Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	A Prospective, Multi-Center Study of the Medtronic Braive™ Growth Modulation System When Used in the Treatment of Pediatric Patients Diagnosed with Juvenile or Adolescent Idiopathic Scoliosis (BRAIVE IDE Study)
Clinical Investigation Plan Identifier	MDT19009SD1901
Clinical Investigation Plan Version	V7.0
Sponsor/Local Sponsor	Medtronic Sofamor Danek USA, Inc. 1800 Pyramid Place Memphis, TN 38132 USA **Local sponsor – EU Legal Representative :** Medtronic Bakken Research Center BV Endepolsdomein 5 6229 GW Maastricht The Netherlands **Local Sponsor - Canada:** Medtronic of Canada ULC. 99 Hereford St. Brampton, ON L6Y 0R3 Canada +1-905-460-3800

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• New Document (Due to lack of oversight the statistical programmer signature was missing. There is no impact for the study since no patients were enrolled yet and no data analysis took place under this version.)	[redacted] M Squared Associates, Inc. Senior Biostatistician
2.0	• Updated to point to V3.0 of the protocol (CIP). (Due to lack of oversight the statistical programmer signature was missing. There is no impact for the study since no patients were enrolled yet and no data analysis took place under this version.)	[redacted] M Squared Associates, Inc. Senior Biostatistician
3.0	Updated to point to CIP V4.0 and ISO 14155 2020 • Changed "Safety Failure" to "Treatment Failure" • Deleted previous statements in the "Center Pooling", no statistical analysis would be performed due to small sample sizes and single arm, but a subgroup analysis by regions will be presented. • Added time courses to "Investigation Plan" section • Modified "Determination of Sample Size" according to CIP 4.0 • Update made in Subgroup Analysis • Safety Evaluation – added 4 types of endpoints and device deficiencies; deleted this statement: "A literature review will be conducted to provide additional supporting evidence of the safety of the device." • Added the definition of the event of clinically significant overcorrection. • Added when to utilize CEC adjudication • Added a new section: algorithm of neurological success in the last section "Statistical Appendices"	[redacted], Medtronic Senior Principal Statistician

Version	Summary of Changes	Author(s)/Title
4.0	• Added observational radiographic endpoints; • Changed the ITT (intent-to-treat) population to the primary analysis population; • Added additional analyses by comparing the postoperative measurements with the measurements prior to discharge • Added an additional subgroup analysis by stratifying the primary endpoint outcome by degree of baseline curve flexibility • Added PedsQL and SRS -22r scoring method	[redacted] Medtronic Senior Principal Statistician
5.0	• Clarified cobb angle to be main thoracic • Added secondary endpoint to assess TL/L cobb angle • Added observational radiographic endpoint to assess PT cobb angle • Added Main Thoracic to cobb angle for clarity considering we are now also assessing PT and TL/L cobb angles. • Added "If there is any additional interim analysis needed, the statistical analysis plan will be updated to document the need." • Added abbreviations for PedsQL and SRS-22 • Added investigator's assessment will be reported for device or procedure-related adverse events	[redacted] Medtronic Senior Principal Statistician
6.0	The content is adapted according to CIP 7.0 to reflect the changes due to the decision to discontinue the BRAIVE program. More specifically: • Updated primary objective from demonstrating efficacy to a primary safety objective to summarize device-related adverse events up to 24-month visit • Main Cobb angle is now a secondary endpoint • Added Instrumented Cobb Angle as an endpoint	[redacted] Senior Statistics Manager

Version	Summary of Changes	Author(s)/Title
	• Added Secondary spine surgery up to 24-month visit and Device deficiency up to 24-month visit as secondary safety endpoints. • Removal of the following endpoints: Individual Subject Success, PedsQL, shoulder imbalance endpoint, T1-L1 length, disc wedging angle and Neurological status. • Sample size changed from 25 to 10. • Removal of the subgroup analyses.	

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigation Plan
SAP	Statistical Analysis Plan
HDE	Humanitarian Device Exemption
GMS	Growth Modulation System
SAE	Serious Adverse Event
PedsQL	Pediatric Quality of Life Inventory™
SRS-22	Scoliosis Research Society 22 Patient Questionnaire

3. Introduction

The Braive™ Growth Modulation System functions by using growth modulation to treat patients with immature spinal anatomy. The system is comprised of a flexible braid, which is affixed to the anterior spinal column using metallic vertebral body screws, plates, and set screws. As the patient grows, the braid maintains compressive forces on the vertebral bodies along the convex side of the curve to correct the curvature of the thoracic spine. The continued growth of the concave side brings the vertebral bodies back into alignment. As with devices that function using growth modulation, no fusion of the spine occurs. The Braive ™ Growth Modulation System is designed to correct and preserve correction in a non-fusion manner to preserve the patient's growth potential.

