APPENDIX

HS# 2789: PULMONARY FIBROSIS CONTACT REGISTRY STUDY PROTOCOL

1.1 Purpose

As the name states, contact registries store contact information from groups of reasonably well-characterized patients who are interested in being informed about ongoing or future research opportunities. Pulmonary fibrosis (PF) is a condition for which effective therapies have remained elusive, making drug trials and interventional research studies a mainstay in the PF arena over the past decade and for the foreseeable future. A PF Contact Registry will be a conduit to collect, analyze, and disseminate deidentified, group-level data on the clinical phenotypes of PF patients and will house contact information from patients who wish to be informed about research opportunities for which they may qualify. Data contained in the registry will help inform research hypotheses and guide investigators as they develop research protocols by providing them with numbers of potential subjects who meet particular inclusion/exclusion criteria. The development of a PF Contact Registry will help study this disabling disease.

1.2 Background and Significance

Pulmonary fibrosis is a horrific, irreversible disease. While shortening patients' survival, PF insinuates itself into their lives, leaving them breathless and unable to perform physical activities.[1] Although understanding of the pathogenesis of PF remains murky, what is clear is that increasing age is a risk factor for PF.[2-4] Because the US population is aging, PF will be an expanding health problem for the foreseeable future. Given its estimated US prevalence of about 50 per 100 000 persons,[5] PF may not be a rampant burden on the US health care system, but it absolutely and unrelentingly weighs down patients. Patients with PF suffer.
They have poor quality of life,[6-7] and as the disease progresses, their ability to perform physical activities dwindles. Many are forced to stop working, and 50% of PF patients face death within 3 years of diagnosis. There are no Federal Drug Administration–approved drugs for PF and, to date, no therapy (medicinal or nonmedicinal) has been indisputably proved to benefit PF patients. Further research is needed to identify new drug treatments for PF, to examine the benefits of existing therapies such as supplemental oxygen, and to improve the quality of life of PF patients and their loved ones.

Having access to certain basic data (eg, demographic, disease status, and contact information) from patients who wish to be contacted about research opportunities is vital to conducting all kinds of PF research studies, particularly those that require large,

demographically diverse samples. A contact registry gives underserved and hard-to-reach populations (eg, rural, minority, or low socioeconomic status)—and patients unwilling or unable to travel to a PF center of excellence—an opportunity to move the PF field by participating in research.

As more and more Americans, including those of underserved populations, are "plugged in" to the internet, a web-based contact registry will afford more PF patients than ever the chance to seek out and participate in groundbreaking research.[8-9] According to the Pew Internet & American Life Project, 81% of American adults use the internet. Moreover, at least half of American seniors aged 65 and older report internet use,9 and 88% of the 79% of caregivers who have access to the internet look online for health information on behalf of someone else. Furthermore, caregivers are more likely than non-caregivers of the same age to use the internet, particularly to get and share health information.[10] Overall, a 2012 poll showed that 72% of all adult internet users reported looking online for health-related information within the previous year of being surveyed.[11] With the internet-savvy population growing (both in numbers and with age), web-based contact registries are more than justified, especially in the field of chronic disease.

1.3 Aims

Specific Aim 1:
Create and maintain a nationwide registry of up to 50 000 people, including PF patients or people who are primary supporters of PF patients, who are willing to be contacted when opportunities arise for participation in clinical research and/or with other forms for data dissemination (ie, with a biannual newsletter detailing study results or advances in PF).

Specific Aim 2:
Use the registry as a source of potential subjects for the study "Observing the Effects of Supplemental Oxygen on Patients With Pulmonary Fibrosis."

Specific Aim 3:
Use the registry as a source of possible subjects for future clinical research studies that require people with PF or their primary supporters.

1.4 Design and Methodology

Who will be in the registry
Anyone at least 18 years of age who either (1) has been diagnosed with PF or (2) is a primary supporter or caregiver of someone living with PF is eligible to enroll in the registry.

