

Assessment of Safety of Air Travel in Patients with Birt-Hogg-Dube Syndrome

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Study protocol

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“Assessment of Safety of Air Travel in Patients with Diffuse Cystic Lung Disease”

Rare Diseases Clinical Research Network
Rare Lung Diseases Consortium
NG Pilot Project
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1.0 Overview

1.1. Protocol Synopsis

Protocol Number:	5714
Protocol Title:	Assessment of Safety of Air Travel in Patients with Diffuse Cystic Lung Disease
Study Chair:	Nishant Gupta, MD
Statistician:	Laura E James
Consortium:	Rare Lung Diseases
Participating Sites:	University of Cincinnati
Activation Date:	December 4, 2015
Sample Size:	300 subjects - 100 with Birt-Hogg-Dubé Syndrome (BHD), 200 with Pulmonary Langerhans Cell Histiocytosis (PLCH)
Target Enrollment Period:	September 2015 – September 2016
Study Design:	This is a questionnaire-based study of patients with diffuse cystic lung diseases (DCLDs) to gather information relevant to safety of air travel, especially pertaining to the risk of pneumothorax associated with air travel. In addition, this study will be used to further characterize clinical aspects of disease and establish a contact registry for patients.
Primary Study Objective(s):	To define the risk of pneumothorax associated with air travel in patients with DCLD.
Secondary Study Objective(s):	<ul style="list-style-type: none"> To establish a contact registry for patients with BHD and PLCH To define the clinical phenotype of each DCLD in their respective cohort of patients To define current screening practices for surveillance of disease-specific anomalies (i.e. renal tumors in BHD)
	<p>The study will enroll participants through the clinic network at the Rare Lung Disease Consortium (RLDC) and through the BHD and PLCH foundation websites. Participants will have access to the questionnaire via REDCap (an online data management system) and each participant will be provided a link to complete the survey. In case of lack of internet access or inability to complete the online questionnaire, a paper survey will be mailed out with a pre-paid envelope to return the survey.</p> <p><u>Inclusion Criteria:</u></p> <ul style="list-style-type: none"> Adult, age 18 or older English literate Signed, dated informed consent; either given electronically or via paper form Diagnosis of BHD, or PLCH as defined by accepted clinical, histopathological and/or genetic criteria. <ul style="list-style-type: none"> ➤ For BHD, diagnosis would include the presence of fibrofolliculomas/trichodiscomas on skin biopsy, or the presence of pathogenic FLCN mutations. ➤ For PLCH, it would include characteristic radiographic findings and tissue biopsy consistent with PLCH (presence of CD1a positive Langerhans cells or stellate fibrosis in late stages). <p><u>Exclusion Criteria:</u></p> <ul style="list-style-type: none"> Inability to give informed consent

Outcome Measures:	Number of pneumothoraces associated with air travel, estimated as a percentage of the number of flights taken.
Statistical Considerations (sample size and analysis plan):	Data from all surveys will be pooled together. The rate of pneumothorax will be estimated as a percentage of the number of flights taken. We will compare other disease and patient characteristics to try to determine factors associated with an increased risk of in-flight pneumothorax.
Variables collected	<ul style="list-style-type: none"> • Contact information • Demographics • Age, gender, ethnicity • Medical history • Diagnosis • Surveillance information for associated clinical anomalies, such as renal tumors in BHD • Evaluation of dyspnea, other pulmonary problems and need for supplemental oxygen • Family history • Smoking history • Pneumothorax information (diagnosis, management, measures to prevent prevention such as pleurodesis, relationship with flights) • Flight history • Effect of pneumothoraces on attitudes towards undertaking air travel
Ethical and Scientific Review Procedures	Institutional Review Board approval will be obtained. Informed consent will be obtained from participants. Every effort will be made to protect participant confidentiality according to privacy laws and medical record confidentiality regulations.
Data Ownership	Nishant Gupta, M.D.
Sponsors (federal, state, foundation and industry support):	National Institutes of Health (NIH) U54

1.2. Lay Summary

Birt-Hogg-Dubé syndrome (BHD) is an uncommon genetic disease characterized by tumors in the hair follicles and kidneys, as well as lung cyst formation. These lung cysts can rupture thus placing patients with BHD at a higher risk for development of pneumothoraces, or collapsed lungs.

Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon disease characterized by the formation of cysts in the lungs, and is strongly associated with smoking cigarettes. Similar to BHD, patients with PLCH have an increased risk of development of pneumothoraces.

