CLINICAL INVESTIGATION PLAN (PROTOCOL)

PEARLE: Prospective, Single Arm, Pivotal Clinical Trial Designed to Assess the Safety and Effectiveness of the Jada™ System In Treating Primary Postpartum Hemorrhage

Short title:	PEARLE Study		
Test device:	Jada System		
Clinical study phase:	Pivotal	Version Date:	25FEB2019
Study no.:	PPH-02	Version No.:	CIP-01 v2.6
Sponsor:	Alydia Health 3475 Edison Way, Suite J Menlo Park, California 94025 USA		
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This study shall be conducted under Institutional Review Board approval and in compliance with United States (U.S.) Food and Drug Administration (FDA) regulations, ISO 14155 (2011), the ethical principles that have their origin in the Declaration of Helsinki and all applicable privacy requirements.

Investigator Certification

Prior to participation in the PEARLE Study as an Investigator, I understand that I must obtain written approval from my Institutional Review Board (IRB).

As an Investigator, I must also:

1. Conduct the study in accordance with the study protocol, United States (U.S.) Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations (CFR) Parts 812, 50, 54, & 56), ISO 14155, the ethical principles that have their origin in the Declaration of Helsinki and all applicable privacy requirements.
2. Complete required study training prior to study participation.
3. Ensure that the study is not commenced until IRB approval has been obtained.
4. Ensure that written informed consent is obtained from each subject prior to enrollment into the study, using the most recently IRB-approved subject Informed Consent Form.
5. Provide all required data and reports and agree to allow source document verification of study data with subject's medical records.
6. Allow Sponsor personnel and its designees, as well as U.S. FDA representatives and representatives from other public health agencies, to inspect and copy any documents pertaining to this clinical investigation.

Investigator Signature
I have read and understand the contents of the PEARLE Study protocol (CIP-01 v2.6) and agree to abide by the requirements set forth in this document.

Signature	Date
Printed name	Institution

Revision History

Version Number	Description of Change	Effective Date
Version 1	Initial release. Note: Initial protocol numbered CIV-PIVOTAL-1.0. Version 030716/S2.	7 April 2016
Version 1.1	Change to informed consent section to allow informed consent to be obtained after the onset of labor. Note: Protocol revision numbered CIV-PIVOTAL-1.1.	20 December 2016
Version 2	Protocol rewrite to change the primary endpoint and statistical analysis plan. Editorial and administrative changes also made. Note: Protocol revision numbering changed to PPH-02 version 2.	24 February 2017
Version 2.1	Minor edits to protocol to clarify primary effectiveness endpoint, add a secondary endpoint for maternal morbidity, clarify the definition of time to hemorrhage cessation, and clarify the statistics section. Edits made in response to FDA Study Design Considerations identified in February 24, 2017 approval letter for S006.	11 April 2017
Version 2.2	Minor edits to protocol to clarify statistical analysis in section 5.3.1. Edits made in response to FDA Study Design Considerations identified in the IDE Approval Letter dated April 11, 2017 for S007.	7 July 2017
Version 2.3	Minor edits to protocol to clarify statistical analysis and sample size in Section 5.3. Edits made in response to FDA Study Design Considerations identified in the IDE Approval Letter dated July 7, 2017 for S008. Additional minor edits made to cover sheet and Section 9 for study consistency.	6 November 2017
Version 2.4	Minor edits to protocol to clarify statistical analysis and sample size in Section 5.3. Edits made in response to FDA Study Design Considerations identified in the IDE Approval Letter dated November 6, 2017 for S010.	19 December 2017
Version 2.5	Edits to clarify inclusion and exclusion criteria and the schedule of assessments. Added the consent bracelet as an identifier for consented subjects. Eliminated OUS sites and increased number of sites to 12. Edits to the risk	17 July 2018

	and potential benefits sections and to the name of the Device. Updated the contact information and other minor corrections. A section on training was included. The secondary endpoint of time to PPH control was refined and the steps of Device use were clarified.	
Version 2.6	Updated name of Sponsor to Alydia Health and name of product to Jada System. Updated picture of consent bracelet. Updated maximum number of sites to 20 in the U.S. or O.U.S. Revised secondary endpoints. Revised one inclusion and one exclusion criterion. Revised poolability section. Added study poster as optional recruitment tool.	25FEB2019

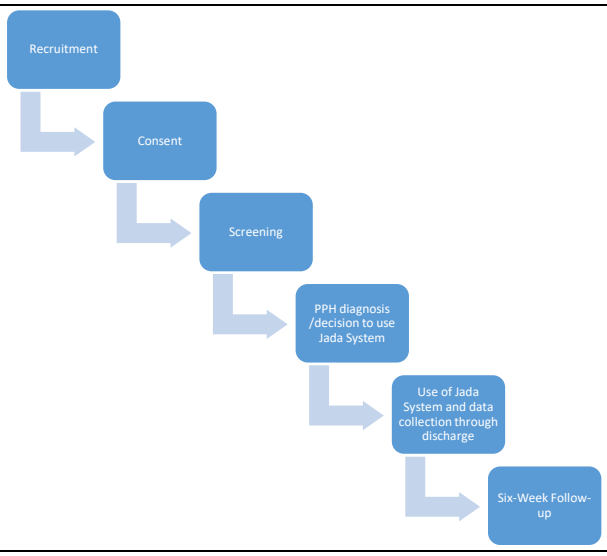
List of abbreviations

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
AMTSL	Active Management of the Third Stage of Labor
CBC	Complete blood count
CRF	Case report form
FDA	Food and Drug Administration
FIH	First-in-Human
GCP	Good clinical practices
GMP	Good manufacturing practices
ICF	Informed consent form
ICU	Intensive care unit
IDE	Investigational device exception
IFU	Instructions for use
IRB	Institutional review board
ISO	International Standards Organization
IV	Intravenous
ITT	Intent to Treat
O.U.S.	Outside the United States
PPH	Postpartum hemorrhage
SADE	Serious adverse device event
SAE	Serious adverse event
SAS	Statistical Analysis System
UADE	Unanticipated adverse device effect
U.S.	United States
WHO	World Health Organization

Table of Contents

1.0 Study Summary

Title:	Prospective, Single Arm, Pivotal Clinical Trial Designed to Assess the Safety and Effectiveness of the Jada System In Treating Primary Postpartum Hemorrhage ("PPH")
Short Title:	PEARLE Study
Design:	Prospective, single-arm, literature-controlled, multi-center study
Purpose:	Evaluate the safety and effectiveness of the Jada System in the control and reduction of primary postpartum hemorrhage.
Inclusion Criteria:	1. Adult Female, 18 years of age or older at time of consent. 2. Able to understand and provide informed consent to participate in the study. 3. Diagnosis of PPH with suspected atony within 24 hours after vaginal or c-section delivery. 4. EBL, to be determined when investigator is ready to have the Jada peel pack opened: Vaginal delivery: 500 – 1500 ml EBL or C-section delivery: 1000 – 1500 ml EBL 5. Failed first-line intervention of uterotonics and uterine massage/bimanual uterine massage to stop bleeding. *Note: Uterotonic administration may continue concomitant with and post Jada use, as long as such use does not exceed the maximum dose of the drug.*
Exclusion Criteria:	1. EBL >1500ml, to be determined when investigator is ready to have the Jada peel pack opened. 2. Delivery at a gestational age < 34 weeks. 3. For C-sections: Cervix < 3 cm dilated before use of Jada. 4. PPH that the investigator determines to require more aggressive treatment, including any of the following: a) hysterectomy; b) b-lynch suture; c) uterine artery embolization or ligation; d) hypogastric ligation. 5. Known uterine anomaly. 6. Ongoing intrauterine pregnancy. 7. Placenta abnormality including any of the following: a) known placenta accreta; b) retained placenta with known risk factors for placenta accreta (e.g. history of prior uterine surgery, including prior c-section and placenta previa); c) retained placenta without easy manual removal. 8. Known uterine rupture. 9. Unresolved uterine inversion. 10. Subject has undergone intrauterine balloon therapy or uterine packing for tamponade treatment of this PPH prior to use of the Jada System. 11. Current cervical cancer. 12. Current purulent infection of vagina, cervix, uterus. 13. Diagnosis of coagulopathy.

