Protocol Title

Impact of Fever Prevention in Brain Injured Patients (INTREPID)

Sponsor

Bard Medical Division
C. R. Bard, Inc.
8195 Industrial Blvd.
Covington, GA 30014

Protocol Number/Version/Date

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Clinical Trial Registration

NCT02996266

BARD MEDICAL DIVISION

CLINICAL STUDY PROTOCOL

Title:	**Impact of Fever Prevention in Brain Injured Patients (INTREPID)**
Protocol Number:	**BMD-1111**
Version:	**7.0**
Study Type:	**Randomized, Controlled Trial; Investigational Device Exemption**
Date:	**March 9, 2020**
Study Device(s):	**Arctic Sun® 5000 Temperature Management System**
Sponsor:	**Bard Medical Division C. R. Bard, Inc. 8195 Industrial Blvd. Covington, GA 30014**
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Protocol Signature Page

The Investigator agrees to conduct the clinical study which is the subject of this protocol in accordance with the Clinical Study Agreement, this protocol, all applicable laws and regulations, and the conditions of approval imposed by the reviewing Ethics Committee or Institutional Review Board.

Agreed to by (Investigator):

_____

Printed Name – Investigator

_____

Signature – Investigator

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Date

Agreed to by (Sponsor):

_____

Printed Name – Sponsor

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Signature – Sponsor

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Date

Protocol Abbreviations/Acronyms

Abbreviation/Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AFC	Aggressive Fever Control
AGP	ArcticGel™ Pads
AS-5000	Arctic Sun® 5000 Targeted Temperature Management System
ASPECTS	Alberta Stroke Program Early CT Score
Bard	C.R. Bard, Inc.
BMD	Bard Medical Division, C.R. Bard, Inc.
CFR	Code of Federal Regulations
CRF	Case Report Form
CV	Curriculum Vitae
DMC	Data Monitoring Committee
EC	Ethics Committee
EOS	End of Study
FDA	United States Food and Drug Administration
F/U	Follow-Up
ICDSC	Intensive Care Delirium Screening Checklist
ICF	Informed Consent Form
ICH	Intracerebral Hemorrhage
ICU	Intensive Care Unit
IFU	Instruction for Use
IRB	Institutional Review Board
IS	Ischemic Stroke
ITT	Intent-to-treat
LKN	Last Known Normal
LTF	Lost to follow-up
MAE	Major Adverse Event
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
MoCA	Montreal Cognitive Assessment
PP	Per protocol
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SAP	Statistical analysis plan
SCA	Sudden Cardiac Arrest
SOC	Standard of Care
TBI	Traumatic Brain Injury
TH	Therapeutic Hypothermia
TTM	Targeted Temperature Management
WBC	White Blood Cell
WFNS	World Federation of Neurological Societies Grading System for Subarachnoid Hemorrhage
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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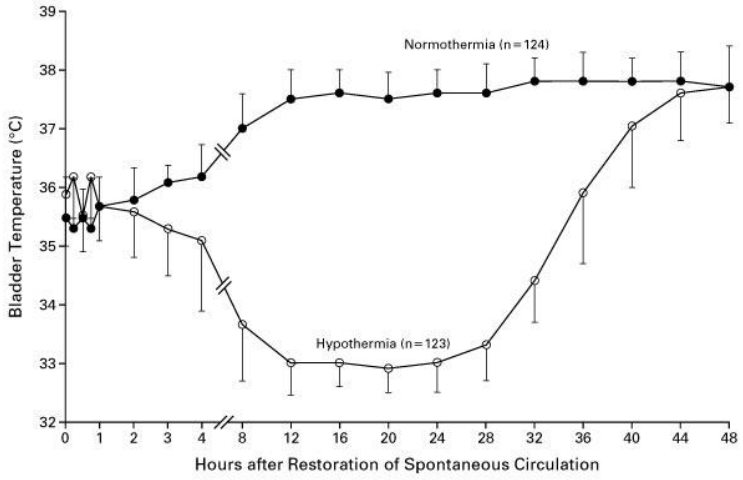
1. INTRODUCTION

There has been significant attention in recent studies exploring the use of therapeutic hypothermia (TH) to improve outcomes in brain-injured patients. In 2002, two studies served as the basis for using therapeutic hypothermia to 32-34°C in post-sudden cardiac arrest (SCA) patients, both showing a significant benefit not only in terms of survival but also functional outcome.[1,2] These studies led to widespread adoption of TH in the post-cardiac arrest population. However, in 2013 the Targeted Temperature Management (TTM) trial showed that cooling patients to 36°C was as effective as cooling them to 33°C,[3] leading to questions regarding the original 2002 studies. Further review of the temperature data from the 2002 trials reveals that many patients in the control "normothermia" group were relatively hyperthermic (see Figure 1). Indeed, it may have been this relative hyperthermia that led to worse outcomes in the control group, rather than a true beneficial effect from the hypothermia used in the treatment group.

Figure 1.



The use of TH is quite likely beneficial in certain populations but is not without its potential adverse effects such as cardiac dysrhythmia and increased infection and bleeding risk. Additionally, significant doses of sedatives and/or paralytics, which can confound neurologic assessment, are often required to control shivering in TH patients. Finally, TH delays drug metabolism and has shown detrimental effects on the ability to prognosticate neurologically, specifically after cardiac arrest.[4,5] Considering the findings of the TTM trial[3], review of the temperature curves from the 2002 SCA studies, and the known adverse effects of TH, controlled normothermia may prove to be an effective method of preventing secondary brain injury and improving neurological outcomes, may reduce potential complications, and alleviate concerns regarding neuro-prognostication.

Approximately 700,000 patients have an ischemic stroke annually in the United States; 5 – 10% of all strokes are subarachnoid hemorrhages and 15% of all strokes are intracerebral hemorrhages.[6,7] Up to 90% of patients develop at least 1 fever within 7 days in the ICU.[8] Regardless of the etiology of the neurological injury, fever or elevated body temperature has been associated with worse outcomes. Clinical studies have explored the effects of fever within acute ischemic stroke, subarachnoid hemorrhage and intracerebral hemorrhage patients.

In ischemic stroke, elevated body temperature on admission is associated with higher mortality (and lower body temperature associated with decreased mortality), and is independently related to stroke severity, infarct size and outcome.[9] For each 1°C increase in temperature, the relative risk of poor outcome rises by 2.2.[10] The odds of short term mortality double when an ischemic stroke patient develops a fever within 24 hours of onset.[11] In a study of 580 subarachnoid hemorrhage (SAH) patients, hyperthermia (>38.3°C) was found to contribute to worse outcomes (odds ratio 2.0), after controlling for higher clinical grade, re-hemorrhage, advanced age, and other comorbid diseases.[12] Studies in intracerebral hemorrhage (ICH) patients have also found an association of fever with poor outcome, including within the first 72 hours of injury.[13] In a study of 266 ICH patients, early neurological deterioration was associated with a temperature >37.5°C.[14]

In 2008, Greer et al performed a comprehensive meta-analysis of 14,431 patients with a variety of neurological injuries. They found that fever/higher body temperature was associated with worse outcomes, regardless of the outcome measure used, compared to patients who were normothermic.[15] The outcome measures examined included mortality, Glasgow Outcome Scale, Barthel Index, modified Rankin Scale, Canadian Stroke Scale, and both intensive care unit (ICU) and hospital length of stay. [15]

Overall, there is strong data that supports the association of poor outcomes with fever in brain injured patients. Despite several studies that have treated fever after its onset, from a physiological perspective, prevention of secondary injury may be a promising approach compared to strategies that are reactive. Fever has been known to increase excitatory neurotransmitters and oxygen free radicals which influence ischemic mechanisms within the penumbra.[16] This can result in higher mortality rates and worse neurological outcomes.[16] By preventing fever the cellular demand for oxygen should be decreased, the blood brain barrier should be stabilized and cell membranes should be stabilized. [16]

