Physiologic and Behavioral Correlates of GERD Symptom Severity

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PRÉCIS

Study Title

Physiologic and Behavioral Correlates of GERD Symptom Severity

Objectives

Primary Aim: To identify the physiologic responses associated with improvement in gastroesophageal reflux disease (GERD) symptom severity in response to two different types of patient-provider interactions.

Secondary Aim: To determine whether an expanded patient-provider visit modeled after an integrative medicine consultation leads to more supportive provider behaviors and improved rapport, engagement, and reciprocity in the patient-provider interaction.

Design and Outcomes

This is a pilot, proof-of-concept randomized controlled trial to assess the physiologic and behavioral mechanisms associated with improved symptom severity in adult patients with GERD-related symptoms in response to enhanced patient-provider interactions.

Subjects will be randomized to receive one of two different semi-scripted visit types – either a "standard visit" modeled after an empathic, conventional primary care evaluation or an "expanded visit" modeled after an integrative medicine consultation. During the visit we will measure heart rate variability (HRV) and galvanic skin response (GSR) in the patient-provider dyads; in addition, we will video record the interactions for later analysis of behavioral responses. Subjects will also complete a daily GERD symptom diary and questionnaires about GERD symptoms before their visit with a study provider and two weeks later. Blood will also be drawn and frozen for later omics-based analyses.

Interventions and Duration

Subjects will have a single visit with a "study provider," a physician or nurse practitioner who they have never previously met. Subjects will complete a daily symptom diary for 2 weeks following this visit and return for a second study-related visit in which they will complete questionnaires and be debriefed by a physician on the study team (not the individual who conducted the study intervention visit).

Sample Size and Population

We plan to enroll to obtain 24 completing subjects with GERD, age 21-70 with heartburn symptoms 3 or more days per week. To permit a spread of physiologic, behavioral, and symptom responses, 16 subjects will be randomized to the expanded visit intervention and 8 subjects will be randomized to the standard visit intervention (2:1 expanded:standard

randomization). We will stratify randomization by study provider such that each provider will see 6 subjects (4 expanded visits and 2 standard visits).

1. STUDY OBJECTIVES

The patient-provider relationship is central to the art of medicine and affects a range of health outcomes. However, the specific benefits, and exact mechanisms, by which this relationship supports the healing process is poorly understood. Emerging data suggests that physiologic biomarkers such as galvanic skin response (GSR) and heart rate variability (HRV) are associated with empathy and correlated with the complex verbal and non-verbal behaviors of patients and providers during an encounter. Physiologic synchrony in patient-provider dyads and supportive non-verbal behaviors may be associated with subsequent health outcomes. This pilot study will test these hypotheses using GERD as a model condition.

1.1 Primary Objective

To identify the physiologic responses associated with improvement in GERD symptom severity in response to two different types of patient-provider interactions.

1.2 Secondary Objective

To determine whether an expanded patient-provider visit modeled after an integrative medicine consultation leads to more supportive provider behaviors and improved rapport, engagement, and reciprocity in the patient-provider interaction.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The patient-physician relationship is central to the art of medicine [1,2]. The quality of this relationship affects a range of health outcomes, from irritable bowel [3] and cold symptoms [4] to blood pressure, pain levels, and diabetes outcomes [5–8]. However, the specific benefits, and exact mechanisms, by which this relationship supports healing remain poorly understood. Previous work has demonstrated that when providers maintain eye contact, actively listen, and express empathy, their patients improve more after receiving a placebo than patients receiving care from apparently more detached providers [3,4]. Though studies have suggested a role for communication skills and both cognitive and emotional components of empathy, the variety of measures used and lack of clarity in definitions have limited the interpretation of this work [5,6,9,10].

In most conventional medical settings, practice demands have resulted in reduced time to focus on relational aspects of care. Concomitantly, medical educators and professional societies have called for greater emphasis on humanism, patient-centered care, and improved patient-provider communication [11,12]. Indeed, patients are frequently stressed/in distress when they visit a physician [13]. Perceived lack of time and anxiety about the visit likely contributes to this stress, one manifestation of which is white coat hypertension [14].

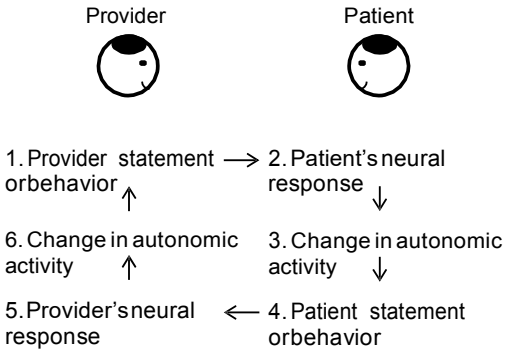
The public has become increasingly interested in complementary and integrative medicine (IM) healing approaches in which patient-provider dynamics often differ substantially from most conventional medical visits [15–19]. IM providers frequently spend more time with patients and ask questions that are quite different from those asked during conventional visits. The IM consultation process may produce enhanced placebo effects [19]. It is unclear whether these effects represent a form of interpersonal healing [20], an enhanced patient-provider relationship (e.g., increased perceived empathy or trust), or simply provide patients with the opportunity to reflect on their symptoms in a safe and non-judgmental space (a form of therapeutic narrative medicine [21]) creating an openness to perceiving symptoms differently and enhancing coping [22]. Some patients feel "more heard" by IM providers [23]. IM providers may make patients feel more "at ease" and relaxed, promoting a physiologic response (e.g., reduced heart rate and blood pressure) similar to that elicited by meditation and other mind body techniques [24]. Feeling less stressed during a medical visit may create an openness to change and improved memory of, and follow-through with, the provider's recommendations [25]. Yet there are few studies of these interactions and they largely rely upon patient interviews or responses to surveys [15–18].

Gastroesphageal reflux disease (GERD) is one of the most prevalent health-related conditions in the Western world with prevalence estimates ranging from 20-40% [26,27]. GERD is primarily a clinical diagnosis, characterized by symptoms of heartburn and acid reflux. It is associated with decreased health-related quality of life and significant healthcare costs and lost productivity [28,29]. Standard treatment includes antacids, H2 receptor blockers, and proton pump inhibitors (PPIs), with the latter generally regarded as the most effective of these therapies. Nonetheless, many patients experience continued symptoms despite taking PPIs [30]. Many patients who do not find relief with PPIs have functional heartburn symptoms and/or co-occurring dyspepsia symptoms (e.g., upper abdominal discomfort, bloating, and gas) that do not respond well to this class of medication [31,32]. Moreover, awareness of the interconnections between the central nervous and gastrointestinal systems has led to the recognition that stress can profoundly affect gastrointestinal (GI) symptoms, such as GERD [33], suggesting that interventions targeting these pathways may improve symptoms [34]. Notably, the placebo response rate in trials of GERD medications can be as high as 40% [35].