Duration of Study:	It is expected to take approximately 12-18 months to enroll, treat, and follow-up all 107 subjects.
Primary Safety Endpoint:	Incidence, severity and seriousness of device-related Adverse Events (AEs).
Primary Effectiveness Endpoint:	Control of postpartum hemorrhage, defined as the avoidance of non-surgical, second-line or surgical intervention to control uterine hemorrhage after the use of the Jada System per the Instructions for Use. Non-surgical, second line procedures include uterine balloon therapy, uterine packing, or uterine artery embolization. Surgical intervention includes procedures such as uterine arterial ligation, uterine compression sutures or hysterectomy. Note: Continuation of the administration of uterotonics concomitant with and post Jada System use is standard of care and does not constitute failure of the primary effectiveness endpoint.
Statistical Analysis Plan Summary:	The primary effectiveness objective of this Pivotal Study is to show that the observed Treatment Success Rate is not worse than the rate reported in the literature. The study is considered a success when the lower bound of the two-sided Exact Clopper-Pearson mid-p 95% Confidence Interval for the Study Treatment Success is greater than or equal to 73.4%.
Study Flowchart:	

2.0 Postpartum Hemorrhage Background

2.1 Definition and Prevalence of Postpartum Hemorrhage

Postpartum hemorrhage (PPH), or excessive blood loss after childbirth, is the leading cause of maternal mortality. PPH is responsible for over a quarter of maternal deaths worldwide.[1] In Africa and Asia, where most maternal deaths occur, PPH accounts for more than 30% of all maternal deaths.[3] It is estimated that PPH afflicts 6% of women giving birth.[2] Africa has the highest rate of PPH, with a

prevalence of 10.5% of women giving birth.[2] Even developed countries are challenged by this life-threatening complication of childbirth, causing 10.6% of maternal deaths in the United Kingdom, and 12% of maternal deaths in the United States.[4]

Although death is the most tragic event reported in obstetrics, severe maternal morbidity related to PPH such as surgical interventions including hysterectomy, disseminated intravascular coagulopathy, transfusions, and Intensive Care Unit (ICU) admissions, are more common than death.[4-6] PPH can also be a cause of long-term severe morbidity, and approximately 12% of women who survive PPH will have severe anemia.[12] Additionally, women who survive an event of severe PPH are significantly more likely to die in the year following the event.[34]

Primary PPH, which is PPH that occurs within 24 hours after the birth of the baby, is the most common form of major obstetric hemorrhage. The most commonly accepted definition for primary PPH is the loss of 500 ml or more of blood from the genital tract within 24 hours after the birth of a baby. Severe primary PPH is commonly defined as loss of more than 1500 ml of blood within 24 hours after the birth of a baby. Alternative standards for defining and diagnosing PPH include changes in hematocrit, rapidity of blood loss and changes in vital signs.[4,7-10]

It is difficult to predict who will develop PPH because most women who have PPH have no risk factors. Many deaths due to PPH could be prevented with timely diagnosis and intervention. A blood loss of more than 1500 ml is usually considered life threatening and triggers a full complement of emergency measures to achieve resuscitation and hemostasis. It would seem appropriate that PPH protocols activate at much lower thresholds to prevent blood loss that requires drastic measures or becomes life threatening.

2.2 Causes of Postpartum Hemorrhage

PPH may be caused by uterine atony, injury to the birth canal, retained placenta, and coagulopathy, among other etiologies.

Uterine atony, or suboptimal uterine contractions after childbirth, is the most prevalent cause, involved in 75% of primary PPH cases.[8] Normally after delivery, the smooth muscle fibers of the uterus contract and constrict the blood vessels that serve the placental bed. If the uterus does not properly contract after delivery, these blood vessels are exposed to the cavity of the uterus, leading to uterine PPH. Atony may result from prolonged labor, prolonged use of uterotonic stimulants, over-distention of the uterus, infection, placental abnormalities, or bladder distention, but the majority (80%) of women with PPH due to uterine atony will have no risk factors.[11]

2.3 Currently Available Treatment and Prevention Strategies

Organizations and associations including the World Health Organization (WHO), International Confederation of Midwives, International Federation of Gynecologists and Obstetricians, American College of Obstetricians and Gynecologists, and Royal College of Obstetricians and Gynaecologists have released guidelines for PPH prevention and management.[13,14,15-18]

The WHO guideline for the Active Management of the Third Stage of Labor (AMTSL) is recommended for all patients in order to prevent PPH. The AMTSL guideline recommends the use of oxytocin, a uterotonic, for the prevention of PPH during the third stage of labor for all births. In settings where skilled birth attendants are available, controlled cord traction may be used in vaginal births. Postpartum abdominal uterine tone assessment is recommended to identify uterine atony prior to the occurrence of PPH.

If AMTSL does not prevent the occurrence of PPH, initial management guidelines include identifying the source of the PPH and implementing appropriate interventions based on the etiology. Manual removal of the placenta is indicated for a retained placenta; vaginal and vulvar lacerations need to be repaired in parallel to treating uterine bleeding. Interventions to treat PPH due to atony generally proceed from less to more invasive. Most guidelines first recommend the use of additional uterotonic agents, which cause the uterus to contract. These medications include oxytocin (Pitocin®), prostaglandin E1/misoprostol (Cytotec®), methylergonovine (Methergine®), prostaglandin 15-methyl F2α/carboprost tromethamine (Hemabate®), and prostaglandin E2/dinoprostone (Cervidil® or Prepidil®).[13-16,24] All of these medications are available in the United States. Only oxytocin, methylergonovine, and carboprost tromethamine are approved by the US FDA specifically for PPH management.

External uterine massage and bimanual uterine massage may also be used as first-line conservative treatments in conjunction with uterotonics. These techniques encourage uterine contractions that counteract atony and assist with expulsion of retained placenta or clots. Initial PPH management also includes intravenous (IV) fluid therapy to expand volume and give access for parenteral medication.

Some institutions use tamponade methods as a second line therapy if the uterotonics fail to take effect. These methods include uterine packing, the use of multiple Foley catheters or condom catheters (not FDA cleared for the treatment of PPH), or the use of a balloon tamponade device cleared specifically for PPH. These methods create tamponade through compression of blood vessels, leading to the control of hemorrhage. Although tamponade may occur, the expansion caused by the packing materials or balloon may interfere with the normal physiologic uterine retraction and constriction of placental bed vasculature that normally follows childbirth. Thus, the uterine musculature can move back to its atonic state, causing blood loss to recur.

If initial conservative management for PPH of uterine origin fails or is slow to take effect, invasive surgical procedures are indicated. Surgical options include uterine curettage to ensure the removal of any residual products of conception, uterine de-vascularization procedures, uterine compression sutures, and, as a last resort, hysterectomy.[13-16] Surgeries can increase the risk of infection, maternal morbidity and other complications, and they may eliminate or adversely affect future fertility and pregnancy.

3.0 Device Description

3.1 Intended Use

The Jada System is intended to provide control or reduction of postpartum uterine bleeding when conservative management is warranted.

3.2 Jada System Description

The Jada System is a 40 cm long intrauterine device made of silicone. The device consists of an elliptical intrauterine loop collared by a donut shaped vacuum seal and a connecting tube that terminates in a male tubing slip vacuum port attachment (see Figure 1). The loop has twenty pores directed towards the interior of the loop that are partially covered by a shield, which creates a channel to prevent plugging with tissue or clots. The connecting tube has a seal port valve that can be attached to a syringe, allowing the vacuum seal to be filled with sterile IV fluid. The various portions of the device are soft enough to reduce the chance of injury or perforation, but firm enough for easy insertion and smooth function without kinking. The Jada is designed to attach to sterile tubing and a regulated vacuum source with an in-line graduated vacuum collection canister.

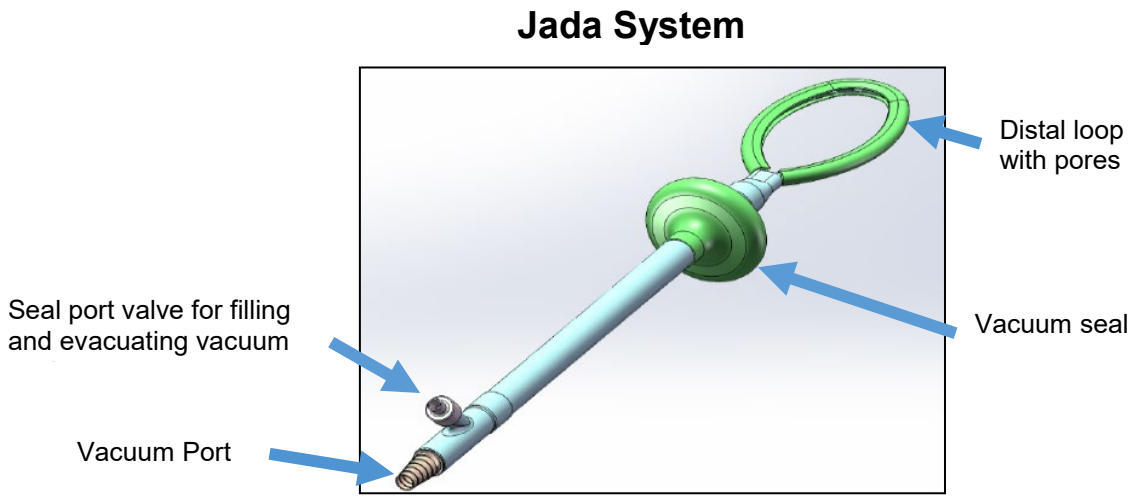


Figure 1: Jada System

3.3 Jada Overview

The Jada System is inserted into a woman's uterus transvaginally in women who have vaginal deliveries and trans-abdominally or transvaginally in women who have Cesarean sections (depending on whether PPH is diagnosed before or after the hysterotomy is closed). The shielded loop of perforated tubing is introduced in the uterine cavity. The vacuum seal is positioned in the upper vagina, against the external cervical os. The male tubing slip vacuum port attachment can then be connected to sterile tubing, regulated vacuum source, and graduated vacuum collection canister. See Figure 2.

