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A Prospective Randomized Efficacy Study Comparing a Pelvic Digital Health System Home Program of Pelvic Floor Muscle Exercise to Kegel Exercises in the Treatment of Stress-Predominant Urinary Incontinence

Statistical Analysis Plan

August 27, 2019

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Secondary analysis of a Prospective, Nested, Randomized Efficacy Study Comparing a Pelvic Digital Health System Home Program of Pelvic Floor Muscle Exercise to Kegel Exercises in the Treatment of Stress-Predominant Urinary Incontinence (Renovia-05) –

Pilot/Feasibility Trail

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1. Objectives

- Assess the feasibility of a randomized trial to test the efficacy of using a novel intravaginal system (leva® Plus Pelvic Digital Health System) to perform pelvic floor muscle exercises (PFME) compared to a Kegel exercise home program in women with stress-predominant urinary incontinence (SUI)
- Assess any technical issues with the digital aspect of the leva® Plus Pelvic Digital Health System
- Evaluate compliance with exercises in the leva® Plus Pelvic Digital Health System arm of the study

2. Design

The initial randomized study was ended early due to technical difficulties. This will be analyzed as a pilot/feasibility trial. Details about the randomized controlled trial study design and study visits can be found in the protocol, Renovia-05 (Sponsor: Renovia Inc.)

The study enrolled 60 women, randomized into the two initial arms (30 women per arm) and followed participants for 8 weeks.

3. Statistical analysis

3.1 Participant description

Baseline characteristics will include demographics (i.e. participant age, race, other measures of SES) and medical history (i.e. gravidity, parity, history of abdominal surgery) as reported on the baseline questionnaires. In addition, the results of the initial exam assessing urinary incontinence (including voiding diary, Pelvic Organ Prolapse assessment (POP-Q), PFDx device assessment) and the results of the questionnaires administered (PFDI, PISQ-IR, McGill Pain Questionnaire, SESPPFE, PGI-S, PGI-I, WHODAS, PFIQ) will be reported for both groups. Available scoring for all validated measures will be used.

3.2 Feasibility

Two aspect of feasibility will be assessed.

3.2.1 Feasibility of randomization

Participant flow will be described in a flow diagram. If available, the flow diagram will describe the number of potential participants approached and the number of participants consented and randomized.

3.2.2. Feasibility of digital health platform

In the leva® Plus Pelvic Digital Health System, the following will be described:

- Number of calls made for technical issues
- If available, categories of technical issues, as well as time since randomization

- Comparison of demographics of participants who called for technical issues vs. participants who did not call for technical issues
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- Comparison of primary study outcomes of participants who called for technical issues vs. participants who did not call for technical issues

3.3 Compliance

Compliance will be assessed by participant report at the 8-week study visit. Participants who report performing the exercises at least 80% of the time will be considered compliant. Exercises using the leva® Plus Pelvic Digital Health System should be performed twice daily, for a total of 14 times per week; therefore, participants who perform the exercise at least 11 times per week will be considered compliant. Exercises in the control (Kegel) arm should be performed three times per day, for a total of 21 times per week; therefore, participants who perform the exercises 17 times per week will be considered complaint.

In addition, for participants in the leva® Plus Pelvic Digital Health System arm, self-report will be validated using data from the device. The distribution of concordance will be reported. Allowing for some error in reporting, reports within 1 exercise per week (over or under report) will be considered concordant. This may be altered based on the data, at which point the statistician and investigators may re-define concordance.

3.4 8-week assessment

The primary outcome, 8-week assessment, will be reported as described below. Efficacy will also be reported as both improvement on the PGI-I and no urinary distress on the PFDI-20. In addition, the results of the PFDI, PISQ-IR, McGill Pain Questionnaire, SESPPFE, WHODAS, PFIQ, PGI-S and clinical assessment of urinary incontinence (voiding diary, POP-Q, PFDx device assessment) will be reported.

Efficacy of leva® Plus Pelvic Digital Health System: Two definitions of efficacy will be reported as two "primary" outcomes. Both will be dichotomous (yes or no). Efficacy will be assessed at the 8-week visit and will be defined as: 1, improvement of symptoms, and 2, no urinary distress.

- "Improvement" will be defined as "much better" or "very much better" on the Patient Global Impression of Improvement (PGI-I) scale. Any other answers will be considered "No improvement".
- "No urinary distress" will defined as a raw score of 2 or less on all six indicators in the Pelvic Floor Disability Index (PFDI-20) Urinary Distress Inventory (UDI-6) subscale. Raw scores of greater than 2 will be considered reports of distress.

Both will be reported as the primary study outcome.

- **Pelvic Floor Disability Index (PFDI):** Obtain the mean value of all of the answered items within the corresponding scale (possible value 0 to 4) and then multiply by 25 to obtain the scale score (range 0 to 100). Missing items are dealt with by using the mean from answered items only. For the summary score, add the scores from the 3 scales together to obtain the summary score

(range 0 to 300). This can be reported as a continuous variable or may be categorized depending on distribution of the data. For the primary outcome, "No urinary distress" will defined as a raw score of 2 or less on all six indicators in the UDI-6 subscale. Raw scores of greater than 2 will be considered reports of distress.

