CELEBRATING

20 YEARS OF NARCOMS
When someone is first diagnosed with MS, they often wonder what their future holds in 10, 20, or 30+ years. Most clinical trials and research projects only follow participants for 2–3 years. What is really needed now is to understand how people living with MS are doing through the course of their lifetime, not just in the early stages of the disease.

NARCOMS is in a unique position to be able to provide this information. While enrolling new participants is important, retaining existing participants is also extremely vital. It is also vital to have 20-year follow-up so that we can understand the evolution of the disease.

Every year, your information adds to the body of research on the disease. Here is where NARCOMS stands as of the Spring 2012 survey:

- 51 participants have completed every update survey since 2000
- 637 participants have completed every update survey since their enrollment after 2000
- 50% of participants have completed at least 5 update surveys
- The average years of follow up on participants that have completed at least one update survey is 6 years
02. **Letter from the Director**: 20 Years of NARCOMS

04. **Feature Focus**: Two New Studies on Interferon-Beta-1b

10. **NARCOMS Q&A**: How We Devise New Questions for Surveys

11. **Survey 101**: Exit Strategies: Please Don’t Go (But if You Do, Let Us Know)!

12. **MS News**: New Oral Therapies to Treat MS; Alemtuzumab Reduces Relapse Rates

14. **MS Reflections**: Progressive MS—The Next Frontier

16. **NARCOMS Snapshot**: The Importance of Follow-Up Surveys

18. **NARCOMS Messenger**: Papers & Presentations Based on NARCOMS Data

20. **Play**: Find These Words: Cheer, Fruitcake, Holly, Icicle, Mistletoe…

21. **Faces of NARCOMS**: A Better Understanding of What it Means to Have MS
Hello,

Welcome to the Winter 2013 issue of NARCOMS Now.

This year marks the 20th anniversary of the NARCOMS Registry! In 1993 the Consortium of Multiple Sclerosis Centers (CMSC) launched the development of NARCOMS. The first participant enrolled in 1996; an additional 760 individuals enrolled that year. As of December 2012, over 36,000 participants from around the world have enrolled. Some of those earliest participants are still helping us by completing update questionnaires—in fact, 51 participants have individually completed all 25 update questionnaires! Of those completing follow up 40% have completed more than 50% of their update questionnaires. This is an invaluable contribution to MS research. Over the course of the year we will share more of the history and future plans of the NARCOMS Registry with you, beginning with this issue’s “NARCOMS Messenger.” We hope that you will enjoy learning about our past as we look toward the next 20 years.

In this issue you will find features regarding progressive MS, and disease-modifying therapies. About 8 or 9 in every 10 people with MS first exhibit a relapsing-remitting disease course characterized by relapses, and periods of remission, in which symptoms are stable.

One or two in every 10 people with MS exhibit a progressive course from onset. Many people with relapsing-remitting MS ultimately develop secondary progressive MS in which disability gradually progresses.

In 1993, the year NARCOMS was launched, the first disease-modifying therapy for MS was approved in the United States. With the approval of interferon-beta-1b (Betaseron), a new treatment era began. Approval of interferon-beta-1a (Rebif, Avonex) and glatiramer acetate (Copaxone) followed shortly thereafter. In our “Feature Focus,” Drs. Gary Cutter and Volker Knappertz discuss their ongoing research about interferon-beta-1b. “MS News” highlights the most recently approved disease-modifying therapy for MS, teriflunomide (Aubagio). It is the second oral therapy for MS, and others are expected to follow. Despite all of these advances for persons with relapsing-remitting MS, effective treatments for primary progressive and secondary progressive MS are lacking. In “MS Reflections,” Dr. Robert Fox, Managing Director of NARCOMS, talks about progressive MS including challenges that need to be tackled, and ways to advance the development of disease-modifying treatments for progressive MS. We look forward to many more advances in MS care.
NARCOMS INFORMATION CORNER

HAVE AN IDEA?

We would love to hear from you! Send us your questions, comments & suggestions.

Call: 1-800-253-7884 (toll-free US)

Email: Narcomsnow@NARCOMS.org
Online: www.narcoms.org/contact

Who you’ll hear on the phone: Chad, Chasity, Jeffry or Desiree

NARCOMS PROMISE

Your personal information is always confidential.

The NARCOMS Global MS Patient Registry facilitates multi-center research on multiple sclerosis, developing collaboration between MS centers of excellence throughout the world to increase knowledge, improve clinical care, and enhance the quality of life for persons with MS.