When the vacuum seal is filled with sterile IV fluid and the vacuum is turned on, the vacuum seal ensures that a vacuum can be created in the uterine cavity.

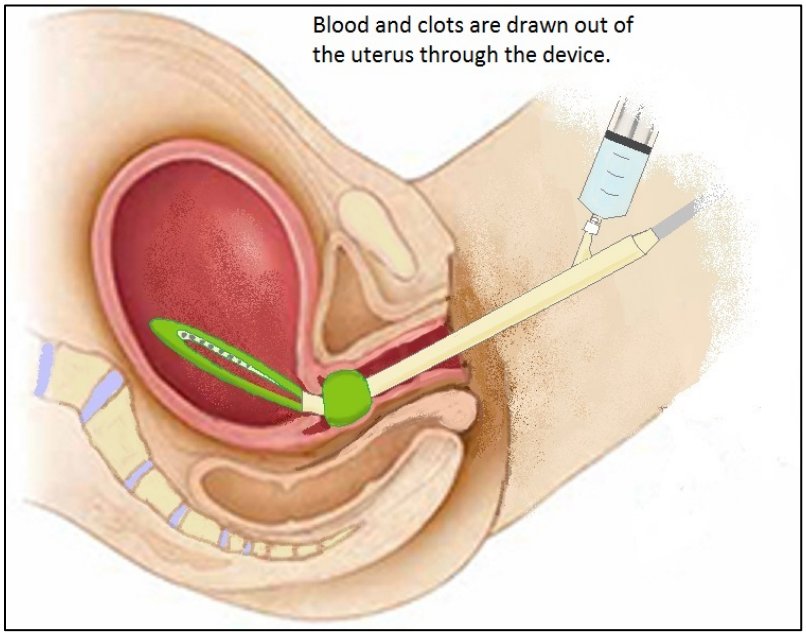


Figure 2: Jada, properly positioned, prior to turning the vacuum on.

Once the vacuum is turned on, residual blood and clots from the PPH are suctioned through the vacuum tube. After the residual materials are suctioned, the continued application of this vacuum force within the uterine cavity will cause the uterus to collapse upon itself, Figure 3. See Section 6.5 for additional detail on the use of the Jada System. See the Instructions for Use for additional instruction on the use of the device.

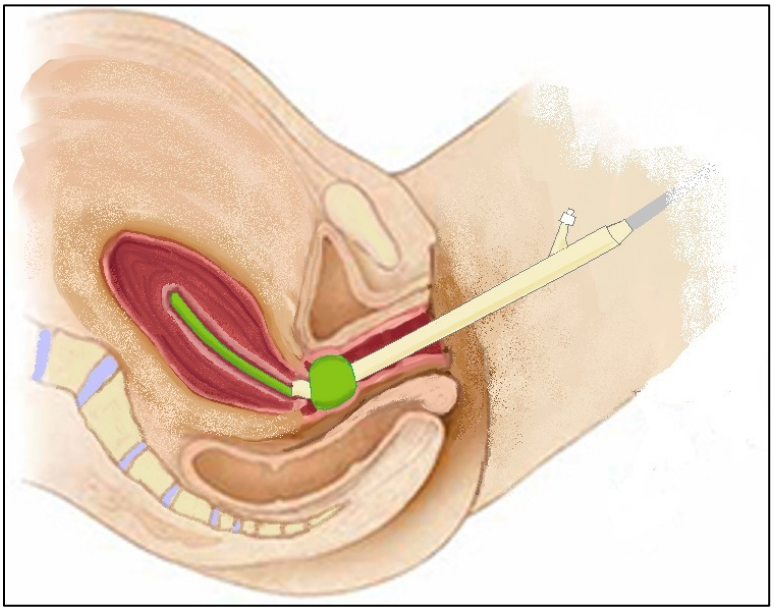


Figure 3: Negative pressure within the uterine cavity causing the uterus to collapse upon itself.

3.3.1 Mechanism of Action

The uterus is composed of a unique interlacing network of muscle fibers. Blood vessels that supply the placental bed pass through this latticework of uterine muscle, Figure 4. After delivery of the infant, when the placenta separates from the uterine wall, these fibers contract causing uterine retraction and constriction of these blood vessels. It is a physiologically efficient method for hemostasis. If the uterine muscle fibers do not contract as normal, PPH may occur.

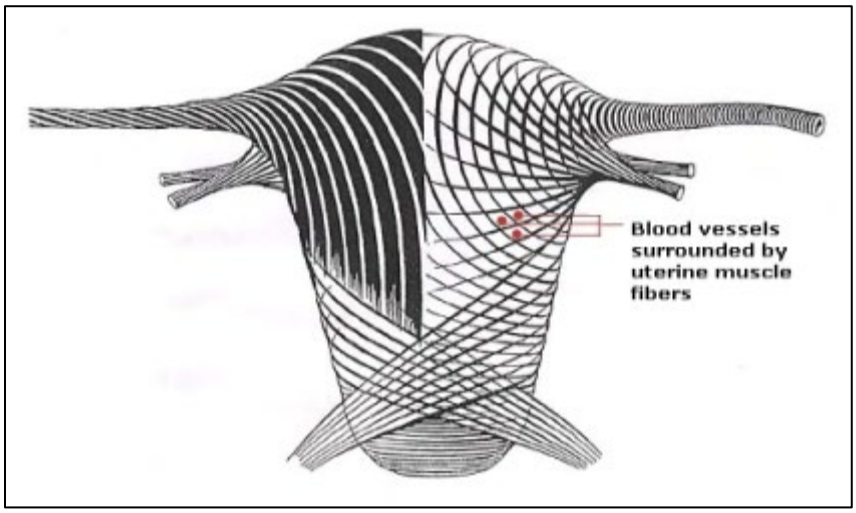


Figure 4: Muscular latticework basket weave diagram of the uterus

The Jada System facilitates an assisted physiologic restoration of normal postpartum uterine mechanisms. Jada establishes negative pressure within the atonic postpartum uterus, causing the uterus to collapse into and onto itself. The inner uterine walls press against one another, producing an immediate tamponade of the uterine cavity that causes rapid hemostasis. In this hemostatic state, the uterus is also stimulated to contract, and can retract down to its normal postpartum size and status without obstruction to optimal postpartum architecture. Additionally, by generating tamponade and stimulating contractions without distension of the uterus, there is no risk of rupturing the scarred or sutured uterus when prior surgery or current Cesarean section is a risk factor.

3.4 Prior Bench and Animal Testing

Benchtop, safety, and animal studies have been performed to verify the functionality and performance of the Jada System.

3.4.1 Benchtop Studies

Functionality Verification was conducted to verify Jada is built to the specifications in the Manufacturing and Functional Specifications documents. The shape integrity of the Jada was tested to verify that it would not collapse or break when being subjected to a vacuum of twice the recommended use. The Flow Rate test verified that the Jada System facilitated a flow rate of at least 400 ml/min when an internal vacuum of 70 mm Hg was applied. The connecting tube was tested to verify that it would facilitate a connection to a hospital-supplied collection vessel and vacuum line. The vacuum seal was tested to verify that it can withstand over-inflation to one and a half times its recommended size. The device was also tested in the presence of heavily clotted pig blood to verify that it can function within the presence of blood clots.

3.4.2 Safety Studies

Table 1: Safety Studies

Test Category	Tests Performed	Testing Performed per Standard		Pass/Fail
Sterilization Validation	Tests performed by SteriPro (through Sterigenics) to substantiate a 25 kGy dose and validate the effectiveness of Gamma batch release for sterilization of the Jada System.	ANSI/AAMI/ISO 11137-2		Pass
Packaging and Shelf Life Validation	Tests performed by Westpak to validate the packaging can withstand shipping & handling, various climates, and support a shelf life of 4 years.	Accelerated Aging	ASTM F1980-07	Pass
		Climatic Conditioning	ASTM D4332-14	
		Initial Manual Handling	ASTM D5276-98	
		Vehicle Stacking	ASTM D642-00	
		Loose Load Vibration	ASTM D999-08	
		Vehicle Vibration	ASTM D4728-06	
		Final Manual Handling	ASTM D5276-98	
		Gross Leak Detection (Bubble)	ASTM F2096-11	
		Seal Strength (Peel)	ASTM F88/F88M-09	
Biocompatibility Validation	Tests performed by NAMSA to validate the materials of the Jada System are biocompatible and nonirritating.	Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract)	ISO 10993-5	Pass
		ISO Maximization Sensitization Study—Extract	ISO 10993-10	

		ISO Vaginal Irritation Study	ISO 10993-10	
		Acute Systemic Toxicity – Extract	ISO 10993-11	

3.4.3 Animal Studies

There is no adequate animal model that duplicates PPH that is observed in humans; however, animal studies were conducted to test technical aspects of the device. In the animal testing that was performed, Jada was evaluated in porcine and ovine bladders. Testing supported the theory that vacuum could contract a sealed organ, thus, could theoretically reduce bleeding.

