# Supplementary Online Content

Amundsen CL, Richter HE, Menefee SA, et al. Effect of onabotulinumtoxinA compared with sacral neuromodulation on refractory urgency urinary incontinence in women: a randomized clinical trial: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.14617

**eAppendix.** Sensitivity Analysis Multiple Imputation Procedure
**eTable1.** Inclusion and Exclusion Criteria
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**eTable3.** Efficacy and Quality of Life Outcomes of Per-Protocol population

This supplementary material has been provided by the authors to give readers additional information about their work.

**eAppendix.** Sensitivity Analysis Multiple Imputation Procedure

Of the 386 randomized participants, 5 had invalid baseline diaries and 16 additional participants provided no follow-up diaries over the first six months, resulting in a total of 21 participants (5.4%) with no useable diary data. Overall, 295 participants (76.4%) provided all six follow-up diaries, another 58 (15.0%) provided 4 or 5 diaries, and 12 (3.1%) provided only 1 to 3 diaries. Missed diaries were fairly evenly distributed among study visits and among individuals that provided any follow-up diary and were primarily due to intermittent missed or out of window visits instead of study drop-out/loss to follow-up.

Based on the masked review of missing diary patterns and the relatively low incidence of missing diaries, the protocol team determined prior to database lock that a relatively simple modeling approach was appropriate for each imputation step within the multiple imputation process. Consequently, the regression-based imputation model used treatment assignment and the randomization stratification factor of age to generate the imputed data. Each month's missing data were imputed independently to generate 10 imputed datasets that had complete diary data (i.e. 6 months of data) for each of the 386 participants The imputation was completed using the procedure MI in SAS using regression based imputation assuming temporal independence across months for the outcome of change from baseline in urgency urinary incontinence episodes. Prior to conducting further analyses, the distributional characteristics of the imputed data sets were evaluated descriptively to confirm that they were consistent with the distributions of the raw data.

For the next step of the imputation process, the mixed effect model used for the primary analysis was run for each of the 10 imputation data sets using the SAS procedure MIXED to generate mean and covariance structure estimates for each parameter of the model. As a final step the parameter estimates and associated covariance structure were used as input for the SAS procedure MIANALYZE to generate estimates of the model parameters and the effects of interest, their covariance estimates and appropriate test statistics. This procedure utilizes standard analytic methods to appropriately account for both the within-imputation data set and between data set variance in generating hypothesis tests and interval estimates of the parameters of interest.

**eTable1. Inclusion and Exclusion Criteria**

**Inclusion Criteria**

- Non-pregnant adult female at least 21 years old, with no plans to become pregnant during the course of the trial— and if of child-bearing potential, with a negative pregnancy test, and if sexually active, must be using medically acceptable contraception
- ≥ 6 urge urinary incontinence episodes on a 3-day baseline bladder diary, with these urge incontinence episodes representing greater than 50% of the total incontinent episodes recorded
- Willing and able to complete all study related items and interviews
- Refractory urinary urge urinary incontinence defined as:

a. Persistent symptoms despite at least one or more conservative treatments (e.g. supervised behavioral therapy, supervised physical therapy); and
b. Persistent symptoms despite the use of a minimum of two anticholinergics, or unable to tolerate medication due to side effects, or has a contraindication to taking anticholinergic medication

- Currently not on an anticholinergic antimuscarinic medication (e.g. oxybutynin, tolterodine, and/or fesoterodine) or be willing to stop medication for 3 weeks prior to completing baseline bladder diary and expected to remain off medications through duration of study
- Demonstrates ability (or have caregiver demonstrate ability) to perform clean intermittent self-catheterization
- Grossly neurologically normal on exam and no gross systemic neurologic conditions believed to affect urinary function
- Urodynamic assessment within the previous 18 months prior to enrollment or done after enrollment, prior to randomization

**Exclusion Criteria**

- Neurologic diseases such as multiple sclerosis, Parkinson Disease, CVA within 6 months prior to enrollment, myasthenia gravis, Charcot-Marie-Tooth disease, clinically significant peripheral neuropathy, and complete spinal cord injury.
- Untreated urinary tract infection (UTI)
- Any prior use of either study therapy for treatment of urinary urge incontinence (Onabotulinumtoxin A or sacral neuromodulation
- Current participation in any other interventional research study.
- PVR >150 ml on 2 occasions within 6 months prior to enrollment (If the PVR value was obtained by ultrasound and was ≥150 ml, the PVR will be confirmed by catheterization which will be the gold standard)
- Subjects with knowledge of planned MRIs or diathermy.
- Current or prior bladder malignancy.
- Surgically altered detrusor muscle, such as augmentation cystoplasty.
- Subjects taking aminoglycosides.
- Currently pregnant or lactating.
- Subjects who are on anticoagulant therapy, including aspirin, who are unable to discontinue treatment for 24 hours prior to bladder injection and staged sacral neuromodulation procedure.

