Fetal Treatment of Galenic Malformations

BCH IRB Protocol Number: P00034727

MGB IRB Protocol Number: 2020P000216

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Version Date: 12-11-2023

NCT Number: NCT04434729

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AUC	Area Under the Curve
BCH	Boston Children's Hospital
BMI	Body Mass Index
BWH	Brigham and Women's Hospital
CBCL	Child Behavior Checklist
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HTN	Hypertension
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IM	Intramuscular
INC	International Neonatal Consortium
IRB	Institutional Review Board
IT	Infant Treatment
LV	Left Ventricle
MFCC	Maternal Fetal Care Center
MFM	Maternal Fetal Medicine
MGB	Mass General Brigham
MRI	Magnetic Resonance Imaging
NAR	Neonatal At Risk
NCI	National Cancer Institute
NICU	Neonatal Intensive Care Unit
OR	Operating Room
PI	Principal Investigator
REEL	Receptive-Expressive Emergent Language Test
RHV	Rotating Hemostatic Valve

RV	Right Ventricle
SAE	Serious Adverse Event/Serious Adverse Experience
SFP	Severe Fetal Presentation
SI	Sponsor-Investigator
UK	United Kingdom
US	United States
VOGM	Vein of Galen Malformation

PROTOCOL SUMMARY

Title:	Fetal Treatment of Galenic Malformations
Summary:	This is a prospective, single-arm non-randomized interventional study of fetuses to assess the safety and efficacy of fetal embolization of VOGM. Subjects will receive a one-time study intervention of fetal embolization. Follow-up assessments will be collected every 4 weeks until delivery, as per standard of care. After delivery, neurological assessments will be performed every 6 months for 2 years (adjusted for gestational age). Data will be compared to historical cohorts.
Objectives:	The objectives for this study are to assess the safety and efficacy of fetal embolization of vein of Galen malformations. **Primary objective:** To evaluate the prenatal safety of fetal embolization for patients with vein of Galen malformations. **Secondary objective:** To evaluate the efficacy of fetal embolization for patients with vein of Galen malformations.
Population:	Fetuses between 23 weeks and term diagnosed with fetal VOGM through fetal MRI and their mothers will be recruited for this study.
Phase:	I/II
Number of Sites:	This study is conducted jointly between Boston Children's Hospital and Brigham and Women's Hospital.
Description of Intervention:	Subjects will undergo transcranial torcular needle puncture and median prosencephalic vein embolization. Detachable platinum coils (Target XL and XXL Detachable Coil, Stryker Neurovascular) will be used to pack the prosencephalic varix.
Study Duration:	We estimate the study duration will be 8 years: ● Recruitment: 5 years ● Patient follow up: 2 years ● Data analysis: 1 year
Subject Participation Duration:	Subjects will be on the study from the time the parents sign consent to two years after delivery.
Estimated Time to Complete Enrollment:	We estimate 5-7 years to complete enrollment.

Schematic of Study Design:

Prior to Enrollment	Obtain informed consent. Screen potential subjects by inclusion and exclusion criteria; obtain history, document.
Visit 1 Baseline	Perform baseline assessments, including detailed pregnancy and medical history, fetal and obstetric ultrasound, fetal MRI, and fetal echocardiogram.
Visit 2 Intervention	Perform study intervention. Mothers will be monitored until at least the morning after the procedure or longer as needed. Fetal echocardiogram, obstetric ultrasound, and fetal MRI will be performed 24-48 hours after the procedure. These assessments will be repeated every 4 weeks until delivery.
	Delivery and post-delivery care will be provided as standard of care as appropriate for gestational age and clinical condition. In particular, all neonates and infants with vein of Galen malformation are closely followed with clinical exam and serial imaging (including MRI) and undergo embolization of the malformation on a timeframe dictated by the clinical status. Data will be abstracted from the medical record.
Visits 3, 4 6 and 12 month follow ups	Neurological assessments (Vineland Adaptive Behavior Scales and REEL) will be performed over the phone or in person. Families will be asked about developmental milestones and incidence of seizures.
Visits 5, 6 18 and 24 month follow ups	Neurological assessments (Vineland Adaptive Behavior Scales, REEL, DAYC-2 and CBCL) will be performed over the phone or in person. If in person, a Bayley examination will also be performed. Families will be asked about developmental milestones and incidence of seizures.

1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Prognosis

Vein of Galen malformation (VOGM) is an arteriovenous vascular lesion of the brain, whereby numerous cerebral arteries abnormally flow directly into the embryological precursor of the vein of Galen – the median prosencephalic vein. The procencephalic vein grows, under these conditions of abnormal high flow and pressure, to form the characteristic massive venous varix in the center of the brain seen in affected infants. Vein of Galen malformations present with a broad range of severity, from fulminant cardiopulmonary failure (due to over-circulation) soon after birth to asymptomatic presentation for the first few months of life. The development of endovascular treatment for vein of Galen malformations (VOGM) in the late 1980's, spearheaded by Pierre Lasjaunias and colleagues, was a major advance, offering the possibility of good outcome in the setting of a diagnosis that had previously been nearly universally fatal, and published series from several centers around the world, including two recent international meta-analyses, reflect this improved prognosis [1-2]. However, even at the most experienced centers, neonates with VOGM presenting with early cardiac failure have a high mortality rate (~50% overall, 100% in neonates with pulmonary HTN in Lasjuanias' cohort [3]); survivors within this cohort typically require several rounds of high-risk embolization in the first 1-2 weeks of life, with a high rate of neurological morbidity and prolonged NICU stay.

It is important to note that all such studies of outcomes after embolization, from Lasjaunias' work in the late 1990's and early 2000's to the recent meta-analyses, consist of cohorts of carefully preselected patients: those who, in the judgment of the treating physicians, were likely to respond to intervention. Virtually all major centers worldwide use the Bicêtre criteria [3] or some variant thereof, to essentially screen out patients whose pathophysiology is too far advanced for a realistic hope of recovery, using optimal current standard of care treatment.

Thus, from the perspective of most non pre-selected neonates or fetuses with a diagnosis of vein of Galen malformation, the prognosis remains guarded or grim. Considering prenatally diagnosed cases from the obstetric literature between 1994 and 2011, a recent review [4] found a 54% mortality rate, a 14% rate of survival with severe neurocognitive compromise, and only a 32% chance of survival with either no impairment or with only minor neurological injury. A pooled study of serial prenatally diagnosed VOGM patients from two referral centers, in Paris and Genoa [5], found a rate of 33% for late termination of pregnancy due to poor fetal prognosis or intrauterine death, a 24% neonatal mortality rate, and a 6% rate of survival with significant neurological compromise, leaving only 37% of the original fetal cohort to survive infancy without significant neurological impairment.

Population studies in the UK, where all cases are referred to and treated at a single national center of excellence (Great Ormond Street Hospital), thus avoiding referral bias and preselection, demonstrate a 40% mortality in the largest cohort of VOGM patients, those treated as neonates [6], with 50% of survivors having moderate to severe neurocognitive compromise. Thus, the entire UK national experience similarly demonstrates that only ~1/3 of neonatally treated patients can expect to survive to adulthood with good neurodevelopmental outcome. In the UK national cohort of VOGM patients who presented in infancy rather than as neonates [7] and thus had less severe early pathology, the overall survival rate was 90%, though even in this

healthier cohort, ~30% had poor neurological outcome, despite expert treatment. Among published studies from neurovascular specialty treating centers, the UK data are unique in reflecting outcomes across an entire population.

As seen in the UK data and in the two recent large meta-analyses, there is a clear bifurcation in outcome among patients, between those requiring urgent treatment as neonates (hereafter referred to as NAR, *neonatal at risk*), who have a high mortality and morbidity, and those in whom treatment can be deferred until infancy (typically age 3-6 months, hereafter referred to as IT, *infant treatment*), whose prognosis is much more favorable. Over the same 10-year period in the UK, 85 VOGM patients presented as NAR (73.3%) and 31 as IT (26.7%). This ratio is similar to our cohort at BCH, with 68.8% presenting as NAR and 31.2% as IT. Given that over 2/3 of all VOGM patients face the grim prognosis of the NAR cohort, an intervention with the potential to alter the pathophysiology such that a greater fraction of patients present as IT could have a major positive impact on overall prognosis for VOGM.

2.1.2 Predicting Aggressive Presentation of VOGM

It has been to this point impossible to predict the postnatal clinical presentation based on prenatal imaging; neither the size of the varix nor the number of arterial feeders nor a benign fetal echocardiogram is predictive of benign clinical presentation. Thus, at most expert centers, including our own, every newborn with VOGM is admitted to the NICU and carefully observed for clinical deterioration, with the team prepared for urgent embolization should aggressive heart failure become manifest, i.e., should the patient present as NAR.

