Qualitative Interviews with Patients with GERD Symptoms
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PRO Consulting

Health Research Associates

Sponsor:

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TABLE of CONTENTS

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1.0 Introduction

Gastroesophageal Reflux Disorder (GERD) is a common condition that results from reflux of gastric contents into the esophagus through the lower esophageal sphincter. Prevalence studies in the Western world have indicated that between 10% and 20% of the population experience heartburn or regurgitation symptoms at least weekly (Dent et al 2005). The corresponding figures in the US are estimated to between 14% and 40%

While Proton Pump Inhibitors (PPIs) are the most widely used and effective therapy to reduce acid secretion, approximately 20 to 30% of the GERD population have only a partial response to PPIs as characterized by persistent GERD symptoms (Fass et al 2007). Most people experience their GERD symptoms both at daytime and night-time. However, some patients experience these symptoms mainly during the day, when they are more aware of them and what might cause them. Others experience symptoms only at night; some when they try to get to sleep, and others are awaken during the night.

AstraZeneca is currently developing a drug for improved treatment of Gastroesophageal Reflux Disease (GERD). The target population is referred to as partial responders to PPI treatment. Partial responders are patients who improved on PPI treatment, but still suffer from GERD symptoms (NB. non-responders are not included in this patient group). These patients often report GERD to have a negative impact on sleep.

This qualitative interview study is being conducted to gather information that will lead to a better understanding of the night time symptoms and their impacts for those patients who are partial responders to PPIs and still experiencing symptoms.

2.0 Study Objectives

Qualitative interviews will be conducted with patients with GERD who are partial responders to PPIs and who are continuously treated with optimized unchanged PPIs and currently experiencing both daytime and nighttime GERD symptoms. The overall goal of the interview study is to understand and document the qualitative and quantitative aspects of nighttime GERD symptoms as well as the differences between daytime and nighttime GERD symptoms. Specific objectives are as follows:

1. To identify GERD symptoms experienced at night:
    a. Document the frequency with which patients report GERD symptoms and determine the words and phrases patients use to describe their GERD symptoms,
    b. Explore which GERD symptoms occur during day and which occur during the night/sleep, and
    c. Determine whether there are qualitative or quantitative differences between patients' reports of daytime and nighttime GERD symptoms.
2. Understand how patients experience and describe the nighttime impacts of GERD symptoms on sleep to gain a better understanding of the potential relationship of GERD symptoms and various dimensions of the patients' nighttime sleep experience.
3. Understand how patients experience and describe the next-day impacts of night-time GERD symptoms , i.e., the next day consequences, to gain a better understanding of the patients' perceptions of the impact of nighttime GERD symptoms on the following day.
4. Evaluate whether the patients' experience of nighttime GERD symptoms are uniquely troublesome relative to daytime symptoms, i.e., evaluate troublesome ratings as a differentiator between daytime and nighttime GERD symptoms and a measure of symptom treatment priority, and
5. Evaluate patients' perceptions of nighttime GERD symptom treatment and what would be a successful treatment to inform which GERD concepts are relevant to improvement in nighttime GERD symptoms.

3.0 Overview of Study Design

This qualitative interview study will enroll approximately 30 patients for individual face-to-face interviews. The interviews will be conducted using a semi-structured concept elicitation (CE) interview guide that is designed to assist interviewers to achieve the specified study objectives and help patients to spontaneously express their experience with GERD and the overall impact of their symptoms on their daily lives. Up to one third of the population (10) will be from the Latino heritage, and bilingual speakers of English and US Spanish. This will provide additional information on whether GERD symptoms are expressed differently by patients of different ethnic groups.

4.0 Methods for Qualitative Interviews

4.1 Subject Recruitment and Site Management

Approximately 30 subjects will be recruited from up to four different clinical sites located in different regions of the United States. Sites will be trained on study execution responsibilities and compensated on a per subject basis for those successfully recruited and participating in the interview sessions.

Staff at each of the sites will be asked to recruit, screen, consent and schedule appropriate patients for the interviews. The interviewer will travel to the clinic site on a pre-determined date to conduct the actual interviews. At least three of the estimated 30 interviews will be video taped and provided for review by the sponsor of this study.

Initial Screening from Patient Records:
Study coordinators at each site will utilize patient records to identify patients who are likely to meet study inclusion/exclusion criteria.

Telephone (or clinic) contact with Patients:
The study coordinator will contact patients identified as potentially eligible for study participation through the chart review process described above to ascertain their interest and complete further screening using the telephone screening section of the Initial Screening Form as a guide. The study coordinator will schedule potentially eligible patients for an in-person enrollment visit.

Enrollment visit:
During the enrollment visit, subjects will complete the Informed Consent document and the demographic form. The study coordinator and clinician will complete the overall eligibility form for the subject. Eligible subjects will be scheduled for an interview session, and given a reminder call within two days of the scheduled date and time.

In order to be eligible for interview, subjects will need to meet all study inclusion criteria and must not violate any exclusion criteria listed below.

