A Prospective, Multicenter, Single Arm Clinical Study Evaluating the Use of the Renuvion APR Device for Improving the Appearance to Lax Tissue in the Neck and Submental Region

Statistical Analysis Plan

Study Protocol No: **VP-1902**

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Confidentiality Statement:

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LIST OF ABBREVIATIONS

AE	Adverse Event
CIP	Clinical Investigational Plan
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DCF	Data Clarification Form
DRM	Data Review Meeting
DR-(S)AE	Device-Related (Serious) Adverse Event
FAS	Full Analysis Set
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICH	International Conference for Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intent-to-Treat
MDD	Medical Device Directive
mITT	Modified Intent-to-Treat
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PP	Per Protocol
PPS	Per Protocol Set
PR-(S)AE	Procedure-Related (Serious) Adverse Event
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect

1 PURPOSE

The purpose of this Statistical Analysis Plan (SAP) is to document the statistical design considerations for the study of a new medical device, the Renuvion APR device to improve the appearance of lax tissue in the neck and submental regions. This SAP documents the sample size estimation, study objectives, endpoints, data collection tools, and analysis plan. The requirements of the United States FDA and European MDD have been considered in the development of this document.

Once the study is completed a 510(k) will be submitted to the agency to request expanding the indications of the Renuvion APR (cleared under K191542).

Note: For marketing reasons that do not affect the safety and effectiveness of the device, we have updated the name from Apyx Plasma/RF to Renuvion APR handpiece. (APR stands for Apyx Plasma/RF).

2 REFERENCE DOCUMENTS

This SAP corresponds to the Apyx Clinical Investigation Protocol (CIP), "A Prospective, Multi-Center, Evaluator-Blinded Study Evaluating the Safety and Effectiveness of the Renuvion APR Device to Improve the Appearance of Lax Tissue in the Neck and Submental Region", Protocol # VP-1902. Because detailed clinical information is included in the study protocol, the clinical aspects are *not* repeated in this SAP document. The information included in this SAP relates to the study design and data analysis.

3 OVERVIEW OF STATISTICAL DESIGN

This is a multi-center, single arm, single-blind (evaluator) prospective study of subjects who are seeking a procedure to reduce the appearance of laxity of the neck and submental regions at up to 8 investigational centers in the United States, with a maximum of 20 study subjects enrolled at each site.

Phase I (n=17) of this study was conducted and provided to the FDA as an interim safety report of safety data including information related to adverse events followed through resolution for all subjects. Phase I of this study was conducted prior to Revision 9 of the study protocol.

Phase II (n=65) of this study will be conducted as the pivotal study to demonstrate the safety and effectiveness of the Renuvion APR Device to improve the appearance of lax tissue in the neck and submental region. Phase II of the study begins with Revision 9 of the study protocol.

Study subjects that meet study eligibility criteria and have provided informed consent will be enrolled in the study. During the procedure, the investigators will use the Renuvion APR handpiece on the neck and submental areas of study subjects with the goal of reducing skin laxity.

Study subjects will be followed immediately following the procedure, and at 1 day, 7 days, 14 days, 30 days, 90 days, and 180 days post-procedure for study assessments. Assessments of

endpoints will use standardized evaluation tools and blinded evaluators as applicable. This includes the use of an independent 3-member evaluation team to eliminate the bias that is likely inherent in the investigators' assessments.

Phase II study enrollment is expected to occur over 6-8 months. Imaging and study assessments will continue through 6 months post-procedure. Total Phase II study duration is expected to be approximately 14 months. The 510(k) application for the device will be submitted based on 180-day post-procedure results. However, this clinical trial will continue until all adverse events are resolved. At that time, the trial will be considered complete, the final results will be determined, and a final report will be prepared.

Table 1 below shows the required evaluations and the schedule on which they are to occur.

