THE NDB Research NEWSLETTER

News for Participants in the National Data Bank for Rheumatic Diseases *July 2007*

Notes from the Director

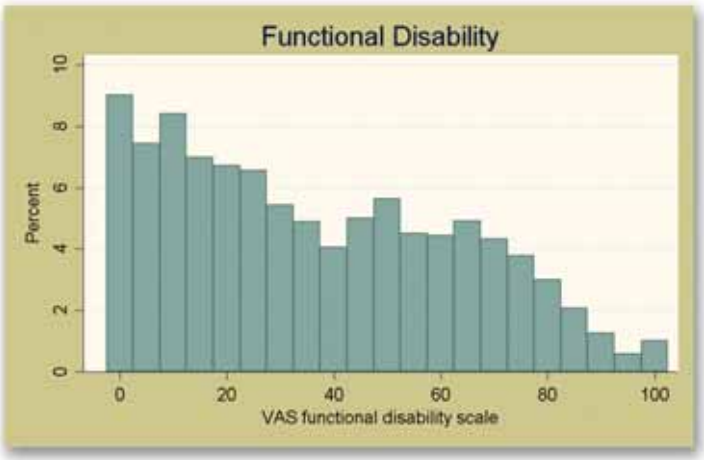
An important aspect of the work of the National Data Bank for Rheumatic Diseases (NDB) is to determine how people with arthritis, lupus, fibromyalgia and similar conditions are doing. By "doing" we mean how well you function, how much pain you have, whether you can work or are working – and similar outcomes. If we know these things we can start to determine how well treatment works. And to really know about treatment effectiveness we also need to collect information about side effects and about costs of treatment.

NDB data (your answers) are special because they measure real life effectiveness, side effects and costs. You might say that we are the "truth squad" for arthritis treatment. This year we published a series of articles in medical journals that deal with effectiveness, the risk of developing cancer as a side effect to treatment, potential complications associated with prednisone, and why you do and do not change medications. Here are some of the issues we approached.

The ideal treatment is effective, free of side effects, and is inexpensive.

Treatments must be effective. Let's consider what we mean by effective. Here's an example. We asked you in NDB questionnaires to put an X in a box that described your functional limitations. One end of the scale was labeled "0" for "No functional limitations" and the other end was labeled "100" for "Severe Functional Limitations." The results are shown in the graph above. About 32% of people had scores less than 20 (Add up the percentages in the first 4 boxes to get this number). Roughly, the scores represent the severity of functional problems expressed as a percent. You can estimate your functional disability score by picking a point between 0 and 100 on the scale that represents your level of functional limitation.

As we look at these results there are several questions we might want to ask. The first is, "what is an 'acceptable' level of functional limitation?" By that we mean, "How much limitation would you be willing to



This graph shows the disability of people in the NDB expressed as a percentage. People with scores of 20 or less (the bottom numbers) generally consider their function to be acceptable.

accept before feeling that the limitation importantly limited your life?" It turns out, by some complicated calculations, that a level less than 20 is roughly the acceptable level. It also turns out that an improvement of 20% or more is the amount of improvement that most people think is important to them. To summarize this, if you receive treatment you would like to end up with a score less than 20. If you didn't end up there, you would like to improve by at least 20%.

Notice that for the improvement we discussed above, you can see or feel how you improve. But could a treatment be helpful if your symptoms and how you feel don't improve or don't improve much? Possibly. Suppose a treatment didn't make you better but prevented you from getting worse or slowed down the progression of your illness. There are other ways treatment could affect your illness. It could make your lab tests better or it could slow down damage to your joints, as seen on x-rays. But regardless of how we measure improvement, the improvement shouldn't just be brief. It should last a long time.

Laboratory or x-ray improvement is only important if it ultimately results in meaningful improvement to you that you can recognize. Improvement in laboratory or x-ray tests is really a future promise — a possibility. To summarize, treatments should provide meaningful improvement that lasts a long time and/or "improvement" that stops or slows the progression of illness. And, that improvement should be noticeable to you not just to your laboratory or x-rays tests.

The second aspect of true effectiveness is side effects. Side effects can range from mild and unimportant to life

continued on page 2

Research Results (continued)

threatening. Sometimes side effects can not be easily identified because there does not appear to be a direct cause and effect. For example, a treatment might increase the risk of pneumonia or increase the risk of fracture in the future, but you would not notice that. When we balance treatment effectiveness we must also add in the risk of side effects. If a treatment is only slightly effective, we would not want to risk any side effects. But if it were very effective we might be willing to risk even serious side effects. Side effects may occur years after the treatment is started. For this reason, NDB data is much better for identifying these side effects than the results of relatively short-term clinical trials.