2.2 Study Rationale

Recent studies are beginning to reveal the neural correlates of empathy, both in general [36] and in patient-provider relationships [37,38]. Activation of specific neural pathways drives changes in autonomic nervous system regulation [39], resulting in downstream changes in physiologic biomarkers such as galvanic skin response (GSR) and heart rate variability (HRV) [40,41]. A growing body of research has identified concordance in physiologic biomarkers between individuals. An excellent review of this topic, also known as "interpersonal autonomic

Figure 1: Proposed model for mechanisms underlying the patient-provider relationship



physiology" or "physiologic synchrony," has recently been published [42]. The authors reviewed 61 studies covering relationships between therapist and client, couples, mother and child, teammates, and other relationships. There were 8 studies of the therapist-client relationship which examined either heart rate (HR) or skin conductance/galvanic skin response (GSR). Multiple studies found positive correlations between empathy ratings and physiologic synchrony. The study I have proposed would be the first to examine physiologic biomarkers in the context of physician-patient interactions in a medical setting.

As illustrated in Figure 1 above, we hypothesize that moment-to-moment autonomic changes in patients and providers over the course of a visit collectively influence perceptions of the encounter (part of the "neural response") and response to treatment and that improved treatment response is associated with increased concordance in these autonomic changes.

GSR and HRV can also be used to assess relative physiologic stress vs. relaxation [43]. Typically GSR and HR decrease and high frequency HRV increases in the relaxed state [24,44,45]. While empathic visits may theoretically reduce patients' allostatic load and distress [46], this hypothesis has not been studied rigorously. Newer computational approaches incorporating complexity theory to the analysis of physiologic data [47] have yielded valuable insights to the study of human disease (e.g., decreased HRV is associated with increased cardiovascular mortality [48,49]) and the effects of integrative modalities such as tai chi [50,51]. There is limited data using these approaches to study client-therapist interactions [52–54].

Social psychologists have developed and validated a variety of coding schemes to analyze providers' verbal and non-verbal behaviors and to link these behaviors with patient satisfaction, understanding, trust, rapport, empathy, and a variety of related factors [9,55–60]. This rich literature has yielded many insights and a variety of tools used in studies of physician-patient communication, but rarely have these tools been linked with physiology or health outcomes [7].

I recently found that an "expanded" provider visit modeled after a visit to an IM provider was more effective in decreasing heartburn and dyspepsia symptoms in patients with GERD than a "standard" provider visit modeled after an empathic conventional medical visit [61]. I used a script of pre-determined questions for each visit type. The standard visit script included questions about GERD history, symptoms, prior evaluation and treatments, and past medical history. The expanded visit script included the same questions plus additional questions that inquired about their GI symptoms, non-GI symptoms, and overall temperament. Thus, the main differences between the visits were the length of time spent with the subject and the additional questions that were asked. Many of the subjects in this study were already taking pharmaceutical medications for GERD, suggesting that symptom improvement resulting from the expanded provider visit may enhance the efficacy of some medications in providing adequate symptom relief.

While some may argue that increasing visit length is impractical in conventional healthcare settings, one reason why payers will not adequately reimburse for increased visit lengths is the lack of data linking visit length with health outcomes. Increased visit length has been associated in clinical practice with reduced number of prescriptions and

increased patient satisfaction, engagement, and quality of care [62–64]. Other studies suggest mechanisms by which provider communication (verbal & non-verbal) may affect health outcomes [65]. Yet we really do not know what makes longer visits more effective. By first better understanding the mechanisms that make the expanded visit intervention effective, I will be able to make informed decisions regarding future changes to this intervention and adaptations that may make it more feasible in today's healthcare environment.

3. STUDY DESIGN

Study design: Single-center, single-blind, pilot randomized controlled trial

Primary outcomes:

1) Correlation between physiologic synchrony in patient-provider dyads (GSR or HRV) and improvement in GERD symptom severity.
2) Correlation between absolute changes in GSR within subjects over the course of the study visit and subsequent changes in GERD symptom severity.
3) Correlation between absolute changes in high frequency HRV within subjects over the course of the study visit and subsequent changes in GERD symptom severity.

Secondary outcomes:

1) The difference in the frequency of supportive provider behaviors between the standard and expanded visit groups.
2) The difference in the ratings of rapport, engagement, and reciprocity between the standard and expanded visit groups.

Study population:

Men and women age 21-70 with heartburn symptoms 3 or more days per week. We will enroll until we reach 24 completing subjects.

Study location:

The Clinical Research Center (CRC) at Massachusetts General Hospital (MGH), the Benson-Henry Institute (BHI) for Mind Body Medicine, or another MGH location.

Length of subject participation: 2 weeks

Length of study enrollment: 12-14 months

Groups:

1) Standard visit (n=8), modeled after an empathic, high quality conventional primary care visit.
2) Expanded visit (n=16), modeled after a visit with an integrative medicine provider

Randomization:

The randomization code will be generated by the study statistician as described below (section 4.3). The study will be single-blinded (study providers and the research team will know what the subject is receiving but the subject will not). Randomization will be

stratified based on study provider. We anticipate 4 providers each seeing 6 subjects (2 standard visits, 4 expanded visits).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Research subjects must meet all of the following inclusion criteria to participate in the study:

- Adults ages 21-70 years old (rationale: population of interest, GERD frequency increases with age; adults 70+ are more likely to have complicated disease and/or meet one or more exclusion criteria)
- Heartburn symptoms 3 or more days per week with an average daily symptom severity of 3 or more on a 7 day baseline symptom diary (see section 6.2.2 for description of instrument; rationale: subjects must be symptomatic enough that improvement in symptoms is detectable. This threshold is similar to that seen in my pilot study [61].)
- English language proficiency (rationale: feasibility)
- Willingness to be videotaped and connected to physiologic monitoring devices during the visit (rationale: feasibility/study procedures)

4.2 Exclusion Criteria

Any candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation.

- Diagnosis of Crohn's disease, systemic sclerosis, known active ulcer disease, gastric cancer, or untreated/active Barrett's esophagitis based on subject self-report and/or medical record review (rationale: heartburn symptoms may be due to another, more serious medical illness)
- Heavy alcohol use (> 6 drinks/week for women and > 13 drinks/week for men) based on subject self-report (rationale: can exacerbate heartburn symptoms)
- Pregnant women. Due to the short nature of the study and lack of interventions that will interfere with pregnancy, we will not screen for pregnancy or request female participants to use contraception (rationale: feasibility/physiology of heartburn is different in pregnant women).
- Dementia or significant memory difficulties as determined by the study team and medical record review (rationale: feasibility and human subjects concerns)
- Severe, unstable psychiatric disease based on subject self-report, study team determination, and/or medical record review (rationale: feasibility and human subjects concerns)
- Greater than 15 doses of nonsteroidal anti-inflammatory drugs (NSAIDS) within the prior 30 days (aspirin ≤ 325 mg daily permitted) or ongoing NSAID use at a

level deemed likely to interfere with the study (rationale: NSAIDS can exacerbate GERD and cause peptic ulcers)