In 2009, Broessner et al, performed a randomized study to assess the safety and efficacy of prophylactic, catheter-based normothermia. [17] While the study demonstrated that prophylactic normothermia significantly reduced fever burden and was not associated with increased major adverse events, it was not powered to detect a difference in clinical outcomes. Additional post-hoc analysis of the study data did however suggest that prophylactic normothermia might be beneficial in selected patients susceptible for fever.[18] Mayer et al performed a study to compare the efficacy of the Arctic Sun

Temperature Management System with conventional measures (cooling blankets) for treating fever in neuro-intensive care unit patients.[19] They demonstrated that patients treated with the Arctic Sun System experienced a 75% reduction in fever burden and also spent less percent time febrile. The authors note that there was a non-significant trend toward greater improvement in Glasgow Coma Scores in Arctic Sun-treated patients. [19] In a case-control study of SAH patients treated with advanced fever control, defined as controlled normothermia with an advanced temperature modulating device, 40 cases and 80 controls were analyzed.[20] All advanced fever control patients were treated with the Arctic Sun Temperature Management System; one patient was also treated with an intravascular system. There was a trend towards a lower rate of poor outcomes in the advanced fever control group at 3-months and a statistically significant lower rate of poor outcomes at 12-months. [20] In a recent review, Bohman and Levine conclude that "The value of therapeutic normothermia in the neurocritical care unit (NCCU) is increasingly accepted, yet prospective trials that demonstrate a functional benefit to patients are lacking."[21]

1.1. Study Rationale

Multiple studies demonstrate that fever / elevated temperature is associated with poor outcomes in brain injured patients; however, there are no conclusive studies that demonstrate that fever prevention/controlled normothermia is associated with better outcomes. This study will be conducted to assess the impact of advanced temperature control to prevent fever in brain injured patients. The fever prevention group will use the Arctic Sun Temperature Management System and will be compared to standard care patients in whom fever may spontaneously develop. If fever develops in a patient in the standard care group, they are treated with standard fever care measures according to a stepwise algorithm, consisting primarily of intermittent antipyretics (e.g., acetaminophen) and cooling blankets and, when necessary, advanced targeted temperature management devices. Outcomes will be measured across a number of assessments including, but not limited to 3- and 6-month follow-up modified Rankin Scale, Barthel Index Scale, Glasgow Outcomes Scale-Extended, Montreal Cognitive Assessment, mortality, delirium, and ICU and hospital length of stay.

1.2. Device Description

1.2.1. Test Device: Arctic Sun® 5000 Temperature Management System

The Arctic Sun® Temperature Management System is intended for monitoring and controlling patient temperature. The Arctic Sun® System is comprised of two main components, the Arctic Sun® 5000 (console) and ArcticGel™ Pads. The Arctic Sun® 5000 (AS-5000) consists of a touch screen used to program therapy, a port where a continuous patient temperature device is connected (e.g., esophageal probe, temperature-sensing Foley catheter, rectal probe), and

a water reservoir. The ArcticGel™ Pads feature a thin hydrogel coating that ensures they maintain contact with the patient's skin throughout the treatment. The conductive property of the pad's mimics water immersion. When connected and in place, the Arctic Sun® System circulates water through the ArcticGel™ Pads at a specific temperature based on the prescribed, programmed therapy and the patient's current temperature. Patient temperature is continuously fed into the AS-5000 and water temperature adjustments are made as required to reach/maintain target temperatures. See Appendix 19.10 for Instructions for Use (IFU).

1.2.2. Control Device(s): Standard Care / Cooling Method

Per the Investigator's discretion, patients randomized to the control arm may be treated with fans, ice packs, and/or any one of the many water or air circulating blankets available in the market (e.g., Soft-Temp® Conductive Warming Blanket, Adroit Medical Systems, Loudon, TN; Maxi-Therm® Lite Hyper-Hypothermia Blanket, Cincinnati Sub-Zero, Cincinnati, OH). Standard cooling blankets usually consist of a control device that circulates cooled air or water through a blanket that is placed over and/or under the patient. These cooling blanket systems do not always incorporate a method to continuously assess patient temperature so the clinician may be responsible for adjusting the air/water temperature up or down.

Investigators will be responsible for obtaining IFU(s) for non-Bard devices used in the study.

2. STUDY OBJECTIVES

The objective of this study is to assess fever burden and the impact on outcomes of fever prevention using the Arctic Sun 5000 Temperature Management System as compared to standard fever care in brain-injured patients.

Assessment of this objective will be performed by evaluating the:

- Fever burden (°C-hour; defined as the area under the temperature curve above 37.9°C);
- 3- , 6- , and 12-month follow-up neurologic assessment;
- Mortality rates [7-day (or hospital discharge), 3-month, 6-month, 12-month]; and
- Intensive care unit and hospital lengths of stay.

See Section 10.3 for a detailed description of study endpoint measures.

3. STUDY DESIGN

This protocol describes a randomized, controlled multicenter clinical investigation designed to assess fever burden and early, short- and long-term clinical outcomes of fever prevention (FP) using the Arctic Sun 5000 Temperature Management System (test device) compared to standard fever care (control device(s)) in the treatment of moderate-to-severe brain injured patients. The target temperature in the FP group is 37.0°C through 336 hours (14 days) or until discharged/deemed medically ready for discharge from the ICU. In this study, fever is clinically defined as ≥38°C.

The primary outcome endpoint is the daily average fever burden (°C-hour) between randomization and through 336 hours (14 days) or ICU exit, whichever comes first. The key secondary outcome endpoint is the level of functional independence at 90 days post-injury (3-month) follow-up based on the modified Rankin Scale. Other secondary endpoints will include additional neurologic outcomes measured at varying time points, mortality, delirium, and ICU and hospital length of stay (see Section 10.3).

The primary safety endpoints will include adverse events, major adverse events, incidence of infection, and incidence of shivering.

The study will follow brain-injured patients throughout their hospital stay and at 3-, 6-, and 12-months post injury for neurologic assessment. After a pre-specified stabilization period, patients meeting inclusion/exclusion criteria will be consented and randomized to either the fever prevention (FP) or the standard care (SC) group. Randomization will be stratified by study site, the type of brain injury (i.e., acute ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage), subject age and injury-specific severity score.

4. STUDY POPULATION

4.1. Number of Subjects

This study is projected to enroll an estimated 1,176 subjects (588 subjects per study group) to yield 1,000 evaluable subjects, with a potential maximum of 2,000 evaluable subjects at up to 50 study sites (U.S. and international) with no more than 20% of the subjects enrolled at any one site.

See Section 10.1 for sample size considerations.

4.2. Study Population

Adult subjects with a primary stroke diagnosis (i.e., acute ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage) will be screened for potential eligibility against the study protocol inclusion and exclusion criteria. Medical records documenting tests, examinations and evaluations may be used as the source documents for the initial screening criteria. Specific screening tests

and/or evaluations, typically performed as standard of care in neurocritical patients, will be recorded and used to verify inclusion/exclusion criteria. Only those patients having gone through the prescribed disease-specific stabilization period will be considered for enrollment.

During the screening and recruitment process, the Investigators or their designees will be responsible for describing the nature of the clinical study to the subject or healthcare proxy, verifying that the eligibility criteria have been met, and obtaining informed consent.

4.3. General Care of Enrolled Subjects

It is understood that care and treatment of the brain injured patient is individualized based on their specific needs and circumstances; however, there is a need to reduce the potential for treatment bias across sites/investigators participating in this study. To that end, when at all possible/reasonable, investigators should follow established society guidelines when caring for enrolled subjects. Appendices 19.11, 19.12, and 19.13 contain a summary of recommendations from the American Heart Association/ American Stoke Association guidelines for management of patients with acute ischemic stroke, spontaneous intracerebral hemorrhage, and subarachnoid hemorrhage, respectively.