3.5 First in Human Study Feasibility Study

A First-in-Human (FIH) feasibility investigational study with Ethics Committee oversight was conducted at two clinical sites in Indonesia. The purpose of the study was to demonstrate the placement, function, and operation of the Jada System to meet its intended use to reduce or control PPH.

Ten women were enrolled between July 2014 and February 2015. None of the subjects presented with a retained placenta, uterine lacerations, uterine scarring, or for any conditions other than atonic post-partum hemorrhage. The Jada was successfully placed and activated in all ten subjects. A vacuum force of 70 mmHg - 90 mmHg was used for treatment. The average time from placement of the Jada to removal was 152.0 ± 111.7 minutes (range 60-390 minutes).

Bleeding was controlled within two minutes for all ten subjects. Evaluation of the primary clinical data safety endpoints determined that: 1) no safety issues were observed relative to the placement, insertion, or removal of the Jada, 2) there were no complications related to delayed arrest of blood loss, 3) there was no damage to the uterus, cervix, or vagina, and 4) no uterine inversion or folding events were observed during the Jada procedure.

3.6 Risk Analysis

A risk analysis has been performed in accordance with ISO 14971 for the Jada System. The safety and risk profile of Jada have been further explored and substantiated in the FIH Feasibility study. Based on the risk analysis and FIH study results, there is no expectation or current evidence to suggest that the risks will be increased with Jada as compared to commercially available tamponade devices. Jada has the potential to work more quickly to treat PPH with less side effects. Thus, the potential benefits of the device are expected to outweigh the risks.

3.6.1 Potential Risks to Study Subjects

Risks due to use of the Jada System and recommended actions are described below.

Bleeding: Bleeding may be observed due to mechanical injury to blood vessels or tissue in the area where the Jada System is inserted and deployed. If bleeding due to the device is suspected, the Investigator should remove the device and repair the injured area, as indicated.

Pain / Cramping: Subjects may experience pain or discomfort during the intervention and possibly post-intervention for a short duration of time. Non-steroidal anti-inflammatory or other analgesic medication may be provided for relief.

Perforation of or injury to uterus, fallopian tubes, and adjacent structures: Perforation or injury to the vagina, uterus, fallopian tubes, or adjacent tissue is a possible risk during insertion of any foreign object into the uterus. If perforation due to Jada is suspected, the Investigator should remove the device and evaluate the subject for further treatment.

Infection: Infection is a possible complication following the placement of any foreign object into the uterus. If infection due to Jada is suspected, the Investigator should evaluate the subject and provide treatment (e.g. antibiotics) as indicated.

Failure to stop PPH: Patient monitoring is an integral part of managing PPH. Signs of deteriorating or non-improving condition should lead to a more aggressive treatment of uterine bleeding. There is a risk that the use of Jada will not achieve its intended goal of stopping the PPH; therefore, other treatments may be required. It is noted that while Jada is designed to stop PPH, it does not treat the effects of blood loss, so is not a replacement for fluid resuscitation and should be used along with proper treatment for blood loss (i.e., transfusions).

Unknown Risks: As with any investigational device, there may be risks that are currently unknown or unanticipated.

Inconvenience: There may be added inconvenience to the study subject for participating in the study. The potential for inconvenience is thought to be very minimal for this study as there are no additional requirements for visits outside of standard of care for study subjects.

Loss of confidentiality: There may be loss of confidentiality of a subject's study-related Protected Health Information (PHI) due to participation in the study. The investigational site and study sponsor will do everything possible to limit this risk by storing research records in secure areas and limited access to these records.

3.6.2 Risk Detection and Mitigation

Several precautionary measures have been built into the investigational protocol to protect the study subjects and to detect any potential adverse effects.

- Inclusion/exclusion criteria were identified to help assure that any study subject who may be at increased risk for an adverse event is not enrolled in the study. Also, study subjects will be observed during and following the intervention to assure that any acute adverse events are detected in a timely manner so that proper medical treatment can be initiated. Subjects will be followed at 6 weeks following the intervention in order to capture other possible intervention-related adverse events that do not manifest immediately.

3.7 Potential Benefits of the Intervention

The potential clinical benefits include:

- Treatment that mirrors the normal postpartum physiology of the body, which may result in a more rapid control of hemorrhage.
- Less invasive device than commonly used surgical interventions.
- Avoidance of the use of some uterotonics or shortening duration of use that have more systemic adverse effects.
- No outward physical pressure on a scarred or sutured uterus unlike other commonly used tamponade devices.
- Ability to measure blood loss after initiation of treatment due to the use of the in-line graduated canister.

If Jada proves effective and safe in treating PPH, there are also larger benefits expected for global health care systems:

- Control PPH rapidly, resulting in reduced costs
- Decrease physician time for the intervention and monitoring
- Reduce use of operating rooms or ICUs and decrease length of hospital stays
- Lower cost product than currently available balloon tamponade devices, allowing Jada to significantly benefit emerging countries.

4.0 Study Objectives

4.1 Purpose of the Study

The purpose of this Pivotal Study is to evaluate the safety and effectiveness of the Jada System in the control and reduction of primary PPH.

4.2 Study Endpoints

4.2.1 Primary Effectiveness Endpoint

Control of postpartum hemorrhage, defined as the avoidance of non-surgical, second line or surgical intervention to control uterine hemorrhage after the use of the Jada System per the Instructions for Use.

Non-surgical, second line procedures include uterine balloon therapy, uterine packing, or uterine artery embolization. Surgical intervention includes procedures such as uterine arterial ligation, uterine compression sutures or hysterectomy.

Note: Continuation of the administration of uterotonics concomitant with and post Jada use is standard of care as long as such use does not exceed the maximum dose of the drug and does not constitute failure of the primary effectiveness endpoint.

4.2.2 Primary Safety Endpoint

Safety: Incidence, severity and seriousness of device-related Adverse Events.

4.2.3 Secondary Endpoints

1. Time to control hemorrhage, defined as the time from turning on the vacuum source until the time the *first* of any of the following occurs:
    - there is no blood being collected in the tubing or canister, or
    - the blood loss is observed as leveled off in the canister, or
    - blood loss is at a rate of < 500 ml in 24 hours.
2. Rate of surgical intervention required to control PPH after Jada use.
3. Rate of non-surgical intervention required to control PPH after Jada use.
4. Assessment of device usability as reported by the clinician using a dedicated data collection form.
5. Rate of blood product transfusion required after Jada use, and number of transfusion units when administered.

4.3 Overall Study Success

A thorough review of all known publications reporting on the use of the Bakri Balloon to treat PPH was performed. A meta-analysis methodology was used to aggregate the studies and provide a numerical estimate of the overall Treatment Success Rate. Based on a random effects model, the estimated pooled proportion of subjects who reached hemostasis (i.e., control of uterine hemorrhaging)

following Bakri Balloon (or equivalent) treatments was 82.0% (95% CI: 73.4% to 89.2%). See the Clinical Evaluation Report (G150265, Attachment H, pages 337-382).

The primary effectiveness objective of this Pivotal Study is to show that the observed Treatment Success Rate is not worse that the rate reported in the literature. The study is considered a success when the lower bound of the two-sided Exact Clopper-Pearson mid-p 95% Confidence Interval for the Study Treatment Success is greater than or equal to 73.4%.

5.0 Study Design

5.1 Overview

This study design is prospective, single-arm, literature-controlled, and multi-center. Since this is a literature-controlled study, meta-analysis methodology was used to establish target endpoints which will demonstrate the safety and effectiveness of the Jada System. See the Clinical Evaluation Report (G150265, Attachment H, pages 337-382).

5.2 Site Selection

The study will be conducted at no less than five and no more than twenty sites, which may include both U.S. and O.U.S sites. Site selection will be conducted in accordance with sponsor Standard Operating Procedures. If O.U.S. sites are enrolled, they will comply with FDA's February 2018 guidance titled "Acceptance of Clinical Data to Support Medical Device Applications and Submissions, Frequently Asked Questions, Guidance for Industry and Food and Drug Administration Staff."

5.3 Study Training

The training program for sites participating in the study will include the following:

1. Didactic training;
2. Hands-on training;
3. Investigator Training Certification Quiz;
4. Procedure Guide Poster.

All investigators will be required to undergo both hands-on training and didactic training and successfully pass the Investigator Training Certification Quiz, which will be administered after the training is complete. The trainee will be considered to have passed the Investigator Training Certification Quiz once all questions have been answered correctly, which may involve a retake of the quiz.

Didactic Training

The didactic training will be performed by Alydia Health staff that are qualified to perform the training. The didactic training will be performed either in person or via videoconference.