VIEW PAST SURVEYS

www.narcoms.org

Click on: Participant Log in Here

Enter your username and password.
Select the correct picture, click Login.
Click the Form Summary link.

Choose the survey you would like to view from the drop down menus and click the View Summary link.
Print like you would any document.

EN ESPAÑOL

Para acceder a nuestro sistema a línea:

www.narcoms.org/es

Nuestro sitio de web es de alto seguridad a para su confidencialidad.

Para solicitar la envía de un cuestionario de inscripción por correo, llame al Registro NARCOMS al (800) 253-7884.

BECOME A PART OF NARCOMS:

WWW.NARCOMS.ORG / 1-800-253-7884

Reminder when Completing Paper Surveys:

Please use pen rather than pencil when filling out NARCOMS paper surveys. Responses are scanned to electronic files for data capture and pen is easier to read. Thanks!
In the past year, 2012, researchers studying multiple sclerosis (MS) produced varying results on the effectiveness of one of the oldest drugs used to treat MS symptoms, interferon beta-1b (IFNβ-1b). One study showed there is a significant survival advantage to patients receiving early IFNβ-1b treatment. The other showed interferon beta does not prolong the time to disability. The conclusion of both studies, however, was that taking the oft-prescribed drug is worthwhile. (Other interferons, such as Rebif and Avonex, have also been shown to reduce attacks.)

Interferon beta-1b, marketed as Betaseron (Bayer) and Extavia (Novartis), is a drug in the interferon family used to treat the relapsing-remitting and secondary progressive forms of MS. It received FDA approval for relapsing MS in 1993, and later received approval for use after a single attack. Administered by subcutaneous injection, interferon beta has been shown to reduce the frequency of attacks.

In April 2012, Neurology published results from the study, “Survival in MS: A Randomized Cohort Study 21 Years After the Start of the Pivotal IFNβ-1b Trial.”1 This 21-year follow-up study set out to look at the long-term outcomes of participants from one of the original randomized controlled studies conducted on interferon.2

The 21-year follow up boasted an astounding 98.4% ascertainment rate, in which the authors were able to determine the status of 366 of the 372 original IFNβ-1b patients. These IFNβ-1b patients started the study an average of 8 years from their diagnosis, making this follow-up nearly 30 years after the onset of their MS. Of those 366 patients, 81 deaths were recorded (22.1%, or 81 of 366). Patients originally randomly assigned to 250 micrograms of IFNβ-1b showed a 46.8% reduction in the rate of death over the long-term follow up, compared with placebo.

Douglas Goodin, MD, Professor of Neurology at the UCSF School of Medicine

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2 http://www.ncbi.nlm.nih.gov/pubmed/8469318
“The conclusion was that there was a significant survival advantage—of nearly 50%—in this group of patients receiving early IFNβ-1b treatment, compared with those taking none at all,” says Gary Cutter, PhD, Professor of Biostatistics at the University of Alabama at Birmingham and Coordinating Center Director for NARCOMS. Anthony Reder, MD, Professor of Neurology at the University of Chicago Medical Center, presented the study results at the CMSC/ACTRIMS joint conference in June 2012.

The original randomized placebo-controlled trial of IFNβ-1b in MS showed clinical and MRI benefits from therapy over five years. This new study investigated whether earlier treatment with IFNβ-1b showed a difference in life expectancy up to 21 years after patient enrollment in the original trial.

“It turns out there’s almost a 50% difference in mortality rate between the active group [those using IFNβ-1b] and the placebo group,” says Volker Knappertz, MD, Head of Central Nervous System Development at MedImmune, a drug discovery company based in Maryland. “There seems to be something in treating patients earlier that really makes a big difference.” What this means is the risk of dying in the 21-year follow up period was reduced by almost 50% for those treated with IFNβ-1b.

““This study came about because we decided it was extremely important to have long-term follow up on the original cohort of patients,” says the study’s lead author Douglas Goodin, MD, Professor of Neurology at the UCSF School of Medicine. “It’s not encouraged enough; all currently conducted clinical trials examine only the short-term outcomes of attack rate, change in disability scores, and MRIs. Nevertheless, it is important to recognize that each of these short-term measures are only surrogates for the long-term outcome that we are hoping to impact favorably with our therapies.”

“There was a significant survival advantage—of nearly 50%—in this group of patients receiving early IFNβ-1b treatment, compared with those taking none at all.”