- Failure to complete the baseline symptom diary for at least 6 of 7 days (rationale: feasibility)
- Change in GERD treatment regimen within the last 2 weeks (subjects may use antacids, H2 receptor blockers, and/or proton pump inhibitors as long as they are symptomatic on a stable regimen; rationale: feasibility, need a stable symptom baseline)
- Allergy to adhesives (rationale: feasibility/study procedures)
- Inability to provide informed consent (rationale: human subjects concerns)
- In the opinion of the investigator, unable to comply with the study protocol or has a condition that would likely interfere with the study (rationale: feasibility)

4.3 Study Enrollment Procedures

Patient Recruitment*:*

Initial recruitment efforts will start with the MGH Internal Medicine Associates (IMA) primary care practice and the Benson-Henry Institute (BHI; clinician referral, flyers in clinic, and posting on the BHI website), but may expand to include a) other MGH primary care practices, b) the MGH gastroenterology clinic, c) Research Study Volunteer Program (RSVP) for Health (an online registry of Partner's affiliated clinical trials), d) the Partners' clinical trials website, e) MGH Broadcast weekly research studies seeking volunteers email, f) clinician referral, g) the Research Opportunities Direct to You (RODY) program, and/or h) flyers posted in clinics and hospital-approved bulletin boards if we are not meeting our recruitment goal of 3-5 subjects/month.

We will begin by identifying potential subjects from the MGH primary care practice-based research network (PBRN) cohort. Potential subjects identified through the PBRN cohort will receive a letter from the study PI informing them of the study and inviting them to participate along with contact information for a study coordinator and a postcard they can mail in if they wish to opt-out and not be contacted. Patients who do not mail back the opt-out card will receive a telephone call from a study team member at least 2 weeks after the letter was mailed. We will seek permission from patients' primary care physicians prior to sending any letters. Letters sent to potential participants that are part of the RODY program will not include an opt-out card, but the study coordinator's number and email with instructions to call or email if they do not wish to be contacted about the study.

Study flyers will be posted in the BHI waiting room to recruit participants. If a patient is interested in learning more about the study, they may request additional information during their appointment or may call the phone number on the flyer. Alternatively, if the investigator sees a patient who may be eligible, she may mention that the BHI is conducting a study for patients with GERD and ask if they would like to receive more information from a study research coordinator. In all cases, prospective subjects will be informed that their decision whether to participate will have no effect on the care they

receive at the Institute. The Investigator will address any immediate questions the prospective subject may have and obtain verbal permission to give their contact information to a study staff member who can provide further details.

Patient Screening*:*

Potential subjects will undergo a telephone prescreen by study staff and have the opportunity to ask questions about the study (see telephone script). Potential subjects will be told that they will not receive specific treatment recommendations for their GERD as part of the study. They will also be informed that the study involves optional blood draws at each visit. If the potential subject receives care at a Partner's Healthcare affiliated institution, their medical record will be reviewed as part of the eligibility assessment. A standardized form (see attached) will be used to ascertain potential eligibility and an electronic screening log will be kept to keep track of reasons for ineligibility. Those who are deemed potentially eligible and are interested in participating will be sent a 7 day baseline symptom diary (by email or via the post office) and scheduled for an intake visit and two week follow-up visit. Potential subjects will be mailed a copy of their medication list (if they are a Partner's patient) and asked to update it or bring a complete list of medications, vitamins, herbs, and supplements that they are taking to the baseline visit. Potential subjects will be called several days after the diary is mailed to ensure that they received it and that the instructions for completing the diary are clear.

Intake Visit and Consent*:*

Subjects will present to the BHI, the CRC at MGH, or another pre-determined MGH location. The baseline symptom diary will be reviewed by a study team physician (one of the study investigators, not a provider delivering the study visit intervention) and potential subjects will be rescreened. If they are deemed eligible, they will have an opportunity to review the written informed consent document, ask any questions, and will be consented by a study team physician.

To avoid alerting subjects to the fact that we are directly studying the effect of the patient-provider relationship on health outcomes (which could influence study results [66,67]), the study team physician will inform subjects during the consent process that 1) talking about their symptoms with a physician may result in improved autonomic nervous system regulation and improvement in GERD symptoms (to set an expectation for possible symptom improvement and explain why GSR and HRV are being monitored) and 2) we are studying whether physicians mirror patients' physiology as has been suggested by some neuroimaging studies [37,68] (to explain why providers are being similarly monitored). While it is challenging to study patient-provider interactions without subjects' direct knowledge, particularly since both are being monitored in this study, we believe that framing the study in this way is the most sensible way to proceed and the least likely to substantively affect the study's results. As the intervention is minimal risk, we believe it meets the federal criteria for modification of informed consent [69], to allow us to conceal from participants that we are studying the patient-provider interaction.

Subjects will also be informed during the consent process that the healthcare provider who will be asking them about their GERD symptoms has been instructed not to provide any specific GERD treatment advice since they will not have the opportunity to follow-up and

because their primary care physician may have a preferred treatment plan for their GERD. We will provide study participants with an informational handout on GERD and possible treatment approaches at the end of the study.

Individuals who sign the informed consent document and elect to participate in the study will be considered enrolled. Only individuals who can provide informed consent will be eligible to participate.

Randomization:

Once enrolled, subjects will be randomized to receive either the standard visit intervention (n=8) or the expanded visit intervention (n=16; section 9.2). They will not know that there are two possible visit choices. This aspect will be revealed to subjects during a debriefing at the follow-up visit. We will stratify by provider and create permuted block sizes of 3 and 6 (2 expanded, 1 standard; 4 expanded, 2 standard) with the intent to enroll 4 providers who will each see 6 subjects. If we can only enroll 3 providers or one provider cannot see 6 subjects then the remaining slots will be divided among the remaining providers.

Provider Recruitment and Screening*:*

We will approach pre-identified MGH internal medicine physicians and ask whether they are interested in participating in the study as providers. If we cannot identify enough interested physicians internally, we may approach colleagues at other Partners-affiliated institutions and/or send an email describing the study to internists within the MGH Division of General Internal Medicine. We may also present the study at practice meetings or division conferences. Providers must be willing to adhere to the study protocol and not provide specific treatment recommendations (pharmacologic or non-pharmacologic) as this is outside the scope of the study and subjects must remain on a stable regimen during the course of the study. Providers must also be willing to receive a brief training to understand how to deliver the standard and expanded visit interventions.

Provider Consent*:*

Participating providers will be consented by the study PI. As study providers will deliver both visit interventions, they will not be blinded as to the study's hypotheses or the group to which a given subject is assigned. They will be notified of which intervention they are delivering immediately before walking into the room to conduct the study visit.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Standard and Expanded Visit Groups

Subjects will be randomized to receive either a "standard visit" or an "expanded visit" with a study provider. The standard visit is based on a high quality, empathic, conventional primary care encounter. The expanded visit is based on an integrative medicine consultation. Both visits are based on a script of questions and statements to the

patient/subject (see Appendix E). The standard visit script includes questions about GERD history, symptoms, prior evaluation and treatments, and past medical history as well as a brief physical exam. The expanded visit script includes the same questions as the standard visit script plus additional questions that inquire about the modalities of their GI symptoms (e.g., nature of the reflux taste, sensation of heartburn pain and/or abdominal fullness, time of day better/worse), details about non-GI symptoms, quality of sleep, the effect of the weather on symptoms, food cravings and aversions, menstrual flow, fears/phobias, and overall temperament. In this way, the expanded visit tries to understand the patient's/subject's constitution in a way that many systems of integrative medicine attempt to do. To reduce the potential for introducing bias by using the words "standard" and "expanded", the visit templates that they study providers will follow will simply refer to the number of questions to be asked on the template (e.g., 6 Question Template).