Hands-On Training

Hands-on training will be provided by qualified persons who are familiar with the Jada System and PPH. Trainees will use demonstration samples of the Jada System in bench models built by Alydia Health to simulate anatomy in both transvaginal placement and transabdominal placement. This clinical experience simulation is intended to ensure operators master the Jada procedural steps prior to live study subject procedures. Trainees will be required to independently and individually demonstrate successful deployment of a minimum of one Jada System in each model before they are approved to use the device. Successful deployment is defined as following all of the procedural steps in

accordance with the Instructions for Use without prompting or correction by the trainer in the transvaginal model, and successfully completing the device positioning steps in the transabdominal model also without prompting or correction by the trainer. This may require more than one deployment attempt.

Procedure Guide Poster
Finally, as a post-training reminder and reference, each site is provided with a Procedure Guide Poster, which serves as a quick reference guide for the procedure.

5.4 Study Population

5.4.1 Number of Subjects and Sample Size Calculation

Up to 107 subjects will be enrolled in the study to ensure that 96 subjects are available for the analysis of the primary effectiveness endpoint. Sites are expected to enroll a minimum of 5 subjects. Site enrollment will be capped at 30% of the total expected enrollment, such that no site will enroll more than 32 subjects.

The study is powered to show that the Treatment Success Rate among the Jada subjects is not inferior to the Treatment Success Rate derived from a meta-analysis performed using all known publications reporting on the use of the Bakri Balloon (and equivalents) to treat PPH.

Based on a random effects model used in the meta-analysis, the estimated pooled proportion of subjects who reached hemostasis (i.e., control of uterine hemorrhaging) following Bakri Balloon treatments was 82.0% (95% CI: 73.4% to 89.2%). See the Clinical Evaluation Report (G150265, Attachment H, pages 337-382).

Non-inferiority will be achieved when the lower bound of the Exact Clopper-Pearson mid-p 95% Confidence Interval for the Study Treatment Success Rate is greater than or equal to the lower bound of the 95% Confidence Interval of the Treatment Success Rate derived in the meta-analysis, or 73.4%. That is:

Statistical Hypothesis:	H_0: $\pi_{Jada} \leq \pi_{Literature\ CI\ LB}$ vs H_1: $\pi_{Jada} > \pi_{Literature\ CI\ LB}$ where π_{Jada} is the Treatment Success Rate for Jada treated subjects and $\pi_{Literature\ CI\ LB}$ is the lower bound of the 95% Confidence Interval for the Treatment Success Rate derived from the meta-analysis of the Bakri Balloon Literature.
Statistical Methodology:	Confidence Interval for π_{Jada}
Expected π_{Jada}:	0.82
Half-width of 95% CI:	0.086
Confidence Level:	Two-sided 95%
Minimum Sample Size:	n = 96 evaluable subjects
Statistical Power:	0.806 that the lower bound will be greater than or equal to 0.734

With 96 evaluable subjects, there is an 80.6% probability that the lower bound of the observed Exact Clopper-Pearson mid-p two-sided 95% confidence interval will be expected to be greater than 0.734 when the Jada Treatment Success is expected to be 82%. (Calculated using SAS v9.4 PROC POWER.)

For safety, with 96 subjects treated with Jada, there is a 95% chance of observing at least one adverse event when the underlying incidence of the event is at least 3.1%.

To account for up to 10% of the subjects withdrawing early or not having data available for the analysis of the primary effectiveness endpoint, a total of 107 subjects will be enrolled.

5.4.2 Source of Subjects

Subjects will be identified and recruited from inpatient and outpatient facilities affiliated with or at study sites. Any recruitment materials used that are intended for use with patients must be approved by the Sponsor and the reviewing IRB prior to use.

5.4.3 Inclusion/Exclusion Criteria

All patients must be carefully screened against all inclusion and exclusion criteria prior to enrollment in the study. Each Jada System will be shipped with a source worksheet listing all eligibility criteria, which should be used to ensure compliance with study eligibility criteria during subject enrollment.

Inclusion Criteria:

1. Adult Female, 18 years of age or older at time of consent.
2. Able to understand and provide informed consent to participate in the study.
3. Diagnosis of PPH with suspected atony within 24 hours after vaginal or c-section delivery.
4. EBL, determined when investigator is ready to have the Jada peel pack opened:
   Vaginal delivery: 500 – 1500 ml EBL or
   C-section delivery 1000 – 1500 ml EBL
5. Failed first-line intervention of uterotonics and uterine massage/bimanual uterine massage to stop bleeding.
   Note: Uterotonic administration may continue concomitant with and post Jada use, as long as such use does not exceed the maximum dose of the drug.

Exclusion Criteria:

1. EBL >1500ml, to be determined when investigator is ready to have the Jada peel pack opened.
2. Delivery at a gestational age < 34 weeks.
3. For C-sections: Cervix < 3 cm dilated before use of Jada.
4. PPH that the investigator determines to require more aggressive treatment, including any of the following:
   a) hysterectomy;
   b) b-lynch suture;
   c) uterine artery embolization or ligation;
   d) hypogastric ligation.
5. Known uterine anomaly.
6. Ongoing intrauterine pregnancy.
7. Placenta abnormality including any of the following:
   a) known placenta accreta;
   b) retained placenta with known risk factors for placenta accreta (e.g. history of prior uterine surgery, including prior c-section and placenta previa);
   c) retained placenta without easy manual removal.
8. Known uterine rupture.
9. Unresolved uterine inversion.

10. Subject has undergone intrauterine balloon therapy or uterine packing for tamponade treatment of this PPH prior to use of Jada.
11. Current cervical cancer.
12. Current purulent infection of vagina, cervix, uterus.
13. Diagnosis of coagulopathy.

5.4.4 Subject Withdrawal and Termination

Subjects will be advised that they may voluntarily withdraw from the study at any time and will be instructed to notify the Investigator immediately if they choose to withdraw. A subject may choose to withdraw for any reason and is not obligated to reveal reason(s) for withdrawal. Any data contributed up to the point of withdrawal will be included in the analyses. In addition, any adverse events that are ongoing at the time of the subject's withdrawal will be marked as such on the Adverse Event case report form. Subjects will be followed until the adverse event is resolved or is not expected to change.

Subjects may also be involuntarily terminated from the study by the Investigator if the Investigator believes it is in the best interest of the subject. This may occur if the investigator believes more aggressive treatment is necessary prior to the use of Jada. This may also occur if the Investigator decides to abort the treatment with Jada after it is inserted. If a Jada is inserted in the subject but treatment is aborted thereafter, the subject will be followed for six weeks.

5.5 Duration of Study and Subject Participation

All eligible study subjects who are enrolled in the study will be expected to continue participation in this clinical study for six weeks following the Jada intervention, except as provided in the section on subject withdrawal and termination. For this study, "enrolled" is defined as: 1) signing the Informed Consent Form and 2) meeting the inclusion/exclusion criteria.

The literature cites PPH prevalence rates ranging from 2% (severe PPH) to 5% (primary PPH) in the United States. This would mean 2000 to 5000 deliveries would be needed to reach the target enrollment of 107 subjects. Consequently, it is anticipated that it will take approximately 12-18 months to screen, enroll, intervene, and follow-up all 107 subjects.

5.6 Justification for Study

A feasibility clinical study of the Jada System has been completed with encouraging results. See the Clinical Evaluation Report (G150265, Attachment H, pages 337-382). In this feasibility study, Jada was used in a limited population of women who had failed first line conservative therapy. This study excluded subjects delivering by Cesarean section and subjects with other major identifiable causes of PPH other than atony. This conservative subject selection process was deliberately chosen to reduce the variance in the treated population in order to clearly demonstrate the device's mechanism of action and allow safety to be elucidated. In all ten subjects, PPH ceased within two minutes. The Jada System was left in place for up to 6.5 hours. None of the subjects experienced a device-related adverse event.

Subsequent to this Feasibility Study, clinical use of vacuum via uterine cannula (different device than the Jada) to create uterine tamponade was reported by Ram et al in 2014.[25] Sixteen women who had vaginal deliveries and four women who underwent Cesarean sections were included in the study. All women received 10 units of oxytocin at the appearance of the baby's anterior shoulder, 5 units of intravenous oxytocin after the delivery of the placenta, and then uterine massage. Carboprost 125 mcg was also given when the bleeding did not stop. All 20 women were then administered the uterine vacuum retraction system via rigid cannula and vacuum forces of 650 mmHg for 10 minutes at a time. Complete cessation of bleeding which was associated with contraction and firm retraction of the uterus

was observed in all women within 4 minutes of initiation of the procedure. The clinical outcomes for the vaginal deliveries and Cesarean sections were comparable. No adverse events were reported.

These early studies demonstrated the safety and initial effectiveness of the use of a vacuum to create uterine tamponade and treat postpartum hemorrhage. This Pivotal Study is designed to gather more data demonstrating the safety and effectiveness of the Jada System in a larger patient population. Meta-analysis methodology was used to establish target endpoints which will demonstrate the safety and effectiveness of the Jada System; as such, the resulting design is a literature-controlled study design.