4.4. Eligibility Criteria

4.4.1. General Inclusion Criteria

A subject must meet all of the following criteria to be entered in the study:

1. Adult patients ≥18 and ≤85* years of age; and

2. Admitted with a primary neurological diagnosis of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage; and

3. Prior to onset of acute symptoms, was considered functionally independent (mRS 0-2)*; and

4. Meets disease-specific criteria. (See section 4.4.3)
*NOTE: For subjects >80 and ≤85 years of age, the qualifying mRS must be = 0

4.4.2. General Exclusion Criteria

A subject must be excluded from study entry if any of the following criteria are met:

1. Fever (≥38.0°C) for more than one hour or more than one instance prior to study enrollment; or

2. Pre-existing neurological, psychiatric, or other condition that would confound neurological assessment or would make it difficult to accurately assess neurologic and/or functional outcome; or

3. Has a pre-morbid condition that in the opinion of the investigator suggests poor likelihood of survival to 6 months; or

4. Has a pre-morbid mRS ≥3 for subjects 18 – 80 years of age or ≥1 for subjects ≥81 years of age; or

5. Diagnosed with brain death; or

6. Is undergoing therapeutic hypothermia therapy; or

7. Has sustained neurological injury felt to be catastrophic with little chance of recovery or is on comfort measures only; or

8. Has a skin condition in which the use of the ArcticGel Pads is contraindicated (i.e., skin that has signs of ulceration, burns, hives, or rash); or

9. Has poor skin integrity or poor tissue perfusion; or

10. Participation in a concurrent investigational / interventional study (medical device or drug); or

11. In the investigator's opinion is likely to require a stay in the ICU ≤72 hours; or

12. Is known to be pregnant, or has a positive pregnancy test (for women of childbearing age); or

13. Fever (≥38.0°C) at time of study enrollment.

14. Fever at the time of randomization.*

*A confirmatory temperature check must be performed no more than one hour prior to randomization to ensure that the subject has not become febrile between enrollment and randomization. Subjects found to be

febrile between enrollment and randomization will be considered screen failures.

4.4.3. Disease Specific Inclusion / Exclusion Criteria

DISEASE STATE*	STABILIZATION PERIOD (Enrollment Timeframe)	INCLUSION CRITERIA	EXCLUSION CRITERIA
Ischemic Stroke	No less than 3 hours but no more than 24 hours from ictus	• Imaging confirmed diagnosis • NIHSS ≥6 at the time of consideration of enrollment** • If performed, IV tPA or endovascular management meets institutional guidelines	• Hemorrhagic conversion of an ischemic stroke is acceptable, provided it meets all ICH inclusion/ exclusion criteria below
Intracerebral Hemorrhage	• No less than 6 hours but no more than 36 hours from last known normal (LKN) time • No less than 4 hours after intracranial procedure to ensure stability post-operatively if surgery performed • Additionally, for patients on anticoagulation therapy, only after serial scans at least 4 hours apart show no further ICH expansion (>5cc)	• Imaging confirmed diagnosis of primary ICH • NIHSS ≥6 at time of consideration of enrollment** • GCS ≥5 at time of consideration of enrollment*** • ICH volume of 1-60 cc	• ICH known to be secondary to neoplasm or trauma
Subarachnoid Hemorrhage	• No less than 4 but no more than 48 hours after stabilization post intracranial endovascular/surgical procedure (if performed) • Within 72 hours of onset of symptoms	• Aneurysmal/ aneurysmal pattern SAH confirmed within 24 hours of symptom onset • Admission imaging shows Fisher Grade 2-4 OR Modified Fisher Scale 1 - 4	• SAH due to trauma • Fisher Grade 1 OR Modified Fisher Scale 0 • Non-securable aneurysm except angiogram negative SAH if all other I/E criteria met

*Note: Randomization is based on the subject's primary diagnosis.
**Note: Guidance for performing NIHSS in comatose patients can be found in Appendix 19.3
***Note: For intubated patients, the verbal portion of GCS may be imputed (see Appendix 19.2).

5. STUDY SCHEDULE

All subjects who sign the informed consent and meet eligibility criteria will be randomized to either the FP or SC group and will be followed as per the protocol defined study procedures and follow-up visit schedule. A confirmatory temperature check must be performed no more than one hour prior to randomization to ensure that the subject does not become febrile. If the subject becomes febrile between enrollment and randomization, they will be considered a screen failure. Randomization and initiation of study procedures (e.g., index procedure, hourly temperature measurements) should take place as close to enrollment as possible.

The study procedures and visit schedules for enrolled subjects is shown in Table 1. With the exception of the post-acute phase visit, all follow-up visits must be scheduled based on the date of symptom onset. If a subject is unable to attend a scheduled study visit, this must be documented in the subject's file and the site should request that the subject return as close to the scheduled visit date as possible.

Note: For the purposes of this study, the definition of "deemed medically ready for discharge" is defined as follows: patient is medically stable and no longer requires critical/intensive level care or observation. For example, a patient may be medically stable and no longer requires critical level care but cannot be discharged from the ICU due to a lack of beds in a standard care unit. In this case, the acute phase of the study would be discontinued and the date the patient was deemed ready for discharge would be recorded in the appropriate case report form.

Should a subject in the Fever Prevention arm prematurely discontinue the Arctic Sun 5000 System OR a subject in the Standard Care arm have a targeted temperature management system initiated for fever control, the subject does not switch arms of the study. All study procedures / assessments should continue as scheduled for their assigned arm.

Should a subject's medical care be changed to comfort-measures only, the acute phase of the study will be discontinued.

Table 1: Study Schedule

	Screening / Enrollment	Acute Phase	Post-Acute Phase Visit	3 Month F/U Visit	6 Month F/U Visit	12 Month F/U Visit
Procedure/Test/Follow-Up Windows	Hospital / ICU Admission	336 Hours (14 Days) [i]	5 Days Post-Acute Phase OR Hospital Discharge[ii] ±1 day	3 mo ±30 days from LKN/Ictus	6 mo±30 days from LKN/Ictus	12 mo ±30 days from LKN/Ictus
Inclusion/Exclusion Criteria	X					
Describe study to potential subject	X					
Informed Consent/Enrollment	X					
Randomization*	X					
Demographics and medical history	X					
Modified Rankin Scale	X (Pre-Morbid)		X	X	X	X[vi]
Glasgow Coma Scale	X					
Intracerebral Hemorrhage Score (ICH Score)	X[iv]					
Barthel Index			X	X	X	
Glasgow Outcome Scale - Extended			X	X	X	
Montreal Cognitive Assessment			X	X	X	
Diagnostic Imaging (CT Scan or MRI)	X[iii]					
NIH Stroke Scale	X[v]	X[vii]	X	X	X	
Daily Intensive Care Delirium Screening Checklist		X				
World Federation of Neurological Surgeons Grading System (SAH subjects only)	X[iii]					
Fever Prevention Index Procedure		X				
Hourly Body Temperature*		X				
Urinalysis (Subjects with Foley catheter)	X	X[viii]				
Daily White Blood Cell Count		X				
Shiver monitoring and control protocol		X				
Antipyretic use / supplemental shiver control		X				
End of full case data download from Arctic Sun		X				
Adverse Events		X	X[ix]	X[ix]	X[ix]	X[ix]

* A confirmatory temperature check must be performed no more than one hour prior to randomization; should they be found to be febrile they will be considered a screen failure
i – Acute Phase will continue through 336 Hours (14 days) for ALL subjects OR until the patient is discharged/deemed medically ready for discharge from the ICU or the subject goes on comfort-measures only, whichever occurs first; neurologic assessments performed during this phase are not blinded
ii - Window will be 5 days after completion of Acute Phase OR at hospital discharge, whichever comes first
iii - Testing performed at admission may be used for screening and as study baseline measures; if not previously performed, tests should be completed for eligibility screen and baseline
iv – For ICH subjects only at screening
v - Only for IS and ICH subjects at screening and enrollment
vi – May be assessed by phone unless an actual visit is otherwise performed within the follow-up window
vii – NIH Stoke Scale will be performed at day 2 and day 5 of the study for IS and ICH subjects when not fully sedated; not blinded assessments
viii – Urinalysis performed at study enrollment, Day 7 (if still in the acute phase) and at the end of the acute phase/time of catheter removal for all catheterized subjects
ix – Limited to MAEs only

6. STUDY PROCEDURES

The study visit schedule outlined in Table 1 summarizes the study procedures to be performed during each study interval or visit. This section provides additional details of the individual study procedures.

6.1. Evaluations

6.1.1. Informed Consent

The Investigator or designee will explain the study to the subject or proxy, answer all of the subject's/proxy's questions, and obtain written informed consent in a language which the subject/proxy is fluent before the collection of any study data or performance of any study procedures.