What has been predictable is a virtually certain grim prognosis in cases where the fetal MR already shows diffuse bihemispheric parenchymal brain injury as well as in cases with in-utero evidence of multi-organ failure (hydrops, pleural effusions, poor ventricular function on fetal echocardiography). Currently available treatment does not alter the near 100% mortality in this small cohort (hereafter referred to as SFP, *severe fetal presentation*), with the few survivors suffering from profound neurodevelopmental impairment. Currently, we recommend comfort care in the NICU after delivery for the SFP cohort.

Our relatively large clinical cohort of VOGM patients referred to the Maternal Fetal Care Center (MFCC), the vast majority of whom delivered at BWH and were treated at BCH, in whom we have detailed imaging and clinical data (32 neonatal patients, 16 with fetal scans), offered us the opportunity to reassess whether clinical prognostication based on imaging criteria might in fact be possible. As step 1 of the analysis, we systematically studied the day-of-life 1 brain MRI, obtained in every patient in the cohort, assessing 18 different neuroanatomical parameters. Our analysis confirmed what others have repeatedly seen, that many vascular anatomic parameters do not correlate with the neonatal clinical severity. However, a subset of the parameters did correlate with clinical outcome (NAR versus IT), and starting with five such significant variables by univariate analysis, multivariable regression analysis confirmed that the caliber of the straight or falcine sinus at its narrowest point provided a highly predictive model (AUC = 0.870, 95% CI: 0.746‑0.994, P<0.001). This makes mechanistic sense: the falcine or straight venous sinus represents the exclusive drainage pathway by which high-pressure, high-flow arterialized blood from the malformation is directed back to the systemic circulation. The narrowest point along this outflow tract represents the likeliest bottleneck shielding the systemic circulation from the effects of the VOGM, and thus it is not surprising that overall clinical status is sensitively dependent on the caliber of this bottleneck.

Armed with this finding in MRI scans in neonates, we then analyzed our cohort of patients who had also undergone fetal MRI. Of the 16 VOGM patients with fetal scans, 11 presented as NAR (68.8%) and 5 as IT (31.2%). We found that in the fetal cohort as well, the maximal diameter and circumference at the narrowest point of the straight/falcine sinus were remarkably predictive of clinical presentation as NAR versus IT: AUC = 0.964, 95% CI: 0.877-1.00, P<0.001 and AUC = 1.00, 95% CI: 1.00-1.00, P<0.001, respectively, for diameter and circumference of this bottleneck point. It is thus possible to generate threshold values for these measurements below which fetal patients are strongly expected to present as IT. Specifically, the likelihood of clinical presentation as NAR as a function of the caliber of the straight or falcine sinus on MRI is summarized in the table below (probabilities determined by logistic regression analysis, where straight sinus diameter on MRI was identified as a multivariable predictor of clinical outcome ($p < 0.001$):

Table 1. Likelihood of NAR as a function of sinus diameter

Straight/falcine sinus diameter (mm)	Probability of NAR	95% Confidence Interval
0	4%	1-30%
1	8%	2-38%
2	14%	3-44%
3	24%	8-52%
4	38%	18-60%
5	53%	33-72%
6	68%	49-83%
7	**80%**	**60-92%**
8	**88%**	**69-96%**
9	**93%**	**75-98%**
10	**96%**	**80-99%**
11	**98%**	**84-99%**
12	**99%**	**87-99%**
13	**100%**	**90-100%**

Thus, novel fetal therapeutic approaches to VOGM can be directed specifically towards those patients who by natural history are likely to have a more moribund clinical course (i.e., NAR). These results have been presented at recent national and international neurointerventional radiology meetings, and is published in the American Journal of Neuroradiology. [8] The target cohort for this study will be subjects whose straight/falcine sinus diameter on fetal MRI measures 7 mm or more (listed in bold text above).

2.2 Scientific Rationale

Given the sobering overall prognosis for fetally diagnosed VOGM, the need for novel treatment approaches that may potentially lower the rates of fetal or neonatal death and severe neurological compromise is apparent. Intervening to significantly diminish the flow through the malformation in the fetal period itself is just such an approach.

Compared to the post-natal situation, the fetal physiology, with its low-resistance placental circulation, is protective of the brain in patients with VOGM. After birth, with loss of the low-

resistance placental circulation, the situation worsens significantly, for both heart and brain, with the low-resistance VOGM collecting as much as 70% of the cardiac output [9]. There is a massive increase in cardiac preload, and with closure of the ductus, pulmonary pressures increase dramatically. The right ventricle dilates and its function becomes impaired. Interventricular septal displacement contributes to left ventricular dysfunction. Diastolic flow reversal is seen in the aorta, due to steal by the VOGM. Thus, cardiac metabolic demands are significantly increased, but coronary artery flow is decreased, resulting in myocardial ischemia and failure [10-11]. Similarly, arterial steal from the cerebral circulation is common, likely exacerbated by intracranial venous hypertension, and bihemispheric parenchymal brain injuries begin to accrue.

Given the high rate of treatment failure once this physiology has taken hold, it is speculated that irreversible changes in the pulmonary vasculature occur early, so that even definitive neonatal closure of the VOGM does not ameliorate the pulmonary hypertension. From a brain perspective, in all newborns, there is a steep physiological increase in brain perfusion 2 days after birth, as an adaptation to postnatal life [12-13]; this is independent of gestational age at delivery. The commonly seen accrual of new parenchymal brain injuries in the first days to weeks postnatally in patients with VOGM and heart failure suggests that this expected uptick in postnatal brain perfusion is lacking in these patients. Thus, early treatment, before postnatal cardiopulmonary and brain circulatory changes occur, could potentially mitigate the often-fatal pathophysiological cascade, even within this high mortality subgroup.

Neonatal trans-torcular embolization of VOGM was the first alternative to open surgery, developed in the mid-1980's [14-15]. This technique involved direct needle puncture of the posterior fontanelle, allowing for coil embolization of the venous varix. Efficacy of the technique in occluding the malformation and in reversing cardiac failure was clear, but the procedure carried an attendant risk of venous infarction and hemorrhage. Thus, at most centers (including ours) the preferred postnatal approach is instead transarterial embolization [3], often using the umbilical artery for catheter access to the brain during the first week of life, and then the femoral artery thereafter. However, transarterial embolization is often less efficacious in reversing cardiopulmonary dysfunction, leading to the relatively high treatment failure rates in the NAR cohort mentioned above. The fetal environment, in the presence of the low-resistance placental circulation, and where the significant postnatal increase in cerebral circulation has not yet occurred, likely provides a far safer environment for the more efficacious treatment approach of direct embolization of the prosencephalic venous varix, with the opportunity for rerouting of the deep venous system before birth, under conditions of an overall lower-flow state to the brain.

Achieving flow diminution through the malformation by partial occlusion of the venous varix in utero would preempt development of pulmonary hypertension and likely protect both brain and heart from steal-related ischemia. As an additional benefit, morbidity to lower-extremity arteries from femoral catheterization in neonates would be avoided. Moreover, as prenatal treatment would be performed under ultrasound rather than fluoroscopy, procedural exposure to ionizing radiation would also be avoided.

BWH MFM and the BCH interventional cardiology group have pioneered fetal cardiac interventions, such as fetal balloon angioplasty for aortic valve stenosis starting in 1999 and have accrued the largest volume of such procedures worldwide, with over 200 cases performed at our center, for aortic stenosis and other indications. Our environment thus offers unequaled expertise in the safe performance of such fetal interventions, including maternal and fetal safety, fetal anesthesia, and percutaneous needle access to fetal anatomic targets. Certain eligibility

requirements and other elements of this protocol are adapted based on the experience from the fetal cardiac interventions.

BCH is a national and international referral center for management of VOGM, with a well-established multidisciplinary consultation pathway at the Maternal Fetal Care Center (MFCC). In 2018, 40 neonatal VOGM embolizations were performed, and 30 in 2017. BCH performs the highest volume of pediatric neuroendovascular and open neurosurgical cerebrovascular procedures in the US (and likely worldwide). Pediatric neuroanesthesia and neurointensive care function together with the proceduralists as a combined center of excellence.

The purpose of this study is to evaluate primarily the safety of fetal transcranial torcular puncture and median prosencephalic vein embolization in fetuses between 23 weeks gestation and term diagnosed with VOGM. We hypothesize that this novel fetal procedure will not pose undue risks to either the mother or the fetus and will be more effective in treating VOGM than the current neonatal embolization techniques. While the Target XL and Target XXL coils that will be used to perform embolization (Stryker Neurovascular) are currently only approved for use in adults, they are frequently used off-label for pediatric embolizations, including VOGM embolization in neonates and infants. An IDE application has been approved by the FDA for the use of these devices in this study.