6.0 Study Procedures

6.1 Subject Recruitment

Participants will not be recruited until the Institutional Review Board governing their treatment facility has approved the study.

The Investigator may begin recruiting participants at any time prior to the diagnosis of PPH in accordance with the requirements of the following section, Subject Consent. The supplied short Patient Study Brochure, the PEARLE Study Poster, or the Patient Study Information Video can be used at this point to introduce the study to all potential participants (provided these recruitment materials have been approved by the IRB at the site), prior to issuing the lengthier informed consent form. Use of the brochure, study poster and video information tools are optional.

6.2 Subject Consent

Principles of Informed Consent

As stated by US FDA,[1] *"To many, the term informed consent is mistakenly viewed as synonymous with obtaining a subject's signature on the consent form. FDA believes that obtaining a subject's oral or written informed consent is only part of the consent process. Informed consent involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject's comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject's voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires. To be effective, the process must provide sufficient opportunity for the subject to consider whether to participate. (21 CFR 50.20.) FDA considers this to include allowing sufficient time for subjects to consider the information and providing time and opportunity for the subjects to ask questions and have those questions answered. The Investigator (or other study staff who are conducting the informed consent interview) and the subject should exchange information and discuss the contents of the informed consent document. This process must occur under circumstances that minimize the possibility of coercion or undue influence."*

Study Requirements

Upon determination of subject eligibility (preliminary completion of study entry criteria), the patient will have the opportunity to discuss any risks, benefits, alternative therapies, and the study requirements with the Investigator prior to signing the informed consent document. Signed informed consent shall be obtained from each study subject prior to use of the investigational device.

[1] Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Draft issued July 2014

Consent Timing

Given the potential for duress, the timing for obtaining informed consent from women undergoing labor and delivery raises unique considerations. As such, considerations and requirements for timing of obtaining informed consent are discussed below.

Informed consent for this study can be obtained during several different phases of interaction with the patient:

Phase 1: At any antenatal obstetrical office visit prior to the onset of labor

Phase 2: After hospital admission, but before the onset of labor, including the following:

- Women making an antenatal visit at the hospital
- Women admitted for labor induction
- Women with ruptured membranes, but who are not in labor

Phase 3: After the onset of labor, **but before the diagnosis of PPH**

In all 3 phases, the patient must be provided adequate time to review the informed consent form and consider whether or not to participate. For women considered high risk for PPH, it is ideal to obtain informed consent during Phase 1. In order to avoid undue anxiety for those women who are not considered at high risk, consent can be obtained later, upon hospital admission, when many possible although unlikely interventions are routinely discussed.

During Phase 3, there is an increased likelihood that the woman will be under periods of duress. As such, the following safeguards will be applied to informed consent that is obtained during Phase 3.

Informed consent will not be obtained when any of the following apply:

1. The patient has been diagnosed with PPH.
2. The patient has arterial bleeding requiring surgical exploration or angiographic embolization.
3. The patient requires immediate life-saving hysterectomy.
4. The patient is in the second stage of labor.
5. The patient is experiencing a contraction.
6. The patient is experiencing pain or discomfort that prevents a lucid discussion of the elements of the informed consent form.
7. The patient is undergoing a gynecological examination.
8. The patient is distracted by the placement or adjustment of fetal or labor monitoring devices.
9. The patient is undergoing administration of an epidural regional anesthetic or spinal anesthetic.
10. The study Investigator believes that the patient's level of mental and/or physical stress prevents a lucid discussion of the elements of the informed consent form.

The patients will be informed by the Investigator or Investigator's designee that they are free to refuse participation in this research study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

The Investigator or the Investigator's designee will inform patients that their medical records will be subject to review by the sponsor and appropriate regulatory bodies. This information will be used during the analysis of the results of the clinical study, but the patients' identities will be treated as confidential. Patients will be assigned a unique study subject code that will not reveal the patient's identity, and this code will be used on all data and data collection forms during the study period.

The Investigator or their designee will explain the conditions of the study, giving the patient sufficient time to ask questions and to consider whether or not they want to participate. If the patient agrees, they shall be given an approved consent form for signature and date. A copy of the consent form will

be given to the patient. The original consent forms will be kept by the Investigator and will be subject to review by the sponsor or a representative of the sponsor, and by the appropriate regulatory bodies.

If the patient signs the informed consent form, the site must place a PEARLE Consent ID bracelet on their wrist to indicate that they have been consented.

Figure 5: PEARLE Consent ID Bracelet

6.3 Subject Pre-Enrollment Screening

All patients must be screened for all inclusion and exclusion criteria prior to being enrolled in the study.

At any time during the consent process or after, if the subject is known to screen fail the study for any inclusion or exclusion criterion, the process of working toward enrollment of that subject should cease. This includes any information that becomes known from subject interview, subject history, or examination at any point after admission. Once a person is known to not fulfill any criterion, the identification of their consent should be removed. For example, if they have a PEARLE Consent ID bracelet on, it should be removed from their wrist.

6.4 Subject Enrollment

The Investigator should consider all possible causes of bleeding, including evaluating for lacerations, retained placenta, broad ligament and vaginal hematomas, uterine rupture, and other causes requiring different treatment pathways. First line therapies should be attempted in accordance with the institution's PPH protocol. After first line therapies have been attempted and failed, the Investigator will make the decision to use Jada to attempt control or reduction of PPH. The subject will be considered "enrolled" after she: 1) signs the Informed Consent Form and 2) meets the inclusion/exclusion criteria.

6.5 Intervention

The Investigator will use Jada in conjunction with the device's Instructions for Use that is included with every device. Following the steps of the IFU and according to their training, the Investigator will place the Jada intrauterine loop into the uterus. For vaginal deliveries, the device will be placed transvaginally; for Cesarean deliveries, the device will be placed trans-abdominally or transvaginally (if the hysterotomy was closed first). The vacuum seal will be filled with 60 ml sterile IV fluid. Vacuum forces will be applied to suction residual blood and debris. Once the residual blood is removed, the pressure gradient from the vacuum creates a uniform mechanical stimulus on the uterus, causing it to collapse into and onto itself. At that time, tamponade occurs and hemorrhage is expected to be controlled. Vacuum forces will be maintained for at least one hour (from the time hemorrhage is controlled) until the subject is stable or until the Investigator determines that hemorrhage was not

controlled and further intervention is needed. If any further intervention is required to treat the PPH, it will be reported on the Procedure case report form, capturing details on the intervention.

Once the Investigator detaches the tubing from the device or "zero's" the vacuum source and the seal is emptied of the fluid, the device should remain in place and taped to the patient's inner thigh for at least 30 minutes, provided the subject is stable and there is no medically valid reason to remove the device. The 30-minute minimum observation period allows for the Investigator to re-initiate treatment should the uterus return to an atonic state with abnormal bleeding.

If the subject remains stable and the PPH does not return for 30 minutes, then the device can be removed and decommissioned (cut up) prior to final disposal. Device pieces should be discarded in accordance with hospital biohazardous waste policies. If there was a device malfunction, the Investigator or designee should wrap the device in a biohazardous disposal bag and contact Alydia Health for further instructions to return the device for evaluation.

Other standard of care medical evaluation and care must be ongoing during the use of the Jada System. If it is determined that blood products must be administered, then the Investigator should follow the local protocol to do so.

6.6 Post-procedure Follow-up

After removal of Jada and before subject discharge from the hospital, additional data collection is required. Information about the following will be collected on case reports forms:

- Physical Examination, including limited Pelvic Examination
- If done, CBC and coagulation panel results
- Clinician Assessment of Device Usability
- Assessment of any adverse events that occur from the beginning of device use to discharge

6.7 Six-week Follow-up

A study follow-up assessment will occur at the subject's normal 6-week postpartum follow-up visit. The following assessments will be performed:

- Physical Examination, including limited Pelvic Examination
- Assessment for any adverse events

Note: If a patient is unable to return for their normal 6-week postpartum visit after three documented attempts to complete the visit, follow-up should occur via phone to gather data related to adverse events from the discharge through this single follow-up time point.

6.8 Summary Table of Clinical Assessments

The schedule of clinical assessment is outlined in Table 2.

Table 2: Clinical Assessment Schedule

Procedure/Assessment	**Baseline**	**Jada Procedure through discharge**	**6-Week Follow-up** *42 days ± 14 days*
Screening for inclusion / exclusion	√		
Informed Consent and HIPAA authorization	√		
Enrollment		√	

Demographics, history and delivery data collection	√		
General exam	√ (after delivery but prior to PPH dx)	√ (after Jada use and prior to discharge)	√
Vital Signs (at admission)	√		
CBC / Coag Panel	√* (at admission)	√* (after Jada use and prior to discharge)	
Jada procedure and endpoint assessment		√	
Investigator assessment of device usability		√	
Adverse Event assessment		√	√
Assessment of medications that may affect bleeding	√	√	
Study exit			√

√* If an Investigator deems it medically important to conduct the CBC or coagulation panel, the results of these should be recorded in the Baseline and Post-Procedure Through Discharge case report forms.