The subject (or subject's legally authorized representative) must be willing and able to sign and date the informed consent form. The original will be retained with the subject records and a copy will be provided to the subject.

6.1.2. Enrollment

Subjects who sign an informed consent will be considered enrolled in this study. Note: For subjects enrolled but not randomized, data collection will be limited to demographics and eligibility information.

6.1.3. Eligibility

The subject's eligibility (inclusion/exclusion criteria) for study enrollment will be reviewed and documented on the appropriate case report form (CRF). At the time of screening, it must be documented that study eligibility criteria were reviewed with the screening results noted. Subjects who fail to meet eligibility criteria must not be enrolled in the study.

A confirmatory temperature check must be performed no more than one hour prior to randomization to ensure that the subject does not become febrile. If the subject becomes febrile between enrollment and randomization, they will be considered a screen failure. This will be documented on the appropriate CRF.

6.1.4. Assignment of Subject Number

A unique identification number will be given to study subjects. Subject numbers will be assigned in sequential order. The subject number will consist of six digits. The first three digits will designate the study site. The last three digits will designate the subject by number in sequential order (i.e., subject

number 101 001 will be the first subject at site 101; 101 002 will be the second subject at site 101, etc.).

6.1.5. Demographics and Medical History

At enrollment, the subject's demographic information and medical history will be documented on the appropriate CRF. Demographic data will include year of birth, gender, race, ethnicity, height and weight.

Relevant medical history will be obtained by the physician including but not limited to the following:

- Primary diagnosis
- Hypertension
- Heart failure
- Ischemic heart disease
- Acute myocardial infarction
- Arrhythmia
- Transient ischemic attack/stroke
- Asthma/chronic obstructive pulmonary disease
- Coagulopathy
- Diabetes
- Previous head trauma/injury
- Neurological status

6.1.6. Diagnostic Testing

Because of the variety of disease states examined in this study, there are several types of diagnostic testing that might be performed as part of the institution's/Investigator's standard of care to confirm clinical diagnosis. Diagnostic tests may include, but are not limited to, computed tomography scan (CT scan), computed tomography angiography (CT angiography), or magnetic resonance imaging (MRI). The type of testing used to confirm diagnosis and study eligibility will be documented.

6.1.7. Baseline Neurologic Assessments

6.1.7.1. Modified Rankin Scale

All enrolled subjects will have a pre-morbid modified Rankin Scale[22] (mRS) documented. See Appendix 19.1 for additional scoring information for Modified Rankin Scale.

6.1.7.2. Glasgow Coma Scale

All enrolled subjects will have a Glasgow Coma Scale[23] documented at baseline. See Appendix 19.2 for additional scoring information for the Glasgow Coma Scale.

6.1.7.3. National Institutes of Health Stroke Scale

Ischemic Stroke and Intracerebral Hemorrhage subjects will have a National Institutes of Health Stroke Scale (NIHSS) [24] documented at baseline. See Appendix 19.3 for additional information on the process for scoring the NIHSS.

6.1.7.4. World Federation of Neurological Societies Grading Scale for Subarachnoid Hemorrhage (WFNS)

Non-traumatic, subarachnoid hemorrhage patients will have a WFNS Scale[25] documented at baseline. This will also be used during randomization as a measure of injury severity. See Appendix 19.4 for additional information on scoring the WFNS Scale.

6.1.7.5. Intracerebral Hemorrhage Score

Intracerebral hemorrhage patients will have an intracerebral hemorrhage score[26] calculated and documented at baseline to be used during randomization as a measure of injury severity. See Appendix 19.5 for additional information on calculating the ICH score.

6.2. Randomization

Randomization will occur after informed consent is obtained, after study personnel ensure the subject meets all general and disease-specific inclusion and none of the exclusion criteria. A confirmatory temperature check must be performed no more than one hour prior to randomization to ensure that the subject does not become febrile. If the subject becomes febrile between enrollment and randomization, they will be considered a screen failure. Randomization and initiation of study procedures (e.g., index procedure, hourly temperature measurements) should take place as close to enrollment as possible.

Using a minimization algorithm, enrolled subjects will be stratified by four factors: neurological diagnosis, investigational site, age (<70 years vs. ≥70 years), and baseline severity and randomized into either the fever prevention group or the standard care group at a 1:1 ratio. Baseline severity for IS subjects will be according to the NIHSS score (<17 vs. ≥17, on a scale of 0-

42, with higher scores indicating greater severity). For ICH subjects, baseline severity will be based on the ICH score (≤2 vs. ≥3, with higher scores indicating greater severity). For SAH subjects, baseline severity will be according to the World Federation of Neurological Societies Grading System for Subarachnoid Hemorrhage (≤III vs. ≥IV, on a scale of I-V, with higher scores indicating greater severity).

The randomization process will be handled via use of an interactive web-based system.

6.3. Physical Examination

For the purposes of the study, a limited physical exam will be performed including height and weight measurements. The limited physical exam must assess, at minimum, all of the systems listed in the case report form.

6.4. Patient Temperature

There are two purposes for measuring/monitoring patient temperature within the study: 1) primary endpoint of fever burden; and 2) control of patient temperature using the Arctic Sun System. For the fever burden endpoint, all subjects must have hourly temperature measured using one standardized thermometry method. Ideally, a continuous core temperature measurement method will be used (e.g., temp-sensing Foley catheter, esophageal probe, or 3M™ BairHugger™ Temperature Monitoring System). So as to more closely mimic standard of care for temperature measurement, each investigative site will be allowed to select the thermometry method they feel is most appropriate to standardize to. This method must be used for all hourly measurement, for all subjects, regardless of the study arm that they are randomized to, and regardless of the continuous thermometer that may be used for controlling the Arctic Sun System. For example, if a subject in the fever prevention group has a temp-sensing Foley catheter in place for control of the Arctic Sun System, but the site has standardized to temporal artery thermometry, the subject must still have hourly temperatures taken using the temporal method. Standardized hourly temperature measurements are required throughout the acute phase of the study (336 hours/14 days), or until the subject is discharged/deemed ready for discharge from the ICU/placed on comfort measures only, whichever comes first).

The second purpose for measuring temperature is for the control of the Arctic Sun System. Subjects randomized to the fever prevention group must have a continuous core temperature probe (i.e., Foley catheter or esophageal probe) (see section 6.8.1 for more detail).

6.5. Medications

Antipyretics and other medications (e.g., antimicrobials) given to treat fever during the acute phase of the study will be recorded. Additionally, medications given to control shivering will be recorded. Because acetaminophen and similar medications/antipyretics may be used either to treat fever or to treat shivering, the specific indication for use will be collected in the appropriate case report form.

6.6. Infection Surveillance

To assist the Investigator in identifying potential infection in enrolled subjects, regular active screening will be performed by the following methods. Investigators should refer to Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America for additional recommendations.

6.6.1. Urinalysis

Urinalysis will be performed for all subjects with a Foley catheter at study enrollment (baseline) or day of catheter insertion, day 7 of the acute phase (if the subject is still in the ICU), and at the end of the acute phase or when the catheter is removed, whichever comes first.

6.6.2. White Blood Cell Count

A white blood cell (WBC) count will be performed daily for all subjects during the acute phase. WBC counts performed as part of complete blood counts collected for other purposes are acceptable if collected within the appropriate timeframe.