Costs are the third part of the treatment equation. They may be particularly important if you pay the costs, or even just pay part of the costs. However, someone pays the costs, and those costs will be reflected in insurance premiums or increased taxes. All things being equal, if two drugs were about equally effective and you were paying out of your pocket, you'd probably pick the least expensive treatment. In most European countries the authorities who approve drugs take costs into consideration. In the graph below, here is a comparison of the annual total medical costs for people taking biologic treatments such as Enbrel, Remicade or Humira compared with those not using these treatments. Annual costs are more than $25,000 greater for biologic users.

… treatments should provide meaningful improvement that lasts a long time and/or "improvement" that stops or slows the progression of illness … improvement should be noticeable to you not just to your laboratory or x-rays tests.

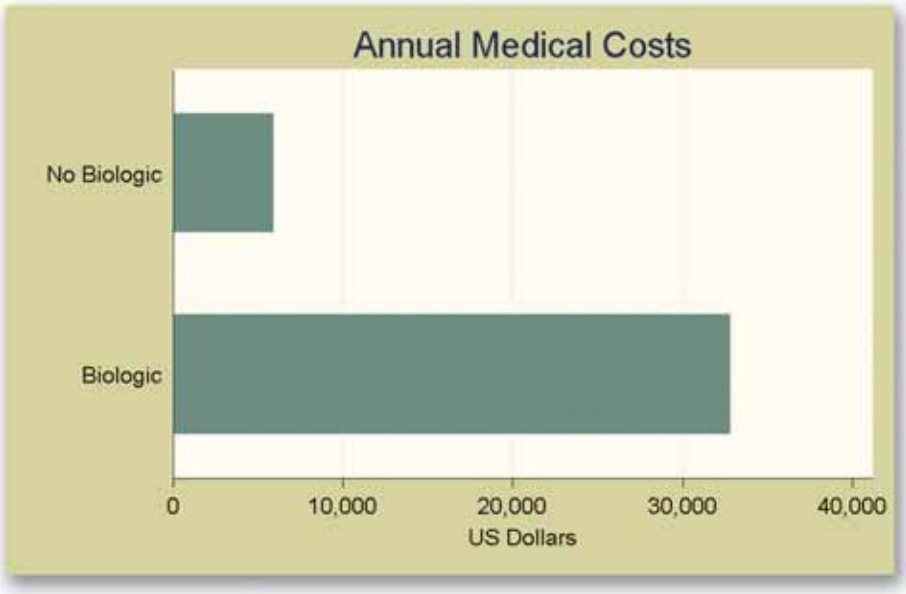
Why is all of this important? Let's take the case of drugs like Vioxx and Celebrex. These drugs are called COX-2 NSAIDs (non-steroidal anti-inflammatory drugs). NDB data show that 44% of you have used either Vioxx or Celebrex. Vioxx is now known to increase the risk of heart attacks. Celebrex contains the following warning in its label, "Like all prescription NSAIDs, Celebrex may increase the chance of a heart attack or stroke that can lead to death." As you'll see elsewhere in the newsletter, we found evidence that Celebrex is associated with heart attacks.

There never was evidence that Vioxx or Celebrex was more effective than less expensive drugs already available, like naproxen or ibuprofen. The main claim of Vioxx and Celebrex was that they reduced stomach ulcers compared with older drugs. But they could cost up to ten times as much and, of course, they turned out to have bad side effects. Most often, these drugs were prescribed to people who were not at risk for stomach ulcers. When this occurred such people received no benefit and paid much more. How could this be?

Next, consider the case of biologic drugs such as Remicade, Enbrel and Humira. NDB data, provided by you, show that they are effective, but much less effective in real life (your use) than the results of clinical trials show. And, of course, we know that they are very expensive. Why do so many people use these drugs?

The reasons that drugs are prescribed are very complicated. But advertising plays a big role. If you have been watching television you will have seen advertising about arthritis and pain directed to you (not your doctor). You may have noticed that the attractive people in the ads seem to have few problems after taking the advertised medications. It's not that way in real life. But advertising sells.

