Milrinone in addition to hyperdynamic therapy in the treatment of vasospasm following aneurysmal subarachnoid hemorrhage

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1.0 Background

Aneurysmal subarachnoid hemorrhage affects 6-8/100,000 people every year[4]. In addition to the various medical comorbidities that accompany this disease, about 50% will experience angiographic narrowing of the cerebral arteries (radiographic vasospasm) and 20-30% will experience delayed ischemic neurologic deficit (DIND, formerly clinical vasospasm)[1]. The onset of vasospasm is most commonly between days 4 and 14 after the hemorrhage. Patients afflicted with DIND may go on to suffer permanent neurologic deficits which can impair their quality of life or be fatal. Although there has been much advancement in the last 15-20 years in the ability to monitor and assess this condition, there has unfortunately been scarce progress in treating it effectively[3].

The current mainstay of therapy is so-called hyperdynamic therapy, in which the patient's blood pressure is augmented and blood volume increased with the hope that resistance to flow can be overcome and the brain perfused[2]. This comes with its own set of complications, such as cardiac injury and fluid overload. It is also important to note that this modality of therapy has never been validated in a randomized, controlled trial, though it is accepted as the standard of care in many institutions[5]. Patients that are refractory to medical therapy may undergo angiographic therapy with infusion of agents such as calcium-channel blockers or papaverine or in extreme cases, balloon angioplasty. Some groups, such as the Montreal Neurological Hospital, have used infusions of the drug milrinone (Hospira, Inc Lake Forest, IL) to counter cerebral vasospasm. The smooth muscle of cerebral blood vessels is rich in phosphodiesterase-III (PDE-III), making it a promising target for this drug[6]. Milrinone is currently FDA approved for the treatment of congestive heart failure as it has both vasodilatory and inotropic effects. It is thought that these same effects may be beneficial in cerebral vasospasm. Milrinone also has anti-inflammatory effects through inhibition of interleukins[5].

Milrinone is known to be safe with a relatively low incidence of complications. The Montreal group had no patients (out of 88 presented) with complications from milrinone infusion for as long as 9 days. To date, no study has compared the current standard-of-care, hyperdynamic therapy, with milrinone in addition to standard treatment.

2.0 Rationale and Specific Aims

The goal of this study is to assess the efficacy of milrinone as an agent to treat cerebral vasospasm by adding it to standard therapy. This will take the form of a randomized, controlled trial in which patients will receive either standard hyperdynamic therapy or hyperdynamic therapy + milrinone. The primary outcome of interest will be modified Rankin Scale (mRS) at 6 months (+/- 60 days). Secondary outcomes assessed will be need for angiographic therapy, mRS at 12 months (+/- 60 days), duration of vasospasm (in days), hospital and ICU lengths of stay, side effects/complications of both modalities of therapy, milrinone dose, name and dose of drug(s) used for intra-arterial injection, number of times angiographic therapy is required, vasopressor usage, and discharge disposition.

3.1 Inclusion/Exclusion Criteria

Inclusion

- Subjects ≥18 years of age
- Aneurysmal subarachnoid hemorrhage, proven on CT angiogram or digital subtraction angiography
- Aneurysm treated, either by endovascular embolization or surgical clip ligation
- Evidence of increased velocities on transcranial dopplers (TCDs) and/or radiographic evidence of vasospasm as seen on angiogram
- Cerebral vasospasm as demonstrated by patient's clinical exam (new focal deficit or change in mental status not attributable to any other cause)

Exclusion

- Recurrent subarachnoid hemorrhage
- Untreated ruptured aneurysm, for any reason
- Patients who die prior to treatment for aneurysm
- Patients who are not able to complete at least 6 months of follow-up
- Patients who are admitted already in vasospasm (i.e. a delayed admission)
- Creatinine clearance less than 20 ml/min
- Women with a positive pregnancy test or who are lactating
- Other comorbidity which may adversely affect patient outcome, at the discretion of the principal investigator

4.0 Enrollment/Randomization

Location: IU Health Methodist Hospital, 1701 N Senate Ave, Indianapolis, IN 46202