4.2 Sample Description (primary characteristics of patients)

Approximately thirty subjects who have been diagnosed with GERD and who have continuously been treated for a minimum of 4 weeks with PPI therapy and who continue to experience both daytime and nighttime symptoms of GERD will constitute the study sample. Up to 30% of the patients will be of Latino origin who are and bilingual speakers of English and US Spanish.
Inclusion/Exclusion Criteria for Eligibility:

Inclusion Criteria

A subject will be eligible if all of the following criteria are met:

1. Male or female between 18 and 75 years of age
2. Subject has a Body Mass Index between 18.5 and 35.0
3. Subject has at least a 6 month history of GERD symptoms (not necessarily consecutive)

4. Subject has a continuous optimized treatment regimen with a proton pump inhibitor (PPI) during the last 4 weeks (optimized means a treatment that according to the physician cannot be further improved by changing brand or dosing of the PPI).
5. If subject has a history of reflux (erosive) esophagitis (EE) they need to have been continuously treated with a PPI for at least 8 weeks prior to interview, the last four being optimized regimen
6. Using a 7-day recall, subject self-reports experiencing a minimum of 3 days of at least mild to moderate and 3 nights of at least mild to moderate severity of heartburn and/or regurgitation as assessed at the enrollment visit with the Inclusion Symptom Questionnaire (ISQ)
7. Subject is able to read the consent document and is willing to provide written informed consent
8. Subject is able to read and write in the English language.
9. Subject is capable of participating in a one-hour interview

Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Subject diagnosed with sleep disorder not related to GERD
2. Subject's GERD symptoms have been completely resolved with PPI treatment
3. Subject has never experienced any GERD symptom improvement at all with PPI Treatment.
4. Subject has prior surgery of the upper GI tract (open, endoscopic or laparoscopic surgery on the esophagus, the stomach and the duodenum with the exception of oversewing or endoscopic treatment of a bleeding ulcer)
5. Subject is currently working a night shift
6. Subject has a history drug addiction, drug abuse (including cannabinoids) or alcohol abuse.
7. Subject has any severe impairment of communication or cognition that, in the judgment of the investigator, precludes participation in the study
8. Subject was involved in the planning or conduct of the study (applies to all AstraZeneca representatives)
9. Subject was enrolled in a previous lesogaberan (AZD3355) study within the past 2 years.

4.3 Data Collection Documents

Concept Elicitation (CE) Interview Guide

The CE interview guide is a document constructed to guide the flow of the semi-structured qualitative interview. It includes broad open-ended questions addressing main areas of inquiry and various interviewer prompts to encourage more detailed discussion around descriptions of the symptoms and symptom-related impacts of GERD. The overall structure of the interview guide is intended to guide the conversation in a way that explores what the patient feels is relevant about their condition and important regarding the effects of treatment. The content areas of exploration of the CE interview guide are informed by current literature and expert input and uses a combination of grounded theory study and phenomenological study methods to elicit the subject responses (Cresswell, 2007).

The semi-structured nature of the CE interview procedure facilitates patients' subjective report of information useful for achieving study objectives at any time during the interview.

Additional data collection forms to be used by the study coordinators, clinicians and interview subjects are the Initial Screening form, Consent form, Clinician Information Form, Demographic form and Overall Eligibility form.

4.4 Interviewer Training and Quality Assurance Procedures

Interview training will be conducted in two parts, using two different trained interviewers for each part. The interviewers will meet to review and clarify the content of the interview guide and will rehearse the logistics of the interview using a process of mock interviews with each other.

Second, two patients similar to those characterized by the present Inclusion/Exclusion criteria and who have previously volunteered to be contacted for pilot studies will participate in a pilot interview. The same study forms and consenting process will be used for the pilot interviews. The pilot interview will be audio recorded as a part of the training process, but the data will not be transcribed or included in the study dataset. At the end of the pilot interview, the subject will be financially compensated in the amount of The interviewers will review pilot results and assess the need for any changes to the interview guide. Changes will be documented, and discussed with the study team prior to implementation.

4.5 The Interview Process

Interviewers will conduct one-on-one interviews, in person, with the subjects from the selected clinical sites using the semi-structured CE interview guide.

Individual interview sessions will last approximately 60 minutes. All interviews will be audio-recorded and transcribed. Three interviews will be video taped in addition to being audio taped. At the end of each interview session, subjects will receive a check for for reimbursement of their time and study participation.

4.6 Analysis of Qualitative Data and Quality Control

4.6.1 Preparation of Concept Elicitation Data

In preparation for data coding, the interview audio files will be transcribed and interviewers will audit the transcripts to delete any mention of subject names, correct spellings, review inaudible fragments or edit out extraneous interruptions.

The primary goal of transcript coding is to identify, catalog, and organize subjects' expressions of concepts. The coded interviews will be analyzed using ATLAS.ti qualitative data analysis software (Version 5; Muir, 2004; Woolf, 2007). The ATLAS.ti software allows the coder to establish unique concept codes which are used by the coder to tag concepts of similar content as it is identified in the transcripts. In the present study, the tagged concepts will organize the primary data (i.e., the transcript text) into unique categories consistent with each of the study objectives and, therefore, will allow for primary analysis of the data (see Analysis of Concept Elicitation Data section 4.6.3).

