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A Pivotal Clinical Trial Evaluating the Safety and Effectiveness of Adherus™ AutoSpray and Adherus™ AutoSpray ET Dural Sealant When Used as a Dural Sealant in Spinal Procedures

Investigational Plan #: HBMT-US-2019-001
[redacted]
Version Date: 26 November 2024

HyperBranch Medical Technology, Inc.
800-12 Capitola Drive
Durham, North Carolina 27713

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1. SYNOPSIS

Title	A Pivotal Clinical Trial Evaluating the Safety and Effectiveness of Adherus™ AutoSpray and Adherus™ AutoSpray ET Dural Sealant When Used as a Dural Sealant in Spinal Procedures
Investigational Device	Adherus AutoSpray and Adherus AutoSpray ET Dural Sealant (Adherus Dural Sealant)
Control	DuraSeal™ Exact Spine Sealant System (DuraSeal Exact) (P080013b)
Study Purpose	To demonstrate that Adherus Dural Sealant is safe and effective at achieving water-tight closure when used as an adjunct to standard methods of dural repair for spinal procedures as compared to DuraSeal Exact.
Proposed Indication for Use	Adherus Dural Sealant is intended as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure during spinal procedures.
Study Design	This is a prospective, randomized, controlled, single-blind, multicenter, pivotal trial that will evaluate the safety and effectiveness of Adherus Dural Sealant when used in conjunction with standard methods of dural repair in spinal procedures. This trial uses the commercially available DuraSeal Exact (P080013) as an active control. The trial is designed to demonstrate non-inferiority of Adherus Dural Sealant to DuraSeal Exact. Subjects who have consented to participate in this study prior to undergoing spinal surgery and experience a durotomy, will be considered for study enrollment. Following a two-tiered inclusion/exclusion consideration, subjects will be randomized intraoperatively using a 1:1 randomization ratio. Up to 90 subjects will be enrolled and randomized to be treated with either Adherus Dural Sealant or DuraSeal Exact. [redacted] Up to 30 investigational sites within the United States will participate in this trial. A primary composite endpoint evaluating safety and effectiveness will be measured within a 90-day required follow-up period post-procedure. Subjects will be followed at discharge or between postoperative days (POD) 1-4 from the index procedure (whichever occurs first) and at 30 days and 90 days post-index procedure.
Study Success Criteria	Adherus Dural Sealant will be considered to have demonstrated adequate safety and effectiveness if the proportion of subjects who are classified as demonstrating success in the composite primary endpoint (see below) at the 90-day follow-up visit is statistically not worse among the Adherus-treated subjects compared to the control subjects based on pre-determined criteria for non-inferiority.

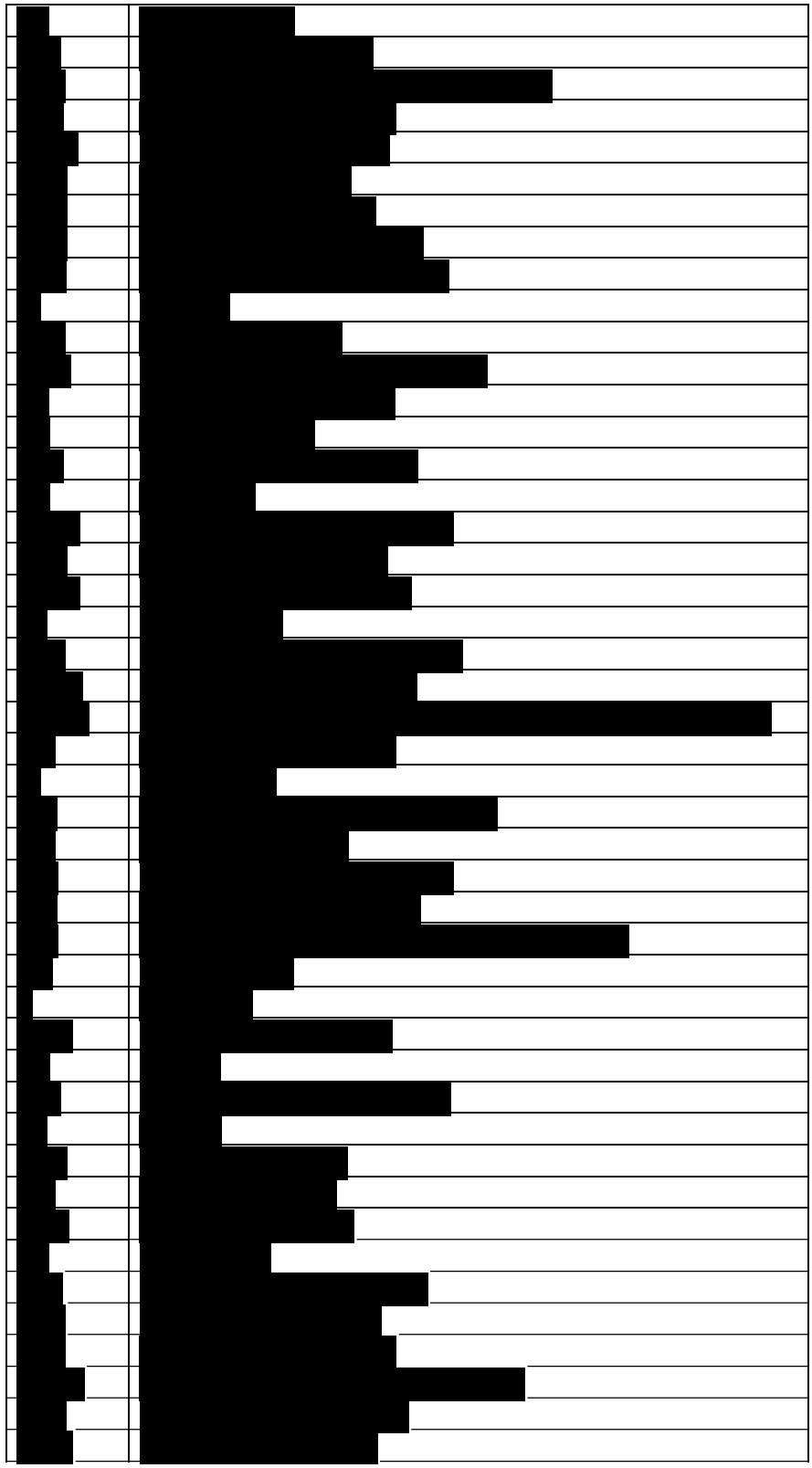
[redacted]