2.3 Prior Experience

Vein of Galen malformation (VOGM) poses a unique anatomical configuration, consisting of a venous varix, massively enlarged in response to chronic inflow of arterial-pressure blood, drained via a venous sinus to an enlarged torcular dural sinus at the posterior aspect of the skull. In the proposed intervention, intravascular access to the malformation is by direct puncture of the torcular, rather than by navigating from a distant site of vessel puncture and coiling of the varix is performed under ultrasound. There is no extant animal model that remotely resembles this anatomic configuration, and thus no available model that is even minimally adequate for performing preclinical studies for investigating fetal interventions for VOGM. Animal aneurysm models, consisting of an elastase-injured or surgically-injured artery, differ fundamentally from the anatomy of VOGM, in that they represent a delicate, injured vascular structure, rather than a massively enlarged venous varix. Direct puncture of an aneurysm dome in such a model would almost certainly lead to rupture, and it is known from clinical practice that within the brain, direct puncture of even a normal arterial wall can lead to uncontrolled hemorrhage. In contrast, access to the fetal intravascular space in the proposed intervention is transcranially through the tough fibrous dura making up the wall of the torcular dural sinus. For the proposed fetal intervention, the needle does not puncture the varix, nor does it puncture the wall of any arteries.

Thus, rather than an animal model dissimilar from the focus of the study, the critical questions of whether a varix with anatomical configuration resembling VOGM can be non-invasively measured accurately, whether the number of coils required for a predetermined packing density can be accurately calculated off these measurements, whether the coiling itself can be performed under ultrasound guidance with good visualization, and whether the efficacy of the treatment can be assessed with non-invasive imaging, can all be squarely addressed with a carefully constructed ultrasound phantom. Once constructed, the phantoms would undergo a pre-treatment MR imaging workup, ultrasound-guided embolization, and post-treatment MR assessment in exactly the manner proposed for the fetal intervention. Additionally, cutting open the phantoms after completion of the process would allow for direct visual verification of the

efficacy of the treatment. The Boston Children's Hospital simulations group has successfully previously designed and built in-house anatomically accurate phantoms for simulating neonatal head ultrasound. The phantoms capture real-life tissue and liquid echogenicities and interfaces with high fidelity and are now in use for radiology house staff education. The phantoms were cast using polyvinyl alcohol (PVA) cryogel (6% by weight PVA dissolved in pure water), as this material had been previously shown to well mimic the ultrasound appearance of brain parenchyma and provides vivid solid-liquid boundaries visible on MR imaging as well.

We capitalized on this experience to build two novel phantoms designed to mimic the salient vasculature of the fetal vein of Galen malformation, embedded in a soft tissue-like cyrogel brain. Accordingly, we designed the phantom as cryogel hemisphere (the flat bottom allowed for placement on the table during embolization of the phantom) with a fluid-filled inner cavity designed to mimic the median prosencephalic varix and with a fluid-filled channel leading from the surface to the central cavity designed to mimic the falcine sinus. The specific dimensions of the central cavity and of the channel were taken directly from fetal MRI scans of patients with vein of Galen malformations. Two phantoms were built, one based on a fetus with a spherical median prosencephalic varix, and the other based on a fetus with a windsock-like configuration. A cryogel plug at the surface, mimicking the posterior fontanelle, provided access to the channel for filling with water. MRI imaging was performed on these phantoms, followed by the ultrasound-guided intervention, exactly as outlined in the protocol. Post-treatment evaluation showed that the intervention was successful in that the coil masses were deposited in compact fashion at the intended target, with no protrusion or complication. [16]

There are no clinical studies investigating fetal embolization for VOGM. However, embolization is performed in neonates with this condition, using the same catheters, wires, and coils as will be used for the fetal intervention. Additionally, BWH MFM and the BCH interventional cardiology group have pioneered fetal cardiac interventions. These two partnered institutions therefore offer unequaled expertise in the safe performance of such fetal interventions, including maternal and fetal safety, fetal anesthesia, and percutaneous needle access to fetal anatomic targets. Certain eligibility requirements and other elements of this protocol are adapted based on the experience from the fetal cardiac interventions.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Risks to the mother include the following:

- Hemorrhage requiring blood transfusion and/or further surgery due to injury of the abdomen, uterus, placenta, and umbilical cord
- Damage to other maternal organs (bladder, bowel) requiring observation, additional surgery
- Placental abruption
    - in certain cases of maternal vascular compromise due to abruption, a hysterotomy, cesarean section and/or hysterectomy may be required, which would impact future reproductive ability
- Death
- Allergic reaction

- Spinal anesthesia risks
- Chorioamniotic separation
- Premature labor /delivery: associated maternal risks of treatment
- Premature rupture of membranes
- Infection

Risks to the fetus include the following:

Risks related to undergoing a fetal procedure:
- Preterm delivery with gestational age associated risks
- Procedure-related fetal death
- Stillbirth
- Fetal paralysis
- Intravascular absorption of narcotic, atropine, or muscle paralytic medication
- Hemorrhage and/or injury of fetal structures, placenta, and umbilical cord
- Foreign body retention
- Infection

Risks related to embolization:
- Intracranial hemorrhage
- Seizures, epilepsy, or other neurological disorders
- Vessel dissection or perforation
- Allergic reaction
- Non-target embolization of the coil
- Brain ischemia
- Inadvertent vessel thrombosis or occlusion

There is no expected radiation risk, as the procedure will be performed under ultrasonographic guidance.

2.4.2 Potential Benefits

The primary benefit to mothers who enroll in the study will be careful monitoring of the pregnancy and fetus using fetal ultrasonography, echocardiography, and MRI. These are all standard of care for monitoring pregnant mothers with fetuses with VOGM at our institution but may exceed the care offered at the subject's non-specialized outside home institutions.

The primary benefit of fetal embolization of VOGM will be the potential avoidance of parenchymal brain injury, cardiopulmonary failure, and other organ failure, and thus potential lowering of significant risk of morbidity and mortality, compared to neonatal VOGM. A secondary benefit may be to improve prognosis after neonatal treatment, in the event such treatment proves necessary despite fetal intervention.

3 OBJECTIVES

3.1 Study Objectives

Primary objective: To evaluate the prenatal safety of fetal embolization for patients with vein of Galen malformations.
Secondary objective: To evaluate the efficacy of fetal embolization for patients with vein of Galen malformations.

3.2 Study Outcome Measures

Primary (safety) endpoint: The procedure is deemed safe if

1) **None** of the following unacceptable events occur within 7 days of fetal embolization:
   a) Fetal death
   b) Fetal intracranial hemorrhage, either parenchymal or extra-axial, other than petechial hemorrhage. A petechial hemorrhage is seen as focal staining of the brain parenchyma by blood products on MRI, is not associated with mass effect, and there are minimal neurologic sequelae. Petechial hemorrhages are usually considered non-serious adverse events in trials.
   c) Maternal death
2) **None** of the following unacceptable events occur between fetal embolization and delivery:
   a) Intra-procedural and post-procedural morbidity to the fetus and mother, probably related to the fetal intervention, e.g. placental abruption with subsequent sequelae
   b) Preterm delivery < 28 weeks, probably related to the fetal intervention
   c) Maternal blood transfusion or unanticipated surgical intervention, probably related to the fetal intervention
   d) Presence of fetal imaging evidence of new brain injury in a location or pattern unexpected for the natural history of vein of Galen malformation, probably related to the fetal intervention

Secondary (efficacy) endpoint: The procedure is deemed efficacious if **none** of the following serious postnatal events occur within 30 days of birth:

1. Urgent neonatal embolization is needed. Without fetal intervention, we'd expect 80% of the cohort to require such intervention.
2. Neonatal death. Without fetal intervention, we'd expect a mortality rate of 40% in this cohort.
3. Brain MRI within the first three weeks after birth reveals parenchymal brain injury (acute infarct or gliosis) affecting > 10% of the supratentorial brain volume. Without fetal intervention, we'd expect 30% of patients in this cohort to show this kind of injury.

Additional efficacy data to be collected includes assessment of the neurocognitive development in the treated cohort. Subjects will be followed and assessed until age 24 months and results will be compared to historical controls of NAR VOGM patients treated using the current neonatal paradigm.

Comparison of outcomes will be made with published (meta-analysis and UK national data [1, 2, 6, 7]) and institutional historical results for fetuses who receive standard neonatal or post-neonatal treatment.

Historically, there has been a dearth of detailed data collected for long-term neurocognitive developmental outcomes for the VOGM patient population. Based on historical data that is available, we expect 30% of patients to survive with good neurological outcomes – these data will be used as a comparator to broadly assess outcomes with this intervention. The detailed data from the neurodevelopmental assessments used in this research will be analyzed as an exploratory outcome.

Technical procedural variables to be collected for the study include:

a) Time for fetal positioning
b) Time to navigate from the torcular to the prosencephalic varix
c) Vessel perforation by wire, microcatheter, or coil
d) Number of coils deployed
e) Change in color Doppler appearance of varix after embolization
f) Change in arterialization of waveform within the varix after embolization
g) Technical fetal embolization procedure success, with time recorded at embolization procedure completion
    1. Technical procedural success will be defined as any fetal vein of Galen embolization procedure in which a microcatheter is successfully positioned in the prosencephalic varix and the pre-planned number of detachable coils is deployed.