—Gary Cutter, PhD, Professor of Biostatistics at the University of Alabama at Birmingham and Coordinating Center Director for NARCOMS.
THE POWER OF FOLLOW UP

Knappertz was heavily involved with researching the status of the 372 individuals in the original trial for the 21-year follow up study.

“These original MS patients were the first clinical trial group treated with interferon beta,” he says, “and we followed them 21 years after their first treatment. The biggest strength of our study was that we found almost all the patients, using diligence, by talking to investigators, and by using internet resources that have become available since the original trial began.” This includes the National Death Index, a registry unique to the United States, which in this case yielded death records on several patients that would otherwise have been lost to follow up.

“The follow up rate in this study is as good as any study that’s ever been done,” says Cutter. “That allows statisticians like myself to know that the people who are missing [6 total] are not going to change the result. We want to promote the fact that in all studies there is an issue of completeness, and good follow up is valuable.”

In comparison with the results of the initial 16-year follow up study in the same patients, the results of this 21-year follow up showed that of the people whose results weren’t ascertained at 16 years, they had twice the mortality of those who were seen. “It showed how much information loss there is when there isn’t a complete data set, and how much it can alter your perception of what is going on,” Cutter says.

“There seems to be something in treating patients earlier that really makes a big difference.”

—Volker Knappertz, MD, Head of Central Nervous System Development at MedImmune, a drug discovery company based in Maryland.

For better or for worse, Knappertz says, “mortality in MS has been somewhat overlooked.” Over the last few years, he says, MS resources online and elsewhere skirted the topic of MS affecting life expectancy, “when in reality it does affect it in many cases.”

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3 Ebers GC, Traboulsee A, Li D, et al; “Investigators of the 16-year Long-Term Follow Up Study.” Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. J Neurol Neurosurg Psychiatry. 2010;81(8):907-912

4 “Association Between Use of Interferon Beta and Progression of Disability in Patients With Relapsing-Remitting Multiple Sclerosis” Afsaneh Shirani, MD; Yinshan Zhao, PhD; Mohammad Ehsanul Karim, MSc; Charity Evans, PhD; Elaine Kingwell, PhD; Mia L. van der Kop, MSc; Joel Oger, MD, FRCPC; Paul Gustafson, PhD; John Petkau, PhD; Helen Tremlett, PhD. JAMA. 2012;308(3):247-256. doi:10.1001/jama.2012.7625.
Winter 2013

The 21-year study provides encouragement, in that it could be there is some benefit to long-term therapy measured in reduction of mortality over the lifetime,” says Cutter. “This is one of the first studies that will contribute in this realm, and others will follow it.”

“We now have another important piece of evidence to treat MS early; earlier treatment already has been demonstrated to reduce attacks, the disease progresses later, and patients’ cognitive function is preserved,” says Knappertz. “We’re telling you you’re going to live longer and your chance of dying is going to be reduced by up to 50%.”

The overall message here is, Knappertz says, “to tell people that MS is not a totally benign disease and that early treatment is very important—don’t delay the start of treatment.”

Next steps Goodin says he hopes to see taken are the long-term follow-up of other disease-modifying therapies for MS such as Avonex, Copaxone, and Rebif. “All of these have been around long enough to warrant follow-up studies if the drug companies wanted to investigate,” he says.

**A DIFFERENT SET OF RESULTS**

On July 18, 2012, the Journal of the American Medical Association published a study (tinyurl.com/ay8pjp5) concluding that interferon beta does not postpone disability. Interferon beta does reduce MS relapses, however, so patients should continue taking it, researchers concluded.

The study included data on nearly 2,700 MS patients from British Columbia, Canada, with relapsing-remitting MS who were followed for 4 to 11 years. About one-third of the patients were treated with interferon beta after it became available in the early 1990s, and one third were not treated. Data were also examined from a third group of MS patients who were diagnosed and followed before interferon beta was a treatment option.

The investigators found no statistically significant difference in how long it took for patients prescribed interferon beta to become disabled, defined as needing a cane to walk 330 feet.

“We were not able to find a significant association between interferon beta exposure and progression to disability,” said Helen Tremlett, an Associate Professor of Neurology at the University of British Columbia.
Several other studies have suggested that interferon beta, by reducing relapses, could also prolong progression to disability, Tremlett said. Still other research has found that brain scans (MRIs) of people taking interferon beta show less damage. About 85 percent of those with MS start with a relapsing-remitting course, in which relapses are followed by partial or total recovery, according to the National Multiple Sclerosis Society.