**eTable1. Inclusion and Exclusion Criteria**

- Serum creatinine level greater than twice the upper limit of normal within the previous year prior to enrollment
- Surgical treatment for stress incontinence (sling, Burch or urethral injection) or pelvic organ prolapse recommended or planned at enrollment by study investigator(s).
- Prior stress incontinence or prolapsed surgery within the last 6 months prior to enrollment.
- Allergy to lidocaine or bupivacaine.
- Prior pelvic radiation.
- Uninvestigated hematuria.
- Greater than or equal to Stage III vaginal prolapse.
- Known allergy to onabotulinumtoxinA .
- Use of a vaginal pessary

**eTable 2. Outcomes: Efficacy and Quality of Life of Clinical Responder Population**

| Outcome | OnabotulinumtoxinA (N=159) | Sacral Neuromodulation (n=139) | Treatment Group Difference (95% CI) | P Value |
|---|---|---|---|---|
| **For those completing at least 4 months of diaries** | | | | |
| Complete resolution of urgency incontinence no./total no. (%)[d] | 34/154 (22%) | 6/134 (4%) | -18 (-29, -6) | <.001 |
| ≥ 75% reduction in urgency urinary incontinence - no./total no. (%)[d] | 80/154 (52%) | 43/134 (32%) | -20 (-31, -8) | .001 |
| ≥ 50% reduction in urge urinary incontinence - no./total no. (%)[d] | 108/154 (70%) | 79/134 (59%) | -11 (-23, 0) | .10 |
| | | | | |
| **For those completing all 6 months of diaries** | | | | |
| Complete resolution of urgency incontinence no./total no. (%)[d] | 26/115 (23%) | 2/80 (3%) | -20 (-34, -6) | <.005 |
| ≥ 75% reduction in urgency urinary incontinence - no./total no. (%)[d] | 63/115 (55%) | 27/80 (34%) | -21 (-35, -7) | .02 |
| ≥ 50% reduction in urgency urinary incontinence - no./total no. (%)[d] | 85/115 (74%) | 47/80 (59%) | -15 (-29, -1) | .07 |

**eTable 2. Outcomes: Efficacy and Quality of Life of Clinical Responder Population**

| Outcome | OnabotulinumtoxinA (N=159) | Sacral Neuromodulation (n=139) | Treatment Group Difference (95% CI) | P Value |
|---|---|---|---|---|
| | | | | |
| Mean change in urgency urinary incontinence through 6 months – Adjusted Mean (95% CI)** | -4.37 (-4.75, -4.00) | -3.69 (-4.10, -3.28) | 0.68 (0.17, 1.20) | .01 |
| Mean change in any urinary incontinence through 6 months– Adjusted Mean (95% CI)** | -4.59 (-5.01, -4.17) | -3.97 (-4.42, -3.52) | 0.62 (0.05, 1.19) | .03 |
| Mean change in nocturia through 6 months– Adjusted Mean (95% CI)** | -0.34 (-0.52, -0.16) | -0.29 (-0.49, -0.10) | 0.04 (-0.20, 0.29) | .73 |
| Mean change in # voids through 6 months– Adjusted Mean (95% CI)** | -0.97 (-1.45, -0.49) | -0.90 (-1.42, -0.38) | 0.07 (-0.58, 0.73) | .83 |
| Mean change in # pads/day through 6 months– Adjusted Mean (95% CI) | -2.33 (-2.64, -2.02) | -1.86 (-2.20, -1.52) | 0.47 (0.04, 0.89) | .03 |
| | | | | |
| Mean change from baseline in score on OABq-SF through 6 months– Adjusted Mean (95% CI) | | | | |
| Symptom-bother | -51.8 (-55.6,-48.0) | -44.8 (-48.9,-40.6) | 7.0 (1.8, 12.2) | .009 |
| Quality of life | 46.4 (42.5, 50.2) | 45.1 (40.9, 49.3) | -1.2 (-6.5, 4.0) | .64 |
| At 6 months OAB SATq¥ - Adjusted Mean (95% CI) | | | | |

