Study Protocol and Statistical Analysis Plan Cover sheet:

Title: Epidermal Permeability Barrier Function and Stratum Corneum Hydration of Rosacea Following Application of Ivermectin

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Principle Investigator: Steven R. Feldman, MD, PhD

Sponsor or funding source: Galderma

Study Rationale:

Facial erythema is the hallmark of rosacea and the mandatory criterion for its diagnosis.(1) It is estimated that rosacea-related erythema affects more than 40 million people worldwide. The repair and maintenance of the epidermal barrier are critically important in the treatment of rosacea. Rosacea lesions can have a defective barrier, characterized by elevated transepidermal water loss (TEWL) rates and reduced levels of stratum corneum (SC) hydration.(2) The skin barrier function is a critical factor for assessing the severity of rosacea. The precise mechanisms underlying the relationship between rosacea and skin barrier function are not yet known. Some argue that impaired skin barrier function is a consequence of inflammation and continuous stimulation, while others attribute it to infection with follicle mites.(3)

Ivermectin possesses anti-inflammatory by effecting cytokines and neutrophils, and anti-parasitic properties by effecting *Demodex* mites. (4, 5) Ivermectin offers a potential treatment option in maintenance therapy. (6) Recent attention has been directed toward the maintenance and prevention of relapse of rosacea. Treatment with ivermectin may decrease follicle mites, thereby decreasing rosacea flares, improving epidermal barrier dysfunction, reduces TEWL, and improves SC hydration.(7) However, topical application of medications can be complicated, time-consuming, and often frustrating. Poor adherence to therapy can lead to treatment failure and poor health outcomes.(8, 9)

Frequent office visits improve adherence, but are rarely feasible in everyday practice.(10, 11) Reminders are helpful for patients who are strongly motivated to take the medication but sometimes forget. For the majority of patients, who have not completely bought into the regimen, a subtler approach appears better. This approach aims at building intrinsic motivation, trust, feelings of being cared for, and accountability through frequent contact. In a pilot study of teenagers with acne, sending weekly surveys querying subjects about perceived burden of treatment, perceived usefulness of the medication, current disease severity, and side effects raised mean adherence to 89%, compared to 33% in the control group.(12) The present study aims to validate a very similar tool for patients at risk for low adherence to ivermectin.

Another limitation to improving patients' adherence to topical treatments is that there has not been a practical way to give patients feedback on the state of their skin barrier. Measuring TEWL rates and SC hydration levels could be a valuable tool to give patients this feedback. We propose to test whether we can improve patients' use of topical ivermectin in subjects with rosacea by using a portable hydration measurement device that simultaneously measures both the TEWL rates and SC hydration levels in a study in which we would objectively measuring adherence to daily ivermectin.(13)

Our primary hypothesis is that weekly digital interactions and routine measurement of TEWL rates and SC hydration levels will promote patient adherence to maintenance ivermectin therapy and prevent disease relapse. The project will consist of a trial in which thirty subjects with rosacea receive ivermectin therapy and are randomized to receive either no intervention, a

weekly digital survey to assess patient's attitudes towards ivermectin therapy, or a portal hydration measurement device that measures TEWL rates and SC hydration levels. We will measure adherence objectively in all groups with electronic monitors attached to the containers of the ivermectin, which all subjects will be told to use daily for maintenance therapy. Additionally, the hydration measurement device can transmit data to an Internet server via a smartphone using Bluetooth technology, thereby allowing providers to monitor a patient's TEWL rate and SC levels.

Objectives:

- Determine the effect of the portable hydration measurement device on treatment adherence to daily ivermectin therapy
- Determine the effect of weekly digital survey on treatment adherence to daily ivermectin therapy
- Determine the effect of daily ivermectin therapy on TEWL rate, SC levels, and rosacea treatment outcomes

Methods and Measures:

Study Design:

Adult subjects will be offered an opportunity to participate in the study. Subjects will either have a diagnosis of rosacea. A total of 30 subjects will be enrolled. After consent and basic demographics, a study team member will use the GPSkin Barrier® to measure the baseline moisture level of the face of all subjects. Subjects will also fill out questionnaires pertaining to quality of life, accountability, patient-physician relationship, and severity of rosacea.