This statistical analysis plan details the planned objectives and analyses to be performed to evaluate the safety and performance of the Braive™ Growth Modulation System when used in the treatment of juvenile and adolescent idiopathic scoliosis. The data obtained from this study may be used for regulatory purposes worldwide, in addition to possible publications.

4. Study Objectives

The purpose of this study was to establish probable benefit and evaluate the safety and preliminary effectiveness of the Braive™ GMS when used in the treatment of JIS and AIS.

In March 2023, Medtronic made the decision to discontinue the BRAIVE program. All sites, therefore, have been notified to discontinue study enrollment and there are no plans at this time to utilize collected data to obtain Humanitarian Device Exemption (HDE) approval.

This decision is not associated with any safety or efficacy observations from the study, and the study has not received stopping recommendations from the Data Monitoring Committee.

5. Investigation Plan

This is a prospective, multi-center, single-arm study of the Medtronic Braive™ GMS. As all subjects will have failed conservative care as per investigator's assessment, they will serve as their own controls. The baseline measurements will be collected prior to implantation of the device and compared against the measurements collected postoperatively. Data will be evaluated mainly for safety. Each subject will be followed until skeletally mature.

Clinical assessments will be completed at baseline (preoperatively), during surgery, and postoperatively at discharge, 3 months, 6 months, 12 months, 18 months, and 24 months, and then annually until subjects reach skeletal maturity (defined as Risser 5 as assessed by the investigator).

6. Determination of Sample Size

This study was designed to show that the investigational device can be used to obtain a statistically significant improvement (>0) in the Cobb angle. The initial sample size required to demonstrate a statistically significant improvement of cobb angle at 24 months as compared to that in the preoperative visit is 24. Medtronic planned to treat 25 subjects (refer to SAP V5.0 for detail). Due to the decision to stop the enrollment early, the sample size is 10 at the time of this decision.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Accountability tables will be generated to show, at each study visit, the number of subjects who might be expected to attend a given visit and the number and proportion who did attend. Visits occurring outside the windows will be considered protocol deviations. However, they will be included in the analysis.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Any deviations from the clinical investigation plan will be summarized and discussed in the clinical study reports.

7.1.3 Analysis Sets

7.1.3.1 Primary Analysis Population

The primary analysis population will include all subjects who are enrolled and undergo the Braive™ GMS surgical procedure. The primary dataset will be used for all the analyses. For subjects who are treatment failures, the last postoperative observation before the first treatment failure will be carried forward for analysis of additional secondary endpoints (see section 7.9.1).

7.2 General Methodology

All data will be analyzed using descriptive statistics including but not limited to mean, standard deviation, frequency, percentage, and 95% confidence intervals, as appropriate for the scale and distribution of the endpoint.

7.3 Center Pooling

Since the sample size is relatively small and the study is a single-arm, it's not applicable to test the site effect. Data from all centers will be pooled together for the analyses.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All analyses will be conducted based on the observed data with no missing data imputation.

7.5 Adjustments for Multiple Comparisons

Since the nature of the analysis is descriptive, no adjustments for multiple comparisons will be made.

7.6 Demographic and Other Baseline Characteristics

Baseline data will include but are not limited to height, weight, age, and preoperative radiographic measurements. Demographics and other pre-treatment characteristics will be summarized and characterized with appropriate descriptive statistics. Categorical variables will be summarized using frequency and percentage. Continuous variables will be summarized using mean, median, standard deviation, minimum, and maximum.

7.7 Treatment Characteristics

Operative data will include but are not limited to patient position, surgical approach, whether an access or general surgeon was used for the approach, number of incisions, total fluoroscopic time, implant details, and imaging system used for intra-op. Operative data will be summarized and characterized with appropriate descriptive statistics. Categorical variables will be summarized using frequency and percentage. Continuous variables will be summarized using mean, median, standard deviation, minimum, and maximum.

7.8 Interim Analyses

Due to the decision to stop the study enrollment, a final analysis will be conducted when all subjects have reached skeletal maturity. An interim analysis may be conducted when everyone reaches 24-month visit in addition to the progress reports required by the FDA.