Additional exploratory outcome measures to be categorized (as absent, mild (i.e. radiographic finding without current clinical impact) or severe) include:

a) Development of new parenchymal brain injuries on fetal MR
b) Growth of brain ventricles or extraaxial CSF spaces on fetal MR or ultrasound
c) Worsening of echocardiographic measures of LV and RV function
d) Development or worsening of sonographic findings including pleural effusions, pericardiac effusions, and hydrops
e) Incidence of non-petechial fetal intracranial hemorrhage (either parenchymal or extra-axial)

Neonatal parameters

a) Postnatal accrual of new parenchymal brain injuries on MR
b) Neonatal demise

4 STUDY DESIGN

This is a prospective, single arm, phase I/II trial to evaluate the safety and efficacy of fetal embolization for patients with vein of Galen malformations. The trial uses a Simon's optimal two-stage design for both the primary safety and secondary efficacy endpoints. More details can be found in the Statistical Considerations section.

Up to 25 subjects will be enrolled in this trial to obtain a cohort of 20 evaluable subjects. The MFCC is an international referral center for management of VOGM. In 2018, 40 neonatal VOGM embolizations were performed, and 30 in 2017. We expect recruitment to take place over 5-7 years. Study participation will extend from the time of consent through approximately 2 years post-birth (adjusted for gestational age) and data analysis will take place for approximately one year after the last subject has completed the study.

5 STUDY ENROLLMENT AND WITHDRAWAL

The intention of the Inclusion/Exclusion Criteria is to ensure evaluation of the safety of fetal embolization of vein of Galen malformation ONLY in fetuses in whom rescue is plausible, NOT in all fetuses in whom the procedure could be performed from a technical standpoint.

The study population will be delineated using the judgment of the principal investigators and an eligibility committee (see below) regarding whether or not (i) the fetus has already sustained irreversible major brain or other organ injury (SFP cohort) and (ii) the vein of Galen malformation has imaging characteristics such that the patient is likely to fall into the IT category and thus has a more favorable prognosis. Because the protocol offers a novel treatment approach with a potential for direct harm to individual fetuses and their mothers, only fetuses with the highest chance of deriving benefit from the procedure will be enrolled (i.e. the NAR cohort and neither the IT nor the SFP cohorts).

An eligibility committee will be consulted to review eligibility for each potential subject. The committee will consist of the principal investigators, Drs. Wilkins-Haug and Orbach, as well as Dr. Joanne Rispoli, a neuroradiologist at BCH, and Dr. Janet Soul, an experienced senior pediatric developmental neurologist, who consults regularly on neurological prognosis at the MFCC. Subjects will only be enrolled if all committee members determine that the eligibility criteria are met.

5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. *Pregnant woman carrying a fetus harboring a vein of Galen malformation in whom the straight sinus or falcine sinus draining the prosencephalic varix measures 7 mm or more on fetal MRI (medio-lateral diameter measured at the narrowest point of the sinus along the rostral-caudal axis, assessed on a T2-weighted coronal slice)*.

2. *Fetal gestational age between 23 weeks and term as determined by clinical information and evaluation of first ultrasound.* Although it is believed that the VOGM forms between gestational weeks 6-11 (the developmental window during which the prosencephalic vein of Markowski is present before involution [17]), diagnosis of the condition by fetal ultrasound has never been reported prior to 22 weeks, likely because of the small size of the varix prior to that point. In principle, embolization of the malformation at any time after identification and prior to delivery could forestall the development of brain, cardiopulmonary, and other organ injury. The presence of the low-pressure placental circulation and the fetal lower-flow baseline cerebral circulation might be protective, in terms of reducing potential morbidity from intracranial hemodynamic shifts that accompany embolization. The suitability for fetal treatment, in terms of technical/positional factors, will be assessed on a case-by-case basis by the MFM, ultrasonographer, and neurointerventionalist participating in the study.

3. *Anatomic diagnosis of fetal vein of Galen malformation.* Various cerebrovascular conditions, such as dural sinus malformation and pial arteriovenous fistula, can result in dilated intracranial vascular structures being visualized in utero. Similarly, fetal dilatation

of the vein of Galen can occasionally be seen without the presence of an arteriovenous lesion at all, as a benign venous variant. This condition is readily distinguishable sonographically from VOGM by virtue of the presence of dilated arterial feeding pedicles, and by the presence of an arterial waveform within the varix. This study is aimed solely at fetuses with an established diagnosis of vein of Galen malformation.

4. *Well preserved brain parenchyma.* In some cases, significant bihemispheric cerebral parenchymal injuries with gliosis are seen at the time of initial fetal diagnosis of vein of Galen malformation (SFP cohort). Such fetuses rarely survive, but if they do, are profoundly neurodevelopmentally impaired: typically blind, mute, quadriparetic, often with unremitting intractable seizures, and permanently bedbound and uncommunicative. As there is no realistic possibility of achieving a good neurological outcome in such patients, fetuses with diffuse bihemispheric brain injury will not be candidates for inclusion. On the other hand, the presence of small and focal brain parenchymal injury on fetal MR (parameters defined below) in a fetus with vein of Galen malformation would not be an exclusion criterion. Given the overall intactness of the brain parenchyma in such fetuses at the time of diagnosis, it is reasonable to expect that treatment of the underlying VOGM in utero might preclude further brain injury.

5. *Maternal age of 18 years and older*

6. *Eligible for continuous lumbar epidural anesthesia*

7. *Able to travel to study site for study evaluation, procedures and visits*

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. *Extensive fetal brain parenchymal injury/gliosis, >10% of supratentorial brain volume (i.e., SFP presentation). This is a degree of fetal brain injury beyond which the risk of significant neurological morbidity is high, based on studies of prenatal ischemic stroke [18-22].*

2. *Irreversible fetal non-brain organ injury (e.g. hydrops fetalis as a manifestation of heart failure, a finding which portends fatal outcome in fetuses with vein of Galen malformation), i.e., SFP presentation.*

3. *Fetus with VOGM in whom the straight sinus or falcine sinus draining the prosencephalic varix measures less than 7 mm on fetal MRI (T2-weighted coronal slice, medio-lateral diameter measured at the narrowest point of the sinus along the anterior-posterior axis), fitting fetal MRI criteria for likely evolution into the IT cohort*

4. *Severe maternal obesity pre-pregnancy as defined by body mass index (BMI) of 40 or greater*

5. *Fetuses with major congenital anomalies*

6. *Evidence of preterm labor, rupture of membranes or abruption*

7. *Maternal coagulopathy: INR > 1.2; PT/PTT above normal ranges for the lab; platelets <100*

8. *Medical disease requiring current anticoagulation including maternal deep vein thrombosis*

9. *Prior maternal medical history that would preclude epidural anesthesia*

10. *Multi-fetal pregnancy*

11. *Placenta previa or accreta*

12. *Participation in another fetal study that influences maternal and fetal morbidity and mortality*

13. *Known maternal hypersensitivity to 316LM stainless steel*

14. *Supine hypotensive syndrome*

5.3 Strategies for Recruitment and Retention

Participation in the study will be offered to patients who seek clinical consultation at the MFCC once fetal diagnosis of VOGM has been made. Additionally, the study will be described on VOGM online family support group sites and at national Maternal Fetal Medicine meetings and forums. A letter will also be sent out to physicians at outside institutions who see high-risk obstetric patients informing them of the study.

In accordance with federal regulations, no inducements, monetary or otherwise, will be offered to terminate a pregnancy; individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and individuals engaged in the research will have no part in determining the viability of a neonate.

5.4 Subject Withdrawal

5.4.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

- Ideal fetal positioning for the procedure cannot be achieved over a duration of 40 minutes with epidural analgesia; a single, separate 40 minute attempt may be undertaken at > 24hrs after the first attempt.
- The fetal embolization procedure is attempted but unable to be completed for any reason.

5.4.2 Handling of Subject Withdrawals

Any subject withdrawn prior to completing the fetal embolization will be replaced. The enrollment goal of the study is to achieve a cohort of 20 evaluable participants who have completed the intervention.

All subjects enrolled in the study will plan to deliver at BWH. In the event that there is an unplanned delivery at an institution other than BWH, the subject will receive standard of care at the outside institution. We will be available for consultation and, as is the case for non-research subjects, would consider the benefits and risks of transfer to BCH versus local treatment, depending on the clinical severity of the neonate. All advice will be purely based on the best medical interest of the baby, and not the research study. We will attempt to collect all relevant clinical information from the outside institution.

5.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to mother or fetus.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

Further information regarding stopping rules can be found in the Statistical Considerations section.

6 STUDY INTERVENTION

6.1 Study Product Description

The investigational devices used in this study as a permanent implant are Target XXL Detachable Coils and Target XL Detachable Coils (Stryker Neurovascular). Target Detachable Coils are stretch resistant, electrolytically detachable coils consisting of a platinum-tungsten alloy coil attached to a stainless-steel delivery wire. Target Detachable Coils are intended to endovascularly obstruct or occlude blood flow in vascular abnormalities of the neurovascular and peripheral vessels. In particular, these devices are currently indicated for endovascular embolization of intracranial aneurysms. Such coils are routinely used in clinical practice for neonatal embolization. However, they have not been previously used in a fetal intervention. More information about the products can be found in the product labeling.