Study Population	Enrolled subjects will be ≥ 18 and ≤ 75 years of age undergoing spinal surgery and will meet all study-specific pre-operative and intra-operative inclusion and exclusion criteria.
[redacted]	[redacted]
Investigational Sites	Up to 30 investigational sites located in the United States will be qualified and activated for this study.
[redacted]	[redacted]
Primary Objective	The primary objective of the study is to demonstrate that the safety and effectiveness of Adherus Dural Sealant is not inferior to DuraSeal Exact Spine Sealant System when used as indicated for spinal procedures.
Primary Endpoint	The primary endpoint is a composite evaluation of the safety and effectiveness of Adherus Dural Sealant for a spinal application. The endpoint will be measured by the proportion of treated subjects who are free from the following: • Cerebrospinal fluid (CSF) leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging study during the 90-day follow-up period of the index procedure. • Unplanned retreatment of the original surgical site adjudicated by the Clinical Events Committee (CEC) to be device-related, other than CSF leak or pseudomeningocele formation or those related to the subject's pre-existing condition, during the 90-day follow-up period including:

	○ treatment for deep infection ○ treatment for meningitis ○ minimally invasive procedures or return to the operating room for neurosurgical complications
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

	
Study Sponsor	HyperBranch Medical Technology, Inc. 800-12 Capitola Drive Durham, North Carolina 27713
Contract Research Organization and Study Monitor	



3. INTRODUCTION AND BACKGROUND

[redacted]

3.1. Adherus Dural Sealant for Cranial Surgery: Pivotal Study Results

Following the successful completion of a feasibility study with satisfactory safety and effectiveness results, HyperBranch conducted a prospective, randomized, single-blind, multicenter, investigational device exemption pivotal study between September 2010 and September 2012 at 17 active study centers (enrolled and treated) in the United States.[20] This pivotal study was designed to demonstrate that the safety and effectiveness of the Adherus Dural Sealant was not inferior to DuraSeal when used as indicated in cranial procedures. Two hundred fifty (250) subjects undergoing planned cranial surgery involving durotomy were enrolled and randomized to receive either Adherus Dural Sealant or DuraSeal (control), which could also

[redacted]

be used with either the standard applicator or a variety of extended tip applicators after satisfying all pre-operative and intra-operative inclusion and exclusion criteria. Following primary dural closure and up to two applications of the assigned treatment, Adherus Dural Sealant was 100% effective (114/114) at achieving intra-operative watertight dural closure and DuraSeal was 99.1% effective (116/117) following a Valsalva maneuver (up to 20 cm H_2O for up to five seconds) for the per protocol analysis set (no missing data imputation). The primary composite endpoint (measured by the proportion of treated subjects who were free of intra-operative CSF leakage from dural repair during Valsalva maneuver, CSF leak/pseudomeningocele, and unplanned retreatment of the original surgical site) for the per protocol analysis (all subjects who received treatment with evaluable 120-day follow-up data) was 91.2% (104/114) in the Adherus group compared to 90.6% (106/117) in the control group. Within this analysis group, Adherus was found to be statistically significantly non-inferior to the control with respect to the overall success rate at 120 days with a non-inferiority margin of 10% (p=0.0049).

Of note, in the early post-surgical period when the sealants are expected to function, post hoc assessments of the overall success rate at the 14-day follow-up on subjects who completed this visit demonstrated the superiority of Adherus over control (p=0.0297).[20] In addition, post hoc assessments of the overall success rate at the 45-day follow-up on subjects who completed this visit trended towards the superiority of Adherus over control superiority (p=0.0561).[20] The freedom from primary endpoint failure analysis also showed that the primary endpoint failures in the control group tended to occur early in follow-up period while a majority of Adherus failures were identified through protocol-required radiographic imaging at the 120-day follow-up visit.

One-hundred subjects (n=100; 80.6%) in the Adherus group and 98 subjects (77.8%) in the control group experienced at least one adverse event (AE) within the 120-day follow-up period. The type and rate of adverse events observed in this study were consistent with the complexity of the surgical procedure performed and the co-morbid condition of the treated subjects and were expected given the severe disease state of the patient population; 66 (55%) Adherus subjects and 60 (49.2%) control subjects in the modified intent-to-treat (MITT) analysis set had an American Society of Anesthesiologists (ASA) score ≥ III at baseline. Most of AEs were mild or moderate in severity, and over half of the AEs in each treatment group had resolved by the date of study completion. The most frequently reported AEs in both treatment groups were classified as 'nervous system disorders' (48.4% Adherus subjects, 44.4% control subjects).

The incidence of serious adverse events (SAEs) was comparable between the two groups. There were 41 SAEs among 33 (26.6%) Adherus subjects, and 40 SAEs among 33 (26.2%) control subjects. Seven (7; 5.6%) Adherus subjects had eight (8) SAEs adjudicated by the Clinical Events Committee (CEC) as device-related and were coded as pseudomeningocele (n=3), convulsion (n=1), dysphagia (n=1), headache (n=1), extradural hematoma (n=1), and respiratory failure (n=1). Five (n=5; 4.0%) control subjects had five device-related SAEs coded as incision site infection (n=2), intracranial venous sinus thrombosis (n=1), infection (n=1), and pseudomeningocele (n=1). Nine (9) deaths occurred over the course of the 120-day study (four Adherus subjects, five control subjects). Deaths among the Adherus subjects were attributed to complications from colitis, stroke, disease progression, and metastatic lung cancer. Deaths among the control subjects were attributed to disease progression (n=2), multi-organ failure and pneumonia, respiratory failure, and posterior herniation with severe brain injury. All deaths were adjudicated as not related to the device. One death in the Adherus group was determined to be definitely procedure-related, and one death in the control group was possibly procedure-related. The remaining seven deaths were adjudicated as not related to the procedure. There were no unanticipated adverse device effects (UADEs).