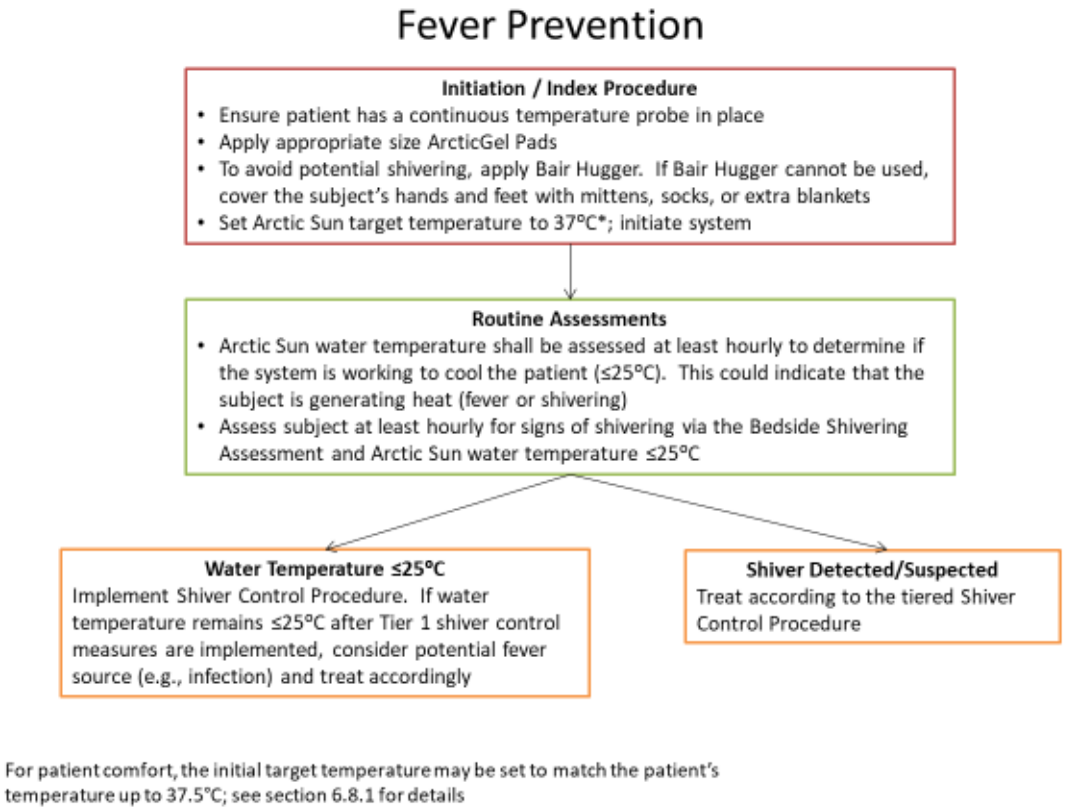
6.7. Adverse Events

Each subject will be monitored for the occurrence of both adverse events (AEs) and major adverse events (MAEs) according to definitions in Section 7. All AEs will be monitored from study randomization through the acute phase of the study (discharge from the ICU) and MAEs will be monitored from randomization through the end of study participation.

6.8. Fever Prevention (FP)

Subjects randomized to the fever prevention group will have the following procedures. See Figure 2.

Figure 2.



6.8.1. Index Procedure

Subjects randomized to the FP group must have a continuous core temperature probe (i.e., Foley catheter; Note: an esophageal probe may be used in intubated patients but will need to be replaced with a Foley catheter when the subject is extubated; rectal probes may not be used) placed prior to initiation of the Arctic Sun System. The appropriately sized ArcticGel Pads will be placed on the subject based on their weight; the pads will be connected to the AS-5000. The target temperature will be set to 37°C and the system initiated and operated according to the Instructions for Use. (*Note: To avoid pressure points, if appropriately sized pads are not immediately available, use the next smaller sized pads; replace pads with appropriately sized pads as soon as possible.)

For patient comfort and to reduce the potential for early onset shivering, counter-warming should be applied concurrently; see section 6.8.4. Additionally, the initial target temperature may be set to match the actual patient temperature up to 37.5°C. If this is done, the patient temperature should be read from the Arctic Sun console. The target temperature should be decreased by approximately 0.1°C after each hour of therapy until the target temperature of 37.0°C is reached (no more than 10 hours). See section 6.10 more information on shiver control procedures.

Short suspensions in therapy for purposes of conducting diagnostic procedures, subject mobilization, etc., are to be expected; however, the duration of these suspensions must be as short as possible. Suspension in therapy ≥1 hour must be documented in the appropriate CRF.

6.8.1.1. ArcticGel Pad Changes

ArcticGel Pads should be changed every 5 days for duration of the subject's participation in the study. During the pad change process, the skin under the pads should be fully assessed for signs of injury. If skin injury is noted, this should be reported as an adverse event. (Note: If cool water is circulating through the pads, it is not uncommon for the skin to appear pink or mottled when the pads are initially removed. If skin injury is suspected, allow the skin to warm and reassess the area prior to reapplication of the pads.)

To avoid subject injury, ArcticGel Pads should not be replaced on skin that has signs of ulceration, burns, hives, or rash or on areas with poor skin integrity or poor tissue perfusion. Additionally, if the subject is suffering from edema, pads should be repositioned frequently to avoid undue tension/stress on the skin or therapy suspended until the edema is controlled.

Note that the use of ArcticGel Pads does not prevent patient turning, physical therapy, and/or mobilization. Pads can be drained and temporarily disconnected from the Arctic Sun console for purposes of mobilization or physical therapy when required.

6.8.2. Monitoring for Heat Generation

Subjects should be assessed hourly for signs of heat generation (fever or shivering) via the Bedside Shivering Assessment and/or assessment of the AS-5000 water temperature. If fever is suspected, the Investigator should perform an appropriate investigation (e.g., cultures) and treat the patient accordingly.

If shivering is detected/suspected, the Shiver Control Procedure should be immediately implemented (See section 6.10).

6.8.2.1. Bedside Shivering Assessment (BSAS)

Score	Definition
0	None: No shivering noted on palpation of the masseter, neck, or chest wall
1	Mild: Shivering localized to the neck and/or thorax only
2	Moderate: Shivering involves gross movements of the upper extremities (in addition to neck and/or thorax)
3	Severe: Shivering involves gross movements of the trunk and upper and lower extremities

6.8.2.2. Arctic Sun 5000 (AS-5000) Water Temperature

The Arctic Sun water temperature should be assessed hourly by the bedside nurse to determine if the system is working to cool the patient (water temperature for a normothermic patient is typically 28°-30°C). If the water temperature is below 25°C this could indicate that the subject is generating heat (fever *or* shivering). Perform a BSAS to determine if shivering is present and at what level. See Appendix 19.14: Guide for Addressing Arctic Sun Water Temperature Below 25°C.

At the end of the fever prevention period, case data for each subject will be downloaded from the Arctic Sun 5000. This data, which contains various performance metrics including, but not limited to water temperature and water flow rate, will be analyzed to determine if the subject had indicators of fever.

6.8.3. Arctic Sun Case Data

At the end of the acute phase, case data for each subject will be downloaded from the Arctic Sun 5000 console and uploaded to a site-specific email address. Data files should be uploaded as soon as possible after the subject completes the acute phase. This data, which contains various performance metrics including, but not limited to water temperature and water flow rate, will be analyzed to determine if the subject had indicators of fever.

6.8.4. Skin Assessment

The skin under ArcticGel Pads should be assessed at least 4 times per day (no less than every 6 hours). Assessment can be performed by gently pulling up a corner of the ArcticGel Pad and visualizing the skin underneath. If skin injury is detected, the pad should be removed, and the injury documented as an adverse event. (Note: If cool water is circulating through the pads, it is not uncommon for the skin to appear pink or mottled when the pads are initially removed. If skin injury is suspected, allow the skin to warm and reassess the area prior to reapplication of the pads.)

To avoid subject injury, ArcticGel Pads should not be placed on skin that has signs of ulceration, burns, hives, or rash or on areas with poor skin integrity or poor tissue perfusion. Additionally, if the subject is suffering from edema, pads should be repositioned frequently do avoid undue tension/stress on the skin or therapy suspended until the edema is controlled.

