld, et al., 2007; Walgaard, et al., 2010; Walgaard, et al., 2011; Walgaard, et al., 2016). However, most of these studies were retrospective, and the findings were derived from relatively small series or selected groups of patients with a short follow-up period using a limited set of suboptimal outcome measures. In addition, the variety in inclusion criteria and methods used in these studies complicates comparing or combining collected data. Moreover, GBS varies considerably between geographical regions (Kuwabara and Yuki, 2013; Mori, et al., 2012; Willison, et al., 2016). Solving these problems requires a prospective study design with standardized collection of clinical data and biomaterials from a large group of well-defined GBS patients with a long follow-up period. The International GBS Outcome Study (IGOS) was initiated to collect the required clinical data and biosamples. After several organizational meetings, a final study protocol was prepared, and local investigators were invited to participate. IGOS is being conducted in collaboration with the Peripheral Nerve Society and Inflammatory Neuropathy Consortium (INC) (www.pnsociety.com/inflammatory-neuropathy-consortium/), an international organization of clinical neurologists and scientists involved in the investigation and care of patients with GBS.

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**Study aim and objectives**

The overall aim of IGOS is to determine the clinical and biological determinants and predictors of the clinical course and outcome of GBS. The objectives are: (1) to define the variation in clinical presentation, subtypes, progression and recovery of GBS in patients from a broad range of geographical areas, (2) to describe the current practice of diagnosis, treatment, and care for GBS, (3) to identify environmental and host factors that determine the disease onset and the variation in clinical course, treatment response and outcome, (4) to develop improved prognostic models to predict the clinical course and outcome in individual patients, and (5) to facilitate the collection of standardized and relevant data and biosamples for future studies of GBS.

**Methods and Materials**

**Study design**

IGOS is an international, prospective, observational, multi-center cohort study. It uses a predefined protocol to collect data regarding baseline characteristics, clinical presentation and course, electrophysiology, diagnosis, treatment and outcome during a follow-up of 1 year with the possibility to extend the follow-up to 2 or 3 years (Figure 1). The protocol specifies the timing of the collection of biosamples, including blood for DNA and serum studies and cerebrospinal fluid (CSF). Predictive models for the clinical course and outcome will be based on results collected in the first two weeks. The first 1000 participants will constitute a derivation cohort. The next 500 or more patients will provide a validation cohort.

**Inclusion and exclusion criteria for patients**

Inclusion requires fulfilling the following criteria:
1. The diagnostic criteria for GBS of the National Institute of Neurological Disorders and Stroke (NINDS) (See supplement 1), or one of the variants of GBS, including the MFS and overlap syndromes (Asbury and Cornblath, 1990; Sejvar, et al., 2011; Wakerley, et al., 2014).

2. Entry within two weeks of onset of weakness (or other symptoms attributed to GBS).

3. Opportunity to continue a follow-up for at least one year.

4. Informed consent of the participant or, for children, the parents or legal guardians.

The aim is to enroll patients representing the full spectrum of GBS. There are no exclusion criteria, and all patients with GBS or its variants, including MFS and overlap forms, may participate, regardless of age, disease severity, or treatment.