In summary, the primary study hypothesis was met following pre-specified imputation rules for missing data in the per protocol analysis set (no missing data imputation). The robustness of study success was further confirmed through analysis of the intent-to-treat analysis set as well as in the summary of other secondary endpoints. The two study treatments (Adherus and control) produced similar risk profiles with no unanticipated adverse device effects. The analysis of this study shows powered, ample, and consistent evidence against the pre-specified success criteria that Adherus can be considered clinically and statistically non-inferior to control when used as indicated for cranial surgeries.

4. DEVICE DESCRIPTION

4.1. Investigational Device Name

The investigational device/s is the Adherus AutoSpray Dural Sealant and Adherus AutoSpray ET Dural Sealant (Adherus Dural Sealant).

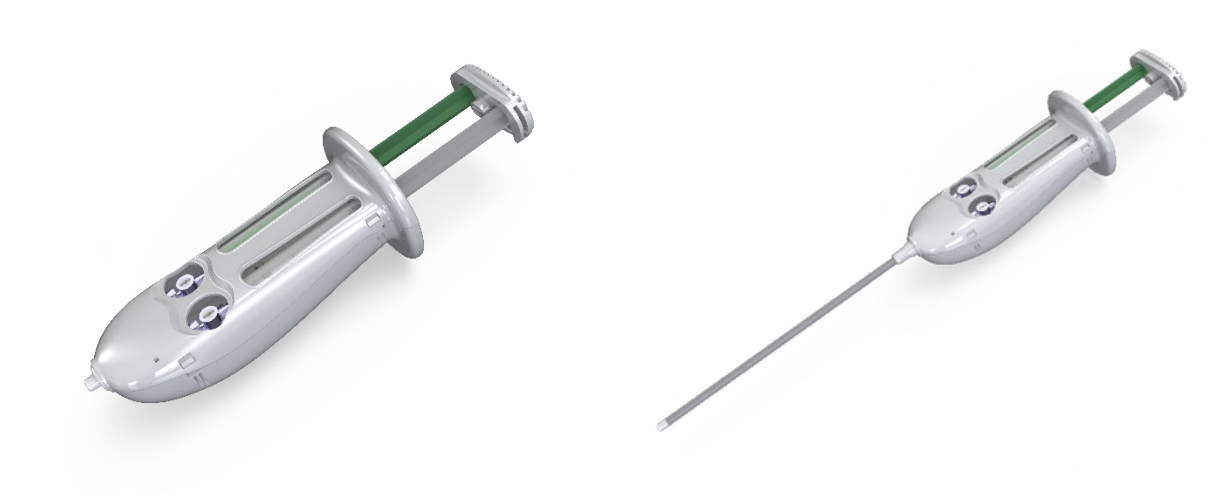
4.2. Investigational Device Description

Adherus Dural Sealant is a hydrogel sealant that polymerizes to form a well-adhered, compliant film when sprayed onto the surgical site. Adherus Dural Sealant is designed to provide a watertight seal until the dura heals.

Adherus Dural Sealant consists of components for preparation of a synthetic, absorbable sealant and an applicator for delivery of the sealant to the target site. The sealant is provided sterile to the user. The sealant is composed of two solutions, a PEG ester solution and a polyethyleneimine (PEI) solution (referred to as the 'green' and 'clear' precursors, respectively). When mixed together, the precursors crosslink to form the hydrogel sealant. The mixing of the sealant precursors is accomplished as the materials exit the tip of the applicator. The hydrogel implant is absorbed within approximately 90 days, sufficient time to allow for dura healing. Each single-use sterile applicator housing contains the batteries, air pump, nozzle, and syringes needed for sealant application.

Adherus AutoSpray Dural Sealant and Adherus AutoSpray Extended Tip (ET) Dural Sealant are each sterile, single-use, electromechanical, battery-operated device with internal system components that provide air flow to aid in the delivery of the same synthetic, absorbable, two-component hydrogel sealant system and allow delivery to be interrupted without clogging.

Figure 1. Adherus AutoSpray and Adherus AutoSpray ET Dural Sealant applicators



Each device (see Figure 1.) is supplied as a pre-assembled applicator and two separate glass vials, one of which is packaged within a foil pouch. The two glass vials contain either an activated PEG ester powder or a PEI dissolved in sterile water. The crosslinking components are reconstituted prior to use by their respective reconstitution buffers which are housed within the applicator. The resulting solutions mix within the applicator and quickly crosslink to form the hydrogel sealant soon after exiting the applicator tip. The delivered solution immediately crosslinks to form a hydrogel sealant which is absorbed over approximately 90 days, sufficient time to allow for healing.

The integrated extended tip nozzle Adherus AutoSpray Extended Tip (ET) is malleable and may be bent or shaped to preference. The extended tip nozzle thoroughly mixes the two sealant solutions and delivers the

mixed solution to the target site through a tight spray pattern. The spray nozzle is integral to the system and is not removable.

4.3. Proposed Indication for Use

The Adherus Dural Sealant System is intended as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure during spinal procedures.

4.4. Control Device Name

DuraSeal™ Exact Spine Sealant System (P080013)

4.5. Control Device Description

The DuraSeal Exact Spine Sealant System (DuraSeal Exact) consists of components for preparation of a synthetic absorbable sealant, and applicators for delivery of the sealant to the target site. The sealant is composed of two solutions, a polyethylene glycol (PEG) ester solution and a buffer solution (referred to as the ‘blue’ and ‘clear’ precursors, respectively). When mixed together, the precursors cross link to form the hydrogel sealant. The mixing of the precursors is accomplished as the materials exit the tip of the applicator. The hydrogel sealant is naturally absorbed in approximately 9 to 12 weeks. The 3mL polymer kit and 5mL polymer kits consist of the Dual Liquid Applicator in the tray. The polymer may be used with either the MicroMyst™ or Extended Tip applicator. The polymer kits and applicators are provided sterile. DuraSeal Exact can be used for up to one hour following reconstitution.

4.6. Control Device Indication for Use

The DuraSeal Exact is indicated for use as an adjunct to sutured dural repair during spinal surgery to provide watertight closure.