In our pilot study [61] we did not limit the amount of time spent with the study subject. On average, the standard visit lasted 18 minutes (range 11-32 minutes) and the expanded visit lasted 42 minutes (range 23-74 minutes). The study providers will be instructed to maintain equal empathy in both groups (e.g., kind and friendly manner, maintained eye contact, active listening and repeating back the patient's words, expressions of empathy). Thus, the main differences between the visits will be the length of time spent with the subject and the additional questions that are asked.

Each study provider will participate in an orientation session to learn how to deliver the standard and expanded visit interventions. Providers will be explicitly instructed not to offer specific GERD treatment advice – either pharmacologic or non-pharmacologic. The study PI will review video recordings of the interactions to offer feedback to study providers and ensure protocol fidelity. As each study provider finishes his/her portion of the study, the PI will interview them to understand their experiences of the study, the two visit types, and their views on the doctor-patient relationship.

We do not anticipate any adverse effects as a result of this intervention.

5.2 Handling of Study Interventions

To minimize potential bias that could affect study staff interactions with subjects, the study provider will open an envelope indicating which visit type he or she is to deliver immediately before conducting the study visit and will receive the appropriate study visit script. At the time of consent, study subjects will not be informed about the two different interview types or that part of the study involves testing the effect of the doctor-patient interaction on response to treatment. Concealment of these aspects of the study protocol is essential to maintaining the validity of the study as data suggests that patients responses change when they know that the doctor-patient interaction is being studied [66,67]. The study PI, or another study team physician, will notify subjects at their follow-up study visit, after the exit interview, that there were two possible types of physician visits, that this aspect of the study was concealed from them initially, and of the rationale for doing so. A script outlining this planned debriefing is present in Appendix G. We believe that this intervention is minimal risk and that our plan meets the federal criteria for permitting alteration of some elements of informed consent [69].

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Subjects are permitted to remain on all baseline medications, over-the-counter products, and dietary supplements, including those used to treat GERD symptoms (e.g., antacids, H2 receptor blockers, and proton pump inhibitors) during the study. We will request that they not change doses of medications used to treat GERD symptoms during the two weeks that they are enrolled in the study.

5.3.2 Required Interventions

None.

5.3.3 Prohibited Interventions

Subjects may not have consumed more than 15 doses of NSAIDS within the prior 30 days (or more than 8 doses during the 2 week study period. Aspirin at doses of 325 mg or less daily is permitted.

We will ask subjects not to change their GERD treatment regimen during the study. This will be monitored via the daily symptom diary.

5.4 Adherence Assessment

Subject adherence is defined by subjects completing at least 12 out of 14 days of their daily symptom diary during the two week study period. Adherence will be assessed when subjects return their symptom diaries at their follow-up visit. For subjects who return incomplete symptom diaries, average daily symptom severity for the days completed will be calculated. If there is insufficient data to make this calculation, we will assume that symptoms are unchanged from baseline.

6. STUDY PROCEDURE

6.1 Schedule of Evaluations for Subjects/Patients

Assessment	Telephone Screening: (Day -30 to -7)	Baseline, Enrollment, Randomization: Visit 1 (Day 0)	Post Intervention: Visit 1 (Day 0)	Follow-up: Visit 2 (Day 13-18)
Prescreen Form	X	X		
GERD Daily Symptom Diary Reviewed		X		X
Informed Consent Form		X		
Current Medication List		X		X
Height and weight		X		
Blood draw		X	X	X
Demographics & Health Behaviors		X		
GERD-Health Related Quality of Life Questionnaire (GERD-HRQL)		X		X
NIH Patient Reported Outcomes Measurement Information System (PROMIS) GERD		X		X
Gastrointestinal Symptom Rating Scale (GSRS)		X		X
Perceived Stress Scale-10 (PSS-10)		X		X
Current Stress Question		X	X	X
NEO Five Factor Inventory (NEO-FFI)		X		
Randomization		X		
HRV, respiratory rate, skin temperature, and GSR		X		
Video recording		X		
Study visit		X		
Consultation And Relational Empathy questionnaire (CARE)			X	
HEAL Patient-Provider Connection			X	
Adverse Events				X
Qualitative Interview				X
Debriefing				X

Schedule of Evaluations for Providers

Assessment	Enrollment	Prior to each subject/patient encounter
Informed Consent Form	**X**	
Interpersonal Reactivity Index (IRI)	**X**	
NEO-FFI	**X**	
Demographics	**X**	
Intervention Training	**X**	
PSS-10		**X**
Current Stress Question		**X**
Fatigue Scale		**X**
Interview at completion of study		

6.2 Description of Evaluations

6.2.1 Telephone Screening (Day -30 to -7)

A standardized form will be used to assess the potential subject's eligibility for the study. See Appendix B.

6.2.2 Enrollment, Baseline, and Randomization (Visit 1, Day 0)

Potential subjects will be rescreened using the pre-screen form by a study physician. The study physician will also review the baseline symptom dairy to ensure that the individual is symptomatic enough to enroll. If the individual is eligible to participate in the study, they will be given a copy of the consent form to review.

Consenting Procedure

Written informed consent will be obtained by a study team physician (see also section 4.3). The subject will be given adequate time to read the consent form, and any questions the subject has will be answered. The study team physician will confirm that the subject understands that he/she will be connected to physiologic monitors during the visit and that the visit will be video recorded. The subject will also have the opportunity to choose whether or not to consent to blood draws as part of the study which will involve two blood draws at the first visit and one blood draw at the second visit. The subject will receive a copy of the consent form and the original signed copy will be kept in a study binder. If the subject agrees to participate and signs the informed consent form, they will be considered "enrolled".

Study providers will be consented by the study PI, following a similar process, using a different written informed consent form.

Baseline Assessments

Evaluations for Study participants/patients:

- Current medication List – will be pulled from Epic and verified with the patient by a study team physician.
- Height and weight – will be obtained by a CRC nurse or study team member.
- Blood draw (optional) – 10 mL of blood will be obtained by a research nurse in the CRC or other appropriate clinician. Blood will be processed to obtain RNA, DNA, and plasma then frozen at -80^{o}C for later omics analyses.
- Demographics and health behaviors – will assess things such as age, gender, race/ethnicity, smoking status, alcohol & caffeine use (see Appendix D)
- Baseline Symptom Diary – 7 day diary indicating the frequency and severity of 9 different GERD and dyspepsia-related symptoms on a 5 point scale as well as any medications, supplements, or other products used to help manage symptoms. The first 3 symptoms (daytime heartburn, nighttime heartburn, and acid reflux) will be used to assess severity of GERD symptoms.