Subjects will be randomized into one of three arms: the control group (n= 10), the digital interaction group (n=10), or the GPSkin group (n=10). All patients will receive ivermectin equipped with an electronic monitor to measure adherence for daily treatment of rosacea. The digital interaction group will receive a survey by email each week asking about their use ivermectin generated by Causa Research. The patients in the GPSkin group will receive the GPSkin Barrier® to measure their moisture level of their face daily. Subjects will be instructed to use the ivermectin once daily. Subjects will return at 3 Months. At this visit, the data from the electronic adherence monitoring will be downloaded, the ivermectin will be weighed, and the patient will fill out the same questionnaires (quality of life, accountability, patient-physician relationship, and severity of rosacea). The intervention subjects will be evaluated on their use of the GPSkin Barrier® to measure their stratum corneum hydration. Participants not randomized to the email intervention group will receive an accountability questionnaire at the beginning and end of the study.

Setting

The study will be conducted at Department of Dermatology at Wake Forest School of Medicine. Data will also be analyzed at Department of Dermatology at Wake Forest School of Medicine.

Subject Selection

Inclusion Criteria

- Subject is 18 years of age or older.
- Subject has a working knowledge of English.
- Subject with a diagnosis of Rosacea
- Subjects without a known allergy to ivermectin
- Subjects with access to a smart phone

Exclusion Criteria

- Subjects under 18 years of age.
- Subject does not have a working knowledge of English.
- Subject with a diagnosed skin condition other than rosacea
- Subjects with a known allergy to ivermectin
- Subjects without access to a smart phone

Intervention and Interactions

Patients will be recruited from the Dermatology Clinic or from the Dermatology Clinic Database. Team members can recruit in-person with patients in the Dermatology Clinic, or by calling patients with a diagnosis of Rosacea (ICD 10: L71.9). Patients will then be brought to the Center for Dermatology Research for their initial screening visit. Demographic data collected from the patient includes sex, age, and ethnicity.

Outcome Measure

Outcomes include adherence (as measured by electronic monitoring), weight of the ivermectin, rosacea severity, quality of life, reporting of adverse effects, accountability questionnaire, and use of the GPSkin Barrier® in the GPSkin group. Data from the clinical study will be analyzed by a biostatistics software. Correlation between demographics will be measured.

Analytical Plan

Data will be analyzed using descriptive statistics on a biostatistics software.

Human Subjects Protection

Subject Recruitment Methods

Subjects who meet the inclusion and exclusion eligibility criteria will be able to participate in the study. Subjects are recruited at a clinic in the Department of Dermatology at Wake Forest School of Medicine or through the Department of Dermatology Database.

Informed Consent

Informed consent will be acquired for this study. The risk of harm or discomfort is not expected to be more than a daily life or routine physical or psychological exam or test. Rights and welfare of subjects will be protected through the use of measures to maintain the confidentiality of study information. No identifying information will be taken from the patient. The only information taken from the patient includes age, gender, ethnicity, location of the skin lesion, and email addresses. The information collected for this research study includes quality of

life, accountability, and severity of rosacea information. Results of the study will be published or presented in lieu of providing individual subjects additional information regarding the study.

Confidentiality and Privacy

Confidentiality will be protected by collecting information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, no subject identifiers will be used. The results of the survey will be presented as an anonymous data set. Data access will be limited to study staff. Data will be kept locked and secured, with computer data password protection. No references to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for monitoring data and safety of subjects. The principal investigator will be assisted by other members of study staff.

Report of Unanticipated Problems, Adverse Events, or Deviations

All unanticipated problems, serious or unexpected adverse events, deviations or protocol amendments will be reported by the principle investigator or designated member of the research team to IRB or appropriate government agency if appropriate.

Appendix

I. **Demographic Questions**
II. **Dermatology Quality of Life Index**
III. **Weekly Accountability Questionnaire for Digital Interaction Group**
IV. **Rosacea Severity Indices**
V. **Accountability Measurement Tool (AMT)**
VI. **Patient-Doctor Relationship Questionnaire (PDRQ-9)**

Appendix I: Demographic Questions for Patients

1. What is your gender?
   - Male
   - Female
   - Other

2. What is your ethnicity?
   - Caucasian
   - African American
   - Asian
   - Native American
   - Other

3. What is your age?
   - Open ended question.

4. Do you regularly use a moisturizer on your skin?
   - Yes
   - No
   - Intermittently

5. If you use a moisturizer, what is the name of the moisturizer?
   - Open ended question.

Appendix II: Dermatology Quality of Life Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score:

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

Appendix III: Accountability Questionnaire – email survey that subjects in digital intervention group will receive weekly

Hi {PARTICIPANT NAME}! Time for a {diagnosis} check in!