**eTable 2. Outcomes: Efficacy and Quality of Life of Clinical Responder Population**

| Outcome | OnabotulinumtoxinA (N=159) | Sacral Neuromodulation (n=139) | Treatment Group Difference (95% CI) | P Value |
|---|---|---|---|---|
| Treatment Satisfaction | 74.0 (69.5, 78.5) | 64.4 (59.4, 69.5) | 9.6 (3.2, 15.9) | .003 |
| Side Effects | 89.9 (86.0, 93.8) | 85.3 (81.0, 89.7) | 4.5 (-0.9, 10.0) | .10 |
| Endorsement | 84.6 (80.4, 88.7) | 72.2 (67.5, 76.9) | 12.3 (6.5, 18.2) | <.001 |
| Convenience | 70.6 (66.4, 74.8) | 71.7 (67.0, 76.5) | -1.1 (-7.0, 4.8) | .71 |
| Treatment Preference[##] – no (%) | 103 (95%) | 80 ( 93%) | -2 (-16, 12) | .64 |
| At 6 months PGI-I:[β] | | | | |
| Urinary leakage – no (%) | 93 ( 77%) | 81 ( 75%) | -2 (-15, 11) | .95 |
| Bladder function – no (%) | 93 (76%) | 83 (78%) | 3 (-10, 16) | .33 |
| At 6 months Sandvik[a] : no (%) | | | | .46 |
| Slight | 29 (28%) | 21 (21%) | | |
| Moderate | 30 ( 29%) | 31 (31%) | | |
| Severe | 20 (19%) | 17 (17%) | | |
| Very Severe | 26 (25%) | 30 (30%) | | |
| Change in UDI-SF[b] at 6 months-Adjusted Mean (95% CI) | -11.1 (-13.7, -8.5) | -10.1 (-13.0, -7.3) | -1.0 (-4.6, 2.6) | .58 |
| Change in IIQ-SF[c] at 6 months-Adjusted Mean (95% CI) | -13.8 (-16.6, -10.9) | -12.4 (-15.6, -9.3) | -1.3 (-5.3, 2.6) | .51 |
| Change in HUI-3[d] at 6 months-Adjusted Mean (95% CI) | -0.007 (-0.026, 0.012) | -0.005 (-0.026, 0.016) | -0.002 (-0.028, 0.024) | .88 |

Table presents results of analyses used in Table 2 repeated on the clinical responder population defined as Women with ≥50% reduction in mean UUIE on a 3-day bladder diary during the 7-14 day testing phase for sacral neuromodulation randomized individuals and one-month post-injection for onabotulinumtoxin A randomized individuals.

ᵈ represents individuals who had this degree of improvement on all their diaries as measured by percentage change in daily average UUI episodes.

** Values for any urinary incontinence, urgency urinary incontinence, nocturia, voids are based on mean number of episodes per day on a 3 day diary captured monthly and are generated from model-based estimates. The adjusted models controlled for the stratification variables of age and clinical site

¥ Values for the Overactive Bladder Satisfaction questionnaire (OAB-SATq) range from 0-100 and includes five subscales; treatment satisfaction, side effects, treatment endorsement, convenience, and patient preference, with higher scores reflecting better satisfaction. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

## Treatment preference is a binary outcome that is classified as yes if a participant answers either “Slight preference for the treatment I am receiving now” or “Definitely prefer the treatment I am receiving now” to the question: “Do you prefer the treatment that you received since entering this study to the treatment you received before the study?” from the OAB SATq. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

β The Patient Global Impression of Improvement (PGI-I) is a patient reported measure of perceived improvement with treatment on a scale of 1 (very much better) to 7 (very much worse). Included here are participants who had adequate improvement, defined as a rating of 1, 2 or 3 (better). Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

a The Sandvik scale has a range of 1-12, with higher scores representing worse outcomes. Results based on adjusted Mantel-Haenszel controlling for the stratification variables of age and clinical site.