IGOS data- and biobank

Baseline, clinical and treatment data

We collect baseline data about the patients’ demography, co-morbidity, family history and antecedent events. In addition, we record the first clinical symptoms and signs of GBS, the timing and key features of the diagnosis, hospital transfers, neurological examination findings and the clinical course. The severity and distribution of clinical manifestations of GBS will be documented in detail, including cranial nerve deficits, limb weakness using the MRC sum score (Kleyweg, et al., 1991) and Rasch-built MRC score (Vanhoutte, et al., 2012), sensory deficits, ataxia, limb tendon reflexes, GBS disability scale (Hughes, et al., 1978), pain, autonomic dysfunction, respiratory failure, and associated medical complications. In addition, we record the occurrence of treatment related fluctuations and transitions to chronic inflammatory demyelinating polyneuropathy (CIDP) (Ruts, et al., 2010). From 4
weeks onward, we collect the following clinical outcome measures: Overall Neuropathy Limitation Scale (ONLS) (Graham and Hughes, 2006), Rasch-built Overall Disability Score (R-ODS) (van Nes, et al., 2011), Fatigue Severity Scale (FSS) (and Rasch-built FSS) (van Nes, et al., 2009) and the EuroQol EQ-5D health questionnaire (Brooks, 1996) (Figure 1). A full neurological examination will be performed at study entry and after 1 week, 2 weeks, 4 weeks, 26 (± 2) weeks and 52 (± 4) weeks. Participants still in hospital at 8 (± 1) weeks and 13 (± 1) weeks will be examined but those who have been discharged have only a telephone assessment of the GBS disability scale, ONLS, R-ODS, FSS and EuroQol EQ-5D. All patient reported outcome measures have been translated (and back translated) into the language of the participants. We collect detailed information about the treatment for GBS including the type, timing, regimen and side-effects of treatment, admission to intensive care, and start and end of mechanical ventilation. If a patient dies, we document the timing and cause of death.

**Electrophysiology data**

We collect the results of the routine diagnostic electrophysiological examinations, including the raw data and the local investigators’ interpretation and classification of the subtype, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), inexcitable nerves, and equivocal or normal results. The study protocol recommends performing electrophysiological studies according to a predefined standard format (see Supplement 2). Some clinics routinely perform a second diagnostic nerve conduction study and we collect these results when available. We document locally used normative values and standard electrophysiology protocols.
**Blood samples**

We collect blood and CSF samples according to a predefined schedule (Figure 1). Blood samples provide serum and DNA. The protocol specifies that the first serum sample is to be collected before the start of treatment, although in some patients treatment is being initiated before study entry (e.g., when patients transfer to a center participating in IGOS after treatment at a local community hospital). Blood samples are frozen and stored at -80°C (or initially stored -20°C for a maximum of 6 months) at the local center or at the center of the country coordinator, and transported on dry ice to a central biobank, at Erasmus MC in Rotterdam, the Netherlands, with a reserve biobank at the University of Glasgow, Scotland, UK.

**Cerebrospinal fluid samples**

If participants have a routine lumbar puncture to examine CSF for diagnostic studies, we keep an aliquot for biomarker studies. In centers participating in an advanced proteomics study, an extra aliquot is sampled (Teunissen, et al., 2009). This study requires centrifugation of the CSF sample within one hour after the lumbar puncture. The supernatant (without pellet) is removed and immediately stored in a polystyrene tube at -20°C until being transferred to the country coordinating center and stored at -80°C. This optional research module requires additional informed consent.

**Extended follow-up of two and three years**

The time course of nerve regeneration and clinical recovery in GBS is unclear. Some patients continue to improve even after one year (Dhar, et al., 2008; Rudolph, et al., 2008). To determine the further recovery and long-term residual deficits, there is an optional long-term follow-up research module with a telephone assessment at 2 years (104 ± 4 weeks) and 3 years (156 ± 4 weeks) after
onset. The data collected then include the GBS disability score, ONLS, R-ODS, FSS (and Rasch-FSS), and EuroQol EQ-5D. Severely affected patients may have more extensive evaluation including neurological examination at each visit. The long-term follow-up requires additional informed consent.

*Children with GBS*

Children with GBS differ from adult patients regarding their preceding infections, clinical features, GBS subtype, treatment and outcome (*Korinthenberg, et al., 2007; Roodbol, et al., 2011*). In children it is more difficult to obtain biosamples and the adult outcome measures have not all been validated. For this reason we are using an adapted protocol for children with age-dependent sampling of biomaterials and clinical assessment scales.