1. **Do you feel the medication is helping your rosacea?**
    a. **Yes, my {diagnosis} is much better**
    b. **Yes, my {diagnosis} is somewhat better**
    c. **I haven't noticed a change in my {diagnosis}**
    d. **No, my {diagnosis} is moderately worse**
    e. **No, my {diagnosis} is much worse**
2. **How many days were you able to use the {medication} this week?**
    a. **Every day**
    b. **I missed 1 or 2 days**
    c. **I missed the majority of this week**
3. **Did you have any difficulty using the {medication}?**
    a. **No- it was very easy to use**
    b. **It was OK**
    c. **I found it inconvenient to use**
    d. **It was difficult to use**
    e. **It was very difficult to use**
4. **Have you had any side effects from using the {medication}?**
    a. **Yes**
        i. **If yes, what side effects did you experience?**
        ii. **Open data entry field for responses**

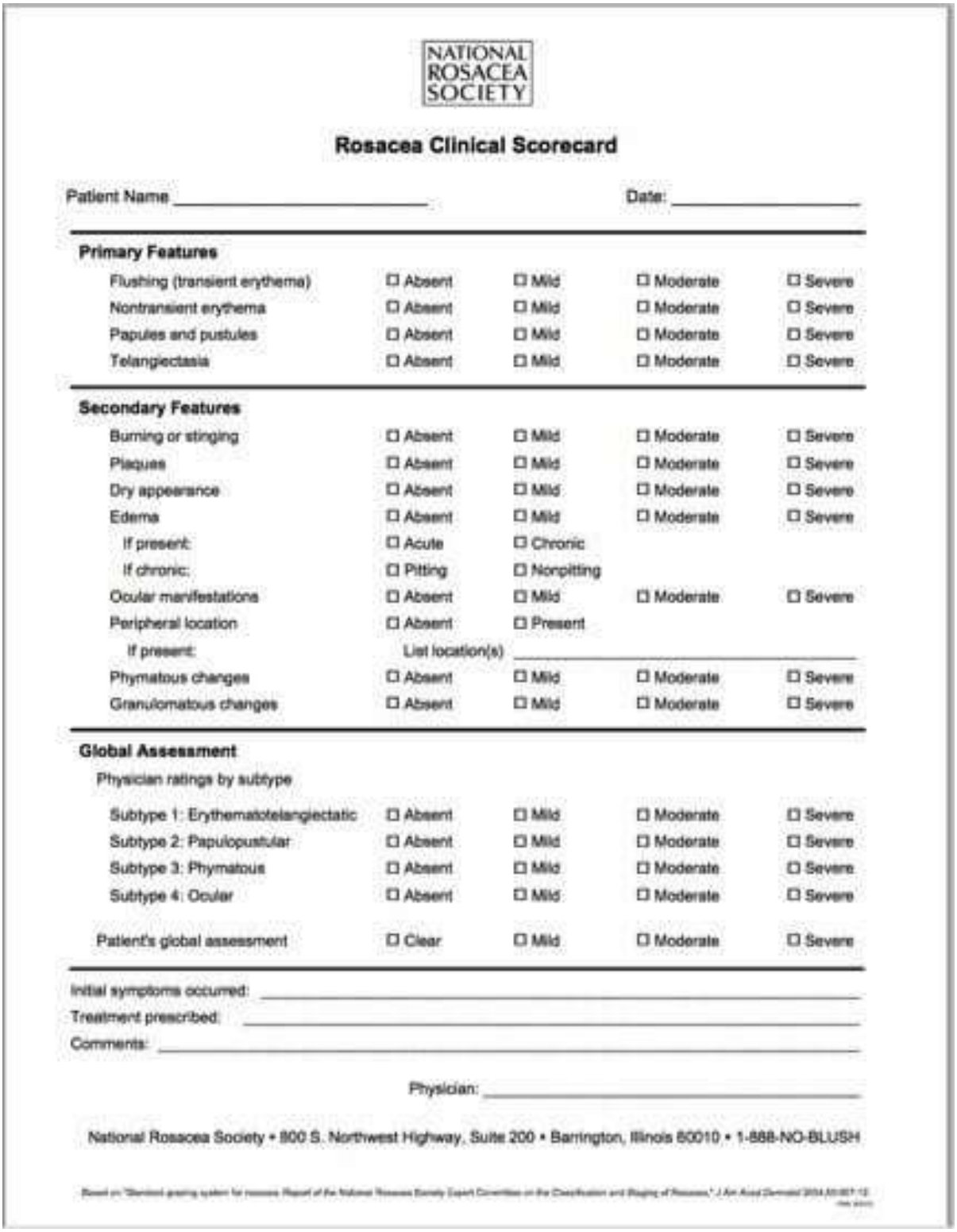
        _____
    b. **No**
5. **Do you use a reminder system of any kind to help you remember to use your {medication}? For example, some of our patients use reminders or applications on a smart phone. Others have told us they keep their medicine somewhere in their home that they can't miss.**
    a. **Yes**
        i. **Please list the methods you use to help you keep track of your medications:**

        _____
    b. **No**
6. **Thinking ahead to next week, how many days do you think you will be able to use your {medication}? We will check in again next week through your weekly survey to see how you're doing.**
    a. **Every day**
    b. **5-6 days per week**
    c. **Other, please list: _____**

Thanks! We'll reach out to you again next week!