b The Urinary Distress Inventory short form (UDI-SF) scale has a range of 0-100, with higher scores representing a worse outcome. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

c The Incontinence Impact Questionnaire short form (IIQ-SF) scale has a range of 0-100, with higher scores representing a worse outcome. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

d The Health Utility Index, Version 3 (HUI 3) scale has a range of 0-1, with higher scores representing a better outcome. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

**eTable 3. Outcomes: Efficacy and Quality of Life of Per- Protocol population**

| Outcome | OnabotulinumtoxinA (N=159) | Sacral Neuromodulation (n=139) | Treatment Group Difference (95% CI) | P Value |
|---|---|---|---|---|
| **For those completing at least 4 months of diaries** | | | | |
| Complete resolution of urgency incontinence no./total no. (%)[d] | 33/152 (22%) | 6/117 (5%) | -17 (-28, -5) | .001 |
| ≥ 75% reduction in urgency urinary incontinence - no./total no. (%)[d] | 79/152 (52%) | 40/117 (34%) | -18 (-29, -6) | .006 |
| ≥ 50% reduction in urge urinary incontinence - no./total no. (%)[d] | 107/152 (70%) | 71/117 (61%) | -10 (-22, 2) | .16 |
| | | | | |
| **For those completing all 6 months of diaries** | | | | |
| Complete resolution of urgency incontinence no./total no. (%)[d] | 26/114 (23%) | 2/68 (3%) | -20 (-34, -5) | .001 |
| ≥ 75% reduction in urgency urinary incontinence - no./total no. (%)[d] | 63/114 (55%) | 23/68 (34%) | -21 (-36, -7) | .04 |
| ≥ 50% reduction in urgency urinary incontinence - no./total no. (%)[d] | 85/114 (75%) | 39/68 (57%) | -17 (-32, -2) | .07 |

**eTable 3. Outcomes: Efficacy and Quality of Life of Per- Protocol population**

| Outcome | OnabotulinumtoxinA (N=159) | Sacral Neuromodulation (n=139) | Treatment Group Difference (95% CI) | P Value |
|---|---|---|---|---|
| | | | | |
| Mean change in urgency urinary incontinence through 6 months – Adjusted Mean (95% CI)** | -4.37 (-4.74, -3.99) | -3.70 (-4.11, -3.28) | 0.67 0.15, 1.19) | .01 |
| Mean change in any urinary incontinence through 6 months– Adjusted Mean (95% CI)** | -4.58 (-5.01, -4.16) | -3.97 (-4.43, -3.51) | 0.62 (0.04, 1.19) | .04 |
| Mean change in nocturia through 6 months– Adjusted Mean (95% CI)** | -0.33 (-0.51, -0.15) | -0.30 (-0.49, -0.10) | 0.03 (-0.21, 0.28) | .79 |
| Mean change in # voids through 6 months– Adjusted Mean (95% CI)** | -0.94 (-1.42, -0.45) | -0.87 (-1.40, -0.34) | 0.07 (-0.60, 0.73) | .84 |
| Mean change in # pads/day through 6 months– Adjusted Mean (95% CI) | -2.30 (-2.61, -1.99) | -1.85 (-2.19, -1.52) | 0.44 (0.02, 0.87) | .04 |
| | | | | |
| Mean change from baseline in score on OABq-SF through 6 months– Adjusted Mean (95% CI) | | | | |
| Symptom-bother | -52.3 (-56.2,-48.5) | -46.0 (-50.2,-41.8) | 6.3 (1.1, 11.6) | .0189 |
| Quality of life | 46.9 (43.1, 50.7) | 46.0 (41.8, 50.2) | -0.9 (-6.2, 4.4) | .7469 |
| At 6 months OAB SATq¥ - Adjusted Mean (95% CI) | | | | |