The study generated some media coverage that in essence reported that the most commonly used MS treatments have no effects on disease outcome. Goodin, Reder, and Cutter, (co-authors of the 21-year follow-up study) took issue with some of the statistical methods used in the Tremlett study, and wrote a letter to JAMA explaining their thoughts. It was published in the journal’s Oct. 24–31, 2012 issue. The basic argument was that individuals who never changed their drugs or those who never received drugs were preselected to do better, since both patients and clinicians often initiate treatment when the disease worsens. Thus, it is difficult to show a treatment benefit when comparing treated patients to those who never received drugs or switched drugs. The authors tried to adjust for variables that might be associated with initiation of treatment, but the patients who went without therapy were still likely to be subject to this bias.

Tremlett and her coauthors published a response to Goodin and his colleagues’ letter in the same issue of JAMA. In it they point out that, “A major strength of our study was the inclusion of both a historical and contemporay control group. As Goodin and colleagues note, around 20% of the patients in the historical untreated cohort were excluded due to subsequent exposure to interferon beta. We did, however, perform a sensitivity analysis including these patients. This did not change our conclusions. Yet, we agree that a cohort that never had access to treatment (if they could be found) might serve as a better control cohort.”

“The 21-year study provides encouragement, in that it could be there is some benefit to long-term therapy measured in reduction of mortality over the lifetime.”

—Gary Cutter, PhD, UAB

The conclusion of all of this research, it seems, is a reinforcement of the need for ongoing studies, both short and long-term, of existing MS treatments on time to disability and life expectancy. Meanwhile the field continues to expand, as several new oral treatments have recently been approved for use in the United States—which themselves merit study.

VICTIMS OF HURRICANE SANDY

Our thoughts go out to those who were affected by Superstorm Sandy. Your safety and well-being are of the highest importance to us at NARCOMS. If you have not been able to complete your Fall 2012 survey and still wish to do so, please let us know and we will make every effort to accommodate you.
FEATURE FOCUS EXTRA: NARCOMS AND MORTALITY

Similar to the study profiled here, NARCOMS has begun to track mortality of participants. Utilizing the National Death Index (NDI), we searched for those participants who have been reported to us as deceased, and for others who were no longer active through 2009, to see if we could match NARCOMS participants in the NDI database. The goal is to study all causes of death and compare NARCOMS with other populations. The graph below is an estimation of the survival for those in NARCOMS. When compared to the U.S. population, it shows a slightly higher percentage deceased at any given age.

THE BRODSKY FAMILY FOUNDATION DONATION

NARCOMS would like to acknowledge the generous support received from Mrs. Shirley Brodsky, her daughter Thea Amr, and the Brodsky Family Foundation over the years. Thank you very much for your continued commitment to NARCOMS research efforts.
**Q:** How are the new questions in each survey chosen? Sometimes they don’t seem related to MS.

**A:** The new questions that appear (usually near the end of a survey) come from one of two places:

1. A member of the NARCOMS research team proposes an idea for a question.

2. An outside researcher submits a proposal to NARCOMS through www.NARCOMS.org/research.

In either case, the NARCOMS Executive Committee reviews the proposal for scientific interest, usefulness in MS research, and to determine if there is enough space in one survey for the questions. If the proposal is accepted the questions will appear in the next survey where there is enough space to ask them.

Sometimes the questions are more appropriate for an outside survey or will need to be asked multiple times to determine if answers change over time. In these cases, you might be invited to participate in this research in addition to the NARCOMS regular surveys.

All questions that appear in a survey have a specific reason for appearing. It might be to compare MS to other disease groups or the general population.

They may be directly related to symptoms, treatment of your MS, other medical conditions or social aspects of MS, but the Executive Committee has determined that the research is of interest to the MS community at large.

As with any of the questions, if you want to know why they are being asked or would like more information on the area of research, please feel free to contact us.

**Q:** What if I filled out my current survey online or mailed it in and realize I made a mistake—how can I change my response?

**A:** This is a bit easier for online participants—just give us a call or send us an email and we can help you correct the mistake.

If you have mailed in your survey, we will need to wait until we have received it to make the change. Depending on where you live, this might take up to 7 days. You can email or call us and let us know you have a correction. Once your survey is received, we can make the change or give you a call to talk about the answer you think you need to fix.

If you have a change to your address or email address, or would like to change how you receive NARCOMS information, you can call or send us an email anytime.