7.0 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse event

An adverse event is any untoward medical occurrence (i.e., any unfavorable and unintended sign, including abnormal laboratory findings, symptom, or disease) in a clinical investigation subject after the subject enrolls in this study. Adverse events will be categorized as serious and non-serious, device-related and non-device-related, and anticipated and unanticipated.

7.1.2 Adverse device effect

An adverse device effect (ADE) is an AE related to the use of the device, including AEs resulting from insufficient or inadequate instructions for use, installation or operation, or any malfunction of the investigational medical device, use error or from intentional misuse of the medical device.

7.1.3 Device deficiency

A device deficiency is an inadequacy of device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse, or use error and inadequate labeling.

7.1.4 Device failure

A device failure is a failure of the device to perform or function as intended, including any deviations from the performance specifications or intended use.

7.1.5 Device malfunction

A device malfunction is a failure of the device to meet its performance specifications or otherwise perform as intended when used in accordance with the Instructions For Use.

7.1.6 Device misuse

A device misuse occurs when the Investigator uses the device in a manner that is contradictory to the Instructions For Use. A device misuse will not be considered a malfunction.

7.1.7 Device-related adverse event

A device-related adverse event is any AE for which a causal relationship between the device and the AE is at least a reasonable possibility (i.e., the relationship cannot be excluded).

7.1.8 Near incident

A near incident is any malfunction or deterioration in the characteristics and/or performance of the device (an ADE) which might have led to death or serious deterioration in health. The incident occurred and is such that if it occurred again, it might lead to death or serious deterioration in health.

7.1.9 Serious adverse device effect

An ADE that results in any of the consequences of a serious adverse event "SAE". The term serious adverse device effect (SADE) is synonymous with "incident".

7.1.10 Serious adverse event (SAE)

Any adverse event that meets at least one of the following criteria (a—f):

a. Results in death.
b. Is life-threatening.
   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization.
   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met: the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR the admission is not associated with an AE (e.g., social hospitalization for purposes of respite care). However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
d. Results in persistent or significant disability / incapacity.
   Disability means a substantial disruption of a person's ability to conduct normal life's functions.
e. Results in fetal distress, fetal death or a congenital abnormality or birth defect.
f. Is considered an important medical event that jeopardizes the health of the subject or requires surgical intervention to prevent one of the outcomes listed above as judged by the Investigator.

7.1.11 Unanticipated adverse device effect

An unanticipated adverse device effect (UADE) is any SADE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, intensity, or degree of incidence in the investigational plan or application or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2 Classifications for Adverse Event Assessment

All AEs from beginning of device use to subject termination will be assessed and documented by the Investigator according to the categories detailed below:

7.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in section 7.1 (Definitions).

7.2.2 Severity

The severity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

7.2.3 Causal relationship

The assessment of the causal relationship between an AE and the device or procedure is a clinical decision based on all available information at the time of the completion of the AE case report form. The assessment is based on the question whether there was a "reasonable causal relationship" to the procedure and/or device.

Possible responses to causal relationship are "related", "possibly related", or "not related".

- An assessment of "not related" would include (1) the existence of a clear alternative explanation (e.g., the subject develops a local infection from an unrelated laceration) or (2) non-plausibility (e.g., the subject is struck by an automobile when there is no indication that the device caused disorientation that may have caused the event).
- An assessment of "possibly related" indicates that there is a reasonable suspicion that the AE is associated with the procedure and/or device, but not definitively so.
- An assessment of "related" indicates that the AE is very likely associated with the procedure and/or device.

Important factors to be considered in assessing the relationship of the AE to the device or procedure include (1) the temporal sequence from the procedure—the event should occur after the procedure is initiated, (2) underlying, concomitant, intercurrent diseases—each event should be evaluated in the context of the natural history and course of the procedure and any other medical conditions the subject may have, and (3) concomitant medications or procedures—any drugs the subject is taking or the additional procedures the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

7.2.4 Anticipated

A list of anticipated adverse events is in Section 3.6.1. For this study, the applicable reference documents are this protocol and the Clinical Evaluation Report (G150265, Attachment H, pages 337-382). Classification of AEs as anticipated and unanticipated will be determined by the Investigator using the reference documents.

7.3 Assessments and documentation of adverse events

The Investigator must collect all AEs for each subject from the time of enrollment through the end of subject study participation, whether or not deemed related to the investigational device or procedure. A hospitalization or surgical procedure that was scheduled prior to subject enrollment should not be deemed an adverse event. All AE data will be recorded on the AE case report form. The Investigator must make an assessment and document it on the AE case report form. The Independent Medical Monitor will adjudicate all reported adverse events.

All AEs will be followed through resolution or until the AE is not expected to change. The subject will be referred to his or her primary care physician for any ongoing medical issues continuing beyond the completion of the study.

7.4 Reporting of serious adverse events and near incidents

The definition of SAE is provided in Section 7.1. These include device deficiencies that may have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

Notification to sponsor: All serious adverse events (whether or not considered device-related) must be reported immediately (within 24 hours) to:

Kathryn D. Wine, MPH
Clinical Operations
415.990.4104
Kathryn@alydiahealth.com
If e-mail receipt is not confirmed, please call to provide notification.

Notification of the IRB: Notification of the IRB about all relevant events will be performed by the Investigator according to all applicable requirements.

7.5 Device Deficiencies

The Investigator must document all device failures, malfunctions, and use errors, including the assessment whether the event is considered a near incident (ADE) using the Device Deficiency case report form. The case report form must be faxed or emailed to the Sponsor within 24 hours of Investigator knowledge of the event. If a device malfunctions, the Investigator must contact the Sponsor to determine if the device should be returned.

7.6 Study Termination

If new information is discovered during the study that indicates that the device or intervention provides an unreasonable risk to subjects, study enrollment will be suspended or discontinued. Enrollment will only be resumed once the risk has been appropriately mitigated and authorization to resume is obtained from FDA and the reviewing IRB. Regardless of ability to resume the study, all treated subjects will be followed as required by the protocol (6 weeks post-intervention).

The study or any clinical study site may also be halted or terminated early by the Sponsor for business reasons.

8.0 Data Collection, Reporting and Quality Assurance

8.1 Case Report Forms

Case report forms will be used to record demographic, intervention, and follow-up data, as well as any protocol deviations, adverse events, or device malfunctions that may occur during the study period.

8.2 Protocol Deviations

A Protocol Deviation Form must be completed for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion/exclusion criteria[2], not performing

[2] There may be times when the pre-treatment EBL is re-estimated after Device use. If the re-estimation of the pre-treatment EBL is greater than the maximum EBL allowed for study entry by ≤ 20% (i.e. the re-estimate was ≤ 1800 ml), then the site is not required to report a protocol deviation to the EBL

required testing, missed follow-up window, etc.). The Investigator must notify the Sponsor and the reviewing IRB of any deviation from the investigational plan that was done to protect the life or physical well-being of a subject (medical emergencies). Such notice should be given within 24 hours after the emergency occurred.

8.3 Efforts to Minimize Data Loss

If a subject fails to comply with the follow up evaluations, the study site must attempt to contact the subject at least three times, including once as a registered letter. In order to minimize loss to follow-up, during the hospitalization, the study coordinator will request that the subject provide names and contact information of two individuals that have a close relationship with the subject. The contacts will be utilized in the event that the subject relocates or cannot be reached by mail or telephone. This information will be treated as confidential and for use by the investigative site only.

8.4 Data Confidentiality

All information and data sent to the Sponsor, Contract Research Organizations, or their designated agents concerning subjects or their participation in this study will be considered confidential and identifying information should be redacted. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The Principal Investigator consents to visits by the staff of the Sponsor and its authorized representatives and the U.S. Food and Drug Administration or any other local governmental body to review the study subjects' medical records including any test or laboratory data.

All information concerning the device, such as patent applications, formulas, manufacturing processes, scientific data, specific study designs, protocols, and formulation information supplied by the Sponsor and not previously published is considered confidential and will remain the sole property of the Sponsor. The Principal Investigator agrees to use this information only in accomplishing the purposes of this study and will not use it for other purposes without the Sponsor's written consent.

8.5 Quality Assurance of the Data

Subject case report forms will be reviewed against source documentation for completeness and accuracy. If any discrepancies are noted, they will be resolved with the Investigator and/or designee. If the data are incomplete, attempts will be made to obtain the missing data.

8.6 Monitoring Procedures

The Alydia Health Vice President of Clinical Operations will have responsibility over the clinical study. Monitors, the Independent Medical Monitor, and associated personnel will be recorded in the Trial Master File.

The Sponsor is responsible for monitoring the study data to verify that the subject rights and well-being are protected in accordance with applicable regulations, GCP, and Sponsor/CRO procedures. The Sponsor, or Sponsor designee, will perform clinical monitoring, including review of case report forms with verification to the source documentation. Both remote and on-site monitoring may be conducted in this study. The Investigator will allow direct access to all relevant subject files for the purpose of verifying entries made in the case report form and assist with the monitor's activities as required. Adequate time, office accommodations, and resources (e.g., copy machine, phone, and/or internet access) for monitoring visits should be made available to the monitor at clinical sites.