*Data collection*

We have developed a web-based data entry system that meets the standards of security and privacy of Erasmus MC, the host institution. The local investigators use this website to enter the data. The information stored is strictly anonymous. All participants have a unique code for use throughout the study. The quality of the collected data is controlled regularly by the IGOS Coordinating Center according to protocol and additional controls will be conducted by the IGOS Expertise Groups.

*Sample size*

The extent of the clinical variation of GBS in the world is currently unknown and limits the possibility to conduct a power calculation. There is only circumstantial evidence available to estimate the required size of the study. It is recommended for the development of predictive logistic regression
models that the smallest outcome group should include at least 100 patients (Vergouwe, et al., 2005). Previous therapeutic trials with GBS defined poor outcome as a GBS disability score of >2 (not being able to walk unaided or worse) (Hughes, et al., 1978). In treatment trials about 10-15% of participants have had a poor outcome after one year (Hughes, et al., 2007; van Koningsveld, et al., 2007). If we aim to include at least 100 participants with a poor outcome defined in this way, the whole study will need at least 1000 participants. Therefore this is the minimum size of the derivation cohort to identify new clinical and biological markers to predict poor outcome or evaluate previously described prognostic factors. In addition, we collect an independent validation cohort of at least 500 patients to validate any new clinical or biomarkers that emerge from the derivation cohort.

Statistical analyses

Descriptive statistics are used to analyze the clinical data. We will develop prognostic models to evaluate the use of biomarkers and clinical characteristics to predict outcome in clinical practice according to our previously published statistical approaches (van Koningsveld, et al., 2007; Walgaard, et al., 2010; Walgaard, et al., 2011). The association between putative prognostic factors and outcome variables will be analyzed using univariate and multivariable logistic regression models. If two similar variables are equally associated with outcome, the variable most easily obtainable in clinical practice will be selected. We will quantify model performance with respect to discrimination (area under receiver operating characteristic curve). Multivariable regression coefficients will be used to develop new prognostic models for GBS.

IGOS Consortium and IGOS Research Policy Agreement
IGOS is conducted by the IGOS Consortium which consists of (1) the members of the Steering Committee, (2) the staff of the Coordinating Center at Erasmus MC, Rotterdam, the Netherlands, (3) the Country Coordinators and (4) their networks of local investigators (see Appendix). To be able to participate in IGOS and to become a member of the IGOS Consortium all participants signed the IGOS Consortium Agreement which defined the conduct of the study. All members of the IGOS Consortium can apply to the Steering Committee to use the IGOS data/biobank to address specific research questions. Research projects are also being conducted by the Expertise Groups, consisting of members of the IGOS Consortium and additional researchers if external expertise is required.

**Ethical regulations**

The IGOS received approval from the Medical Ethics Review Committee of the Erasmus MC Medical University Rotterdam in 2012. Each participating center also had approval from their local Institutional Review Board (IRB). The IGOS is being conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and the Medical Research Involving Human Subjects (WMO). The procedures set out in this protocol were designed to ensure that the investigators abide by the principles of the GCP guidelines of the European Community (ICH topic E6, CPMP/ICH/135/95, Directive 2001/20/EC) in the conduct, evaluation and documentation of this study. Inclusion in IGOS requires informed consent from each participant or their legal representative. IGOS was registered before the start of the study at ClinicalTrials.gov (NCT01582763).
Discussion

IGOS started in May 2012 and in June 2015 IGOS had enrolled 1000 patients who will form the derivation cohort (Figure 2). By January 2017, more than 1400 patients with GBS had been included in IGOS by 143 active sites from 19 countries across five continents (Figure 3). We are continuing to recruit more patients to complete the independent validation cohort, and anticipate enrollment of 1500 patients by July 2017.