How the registry works

Patients with PF consent to be enrolled in the registry and may consent to be contacted by registry personnel about opportunities for them to participate in research studies. Some of these studies (eg, "Observing the Effects of Supplemental Oxygen on Patients With Pulmonary Fibrosis") will be conducted by Dr. Swigris and his research team—these studies will be considered registry-affiliated. Registry participants are free to enroll in any study they wish— whether registry affiliated or conducted by investigators not affiliated with the registry (that is, non–registry affiliated studies). It is assumed the investigators conducting those studies will adhere to regulations governing the protection of human subjects in research. Consider a hypothetical example: An investigator in Michigan is conducting a study of the effects of oral honey on PF-related cough and would like registry participants to consider enrollment. The investigator would petition the registry and, if approved by the Registry Oversight Committee, registry personnel would contact potentially eligible registry participants to inform them of the study. The participants would then decide whether to contact the investigator in Michigan to be considered for enrollment. The investigator in Michigan would be responsible for discussing the study with any potential subject, obtaining informed consent, and conducting the study. All of these actions fall outside the purview of the registry or its personnel.

How subjects will enroll in the registry

Eligible participants must fill out an intake questionnaire/consent form. Contact information provided to receive a questionnaire is not stored by the registry data coordinating center (DCC) or by the study coordinator. Subjects have 4 options to obtain the intake questionnaire, complete it, and submit it:

- Complete the questionnaire/consent form and submit it online at http://www.pfresearch.org/p3f-Registry/Registry.htm. Participants will be encouraged to print a copy for their records.
- Enter a mailing address onto an online form (-Registry/HardCopy.htm) and have a hard copy mailed to the subject. Once a signed questionnaire/consent has been sent back to the study coordinator, a copy will be made and mailed back to the subject for his or her records.
- Download a PDF file of the questionnaire/consent form from http://pfresearch.org/p3f-Registry/downloadform.htm and mail the completed questionnaire to the study coordinator, who will then hand it off to the DCC at National Jewish Health. Subjects will be encouraged to print a copy for their records.
- Call the study coordinator at a toll-free number (1-855-609-0010) and have him or her mail a hard copy of the questionnaire/consent form to the subject. Once a signed questionnaire/consent has been sent back to the study coordinator, a copy will be made and mailed back to the subject for his or her records.

Registry intake questionnaire/consent form

The information collected from registry participants will be submitted on the registry intake questionnaire/consent form. The following information will be included:

- Informed consent
- Demographics
- Contact information (primary, alternative, address, email, phone number)
- Cause of PF (if applicable)
- Medical symptoms related to PF (if applicable)
- Diagnostic tests
- Supplemental oxygen use

- Smoking history
- Medication
- Family history

Registry newsletter

To stimulate study enrollment and discourage attrition rates, a biannual newsletter will be sent out to registry participants electronically. On the intake questionnaire, registrants will be able to give an email address where they wish to receive the newsletter. If they do not provide their e-mail address, they will not receive the newsletter. With this newsletter, a request will be made to participants to update their contact information. Contact information for study personnel will be included in the newsletter. The newsletter will contain information relevant to PF, including research updates/results, information on interventions, resources, etc.

Subject discontinuation

Subjects' participation in the registry is voluntary. Any subject may decline or discontinue participation in the registry at any time. Requests for discontinuation and removal of data from the registry must be made by phone or in writing. The registry will notify the DCC immediately of a subject's withdrawal from the registry, and the DCC will delete all data related to the subject.

If a subject requests information about a particular non–registry affiliated study, enrolls in that study, and then later wishes to withdraw from that study, he or she must contact the study investigator and request to have his or her data removed from the study database. The registry and its personnel are not responsible for removing data collected in any non–registry affiliated study.