Table 1: Study Required Procedures

	Baseline/ Pre-Procedure Screening[1]	**Procedure (Day 0)**	**1 Day** 1-3 days	**7 Days** 6-8 days	**14 Days** 11-17 days	**30 Days** 23-37 days	**90 Days** 80-100 days	**180 Days** 165-195 days
Informed Consent	X							
Assess Inclusion/Exclusion Criteria	X							
Urine Pregnancy Test[2]	X	X						
Medical History	X							
General Physical Exam	X							
Review Medications	X		X	X	X	X	X	X
2D/3D Photographic Images[3]	X[6]	X[8]		X	X	X	X	X
Numeric Rating Scale (11-point NRS)[4]		X[7]	X	X	X	X	X	X
Study Procedure		X						
Adverse Event Assessment		X	X	X	X	X	X	X
TEN Testing of Sensory Nerves		X	X	X	X	X	As Needed	As Needed
Examination of Facial Motor Nerves		X	X	X	X	X	As Needed	As Needed
Burn Depth Assessment		As Needed	As Needed	As Needed	As Needed	As Needed	As Needed	As Needed
Modified Global Aesthetic Improvement Scale (GAIS)[5]							X	X
Subject Diary		X			X			
Subject Satisfaction Survey								X

[1] Pre-procedure Screening assessments to take place within 30 days prior to undergoing the procedure.
[2] Up to two urine pregnancy tests must be obtained prior to study procedure for females with child-bearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure if screening and procedure are not performed on the same day).
[3]Digital photographs will be taken and labeled according to Photography Instructions. 2D images will be extracted from 3D imaging. Both 2D and 3D images will be used for quantitative assessments. Standard positioning and lighting will be used for all photographs.
[4] To be completed by the study subject on a day of the procedure (prior to the procedure and immediately following the procedure) and at all follow-up visits.
[5] To be completed by Investigator and study subject at day 90 and day 180 follow-up visits.
[6] Grimace image taken in addition to standard images at Baseline only.
[7] NRS pain score will be captured prior to study treatment and immediately (within 60 minutes) after procedure.
[8] Pre-procedure images may be taken if Baseline/Screening images are not considered acceptable by the quality review team, however if the Baseline/Screening image is acceptable by the quality review team, no additional pre-procedure image needs to be taken.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Effectiveness Objective and Endpoint

The primary effectiveness endpoint is improvement in the appearance of lax tissue in the neck and submental region at 180-days as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers.

The primary effectiveness objective is to demonstrate that the proportion of successful subjects exceeds the performance goal (PG).

$$\text{Ho: } P \leq PG \quad \text{vs} \quad \text{Ha: } P > PG$$

Where P is the proportion of successful subjects and PG is the performance goal.

Three experienced, blinded photographic reviewers will perform a qualitative analysis/review of the pre-treatment and post-treatment sets of images of each subject in a blinded and randomized order. Each blinded reviewer will choose which image is the post-treatment image. Success of a subject will be the correct post-treatment image selection by at least 2 of the 3 reviewers. The percentage of subjects with successful post-treatment image selection will be calculated.

4.2 Primary Safety Objective and Endpoint

The primary safety endpoint is the level of pain and discomfort after treatment as reported by the subject on a Numeric Rating Scale (NRS) through the 1-week follow-up visit.

The primary safety objective is to demonstrate that the proportion of subjects with none-to-moderate pain exceeds the performance goal (PG).

$$\text{Ho: } P \leq PG \quad \text{vs} \quad \text{Ha: } P > PG$$

Where P is the proportion of subjects with acceptable pain and PG is the performance goal.

4.3 Additional Endpoints

Other endpoints to be evaluated include:

1. The improvement in the appearance of lax tissue in the neck and submental region at 90 days compared to baseline as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers.
2. Subject Modified Global Aesthetic Improvement Scale (GAIS) at 90-day and 180-day FUV.
3. Investigator Modified GAIS at 90-day and180-day FUV.
4. Subject satisfaction with procedure recorded at the 180-day FUV.
5. Quantitative improvement in overall lift of the submental area at 180 days as determined by quantitative assessment based on 2D photography.
    a) The analysis will describe the population of subjects who respond to treatment by achieving at least 20 mm^2 of lift of the submental region. Responders will be

determined based on change from baseline of area as measured by 2D photography in standard lighting conditions.

b) For the quantitative assessment, fixed landmarks on the subject's face will be used to systematically place a horizontal line, including the point where the chin meets the neck and 35 mm beyond. At this point, a vertical line will be placed and the area of submental skin between the two lines will be calculated. An area reduction of more than 20 mm^2 will be considered to be an improvement.