Process: Patients diagnosed with aneurysmal subarachnoid hemorrhage will be identified at the time of diagnosis and the research team will be contacted by the admitting team to monitor the patient. The patients will be consented and enrolled into the study as soon as possible following surgery or endovascular intervention, if the PI (or his assigned designee) determines the patient to meet all criteria other than evidence of vasospasm. A subject ID number, which is arbitrary, will be assigned to the patient once consented so that patient confidentiality may be protected. They will not, however, be randomized at this point. The patient's Legally Authorized Representative (LAR) will be contacted for consent if the patient is unable to provide it. If a LAR is not present at the bedside, initial contact may take place over the phone to establish a time to discuss the study and obtain consent in person. At the time of diagnosis of clinical vasospasm, the treating physician(s) will notify the research team. At this time, eligibility will again be reviewed with the PI (or his assigned designee) and the protocol orders will be signed and scanned to the pharmacy where they will be entered into CERNER and the pharmacy will randomize the patient to standard hyperdynamic therapy with placebo (normal saline) or standard therapy + milrinone. Randomization will take place at the time of protocol entry into CERNER. The diagnosis will be at the judgment of the treating physician and confirmed by the PI (or his assigned designee). Providers and patients will remain blinded to the drug. An index of which patients received the drug will be maintained by pharmacy services.

5.1 Study Procedures (see Figure 1)

Every effort will be made to initiate the protocol as soon as possible following confirmation of diagnosis and all eligibility criteria and to deliver the drug or placebo to the patient within two hours of order placement/protocol initiation. Diagnosis of clinical vasospasm will be at the

discretion of the treating physician or practitioner, and verified by the PI (or his assigned designee). The pharmacy services will then randomize the patient to receive either milrinone or placebo (normal saline). All patients will undergo treatment per the institutional protocol, which is to infuse fluids (crystalloid or colloid) at an increased rate to maintain a central venous pressure greater than 8 mmHg and progressive increase in blood pressure either by removing antihypertensive medications or using vasopressors, with the addition of milrinone or placebo based on randomization. Standard protocol in our institution calls for progressive increase of systolic pressure until symptoms subside, up to 220 mmHg. All patients will receive an infusion of milrinone or placebo at 0.75 mCg/kg/min. If no improvement is noted within 24 hours, the infusion will be increased to 1.25 mCg/kg/min. All patients in both groups will receive the same infusion at the same rate with the same parameters for increase of dose and for weaning (see below). The drug will be ordered by the physician and provided by pharmacy services in the standard institutional preparation. These parameters are the same as those used at the Montreal Neurological Hospital.

Once the patient is randomized in the study, they will continue to undergo TCDs on a three times per week basis as per institutional protocol. This number, along with the patient's clinical status, will be followed until symptoms resolve. Angiographic therapy may be utilized as needed based on the patient's needs and judgment of the treating physician. If no symptoms are evidenced for 72 hours, then the milrinone/placebo infusion will be weaned at a rate of 0.25 mCg/kg/min every 24 hours until a rate of 0.25 mCg/kg/min is reached, then the infusion will be turned off after 24 hours at this rate. For patients receiving an initial dose of 0.25 mCg/kg/min and titrated up to 0.375 mCg/kg/min, the infusion will be weaned to 0.125 mCg/kg/min for 24 hours then turned off. The weaning will not occur at a rate faster than 0.75 mCg/kg/min over 72 hours. HHH therapy will be weaned according to the standard institutional protocol. If symptoms recur, the protocol will be restarted. Patients with severe, refractory symptoms may still undergo angiographic rescue therapy. Special dosing will be followed for patients with impaired renal function, based on creatinine clearance (CrCl), checked at some point during the current hospital admission and prior to study drug initiation. This will be as follows:

CrCl (mL/min)	**Initial Dose**	**Titration Dose**
Greater than 50 mL/min	0.75 mCg/kg/min	1.25 mCg/kg/min
41- 50 mL/min	0.5 mCg/kg/min	0.75 mCg/kg/min
31-40 mL/min	0.375 mCg/kg/min	0.5 mCg/kg/min
21-30 mL/min	0.25 mCg/kg/min	0.375 mCg/kg/min

Table 1 – Renal dosing parameters

This dosing schema is reflective of the Montreal protocol[5]. While the initial dose of 0.75 mcg/kg/min is less than the currently maximum approved dose of 1.13 mcg/kg/min for congestive heart failure, the maximum titration dose of 1.25 mcg/kg/min is above this. The Montreal group presented 88 patients who were given this same dosing titration with minimal side effects[5], so the investigators believe this procedure to be safe.