Receiving protected health information

As a part of the intake questionnaire/consent form, enrolling participants with PF (recall, primary supporters/caregivers may enroll as well) will have the option of filling out a HIP-024 form, which will allow registry personnel to obtain certain diagnostic and physiologic data from the participant's health care provider. The registry study coordinator will oversee the collection of data on date of diagnosis, symptom onset,

pulmonary physiology, chest imaging studies, lung biopsy reports, and supplemental oxygen use. We will not request such data for primary supporter/caregiver registry participants. All data collected will be stored in the registry by the DCC.

1.5 Data Entry, Editing, and Storage

Data will be collected, processed, and stored by the DCC in the Biostatistics Department of National Jewish Health (NJH) in Denver, Colorado.

The registry questionnaires are processed by Cardiff TeleForm^{TM} Verification software.

Forms that are submitted in paper format are faxed to a computer fax machine and converted into images. The software package includes character recognition, which attempts to convert handwriting into text. These images are verified by DCC staff, using the TeleForm software. If the interpreted text is incorrect, the verifier can type in corrections, based on visual inspection of the form. Forms that are submitted electronically, including the website HTML form and PDF, are processed by the TeleForm software without human verification. The TeleForm software exports the data directly into a Microsoft SQL 2005 database.

Data written on the registry intake questionnaires is self-reported and voluntary. The respondent must sign and date the first section of the questionnaire; if a signature and date are not provided, the questionnaire will not be accepted into the system, the individual will not be able to participate in the registry, and the record will be deleted immediately.
Electronic questionnaires that lack an electronic signature and date will not be saved in the system. Print questionnaires that lack a signature and date will be shredded, and the respondent will be notified that he or she needs to fill out another questionnaire if he or she wishes to participate. In general, the respondent may leave questions blank. The DCC may contact respondents to correct data if questions are left blank or if conflicting data are recorded. A maximum of 2 attempts to correct the data may be made via telephone, email, or mailings. The DCC is responsible for restoring any lost data by manual entry from questionnaires, if needed.

1.6 Data Security

Information given by registry participants will be maintained in a secure storage as described below. Likewise, any data collected from the participant's health care provider (assuming the participant has signed a HIP-024 form) will be entered into the electronic database, and the hard copy will be securely filed. Paper consent or

questionnaire forms (or any other hard copies with identifying or potentially identifying information) will be stored in locked file cabinets in locked offices at NJH's main campus. Images of electronically submitted forms are stored on a secure server for future reference if errors in the data are found and confirmation of accuracy is desired.

Access protection
Access to the registry database is granted to the director of the DCC, the principal investigator (PI), and the registry coordinators. The registry database will be kept on a secure server; security consists of physical security measures, software security protections, database backup protections, and policies to ensure authorized use of the database. Each registry coordinator and the PI will have an individual password to the registry database.
Assigned passwords must never be disclosed to anyone other than the intended user. Password(s) will be disabled immediately when no longer needed by registry personnel. Only the database administrator has the access needed to change passwords.

Software security protections
The director of the DCC or his or her designee will have administrative control of the registry database. The registry will remain on a server on the secure NJH network behind the NJH firewalls. The server, firewalls, and database will each remain password protected at all times.

Web applications' security
The DCC will develop a password-protected, limited-access website for the registry that is located at a secure https URL. By definition, https websites are secured using Secure Sockets Layer (SSL) or Transport Layer Security technology standards. SSL is used to encrypt data transmissions between the web server and a user's computer. In addition, the DCC maintains a security certificate that authenticates the website that resides within NJH.

1.7 Data Release of Deidentified Information

Deidentified, group-level data can be given to researchers on written request to—and approval by—the Registry Oversight Committee. These data will not include any individual protected health information (PHI). They may be used by researchers to learn about a larger PF patient population. This information may also help inform possible research hypotheses, assist with the creation of therapeutic clinical trials, and more.

No queries about subject-specific data will be accepted from any source.