IGOS has important advantages over previous observational studies of GBS. First, IGOS already includes the largest number of prospectively collected patients with a confirmed diagnosis of GBS. Second, there was no selection of patients based on age, clinical subtype or severity, aiming to investigate the full range of variants within the spectrum of GBS. Third, we collected data from patients from various geographical regions, including high- and low-income countries using the same protocol and will be able to compare and contrast various attributes of the condition worldwide. Fourth, IGOS has a long follow-up period and uses several well-defined and validated outcome measures to assess the long-term outcome of GBS. Fifth, we are collecting biosamples prospectively according to the protocol at recruitment and follow-up visits coinciding with clinical assessments. We will use these samples to study preceding infections, antibodies to peripheral nerves and other immunological factors, pharmacokinetics, genetic factors, and other potential biomarkers for correlation with clinical features. Because of these advantages, IGOS will provide the most extensive research data- and biobank of GBS patients collected so far. This will enhance our understanding of the pathogenesis and the individual clinical course, prognosis, treatment response and outcome. The overall aim is to develop more effective personalized treatment regimens based on a better understanding of the variation of the disease.
IGOS has already enhanced international collaboration in research into the cause and treatment of GBS by strengthening international networks. Expertise Groups will be formed on various topics including (1) emerging preceding events related to GBS, (2) diagnostic criteria and protocols for GBS, (3) electrophysiological subtypes of GBS, (4) biological determinants including genetic polymorphisms, preceding infections and serum antibodies in the pathogenesis of GBS and its subtype, (5) biomarkers for monitoring treatment, pharmacokinetics and disease activity, (6) validating and improving outcome measures, (7) long-term outcome, (8) prediction of prognosis, and (9) improving treatment.

By providing an infrastructure for standardized collection of data and biomaterials, IGOS will facilitate international research projects on emerging infections associated with GBS, such as the recent outbreak of Zika virus infection (Cao-Lormeau, et al., 2016; Parra, et al., 2016). This infrastructure will also help to record other emerging preceding events that have been previously related to the development of GBS, including vaccinations. Our aim is also to use the international expertise involved in IGOS and the collected materials to compare and standardize assays for relevant biomarkers in GBS including preceding infections, antibodies, genetic polymorphisms and pharmacokinetic analysis. The extensive recording of the clinical course and outcome at serial visits during long-term follow-up provides a unique opportunity for international validation of outcome measures that so far have been developed in limited regions only. The IGOS data- and biobank provide an easily accessed source of control natural history data for modelling studies and comparison with patients treated with novel treatment regimens. One ongoing study is already comparing one with two courses of IVIg in patients with a poor predicted outcome (International Second IVIg Dose GBS Study). A second observational study within IGOS is comparing IVIg treatment with supportive care alone for patients with initially mild GBS. IGOS provides an exciting opportunity
to support future clinical trials. The consortium is open to collaboration with other academic partners and with pharmaceutical companies interested in improving the treatment of GBS.

**Funding**

The IGOS study protocol was developed without external financial support. The development of a web-based data entry support was supported by funding from the GBS-CIDP Foundation International (https://www.gbs-cidp.org/). Additional funding to support the conduct of IGOS for specific countries or projects was received from gain (http://www.gaincharity.org.uk/), Erasmus MC, Rotterdam, The Netherlands, University of Glasgow, Glasgow, United Kingdom, Grifols, CSL Behring, Shire Pharmaceuticals and Annexon. IGOS is scientifically independent, and the funding agencies have no influence on the study and infrastructure design of IGOS, nor on the collection, statistical analysis and interpretation of the data collected in IGOS, nor on the writing, publication of manuscripts or other presentations based on these data.
References


Figures

**Figure 1.** Time schedule of research protocol for the IGOS database and biobank.

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Legend figure 1.

The filled blocks refer to obligatory studies, the striped to optional substudies. The timeline represents the follow-up period after study entry in weeks. The first 2 weeks focus on collecting data and biomaterials to predict the clinical course and outcome in the period after 2 weeks. Blood samples are obtained as indicated for serial serological studies and for DNA extraction. Routine diagnostic electrophysiology will be conducted in the first or second week, and as an optional study at 4 weeks. * At 8 weeks and 13 weeks patients admitted at the hospital will have a full examination.
and serum sampling but discharged patients will have telephone assessment only and no serum sampling.