- GERD-HRQL - a validated 11 item scale for assessing the impact of GERD symptoms on health-related quality of life [70].
- NIH PROMIS GERD scale – a validated 13 item instrument assessing frequency and severity of GERD symptoms over a 7 day recall period [26].
- GSRS: The Gastrointestinal Symptom Rating Scale is a validated 15 item instrument for measuring the severity of gastrointestinal symptoms [71]. It contains 5 subscales: abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome, and constipation syndrome.
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress).
- Perceived Stress Scale (PSS) – a widely used 10 item measure of perceived stress that has been shown to correlate with a variety of different health outcomes [72]. We have adapted the originally validated measure to ask about stress over the past week (7 days), rather than the past month, to better fit the timeframe of the study. We have used this timeframe in other studies.
- NEO Five Factor Inventory (NEO-FFI) – a validated 60-item instrument that measures five major dimensions of personality: extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience [73]. Some dimensions have been associated with response to enhanced patient-provider interactions in others studies [74].
- Physiologic Measures and Video Recording: During the intervention we will measure HRV, respiratory rate, skin temperature, and GSR in both study patients and study providers. The study visit will also be video recorded.

Evaluations for Study providers:

- Interpersonal Reactivity Index (IRI) — a validated 28 item self-assessment of cognitive and affective components of empathy [75].
- NEO Five Factor Inventory (NEO-FFI) – a validated 60-item instrument that measures five major dimensions of personality: extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience [73]. Some dimensions have been associated with response to enhanced patient-provider interactions in others studies [74].
- Demographics and practice– will assess things such as age, gender, race/ethnicity, and clinical experience (see Appendix D)
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress). Study providers will complete this question immediately prior to each study subject visit.
- Perceived Stress Scale (PSS) – a widely used 10 item measure of perceived stress that has been shown to correlate with a variety of different health outcomes [72].Study providers will complete this questionnaire immediately prior to each study subject visit.

- Fatigue Scale – 1 item self-report measure of the current fatigue level on a scale of 0 (no fatigue) to 10 (extreme fatigue). Study providers will complete this question immediately prior to each study subject visit.

Randomization

Subjects will be randomized on the day of their baseline visit (Visit 1), following consent, to receive either the standard or expanded visit with the particular provided that they are scheduled to see that day. We will stratify randomization by provider so that each provider does the same proportion of standard and expanded visits. Randomization will occur after subjects have completed their optional first blood draw and baseline questionnaires, immediately prior to the study visit. Study providers will open an envelope instructing them which study visit intervention to deliver.

6.2.3 Blinding

This is a single-blinded study. Subjects will be unaware of the possibility for two different types of study visits. Study providers and staff will be aware of the study intervention delivered, but only immediately prior to the study visit to decrease the potential for introducing bias in how study staff interact with subjects during recruitment and consent. Subjects will be debriefed at the end of the Visit 2 regarding the nature of the study and the intervention that they received. Data will be analyzed in a blinded fashion, also to avoid introducing bias. Given the low-risk nature of the study, we do not anticipate a need to break the blind while a subject is enrolled.

6.2.4 Post Intervention Measures (Day 0)

Immediately following the study physician visit, subjects who consented to blood draws will be asked to have another 7.5mL sample of blood taken (to obtain RNA and plasma) and all subjects will be asked to complete the following questionnaires:

- CARE – Consultation And Relational Empathy questionnaire, a validated and commonly used 10 item measure for assessing the quality of the patient encounter and perceptions of empathy from the treatment provider [76]. I used it in my pilot study.
- HEAL Patient-Provider Connection – a subset of the Healing Encounters and Attitudes List, a recently validated 7-item measure of the patient-provider connection. This is a patient-reported outcome developed as part of a set of tools to measure non-specific factors in treatment using the NIH PROMIS methodology [77].
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress).

6.2.5 Telephone check-in

Study coordinators will call enrolled subjects who have completed study visit 1 approximately half-way between the first and second study visits. These telephone check-ins will a) serve as a reminder to participants to complete their daily symptom diary, b) address any participant questions or concerns, and c) remind/confirm participants' second study visit appointment.

6.2.6 Completion/Final Evaluation

We will attempt to schedule subjects' Visit 2 appointments as close to the 2 week window as possible, but will allow a window of 13-18 days. Visit 2 will be scheduled simultaneously with Visit 1 to help promote adherence to this timeline.

- Current medication List – will be pulled from Epic or the prior visit and verified with the subject by a study team physician.
- Blood draw (optional) – 7.5mL of blood will be obtained by a research nurse in the CRC or other appropriate clinician. Blood will be processed to obtain RNA, and plasma then frozen at -80^{o}C for later omics analyses
- GERD-HRQL - a validated 11 item scale for assessing the impact of GERD symptoms on health-related quality of life [70].
- NIH PROMIS GERD scale – a validated 13 item instrument assessing frequency and severity of GERD symptoms over a 7 day recall period [26].
- GSRS: The Gastrointestinal Symptom Rating Scale is a validated 15 item instrument for measuring the severity of gastrointestinal symptoms [71]. It contains 5 subscales: abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome, and constipation syndrome.
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress).
- Perceived Stress Scale (PSS) – a widely used 10 item measure of perceived stress that has been shown to correlate with a variety of different health outcomes [72].
- Adverse events – study staff will ask subjects if they experienced any adverse events and ask about any hospital or emergency room visits since enrollment.
- Daily symptom diary – Identical in content to the baseline symptom diary, this 14 day diary allows subjects to track the frequency and severity of 9 different GERD and dyspepsia-related symptoms on a 5 point scale as well as any medications, supplements, or other products used to help manage symptoms.
- Qualitative interview – a study team member will conduct a semi-structured qualitative interview (see Appendix F) with each subject after the subject has completed questionnaires and prior to the debriefing. These interviews will be audio recorded and will include questions about their perceptions of their interaction with the study provider and with healthcare providers in general and their experience participating in the study.
- GERD handout – an informational handout on GERD and possible treatment approaches will be provided to subjects. See Appendix I.
- Debriefing – a study team physician will debrief with each subject regarding the actual nature of the study. See Appendix G for a debriefing script.