6. Quantitative improvement in submental volume at 180-days as determined by quantitative assessment based on 3D photography.
7. The evaluation of adverse events up to the 180-day visit following treatment.
8. The evaluation of pain scores through the 30-day follow-up visit as reported by the subject on a Numeric Rating Scale (NRS).

5 EVALUATION TOOLS

The following evaluation tools will be used in this study:

- 2-Dimensional and 3-Dimensional Photography
- Independent Photographic Assessments
- Quantitative Assessment of Lift
- Quantitative Assessment of Volume
- Modified Global Aesthetic Improvement Scale (GAIS)
- Subject Satisfaction Survey
- Numeric Rating Scale (NRS) for pain
- Subject Diary
- Adverse Event Reporting
- TEN Testing of Sensory Nerves
- Examination of Facial Motor Nerves
- Burn Depth Assessment (Burn Adverse Events Only)

More information about the evaluation tools, including how to administer them, is included in the study protocol. The schedule on which they are administered is provided in **Table 1**.

6 ADVERSE EVENTS ASSESSMENT REPORTING

The definitions of adverse events (AEs) and the subtypes are provided in the study protocol. Adverse events will be classified by the investigator as to:

- Anticipated vs unanticipated
- Serious vs not serious
- Expected Treatment Effect (ETE) vs Adverse Event (AE)
- Severity: mild, moderate, severe
- Device causality: not related, related, undetermined
- Procedure causality: not related, related, undetermined.

7 SAMPLE SIZE ESTIMATION

7.1 Determination of Sample Size

7.1.1 Primary Effectiveness Hypothesis Test

The primary effectiveness objective of this study is to demonstrate response to treatment with the Renuvion APR handpiece. The 3 IPRs will assess each subject's pre-treatment and post-treatment images in blinded random order and independently record which image they believe is the "post-treatment" image. The proportion of subjects achieving at least 2 out of 3 correct IPR assessments will be calculated; this is the proportion of treatment successes.

The sample sizes were estimated using PASS 2019[1] with the following parameters (See **Table 2**):

- A performance goal (PG) of 55% success.
- A one-sample, one-sided binomial exact test against the PG.
- $\alpha = 0.025$.
- Power = 90%
- Plasma/RF success proportions (P) of 75%
- The test is the binomial Exact Test.

*Table 2: Numeric Results for Testing One Proportion using the Exact Test**

Alternative Hypothesis: One-Sided (H0: P ≤ P0 vs. H1: P > P0)						
Power	**N**	**Performance Goal (PG)**	**Renuvion APR Proportion**	**Δ = Renuvion APR - PG**	**Alpha**	**Reject Ho if Successes ≥**
0.90752	60	0.55	0.75	0.2	0.025	41

*using the Normal approximation, which should be acceptable given the moderate probabilities.

In Phase II, a total of 65 subjects will be treated to accommodate dropouts and losses to follow-up.

7.1.2 Primary Safety Hypothesis Test

The sample size was also calculated for the primary safety hypothesis. Coincidentally, the parameters were identical to those for the primary effectiveness hypothesis, so the sample size was an identical test.

7.2 Performance Goal Rationale

7.2.1 Primary Effectiveness Hypothesis

A Performance Goal (PG) of 55% will be used for testing. A PG of 55% is clinically relevant to ensure that there are significant benefits of the procedure to outweigh its risk. The lower bound of the confidence interval of the proportion of subject achieving treatment successes will be compared against this Performance Goal. This primary effectiveness endpoint definition and performance

[1] PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

goal is more conservative and supported by the results of the Ulthera System study that was conducted to support equivalent indications cleared under K121700. Moreover, this PG is supported by the hypothesis and results of the clinical studies conducted to support the following cleared devices and studies published in clinicaltrials.gov as summarized in **Table 3**.