5. STUDY PURPOSE

To demonstrate that Adherus Dural Sealant is safe and effective at achieving water-tight closure when used as an adjunct to standard methods of dural repair for spinal procedures as compared to DuraSeal Exact.

6. STUDY DESIGN

This is a prospective, randomized, controlled, single-blind, multicenter, pivotal trial that will evaluate the safety and effectiveness of Adherus Dural Sealant when used in conjunction with standard methods of dural repair in spinal procedures. This trial uses the commercially available DuraSeal Exact as an active control. The trial is designed to demonstrate non-inferiority of Adherus Dural Sealant to DuraSeal Exact.

Subjects who have consented to participate in this study prior to undergoing spinal surgery and experience an intended durotomy, will be considered for study enrollment. Following a two-tiered inclusion/exclusion consideration, subjects will be randomized intraoperatively using a 1:1 randomization ratio. [redacted] Up to 30 investigational sites within the United States will participate in this trial.

A primary composite endpoint evaluating safety and effectiveness will be measured within a 90-day required follow-up period post-procedure. Subjects will be followed at discharge or between post-operative days (POD) 1-4 from the index procedure (whichever occurs first) and at 30 days and 90 days post-index procedure. The trial will enroll up to 90 subjects to allow for up to 5% estimated attrition to ensure that 84 evaluable subjects complete the 90-day primary study follow-up period.

6.1. Study Success Criteria

Adherus Dural Sealant will be considered to have demonstrated adequate safety and effectiveness if the proportion of subjects who are classified as demonstrating success in the composite primary endpoint (see below) at the 90-day follow-up visit is statistically not worse among the Adherus-treated subjects compared to the control subjects based on pre-determined criteria for non-inferiority.

[redacted]

6.4. Randomization

Subjects meeting the general and intraoperative inclusion/exclusion criteria will be assigned to receive Adherus Dural Sealant or DuraSeal Exact (control) with equal chance (1:1 randomization) using a computer-generated randomization scheme stratified by center and level treated. A permuted-block randomization scheme will be implemented to balance treatment assignments over time. Treatment assignments will be assigned via study database accessed in the operating room as soon as the durotomy edges are approximated and the need for a dural sealant is determined. The investigator will remain

[redacted]

masked to the treatment assignment until the subject is confirmed to meet all intraoperative inclusion/exclusion criteria. The assigned treatment will be prepared after determination of the randomization assignment. Subjects excluded intraoperatively will be classified as screen failures and will be terminated from further study participation.

Subjects must receive the device as assigned by the randomization scheme. Implantation of the incorrect device is a protocol deviation and must be entered into the study database such by completing the Protocol Deviation electronic case report form (eCRF).

[redacted]

6.5. Treatment Masking

While the subjects will be masked to the study treatment assignments, it is not possible to mask the investigators who apply the treatment and perform most of the follow-up evaluations due to the distinctive applicator and color differences between the study treatments. As a result, this clinical trial is considered a single-blind trial.

7. STUDY OBJECTIVES

7.1. Primary Objective

The primary objective of the study is to demonstrate that the safety and effectiveness of Adherus Dural Sealant is not inferior to DuraSeal Exact when used as indicated for spinal procedures.

[redacted]

8. STUDY ENDPOINTS

8.1. Primary Endpoint

The primary endpoint is a composite evaluation of the safety and effectiveness of Adherus Dural Sealant for a spinal application. The endpoint will be measured by the proportion of treated subjects who are free from the following incidences:

- CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging study during the 90-day follow-up period following the index procedure
- Unplanned retreatment of the original surgical site adjudicated by the CEC to be device-related, other than CSF leak or pseudomeningocele formation or those related to the subject's pre-existing condition, during the 90-day follow-up period including:
  - treatment for deep infection
  - treatment for meningitis
  - minimally invasive procedures or return to the operating room for neurosurgical complications

[redacted]



9. INVESTIGATIONAL CENTERS

This study will be conducted at up to 30 investigational sites within the United States. The investigational sites and investigators will be qualified using predetermined criteria to ensure they have the appropriate neurosurgical and/or orthopedic experience and expertise to perform spinal surgeries with the study devices and to conduct human clinical research with careful adherence to applicable federal regulations. Sites will be required to demonstrate that they have qualified neurosurgeons, orthopedic spine surgeons, and research staff to ensure proper study conduct, including the safeguarding of subject rights and compliance to federal regulations, this investigational plan, the investigator agreement, and the temporal requirements for this study for enrollment.

[redacted]

11. STUDY POPULATION

Enrolled subjects will be ≥ 18 and ≤ 75 years of age undergoing spinal surgery and will meet all study-specific pre-operative and intra-operative inclusion and exclusion criteria. Subjects who have consented to participate in this study prior to undergoing spinal surgery and experience a durotomy, will be considered for study enrollment and will be informed about the study by trained site personnel. Consented subjects who do not meet intraoperative inclusion/exclusion criteria will be considered as screen failures, will not be randomized, will not receive Adherus Dural Sealant, and will be terminated from the study. Following a two-tiered inclusion/exclusion consideration, subjects will be randomized intraoperatively using a 1:1 randomization ratio.

[redacted]

Up to 30 investigational sites within the United States will participate in this trial.

[redacted]

11.1. Inclusion Criteria

Enrolled subjects must meet the following inclusion criteria for enrollment; all criteria must be answered "yes":

1. Subject is ≥ 18 and ≤ 75 years old.
2. Subject is scheduled for an elective spinal procedure that will require a planned durotomy.
3. Subject requires a procedure involving a Class I/clean wound (uninfected surgical wound in which no inflammation is encountered).
4. Subject is able and willing to provide informed consent and HIPAA authorization.
5. Subject is able and willing to meet all study requirements, including attending all post-index procedure assessment visits and radiological tests.