1 Patient reported outcome measures (PROM) used are R-ODS, FSS, Rasch-FSS, EuroQol EQ-5D.

**Figure 2.** Countries with hospitals participating in IGOS.

Legend figure 2

Worldwide representation of IGOS in 19 countries (indicated in orange) including Argentina, Australia, Bangladesh, Belgium, Canada, China, Denmark, France, Germany, Greece, Italy, Japan, Malaysia, Netherlands, South Africa, Spain, Taiwan, United Kingdom and United States of America.
Figure 3. Quarterly number of patients included in IGOS.

Figure 4. Logo for the International GBS Outcome Study (IGOS).
Appendix: Persons involved in IGOS Consortium

IGOS Steering committee
B.C. Jacobs (chair)\textsuperscript{1,2}, R.A.C. Hughes\textsuperscript{3}, D.R. Cornblath\textsuperscript{4}, K.C. Gorson\textsuperscript{5}, H.P. Hartung\textsuperscript{6}, S. Kusunoki\textsuperscript{7}; P.A. van Doorn\textsuperscript{1}, H.J. Willison\textsuperscript{8}

IGOS Coordinating Center at Erasmus MC, Rotterdam, the Netherlands
M. van Woerkom\textsuperscript{1}, B. van den Berg\textsuperscript{1}, C. Verboon\textsuperscript{1}, J. Roodbol\textsuperscript{1}, B.C. Jacobs\textsuperscript{1,2}

IGOS Country coordinators
Argentina: R.C. Reisin\textsuperscript{9}, Australia: S.W. Reddel\textsuperscript{10}, Bangladesh: Z. Islam\textsuperscript{11}, B. Islam\textsuperscript{11}, Q.D. Mohammad\textsuperscript{12}; Belgium: P. van den Bergh\textsuperscript{13}; Canada: T.E. Feasby\textsuperscript{14}; China: Y.Z. Wang\textsuperscript{15}; Denmark: T. Harbo\textsuperscript{16}; France: Y. Péréon\textsuperscript{17}; Germany: H.P. Hartung\textsuperscript{6}, H.C. Lehmann\textsuperscript{18}; Greece: E. Dardiotis\textsuperscript{19}; Italy: E. Nobile-Orazio\textsuperscript{20}; Japan: S. Kusunoki\textsuperscript{7}; Malaysia: N. Shahrizaila\textsuperscript{21}; the Netherlands: B.C. Jacobs\textsuperscript{1,2}, B. van den Berg\textsuperscript{1}, C. Verboon\textsuperscript{1}; South-Africa: K. Bateman\textsuperscript{22}; Spain: I. Illa\textsuperscript{23}, L.A. Quero\textsuperscript{23}; Taiwan: S.T. Hsieh\textsuperscript{24}; United Kingdom: H.J. Willison\textsuperscript{8}, G. Chavada\textsuperscript{8}, A. Davidson\textsuperscript{8}; United States of America: K.C. Gorson\textsuperscript{4}

Affiliations:
Dept. of \textsuperscript{1}Neurology and \textsuperscript{2}Immunology, Erasmus Medical Center, Wytemaweg 80, 3015 CN, Rotterdam, The Netherlands
\textsuperscript{3}MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, PO Box 114, Queen Square, London, WC1N 3BG, United Kingdom
Dept. of Neurology, Johns Hopkins University, Meyer 6-181a, Baltimore, MD 21287-7681, United States of America

Dept. of Neurology, Tufts University, School of Medicine, 736 Cambridge Street, MA 02135 Boston, United States of America

Dept. of Neurology, University of Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany

Dept. of Neurology, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan

Dept. of Neurology, University of Glasgow, Glasgow G12 8QQ, United Kingdom

Dept. of Neurology, Hospital Britanico, Ambrosetti 618. 3rd Floor. Buenos Aires (1405), Argentina