For people with RA, the ads point out that treatments prevent joint damage and improve your function and pain. Who would not want such treatments? But the ads exaggerate effectiveness and



In this graph it's easy to see how much the new biologic treatments add to a person's yearly medical costs. But the cost is only one piece of information when deciding if a treatment is appropriate and worth it.

continued on page 6

LATEST RESEARCH

Heart attack and arthritis medications

Ever since the news of increased heart attack risk came to light with the COX-2 inhibitor drug Vioxx and then later that drug's removal from the market, rheumatologists and researchers have been working to understand the effect of arthritis medications. The main questions are: Which medications present an increased risk of heart attack? How great is that risk? And, does the risk justify the benefit the drugs provide?

Using answers you provided, we took a look at the first of those questions. We analyzed records from more than 25,000 individuals with rheumatic diseases. To begin, simply having rheumatoid arthritis (RA) increases the risk 1.6 times over individuals without RA. Then we looked at other factors thought to increase risk. We found the increased risk to be associated with general health, prednisone use, and heart risk factors such as high blood pressure, diabetes, smoking history and prior heart attacks.

Looking at the COX-2s, rofecoxib (Vioxx) increased the risk 2.8 times. Valdecoxib (Bextra) users had a 2.3 times greater risk of heart attack. Both Vioxx and Bextra have been removed from the market.

Celecoxib (Celebrex), which is still available on the market, showed a risk of 1.3 times for the normal dose, and 1.6 times for high dose.

Two new COX-2s have been in development: lumiracoxib (Prexige) and etoricoxib (Arcoxia). Recently the US Food and Drug Administration (FDA) refused to approve Arcoxia because of the risk of side effects.

But not all arthritis medications increase the risk of heart attack. The pain killers naproxen, diclofenac, ibuprofen and acetaminophen had no increased risk in our study. These medications have their own side effects, most notably stomach problems.

Further, biologic (anti-TNF) therapy, including the drugs adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade), was associated with a reduced risk of heart attack.

We hope this information will be useful to doctors and people with arthritis as they weigh risk against benefit while making individual treatment decisions.

What happens to anti-TNF results in the real world?

As part of the drug approval process, new medications go through stages of tests and studies to determine safety and effectiveness. Perhaps the best known of these stages is the randomized clinical trial, where medications are given to real people to see how they perform. Half of the participants in these trials are given placebos, and no one knows whether the placebo or the real drug is being taken.

Do results from clinical trials, which are time-limited and carefully controlled, hold up in the real world? We took a look at this question and applied it to anti-TNF medications. Because medications are often dispensed free in clinical trials, we also calculated real world costs.

From your answers to the semiannual NDB questionnaires, we compared 3,257 people who began taking anti-TNF treatment with 10,794 people who have never had that treatment. The time span studied averaged 4.4 years per person.

Although NDB research methods vary from clinical trial methods in several ways, we found that people do see benefits from anti-TNF therapy, but the benefits are not as great in the real world as those reported in clinical trials.

On average, a person's medical costs increased $20,207 per year when beginning anti-TNF therapy.

SLEC taking shape

About a year ago the NDB formed a group of researchers and rheumatologists with the purpose of studying lupus in the community. The project called SLEC, for Systemic Lupus Erythematosus in the Community, saw usefulness in applying the NDB's patient-reported research methods to lupus. Nearly all lupus research takes place in clinics and specialized research centers. SLEC is attempting to study various aspects of lupus, its treatment and results from treatment by going directly to people with the disease, just as the NDB does with arthritis.

Since starting, more than 1,100 people with lupus have joined the project. About 800 were referred to the project by their doctors, and the other 300 found the project on their own in other ways, including magazine and internet notices and advertising, and information at doctors' offices. We wanted to see how the doctor-referred group compared to the self-referred group to understand what differences might affect future SLEC research.

In general the groups are very similar, including treatments, medical costs and work disability. On average, self-referred participants tended to be slightly younger, with a small increase in kidney problems, shortness of breath and feelings of depression.

The near match-up of the two groups leads us to the conclusion that patient-reported research projects like SLEC will be a useful tool in the study of lupus.

First SLEC, now SLAQ

Those of you who participate in the NDB have probably noticed that we ask you sets of questions each time, and that these questions don't really change much. The NDB questionnaire is mostly a group of standardized questionnaires that researchers use around the world. Because all researchers use the same questionnaires, they are able to compare results and make faster progress in treatment and understanding of rheumatic conditions.

Lupus has its own standardized questionnaire, the Systemic Lupus Activity Questionnaire, or SLAQ, which focuses on common lupus symptoms. The SLAQ is usually administered by doctors during patient visits.