Intra-Operative Inclusion Criteria:

6. Subject has durotomy edges that can be re-approximated using the investigator's standard methods of dural repair.

11.2. Exclusion Criteria

Enrolled subjects cannot meet any of the following exclusion criteria; all criteria must be answered "no":

1. Subject has clinically significant hydrocephalus or clinical evidence of altered CSF dynamics.
2. Subject has a pre-existing external lumbar CSF drain or internal CSF shunt.
3. Subject has experienced previous CSF leak (secondary to trauma, neoplasm, surgery or other etiology).
4. Subject is undergoing a Chiari malformation procedure.
5. Subject has undergone a previous spinal procedure in the same anatomical location.
6. Subject has had radiation treatment to the surgical site, or standard fractionated radiation therapy is planned within ten days post index-procedure.
7. Subject has spinal metallic implants that may cause significant imaging artifact on the MRI evaluation of the spine.

[redacted]

8. Subject has metallic implant(s) that are not compatible with magnetic resonance imaging [(MRI), e.g., cochlear implant, neurostimulator, stent, surgical clip, cardiac pacemakers, or other non-MRI compatible implants], or an elective implant of such devices is planned during the course of the study. Note: mercury amalgam dental fillings or similar metallic dental prostheses are not an exclusion criterion.
9. Subject has a known malignancy or another condition with anticipated survival shorter than six months.
10. Subject has undergone chemotherapy treatment, excluding hormonal therapy, within three weeks prior to the planned index procedure, or chemotherapy treatment is planned within two weeks after the index procedure is performed.
11. Subject has been treated with chronic steroid therapy (defined as regular (daily) administration of steroid agent(s) for ≥ 8 weeks) unless discontinued greater than four weeks prior to the planned index procedure. Note: standard acute perioperative steroids are permitted; administration of steroid agents for < 8 weeks duration prior to the planned index procedure is permitted.
12. Subject has received warfarin, heparin, other anticoagulant agents, aspirin or non-steroid anti-inflammatory agents on a daily basis and pre-surgical, standard of care drug wash-out did not occur.
13. Subject has a compromised immune system or autoimmune disease or is on chronic immunosuppressant agents at baseline.
14. Subject has a systemic infection or evidence of any infection near planned operative site.
15. Subject has a serum creatinine level > 2.0 mg/dL.
16. Subject has a serum total bilirubin > 2.5 mg/dL at baseline.
17. Subject has uncontrolled diabetes as evidenced by an HbA1c > 7% prior to surgery.
18. Subject has a known allergy to FD&C Blue #1 and/or FD&C Yellow #5 or any of the constituents of the dural sealants.
19. Subject is pregnant, breast-feeding, or intends to become pregnant during the course of the study.
20. Subject is participating in a clinical trial of another investigational drug or device and has not completed the required follow-up period.

Intra-Operative Exclusion Criteria:

21. Subject has an incidental finding that meets any pre-operative exclusion criterion listed above.
22. Subject's dural defect cannot be closed with suture and/or duraplasty material.
23. Subject has a gap > 2 mm present between dural edges, or between the edge of dura and duraplasty material, based on visual estimate by surgeon before application of the surgical sealant.
24. Subject had undergone laminoplasty decompression.
25. Subject had undergone a syringomyelia procedure where the shunt is not placed in the subarachnoid position.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

In the event of death for any subject who expires during their participation in the study, an Adverse Event

[redacted]

13. ADVERSE EVENTS

13.1. Adverse Event Overview

All adverse events (regardless of suspected causality) will be assessed from the time the Informed Consent Form is signed through the termination of the subject from the study. Adverse events (AE) will be assessed at all follow-up visits, unscheduled visits and at the time they occur or are discovered by study staff.

All adverse events will be assessed by the investigator according to:

- Whether the event is an unanticipated adverse device effect (UADE);
- Whether the event is serious (SAE);
- The severity of the event (mild, moderate, severe); and
- The relationship of the event to the investigational or control device and/or procedure (not related, possibly related, definitely related, or unknown).

[redacted]

13.2. Definitions

Adverse Event (AE)

An adverse event is defined as any undesirable clinical occurrence or change from subject's baseline (i.e., prior to sealant application to the dura) condition, whether it is considered to be related to the procedure or assigned study treatment.

Not an Adverse Event: For purposes of this study, the following events will not be considered adverse

[redacted]

Serious Adverse Event (SAE)

An adverse event is considered serious if it meets at least one of the following criteria:

- Results in death.

[redacted]

- Is actually or potentially life-threatening.
- Requires inpatient hospitalization ≥ 24 hours*, or prolongation of an existing hospitalization.[4]
- Results in permanent impairment of a body structure or a body function.
- Requires medical or surgical intervention to prevent one of the above outcomes.

The investigator must follow all serious adverse events until the event is resolved or stabilized, the subject is lost to follow-up, withdrawn consent or completes the study.

Event Severity

Adverse events will be categorized by the investigator as mild, moderate, or severe, depending on the event's impact on the subject's daily activity level:

- Mild – Usually transient, requiring no special treatment; does not interfere with the subject's daily activities.
- Moderate – Low-level inconvenience or concern to the subject; may interfere with daily activities, usually resolved by simple therapeutic non-interventional methods.
- Severe – Interruption in subject's daily activity requiring systemic drug therapy or other treatment.

Event Relatedness

Adverse events will be judged by the investigator as to their relatedness to the study device or procedure using the following classifications:

- Not Related: The event has no relationship to the study devices or procedure.
- Possibly Related: The event has a strong temporal relationship to the study devices or procedure and alternative etiology is equally or less likely compared to the potential relationship to the study devices or procedure.
- Definitely Related: The event is clearly caused by the study devices or procedure and another etiology is unlikely.
- Unknown: Relationship of the event to study devices or procedure and alternative etiology is unknown. There is no evidence or relevant data available to assess the relationship between the event and the device or procedure.