Researchers who are granted access to deidentified, group-level data by the Registry Oversight Committee will be required to take the following actions:

1) A confidentiality and nondisclosure agreement must be signed by both NJH and the recipient institution/entity.
2) Researchers must agree to delete study subjects when notified of withdrawal and comply with human subjects protection.
3) The study investigator must maintain an up-to-date address and telephone number with the registry coordinator. This will enable the registry coordinator to provide subjects with the researchers' direct contact information.

After a study investigator receives approval from the oversight committee for receipt of deidentified, grouped data, the DCC will create a password-protected and locked Excel file of the selected data from the secure database. The password-protected and locked Excel file will be sent to the researchers from the DCC. It is the researchers' responsibility to store the Excel file in a secure location.

1.8 Linkage to Other Future Clinical Research Studies

Researchers who would like to have registry subjects contacted concerning a research study will make a formal request by letter or email to the chair of the Registry Oversight Committee. This formal request for registry subject contact must include the following information:

a) A research protocol that demonstrates a scientifically valid research proposal with eligibility criteria and details of human subjects protection
b) Current curriculum vitae for the PI that documents relevant research and publications
c) Documentation of IRB approval at the research sites
d) Letter of institutional support from a division chair, program director, or office of sponsored research that indicates home institution approval of the use of space, PI time, and use of equipment or services

The chair may also request additional information, including the following:

a) Funding source(s)
b) Research support personnel's qualifications
c) Anticipated outcomes
d) Researchers' previously published work

Once a researcher has been granted approval by the Registry Oversight Committee, the study coordinator will contact registry participants about the opportunity to take part in the clinical research. This contact will be made via email, mail, or phone. Contact information for the researcher will be provided to registry participants, and it

is the responsibility of the registry participants to establish contact with the researcher.

1.9 Monitoring and Quality Assurance

Registry Oversight Committee
The Registry Oversight Committee will oversee the implementation, maintenance, and use of the registry. The committee may meet in person or via teleconference as needed, to be determined by the registry director. The following are the 4 primary functions of the committee:

a) Review and maintain the Pulmonary Fibrosis Registry Policies and Procedures
b) Provide oversight for Registry Data Coordinating Center
c) Review and take actions based on the Data Coordinating Center's reports
d) Review and make approval decisions on proposed clinical studies that would use registry data

Members of the committee

Jeffrey Swigris, DO, MS
Chair of the Registry Oversight Committee
Autoimmune Lung Center and Interstitial Lung Disease Program Associate Professor of Medicine

National Jewish Health

Fred Wamboldt, MD
Codirector, Center for Health Promotion Professor of Medicine
National Jewish Health

Amanda Belkin, MPH Clinical Research Coordinator National Jewish Health

Kaci Chacon, BSN Registered Nurse
Interstitial Lung Disease Program National Jewish Health

Brenda Crowe, CRT
Lung Health Educator, Manager Pulmonary Rehabilitation Dept. Exempla Lutheran Medical Center

Susan Baird, PhD Community Consultant Living With PF

John Osborne, DDS, MSD Retired Professor of Dentistry Living With PF

1.10 Registry Reports

The DCC will provide reports to the Registry Oversight Committee 3 times a year. These reports will include the number of participants and their age (all subjects older than the age of 89 will be labeled as 90+), sex, and state of residence. None of these reports will include PHI.

A quarterly progress report on the status of the Data Coordinating Center will be emailed to the chair of the Registry Oversight Committee. The DCC and registry research staff will maintain an accurate and complete file of these reports. The frequency of this report can be decreased with concurrence of all parties. The Registry Data Center director will remain available to discuss any concerns of the Registry Oversight Committee.

2.1 Inclusion Criteria

Anyone who self-reports a diagnosis of pulmonary fibrosis and is older than 18 years of age will be included in the registry.
Anyone who self-reports being a primary supporter or caregiver of someone living with pulmonary fibrosis and is older than the age of 18 will be included in the registry.

Those who consent to be enrolled in the registry will presumably be able to read and write in English.