Table 3: Performance Goal Support

Trial	Sample size	Successes	Success rate	Exact (Clopper-Pearson)[2] 95% lower CI
Ulthera K121700.	70	43	61%	51%
Ulthera K134032	54	37	68%	57%
SofWave NCT04146584	112	56	50%	42%
Evolve System NCT04124419	20	14	70%	49%
COMBINED (weighted)	**256**	**150**	**58%**	**48%**
COMBINED (unweighted)	**256**	**150**	**63%**	**50%**

7.2.2 Primary Safety Hypothesis

A PG of 55% was also established for the primary safety hypothesis test. There were two parts to establishing the PG:

1. Determining which values on an 11-point NRS scale correspond to mild pain and which to moderate.
2. Determining what percentage of patients with no-to-moderate pain through 7-days is minimally acceptable for a cosmetic procedure.

The first part was answered by Boonstra et al (2016)[3], who showed that on a 11-point NRS, cut-off points of 5 for mild pain and 7 for moderate pain were appropriate. The second part was answered by Broughton et al (2006)[4], who estimated that approximately 55% of subjects reported no-to-moderate pain during the first week post-procedure.

The Broughton estimate was taken from Table 3 of the journal article (see **Table 4)**, which tabulated the percentages of patients reporting pain levels following liposuction by time following the procedure and number of treatment areas. Using the data for subjects receiving treatment in 1-2 areas, we found that 53.4% of subjects reported no higher than moderate pain during the first week post-procedure:

[2] Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika. 26 (4): 404–413. doi:10.1093/biomet/26.4.404

[3] Boonstra AM, Stewart RE, Koke AJA, et al. Cut-Off Points for Mild, Moderate, and Severe Pain on the Numberic Rating Scale for Pain in Patients with Chronic Musculoskeletal Pain: Variability and Influence of Sex and Catastrophizing. Front Psychol 2016; 7: 1466.

[4] Broughton G II, Horton B, Kipschitz A, et al. Lifestyle Outcomes, Satisfaction, and Attitudes of Patients after Liposuction: A Dallas Experience. Plast. Reconstr. Surg. 2006; 117: 1738-1749.

Table 4: Exert of Table 3 Broughton article

Table 3: 1-2 Areas Liposuctioned
Discomfort Level by Final Report (per Subject)

	None	Mild	Moderate	Severe*	TOTAL
1 day	0.023	0.023			
2-3 days		0.093	0.047		
4-7 days		0.209	0.139	0.047	
TOTAL	0.023	0.325	0.186	0.047	.534
> 7 days*	0.023	0.093	0.093	0.209	0.418

* Gray cells not used in calculations.

Therefore, we set our PG at 55%. The null hypothesis test is that Renuvion APR results in fewer than 55% of subjects with maximal pain of "moderate" during the first week post-procedure (i.e., more than 45% have severe pain). The alternative is that more than 55% have moderate or less pain, and fewer than 45% have severe pain.

8 ANALYSIS POPULATIONS AND HANDLING MISSING DATA

8.1 Analysis Sets and Handling of Missing Data

8.1.1 Full Analysis Dataset
(Intent-to-Treat Sample, ITT)

The ITT sample will be used in the primary safety analysis. This is defined as the subjects who enrolled in the trial and on whom the procedure was initiated at least to the point where energy from Renuvion entered the subject's skin.

8.1.2 Primary Modified Analysis Dataset
(Primary Modified Intent-to-Treat Sample, PmITT)

The PmITT sample will be used in the primary effectiveness analysis. Participants enrolled in the study who had baseline photographs taken, completed the study procedure, and have at least one post-treatment photograph at or between 90 and 180 days will be included in the ITT sample.

8.1.3 Secondary Modified Analysis Datasets
(Secondary Modified Intent-to-Treat Samples, SmITTs)

The SmITTs datasets will be used in the secondary and additional analyses. Participants enrolled in the study who had baseline data and the endpoint data in question will be included. No imputation will be done for missing endpoints unless there is evidence that the endpoint is *missing for cause*. The reason that there are more than one SmITT data set is that the data set is dependent upon the endpoint in question; only those subjects with baseline and endpoint data *for that endpoint* will be included in the analysis.