[redacted]

[redacted]

Unanticipated Adverse Device Effect (UADE)

An adverse device effect is any untoward and unintended response to a medical device or as a consequence of inadequate labeling. A UADE is any adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death that is not previously identified in nature, severity, or degree of incidence in this investigational plan or informed consent, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.7. Device Malfunction

Device malfunctions of the Adherus Dural Sealant and DuraSeal Exact are required to be documented on the Device Deficiency eCRF. In the event of a suspected malfunction or device problem, the investigational device shall be returned to the sponsor for analysis. Instructions for returning the investigational device are included in the eTMF

[redacted]

14. STATISTICAL CONSIDERATIONS

This section presents a summary of the Statistical Considerations for this trial[redacted]

14.1. Endpoints and Hypotheses

14.1.1. Primary Endpoint

The primary endpoint will be measured in success or failure of individual subjects encountering either of the following events:

- CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging study during the 90-day follow-up period following the index procedure
- Unplanned retreatment of the original surgical site adjudicated by the CEC to be device-related, other than CSF leak or pseudomeningocele formation or those related to the subject's pre-existing condition, during the 90-day follow-up period including:
  - treatment for deep infection
  - treatment for meningitis
  - minimally invasive procedures or return to the operating room for neurosurgical complications

Subject success is defined as a subject who is free from both listed events through the 90-day follow-up period. That is, a subject will be considered a success for the primary endpoint if they do not experience a CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging study within 90 days of the index procedure and they do not experience a device-related event as defined above.

Safety and effectiveness of the Adherus Dural Sealant will be measured by the proportion of successful subjects treated with the Adherus Dural Sealant compared to those treated with the DuraSeal Exact (active control).

We seek to reject a null hypothesis that says the success rate of Adherus Dural Sealant is unacceptably worse than the success rate of DuraSeal Exact and support the alternative hypothesis that says the success rate of Adherus Dural Sealant is not unacceptably worse than the success rate of DuraSeal Exact, i.e.,

$H_0: \pi_A \leq \pi_D - \delta$ vs. $H_1: \pi_A > \pi_D - \delta$

where:

π_A = success rate of subjects randomized with Adherus Spinal Sealant

π_D = success rate of subjects treated with DuraSeal Exact

δ = the pre-determined non-inferiority margin (δ = 13%)

[redacted]

Post-operative CSF leak or pseudomeningocele will be evaluated by the proportion of subjects free of CSF

[redacted]

[redacted]

14.2. Study Success

This clinical trial uses a randomized controlled design to compare Adherus Dural Sealant System and DuraSeal Exact Spine Sealant as a concurrent active control for non-inferiority. The study will be considered a success if the proportion of subjects achieving an individual successful outcome on the primary endpoint that received treatment with the Adherus Dural Sealant is statistically significantly non-inferior to the proportion of subjects achieving individual success when treated with the DuraSeal control. Statistical significance is defined as a p-value resulting from the primary endpoint analysis using a one-sided normal approximation (z-test) for comparing two proportions that is ≤ 0.05. After the claim of study success is made, a test will be performed for a superiority claim by using the same statistical methodology.

[redacted]

[redacted]

14.4. Analysis Sets

The primary analysis will be based on the intent to treat (ITT) principle, and will include all randomized subjects. Subjects randomized and treated will be analyzed per their randomized assignment, regardless of actual treatment received.

Analysis of the primary and secondary endpoints may also be performed on the per-protocol (PP) analysis set if there are subjects excluded from the ITT analysis set. The PP analysis set is defined as all subjects who receive the treatment to which they were randomized and without protocol deviations that could impact the study outcomes.

14.5. Missing Data Management

Follow-up compliance of treated subjects is expected to be very good for this study based on observation from similar studies, evaluation of the safety and effectiveness of DuraSeal Sealant (P080013b) and evaluation of the safety and effectiveness of the Adherus Autospray Dural Sealant (P130014), and the relatively short follow-up period. Nevertheless, all efforts will be used to minimize missing data.[9, 22]

For the analysis of primary and secondary endpoints based on the ITT analysis set, multiple imputation will be used to impute missing values for subjects who do not contribute to specific endpoint. Any analyses based on Per Protocol analysis set will include available data only, with no planned imputation for missing values.

A sensitivity analysis for the overall study conclusion (primary endpoint analysis) will be conducted to assess the robustness of the results by using a tipping point analysis.

Additional endpoints, and other analyses of primary and secondary endpoints will be analyzed using available data only. No further missing data imputation for individual observations is planned.

14.6. Pooling Data Across Centers

All study data will be pooled across study centers to facilitate hypothesis testing in accordance with the sample size estimation and power analysis. Comparability between study sites may be examined using summary statistics calculated by site.

Homogeneity of the primary endpoint results among centers will be assessed based on the Breslow-Day test. Centers with less than 10 subjects will be combined into virtual centers (one or more) based on geographic location for the poolability assessment. If the results of the test show evidence of heterogeneity across centers (i.e., p-value < 0.15), the treatment effect will be evaluated by center or by grouping of certain centers.

[redacted]

[redacted]

14.8. Analysis Methods

14.8.1. Primary Endpoint

The primary endpoint of treatment success through 90 days will be analyzed by comparing treatment success rates between the Adherus and the control groups using Blackwelder methods for testing non-inferiority between two proportions.[21] The difference in success rates (proportions) between treatment groups will be calculated (Adherus – DuraSeal Exact), and a one-sided 95% confidence interval will be constructed. If non-inferiority is concluded, a subsequent superiority test will be performed using the same methodology.

The primary analysis of the primary endpoint will be based on all randomized subjects (ITT), with multiple imputation used to account for missing values.

A sensitivity analysis will be performed to assess the robustness of the inferences from the analysis of the primary endpoint as described in Section 14.5.

[redacted]

14.9. Demographic and Baseline Characteristics

Demographic and baseline characteristics and the comparability of the Adherus Dural Sealant subjects to control subjects will be summarized using frequencies and percentages for categorical measurements and mean, median, standard deviation, minimum and maximum for continuous measurements.

[redacted]

will be analyzed by first computing the success rates for intra- and post-operative CSF leak or [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

16. MONITORING PROCEDURES

HyperBranch Medical Technology, Inc., has contracted with [redacted] to monitor this study. The study will be monitored according to the study-specific Monitoring Plan.

16.1. Study Monitors

Monitors for this study must be qualified by education, experience, and training to serve in the role of a Study Monitor. The qualifications of monitors will be on file[redacted] Study Monitors will follow [redacted] tandard operating procedures and the written Monitoring Plan for this study. The Monitoring Plan will specify the relative frequency, scope, and general conduct of monitoring visits as well as identify any relevant study-specific Study Monitor responsibilities.