2.2 Exclusion Criteria

Anyone younger than the age of 18 will not be included in the registry.
Anyone who does not self-report having PF or being a primary supporter or caregiver of someone living with PF will not be included in the registry.

Anyone who does not read and write in English will not be included in the study. It will be assumed that anyone who cannot read or write in English will not be able to fill out the form correctly and therefore will not make it into the registry.

2.3 Determining Eligibility

DCC staff will determine eligibility by the completeness of questionnaires/consents. Potential participants whose questionnaires/consents are not filled out appropriately (eg, missing a signature), will not be considered eligible to be in the registry.

3.0 Consent

All individuals whose data are maintained in the registry will have given their consent to participate in the registry, as well as their consent to store PHI in a database and to be contacted for future studies. The consent process is integral to the submission of their data to, and storage of their data by, the DCC. If an electronic questionnaire is submitted without providing a signature and date in the first section, the form will not be accepted into the system and no identifying information will be retained. If a print questionnaire is submitted without a signature and date in the first section, the form will be shredded and no identifying information will be retained. The questionnaire form includes a prompt before the signature block that advises participants to retain a copy for their records. Data from the intake questionnaires will be entered into the database after the forms are sent to the DCC. Participants may withdraw their information from the registry at any time by contacting registry personnel or the DCC either by phone or in writing.

3.1 Research Procedures

The information collected from registry subjects will be submitted on the registry intake questionnaire/consent form. This information includes the following:

- Informed consent
- Demographics
- Contact information (primary, alternative, address, email, phone number)
- Cause of PF (if applicable)
- Medical symptoms related to PF (if applicable)
- Diagnostics
- Supplemental oxygen use
- Smoking history
- Medication
- Family history

4.0 Administration and Enrollment

The web page for the Participation Program for Pulmonary Fibrosis (P3F) will advertise the registry and provide enrollment instructions and access to the online version of the intake questionnaire/consent form.

5.0 Advertising

Advertising for the registry will be done through the P3F website, flyers,

announcements, newsletters, and word of mouth with the help of National Jewish Health, the Pulmonary Fibrosis Foundation, the Coalition for Pulmonary Fibrosis, www.clinicaltrials.gov, and other PF patient advocacy groups. Letters to colleagues across the United States will also be sent requesting advertisement of the P3F and the registry at local clinics.

6.0 References

1. Bye PT, Anderson SD, Woolcock AJ, Young IH, Alison JA. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. *Am Rev Respir Dis.* 1982;(126):1005-1012.
2. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. *Am J Respir Crit Care Med.* 2007;(176):277-284.
3. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. *Am J Respir Crit Care Med.* 2010.
4. Swigris JJ, Olson AL, Huie TJ, et al. Sarcoidosis-related mortality in the United States from 1988 to 2007. *Am J Respir Crit Care Med.* 2011;(183):1524-1530.
5. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2006;(174):810-816.
6. Swigris JJ, Gould MK, Wilson SR. Health-related quality of life among patients with idiopathic pulmonary fibrosis. *Chest.* 2005;(127):284-294.
7. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. *Thorax.* 2005;(60):588-594.
8. Smith A, Zickuhr K. Digital differences, Pew Internet & American Life Project. http://pewinternet.org/Reports/2012/Digital-differences.aspx. Published April 13, 2012. Accessed May 25, 2013.
9. Madden M, Zickuhr K. Older adults and internet use. Pew Internet & American Life Project websit-use.aspx. Published June 6, 2012. Accessed May 25, 2013.
10. Brenner J, Fox S. Family caregivers online. Pew Internet & American Life Project website. http://pewinternet.org/Reports/2012/Caregivers-online.aspx. Published July 12, 2012. Accessed May 25, 2013.
11. Duggan M, Fox S. Health online 2013. Pew Internet & American Life Project website. http://pewinternet.org/Reports/2013/Health-online.aspx. Published January 15, 2013. Accessed May 25, 2013.