7. SAFETY ASSESSMENTS

Expected risks to subjects are as follows:

- Study questionnaires: Symptom and behavioral data collection involves virtually no risk; however, psychosocial tests or questions about symptom intensity may cause minor emotional distress. Because participants are free to stop at any time and will be reminded of this throughout the assessment process, the risk of distress is low. In our experience, such questionnaires are well tolerated and complications are extremely rare.
- Discomfort from ECG/GSR leads and physiologic monitoring: Some participants may experience minor skin irritation due to the adhesive used to apply leads for physiologic monitoring. Subjects with known adhesive allergies will not be eligible to participate in the study. Some participants may experience psychological distress knowing that their physiology is being monitored. The physiologic monitoring will be described in the consent document and care will be taken to minimize such distress. Participants will be free to stop at any time. In general, such monitoring is well-tolerated.
- Discomfort from blood draws: some participants may have an aversion to needles, blood, and/or the drawing of blood. Blood will be drawn by experienced nurses at the MGH CRC and care will be taken to minimize discomfort to participants. Blood draws are generally well-tolerated, although occasionally there may be bruising or discomfort at the site. Rarely an infection can occur. The blood draw will be an optional component of the study, and if an enrolled subject consents to the blood draw and is particularly challenging to draw blood from, we will not require a successful blood draw to be a condition of continued enrollment in the study.
- Videotaping: Some participants may experience psychological distress knowing that they are being videotaped. Participants will be free to stop at any time. In general, videotaping is generally well-tolerated.
- Deception: Subjects may experience minor psychological distress at study visit 2 when they learn that some information was withheld from them at enrollment. Based upon our experience with our prior study, we feel this is unlikely to happen or to be problematic as we have experience conducting such debriefings and subjects generally understand why such information was withheld initially.

7.1 Specification of Safety Parameters

Blood will be drawn by experienced nursing staff and samples will be processed then frozen for later analysis. There will be no immediate laboratory analysis of the samples collected.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

When subjects return for their follow-up visit, a study team member will inquire about any changes to their health or medical visits (including emergency room visits or hospitalizations) since their initial study visit. We do not anticipate any issues that will be causally related to the study. If a subject reports a new or worsening symptom that is medically concerning (e.g., bright red blood per rectum), they will be referred to their

usual healthcare provider for further evaluation.

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is any unfavorable or unintended diagnosis, symptom, sign, syndrome or disease which either occurs during the study (having been absent at baseline), or if present at baseline, appears to worsen.

A **serious adverse event (SAE)** is any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

During the follow-up visit, the study team member will specifically ask about any new or worsening symptoms in the last 2 weeks, unanticipated medical appointments, emergency room, or hospital visits.

In addition, during telephone check-ins, the study research coordinator will record any health concerns reported by subjects (not specifically solicited) and report these to the study PI. If there are any signs or symptoms of concern or that require further clarification, the study PI will contact the subject.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the National Center for Complementary and Integrative Health (NCCIH) Program Officer, Independent Safety Monitor(s), and Partner's IRB within 3 business days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 5 business days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH and the Partner's IRB on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed (see Data Safety and Monitoring Plan).

7.4 Reporting Procedures

Study staff and visit intervention providers will be instructed to report all adverse events (or potential AEs) to the study PI (Dr. Dossett). Determination of relatedness will be made in conjunction with Dr. Denninger and/or Dr. Hur. An electronic log of various types of AEs will be kept and updated by study staff, including the PI.

7.5 Follow-up for Adverse Events

AEs will be followed-up by the study PI by phone calls to the subject and/or monitoring of the medical record until they are resolved or considered stable. Formal AE follow-up will end with subjects' follow-up visit unless they have an ongoing issue or call to report

an event after completing the study.

7.6 Safety Monitoring

Please see the separate data safety and monitoring plan for this study, found in Appendix H.

8. INTERVENTION DISCONTINUATION

We will discontinue the intervention for any subject who declines or is unable to complete the study questionnaires, physiologic monitoring, and/or video recording. Any subjects who are disruptive or felt to pose a threat to study staff will also be discontinued. Given the nature of the study intervention and outcomes, we will not continue to follow subjects who discontinue the study, unless it is for a health-related reason to monitor an adverse event.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Design: This is a pilot, proof-of-concept, single-blinded randomized controlled trial in which subjects will be randomized in a 2:1 fashion to receive either an expanded or standard visit intervention. We are including both types of visit interventions and randomizing subjects in this way to maximize our potential to measure a wide range in physiologic concordance within the patient-provider dyads so we can best assess our hypotheses.

Primary hypotheses:

1. Subjects in patient-provider dyads with higher levels of concordance in GSR or HRV (i.e., where patient and provider GSR or HRV change in concert) will demonstrate greater improvement in GERD symptom severity than subjects in patient-provider dyads with lower levels of concordance in these measures.
2. Subjects who experience physiologic changes similar to those elicited by mind-body techniques (i.e., decreased GSR and increased high frequency HRV) over the course of their visit will demonstrate greater improvements in GERD symptom severity than subjects who do not.

Secondary hypothesis:

1. As the expanded visit unfolds, providers will demonstrate significantly more patient-centered, nonverbally supportive behaviors and have higher global impression ratings of rapport, engagement, and reciprocity compared to early in the expanded visit and both early and late in the standard visit.

Primary outcomes:

1. Correlation between physiologic synchrony in patient-provider dyads (GSR or HRV) and subsequent improvement in GERD symptom severity.
2. Correlation between absolute changes in GSR within subjects over the course of the study visit and subsequent changes in GERD symptom severity.

3. Correlation between absolute changes in high frequency HRV within subjects over the course of the study visit and subsequent changes in GERD symptom severity.

Secondary outcomes:

1. The difference in the frequency of supportive provider behaviors between the standard and expanded visit groups.
2. The difference in the ratings of rapport, engagement, and reciprocity between the standard and expanded visit groups.

Validity and reliability of outcome measures:

1. Assessment of physiologic concordance has been described by a number of groups and we will be using similar methodology [42,78].
2. GERD symptom severity will be assessed by a daily symptom diary used by a number of other groups in medication trials and in our previous study [61,79,80]. The average daily GERD symptom severity is based on the daily sum of scores from the first three questions assessing severity of daytime heartburn, nighttime heartburn, and acid reflux averaged over a 7 day period. The change in GERD symptom severity is calculated by subtracting the average daily GERD symptom severity score during the last 7 days of the study from the average daily GERD symptom severity score at study enrollment. The other GERD symptom questionnaires we are using have also been validated [26,70,71].
3. Social psychologists have developed and validated a variety of coding schemes to analyze providers' verbal and non-verbal behaviors and to link these behaviors with patient satisfaction, understanding, trust, rapport, empathy, and a variety of related factors [9,55–60]. We will use a subset of these validated coding schemes. Thin slices have shown high reliability and validity for behaviors such as gaze, nods, and smiles [81].

9.2 Sample Size and Randomization

This is a pilot study whose aim is to identify features on which to focus in subsequent studies. For the primary outcome, we would consider an observed correlation greater than r = 0.20 adequate evidence of a positive association worthy of further investigation. With a sample size of 24 patient-provider dyads, the study will have an 80% probability of obtaining an estimated correlation between physiologic concordance and changes in GERD symptoms (our primary outcome) greater than r = 0.20 if the true correlation is at least rho = 0.36. The study will have 80% power to declare the correlation significantly greater than zero based on a two-sided alpha = 0.05 if the true correlation is at least rho = 0.54.

Treatment Assignment Procedures

A randomization scheme will be devised before the start of the study by the study biostatistician who will retain the code and will be responsible for breaking the blind at the end of the study. We do not anticipate a need to break the blind during the study because

we are not expecting serious adverse events to occur more frequently in one visit group than another. Randomization will be stratified by provider, with a goal to have 4 providers each see 6 subjects (4 expanded and 2 standard visits each). If a provider cannot commit to this many visits, the study biostatistician may need to adjust the randomization scheme.