- **Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-IR)**: Validated scoring available from Constantine, M.L., Pauls, R.N., Rogers, R.R. et al. Int Urogynecol J (2017) 28: 1901.
- **McGill Pain Questionnaire**: The level of pain for each word can be reported as None, Mild, Moderate, Severe. Collapsing of responses is also possible (pain vs. no pain, no/mild pain vs. moderate/severe pain). Reporting of the visual analogue scale will depend on data recording. Reports of pain location will need to be manually reviewed and categorized.
- **Self-Efficacy Scale for Practicing Pelvic Floor Exercises (SESPPFE):** Sum all of the scores to calculate total score for the scale. This can be reported as a continuous variable or may be categorized depending on distribution of the data.
- **Patient Global Impression of Improvement (PGI-I) Scale:** This is only a single question and will be dichotomized as improvement ("very much better" or "much better") vs. no improvement (all other non-missing answers).
- **Patient Global Impression of Severity (PGI-S) Scale:** This is only a single question and can be reported as is.
- **World Health Organization Disability Assessment Schedule (WHODAS):** Two options are available for scoring the WHODAS. The first is a simple summary score as a continuous variable. The second option is to use the available coding provided by the WHO (http://apps.who.int/iris/bitstream/handle/10665/43974/9789241547598_eng.pdf;jsessionid=680B7F5F1FC5DE085FA4DCFD302F1176?sequence=1). A score of 17 or greater constitutes significant disability.
- **Pelvic Floor Impact Questionnaire (PFIQ)**: Obtain the mean value for all of the answered items within the corresponding scale (possible value 0 – 3) and then multiply by (100/3) to obtain the scale score (range 0-100). Missing items are dealt with by using the mean from answered items only. To obtain a summary score, add the scores from the 3 scales together (range 0-300). This can be reported as a continuous variable or may be categorized depending on distribution of the data.
- **Pelvic Organ Prolapse assessment (POP-Q)**: Assessment of pelvic organ prolapse will be conducted as medically directed. POP-Q stages may be reported as 0-IV, dichotomized as greater than or equal to Stage II vs. less than Stage II, or categorized depending on distribution of the data.
- **PFDx:** Assessment of baseline angle (rest angle), maximum angle (maximum squeeze), duration of pelvic floor lift (in seconds), valsalva angle (minimum angle), number of pelvic floor lift/relax repetitions in 15 seconds. All of these data will be reported as continuous.
- **Brink Score:** Scoring will be conducted as medically directed. All of the ratings will be summed and reported as a continuous variable.

3.5 General statistical analysis guidelines

The analyses will be conducted in the entire population. The denominator for all data will be the total number of women randomized to each group. Two-sided p-values less than 0.05 will be considered statistically significant.

Normality of continuous variables will be assessed using the Shapiro-Wilkes test and a visual inspection of the data distribution. Continuous variables that are normally distributed will be reported as means ± standard deviation. Non-normally distributed data will be reported as median and interquartile range (25^{th} and 75^{th} percentile). Categorical variables may be collapsed as necessary depending on data distribution, although all efforts will be made to maintain pre-determined categories. Categorical variables will be presented as n (%).

Data will be examined descriptively. Crude proportions of the primary and secondary outcomes at 8 weeks will be reported. Log-binomial regression will be used to calculate risk ratios and 95% confidence intervals (CIs) to assess whether the intervention was efficacious. We will assess each portion of efficacy separately (improvement and distress) as well as combined. If differences between the intervention and control groups as seen as baseline, these may be adjusted for in a log-binomial regression.

Chi-square or Fisher's exact tests may be used to calculate p-values to assess differences between categorical variables, as appropriate based on distribution of the data. To assess differences in normally distributed continuous variables between groups, the Student's T-test will be used to calculate p-values. To assess differences in non-normally distributed continuous variables between groups, the Wilcoxon rank-sum test will be used. Log-binomial regression will be used to calculate risk ratios and 95% CIs to assess the association between the intervention and all categorical variables. Linear regression will be used to calculate difference in means and 95% CI to assess the relationship between the intervention and all continuous variables.

In the event that the log-binomial regression does not converge, modified Poisson regression with robust standard errors will be substituted. If this is consistent problem, the statistician may decide to use this approach for all calculations of risk ratios and 95% CIs.

Due to the nature of the pilot/feasibility study, results of the primary analysis should be reported with caution. The initial sample size and follow up time was not achieved.

4. Additional comments

4.1 Reporting of statistical analyses

All reporting of statistical analyses will be in accordance with the CONSORT guidelines (http://www.consort-statement.org/consort-2010).

4.2 Additional analyses

Additional analyses may be conducted as needed based on data at the discretion of the statistician/investigator. Study questions not addressed in this document may require additional analysis plans.