Additional devices being used off-label during the investigational procedure include:

ASAHI Neurovasculature Guide Wire: ASAHI CHIKAI Black 18 Soft Tip (K171613)
Headway 21 Microcatheter, Model MC21250S (K093160)
Bard TruGuide Coaxial Biopsy Needle, 19Ga 17.8 cm, Model C2020A (K936194)

However, these devices are used during the procedure for the delivery of the implanted coils and are entirely removed from the subject at the end of the procedure.

6.1.1 Acquisition

The coils will be purchased directly from the manufacturer, Stryker Neurovascular.

6.1.2 Formulation, Packaging, and Labeling

The devices will be provided with the commercial label.

6.1.3 Product Storage and Stability

Prior to each procedure, the manufacturer will provide a supply of XL and XXL coils. These coils are stored in the Interventional Radiology area at BCH separately from the clinical stock.

6.2 Accountability Procedures for the Study Product

The product is for single use only. Once the procedure is over, any unused and unopened coils and leftover materials, including the detachment system and packaging will be returned back to the manufacturer. Each coil is individually labeled with a bar code, scanned in after the procedure for tracking purposes by Children's Hospital and the coil vendor (per standard clinical protocol for all intracranial coils deployed in patients).

6.3 Concomitant Medications/Treatments

Concomitant medications taken by the mother will be recorded only if they are directly related to any AE. This information will be abstracted from the medical record.

All concomitant medications taken by the neonate will be abstracted from the medical record from birth through discharge. After discharge, information on concomitant medications for the baby will be collected by asking the family during the follow up visits or phone calls.

For concomitant medications, the medication name, dose, indication, and start and stop dates will be recorded.

6.4 Study Procedural Intervention Description

The study involves a single fetal intervention of maternal transuterine, fetal transcranial torcular puncture and median prosencephalic vein embolization. Detachable platinum coils (Target XL and XXL Detachable Coil, Stryker Neurovascular) will be used to pack the prosencephalic varix. This procedure will take place in an OR at either Brigham and Women's Hospital or Boston Children's Hospital.

6.5 Administration of Procedural Intervention

Mothers will undergo epidural anesthesia and then be positioned with left uterine displacement. After induction of maternal regional analgesia, the location of the placenta and the fetal orientation will be established using conventional ultrasonographic techniques. External and/or transvaginal fetal manipulation will then be employed to produce an ideal, or nearly ideal, fetal position for transcranial torcular puncture and subsequent median prosencephalic vein embolization.

While it is impossible to continuously monitor fetal heart rate during the intervention, as the ultrasound signal emitted by the heart rate doppler monitor interferes with the ultrasound probe used for visualization of the fetal head, the fetal heart rate will be checked frequently throughout the procedure – at least every five minutes, as well as after positioning the fetus appropriately for the intracranial intervention, even if the heart rate was checked less than five minutes prior to the repositioning. In order to ensure that these fetal heart rate checks occur without fail, one team member will be designated to monitor a 5-minute timer throughout the case and call out to the team when the time to check the heart rate has arrived. A second team member will be tasked with turning on a hand-held heart rate monitor at that moment and calling out the fetal heart rate once a reading is obtained. After that, the ultrasound-guided procedure at the fetal head will continue.

If an ideal or near-ideal fetal position cannot be obtained within 40 minutes of transcutaneous and transvaginal fetal manipulation, no attempt to perform fetal VOGM embolization will be made, and the procedure will be terminated. If, in the judgment of the clinical team, the subject remains a viable candidate for intervention, another attempt at fetal embolization may be made on a separate day.

Once ideal fetal positioning has been achieved, prior to needle insertion through the fetal posterior skull, an intramuscular injection will be administered to the fetus to provide fetal analgesia and fetal immobility. The interventional procedure will proceed using fetal sonographic visualization.

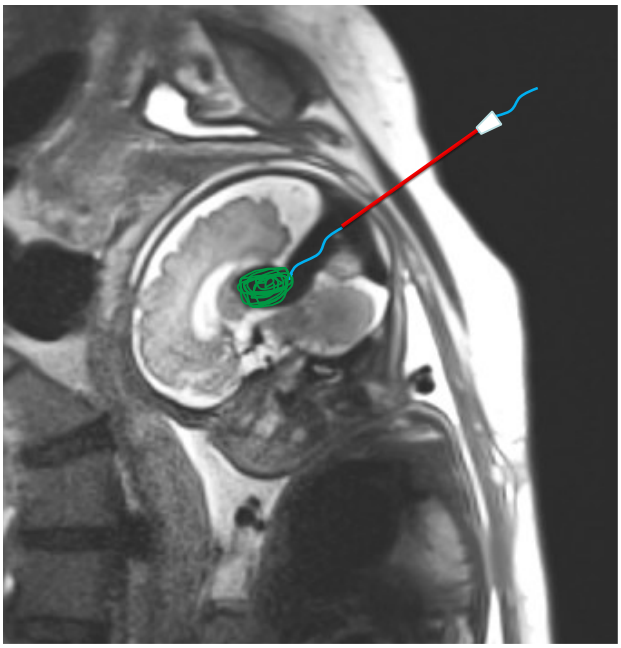

Figure 1

After transcranial access to the torcular has been achieved using an 18 or 19G needle (red line in Figure 1 above), the needle hub will be attached to extension tubing connected to a continuous perfusion heparinized saline drip via a rotating hemostatic valve (RHV). A microcatheter (blue), attached to a second pressurized continuous perfusion heparinized saline drip, will be introduced via the RHV, and navigated over a 0.018” microwire from the torcular through the falcine or straight sinus into the median prosencephalic varix, using sonographic visualization.

For vascular structures in vivo, achievable packing densities of the total volume of the viscus using metallic coils are on the order of 15-25%. For brain aneurysms, where the goal is complete exclusion of the aneurysm dome from the arterial circulation in order to minimize the risk of rupture, densities of 20-25% are typically the goal [23]. In contradistinction, the goal in VOGM embolization of the varix is to achieve significant diminution in flow through the malformation rather than complete exclusion from the circulation. In fact, we calculated the packing density in six neonatal patients in whom successful coil embolization of the varix was carried out in order to alleviate heart failure and found that a packing density of 13-22% resulted in excellent clinical outcome. As such, our target packing density for the fetal interventional procedure, where the explicit goal is to reduce flow through the malformation and thereby increase the ratio of IT to NAR neonates, will be ~15%.

The number of detachable platinum coils (Target XL and XXL Detachable Coil, Stryker Neurovascular) needed to achieve a packing density of ~15% within the varix will be calculated using standard neurointerventional software designed for such calculations. The caliber of the prosencephalic varix will be measured along three axes on fetal MR, and overall volume calculated. The predetermined number of coils will be deployed within the varix under ultrasound (shown in green in Figure 1 above). Target XL and XXL are optimized for large and

giant brain aneurysms, have been chosen for a combination of relatively large diameter of coil filament, resulting in efficient packing, combined with increased softness, lowering the risk of iatrogenic trauma during deployment. Note that only one single session of deployment of coils will be performed per pregnancy as part of this study.

Color doppler ultrasound will be used to visualize flow and to characterize the waveform within the prosencephalic varix prior to and after embolization. In order to minimize the total Doppler exposure and thus thermal transfer, the field of view of the ultrasound probe will remain on the anatomic region being treated, the prosencephalic varix, and Doppler assessment of flow in the internal carotid arteries and circle of Willis will not be measured; the Thermal Index (TI) will be kept at less than 1.0. We anticipate up to approximately one hour of total ultrasound imaging, with the color and spectral Doppler involving less than 10-15 minutes of that time. This falls well under AIUM recommended maximum scanning time for TI of 1 (less than 60 minutes). In addition to the above thermal considerations, there is no a priori expectation of how the circle of Willis arterial flow velocity might change immediately as a result of the embolization, and thus no clinical or technical benefit accruing to the procedure.

In accordance with our fetal cardiac interventional experience, the entire procedure is expected to take <2 hours, which includes time for fetal positioning.

After embolization, mothers will be monitored either at BCH or at the Brigham and Women's Hospital until at least the morning after the procedure, or longer, if necessary. Fetal heart rate is monitored continuously after the procedure, and a focused ultrasound to check placenta, cervix, and the fetal brain will be performed 3-6 hours post-procedure. The measurement will conform to the AIUM official statement on measurement of fetal heart rate. Mothers will receive tocolytic medication perioperatively and continued for 12 hours (po). Continuation of tocolytics past 12 hours will be on an individualized basis, as determined by the maternal fetal specialist. A follow-up fetal echocardiogram, obstetric ultrasound including cervical length, and fetal MRI will be repeated 24-28 hours after the procedure. Maternal activity will be increased gradually, depending upon maternal symptoms and cervical ultrasound findings.