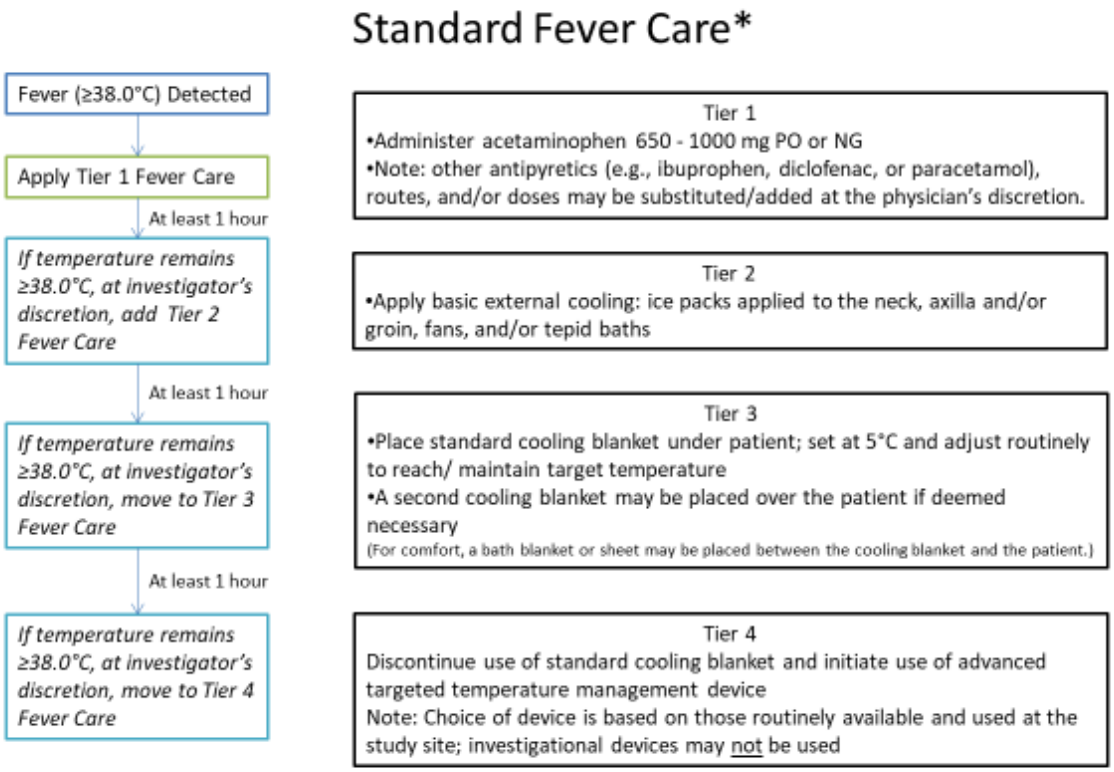
6.8.5. Counter-Warming

In order to reduce the potential for shivering, a Bair-Hugger should be initiated concurrently with the AS-5000. If the Bair-Hugger is not tolerated by the subject or may interfere with other devices and/or procedures, the subject's hands and feet should be covered with mittens, socks, or extra blankets at the time the AS-5000 is initiated. Additional counter-warming measures should be implemented according the Shiver Control Procedure if shivering is detected/suspected (See section 6.10).

6.9. Standard Care

Subjects randomized to the standard care group may be medically managed according to the institution's/Investigator's standard approach unless/until they develop fever. Should the subject develop fever, defined as ≥38°C, the subject will have their fever managed in a standardized, escalating fashion as described below. The decision to initiate treatment or advance to the next tier in the treatment plan is at the investigator's discretion; however, it is recommended that at least one hour should elapse between tiers to allow each individual intervention to take effect. Tiers are intended to be implemented consecutively. See Figure 3. Alterations to tiers should be pre-specified and reviewed and approved by the study Coordinating Investigators.

Figure 3.



*The decision to initiate treatment or advance to higher tiers is at the investigator's discretion.

6.9.1. Tier 1: Antipyretic Therapy

To treat active fever, subjects in the SC group will have PRN acetaminophen 650 - 1000 mg PO or NG administered. If the subject's temperature drops below 38.0°C they can be maintained on PRN acetaminophen therapy. Other antipyretics (e.g., ibuprofen, diclofenac, or paracetamol), routes, and/or doses may be substituted/added at the physician's discretion.

6.9.2. Tier 2: Basic External Cooling

At the investigator's discretion, if the subject's temperature remains ≥38.0°C after administration of Tier 1, ice packs applied to the neck, axilla and/or groin, fans, and/or tepid baths may be added. If the subject's temperature drops below 38.0°C the ice packs, fans, and/or tepid baths will be discontinued. Basic external cooling can be used PRN to supplement antipyretic therapy.

6.9.3. Tier 3: Cooling Blankets

At the investigator's discretion, if the subject's temperature remains ≥38.0°C after application of Tier 2, a standard cooling blanket (e.g., Soft-Temp® Conductive Warming Blanket, Adroit Medical Systems, Loudon, TN; Maxi-Therm® Lite Hyper-Hypothermia Blanket, Cincinnati Sub-Zero, Cincinnati, OH) may be placed under the subject and set to the lowest temperature allowed according to hospital protocol. A bath blanket or sheet may be placed between the cooling blanket and the subject for comfort if desired. To reduce the potential for shivering, the subject's hands and feet may be covered with mittens, socks, or extra blankets at the time the cooling blanket is applied. If the subject's temperature drops below 37.5°C the water temperature should be adjusted up to maintain them at normothermia (to avoid overshoot).

Should the subject's temperature remain ≥38.0°C after the cooling blanket is placed under them, a second blanket may be placed on top of them.

6.9.4. Tier 4: Advanced Targeted Temperature Management

At the investigator's discretion, if the subject's temperature remains ≥38.0°C after application of Tier 3, an available advanced targeted temperature management device with feedback loop and continuous patient temperature monitoring (e.g., Arctic Sun 5000, Blanketrol System, MediTherm System) may be applied.

6.9.5. Monitoring for Shiver

Subjects undergoing fever treatment should be assessed hourly for signs of shivering via the Bedside Shivering Assessment. If shivering is detected/suspected, the Shiver Control Procedure should be immediately implemented (See section 6.10).

6.9.6. Skin Assessment

The skin under external cooling devices (e.g., cooling blankets) should be assessed at least 4 times per day (no less than every 6 hours). Assessment can be performed by lifting the devices and visualizing the skin underneath. If skin injury is detected, the device should be removed, and the injury documented as an adverse event.

6.10. Shiver Control Procedure

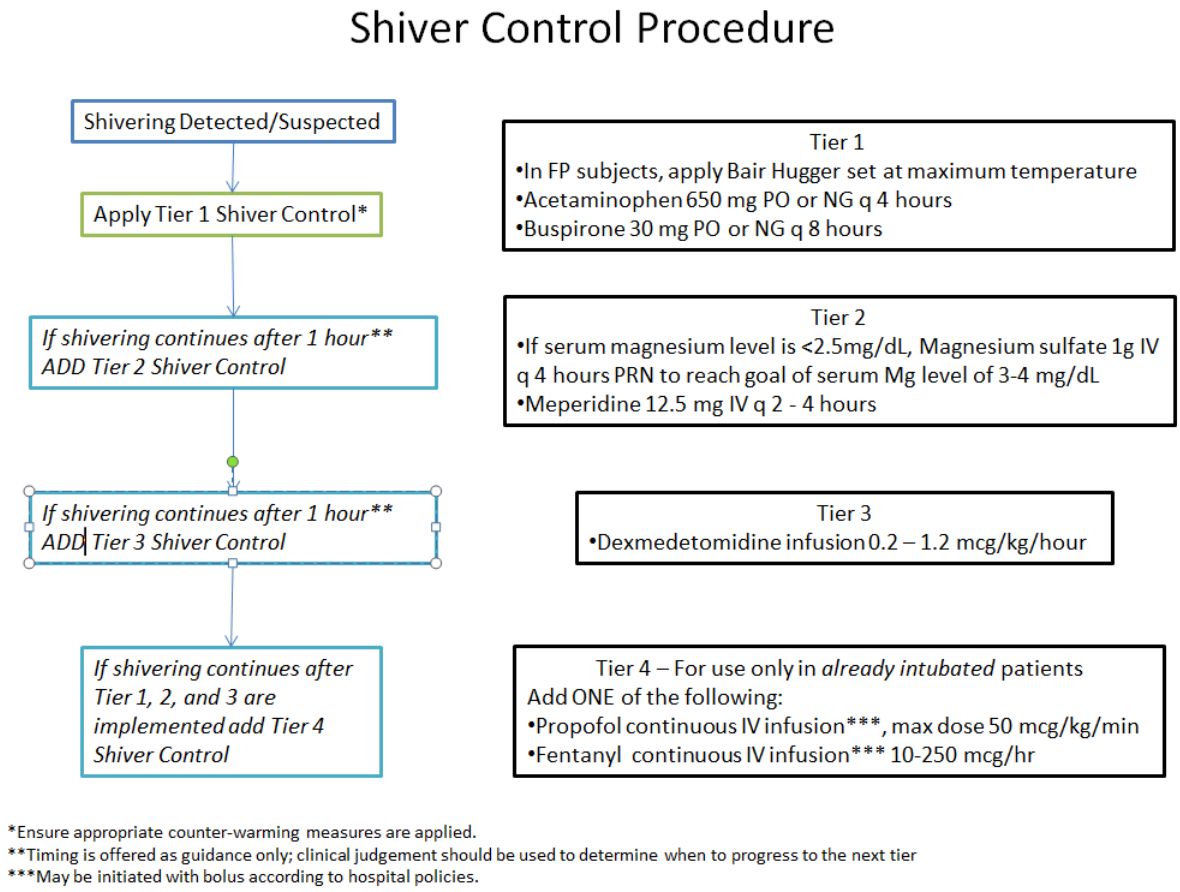
Subjects in the FP group and those undergoing fever treatment in the SC group shall be monitored at least hourly for shivering. If detected/ suspected, subjects will have their shivering managed in a standardized, escalating fashion as described below. *See Figure 4. Addressing and/or controlling shiver in its earliest stages may potentially reduce the need to escalate to additional control tiers, may reduce subject discomfort, and may reduce the incidence of shiver-related adverse events.