The safety of air travel in patients with BHD and PLCH is not established. The concern with air travel in these diseases is related to the risk of cyst expansion with decreasing atmospheric pressure, which could lead to cyst rupture causing a pneumothorax. Safety of air travel has been studied for patients with lymphangioleiomyomatosis (LAM), another rare cystic lung disease. Based on the results from studies done in patients with LAM, recommendations regarding air travel are provided to patients with BHD and PLCH. The aim of this study is to conduct a survey-based assessment of patients with BHD and PLCH and establish the risk of pneumothorax associated with air travel in these diseases.

As a follow up to the original protocol, we plan to re-contact all patients who gave us permission in the survey to contact them again. We will obtain results of their lung function tests and images of CT chest to correlate PFT data and cyst preponderance (size, number, volume etc.) with the risk for spontaneous pneumothorax.

1.3. Detailed Description

The aim of this study is to conduct survey-based assessments for the safety of air travel in patients with BHD and PLCH. The study will enroll patients through the clinic network at Rare Lung Disease Consortium (RLDC) and through the BHD and PLCH foundation websites. Patients will have access to the questionnaire via REDCap (an online data management system) and each patient will be provided with a link to complete the survey. In case of lack of Internet access or inability to complete the online questionnaire, a paper survey will be mailed out with a pre-paid and addressed envelope to return the survey. Paper surveys returned to Nishant Gupta, MD 231 Albert Sabin Way, ML 0564, Cincinnati, OH 45267-0564 will be entered into REDCap by the clinical research coordinator. We plan on enrolling approximately 100 patients with BHD and 200 patients with PLCH for the purpose of this study. Secondary aims of this study include further characterization of the clinical aspects of disease and to establish a contact registry for these patients, in order to facilitate future studies.

This research will be accomplished as part of the Rare Lung Disease Clinical Network Consortium, with data stored and analyzed by the Data Management and Coordinating Center (DMCC) at the University of South Florida as part of the NIH-supported Rare Disease Consortium.

1.4. Participating Investigators and Institutions (Contact Information)

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2.0 Specific Aims (Hypothesis and Objectives)

2.1. Hypothesis

The hypothesis to be tested is that air travel is safe in patients with diffuse cystic lung diseases, and there is no increased risk of pneumothorax in this disease population related to air travel.

2.2. Objectives

1. To define the risk of pneumothorax related to air travel in patients with BHD and PLCH.
2. To establish a contact registry for patients with BHD and PLCH, in order to facilitate participation in future trials.
3. To describe the demographic and clinical characteristics of patients with BHD and PLCH, as well as ascertain clinical practices related to management and surveillance of related medical conditions, such as surveillance of renal tumors in patients with BHD.
4. To determine the relationship between lung function, and radiographic cyst characteristics and the risk of spontaneous pneumothorax in patients with BHD and PLCH.

3.0 Background

BHD is a rare, autosomal dominantly inherited genodermatosis characterized by the formation of hair follicle tumors, kidney tumors, and pulmonary cysts ¹. Pulmonary cysts are seen in 80-100% of patients with BHD ^{2,3}, and lead to an increased risk of development of pneumothorax in these patients ². Zbar et al., have reported that the risk of development of pneumothorax is 32-fold higher in patients with BHD as compared to the general population ⁴.

Atmospheric pressure changes have the potential to cause cyst expansion leading to an increased chance of cyst rupture causing a pneumothorax. Based on this risk, patients with BHD are advised to not undertake scuba diving ⁵, although no disease specific data exists for this recommendation. In general, air travel is considered to be safe in patients with diffuse cystic lung diseases ⁶, although disease specific data for safety of air travel in BHD are lacking.

PLCH is a rare diffuse cystic lung disease seen most commonly in young-middle aged adults, and is associated with exposure to cigarette smoke in greater than 90% of patients ⁷.

Approximately 15% of patients with PLCH develop a pneumothorax over their lifetime, with a recurrence rate of approximately 60% after a sentinel event ⁸. Similar to BHD, recommendations regarding air travel are given to patients with PLCH on the basis of extrapolation from other diseases.

Having specific information about safety of air travel in BHD and PLCH will help these patients make informed decisions about air travel. We aim to conduct a questionnaire-based assessment of patients with BHD and PLCH to ascertain the risk of pneumothorax related to air travel. In the first part of this study we will distribute the questionnaires for BHD, followed later by the PLCH survey. In addition, we aim to establish a contact registry for these patients in order to answer future clinical questions.

With the current amendment, we will re-contact patients with BHD and PLCH, who gave us the permission to contact them in future for other projects. We will ask permission to obtain their medical records, specifically their pulmonary function tests (PFTs), and CT scan(s) of the chest. We will correlate the PFT data and cyst features such as cyst number, size, and volume with the risk of spontaneous pneumothorax. These results will provide us the ability to do individual, patient-specific risk stratification for spontaneous pneumothorax in patients with BHD and PLCH.