Data will be collected and entered into the study database. See Appendix A for a list of data points that will be collected. mRS collection will be carried out at follow-up appointments in the office or over the phone depending on patient availability.

The infusion of the drug may pose risks, including hypotension, arrhythmias, tachycardia, chest pain, and headache. In a very small number of cases, patients may develop severe arrhythmias

or anaphylaxis if allergic to the compound or an ingredient in the preparation. Any patients with low blood pressure will be treated with increased rates of intravenous (IV) fluids and vasopressor agents to raise the blood pressure. This is standard of care for patients suffering from vasospasm already. At the discretion of the treating provider, any patients with dangerously low blood pressure, or other symptoms of shock, will have milrinone/placebo discontinued, however, their data will still be used in final analysis. Final outcome data will also still be collected on these patients.

Angiographic therapy may include:

- Diagnostic angiogram (using dye in the artery to look at blood flow in the brain)
- Use of medications injected into the arteries to dilate the arteries and relieve spasm
- Use of a balloon to dilate parts of the artery that are very tight.

The type of angiographic therapy that is used will be at the discretion of the treating provider. This is standard of care for patients with subarachnoid hemorrhage.

Women of childbearing age will receive a urine pregnancy test when they present to the hospital/emergency room as standard of care. This will occur prior to being approached by the research team.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

6.1.1 Adverse Event (AE)

An adverse event is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to study intervention, or it has worsened in intensity or frequency following study intervention. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0 and will be logged for all patients in both arms of the study. The following grading scale will be used:

0 = No adverse event or within normal limits
1 = Mild adverse event
2 = Moderate adverse event
3 = Severe and undesirable adverse event
4 = Life-threatening or disabling adverse event
5 = Death related to adverse event

6.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 28 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to first administration of study drug

    - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

6.1.3 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

6.1.4 Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Table 2 – Adverse event relationships

Relationship	**Attribution**	**Description**
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly NOT related
	Unlikely	The AE is doubtfully related
Related to investigational agent/intervention	Possible	The AE may be related
	Probable	The AE is likely related
	Definite	The AE is clearly related

6.2 Adverse Event (AE) Reporting Requirements

Adverse events (AEs) will be recorded from the time of first study drug administration and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

6.2.1 Reporting to the IRB

1. Unanticipated problems involving risks to subjects or others will be reported promptly to the IRB if they:
    - were unexpected;

- were related or possibly related to the research; and
- suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

  If the adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

2. Prompt reporting of adverse events to the IRB is defined as within 5 days for on-site studies and 5 days for offsite studies.

6.3 Data Safety Monitoring Board

A board to monitor safety of the intervention will be convened when 10 patients have been enrolled into the study, or at 3 months after the initiation of enrollment, whichever comes first. At the initial meeting, the DSMB will determine its meeting schedule for the remainder of the study. This board will consist of one intensive care physician, one pharmacist, one interventional neuroradiologist, and a statistician will be consulted to assist with data analysis. All adverse events will be reviewed by the board and summarized to be reported to the Indiana University IRB. The board will reserve the right to terminate the study based on quantity and severity of SAEs or if the data reveals there is no benefit.

7.0 Study Withdrawal/Discontinuation

Any participant or family member wishing to withdraw themselves from the study may alert the treating nurse, physician, or study coordinator at any time during their course. If a participant wishes to withdraw, this will be noted on the study database, no further information will be collected from that patient, however data collected up to that point may be used in final analysis. The investigators reserve the right to withdraw any patient it if is felt that further participation in the study will endanger the patients' health. If a patient is withdrawn by the investigator, the study team will still collect outcome data and all data collected may be used in final analysis. If a subject voluntarily withdraws from the study, they will be presented with the option to consent to continued data collection via a separate informed consent document. If they decline, no further data collection will occur.

8.0 Statistical Considerations

Sample size justification: Literature on the natural history and outcomes specifically of patients who suffer DIND is sparse. Based on our own experience, we expect to see mRS of 2 or less in approximately 50% of patients in the control group. With a sample size of 59 patients per group, the study will have 80% power to detect a 25% difference between the experimental and control groups (75% vs. 50% with mRS of 2 or less), assuming a two-sided chi-square test conducted at a 5% significance level.