8.1.4 Per Protocol Dataset

(Per-Protocol Sample, PP)

This will be a subset of the PmITT analysis dataset comprising participants without deviations from the protocol that affect the scientific soundness of the primary safety and effectiveness objectives (i.e., the ability to estimate the effectiveness of Renuvion in reducing submental laxity or to estimate its safety). Participants with protocol deviations that affect this ability will be identified at the data review meeting that takes place before database lock. The effectiveness and safety analysis will also be performed in this Per-Protocol population if the effectiveness and/or safety primary hypotheses are not passed.

8.1.5 Imputation of Missing Values

Those with missing post-treatment photographs at the 180-day visit will have their last post-treatment photograph (such as the 90-day follow-up image) carried forward for use in the IPR assessment for the primary effectiveness endpoint. Since generally the appearance of lax tissue in the neck and submental regions will continue to improve for up to 180 days post-procedure, post-treatment photographs taken at a time point earlier than the 180-day visit will not show more improvement than the missing 180-day photographs. Therefore, the last-value-carried-forward (LVCF) imputation is conservative.

For those subjects with missing primary endpoint data at the 180-day visit and no follow-up images available to carry-forward, the primary effectiveness objective will have the missing data multiply imputed using the patient's baseline characteristics and follow-up evaluations before and after the missing data.

The primary effectiveness hypothesis test will use this data set with a combination of LVCF and multiply imputed values carried out on the PmITT analysis set.

Those with missing endpoint data at the 7-day FUV for the primary safety objective will have the missing data multiply imputed using the patient's baseline characteristics and follow-up evaluations before and after the missing data. The primary safety hypothesis test will use this data set carried out on the ITT analysis set.

8.1.6 Sensitivity Analysis (of Missing Data)

To assess the effects of the imputed data on the results of the primary hypothesis tests, each primary objective will be subjected to a tipping-point analysis. The following description of a tipping point analysis applies to each primary endpoint; two separate tipping-point analyses will be performed.

8.1.7 Procedure for Tipping-Point Analyses

A tipping point analysis will only be performed if the primary hypothesis test rejects the null hypothesis. In this case, the tipping point analysis replaces imputed data points with a value representing failure:

- For the primary effectiveness endpoint, failure is choosing the "pre-procedure" image instead of the "post-procedure" image;
- For the primary safety endpoint, failure is experiencing severe pain within one week of the procedure.

In step 1, one missing (imputed) endpoint is chosen at random and replaced with a failure value. The hypothesis test is re-run. If the null hypothesis is rejected, a second missing endpoint is chosen at random and the analysis is re-run with the two additional failures. As long as the null hypothesis is rejected, the process is repeated on the missing (imputed) data points. Once the null hypothesis is no longer rejected, the analysis results are said to have "tipped", and the process stops.

8.1.8 Subjects not Included in the mITT and PP Samples

Participants enrolled in the study who were excluded from any of the mITT or PP samples will have their reasons for missing data or protocol violations examined and reported.

9 ANALYSIS OF STUDY ENDPOINTS AND OTHER DATA

9.1 Descriptive Statistical Analysis

Demographic data will be analyzed using descriptive statistics and reported. Descriptive statistics will also be used for the Additional Endpoints, and for adding complementary information to the hypothesis tests for the primary endpoints.

- Continuous variables (e.g. age) will be reported as the mean, number of observations, standard deviation, minimum, maximum, and 95% confidence interval (CI) of the mean.
- Categorical variables (e.g. sex) will be reported as the percentage and number of observations in each category and the 95% CI of the percentage.
- Time-to-event variables (e.g. time since study procedure) will be reported by the number at risk, the event rates over time and their 95% confidence intervals (CIs). Kaplan-Meier time-to-event analysis will be used to make the estimates.
- Count variables (e.g. number of hospitalizations in the last year) will be reported by the frequency and percentage in each count category, and the 95% CI of each. Poisson regression or negative binomial regression will be used to make the estimates; the method will depend on data dispersion.