6.6 Procedures for Training of Clinicians on Procedural Intervention

The study procedure will be conducted by licensed clinicians. An obstetric anesthesiologist will administer the maternal anesthesia. The administration of the fetal intramuscular anesthetic and paralytic will be overseen by a fetal anesthesiologist credentialed at both BWH and BCH. A radiologist with ultrasound specialization and extensive experience with invasive fetal procedures will perform the fetal ultrasound throughout the procedure at BWH, while at BCH a maternal-fetal medicine specialist will provide ultrasound guidance. BWH and BCH maternal-fetal medicine credentialing includes the ability to perform invasive fetal procedures, and MFM physicians with experience with invasive fetal cardiac procedures and credentialed at BWH and BCH will be present and participate in each procedure, positioning the fetus and directing the transuterine needle transcranially into the fetal torcular. The microcatheterization and coil deployment will only be performed by Dr. Darren Orbach, credentialed at both BWH and BCH.

7 STUDY SCHEDULE

7.1 Screening, Enrollment, and Baseline (Visit 1)

Screening

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review prior fetal ultrasounds, fetal echocardiography, and fetal MRI to determine eligibility based on inclusion/exclusion criteria.

Enrollment

- Obtain and document informed research consent from both parents of the fetal subject.

Baseline

- Perform a physical exam
- Obtain demographic information and medical history
- Perform fetal ultrasound, fetal echocardiogram, and fetal MRI

7.2 Study Intervention (Visit 2)

Study Procedure Visit

- Perform a preprocedure assessment on the mother
- Obtain clinical procedural consent and anesthesia consent
- Perform the study intervention

After the intervention

- Mothers will be monitored at least overnight at BWH or BCH, or longer if needed
- Tocolytic medication will be administered perioperatively and as needed for the first 12 hours post-intervention
- Fetal heart rate will be monitored continuously after the procedure
- Focused ultrasound to look at cervix, placenta and fetal brain will be performed 3-6 hours post-procedure
- Fetal ultrasound, fetal echocardiogram, and fetal MRI will be performed 24-28 hours after the procedure
- Fetal distress will be addressed clinically and as appropriate for gestational age and status of vein of Galen malformation
- Preterm labor, rupture of membranes and abruption will be addressed clinically, as appropriate for gestational age

7.3 Pre-Delivery Follow up visits

If more than 4 weeks remain before expected delivery, the following assessments will be repeated every 4 weeks until delivery:

- Fetal ultrasound, fetal echocardiogram, and fetal MRI

7.4 Delivery

Plans will be made for all subjects to be delivered at BWH. The mode of delivery is not impacted by the fetal intervention and will be determined based on clinical criteria. Likewise, gestational age of delivery will be determined clinically. Depending on the specifics of each case, including how far along the pregnancy is, how severely affected the fetus is, and other factors, in some cases, early delivery would be the chosen option, while in others, termination might be the recommended option, as previously discussed by the subject with the clinical care team. A recommendation of termination of pregnancy would result from major cerebral injury (intracranial hemorrhage other than petechial or parenchymal infarct >10% of the supratentorial brain volume) visualized on fetal imaging, in the setting of a gestational age young enough that termination remains an option. As such major cerebral injury is one of the unacceptable safety events mentioned above in Section 3.2 and below in Section 11.3, the subject in question would be included in the calculations related to the two-stage study design for safety. However, since fetal death would not have been spontaneous but rather by termination of pregnancy, the subject would not be counted towards the fetal deaths in the study.

If no such situation arises, elective delivery will be performed on a date chosen by the obstetrician as optimal in terms of safety for the mother and baby, in the same way that delivery dates are chosen for patients with vein of Galen malformations who do not undergo fetal intervention.

The newborn will be admitted to the NICU, as per the current practice for all patients with VOGM. As per clinical care, an MRI and echocardiogram will be performed as soon as possible after delivery, typically on day 1 of postnatal life. All care, including additional embolization procedures and additional imaging, will be done per standard of care for this patient population. Per our protocol (and similar to that of most major referral centers for VOGM), if a neonatal patient is unable to be extubated or is not stable enough on medications to be discharged from the NICU within a week due to cardiopulmonary failure, this indicates a need for urgent neonatal embolization.

At our center, extubation criteria in neonates without an underlying lung disease include:

- Patient awake with spontaneous and regular breaths, and
- Mean airway pressure on the ventilator < 10 cmH_2O and FiO_2 < 0.25
- Hemodynamical stability with normal heart rate and blood pressure

At our center, NICU discharge criteria include:

- Absence of respiratory difficulties with respiratory rate consistently under 60/min and without any periodic breathing
- Feeding well (bottle or breast feeding) with good weight gain
- Maintaining temperature in open crib

There are no study-specific requirements or procedures at this point, but data will be collected regarding the subjects' medical care and any adverse events that occur while inpatient in the NICU.

7.5 Follow up Visits

All neonatal subjects will be followed for 2 years post-birth. Families will be contacted by a study investigator every 6 months, ± 1 month, in order to collect information about the neurological and overall developmental status. If the patients undergo cardiology evaluations as part of their clinical care, the clinical information from these evaluations will be collected as well. Since many subjects are expected to reside a long distance from Boston Children's Hospital and will not be able to attend in-person follow up visits every 6 months, the assessment of neurodevelopmental and health status is designed to be conducted by telephone as needed. The following neurodevelopmental assessment tools will be used according to the schedule outlined below:

1. Vineland Adaptive Behavior Scales for assessment of overall development in the four major domains of neurologic function (communication, motor, socialization and daily living skills)
2. REEL (Receptive-Expressive Emergent Language Test) for more in depth evaluation of language skills
3. Child Behavior Checklist (CBCL) to assess emotional and behavioral function
4. DAYC-2 cognitive assessment: The Development Assessment of Young Children-Second Edition (DAYC-2). The DAYC-2 Cognitive domain will be used to assess cognitive development in infant at 18 and 24 months.
5. Bayley examination (in-person only): The Bayley Scales of Infant and Toddler Development is an assessment instrument designed to measure physical, motor, sensory, and cognitive development in babies and young children. It involves interaction between the child and examiner and observations in a series of tasks.

Visit 3: 6 month visit (± 1 month):

- Ask families about developmental milestones, any early interventions, and incidence of seizures/epilepsy and their treatment
- Vineland Adaptive Behavior Scales
- REEL

Visit 4: 12 month visit (± 1 month):

- Ask families about developmental milestones, any early interventions, and incidence of seizures/epilepsy and their treatment
- Vineland Adaptive Behavior Scales
- REEL

Visit 5: 18 month visit (± 1 month):

- Ask families about developmental milestones, any early interventions, and incidence of seizures/epilepsy and their treatment
- Vineland Adaptive Behavior Scales
- REEL
- Child Behavior Checklist
- DAYC-2 cognitive assessment
- Bayley examination (if in-person)

Visit 6: 24 month visit (± 1 month):

- Ask families about developmental milestones, any early interventions, and incidence of seizures/epilepsy and their treatment
- Vineland Adaptive Behavior Scales
- REEL
- Child Behavior Checklist
- DAYC-2 cognitive assessment
- Bayley examination (if in-person)

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

All adverse events of Grade 2 or higher that occur in mothers, fetuses, or neonates and which could plausibly be related to the procedure, based on their nature or temporal relationship to the procedure, will be recorded. The occurrence of events will be assessed during the procedure, at the time of hospital discharge, at each follow-up visit (including imaging results), at delivery/birth, while the neonate is inpatient, and at discharge from the NICU. All subjects will be questioned for adverse events at the time of their follow-up studies (see above) or fetal or neonatal demise. The data collected will be recorded using an Adverse Event form, which will record a description of the event, time of onset in relation to the procedure, the severity of the adverse event, the treatment required, and the outcome.

Preliminary classification of adverse events will be made by the obstetrician for the mother and by the neurointerventionalist for the fetus/neonate. All events will be subsequently reviewed by the DSMB.

Adverse events will be classified as occurring in the mother, or the fetus/neonate, and as most plausibly related to one of the following, based on timing and physiology:

a) Maternal anesthesia
b) Fetal positioning or manipulation
c) Fetal paralysis or analgesia
d) Needle passage through maternal abdomen, uterus, or placenta
e) Needle passage into the fetal cranium or other fetal structures
f) Microcatheter/microwire navigation from the fetal torcular to the prosencephalic varix
g) Coil deployment within the prosencephalic varix
h) Needle withdrawal
i) Other
j) Unknown

8.1.1 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.1.2 Serious Adverse Events

A serious adverse event, including a serious suspected adverse reaction or serious adverse reaction as determined by the Investigator or the sponsor is any event that results in any of the following outcomes:

1. Death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the intervention (e.g., a car accident). If a study subject dies during the study and an autopsy is performed,

the autopsy results will be attached to the study subject's Case Report Form (CRF). Possible evidence of organ injury and the potential relationship of the injury to the intervention are of particular interest. The autopsy report should distinguish the relationship between the underlying diseases, their side effects, and the cause of death.