The experimental and control groups will be compared for differences in baseline demographics and clinical characteristics using chi-square tests for categorical variables and Wilcoxon Rank Sum tests for ordinal and continuous variables. The primary outcome, mRS 2 or less at 6 months, will be compared between groups using chi-square tests. Secondary outcomes, including need for angiographic therapy, mRS 2 or less at 12 months, presence of side effects/complications, and discharge disposition will be compared between groups using chi-square tests, and mRS scores at 6 and 12 months, duration of vasospasm, and hospital and ICU lengths of stay will be compared between groups using Wilcoxon Rank Sum tests.

9.0 Privacy/Confidentiality Issues

All medical information about patients will be maintained in secure and encrypted electronic medical record systems. As mentioned above, each patient will be assigned a unique and arbitrary identifier. The index for the identifiers will be maintained on a secure device which is encrypted and kept behind a firewall at all times. All efforts will be made to prevent transmission of this information, however if it should need to be transmitted, encryption will be used. All efforts will be made to minimize dissemination of this information. All paper records will be kept stored in secure locations with locking enclosures.

10.0 Follow-up and Record Retention

The duration of the study will be 3 years or as long as needed to enroll the required number of patients to meet the power analysis above. Minimum follow-up will be 6 months, and 12 month follow up will also be of interest for the study. The database generated from the study will be maintained indefinitely for possible future retrospective analyses.

References

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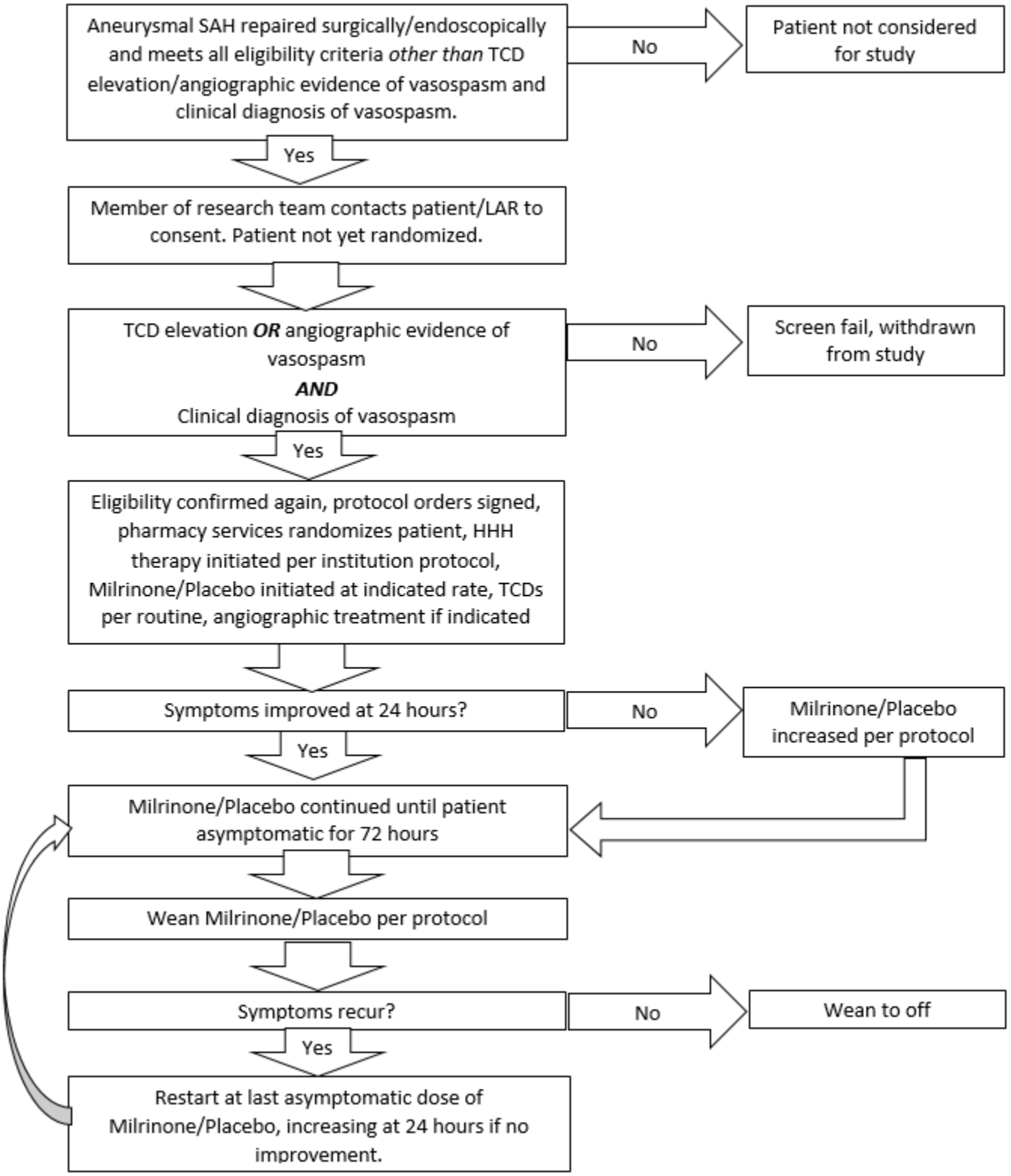
Appendix A – Data Points for Milrinone Protocol