9.2 Statistical Analysis of Primary Effectiveness Endpoint

Proportion of Successes

For the primary effectiveness endpoint, the proportion of successful patients (P) will be tested against the PG. If the lower bound of the two-sided 95% confidence interval of the proportion of subject achieving treatment successes is greater than the Performance Goal, the effectiveness endpoint would be met. The statistical test will be a one-sided Fisher's Exact Test at $\alpha = 0.025$. For the effectiveness endpoint to be met, Ho must be rejected.

$$\text{Ho: } P \leq 55\% \quad \text{vs.} \quad \text{Ha: } P > 55\%$$

Standard descriptive statistics will also be reported; see **Section 9.1** for a list of descriptive statistics.

9.3 Statistical Analysis of Primary Safety Endpoint

NRS Pain through the 7-day Follow-up Visit

The 11-point NRS is used to measure facial, submental, and neck pain prior to procedure, within 60 minutes of treatment and at all follow-up visits. Note that the pain scale is 11 points: 0 through 10. The 0 value represents no pain. Levels 1 through 5 represent mild pain and levels 6 and 7 represent moderate pain. Patients who experience pain no higher than 7 through the 7-day visit post-procedure will be classified as "acceptable pain" patients.

For the primary safety endpoint, the proportion of patients with acceptable pain (P) will be tested against the PG. If the lower bound of the two-sided 95% confidence interval of the proportion of subject achieving treatment successes is greater than the Performance Goal, the primary safety endpoint would be met. The statistical test will be a one-sided Fisher's Exact Test at $\alpha = 0.05$. For the primary safety endpoint to be met, Ho must be rejected.

$$\text{Ho: } P \leq 55\% \quad \text{vs.} \quad \text{Ha: } P > 55\%$$

Standard descriptive statistics will also be reported; see **Section 9.1** for a list of descriptive statistics.

9.4 Statistical Analysis of Additional Endpoints

These analyses will be performed by data type as described in **Section 9.1** of this SAP. All analyses will be descriptive (i.e., no hypotheses will be tested). All of the various AE rates will be estimated using methods for time-to-event data for each category of AE, with emphasis on all device- and procedure-related AEs, and serious device- and procedure-related AEs. Analyses are planned as per **Table 5**.

The assessment tools (e.g. the GAIS and Subject Satisfaction Survey) can be found in the study protocol.

Table 5: Analyses of Additional Endpoints

Endpoint Number	Endpoint	Type of Analysis	Comments
1	The improvement in the appearance of lax tissue in the neck and submental region at 90 days compared to baseline as determined by qualitative 2D photography assessment by blinded Independent Photographic Reviewers.	Categorical	This endpoint is identical to the primary effectiveness endpoint except that it is at 90 days; however, no hypothesis will be tested.
2	Subject Modified Global Aesthetic Improvement Scale (GAIS) at 180-day FUV	Categorical	
3	Investigator Modified GAIS at 180-day FUV	Categorical	
4	Subject satisfaction with procedure recorded at the 180-day FUV on the Subject Satisfaction Survey	Categorical and Continuous	Categorical on 1-4 and Continuous on 5

Endpoint Number	Endpoint	Type of Analysis	Comments
5	Quantitative improvement at 180-days as determined by quantitative assessment based on 2D photography: a) Proportion responders (those achieving at least 20 mm^2 of lift of the submental region). b) Average mm^2 of improvement.	Categorical and Continuous	Categorical on a and Continuous on b
6	Quantitative improvement at 180-days as determined by quantitative assessment based on 3D photography - Average cc of Total Volume change.	Categorical and Continuous	Categorical on a and Continuous on b
7	The evaluation of adverse events up to the 180-day visit following treatment.	Time-to-event	
8	The evaluation of pain scores through the 30-day follow-up visit as reported by the subject on a Numeric Rating Scale (NRS).	Categorical	

9.5 Subgroup Analyses

Subgroup analyses will be performed to understand the effect of demographic and other patient-level variables on the probability of the primary endpoint improvement. A logistic regression will be used to model the effect of age, gender, race/ethnicity, and other baseline variables. (Age *et al* are the "independent variables" and the change (improvement or not) is the dependent or response variable.

If any of the independent variables are significant, the effect size and better responders will be reported. Also, the possibility of clinically relevant interaction terms will be tested.