2. Life-threatening. This includes any AE during which the study subject is, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This definition does not include any event that may have caused death if it had occurred in a more serious form.
3. Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
4. Inpatient hospitalization or prolongation of existing hospitalization beyond the expectation for delivery, except for admission for elective surgery.
5. Important medical event that may not result in one of the above outcomes, but which may jeopardize the health of the study subject or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

It is anticipated that all neonatal subjects on this study, as patients with vein of Galen malformations, will be hospitalized during the course of treatment. Therefore, regarding the hospitalization criterion for seriousness, only AEs that clearly result in the *prolongation* of hospitalization, not related to typical NICU events (e.g. reintubation, poor feeding, apnea of prematurity, etc.) or which are life-threatening should be considered serious for this study.

8.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded throughout the study.

Reportable events will be recorded starting at the time of the start of the study procedure through subject discharge from the NICU. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Characteristics of an Adverse Event

8.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

8.3.2 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.3.3 Severity of Event

We will assign toxicity grades to indicate the severity of adverse experiences and toxicities. For maternal adverse events, toxicity grading consistent with NCI-CTCAE v 5.0 will be used for this protocol. The purpose of using the NCI-CTCAE system is to provide standard language to describe toxicities and to facilitate tabulation and analysis of the data and assessment of the clinical significance of treatment-related toxicities.

Any adverse events not included in the NCI-CTCAE listing will be recorded and graded 1 to 5 according to the General Grade Definition provided below:

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required, hospitalization, or hospice care probable.
Grade 5	Death	Death

For additional information and a printable version of the NCI-CTCAE v. 5.0 manual, consult the NCI-CTCAE website,
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

The NCI-CTCAE system has not been validated for neonatal subjects. Therefore, neonatal adverse events will be graded according to the International Neonatal Consortium (INC) Neonatal Adverse Event Severity Scale [24].

Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior; no change in baseline care or monitoring indicated
Grade 2	Moderate	Moderate; resulting in minor changes of baseline age-appropriate behavior; requiring minor changes in baseline care or monitoring
Grade 3	Severe	Severe; resulting in major changes of baseline age-appropriate behavior or non-life threatening changes in basal physiological processes; requiring major change in baseline care or monitoring
Grade 4	Life-threatening	Life-threatening; Resulting in life-threatening changes in basal physiological processes; requiring urgent major change in baseline care
Grade 5	Death	Death related to AE

More information regarding this scale can be found here:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943241/#SP6

8.4 Reporting Procedures

All AEs, except as defined above, will be followed until the time the event is resolved or medically stable, or until subject is discharged from hospital, whichever comes first. AEs may be discovered through any of these methods:

- Observing the subject
- Questioning the subject, which will be done in an objective manner
- Receiving an unsolicited complaint from the subject
- Review of medical records/source documents

All AEs must be recorded accurately on the Adverse Event log for each study subject. The date of onset and duration of the AE, grade, whether it was expected or unexpected, action taken, date of resolution (if applicable) and outcome of the event must be recorded. The investigator will treat subjects experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes or they are discharged from the hospital.

SAEs and unanticipated problems will be reported promptly to the IRB(s) according to local regulations and guidelines.

The PI and delegates are responsible for notifying the DSMB chair of all SAEs. The DSMB will evaluate the relationship of the SAE to the underlying disease. The PI, in cooperation with the DSMB, will determine whether the SAE is unexpected in nature and make a recommendation for any further action. The primary consideration is the study subjects' safety. All other AEs will be reported to the DSMB for review and adjudication at regular intervals.

8.4.1 Reporting of SAEs and AEs to the FDA

The Sponsor-Investigator (SI) will report unanticipated adverse device effects to the FDA and other applicable health authorities within the required timelines, as specified in 21 CFR 812.150, within 10 working days of the SI becoming aware of the event. As defined in 21 CFR 812.3(s) an unanticipated adverse device effect means any serious adverse 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 was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.5 Halting Rules

The study will be stopped if there is one maternal death occurring within 48 hours of the embolization procedure that is determined by the DSMB to be plausibly related to the study procedure.

More information regarding study stopping rules can be found in the Statistical Considerations section.

9 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of five senior faculty of medical schools not affiliated with the study. Members will have expertise in pediatric neurointerventions, management of vein of Galen malformations, neonatology, maternal-fetal medicine, and fetal/neonatal cardiology. The DSMB will meet as outlined in the DSMB charter.

The DSMB will make recommendations to the PI and the Institutional Review Boards at Boston Children's Hospital and the Brigham and Women's Hospital about protocol changes necessary to protect the scientific validity of the study or to protect study participants, including study termination. The DSMB will meet by phone or video conference at least twice a year after the start of patient enrollment to review all procedures. All serious adverse events will result in notification of the DSMB, which will evaluate the severity of the event, the relationship to the study intervention, and whether stoppage criteria have been met. The DSMB charter indicates additional time points when a DSMB meeting may need to be convened for evaluation of continuation of the study.

10 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by an independent qualified monitor. The monitor will evaluate study processes and documentation based on the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in the Monitoring Plan. The Monitoring Plan will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. The monitor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the MP. Documentation of monitoring activities and findings will be provided to the site study team and the study PIs.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Primary objective (safety):

Null hypothesis: Rate of unacceptable safety events is P>30%
Alternative hypothesis: P<5%

Secondary objective (efficacy):

Null hypothesis: Response rate is P≤40%
Alternative hypothesis: P≥70%

11.2 Sample Size Considerations

We estimate, based on published results and our own experience, that 65% of all neonates born with vein of Galen malformation require urgent neonatal intervention (i.e. are NAR), under current standard of care. Thus, in order to achieve a cohort size of 20 treated patients, we expect to consent and screen 28-30 fetal patients. We expect to enroll 25 participants to account for withdrawals prior to completing the intervention (due to failure to achieve near ideal fetal position or other reasons). The study will be closed to enrollment once 20 participants have completed the intervention. Using the prescreening technique we have developed based on fetal MRI measurement of straight sinus or falcine sinus caliber at the narrowest point, we can estimate that 80% of all such fetal VOGM patients will progress to NAR status without fetal intervention. Setting a goal of reducing this fraction to 30% NAR status after fetal intervention (i.e., a 50% absolute reduction), the proposed sample size will provide 80% power to detect a significant effect of fetal intervention.

11.3 Safety Review

Two-stage design for safety endpoint

In Stage 1, up to 11 evaluable patients will be enrolled (**Table 2**). Out of 11 patients, if 3 or more patients experience an unacceptable event (see definition in Section 3.2 above and recapitulated below Table 2), the intervention is unsafe and not worthy of further study. If 2 or fewer experience any unacceptable event, the trial will proceed to Stage 2, where an additional 9 evaluable patients will be enrolled, for a total of N=20 evaluable patients. Out of N=20 patients, if 4 or more patients experience any unacceptable event, the intervention is unsafe and not worthy of further study. If 3 or fewer patients experience any unacceptable event, the intervention is sufficiently safe and worthy of further study. In addition, in case of a single maternal death, the study will be halted pending review by the DSMB and the FDA.

This design tests the null hypothesis that the rate of unacceptable events is P>30% versus the alternative that P<5%. The total type I error rate is 0.097 and the power is 97.5%. If the intervention is truly unsafe, there is a 68.7% probability of early trial termination.

Table 2: Decision rules for safety based on the optimum two-stage design.

	Cumulative number of patients with unacceptable events	**Decision**
Stage 1: Enroll 11 patients	3 or more	Terminate the trial: agent not worthy of further study
	2 or fewer	Inconclusive result: proceed to Stage 2
Stage 2: Enroll 9 additional patients	4 or more	Terminate the trial: agent not worthy of further study
	3 or fewer	Trial concludes: agent worthy of further study

1) Unacceptable events within 7 days of fetal embolization include:
   a) Fetal death
   b) Fetal intracranial hemorrhage, either parenchymal or extra-axial, other than petechial hemorrhage. A petechial hemorrhage is seen as focal staining of the brain parenchyma by blood products on MRI, is not associated with mass effect, and there are minimal neurologic sequelae. Petechial hemorrhages are usually considered non-serious adverse events in trials.
   c) Maternal death
2) Unacceptable events occur between fetal embolization and delivery include:
   a) Intra-procedural and post-procedural morbidity to the fetus and mother, probably related to the fetal intervention, e.g. placental abruption with subsequent sequelae
   b) Preterm delivery < 28 weeks, probably related to the fetal intervention
   c) Maternal blood transfusion or unanticipated surgical intervention, probably related to the fetal intervention
   d) Presence of fetal imaging evidence of new brain injury in a location or pattern unexpected for the natural history of vein of Galen malformation, probably related to the fetal intervention

11.4 Efficacy Review

Two-stage design for efficacy endpoint

In Stage 1, up to 11 evaluable patients will be enrolled (**Table 3**). Out of 11 patients, if 5 or fewer patients respond, i.e. do not experience a serious postnatal event (see definition in Section 3.2 above), the intervention is not efficacious and not worthy of further study. If 6 or more respond, the trial will proceed to Stage 2, where an additional 9 evaluable patients will be enrolled, for a total of N=20 evaluable patients. Out of N=20 patients, if 10 or fewer patients respond, the intervention is not sufficiently efficacious and not worthy of further study. If 11 or more patients respond, the intervention is sufficiently efficacious and worthy of further study.