Dept. of Neurology, Concord Repatriation General Hospital, Hospital Road, Concord NSW 2139, Sydney, Australia

Dept. of Emerging Disease and Immunobiology Research Group, ICDDR,B, 68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka-1212, Bangladesh

Dept. of Neurology, Dhaka Medical College & Hospital, Dhaka 1000, Bangladesh, Bangladesh

Dept. of Neurology13, University Clinic St. Luc, Avenue Hippocrate 10 – 1200 Brussels, Belgium

Dept. of Clinical Neurosciences, University of Calgary, Room 3D08, TRW Building 3330 Hospital Drive, NW, Calgary, Alberta T2N 4N1, Canada

Dept. of Neurology, Affiliated Hospital of Jining Medical College, 89 Guhuai Road, Jining City, Shandong Province, China

Dept. of Neurology, Aarhus University Hospital, Nørrebrogade 44, DK – 8000 Aarhus, Denmark

17Reference Centre for Neuromuscular Disorders Loire-Bretagne - Filnemus, Nantes University Hospital, CHU Nantes, France

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Dept. of 18Neurology, University Hospital of Cologne, Universitätsklinikum Köln, Kerpener Straße 62
D-50937 Cologne, Germany

Dept. of 19Neurology, University of Thessaly, Hospital of Larissa, Mezourlo, 41110, Larissa Thessaly, Greece

Dept. of 20Neurology, Milan University, Via Manzoni 56, 20089 (Rozzano) Milan, Italy

Dept. of 21Neurology, University of Malaya, Department of Medicine, Faculty of Medicine Building, 50603 Kuala Lumpur, Malaysia

Dept. of 22Neurology, Groote Schuur Hospital, University of Cape Town, E8, Neurology Division, Observatory, 7935, Cape Town, South Africa

Dept. of 23Neurology, Hospital Santa Creu i Sant Pau, Sant Antoni M. Claret 167, 08025 Barcelona, Spain

Dept. of 24Neurology, National Taiwan University Hospital, Department of Neurology, 7 Chung-Shan S. Road, Taipei 10002, Taiwan

IGOS Local Investigators

J.M. Addington, USA; S. Ajroud-Driss, USA; H. Andersen, Denmark; G. Antonini, Italy; S. Attarian, France; U. Badrising, The Netherlands; F.A. Barroso, Argentina; L. Benedetti, Italy; A. Beronio, Italy; M. Bianco, Italy; D. Binda, Italy; C.Briani, Italy; J. Bürmann, Germany; I.R. Bella, USA, T.E. Bertorini, USA; R. Bhavaraju-Sanka, USA; T.H. Brannagan, USA; M. Busby, UK; S. Butterworth, UK; M. Campagnolo, Italy; C. Casasnovas, Spain; G. Cavaletti, Italy; C.S. Chao, S. Chen, USA; S. Chetty, South-Africa; K.G. Claeys, Germany and Belgium; J.A. Cohen, USA; M.E. Conti, Argentina; J.S. Cosgrove, UK; M.C. Dalakas, USA; M.M. Dimachkie, USA; U. Dillmann, Germany; C. Domínguez González, Spain; K. Doppler, Germany; C. Dornonville de la Cour, Denmark; A. Echaniz-Laguna, France; F. Eftimov, The
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Supplement Table 1: Diagnostic criteria for Guillain-Barré syndrome (GBS)

Features required for diagnosis
Progressive weakness in both arms and legs (might start with weakness only in the legs)
Areflexia (or decreased tendon reflexes)

Features that strongly support diagnosis
Progression of symptoms over days to 4 weeks
Relative symmetry of symptoms
Mild sensory symptoms or signs
Cranial nerve involvement, especially bilateral weakness of facial muscles
Autonomic dysfunction
Pain (often present)
High concentration of protein in CSF
Typical electrodiagnostic features