7.9 Evaluation of Objectives

The primary objective of this study has been changed from demonstrating efficacy to a primary safety objective to summarize device-related adverse events up to 24-month visit. Please refer to section 7.10 Safety Evaluation for detail.

7.9.1 Analysis for Additional Secondary Endpoints

Additional secondary endpoints in addition to the secondary safety endpoints outlined in the section 7.10.2 are listed below:

- Change from baseline in main thoracic Cobb angle at all available postoperative time points
- Change from baseline in proximal thoracic Cobb angle at all available postoperative timepoints
- Change from baseline in thoracolumbar/lumbar Cobb angle at all available postoperative timepoints
- Change from post-op baseline in Instrumented Cobb Angle at all available postoperative time points
- Change from baseline in thoracic kyphosis at all available postoperative timepoints
- Change from baseline in Lumbar Lordosis at all available postoperative timepoints
- Change from baseline in coronal balance at all available postoperative timepoints
- Change from baseline in Sagittal Balance at all available postoperative timepoints
- Change from baseline in total vertical thoracic spine height (T1- T12) at all available postoperative timepoints
- Change from baseline in total vertical spine height (T1-S1) at all available postoperative timepoints
- Change from baseline in Scoliosis Research Society-22 Patient Questionnaire (SRS-22) at all available postoperative timepoints
- Status of return to full activity within 3 months per SRS-22

For the additional secondary endpoints related to the change from the baseline, when the distribution of data is approximately normally distributed, the change from baseline will be tested using a paired-

sample t-test. When the distribution of the data is non-normal, a Wilcoxon signed-rank test may be used in place of the paired t-test. In addition, the descriptive statistics including but not limited to mean, standard deviation, median, minimum and maximum will be calculated and presented. For "Status of return to full activity within 3 months per SRS-22", the number and percentage of subjects returned to full activity within 3 months will be calculated and presented.

Additional analysis will be performed by comparing the postoperative measurements at follow-up visits with the measurements at immediate post-op.

7.9.2 Subgroup Analyses

No subgroup analysis will be conducted.

7.10 Safety Evaluation

All adverse events will be reviewed by Medtronic safety representative for safety assessments.

7.10.1 Primary Safety Endpoint

The primary safety endpoint is device-related adverse events up to 24-month visit postoperatively. Sponsor's classification and investigator's assessment will be used for this endpoint. The event rate along with the 2-sided 95% confidence interval will be calculated and presented.

In addition, all device-related adverse events up to skeletal maturity (Riser score 5) will be summarized.

7.10.2 Secondary Safety Endpoint

The secondary safety endpoints include

- Procedure-related adverse events up to 24-month visit. Sponsor's classification and investigator's assessment will be used for this endpoint.
- Secondary spinal surgeries related to the device up to 24-month visit. Sponsor's classification and investigator's assessment will be used for this endpoint.
- Device deficiency up to 24-month visit.

For these secondary safety endpoints, the event rate along with the 2-sided 95% confidence interval will be calculated and presented.

In addition, all procedure-related adverse events up to skeletal maturity, all secondary spinal surgeries related to the device up to skeletal maturity and device deficiency up to skeletal maturity will be summarized.

7.10.3 Adverse Events and Device Deficiencies

A listing of all AEs, SAEs, device or procedure related AEs and SAEs and device deficiencies, secondary spinal surgeries and death will be generated. In addition, summaries of AEs, both overall and by visit, will be provided.

Summaries will be presented for all AEs, SAEs, device or procedure-related AEs, device or procedure-related SAEs and device deficiencies. Time course distributions will be provided in addition to cumulative summaries. Time course distributions will be based on the surgery date of the subject and onset dates of AEs, resulting in continuous time intervals. For overall summaries, a subject reporting the outcome at least once during the study period will be included in the frequency count. The percentage of subjects reporting the event at least once at up to 12-month visit, 24-month visit and skeletal maturity will be reported, and the denominator used in this calculation will be the total number of subjects who are enrolled and who receive the study treatment.

7.10.4 Secondary Spinal Surgeries and Treatment Failures

Secondary spinal surgeries and treatment failures will be summarized in a similar way as for AEs. The summary will list different types of secondary surgeries. The numbers of events and subjects who undergo secondary spinal surgeries and the associated time course distribution will be presented.

7.10.5 Change of Neurological Status

For each component of neurological status including motor, sensory, reflexes and straight leg raise, the change at each visit from baseline will be summarized in categories of “improved”, “maintained” and “deteriorated”. For overall neurological status, the change from baseline will be summarized in the categories of “success” and “failure”. The overall neurological status is deemed a success if, and only if all four components are “maintained” or “improved”. If any one of the components is “deteriorated”, the overall neurological status is a failure.