We enjoy hearing from you. If you have a question or comment, please email Narcomsnow@narcoms.org or call toll free at 1-800-253-7884.
Exit Strategies – Why It Is Important to Tell Us If You Leave NARCOMS

Since spring 2000, NARCOMS has administered 25 semi-annual update surveys, and 51 amazing NARCOMS participants have completed them all! In fact, we have collected 10-year follow-up data from more than 650 NARCOMS participants and 5-year follow-up data on almost 50% of all participants.

Despite this, we lack follow-up information on more than 10,000 enrollees. From a research point of view, a main criticism of longitudinal studies in MS is that the missing follow-up information could change study results.

This concern contributed to the rationale for conducting the follow-up study described in “Feature Focus” (pg. 4). It is also the reason why it is so important to continue completing the NARCOMS follow-up surveys year after year. But what if you can no longer or do not wish to continue?

There are three things we would like you to consider before you decide to end your participation in NARCOMS:

1. You can request help for completing your surveys, from a family member, a friend, a caregiver, or by calling us.

2. While receiving an update every 6 months is our preference and provides the most accurate information, we will happily accept survey responses once a year.

3. It doesn’t matter how long it has been since you last completed a survey—we will welcome you back to NARCOMS anytime!

However, if there comes a time when you do wish to withdraw from NARCOMS, we encourage you to contact us and let us know the main reasons for doing so.

Here’s why, if you are withdrawing because:

• of your MS disability, it is important for statistical purposes to record that.

• of another medical condition, it would be very helpful to know the condition, as there are many conditions related to MS than can affect disability progression.

• you simply no longer wish to participate in NARCOMS, specific reasons can help us enhance the program and make it better for current and future participants.

In addition to more than 36,000 enrollment surveys, the NARCOMS database has follow-up information for more than 25,000 people. All of them are as important as the next 25,000 follow-up surveys we hope to record in the coming years!

Your help and participation are truly appreciated, as NARCOMS research is a direct result of your dedication.

Thank you—and please look for the Spring 2013 survey in mid-April.
GROWING CADRE OF ORAL TREATMENTS FOR RELAPSING-REMITTING MS

In late September, the U.S. Food and Drug Administration approved teriflunomide once-daily pills (Aubagio, developed by Genzyme, a Sanofi company) to treat relapsing forms of MS. The therapy became available by prescription in October in the U.S., and the company has applied for regulatory approval in other parts of the world. Teriflunomide is thought to alter the immune system by blocking the synthesis of DNA, which reduces immune cell production in the bone marrow.

Results from three phase III studies on the drug have been released. For the TOWER trial, 1,169 people with relapsing MS were randomly assigned to receive Aubagio 7 mg or 14 mg, once daily by mouth, or inactive placebo, for 48 weeks. According to a company press release, Aubagio 14 mg reduced relapses by 36.3% versus placebo. In the 14 mg-group, the risk of 12-week sustained accumulation of disability progression was reduced by 31.5%, compared to placebo.

In the TEMSO trial, 1,088 people with relapsing MS were randomly assigned to receive 7 mg or 14 mg of Aubagio, or inactive placebo for 108 weeks; 796 (73.2%) completed the study. After two years, both doses of Aubagio significantly reduced the average number of relapses in a year by as much as 31.5% over placebo. Fewer of those on the higher dose (14 mg) experienced progression of disability compared with those on placebo (20.2% progressed on therapy vs. 27.3% on placebo). On MRI, the total volume of tissue damage and active areas of inflammation were reduced in both Aubagio groups compared to the placebo group.

For the TENERE trial, 324 people with relapsing MS were randomly assigned to receive Aubagio 7 mg or 14 mg, or Rebif (interferon beta-1a, EMD Serono Inc. and Pfizer) 44 mcg three times per week subcutaneously for 48 weeks. The primary endpoint was “risk of failure,” meaning the first occurrence of a relapse, or permanent discontinuation of the study treatment, whichever came first. There was no significant difference in the numbers of participants who experienced this definition of treatment failure among the Aubagio and Rebif groups, according to a company press release. Relapse rates did not differ significantly either. Common side effects of Aubagio include liver irritation and hair thinning, and animal studies have found an increased risk of birth defects in offspring of animals exposed to Augabio.