- **Demographics**
  - Name
  - DOB
  - Age
  - MRN
  - Study ID#
  - Gender
  - Ethnicity
  - Race
- **Past Medical History**
  - HTN
  - Smoker
- **Presentation/Pre-Intervention Data**
  - Date of SAH symptom onset
  - Date of hospital admission
  - Time of hospital admission
  - Hunt/Hess score on admission
  - Fischer score on admission
  - Location of aneurysm (side and vessel)
  - Size of aneurysm
  - # of aneurysms
  - Modality of treatment indicated (clip/coil/both)
  - Date of treatment procedure
  - Time of treatment procedure
- **Post-Intervention Data**
  - First date of elevated TCD
  - Time of first elevated TCD
  - Measurement of first elevated TCD
  - Severity of spasm
  - Mean TCD throughout hospitalization
  - Max TCD throughout hospitalization
  - Need for EVD
  - Date of clinical diagnosis of vasospasm
  - Time of clinical diagnosis of vasospasm
  - Duration of spasm
  - Date of end of spasm
  - Evidence of ischemic changes on CT prior to study drug initiation (date/time)
  - Evidence of ischemic changes on CT any time during hospitalization (date/time)
  - Vasopressor usage
    - Drug(s) used
    - Duration of use
- **Study Drug Data**
  - Date study drug initiated
  - Time study drug initiated
  - Duration of study drug exposure
  - Study drug dose at initiation
  - Was study drug titrated up?

- Hemodynamic parameters
- Creatinine clearance checked during current admission prior to study drug initiation
- Was study drug discontinued early due to complications?

- **Angiographic Therapy Data**
  - Results of angiogram
  - Severity of spasm on angiogram
  - Intra-arterial drug use?
  - Number of times angiographic therapy required
- **Complications**
  - Hypotension
  - Tachycardia
  - Arrhythmias
  - Chest pain
  - Others at discretions of provider
- **Outcomes**
  - Length of ICU stay
  - Date of transfer to floor
  - Date of discharge
  - Length of hospital stay
  - Discharge disposition
  - Modified Rankin Score at 6 months
  - Modified Rankin Score at 12 months
  - Whether patient received milrinone or placebo

Figure 1


Aneurysmal SAH repaired surgically/endoscopically and meets all eligibility criteria *other than* TCD elevation/angiographic evidence of vasospasm and clinical diagnosis of vasospasm.
No
Patient not considered for study
Yes
Member of research team contacts patient/LAR to consent. Patient not yet randomized.
TCD elevation ***OR*** angiographic evidence of vasospasm
AND
Clinical diagnosis of vasospasm
No
Screen fail, withdrawn from study
Yes
Eligibility confirmed again, protocol orders signed, pharmacy services randomizes patient, HHH therapy initiated per institution protocol, Milrinone/Placebo initiated at indicated rate, TCDs per routine, angiographic treatment if indicated
Symptoms improved at 24 hours?
No
Milrinone/Placebo increased per protocol
Yes
Milrinone/Placebo continued until patient asymptomatic for 72 hours
Wean Milrinone/Placebo per protocol
Symptoms recur?
No
Wean to off
Yes
Restart at last asymptomatic dose of Milrinone/Placebo, increasing at 24 hours if no improvement.