Features that should raise doubt about the diagnosis
Severe pulmonary dysfunction with limited limb weakness at onset
Severe sensory signs with limited weakness at onset
Bladder or bowel dysfunction at onset
Fever at onset
Sharp sensory level
Slow progression with limited weakness without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or CIDP)
Marked persistent asymmetry of weakness
Persistent bladder or bowel dysfunction
Increased number of mononuclear cells in CSF (>50×10^6/L)
Polymorphonuclear cells in CSF

Legend supplement Table 1
Adapted from Asbury and Cornblath et al. (Asbury and Cornblath, 1990)
Supplement Table 2: Recommended protocol for routine diagnostic electrophysiology
### Motor nerve conductions studies

<table>
<thead>
<tr>
<th></th>
<th>Responsive (yes/no)</th>
<th>DML (ms)</th>
<th>Distal CMAP amplitude (baseline-peak) (mV)</th>
<th>Prox. CMAP ampl. I (baseline-peak) (mV)</th>
<th>Prox. CMAP ampl. II (baseline-peak) (mV)</th>
<th>NCV I (m/s)</th>
<th>NCV II (m/s)</th>
<th>Minimal F-wave latency (&gt;10) (ms)</th>
<th>H-M lat (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Median nerve–APB (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2. Ulnar nerve–ADM (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3. Peroneal nerve–EDB (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>4. Other nerve*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>5. H-reflex m. soleus (nd)</td>
<td>X</td>
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<td></td>
<td></td>
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</table>

### Sensory nerve conductions studies

<table>
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<tr>
<th></th>
<th>Responsive (yes/no)</th>
<th>DSL (ms)</th>
<th>Distal SNAP amplitude (baseline-peak) (μV)</th>
<th>Prox. SNAP ampl. I (baseline-peak) (μV)</th>
<th>Prox. SNAP ampl. II (baseline-peak) (μV)</th>
<th>NCV I (m/s)</th>
<th>NCV II (m/s)</th>
<th>NCV III (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Median nerve–dig II (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2. Ulnar nerve–dig V (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>3. Sural nerve (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>4. Optional radial nerve (nd)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

### Optional needle EMG

<table>
<thead>
<tr>
<th></th>
<th>Fibrillations (yes/no)</th>
<th>Positive sharp waves (yes/no)</th>
<th>Polyphasic MU (yes/no)</th>
<th>Increased size MU (yes/no)</th>
<th>Decreased MU recruitment (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dorsal Interosseus I muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. Anterior tibial muscle</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>3. Proximal arm muscle (deltoid or biceps muscle)</td>
<td></td>
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<tr>
<td>4. Proximal leg muscle (vastus lateralis muscle)</td>
<td></td>
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</tbody>
</table>
Legend supplement Table 2.

Local investigators are free to conduct the nerve conduction studies according to their local routine standards but recommended in IGOS is to perform a complete electrophysiological examination at two separate time points: the first within 7 days of admission or registration in IGOS, and the second at four weeks after admission or registration in IGOS. The collected data should include sensory studies in legs and arms (3-4 nerves), motor studies with F waves (3-4 nerves), tibial H-reflexes and EMG of a proximal and distal muscle in an arm and leg. Normative data and pictures of the waveforms will also be included in the report.

nd = non-dominant side

* = other nerve (median, ulnar or peroneal nerve on dominant-side or tibial nerve on dominant side) (Uncini and Kuwabara, 2012)
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9500 Gilman Drive
La Jolla, CA 92093-0629
USA
Author/s:
Jacobs, BC; van den Berg, B; Verboon, C; Chavada, G; Cornblath, DR; Gorson, KC; Harbo, T; Hartung, H-P; Hughes, RAC; Kusunoki, S; van Doorn, PA; Willison, HJ

Title:
International Guillain-Barre Syndrome Outcome Study: protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barre syndrome

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Citation:

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