Because the NDB does not get to meet each participant, we rely on you to give us accurate answers to the SLAQ and the other questionnaires. We know from experience that doctors and patients often see things differently. But, just because they do see things differently doesn't make doctors always right or patients always right. It's a matter of perspective.

Still, it's important to see how a questionnaire like the SLAQ works when it is self-administered. We want to know whether lupus can be identified by how people answer the SLAQ.

We looked at your answers and compared people with lupus in our databank to people with RA and a third group who have fibromyalgia. We were able to determine that the SLAQ can be used to distinguish people with lupus from people with RA. However, we found that it isn't quite possible to distinguish lupus from fibromyalgia using the SLAQ alone. There were many symptoms common to both conditions, including fatigue, headaches, stroke/numbness, cognitive problems, joint pain, and abdominal pain.

Drs. Robert Katz, Michelle Petri, Elizabeth Karlson, Graciela Alarcon, Eliza Chakravarty and John Goldman contributed to this study.

Abatacept used as directed

The newest biologic medicine on the market, abatacept (Orencia), is designated for RA patients who have had only limited or no success with previous treatments. Just over one year after abatacept became available, we decided to check how rheumatologists are prescribing the drug.

For this study we compared 166 people who began abatacept treatment with 965 who began other biologic treatment during the same time period.

We found that it is being prescribed according to the drug's instructions. We made this assessment after comparing abatacept to people who initiated other biologic treatment. Those taking abatacept have had more severe RA in the past, had more severe RA when initiating the treatment, and they had greater prior use of biologics and other RA medications. 99% of patients taking abatacept had previously tried other biologic treatment.

E S E A R C H

Doctor referral and self referral in fibromyalgia

The NDB uses a few methods to recruit patients for our ongoing research. Primarily, doctors refer patients to the study. But more and more we are reaching out directly to people with rheumatic conditions using magazine and internet advertising. People who come to the study this way are called self-referred.

We wondered if there might be any significant differences between doctor-referred and self-referred groups, so we looked at people with fibromyalgia to compare the two.

We found some similarities, but many differences. People with fibromyalgia identified by self-referral have characteristics that differ substantially from those of patients referred by doctors. In general they have more symptoms and greater symptom severity. These observations suggest that self-referred participants represent a subset of patients with fibromyalgia, and they may not be representative of all fibromyalgia patients.

Do anti-TNF drugs affect work disability?

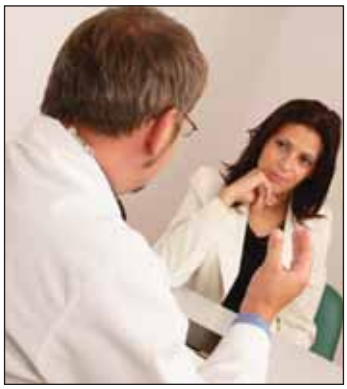
Many people are willing to undertake the expense and effort of taking anti-TNF drugs to enable them to live a more normal life. We wanted to put to the test whether these drugs have an effect on how people do in their working lives.

We looked at about 8,000 RA patients who were employed when RA was first diagnosed.

At 12.8 years after RA onset, 56.2% were still employed, 43.8% were not working, and 22.7% considered themselves disabled. In addition, 30.5% had stopped work over their lifetimes for health reasons and 20.6% were currently receiving Social Security Disability payments.

Work disability occurs in 2.5% of RA patients each year, and 1.9% begin Social Security Disability. This represents an improvement over previous studies, perhaps reflecting overall improvement in RA therapy. But we could not find a protective effect of anti-TNF therapy on the risk of work disability. This could indicate that anti-TNF therapy does not have a strong enough protective effect to show up in the results, or that further study is needed to eliminate other factors that may affect the outcomes.

Duration of anti-TNF treatment



One way that doctors and researchers learn about the effectiveness of a treatment is to see how long people stay on that treatment. We applied this to the anti-TNF drugs adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade).

We looked at about 5,000 patients for up to 7.3 years. Half of persons on these treatments stop them at between 3 and 5.5 years. That shows pretty good acceptability of the treatment. However, it's not possible to eliminate some outside factors that may affect duration, like advertising and recommendations from doctors and other experts. We did find that patients who remained on the therapy improved, but, as mentioned above, not as much as in clinical trials.

Welcome New Participants!