The study biostatistician will create numbered envelopes that will indicate which intervention is to be delivered. After a subject has consented to participate in the study, while he or she is completing the baseline questionnaires, immediately prior to the actual visit intervention, the envelope corresponding to the enrolled subject will be opened to reveal which intervention is to be delivered.

If a subject drops or is unable to complete the study, the statistician may need to rebalance the randomization scheme within a stratum.

Subjects will be informed of their "treatment" assignment during a debriefing at the end of the second study visit.

9.3 Definition of Populations

For analyses including intervention group, we will analyze our data according to which visit intervention subjects received (standard or expanded). We do not anticipate any discrepancies between what subjects were assigned to receive by randomization and what they actually received. Study visit type will be guided by a written script that the providers will follow during the visit. The actual intervention received will also be verified by reviewing study video recordings.

9.4 Interim Analyses and Stopping Rules

As this is a pilot study, the study PI will review video recordings of visit interventions as the study progresses to offer feedback to the study intervention providers. To ensure that we will have an adequate response rate to analyze our outcomes of interest, we will analyze changes in GERD symptom improvement after 6 subjects have completed the expanded visit intervention (we will not break the blind for unenrolled subjects). If there are not at least 2 subjects with a 50% or greater improvement in GERD symptoms and it is deemed that the study providers are delivering the standard and expanded interventions appropriately, we may consider protocol amendments to improve subject expectancy for symptom improvement.

9.5 Outcomes

Assessment	Time Points Collected	Analysis Plan	Section
Demographics, health behaviors, height & weight	Visit 1	Descriptive statistics	9.6
Daily GERD Symptom Diary	Visit 1 & Visit 2	Primary Outcome - Pearson correlation between change in GERD symptom severity and physiologic concordance in patient-provider dyads	9.5.1
GERD-HRQL	Visit 1 & Visit 2	Descriptive statistics and secondary measures of GERD symptom severity	9.6
NIH PROMIS GERD			
GSRS			
Current Stress	Visit 1 (both before & after provider visit) &Visit 2		9.6
PSS-10	Visit 1 (before provider visit) &Visit 2	Generalized linear model to determine whether perceived stress is a modifying factor for change in GSR and HRV in the context of the visit intervention	9.6
FFI	Visit 1	Generalized linear model to determine whether personality is a modifying factor for change in GERD symptoms in the context of the visit intervention	9.6
GSR & HRV	Visit 1	Primary Outcome - Pearson correlation between change in GERD symptom severity and physiologic concordance in patient-provider dyads	9.5.1
Video Recording	Visit 1	Secondary Outcomes - generalized linear mixed models to compare the frequency of supportive provider behaviors and ratings of rapport, engagement, and reciprocity between the standard and expanded visit groups.	9.5.2
CARE	Visit 1, post-intervention	Generalized linear model to determine whether empathy and the patient-provider connection modify change in GERD symptoms in the context of the visit intervention	9.6
HEAL Patient-Provider Connection			
Qualitative Interview	Visit 2	Qualitative analysis to understand subjects' experiences of the study and with healthcare providers generally	9.6

9.5.1 Primary Outcomes

1. Pearson correlation between concordance in GSR or HRV within patient-provider dyads and improvement in GERD symptom severity in the patient. Changes in GERD symptom severity will be calculated from the GERD symptom diaries collected at the first and second study visits. HRV and GSR will be measured during the visit intervention (first study visit).

   We will calculate Pearson correlations between the slopes of time-locked patient and provider GSR data in 15 second intervals after smoothing. An index of concordance in GSR responses for each patient-provider dyad will be calculated as the natural logarithm of the sum of the positive correlations from the entire session minus the natural logarithm of the sum of the absolute value of negative correlations across the session [78]. Dyads with a more positive index demonstrate greater concordance, and the subjects in these dyads would be expected to demonstrate greater improvement in GERD symptom severity.

   I will also perform an analysis using a similar approach to analyze the HRV data – comparing variation in the beat-to-beat intervals over short segments of time and calculating Pearson correlation coefficients for time-locked patient and provider data for these intervals.

2. Correlation between change in GSR (or high frequency HRV) and subsequent changes in GERD symptoms. We will calculate absolute changes in GSR, and also for high frequency HRV, within study subjects from the beginning to the end of the study visit and determine the Pearson correlation between these changes and reported changes in GERD symptom severity. As a secondary analysis, I will test whether changes in GSR and HRV are a function of baseline perceived stress and if that relationship differs between the standard and expanded visit interventions.

   The average daily GERD symptom severity score is derived from the daily symptom diaries (sections 6.2.2 and 6.2.5) that subjects complete. The average daily GERD symptom severity is based on the daily sum of scores from the first three questions assessing severity of daytime heartburn, nighttime heartburn, and acid reflux averaged over a 7 day period. The change in GERD symptom severity is calculated by subtracting the average daily GERD symptom severity score during the last 7 days of the study from the average daily GERD symptom severity score at study enrollment. The GERD symptom severity score has been used in many GERD medication studies and was the primary outcome measure in my pilot study [61].

9.5.2 Secondary Outcomes

1. The difference in the frequency of supportive provider behaviors between the standard and expanded visit groups.
2. The difference in the ratings of rapport, engagement, and reciprocity between the standard and expanded visit groups.

The number of nonverbally supportive behaviors and impression ratings of the patient-provider interaction will come from coding of video recordings of the patient provider interactions (study visit 1).

We hypothesize that the frequency/intensity of supportive provider behaviors increases as the expanded visit unfolds, compared to the standard visit, as rapport, engagement, and reciprocity between patient and provider increase. Briefly, thin slices (1.5 minutes) of video occurring near the beginning and end of the standard visit (and also a time point in the middle of the expanded visit roughly equivalent to the end of the standard visit) will be analyzed by trained coders, blinded to the study hypotheses, for the presence of 1) micro-level nonverbally supportive behaviors (e.g., friendly voice quality, leaning forward, open body posture, eye contact, nod, smile, and gestures) as well as 2) macro-level impression ratings of the interaction (e.g., rapport, engagement, reciprocity).

The PI will meet weekly with the coders to review findings and resolve areas of disagreement until greater than 80% concordance is achieved between coders. Frequency of supportive behaviors and ratings of interactions will be compared using generalized linear mixed models as appropriate for each outcome (e.g., occurrence of binary events, counts of discrete events, ordinal ratings of rapport or engagement). The models will include terms for time-point, visit group assignment, and their interaction.

9.6 Data Analyses

We will perform descriptive statistics on the sample demographics similar to our prior paper [61] including age, gender, race, ethnicity, body mass index (BMI), smoking status, and current medication use for GERD symptoms. We will also assess whether perceived stress, perceived empathy (both patient and provider), or personality type (five factor inventory) modify improvement in GERD symptoms using generalized linear models. We will use the GERD-HRQL, NIH PROMIS GERD, and GSRS as adjunct/corroborating measures of GERD symptom severity. We will also assess whether subject gender or race modifies our results. For all of these analyses, there is a risk that we will be underpowered for detecting significant effects. Qualitative interviews will be audio recorded, transcribed, and coded using standard qualitative methodologies and a grounded theory-based approach [82]. Blood samples will be processed and stored at -80ºC for later omics-based analyses that will be the subject of a future grant/study.