Open text field

Appendix IV: Rosacea Indices



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Rosacea Clinical Scorecard

Patient Name _____ Date: _____

Primary Features				
Flushing (transient erythema)	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Nontransient erythema	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Papules and pustules	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Telangiectasia	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Secondary Features				
Burning or stinging	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Plaques	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Dry appearance	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Edema	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
If present:	☐ Acute	☐ Chronic		
If chronic:	☐ Pitting	☐ Nonpitting		
Ocular manifestations	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Peripheral location	☐ Absent	☐ Present		
If present:	List location(s)	_____		
Phymatous changes	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Granulomatous changes	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Global Assessment				
Physician ratings by subtype				
Subtype 1: Erythematotelangiectatic	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Subtype 2: Papulopustular	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Subtype 3: Phymatous	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Subtype 4: Ocular	☐ Absent	☐ Mild	☐ Moderate	☐ Severe
Patient's global assessment	☐ Clear	☐ Mild	☐ Moderate	☐ Severe

Initial symptoms occurred: _____

Treatment prescribed: _____

Comments: _____

Physician: _____

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Based on "Standard grading system for rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea," J Am Acad Dermatol 2004;50:907-12.

Investigator Global Assessment

Scores		
0	Clear	No inflammatory lesions present, no erythema
1	Almost Clear	Very few small papules/pustules present, very mild erythema
2	Mild	Few small papules/pustules, mild erythema
3	Moderate	Several small or large papules/pustules, moderate erythema
4	Severe	Numerous small and/or large papules/pustules, severe erythema

Patient Self-Assessment

Scores		
0	Clear	No Redness
1	Almost Clear	Very Mild Redness
2	Mild	Mild Redness
3	Moderate	Moderate Redness
4	Severe	Severe Redness

Appendix V: Accountability Measurement Tool (AMT)

Accountability Measurement Tool

Please circle one option for each question.

1 = Strongly disagree
2 = Disagree
3 = Neutral
4 = Agree
5 = Strongly agree

1) I feel guilty if I do not follow my doctor's recommendations.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

2) I am afraid of disappointing my doctor by not following his/her recommendations.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

3) I am concerned that my doctor may be disappointed if I do not follow his/her recommendations.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

4) I feel proud showing my doctor how well my condition has improved.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

5) I am pleased letting my doctor know how well I have taken my medication.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

6) I look forward to letting my doctor know how well I have taken my medication.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

7) All in all, I feel accountable towards my doctor.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

8) An upcoming office visit with my doctor motivates me to follow my doctor's recommendations.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

9) I would feel guilty if [I thought] the doctor believed I wasn't following his/her directions.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

10) I don't want to let my doctor down by not taking my medicine well.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

11) I am concerned of how I would be perceived if my doctor thought I didn't do a good job taking my medication.
    a. 1 = Strongly disagree
    b. 2 = Disagree
    c. 3 = Neutral
    d. 4 = Agree
    e. 5 = Strongly agree

12)I try to take my medication regularly because I have a doctor’s visit coming up.

a. 1 = Strongly disagree
b. 2 = Disagree
c. 3 = Neutral
d. 4 = Agree
e. 5 = Strongly agree

Appendix VI: Patient-Doctor Relationship Questionnaire (PDRQ-9)

PDRQ-9

Instruction:

You will read nine statements that a person can make about his/her physician. Please choose the appropriateness of each statement for your physician by marking one number per statement. The meaning of the numbers is as follows:

1 = not at all appropriate

2 = somewhat appropriate

3 = appropriate

4 = mostly appropriate

5 = totally appropriate

1 My physician helps me	1 2 3 4 5
2 My physician has enough time for me	1 2 3 4 5
3 I trust my physician	1 2 3 4 5
4 My physician understands me	1 2 3 4 5
5 My physician is dedicated to help me	1 2 3 4 5
6 My physician and I agree on the nature of my medical symptoms	1 2 3 4 5
7 I can talk to my physician	1 2 3 4 5
8 I feel content with my physician's treatment	1 2 3 4 5
9 I find my physician easily accessible	1 2 3 4 5

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