4.0 Study Design and Methods

4.1. Overview

Online surveys will be created in REDCap, a password protected data management software, and the links distributed to all patients via email. In case of lack of Internet access or personal preference, paper copies of the surveys will be mailed out to the patients along with a prepaid, addressed return envelope.

4.2. Inclusion Criteria

- Adult, age 18 or older
- English literate
- Signed, dated informed consent; either given electronically or via paper form;
- Diagnosis of BHD, or PLCH as defined by accepted clinical, histopathological and/or genetic criteria
 - *For BHD, diagnosis would include the presence of fibrofolliculomas/trichodiscomas on skin biopsy, or the presence of pathogenic FLCN mutations.*
 - *For PLCH, diagnosis would include characteristic radiographic findings and tissue biopsy consistent with PLCH (presence of CD1a positive Langerhans cells or stellate fibrosis in late stages).*

4.3. Exclusion Criteria

- Inability to give informed consent

4.4. Recruitment of participants

Participants will be recruited from the network of clinics at the Rare Lung Disease-Clinic Network (RLD-CN). The RLDC is a collection of 30 LAM foundation clinics in US and 19 worldwide. These clinics are a hub of many of the rare lung disease we wish to study. A survey of the clinic directors at the RLD-CN suggests that there are over 300 patients with BHD and greater than 700 patients with PLCH being followed currently in this network. In addition, we will seek assistance from the patient advocacy partners such as the BHD Foundation and the Histiocytosis Association to help with recruitment. We will also present our study to patients at national and regional meetings to encourage recruitment. For example, we will take our questionnaires to the International BHD symposium in September 2015 at Syracuse, NY to enable participants to enroll in the study and complete questionnaires at the conference.

4.5. Participant Retention

This study does not require follow-up after completion of the survey, however participants may be contacted in the future to verify and update the contact information they provided for the registry.

4.6. Data Elements

Data elements for this study include the following information about study participants:

- Contact information
- Demographics
- Age, gender, ethnicity
- Medical history
- Patient reported elements of diagnostic criteria and other clinical manifestations
- Surveillance information for associated clinical anomalies, such as renal tumors in BHD
- Evaluation of dyspnea, other pulmonary problems and need for supplemental oxygen

- Family history
- Smoking history
- Pneumothorax information (diagnosis, management, measures to prevent prevention such as pleurodesis, relationship with flights)
- Flight history
- Effect of pneumothoraces on attitudes towards undertaking air travel
- Pulmonary function tests
- CT scans

4.7. Schedule of Events

September 2015: Distribute links and paper copies of the questionnaires

November 2015: Resend links and surveys to increase recruitment

January 2016: Data Analysis

April 2016: Manuscript submission

April 2017: Contact patients and start obtaining medical records

November 2017: Data Analysis

April 2018: Manuscript submission

NIH Approved 02-28-17

5.0 Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to the University of Cincinnati's IRB and the University of South Florida (USF) for approval. Participant enrollment may only begin with IRB approved consent forms. This is an observational study that meets the federal definition of minimal risk.

Since this is a survey based registry study, traditional study monitoring will not occur. We do not expect any adverse events (AEs) nor will we solicit them. If participants contact USF to report an adverse reaction to participation on this registry, USF will report the adverse event to the USF IRB and the Consortium. Otherwise patients will not be solicited for adverse events. The questionnaire data will be stored in a password protected electronic format in REDCap. Only the investigators will have access to the data files. Paper files will be kept in a locked cabinet in a locked office.

The medical records will only be obtained after getting the required permissions from the patients. Since no intervention is being planned for the participants, there will be minimal risk, and we do not expect any adverse effects. The patient records will be kept in a locked cabinet at all times, and access restricted only to the study personnel.

5.1. Study Oversight

The Study Chair has primary oversight responsibility of this study.

5.2. Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "...an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

An unexpected adverse event is defined as any adverse experience...the specificity or severity of which is not consistent with the risks of information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study

All reported adverse events will be classified using the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute. Only those events associated with the conduct of the study and as defined above are reportable.

5.3. Reporting Timeline

Within **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:

Is considered life-threatening/disabling or results in death of subject

-OR-

Is Unexpected/Unanticipated

Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).

All other (suspected) reportable AEs must be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any CRU oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.4. RDCRN Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event, the DMCC created Adverse Event Data Management System (AEDAMS) will immediately notify the Study Chair, site PIs, the Medical Review Officer, and any additional agencies of any reported adverse events via email.