**eTable 3. Outcomes: Efficacy and Quality of Life of Per- Protocol population**

| Outcome | OnabotulinumtoxinA (N=159) | Sacral Neuromodulation (n=139) | Treatment Group Difference (95% CI) | P Value |
|---|---|---|---|---|
| Treatment Satisfaction | 74.4 (69.8, 79.0) | 64.1 (58.8, 69.5) | 10.3 (3.7, 16.9) | .002 |
| Side Effects | 89.1 (85.3, 93.0) | 85.6 (81.1, 90.1) | 3.6 (-1.9, 9.0) | .20 |
| Endorsement | 85.6 (81.4, 89.7) | 73.0 (68.2, 77.8) | 12.6 (6.7, 18.4) | <.001 |
| Convenience | 70.4 (66.2, 74.6) | 71.5 (66.6, 76.5) | -1.1 (-7.1, 4.9) | .72 |
| Treatment Preference[##] – no (%) | 101 (95%) | 71 (93%) | -2 (-16, 13) | .83 |
| At 6 months PGI-I:[β] | | | | |
| Urinary leakage – no (%) | 91 (77%) | 70 (74%) | -3 (-17, 10) | .6293 |
| Bladder function – no (%) | 91 ( 76%) | 74 (79%) | 3 (-11, 16) | .5390 |
| At 6 months Sandvik[a] : no (%) | | | | .3468 |
| Slight | 28 (27%) | 20 23%) | | |
| Moderate | 29 (28%) | 26 (30%) | | |
| Severe | 20 (20%) | 15 (17%) | | |
| Very Severe | 25 (25%) | 26 (30%) | | |
| Change in UDI-SF[b] at 6 months-Adjusted Mean (95% CI) | -11.2 (-13.8, -8.6) | -9.6 (-12.5, -6.7) | -1.6 (-5.2, 2.1) | .40 |
| Change in IIQ-SF[c] at 6 months-Adjusted Mean (95% CI) | -13.9 (-16.7, -11.0) | -12.2 (-15.4, -9.0) | -1.7 (-5.7, 2.3) | .40 |
| Change in HUI-3[d] at 6 months-Adjusted Mean (95% CI) | -0.007 (-0.026, 0.012) | -0.004 (-0.026, 0.018) | -0.003 (-0.030, 0.024) | .78 |

Table presents results of analyses used in Table 2 repeated on the per-protocol population defined as participants receiving complete study therapy who, based on review masked to treatment arm and outcome, did not substantially deviate from the protocol in a manner that impacted study outcome or treatment receipt.

ᵈ represents individuals who had this degree of improvement on all their diaries

** Values for any urinary incontinence, urgency urinary incontinence, nocturia, voids are based on mean number of episodes per day on a 3 day diary captured monthly and are generated from model-based estimates. The adjusted models controlled for the stratification variables of age and clinical site

¥ Values for the Overactive Bladder Satisfaction questionnaire (OAB-SATq) range from 0-100 and includes five subscales; treatment satisfaction, side effects, treatment endorsement, convenience, and patient preference, with higher scores reflecting better satisfaction. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

## Treatment preference is a binary outcome that is classified as yes if a participant answers either "Slight preference for the treatment I am receiving now" or "Definitely prefer the treatment I am receiving now" to the question: "Do you prefer the treatment that you received since entering this study to the treatment you received before the study?" from the OAB SATq. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

β The Patient Global Impression of Improvement (PGI-I) is a patient reported measure of perceived improvement with treatment on a scale of 1 (very much better) to 7 (very much worse). Included here are participants who had adequate improvement, defined as a rating of 1, 2 or 3 (better). Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