*Note: Based on hospital-specific formularies and/or protocols, alternative drugs and/or dosing may be substituted for those listed in tiered shiver control (e.g., Buspirone mg PO or NG q 8 hours vs PRN). Substitutions should be pre-specified and reviewed and approved by the study Coordinating Investigators.

Additionally, according to existing hospital protocols, tier 1 shiver control procedures may be considered and implemented in patients randomized to the fever prevention arm prior to the onset of shiver. The timing between tiers is offered as guidance and clinical judgement should be used to determine how quickly to escalate to a higher tier when shivering continues or is considered to be severe. Because they act synergistically, when moving from one tier to another, interventions from prior tiers should be continued.

Also note that, consistent with hospital protocols, patients sedated or paralyzed for ventilation, shiver control, or other reasons should periodically undergo a “sedation holiday” where sedation is weaned or turned off to allow for neurologic assessment as well as assessment of readiness for extubation. This applies to patients who, in the investigator’s opinion, are hemo-dynamically stable enough to tolerate being off sedation. For intubated patients, if sedation for shiver control is precluding extubation, devices such as cooling blankets or Arctic Sun should be temporarily suspended. These devices and necessary shiver control measures (up to, but not including Tier 4) may and should be restarted once the patient is extubated and deemed stable and appropriate by the treating team but optimally no greater than 6 hours post-extubation.

Figure 4.



6.10.1.1. Tier 1 Shiver Control

If shivering is detected/suspected, institute the following:

- Ensure appropriate counter-warming measures are applied. For FP subjects only (those with AS-5000), if not already in place, apply a Bair Hugger and set it on the maximum temperature (temperature can be lowered if not tolerated by the patient)
- Acetaminophen 650 mg PO or NG q 4 hours
- Buspirone 30 mg PO or NG q 8 hours

6.10.1.2. Tier 2 Shiver Control

If shivering continues 1 hour after Tier 1 measures are implemented, add the following:

- If serum magnesium level is <2.5mg/dL, magnesium sulfate 1g IV q 4 hours PRN to reach goal of serum Mg level of 3-4 mg/dL
- Meperidine 12.5 mg IV q 2 - 4 hours

6.10.1.3. Tier 3 Shiver Control

If shivering continues after Tier 2 measures are implemented, add the following:

- Dexmedetomidine infusion 0.2 – 1.2 mcg/kg/hour

6.10.1.4. Tier 4 Shiver Control (Intubated Subjects Only)

If the subject is *already intubated* and if shiver continues after Tier 1, 2, and 3 measures are implemented, one of the following may be added:

- Propofol continuous infusion, max dose 50 mcg/kg/min
- Fentanyl continuous infusion 10-250 mcg/hr

6.10.1.5. Arctic Sun Target Temperature Adjustment

There are several instances in which the Arctic Sun target temperature may be adjusted. For patients being initiated on Arctic Sun, if the patient's starting temperature is above the target of 37.0°C, Arctic Sun will work to "cool" them to target temperature. In this case, for patient comfort and to reduce the potential for early onset shivering, the initial Arctic Sun target temperature may be set to match the actual patient temperature up to 37.5°C. If this is done, the patient temperature should be read from the Arctic Sun console. The target temperature should be decreased by approximately 0.1°C after each hour of therapy until the target temperature of 37.0°C is reached (no more than 10 hours).

Additionally, for patients already on Arctic Sun, when the water temperature drops below 25°C, it indicates that the machine is working to actively decrease the patient's temperature or to control temperature in a patient generating heat (shiver or fever). If shivering is detected/suspected, the tiered shiver control approach outlined above should be implemented. If shivering is BSAS ≥2, the Arctic Sun target temperature can be temporarily increased up to 37.5°C until shivering is controlled. If shivering is not detected and Tier 1 shiver control procedures do not affect the Arctic Sun water temperature, fever is the most likely source of heat generation and should be addressed accordingly. For patient comfort and to reduce the potential for new onset of shivering, the Arctic Sun target temperature can be temporarily increased up to 37.5°C until treatment of the fever is initiated. After shiver is controlled or fever treatment initiated, the target temperature in Arctic Sun should be decreased by 0.1°C after each hour of therapy until 37.0°C is reached (no more than 10 hours). Suspension in Arctic Sun therapy ≥1 hour must be documented in the appropriate CRF.

6.11. Fever Prevention Initiation / Standard Care Fever Treatment Initiation

Procedural details to be recorded for FP subjects and SC subjects may include but not be limited to:

- Date and time of initiation;
- Patient core temperature at initiation;
- Antipyretic medications; and
- Supplemental external fever control methods (e.g., fan, ice pack; cooling blanket).

6.12. Acute Phase Routine Assessments

Assessments including, but not limited to hourly core body temperature, anti-pyretic medications, and shivering control medications will be documented for all subjects through the acute phase of the study.

6.13. Follow-Up Neurologic Assessments

Follow-up neurological assessments will be performed by study personnel certified in the procedures and/or scoring of the assessments. Assessments performed during the acute phase of the study will not be blinded. Personnel performing assessments during the Post-Acute Phase visit and/or 3-, 6-, and 12-month visits will be blinded to treatment assignment.

Note: Should subjects be physically unable to return for 3- and 6-month follow-up visits, alternate arrangements may be made per the Sponsor's determination. Sites shall contact the Sponsor for guidance.

6.13.1. Modified Rankin Scale

Subjects will have a modified Rankin Scale documented in the Post-Acute Phase and at the 3-, 6-, and 12-months follow-up visits. For the 12-month visit, this assessment may be performed remotely (e.g., telephone call). Scoring of Modified Rankin Scale is provided in Appendix 19.1.

6.13.2. National Institutes of Health Stroke Scale

Ischemic stroke and intracerebral hemorrhage subjects will have a NIHSS documented at days 2 and 5 during the acute phase of the study. If the subject is sedated at a level that precludes day 2 and/or day 5 NIHSS, the assessment may be skipped and documented in the appropriate CRF.

Additionally, all subjects will have a NIHSS documented in the Post-Acute Phase and at the 3- and 6-months follow-up visits. NIHSS scoring is provided in Appendix 19.3.

6.13.3. Intensive Care Delirium Screening Checklist (ICDSC)

Subjects will have an ICDSC[27] documented daily during the acute phase of the study. Additional information on calculating the ICDSC score can be found in Appendix 19.6.

6.13.4. Barthel Index

Subjects will have a Barthel Index[28] assessment documented in Post-Acute Phase and at the 3- and 6-months follow-up visits. Additional information on how the Barthel Index score is calculated can be found in Appendix 19.7.