Serious adverse events: The committee appointed Medical Review Officer (MRO) determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The MRO may request changes to the protocol or consent form as a consequence of the adverse event. A back-up notification system is in place so that any delays in review by the MRO beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. The DMCC will post aggregate reports of all adverse events (serious/not serious and expected, unexpected) for site investigators and IRBs.

5.5. Known Risks/Discomforts Associated with Study and Procedures

There is a risk of breach of confidentiality. The risks of completing the questionnaires include fatigue, anxiety and the perception on the part of the patient that questions may be too personal. The patients will be informed in the consent that they can skip any questions they like, or opt out of the questionnaire portion of studies.

5.6. Study Discontinuation (Observational)

This study will not have study discontinuation rules as it is a survey based registry study. The NIH and local IRBs (at their local site) have the authority to stop or suspend this trial at any time.

5.7. Subject Discontinuation

All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent.

- Withdrawal of consent
- Withdrawal by the participant
- Withdrawal by the investigator

5.8. Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether independent range and/or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

6.0 Statistical Considerations

Data from all surveys will be pooled together. The rate of pneumothorax will be estimated as a percentage of the number of flights taken. We will compare other disease and patient characteristics to try to determine factors associated with an increased risk of in-flight pneumothorax. All analyses will be done by using SAS for Windows, version 9.4, Cary, NC.

NIH Approved 02-28-17

7.0 Data Management

All study data will be collected via systems created in collaboration with the RDCRN Data Management and Coordinating Center and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

7.1. Data Management Responsibilities

Data to be obtained for each study participant in this study will be collected via REDCap. This data will subsequently be transmitted to the DMCC at the University of South Florida by distinct mechanisms using methods that are set forth by DMCC.

Confidentiality: Only investigators and other key personnel involved in the study will have access to individually identifiable private information about human subjects.

7.2. Data Entry

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

NIH Approved 02-28-17

8.0 Human Subjects

8.1. GCP Statement

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

8.2. Risks

All efforts will be made to ensure that the data is secure and the privacy is maintained. There is a risk of breach of confidentiality. The risks of completing the questionnaires include fatigue, anxiety and the perception on the part of the patient that questions may be too personal. The patients will be informed in the consent that they can skip any questions they like, or opt out of the questionnaire portion of studies.

8.3. Benefits

There are no direct benefits for participants from their involvement in this study. The answers obtained from these studies could potentially help patients through informing clinical recommendations, for example, weighing the risk of travel given the risk of developing a pneumothorax associated with air travel. No compensation or incentives will be provided.

8.4. Recruitment

Patients with BHD and PLCH will be recruited with the help of the RLD-CN and the respective patient advocacy groups, the BHD Foundation and the Histiocytosis Association. We expect to enroll over 100 patients with BHD and over 200 patients with PLCH in this study. Adult patients (18 years and older) will be eligible to participate in the study.

8.5. Written Informed Consent

Written informed consent will be obtained from each participant before participation in the study. For the online survey, the informed consent portion will immediately precede the survey in REDCap. Participants will be able to begin the survey only after certifying that they have read and understood the informed consent for the study.

For those using paper forms, the participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original signed consent forms and copies will be given to the participants.

8.6. Process of Consent

Subjects are required to sign an informed consent prior to undertaking the survey in accordance with International Conference on Harmonization (ICH) E6; 4.8, "Informed Consent of Trial Subjects."

It will be clearly explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants

9.0 References

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8. Mendez JL, Nadrous HF, Vassallo R, Decker PA, Ryu JH. Pneumothorax in pulmonary Langerhans cell histiocytosis. Chest 2004;125:1028-32.

10.0 Appendices

Appendix 1. Protocol Amendment History

Date	Protocol Version	Summary of Changes
02-23-17	Amendment 1	<ul style="list-style-type: none">• Re-contact patients with BHD and PLCH who gave us permission to contact them again for future studies• Obtain permission to gather pulmonary function tests and CT chests• Correlate PFT data and cyst features with the risk of spontaneous pneumothoraces• Add Scott Merriman as a co-investigator to the protocol• Updated statistician to Laura E James

Appendix 2. Investigator Agreement and Signature Page

Protocol Title: Assessment of Safety of Air Travel in Patients with Diffuse Cystic Lung Disease

RDCRN protocol number: 5714; UC IRB number:

Amendment number:

UC IRB Approval Date: _____

The Institutional Review Board of the University of Cincinnati has approved this study and protocol. The signature of the Study Chair below documents this approval.

Study Chair (Printed)

Date

Study Chair (Signature)

NIH Approved 02-28-17