Aubagio is the second oral disease-modifying therapy approved for the treatment of MS, joining fingolimod (Gilenya; made by Novartis). Meanwhile, a third oral drug therapy—dimethyl fumarate (BG-12)—is generating news as it nears the end of its FDA review, which is expected by March 2013. In September Biogen Idec published the results of phase III clinical trials of BG-12 in people with relapsing-remitting MS, which suggest that this twice-daily oral therapy significantly reduced relapses and disease activity as detected by MRI. In one trial, BG-12 also reduced disability progression. The results were previously reported at medical meetings, and lead authors Ralf Gold, MD (Ruhr-University Bochum) and Robert J. Fox, MD (NARCOMS Managing Director, Cleveland Clinic) and colleagues have now published complete results in The New England Journal of Medicine (2012; 367: 1087-97 -tinyurl.com/cv7jng & 1098-107 - tinyurl.com/bnfa4xu).
How exactly dimethyl fumarate works is not entirely clear, but it may involve the activation of a cellular pathway involved in cellular protection and anti-inflammation. In two Phase 3 clinical trials in relapsing-remitting MS, dimethyl fumarate showed a reduction in the frequency of relapses and new lesions on MRI. Like teriflunomide, one of the two trials also found that dimethyl fumarate slowed the progression of disability. The main side effects of dimethyl fumarate include skin flushing and gastrointestinal symptoms, such as cramps, abdominal pain, and diarrhea, which typically improved after the first few weeks.

As with any new treatment, the long-term risks of these two new therapies are not well understood. It will require many years of observation to know if their safety profiles are similar to the excellent long-term safety profile of the injectable therapies (interferon-β1 and glatiramer acetate). Similar to any other treatment, you would need to discuss with your doctor whether any of these therapies would be appropriate for you and your MS.

**ALEMTUZUMAB SHOWN TO SIGNIFICANTLY REDUCE RELAPSE RATES**

On November 1, 2012, published results of two large, phase III clinical trials confirmed the ability of alemtuzumab (Genzyme, a Sanofi company) to significantly reduce relapse rates over two years over standard subcutaneous dosing of Rebif (interferon beta-1a, EMD Serono Inc. and Pfizer). One of the studies also suggests that alemtuzumab may significantly reduce worsening of disability. The results were previously reported at medical meetings, and lead authors Alasdair Coles, FRCP (University of Cambridge) and Jeffrey Cohen, MD (Cleveland Clinic) and colleagues have now published complete results of CARE-MS I [tinyurl.com/bmo3c6f] and CARE-MS II [tinyurl.com/c457qu9] in *The Lancet*. Data were submitted to the FDA in an application for marketing approval. The FDA has asked for revisions, so the timeline for its review is not yet established.

In an editorial accompanying the new publication, *The Lancet* points out that alemtuzumab, licensed for the treatment of leukemia, had been used off-label in MS for many years, although now is no longer available. The CARE-MS trials “have been keenly awaited by clinicians and patients wishing to establish evidence for this practice,” the editorial notes.

Alemtuzumab is a humanized monoclonal antibody directed at CD52 (a protein on the surface of immune cells). It was originally approved for the treatment of B-cell chronic lymphocytic leukemia. Its ability to target immune cells led investigators to test its potential as a treatment for relapsing-remitting MS. Alemtuzumab is given by infrequent intravenous infusion—for 5 days initially and for 3 days one year later. Side effects include auto-immune conditions targeting the thyroid, and rarely against platelets (part of the blood that helps with clotting) and kidneys.
With nine FDA-approved therapies for relapsing forms of MS and two others currently under FDA review, we have many different weapons to fight the relapsing form of the disease. There are good animal models to study the immune response in the brain and screen new therapies. MRI is the standard outcome for early-stage clinical trials testing new therapies, identifying with great accuracy the treatments with the greatest potential for decreasing relapses and slowing progression of disability. MRI is also widely used in monitoring the response to these “immunomodulating” therapies, where new lesions suggest that treatment is sub-optimally controlling inflammation. We haven't cured relapsing MS, but we have created a pipeline to develop therapies and get them into the clinic.

In contrast to the successes with treatments for relapsing MS, however, the story in progressive MS—both primary progressive and secondary progressive MS—has been disappointing. The only clinical trials that showed benefit in slowing the progression of disability in progressive MS enrolled patients with active inflammation. This inflammation was defined by either clinical relapses immediately prior to the trial, or active inflammation on MRI at the start of the trial. In the absence of active inflammation, the trials of interferon, glatiramer acetate, and rituximab have been uniformly disappointing. Adding to the challenge, the animal models of active inflammation do not characterize what is taking place in progressive MS. The MRI measures that are so useful in early stage trials of relapsing MS do not work in progressive MS. Not only do we lack effective treatments; we do not have an effective method to develop treatments. Admittedly, there have been successes. While the FDA has approved treatments for spasticity, walking problems, and bladder symptoms, we still have a long way to go in developing therapies for progressive MS. So what are we to do?