As Dr. Dossett has moved and now has a faculty appointment at the University of California, Davis (UC Davis), some data analysis will occur there under her supervision at that location. Dr. Dossett and her team at UC Davis will continue to collaborate with her mentor, Dr. Denninger who serves as the site PI at MGH, on this project.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Blood samples will collected at the MGH CRC. Questionnaire data will be collected on iPads at the MGH CRC or Benson-Henry Institute using Research Electronic Data Capture (REDCap; http://project-redcap.org/) forms, with the exception of GERD

symptom dairies which subjects will complete either online (REDCap) or in paper format daily. Paper data will be doubled entered into a REDCap database by study personal and checked for consistency. REDCap is a secure, web-based application developed by Vanderbilt University for electronic collection and management of clinical research study data. In collaboration with Harvard Catalyst, Partners Research Computing locally hosts REDCap.

Study staff will maintain an electronic screening file and enrollment log file and paper files of consent forms.

Study participant confidentiality will be maintained by a unique identifier. An electronic file linking participants' personally identifying information and study ID will be password protected. All paper data will be stored in a locked filing cabinet. Only study affiliated personal will have access to the study database and associated files. Electronic communication with collaborators will only involve deidentified information. All published data will be presented in aggregate format and deidentified.

10.2 Data Management

All paper symptom diaries will be reviewed in real time with subjects to ensure that data can be transferred completely and accurately to electronic form. Such data will be double entered and cross checked as described above. All data (questionnaire, physiologic, video) will be cleaned by study staff and reviewed every 1-2 months by the study PI to ensure accuracy, completeness, and timeliness of subsequent analyses. All biological samples will be labeled with PIDs, logged, tracked, and stored in a securely locked specimen freezer at the BHI.

10.3 Quality Assurance

10.3.1 Training

The study PI will personally train and supervise all research coordinators and interns working on the study in collaboration with relevant consultants to ensure that study measures are collected appropriately. All research coordinators/interns will have completed the appropriate human subjects and Partners' research training programs and may complete additional training depending upon the capacity in which they will serve in the study.

10.3.2 Protocol Deviations

Protocol deviations will be documented and reported using Partners' Insight/Institutional Review Board (IRB) service as an Other Event. Unapproved major protocol deviations will be reported to the IRB and NCCIH within 5 business days of discovery. Unapproved minor protocol deviations will be reported to the IRB at the time of the annual continuing review and to NCCIH annually as well. Should a protocol deviation become repetitive and/or problematic, the investigational team may consider submitting a protocol amendment to adjust study procedures.

10.3.3 Monitoring

The study PI will regularly review study questionnaires, HRV and GSR data, video recordings, and logs for completeness and quality. Such review will follow each subject initially but will occur at least every 1-2 months for the duration of the study.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the Partner's IRB.

11.2 Informed Consent Forms

Written informed consent will be obtained by a study team physician at the initial study visit after reviewing inclusion and exclusion criteria, the participant's symptom diary, and the electronic medical record if the participant is a patient at a Partner's affiliated hospital. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Participants will have the opportunity to ask questions. A copy will be given to each participant and this fact will be documented in the participant's record. Participants who cannot consent for themselves or who are not fluent in English will not be eligible to participate due to the nature of the study.

11.3 Participant Confidentiality

Study visits will be conducted in a private setting. Whenever possible, questionnaire data will be collected electronically using REDCap. REDCap is a secure, web-based application developed by Vanderbilt University for electronic collection and management of clinical research study data. In collaboration with Harvard Catalyst, Partners Research Computing locally hosts REDCap. All electronic data not gathered using REDCap (symptoms diaries, physiologic data, video recordings) will be stored on a Partners Research Computing shared drive which is backed up nightly to protect against data loss and is behind the Partner's firewall. Any data that cannot be collected directly onto a shared drive (i.e., must be saved on a local hard disk during data collection) will be collected on an encrypted laptop, transferred to a Partner's-affiliated server shortly after collection, and then removed from the laptop. Any paper questionnaire data will be stored in a locked filing cabinet at BHI.

Only those researchers involved in the study will have access to electronic and paper data. The file linking participants' personally identifiable information with their participant identification number (PID) will be password protected and access will be restricted to the fewest number of staff required but will include at least the PI and a research coordinator. Electronic access to videos will also be password protected. All paper records will be kept in a locked file cabinet. All computer entry and analysis will be done using PIDs only. Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a PID to maintain confidentiality. Digital video files may be stored for up to 12 years but may be destroyed sooner.

For analysis of video-recorded data, we will be collaborating with Dr. Judy Hall at Northeastern University. Video file names will be coded with participant ID numbers. We may share video data with Dr. Hall and her team using an application supported by Partners Research Computing that is similar to Dropbox but HIPAA compliant. The only personally identifiable information that will be available will be subjects' images in the

videos. All individuals who will be accessing this data will be added to the protocol and educated in the importance of subject privacy and confidentiality.

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the Office of Human Research Protections (OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12. POTENTIAL BENEFITS

12.1 Potential Benefits to Participating Individuals

Study subjects ("patients") may experience improvement in their GERD symptoms by participating in this study. The placebo response in GERD-related trials may be as high as 40% [35] and our prior data suggests that a therapeutic encounter such as the expanded visit can result in at least temporary symptom improvement for some individuals [61]. It is also possible that subjects may not experience any direct benefit from participating in this study. Participants will be remunerated for their time ($50 per visit) and receive a parking voucher.

Participating study providers will also be remunerated for their time ($80 per visit) and may benefit by learning skills for relating to patients more effectively.

12.2 Potential Benefits to Society

This study will provide insights on the physiologic and behavioral mechanisms that result in improved health outcomes from enhanced patient-provider relationships that may be applicable to a range of different medical conditions.

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14. LIST OF SUPPLEMENTS/APPENDICES

Appendix A: Recruitment Materials
- A.1 Study invitation letter to prospective participants
- A.2 Study flyer
- A.3 Study invitation letter to prospective participants who have agreed to direct contact
- A.4 Partners Clinical Trials website posting
- A.5 Provider Study Flyer

Appendix B: Screening Documents
- B.1 Telephone script for pre-screening
- B.2 Screening form

Appendix C: GERD Daily Symptom Diary

Appendix D: Study Questionnaires

Appendix E: Standard and Expanded Visit scripts
- E.1 Standard Visit Script
- E.2 Expanded Visit Script

Appendix F: Semi-Structured Qualitative Interview
- F2: Semi-Structured Interview of Study Providers

Appendix G: Debriefing Script

Appendix H: Data Safety and Monitoring Plan

Appendix I: GERD Information Handout

Appendix J: Provider recruitment emails

Appendix K: Opt-out post card