Everyone who works for the NDB and all of the doctors and researchers who benefit from our research are extremely grateful for your dedication in helping this project. Many of you have been with us for several years or more. But every 6 months we are also glad to see many new people join us. Here is a quick primer on the NDB for the new and a refresher for the returning.

The NDB is a non-profit organization that performs research in rheumatoid arthritis, osteoarthritis, fibromyalgia, lupus and other rheumatic diseases. The research is designed to improve the treatment and outcomes of these conditions.

The NDB is an independent organization that conducts its own research without influence from pharmaceutical, insurance, financial or other outside interests. Our research is so well respected that we are often hired to provide independent drug safety verification to the government.

Your personal information will always remain private. We do not sell or share any identifying information about NDB participants. Before we work with researchers or collaborate with other research groups we remove any of your answers that could be used to identify you.

Nearly all of our research is available for you to read on our website.

We are glad to answer your general questions about rheumatic diseases and treatments, but we are not able to give personal medical advice.

NDB research is different in an important way: Participants report on themselves; data is not collected by doctors or medical staff. With patient-reported data, researchers get a perspective that short, small clinical trials can not provide. Our long-term study offers a much broader view of treatment and results. Clinical trials are good at identifying common side effects, but rare or subtle problems, or problems that take longer to develop, are better detected by studies like the NDB. The same is true of long-term effectiveness of a treatment.

So, welcome to the NDB, or thanks again for your continuing participation! If you ever have any questions or need help with your questionnaire, feel free to contact us.

FOR MORE INFORMATION OR TO PARTICIPATE

Arthritis Research Center Foundation, Inc.

1035 North Emporia • Suite 288, Wichita, KS • 67214

Director: Frederick Wolfe, MD

Executive Director: Rebecca Schumacher

Please call 1-800-323-5871 ext. 140 or email info@arthritis-research.org

Research Results (continued from page 2)

they promise unknown future benefits. The main purpose of advertising is not altruistic. It is to sell drugs.

So be cautious about treatments. Watch out for marketing. Ask hard questions. Find out how much better the new drug is than the previous treatment. Find out about potential side effects and costs. Be cautious about future promises. They rarely are true. In the end, if you receive a new drug, see if it really improves you. You can tell: it has to improve your symptoms.

One way to test how you are doing is to use our on-line assessment tool. You can find it at www.ndbrally.org. By the way, in the last year we have published much about the issues discussed above. You can find these articles on our web site at www.arthritis-research.org in the research library. Look in the list of links in the physicians or researchers sections. Thanks for what you have done to enable NDB to communicate real life data to the medical world and to you.

Below are the research articles mentioned in Dr. Wolfe's Notes. We will make these available on our website in the newsletters section. Contact us if you have questions.

L. Caplan, F. Wolfe, A. S. Russell, and K. Michaud. **Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes.** J Rheumatol 34 (4):696-705, 2007.

F. Wolfe and K. Michaud. **The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation.** Arthritis Rheum 56 (5):1433-1439, 2007.

Biologic Treatment of Rheumatoid Arthritis and the Risk of Malignancy: Analyses from a Large U.S. Observational Study. Arthritis.Rheum. 2007.(In Press)

F. Wolfe and K. Michaud. **Resistance to Changing Therapy: Discordance Between RA Activity and Patients' Treatment Choices.** Arthritis.Rheum. 2007.(In Press)

F. Wolfe. **Minimal disease activity (MDA), remission and the long-term outcomes of rheumatoid arthritis (RA).** J Rheumatol 2007. (In press)

Meet the NDB

Kimberly Harp, SLEC Project Manager

Kim Harp has been with the NDB for six years managing various research projects. Currently she's the project manager for SLEC (Systemic Lupus Erythematosus in the Community).

If you're in the SLEC study, either as a participant or a physician/researcher, you've probably talked to Kim on the phone. You might be interested in learning more about Kim and her work.

Kim lives in Wichita, Kansas, where the NDB is based. She is a graduate of Friends University in Wichita, and is currently working on a masters degree at Emporia State University. Kim has five children, one grandchild and a silky terrier puppy.

Her activities include volunteering at church and school. She likes to read, garden, and play board games, especially Scrabble.

Kim's job at the NDB is to work with physicians and their staff to assist them in enrolling their lupus patients in the study. She talks to participants over the phone to answer any questions they might have about the study, and also to enroll them in the study. She assists in processing the lupus forms that are used for the study to ensure quality and accuracy of the data that is being collected.

In talking to people on the phone, Kim says there are a few questions that come up often.

Q: Are there any new medicines for lupus?