[redacted]

[redacted]

16.3. Investigational Site Training

Study conduct-specific training of clinical trial personnel is the responsibility of the Study Monitor, HyperBranch Medical Technology, and the investigator. Study training will occur before the first device use.

16.4. Monitoring Visits

This study will be conducted and monitored in accordance with FDA regulations for investigational device exemption (IDE) studies including 21 CFR 50, 54, 56, and 812; this investigational plan; HIPAA; and [redacted] Inc. standard operating procedures.

The study sites will undergo a combination of on-site and remote interim monitoring visits for evaluation of appropriate conduct and documentation of informed consent, timeliness of data form completion, data accuracy, traceability of investigational devices, and investigational plan and regulatory compliance.

[redacted] [redacted] [redacted]

17. INVESTIGATIONAL PLAN MODIFICATIONS

17.1. Amendments to the Investigational Plan

During the course of this investigation, it may become necessary to amend this investigational plan. Such amendments will be made by the sponsor and approved by the FDA, if required. Investigational plan amendments will be forwarded to the site IRB by study personnel as required for approval.

17.2. Deviations to the Investigational Plan

The investigator and other study personnel may deviate from the requirements of this investigational plan without prior approval of the sponsor only in an emergency to protect the life or well-being of participant or study personnel. All investigational plan deviations (either emergent or non-emergent) must be documented on the eCRF Protocol Deviation Form.

18. STUDY ADMINISTRATION

The following records and reports must be created and/or maintained by the parties as specified below. This study uses an eTMF, which is the official repository of all study documents. The eTMF will be reviewed by the monitor throughout the study for completeness and will be inspected by FDA during a Bioresearch Monitoring (BIMO) inspection(s), if is conducted by the agency.

18.1. Investigator Records

Records to be maintained by the investigator in the study's eTMF include:

- Subject Screening Log
- Training Log
- Visitor Log
- Delegation of Authority/Site Signature Log
- Device Accountability Log
- CVs and licenses for all study personnel
- Financial Disclosure Forms
- Device information
    - Investigational device accountability log including date, quantity, lot numbers of all devices, identification of all persons the device was used on, and final disposition
    - Shipping documents
- Investigational Plan and amendments
- IRB communications
    - Submissions to IRB
    - Approval letters
    - Notification of unanticipated adverse device events and protocol violations
    - Study updates/reports (including annual reports and a final report from the investigator)
- Informed Consent/HIPAA Form
    - IRB approved copy
    - Revised approved, consent forms
- Agreements
    - Confidentiality agreement (signed)
    - Clinical trial and/or investigator agreements (signed)
    - Financial disclosure forms

Instructions for use for the two study devices

Correspondence with the IRB, sponsor, [redacted]., and CEC

The following records must be maintained for each subject enrolled in the trial:

- Signed Informed Consent/HIPAA Forms
- Completed eCRFs and Data Clarification Forms

- Completed Protocol Deviation Forms
- Complete medical records, including procedure reports, lab reports, professional notes, etc., for participating subjects.
- Records pertaining to subject death during the investigation (including death records, death certificate, and autopsy report, if performed)

18.2. Investigator Reports

The investigator is required to prepare and submit to HyperBranch Medical Technology [redacted] complete, accurate, and timely reports on this investigation when necessary. The types of reports to be submitted include reports pertaining to unanticipated adverse device effects, major adverse events, withdrawal of IRB approval, and deviations from this investigational plan. If a deviation occurs in order to protect the life or well-being of a subject in an emergency, the investigator must notify the sponsor, [redacted] and IRB immediately but no later than five (5) working days after the emergency occurs.

The investigator is required to submit an annual and final report to the site's Institutional Review Board with a copy to the sponsor and [redacted]. Input from the investigator for the reports will include the following topics at a minimum:

- Number of subjects screened, enrolled, withdrawn, and completed.
- Number of devices received, used, and returned.
- Summary of all adverse events (anticipated and unanticipated).
- Summary of all investigational plan deviations.
- Brief statement of results, outcomes, and conclusions.

HyperBranch Medical Technology reserves the right to perform study monitoring and secure data clarifications and additional medical documentation on subjects enrolled in this trial at any time.

18.3. Sponsor Records

The sponsor [redacted] is required to maintain the following records in the eTMF:

- Investigational plan and all amendments
- Signed Clinical Trial Agreements
- Institutional Review Board approval letters, including a copy of the approved consent form(s)
- All correspondence relating to this study between the sponsor, [redacted] and the investigational site, Institutional Review Board, Study Monitor and FDA
- CVs and licenses for all study personnel
- Site personnel signatures and responsibility lists
- Investigational device inventory log, including date, quantity, and lot numbers of product shipped and received.

18.4. Sponsor Reports

The sponsor (or delegate CRO) is required to prepare and submit the following reports:

- UADE evaluations to FDA, IRB and investigator – 10 working days of notice
- Withdrawal of IRB approval to FDA, other IRB and investigator – 5 working days
- Withdrawal of FDA approval to IRB and investigator – 5 working days

- Current investigator list to FDA every 6 months
- Progress reports at least annually to FDA and IRBs
- Device returns or recalls to FDA and IRB - 30 days
- Notice of significant risk study completion to FDA - 30 days
- Final report to FDA, IRB and investigator - 6 months
- Notify FDA of study termination – 30 working days
- Failure to obtain informed consent to FDA - 5 working days of notice

18.5. Record Retention

All subject study records, correspondence files, all supporting study documentation, and reports must remain on file at the investigational site, at the sponsor, delegate CRO and contractors for a minimum of two (2) years after the completion/termination of this study or when the files are no longer needed to support a USA marketing application, whichever is later.

The investigator must contact the sponsor before destroying or archiving off-site any records and reports pertaining to this trial to ensure that they no longer need to be retained on site. The sponsor must be contacted if the investigator plans to terminate his association with the investigational site to ensure that arrangements for a new investigator are made prior to the investigator's departure.

18.6. Early Termination or Suspension of Study

The sponsor of this trial has the sole responsibility for any decision to suspend or terminate this study. Notice of any decision to suspend or terminate the trial will be immediately forwarded by express delivery to the FDA, sponsor, [redacted]., investigators, Study Monitors and Institutional Review Boards.