Novel concept codes are generated throughout the coding process as new concepts appear in the transcript database. Concept codes reflect actual subject language obtained during the interviews and will allow for this language to be apparent in result report tables (e.g., in this way, the frequency of subject mentions of each concept can be specified as well as the type of subject language used to express that concept). A preliminary coding dictionary will be developed based on concepts known to be important to the experience of GERD based on existing literature and input from key opinion leaders in the field of GERD. The preliminary draft of the coding dictionary will be used to code two transcripts, and then will be reviewed and adjusted to incorporate new concepts found in the interview transcripts. While the preliminary coding dictionary will serve as an organizing guide for the coders to reference at the outset of coding, it will also change, grow, and expand as potentially new concepts are uncovered in the transcripts. The coding dictionary is incomplete until all transcripts have been coded which allows for the identification and integration of concepts not previously specified.

To ensure agreement on the identification of all relevant content and the coding of that content, the results of the coding process will be evaluated using an inter-rater agreement (IRA) analysis.

The final coded qualitative database will be organized into frequency tables showing proportionate percentages of subject mentions of concepts in the transcripts.

Preparation of Other Study Data
Descriptive data from the demographics clinic forms and screening documents will be tabulated and presented in table format to characterize the population.

All documents will be available for use in the final report as embedded PDF files, and all transcripts will be available on separate CDs as PDF files.

4.6.2 Evidence of Saturation of Concept

Saturation is reached when no new concepts can be identified from the data (McColl, 2005). It is expected that saturation will be achieved with a sample of up to 30 interview subjects. A multiple step process is taken to evaluate saturation in the present study. First, the transcripts will be ordered in chronological sequence according to the order they are completed and divided into quartiles. Each sub-group will be assessed against the previous sub-group for the appearance of new concept codes.

Saturation of concept is evidenced when no new concept codes appear in the last transcripts sub-groups. The appearance of new concepts will be documented in a saturation table showing the proportionate number of new concepts elicited by each sub-group.

5.0 Ethical and Regulatory Obligations

5.1 IRB Process

The study will be performed in accordance with the principles stated in the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements.

An application to obtain approval from an IRB for the qualitative interview work will be developed. Study documents to be included in the application are the following: the study protocol, the Concept Elicitation Interview Guide, Initial Screening Form, IRB Consent Form, Clinician Information Form, Demographic Form, and Overall Eligibility Form.

5.2 Informed Consent

In accordance with the ethical principles of the Declaration of Helsinki and to remain consistent with local and national regulatory requirements, written informed consent for all subjects will be obtained prior to study participation. At the enrollment visit, the recruiting clinician or coordinator will obtain written

informed consent from the subject after the aims, methods, anticipated benefits, and potential hazards of the study have been adequately explained.

There are no known risks to the subjects; however, during or after the interviews, subjects may become more aware of their symptoms or discomfort. Subjects will be encouraged to talk with their physicians about their questions or concerns.

All data collected in this study will be strictly confidential in accordance with local, state, and federal law. Personnel from the following organizations may examine the research study documents: the interviewers, data analysts and report authors from the study consultancy, the scientists and project managers from the patient-reported outcomes consultancy, regulatory agencies (e.g., FDA), and IRBs. The summary transcripts, coded data, and reports generated from the interviews will not contain individual identifying information and, in addition to the organizations above, these documents will be available to the study sponsor.

5.3 Study and Data Management

No subject identifiers will be used during the process of transferring, analyzing or reporting of study data and results. The study will be conducted in compliance with HIPAA (Health Insurance Portability and Accountability Act) regulations.

The original data collection documents for this study will be kept at the clinical site with the subject records. Copies will be stored at Health Research Associates, inc. in locked files until they are packaged for storage in an off site archive facility, where they will remain for a period of seven years and then be destroyed. Electronic files are all stored on password protected computers with routine back up onto a secure, firewalled server system. Individual files are password protected when shipped outside the secured server system.

The voice files from the audio recordings are placed on a secure FTP site where they can be accessed by password by the transcription vendor. Transcripts are returned via the FTP site and downloaded for transcription inside the study team's secure server system. PDF files are produced from each transcript and burned onto a CD that is included in the final report book that is sent by express mail to the sponsor under a tracking number. The three video DVD files will be limited to possession by HRA and the sponsor only. The video DVD files will not be transmitted electronically. While in development, the final report document is transferred between members of the study team, including sponsor, via email inside each party's secured internet system.

6.0 Documentation

The documentation to provide supportive evidence to comply with the recent FDA PRO Guidance document (Patrick et al., 2004; US Dept. of Health and Human Services FDA, 2009) will include the following:

- Chronology for Qualitative Process
- Protocols for qualitative interviews and any other research used to identify concepts, including training of interviewers
- Population descriptions (numbers, characteristics, location)
- Description of concept elicitation subject pilot test
- Concept elicitation transcripts for each qualitative interview
- Summary of qualitative findings
- Description of how saturation was achieved including final saturation results
- Final report of methods and results

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