8. Validation Requirements

Independent validation will be performed for each analysis output and relevant publications.

9. References

The following reference was mentioned in the previous version of SAP

Newton, P. O. (2018). Anterior Spinal Growth Tethering for Skeletally Immature Patients with Scoliosis. THE JOURNAL OF BONE AND JOINT SURGERY, INCORPORATED, 100:1691-7.

10. Statistical Appendices

10.1 Algorithm of Neurological Success:

Neurological status is based on four components: motor function, sensory function, reflexes and straight leg raise. For each component, if at least one element worsens from the baseline evaluation, the status will be considered as deteriorated; if at least one element improves from the baseline evaluation and

the remaining elements are the same as the baseline assessment, the status will be considered as improved. If an element assessment is the same as the baseline evaluation, the status of the element will be considered as maintained. The component with all elements either “maintained” or “improved” from the time of the baseline evaluation to the time period evaluated is considered as a success.

The coding for each component of the neurological status is as follows. A change from a smaller number to a larger numerical number in the scale for motor function, sensory function, and straight leg raise indicates an improvement. For reflexes, the change status is stated in the table 1 “Change Status on Reflexes”

Table 1 : Change of Status on Reflexes

	0	1	2	3
0	Maintain	Improve	Improve	Improve
1	Deteriorate	Maintain	Improve	Maintain
2	Deteriorate	Deteriorate	Maintain	Deteriorate
3	Deteriorate	Maintain	Improve	Maintain

The overall neurological status is deemed a success if, and only if all four components are successes. If any one of the components is a failure, the overall neurological status is a failure.

Sensory: Coding scores as follows:
1 = Absent
2 = Impaired
3 = Normal

Motor: Coding scores as follows:
0 = Total Paralysis
1 = Palpable or Visible Contraction
2 = Active Movement, Gravity Eliminated
3 = Active Movement, Against Gravity
4 = Active Movement, Against Some Resistance
5 = Active Movement, Against Full Resistance (full strength)

Reflexes: Coding scores as follows:
0 = Absent
1 = Hypo-reflexia
2 = Normal
3 = Hyper-reflexia

Straight Leg Raise: Coding scores as follows:

1 = Positive

2 = Negative (Normal)

10.2 SCALING AND SCORING OF THE Pediatric Quality of Life Inventory™ - PedsQL™

The Child and Parent Reports of the PedsQL™4.0 (PedsQL.org, version17; May 2017) Generic Core Scales for:

- Children (ages 8-12), Teens (ages 13-18), and Parents are composed of 23 items comprising 4 dimensions.

DESCRIPTION OF THE QUESTIONNAIRE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	*Higher scores*
Emotional Functioning	5	1-5	1-5	*indicate better*
Social Functioning	5	1-5	1-5	HRQQL
School Functioning	5	1-5	1-5	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed, • Mean score = Sum of the items over the number of items answered. **Psychosocial Health Summary Score** = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. **Physical Health Summary Score** = Physical Functioning Scale Score **Total Score**: Sum of all the items over the number of items answered on all the Scales.

Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

10.3 SRS-22r Patient Questionnaire Coding and Scoring Method:

Note, the value of each response listed (in bold) indicates the coding score of each response.
(Score5 Best- 1 Worst)

1. Which one of the following best describes the amount of pain you have experienced during the past 6 months?
   - **5** None
   - **4** Mild
   - **3** Moderate
   - **2** Moderate to severe
   - **1** Severe

2. Which one of the following best describes the amount of pain you have experienced over the last month?
   - **5** None
   - **4** Mild
   - **3** Moderate
   - **2** Moderate to severe
   - **1** Severe

3. During the past 6 months have you been a very nervous person?
   - **5** None of the time
   - **4** A little of the time
   - **3** Some of the time
   - **2** Most of the time
   - **1** Most of the time

4. If you had to spend the rest of your life with your back shape as it is right now, how would you feel about it?
   - **5** Very happy
   - **4** Somewhat happy
   - **3** Neither happy nor unhappy
   - **2** Somewhat unhappy
   - **1** Very unhappy

5. What is your current level of activity?
   1 Bedridden
   2 Primarily no activity
   3 Light labor and light sports
   4 Moderate labor and moderate sports
   5 Full activities without restriction