INTERNATIONAL COLLABORATION

Recognizing that this challenge requires resources beyond the capacity of a single country, six MS foundations from around the world have combined forces to tackle this problem.

Dr. Robert Fox is the Managing Director of NARCOMS, the Medical Director at the Mellen Center for Multiple Sclerosis and a practicing neurologist at the Cleveland Clinic in Ohio.
Through a series of meetings over the course of a year, representatives from the national MS societies of the United States, Canada, United Kingdom, Italy, and the Netherlands, and the Multiple Sclerosis International Federation, developed an international collaborative—the International Progressive MS Collaborative (IPMSC)—with a mission to expedite the development of therapies for effective disease modification and symptom management in progressive MS. Embracing Albert Einstein’s idea that, “the mere formulation of a problem is far more essential than its solution,” they focused on where the challenges in progressive MS really lie. In a report published this fall (available at www.narcoms.org/narcomsnow), the IPMSC identified five key priority areas for research in progressive MS (Table). These five areas represent opportunities and obstacles where focused effort could make the largest impact in finding effective therapies for progressive MS.

Based on this report, the IPMSC commissioned five “Working Groups” of international experts to focus on each area, to identify specific strategies and research priorities to within each. Representatives from all five Working Groups came together in London in November 2012 to integrate their recommendations into focused research opportunities addressing knowledge gaps. A larger meeting is planned for early 2013. Also in 2013, the Multiple Sclerosis International Federation will lead an international funding effort to solicit financial support from government, corporate, and private funding organizations worldwide.

With international collaboration, there is renewed hope that an organized, focused effort can accelerate the development of effective therapies for progressive MS. Instead of saying, “Hey, what about me?” when every relapsing MS trial is announced, those with progressive MS will say, “Hey—that’s for me!”


http://msj.sagepub.com/content/18/11/1534.full
NARCOMS UPDATE SURVEYS: 205,000 AND COUNTING!

Thanks to you, NARCOMS is celebrating our 20th Anniversary! Update surveys began only 12 years ago in 2000 and collected over 13,000 updates in the first year, and annual totals have remained over 15,000 update surveys since 2004. Today we have more than 200,000 update surveys from 25,000 users, helping NARCOMS become the largest patient-driven MS registry!

THE PATIENT DETERMINED DISEASE STEPS (PDDS)

Collected since 2000, the PDDS is how we track overall disability in participants over time. The PDDS allows NARCOMS participants to be compared to other MS populations that have related measures, such as the Expanded Disability Status Scale (EDSS) Since 2001, every survey contains responses from 0 (Normal) up to 8 (Bedridden), and the most common PDDS score reported is a 4 (Early Cane Use).

On average the time to go from a PDDS of 0 to at least a 4 for the first time is about 6½ years, but ranges from 1 to 14 years*.

*467 participants enrolling in NARCOMS with PDDS = 0 and at least 1 follow-up survey with a PDDS ≥ 4
FIVE- AND TEN-YEAR FOLLOW UP

NARCOMS has 5-year update PDDS scores for over 10,000 participants, and 10-year scores for over 5,800 participants. While the average change at 5 years is half a point, the change depends upon what the PDDS score was at enrollment. For example, those that enrolled with a PDDS of 0, on average increase to a PDDS score of 1 by 5 years. Those at higher PDDS scores at enrollment see less of an increase at 5 years.

The pattern is similar at 10 years, with an average increase of about 1 point for all groups at 10 years, except those in the 7-8 group show no overall change.

![Graphs showing PDDS change over time]

Remember, long-term follow up is the key to understanding MS, so please keep contributing to NARCOMS!

OUR COMPLIMENTS!

For those who called about the PRIME clinical trial last fall, the clinical study coordinators were very impressed with the level of knowledge among NARCOMS participants.

Most of the sites are still open for enrollment, so if you experience neurological pain related to MS and are interested in finding out more about the trial just call (855) 722-7222 or visit www.AvanirClinicalTrials.com.
NARCOMS PAPERS & PRESENTATIONS UPDATE 2012

Since 1999, researchers have utilized data collected through NARCOMS in 185 presentations and papers. In 2012 alone, 6 papers were published in medical journals and 23 presentations were given in the United States and Europe.