A: There are some drugs being tested in lupus studies but we don't know when they will become available to the general public as they are still in the early clinical trial phase.

Q. How many people are in this study?

A: Over 1,100 people are currently participating in our SLEC study.

Q. Do I have to pay anything to be in the study?

A: No. The study does not cost participants anything except a little bit of their time.

Kim's job really fits in with her personality. "I don't feel like I am just doing 'a job.' I really like being able to help people, and it is truly rewarding to see results of our research efforts."

The type of research that the NDB performs can take some time to have an effect on individuals with rheumatic disorders like lupus. When asked about this, Kim tells people that this is an ongoing study and, "it is important for people not to give up because over time we can see trends and have results more quickly, which is simply due to the large number of people who participate. The results may help future generations of people with lupus."

What are the qualities that make people want to join a long term study? "People in the study live daily with the ups and downs of lupus, or they are the physicians and staff who treat lupus patients. Often, the people I speak with are appreciative of our research efforts and they want to be involved. Sometimes, they know other people with lupus, or they have family members with lupus, and they want to be able to help them in some way. The people in our lupus study have big hearts and are willing to commit and make a difference in lupus research outcomes."

Kim has important advice for people who are considering joining NDB research or other medical research.

"Please don't wait to join! It only takes a small amount of time to accomplish a huge amount of good. We treat people like family and we respect the privacy of all people. There is no better time than now to step up and be willing to help with lupus research."

Lottery Winners!

Return your research questionnaire within two weeks of receiving it and be eligible for one of three $1,000 awards. The research data bank can best contribute to research when the questionnaires are completed and returned as soon as possible. Anyone who completes the questionnaire within two weeks of receiving it will be eligible for the award – given as a token of our gratitude in help with rheumatology research. The $1,000 winners from the last questionnaire were Doris Detherage, Lawrence, KS; Julia Spears, Lexington, KY; Rene Brule, N Providence, RI. Winning smaller amounts were Rosemarie Milton, Geneva AL; Ella Rice, Marshall NC; Frances Wolfe, Lake Lyme, PA., Raleigh Greene, Flint, TX.

Congratulations to all!

Important Information about Email

For participants using WebQuest, email is our primary method of getting in touch with you. Even if you're not using WebQuest, we'd like to be able to send you important information by email.

We cannot emphasize enough how important it is for you to let us know whenever you change your email address. To update your email address go to our website and look in the participant's links, or call us at 1-800-323-5871.

Here's a **VERY IMPORTANT** step you can take to make sure our email gets to you: Add us to your email address book. Our address is webquest@arthritis-research.org. This will ensure that our mail makes it through the spam blockers. You will need to do this every time you change your email address. Thank you!

Helping the NDB in other ways

Achieving the NDB's goals of telling the rheumatology community about patient experience depends on a large group of participants. Here is another way you can help.

Now available for your support group or arthritis, fibromyalgia or lupus meetings....Our pamphlets explain what we do and how you can help. Each one has a postage-paid postcard to request more information or an enrollment form to join the project. The pamphlets and a small table-top stand are available free from the NDB. Just contact us at info@arthritis-research.org or 800-323-5871 ext. 133 or 140. Thank you!

Questionnaire changes

Participants in the RA, osteoarthritis, fibromyalgia and other rheumatic diseases will see only three new questions this time. Lupus participants will have a section of new questions called the Lupus Status Index. This may or may not become a regular section of the questionnaire. While working on the Lupus Status Index, don't worry if you see any unfamiliar medical terminology. This usually means you don't have the problem being asked about.

WebQuest

WebQuest is the online version questionnaire. The questions are the same as what you get on the paper questionnaire. People who are comfortable using computers should find it easier than the paper version. If you would like to try it, follow the links from our home page, www.arthritis-research.org and make the request, or send us an email at webquest@arthritis-research.org.

Reminders

While working on your questionnaire, if you have ANY questions about the questionnaire, please contact us right away by email or phone. These might be about technical difficulties or how to interpret a question. If you put your immediate questions in the comments section we probably won't see it in time to answer.

Please use the comments section for any information you think we should have that isn't covered in the questionnaire. This could be about a change in medication that needs explanation or information about other considerations of your condition that you think we need to know. You may also ask general questions that don't require an immediate answer.

Refer a Friend

Here's a really easy way to let a friend know about the NDB. Just give us your friend's email address and we'll send out an email invitation to join the study. Go to http://www.arthritis-research.org/enrollfriend.htm