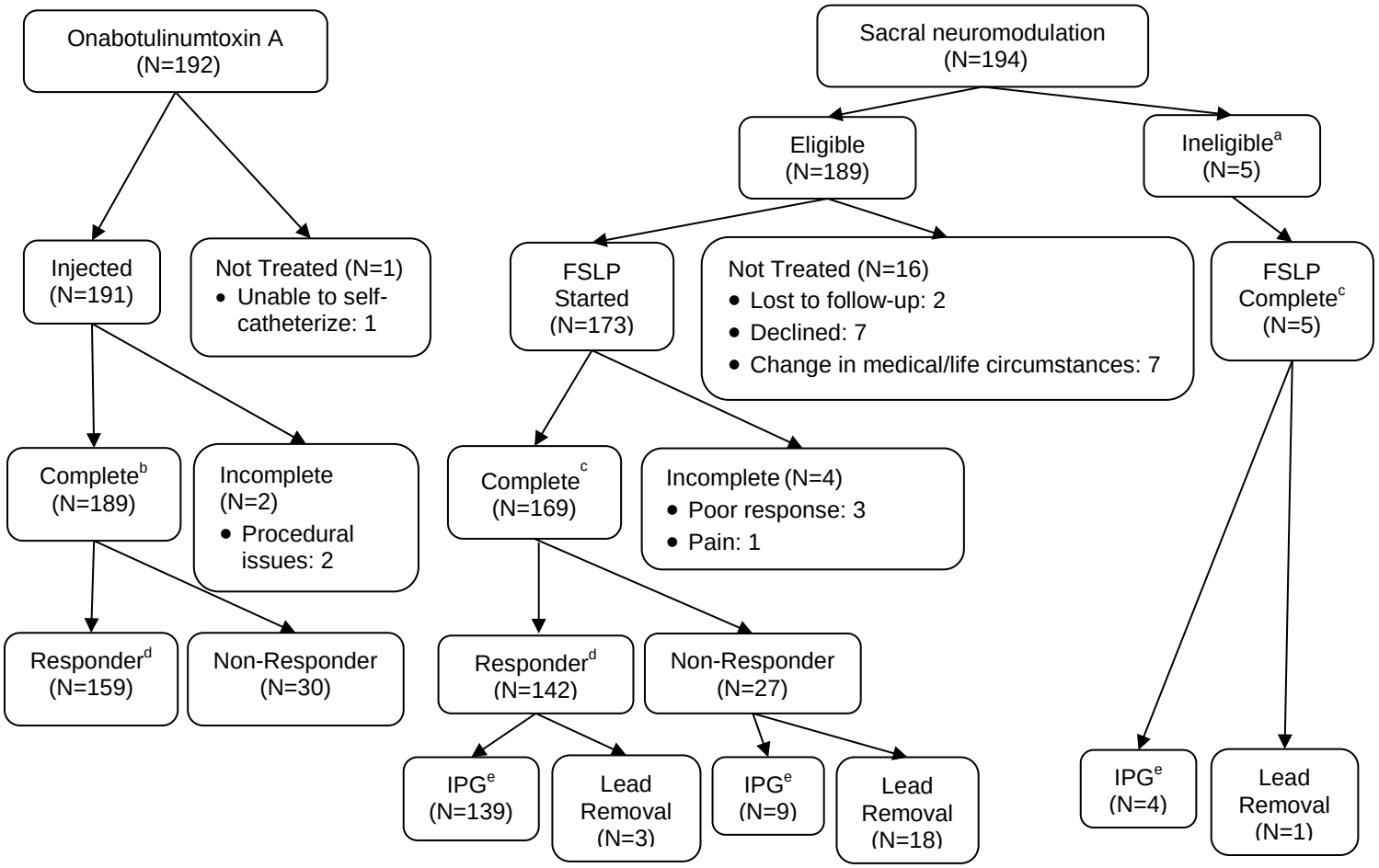
a The Sandvik scale has a range of 1-12, with higher scores representing worse outcomes. Results based on adjusted Mantel-Haenszel analyses controlling for the stratification variables of age and clinical site.

b The Urinary Distress Inventory short form (UDI-SF) scale has a range of 0-100, with higher scores indicating greater distress. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

c The Incontinence Impact Questionnaire short form (IIQ-SF) scale has a range of 0-100, with higher scores representing a worse quality of life. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

d The Health Utility Index, Version 3 (HUI 3) scale has a range of 0-1, with higher scores representing a better health. Estimates based on adjusted models controlling for the stratification variables of age and clinical site.

**eFigure. Flow diagram of study treatment receipt details and clinical response to treatment status in the randomized study population**




[a] Five baseline diaries were identified as being invalid during a data quality audit that occurred after randomization. All 5 individuals were treated and included in safety analyses but excluded from all analyses of efficacy.
[b] Injection completed if received the full dose of 200 U of injected onabotulinumtoxin A and incomplete if received an injection with a dose less than 200 U.
[c] First stage lead placement (FSLP) complete if surgery performed and lead successfully implanted and incomplete if surgery was attempted but lead was not successfully implanted.
[d] Responder defined as 50% or more reduction in mean UUIE on a 3-day bladder diary during the 7 to 14 day testing phase for sacral neuromodulation randomized individuals and one-month post-injection for onabotulinumtoxin A randomized individuals. Clinical responders in the sacral neuromodulation group were eligible for full implantation of the device while non-responders were expected to have the lead removed. Clinical responders in the onabotulinumtoxin A group were eligible for re-injections after completion of the initial 6 month follow-up period.
[e] Implantable pulse generator (IPG) implantation 2nd stage surgery completed