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eligibility criteria. If the re-estimated pre-treatment EBL is >1800 ml, then it must be reported as a protocol deviation.

Monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor's requirements.

The Sponsor/designee will periodically monitor the site activity to verify:

- Data are authentic, accurate and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol).
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The Investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

8.7 Publication Policy

The Principal Investigator may not publish information obtained during this study prior to obtaining the review and approval of the Sponsor, which shall be in writing. The Sponsor reserves the right to assert its proprietary interests regarding any confidential, technical or proprietary information that the Sponsor may have furnished the Principal Investigator in order to facilitate clinical studies under this agreement.

9.0 Statistical Analysis Plan

9.1 Introduction

This is a prospective, single-arm, literature-controlled, multi-center trial designed to assess the safety and effectiveness of the Jada System when treating primary PPH. The study is designed to demonstrate that Jada provides safe and effective control or reduction of primary PPH. Safety will be evaluated by analyzing all adverse events for device relatedness, seriousness, severity, and whether or not they were anticipated.

Up to 20 study sites will enroll a total of up to 107 subjects in the study to ensure that 96 subjects are available for the analysis of the primary effectiveness endpoint. Qualified sites will be located in the U.S. and potentially O.U.S. as well. Sites are expected to enroll a minimum of 5 subjects. Site enrollment will be capped at 30% of the total expected enrollment, such that no site will enroll more than 32 subjects. Also, no more than 50% of the study data will come from O.U.S. sites.

9.2 Study Endpoint Analysis

Reported Adverse Events

Adverse events will be categorized as:

- serious or non-serious,
- severe, moderate or mild,
- device-related, possibly device-related or non-device-related,
- anticipated or unanticipated.

The frequency of each event will be summarized according to the above categories. Since some subjects may report the same event several times (e.g., headache), the first occurrence of the worst reported case of the event will be used for the purpose of analysis**.**

9.3 Primary Effectiveness Endpoint – Treatment Success

Control of postpartum hemorrhage, defined as the avoidance of non-surgical, second line or surgical intervention to control uterine hemorrhage after the use of the Jada System per the Instructions for Use.

Non-surgical, second line procedures include uterine balloon therapy, uterine packing, or uterine artery embolization. Surgical intervention includes procedures such as uterine arterial ligation, uterine compression sutures or hysterectomy.

Note: Continuation of the administration of uterotonics concomitant with and post Jada use is standard of care as long as such use does not exceed the maximum dose of the drug and does not constitute failure of the primary effectiveness endpoint.

9.4 Study Success

A thorough review of all known publications reporting on the use of the Bakri Balloon and other balloon tamponade methodologies to treat PPH was conducted. A meta-analysis methodology was used to aggregate the studies and provide a numerical estimate of the overall Literature Treatment Success Rate. Based on a random effects model, the estimated pooled proportion of subjects who reached hemostasis (i.e., control of uterine hemorrhaging) following Bakri Balloon treatments was 82.0% (95% CI: 73.4% to 89.2%). See the Clinical Evaluation Report (G150265, Attachment H, pages 337-382).

The primary effectiveness objective of this Pivotal Study is to show that the observed Study Treatment Success Rate is not worse that the rate reported in the literature. The study is considered a success when the lower bound of the two-sided Exact Clopper-Pearson mid-p 95% Confidence Interval for the Study Treatment Success is greater than or equal to 73.4%.

9.5 Secondary Endpoints

1. Time to control hemorrhage, defined as the time from turning on the vacuum source until the time the *first* of any of the following occurs:
    - there is no blood being collected in the tubing or canister, or
    - the blood loss is observed as leveled off in the canister, or
    - blood loss at a rate of < 500 ml in 24 hours.
2. Rate of surgical intervention required to control PPH after Jada use.
3. Rate of non-surgical intervention required to control PPH after Jada use.
4. Assessment of device usability as reported by the clinician using a dedicated data collection form.
5. Rate of blood product transfusion required after Jada use, and number of transfusion units when administered.

The secondary endpoints will be summarized, and confidence intervals will be provided to support interpretation of the results. No specific hypothesis tests will be performed for the secondary endpoints.

9.6 Analysis Cohorts

Different groups of subjects, or Analysis Cohorts, will be identified depending on the type and extent of analysis being performed.

Only subjects from study centers located within the United States and study centers located O.U.S. that have been enrolled under this version of the protocol (2.6) will be included in the analyses and data presentations defined in this protocol.

Screening Cohort
All subjects who are consented and screened for the study will be included in the Screening Cohort. Subjects excluded during the procedure from receiving Jada treatment for non-device related reasons are included in this Cohort. Only an accounting of the numbers of subjects screened in the study, plus the reasons given for subjects not enrolled in the study will be performed on this Cohort.

Safety/ITT (Intent to Treat) Cohort
All subjects in whom treatment was attempted with Jada (device inserted and vacuum turned on) are included in the Safety/ITT Cohort.

Per-Protocol Cohort
The Per-Protocol Cohort is defined as the group of subjects who are treated and complete treatment with the Jada System per the device's Instructions for Use, and who complete their 6-week visit without any major protocol deviations.

Cohort for Primary and Secondary Effectiveness Endpoints
Analyses of all primary and secondary effectiveness endpoints will be repeated both for the Safety/ITT Cohort and for the Per-Protocol Cohort. Study Success will be based on the Safety/ITT Cohort.

Cohort for Safety Endpoints
Analyses for all safety related endpoints will be performed using the Safety/ITT Cohort.

9.7 Derived Data – Change-from-Baseline Parameters

Within-subject change-from-baseline (pre-treatment baseline) values for a parameter are calculated as:

Change-from-Baseline = Pre-Treatment value – Follow-Up value

such that a positive value indicates a reduction from the pre-treatment value to the follow-up value, whereas a negative result indicates the opposite.

9.8 Statistical Methods

Categorical data will be summarized using frequency tables, presenting the subject counts and relative percentages. McNemar's chi-square may be used to assess within-subject changes in a bivariate response variable.

Continuous variables will be summarized by the mean, standard deviation, median, minimum and maximum. Within-subject changes (Change-from-Baseline) will be analyzed parametrically using the Paired t-test if the differences are normally distributed, or non-parametrically using the Sign-Rank Test if the differences are not normally distributed.

The SAS system or equivalent statistical package will be used to perform all analyses. Exact confidence intervals will be generated for estimates of proportions. Asymptotic confidence intervals will be generated for estimates of means. The p-values of all tests will be reported without any correction for the multiplicity of tests performed.

9.9 Subgroup Analysis

Analysis of the primary safety and effectiveness endpoints will be repeated for two subgroups of subjects: subjects with vaginal delivery and subjects with surgical delivery by Cesarean section.

9.10 Poolability

Data will be pooled from multiple study sites for this analysis. The justification for pooling is made on a clinical basis[3]. The basis for pooling comes from three critical factors: the study sites must implement one common protocol; the sponsor must provide monitoring of study site compliance; the study sites must use common data collection procedures.

Poolability across study sites will be assessed by presenting Treatment Success Rates by site and analyzing site-to-site differences using the Chi-square Test. Other methods for assessing site-to-site differences in Treatment Success Rates will be considered if the assumptions underlying the Chi-square Test are not met. Site-to-site differences will be assessed at a 0.15 level of significance. A non-significant site-to-site effect will support poolability of study sites. Note that prior to assessing site-to-site differences, sites with less than 5 subjects will be combined. To avoid the scenario that the data from the combined super-site dominate the trial conclusion, sites with less than 5 enrolled subjects be combined according to their geographical closeness, and once a super-site has five or more enrolled subjects, then the forming of this super-site will stop and the forming of a new super-site will start. Site-to-site differences of a quantitative nature, (e.g., all sites show the treatment to be beneficial, but perhaps to a different degree by study site) will not be considered to be an impediment to pooling. Site-to-site differences qualitative in nature (e.g., the vast majority of sites show the treatment to be beneficial, but one or more sites show the treatment to be detrimental) will require extensive evaluation of the sites with contrary results to attempt to determine what factors at those sites led to the result.

9.11 Lost to Follow-up

Data on subjects who are lost to follow-up or who withdraw from the study will be maintained and analyzed up to the point at which they discontinued. The reason for withdrawal will be recorded if known. Subjects who discontinue participation, for whatever reason, will remain in the study and be subject to follow-up in the same manner as those who complete the study except as noted above. The only confirmed lost to follow-up subject will be a subject who dies or refuses to continue to participate in the study and thereby withdraws.

9.12 Dropout Mechanism and Analysis

Subjects who are missing data necessary to assess Treatment Success will be considered a failure (Treatment Success = No) in the analysis of the primary effectiveness endpoint. If the subject withdraws from the study prior to completing the assessment of Treatment Success, it will be considered missing data. All other endpoints will be analyzed "as-is" without any special data imputation methods used to replace missing data.

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