6. How do you look in clothes?
   5 Very good
   4 Good
   3 Fair
   2 Bad
   1 Very bad

7. In the past 6 months have you felt so down in the dumps that nothing could cheer you up?
   1 Very often
   2 Often
   3 Sometimes
   4 Rarely
   5 Never

8. Do you experience back pain when at rest?
   1 Very often
   2 Often
   3 Sometimes
   4 Rarely
   5 Never

9. What is your current level of work/school activity?
   5 100% normal
   4 75% normal
   3 50% normal
   2 25% normal
   1 0% normal

10. Which of the following best describes the appearance of your trunk; defined as the human body except for the head and extremities?
    5 Very good
    4 Good
    3 Fair
    2 Bad
    1 Very bad

11. Which one of the following best describes your pain medication use for back pain?
    - **5** None
    - **4** Non-narcotics weekly or less (e.g., aspirin, Tylenol, Ibuprofen)
    - **3** Non-narcotics daily
    - **2** Narcotics weekly or less (e.g. Tylenol III, Lorcet, Percocet)
    - **1** Narcotics daily

12. Does your back limit your ability to do things around the house?
    - **5** Never
    - **4** Rarely
    - **3** Sometimes
    - **2** Often
    - **1** Very Often

13. Have you felt calm and peaceful during the past 6 months?
    - **5** All of the time
    - **4** Most of the time
    - **3** Some of the time
    - **2** A little of the time
    - **1** None of the time

14. Do you feel that your back condition affects your personal relationships?
    - **5** None
    - **4** Slightly
    - **3** Mildly
    - **2** Moderately
    - **1** Severely

15. Are you and/or your family experiencing financial difficulties because of your back?
    - **1** Severely
    - **2** Moderately
    - **3** Mildly
    - **4** Slightly
    - **5** None

16. In the past 6 months have you felt downhearted and blue?
    - **5** Never
    - **4** Rarely
    - **3** Sometimes

2 Often
1 Very often

17. In the last 3 months have you taken any days off of work, including household work, or school because of back pain?
    5 0 days
    4 1 day
    3 2 days
    2 3 days
    1 4 or more days

18. Does your back condition limit your going out with friends/family?
    5 Never
    4 Rarely
    3 Sometimes
    2 Often
    1 Very often

19. Do you feel attractive with your current back condition?
    5 Yes, very
    4 Yes, somewhat
    3 Neither attractive nor unattractive
    2 No, not very much
    1 No, not at all

20. Have you been a happy person during the past 6 months?
    1 None of the time
    2 A little of the time
    3 Some of the time
    4 Most of the time
    5 All of the time

21. Are you satisfied with the results of your back management?
    5 Very satisfied
    4 Satisfied
    3 Neither satisfied nor unsatisfied
    2 Unsatisfied
    1 Very unsatisfied

22. Would you have the same management again if you had the same condition?
    5 Definitely yes

4 Probably yes
3 Not sure
2 Probably not
1 Definitely not

There are five domains:

Domain Name	Question number included in the Domain
Function	5, 9, 12, 15, 18
Pain	1, 2, 8, 11, 17
Self-Image	4, 6, 10, 14, 19
Mental Health	3, 7, 13, 16, 20
Satisfaction/Dissatisfaction with management	21, 22

Score calculation Instructions (Score 5 Best- 1 Worst):

- If three or more questions are missing for each domain among Function, Pain, Self-Image and Mental Health, the domain can't be scored
- The sub total score could not be obtained if scores on more than two domains in the four domains (Function, Pain, Self-Image and Mental Health) were missing.
    - Note: In the situation where the sub total-score can be calculated, it will be the sum of all responses of the 4 domains /number of all questions answered in the 4 domains. For example, in a situation where the domain score for Pain, Self-Image and Mental Health can be calculated and the Function domain score is missing because only question 5 and 9 were answered, when we calculate the sub total score, the response to these two questions (5 and 9) in the "Function" domain will still be used in the calculation of the sub total score.
- The total score could not be obtained if the sub total score is missing. In addition, if more than 2 domains in the five domains (Function, Pain, Self-Image, Mental Health and Satisfaction) are missing, the total score is missing.
- If the answer to both questions is missing for satisfaction domain, then satisfaction domain can't be scored.

Score for each domain = sum of all responses of the domain / number of questions answered in the domain

Sub Total Score = sum of all responses of the 4 domains (Function, Pain, Self-Image and Mental Health) / number of all questions answered in the 4 domains

Total Score = sum of all responses / number of all questions answered