This design tests the null hypothesis that the response rate is P≤40% versus the alternative that P≥70%. The total type I error rate is 0.099 and the power is 90.2%. If the intervention is truly not efficacious, there is a 75.3% probability of early trial termination.

Table 3: Decision rules for efficacy based on the optimum two-stage design.

	Cumulative number of responses	**Cumulative number of non-responders (patients with serious postnatal events)**	**Decision**
Stage 1: Enroll 11 patients	5 or fewer	6 or more	Terminate the trial: fetal intervention not worthy of further study
	6 or more	5 or fewer	Inconclusive result: proceed to Stage 2
Stage 2: Enroll 9 additional patients	10 or fewer	10 or more	Terminate the trial: fetal intervention not worthy of further study
	11 or more	9 or fewer	Trial concludes: fetal intervention worthy of further study

11.5 Timing of safety and efficacy rules

The safety endpoint is observed from Day 0 (the day of fetal intervention) to Day 7 post-intervention. The efficacy endpoint is observed from the birth to Day 30 of life. Both safety and efficacy decision rules must be satisfied before enrollment to Stage 2 is allowed. Prior to initiating accrual at Stage 2, a sensitivity analysis will be performed to determine if both the safety and efficacy rules would be triggered. Hence, trial enrollment for Stage 2 may be suspended after the enrollment of the 11^{th} patient to allow observation up to Day 30 of life of the most recently treated patient.

The safety and efficacy rules are to be interpreted as specifying that the trial will stop as soon as either criterion is reached; e.g., if the first 3 evaluable patients experience unacceptable prenatal events (safety rule), or the first 6 patients experience serious postnatal events (efficacy rule), then the trial stops immediately. Beyond the 11^{th} patient, the trial halts as soon as 4 unacceptable prenatal events or 10 serious postnatal events occur.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

13.3 Informed Consent Process

Both parents of fetuses who meet all entry criteria for fetal intervention and who wish to continue in the enrollment process will undergo a formal Informed Consent discussion and will both be required to sign the consent form in order to participate in the study.

The father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or if the pregnancy resulted from rape or incest.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

13.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

13.5 Future Use of Identifiable Data

Identifiable data from this study will be stored for future use and future research. Subjects will be informed of this in the informed consent form. Any data that is shared outside of the study will be labeled with a code. The key to the code will be kept on a password-protected computer.

14 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

14.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

14.2 Data Capture Methods

Data will be entered into REDCap Cloud, a 21 CFR 11 FDA-compliant electronic database.

14.3 Study Records Retention

Record retention: An investigator shall retain records required to be maintained for a period of 2 years after the latest of the following dates: (a) date on which clinical investigation is terminated; or (b) data is no longer required to support FDA pre-market approval application, or the FDA is notified of discontinuation of application.

IRB records: The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the appropriate department or agency at reasonable times and in a reasonable manner.

14.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to the IRB, according to their requirements.

LITERATURE REFERENCES

1. Yan et al., Outcome and complications of endovascular embolization for vein of Galen malformations: a systematic review and meta-analysis. J Neurosurg 2015, 123:872-890.
2. Brinjikji et al., Endovascular Treatment of vein of Galen malformations: a systematic review and meta-analysis. AJNR 2017, 38:2308-14.
3. Lasjaunias et al., The management of vein of Galen aneurysmal malformations. Neurosurgery 2006, 59:S3-184-S3-194.
4. Deloison et al., Hidden mortality of prenatally diagnosed vein of Galen aneurysmal malformation: retrospective study and review of the literature. Ultrsound Obstet Gynecol 2012, 40:652-658.
5. Paladini et al., Vein of Galen aneurysmal malformation (VGAM) in the fetus: retrospective analysis of perinatal prognostic indicators in a two-center series of 49 cases. Ultrasound Obstet Gynecol 2017, 50:192-199.
6. Lecce et al., Cross-sectional study of a United Kingdom cohort of neonatal vein of Galen malformation. Annals of Neurology 2018, 84:547-555.
7. Gopalan et al., Presentation, course, and outcome of postneonatal presentations of vein of Galen malformation: a large, single-institution case series. Developmental Medicine & Child Neurology 2018, 60:424-429.
8. Arko L, Lambrych M, Montaser A, Zurakowsk D and Orbach DB. Fetal and neonatal MRI predictors of aggressive early clinical course in Vein of Galen malformation. American J of Neuroradiology. June 202, 41(6): 1105-1111; DOI: https://doi.org/10.3174/ajnr.A6585
9. Chevret et al., Severe cardiac failure in newborns with VGAM. Intensive Care Medicine 2002, 28:1125-30
10. Wong et al., Hemodynamic disturbances associated with endovascular embolization in newborn infants with vein of Galen malformation. Journal of Perinatology 2006. 26:273-8
11. Patel et al., Systemic hemodynamics in infants with vein of Galen malformation: assessment and basis for therapy. Journal of Perinatology 2007. 27:460-63
12. Meek et al., Cerebral blood flow increases over the first three days of life in exteremely preterm neonates. Arch Dis Child Fetal Neonatal Ed 1998, 78:F33-37
13. Kehrer et al., Development of cerebral blood flow volume in preterm neonates during the first two weeks of life. Pediatric Research 2005, 58:927-30
14. Mickle et al., The transtorcular embolization of vein of Galen aneurysms. J Neurosurgery 1986, 64:731-5
15. Hanner et al., Gianturco coil embolization of vein of Galen aneurysms: technical aspects. Radiographics 1988, 8:935-46
16. Orbach DB, Wilkins-Haug LE, Benson CB, Rangwala SD, Pak C, Saffarzadeh M, Weinstock P. Overcoming roadblocks in clinical innovation via high fidelitysimulation: use of a phantom simulator to achieve FDA and IRB approval of a clinical trial of fetal embolization of vein of Galen malformations. J of Neuroinventional Surgery. 2023; 0:1-7. DOI: http://dx.doi.org/10.1136/jnis-2022-019658
17. Raybaud et al., Aneurysms of the vein of Galen: embryonic considerations and an atomically features relating to the pathogenesis of the malformation. Neuroradiology 2989, 31:109-28
18. Mercuri E, Rutherford M, Cowan F et al. (1999) Early prognostic indicators of outcome in infants with neonatal cerebral infarction:a clinical EEG and MRI study. Pediatrics **103**, 39–46.
19. Dyet LE, Kennea N, Counsell SJ, Maalouf EF, Ajayi-Obe M, Duggan PJ, Harrison M, Allsop JM, Hajnal J, Herlihy AH, Edwards B, Laroche S, Cowan FM, Rutherford

MA, Edwards AD. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics. 2006 Aug;118(2):536-48.
20. Ozduman K, Pober BR, Barnes P, Copel JA, Ogle EA, Duncan CC, Ment LR. Fetal stroke. Pediatr Neurol. 2004 Mar;30(3):151-62. Review.
21. Roelants-van Rijn AM, Groenendaal F, Beek FJ, Eken P, van Haastert IC, de Vries LS. Parenchymal brain injury in the preterm infant: comparison of cranial ultrasound, MRI and neurodevelopmental outcome. Neuropediatrics. 2001 Apr;32(2):80-9.
22. Zecavati N, Singh R, Farias-Moeller R, Olsen C, Carpenter JL, Kadom N. The utility of infarct volume measurement in pediatric ischemic stroke. J Child Neurol. 2014 Jun;29(6):811-7.
23. Sluzewski et al., Relationship between aneurysm volume, packing, and compaction, in 145 cerebral aneurysms treated with coils. Radiology 2004, 231:653-658.
24. Salaets T, Turner MA, Short M, et al. Development of a neonatal adverse event severity scale through a Delphi consensus approach. *Arch Dis Child*. 2019;104(12):1167–1173. doi:10.1136/archdischild-2019-317399

APPENDIX A: SCHEDULE OF EVENTS

Procedures		Screening and Baseline (Visit 1)	Study Intervention (Visit 2)	Pre-delivery follow up visits (clinical care)	6 month visit (Visit 3) ± 1 month	12 month visit (Visit 4) ± 1 month	18 month visit (Visit 5) ± 1 month	24 month visit (Visit 6) ± 1 month
Signed Consent Form		X						
Assessment of Eligibility Criteria		X						
Review of Medical History		X						
Review of Concomitant Medications		X	X	X	X	X	X	X
Study Intervention			X					
Fetal ultrasound, fetal echocardiogram, and fetal MRI		X		X				
Assessment of Adverse Events			X	X	X	X	X	X
Neurological assessments	Vineland Adaptive Behavior Scales				X	X	X	X
	REEL				X	X	X	X
	CBCL						X	X
	Bayley Exam						X*	X*
	DAYC-2						X	X

*Only performed if visit is in person.