Sharing NARCOMS data results with the scientific community via a wide range of journals and conferences is an important way to both spread the knowledge and insight gained from analyzing the Registry data, and to inspire further studies in MS. It also helps practitioners get the latest information as quickly as possible, while providing a reliable source of information for health care policy and advocacy initiatives.

NARCOMS INTERVIEW FROM ECTRIMS MEETING IN LYON, FRANCE

A video interview with NARCOMS researcher Amber Salter, MPH regarding her work, “How do multiple sclerosis patients in the NARCOMS registry navigate their treatment options beyond first-line therapies?” can be found at www.narcoms.org (lower left corner of main page).
**NARCOMS RESEARCH AREAS**

NARCOMS information has been used to study a wide variety of MS-related topics. Of the 55 full-length publications that have used NARCOMS registry data, 10 have focused on MS symptoms, with 9 focusing on non-MS diseases that are prevalent in the MS community.

![Bar Chart](image)

*Symptoms include: depression, fatigue, pain, bowel, bladder, spasticity*

**NARCOMS-RELATED DATA IN 2013 – PAPERS, MEETINGS & NEW IDEAS**

Three papers utilizing NARCOMS data have already been accepted for publication in 2013 in the areas of vision, dizziness and cognition in MS. In addition, plans are in place to attend the four major MS meetings in the US and Europe (AAN, CMSC, ACTRIMS & ECTRIMS). If you have an idea for research you would like to see conducted by NARCOMS, please contact us. After all, those living with MS are the best resource!

Abstracts or full-length articles on most of the NARCOMS publications are readily available with search word “NARCOMS” at [www.pubmed.gov](http://www.pubmed.gov). For assistance in locating these, please contact us at 1-800-253-7884 or Narcomsnow@narcoms.org.
Find the following hidden words:

- candle, candycane, caroling, cheer, family, friends, fruitcake, holly,
icicle, mistletoe, presents, resolution, scrooge, snowball, travel

Answers to the current issue of Play can be found at:
www.narcoms.org/narcomsnow/play/winter2013/page2
The majority of us take the simple things in life—like buttoning a shirt or tying our shoes—for granted. I have to admit; I was one of these people, completely oblivious to the fact that one of my very own family members is unable to complete these tasks in a timely manner. How many of us really know what MS is? Some of us may know that it stands for Multiple Sclerosis, but can we properly define it? It wasn’t until October 11th, 2009, that I could do so. Here is what happened on that day.

For as long as I can remember, I’ve known that my Uncle George has MS—but I didn’t know how serious a disease it actually is. My father moved into the same building as my uncle, and the more I visited them, the more I began to notice my uncle struggling to do the simplest tasks.

“Hey, Uncle George, do you want a Butterfinger?” I asked. “No thanks, I’m good,” he replied. “Oh, come on!” I goaded. “Okay, but only if you open it for me,” he responded.

I was about to call him a lazy bum, until my father reminded me that my uncle was physically unable to tear open the bite-sized candy bar. Now that I think back, I realize there were many signs of his disease getting worse that I failed to notice. About a year ago, my younger brother was testing out a joke pen that delivers a small shock when touched. When he tried it on George, nothing happened. I thought he was just being a tough guy, but it turns out that the sensation in his hands is weakened to the point that he simply did not feel the painful jolt the rest of us felt.

I asked my uncle if I could observe him with the intention of writing a paper about him and his illness. On October 11, I went over to my father’s to celebrate his birthday, and my Uncle George was there. He came downstairs and eagerly asked me when I wanted to come up and observe him. I said “Now!” I slowly followed him up the stairs—slowly, because that’s how he walked. The MS has caused him to lose balance and sensation in his feet, resulting in his slow movement and stumbling around the house, especially on the stairs.

As we sat down, Uncle George handed me two magazines that were all about MS. He told me he subscribes to many of them so that he can stay up to date on new studies and information about the disease. George’s loving wife Nancy, along with his supportive friends and family, stand behind him one hundred percent. Nancy cuts his pills and gives him his daily injections, among many other things she does to keep her husband as healthy as possible. Along with the love and support George receives from friends and family, he has found an additional way to keep himself healthy. With the warmest sincerity in his voice my uncle shared with me, “I never let MS get me down. I keep moving forward.”

—Ed T.

Please note: The names of some individuals in this story were changed to protect their privacy.