The sponsor retains the right to suspend or terminate the participation of a study investigator for non-compliance to this investigational plan, the investigator Agreement, inability to successfully implement this investigational plan, falsification of data, or any other breech of federal regulations, ethics or scientific principles.

An investigator may terminate participation in this study for due cause with prior notification to the sponsor and [redacted] She/he will also notify the IRB of study termination. The sponsor will notify the FDA of the investigator's intent within five (5) working days of receiving notification. In the event of study termination by the investigator, she/he is still obligated to continue to follow all study subjects as prescribed by this investigational plan and to adhere to all other investigational plan requirements, including data collection, adverse event notification and to allow monitoring visits by the Study Monitor.

18.7. Publication Policy

It is expected that the results of this study will be presented at scientific meetings and/or be published in peer-reviewed scientific journals. HyperBranch Medical Technology, Inc. retains the rights to all data and information generated by this study. HyperBranch Medical Technology, Inc. retains the right to review and edit all proposed manuscripts, abstracts, publications, and presentations based upon this study or its results prior to submittal to any organization, business, agency, person, publisher, society, or other entity.

19. REGULATORY COMPLIANCE

The investigator and all research staff participating in this investigation are expected to adhere to this investigational plan, applicable privacy laws, any approval requirements imposed by the IRB or FDA, as well as all other pertinent laws and regulations. The investigator has the further responsibility of adherence to the investigator Agreement and to maintain the required documents in the eTMF.

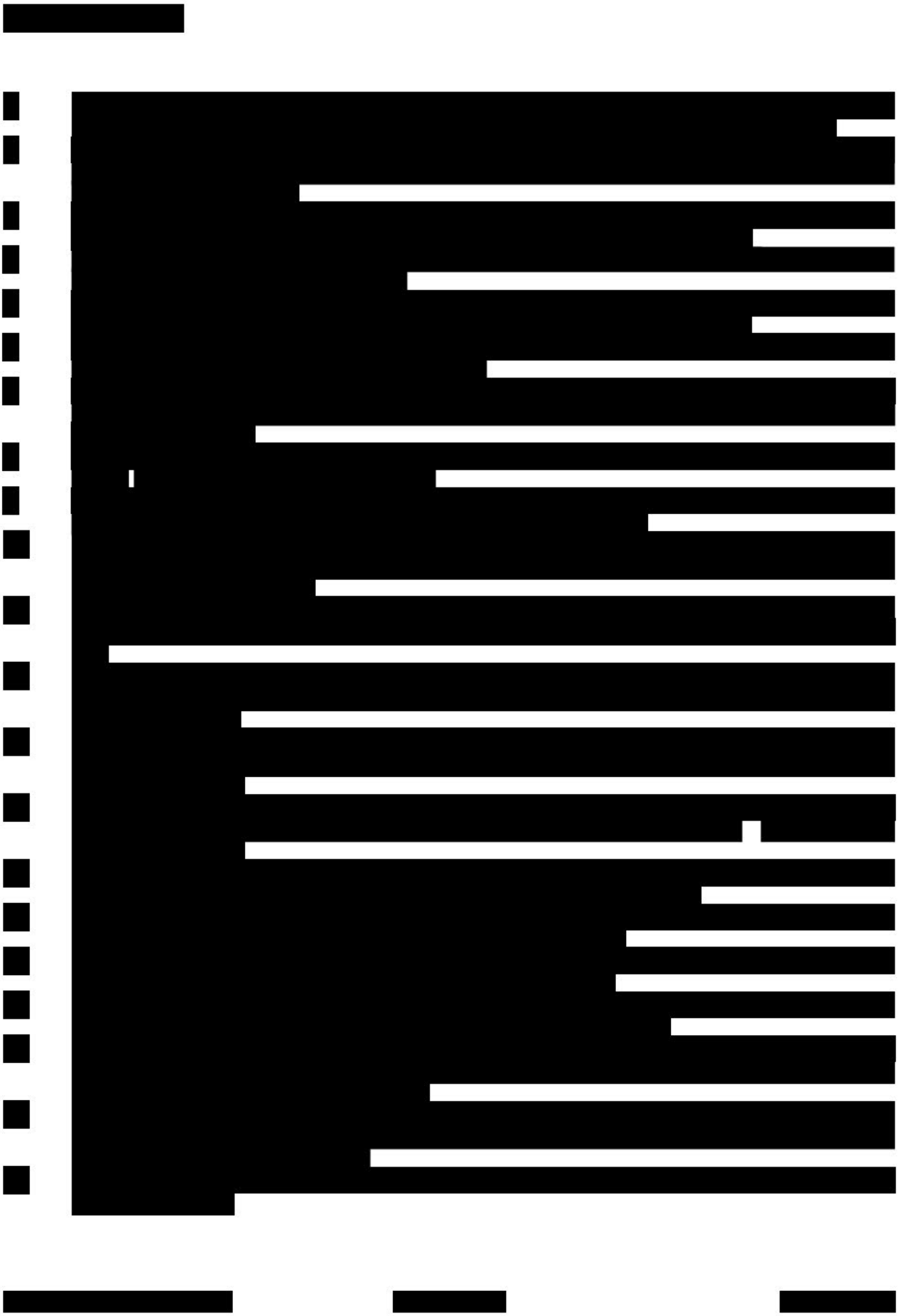
19.1. Institutional Review Board (IRB) Approval

Subjects must not be enrolled into this study by the investigator until authority to do so has been granted by the site's authorized IRB [redacted] A copy of all IRB approval letters and correspondence must be maintained in the eTMF.

19.2. Investigator Agreement and Financial Disclosure

A study-specific investigator agreement (may be part of the clinical trial agreement) will be provided by the sponsor for signature. The investigator agreement must be executed prior to the investigator's enrollment of patients. This document will signify the investigator's agreement to comply with this investigational plan as well as all pertinent regulations and laws.

Prior to study participation, the investigator is required to complete a financial disclosure form from Fortrea Inc., which describes any financial arrangements with the sponsor. This information is to be updated as appropriate for one year after study completion.



[redacted]