6.13.5. Glasgow Outcome Scale Extended

Subjects will have a Glasgow Outcome Scale Extended[29] documented in the Post-Acute Phase and at the 3- and 6-months follow-up visits. Additional information on scoring the Glasgow Outcome Scale Extended can be found in Appendix 19.8

6.13.6. Montreal Cognitive Assessment

Subjects will have a Montreal Cognitive Assessment (MoCA)[30] documented in Post-Acute Phase and at the 3- and 6-months follow-up visits. Additional information on calculating the MoCA score can be found in Appendix 19.9.

6.14. Subject Discontinuation

Subjects may be discontinued for the following reasons:

- Subject is Lost to Follow-Up (LTF): A subject may be considered LTF if the investigational site personnel are unable to locate the subject despite two documented attempts to notify the subject via all means (telephone, e-mail, and/or text) and a third attempt by certified mail. Where the subject has given prior permission, a designated representative (e.g., spouse, relative) will also be contacted. Additionally, where prior permission has been granted, the subject's primary care physician may be contacted for outcome information.
- Subject consent is withdrawn: The subject requests to terminate his/her participation in the study (the Investigator must attempt to identify and

document the reasons for termination). Subjects will be informed that they have the right to withdraw from the study at any time, for any reason, without affecting their future care.

- Investigator decision**:** Participation may be immediately terminated by the Investigator if, in the opinion of the Investigator, the subject would be exposed to inappropriate risk by continuing in the study.

- Death: The subject becomes deceased. If available, the date and cause of death should be documented.

- Study termination: The study is terminated by Sponsor.

Once a subject discontinues from the study, the Investigator must complete a Study Completion CRF and the reason for subject discontinuation must be fully documented.

6.15. Replacement of Subjects

A subject that discontinues from the trial will not be replaced.

7. ADVERSE EVENTS

The Principal Investigator is responsible for the detection and documentation of all adverse events meeting the criteria and definition of an adverse event or serious adverse event. When possible, the Investigator should report a diagnosis as the event term(s). If a definitive diagnosis cannot be made, signs, symptoms, and abnormal laboratory values should be reported as the event term(s). Skin injuries that are suspected to be associated with the use of ArcticGel Pads (including bruising, tearing, skin ulcerations, blistering, and necrosis) should be reported as adverse events related to the study device.

While instances of shiver are being captured and reported as a study endpoint, there may be instances that potentially meet the definition of serious injury (i.e., necessitates medical or surgical intervention to preclude permanent impairment of a body function). As such, any instance of shiver requiring Tier 4 treatment must be reported as an adverse event.

All AEs will be monitored from study randomization through the Acute Phase of the study (336 hours/discharge from the ICU/deemed ready for discharge from ICU/placed on comfort measures only, whichever comes first) and MAEs will be monitored from randomization through the end of study participation. Adverse events will be documented in the medical record or source documentation and on the study appropriate CRF(s). All events will be followed through resolution. Events with an onset prior to randomization should be reported in the subject's medical history.

7.1. Definition of Adverse Events (AE) and Serious Adverse Event (SAE)

In this study, an adverse event is defined as any untoward medical occurrence, unintended disease or injury, or unanticipated complication per the Investigator's assessment regardless of relationship to the investigational device. A serious adverse event is defined by ISO 14155 and/or 21 CFR 803.3 as an adverse event that: a) led to death; b) led to serious deterioration in health that resulted in life-threatening illness or injury, resulted in permanent impairment, required inpatient hospitalization/prolonged hospitalization, or resulted in medical/surgical intervention to prevent life-threatening illness/injury or permanent impairment; or c) led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A pre-existing condition should not be reported as an AE unless there has been a substantial increase in severity or frequency of the condition, which has not been attributed to natural history. Pre-existing conditions should be considered as part of the subject's medical history. Exacerbation of an existing condition should be reported as an AE, if the event meets the protocol definition of an AE.

7.2. Definition of Adverse Device Effect (ADE) and Serious Adverse Device Effect (SADE)

An adverse device effect is defined as any adverse event that is considered to be related to the use of an investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, or operation or any malfunction of the investigational device (study device) and includes any event that is a result of a user error. A serious adverse device effect is defined as any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less than opportune.

7.3. Definition of Major Adverse Events (MAE)

In this study, an MAE will be defined as one of the following:

- Pneumonia;
- Sepsis;
- Malignant cerebral edema; or
- Death

See Appendix 19.15 for guidance regarding MAE definitions.

7.4. Definition of Unanticipated Adverse Device Effect (UADE) and Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated adverse device effect is defined by 21 CFR 812.3 as 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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. An unanticipated serious adverse device effect is defined by ISO 14155 as a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Refer to the product IFUs for a list of AEs that are expected or associated with the use of the study device(s).

7.5. Relationship of Adverse Event To Device/Procedure

The determination of the relationship of an AE to the device or procedure must be made by the physician Investigator and the following guidelines should be used:

- Device: This category should be restricted to AEs directly attributable to devices used for study conduct during the Acute Phase of the study, including but not limited the Arctic Sun System, temperature probes used to operate Arctic Sun, thermometers for hourly temperature assessments, or standard cooling blankets. (E.g., skin injury under ArcticGel Pad)

- Procedure: A procedure includes any study-related activity performed during the Acute-Phase of the study (e.g., hourly temperature measurement; urethral trauma associated with temp-sensing Foley catheter insertion; maintaining normothermia (e.g., severe shivering requiring Tier 4 treatment)).

The following categories should be used by the physician Investigator for assigning the certainty of relatedness:

- Definitely Related: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.

- Possibly Related: An AE is possibly related if it is capable of being related but relatively unlikely.

- Not Related: An AE is not related if it is determined that there is no plausible association.

7.6. Severity of Adverse Events

Each AE should be assessed for its severity, or the intensity of an event, experienced by the subject.

- Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient and is resolved without treatment or sequelae.

- Moderate: May interfere with the subject's activity and require additional intervention and/or treatment and may have additional sequelae.

- Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

7.7. Reporting of Adverse Events

7.7.1. Reports of Adverse Events, Serious Adverse Events and Unanticipated Adverse Device Effects

The procedure for reporting AEs, SAEs, SADEs or USADEs is as follows:

- If an AE or SAE occurs during the Acute-Phase of the study, all sections of the appropriate CRF(s) must be completed.
- All SAEs occurring during the Acute-Phase of the study, including SADEs, and UADEs (including initial reports and follow-up reports with additional event details) must be reported to the Sponsor within 24 hours of the investigational site becoming aware of the event(s). The Intrepid Event Notification Form may be emailed to BMD-INTREPID@crbard.com
- De-identified copies of all requested relevant documentation should be submitted to the Sponsor within 72 hours of knowledge, as appropriate.

Reporting of adverse events to individual Institutional Review Boards (IRBs)/Ethics Committees (ECs) and/or regulatory authorities will follow the local regulations in each participating country.

7.8. Adjudication of Adverse Events

To ensure consistency in determination of relatedness of adverse events, a Clinical Events Committee (CEC) will adjudicate all AEs determined by the site investigator to be related or possibly related to a study device or procedure. Additionally, the CEC will adjudicate all SAEs and MAEs.

The CEC will be comprised of at least three (3) members (neurointensivists, neurologists, or neurosurgeons) who are not directly involved in the conduct of the study. The CEC will be responsible for the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study as determined by the CEC charter.

8. MECHANICAL FAILURES, MALFUNCTIONS AND DEFECTS

The Investigator will record if a Bard device (Arctic Sun 5000 System, ArcticGel Pads) used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction or defects. This applies to: devices used to treat the subject, or devices in which the package was opened, but the device was not used for treatment, or devices with which treatment was attempted, but the device did not remain through the entire study period.

All mechanical failures, malfunctions, missing components, foreign matter inclusion or any other defects of the study device or any components of the device kit that do not perform to specifications will be recorded on the "Device Failure" Case Report Form.

Devices meeting any of the above criteria will be labeled "Biohazard." BMD will contact the site and provide specific shipping instructions and packaging materials, including a pre-paid Federal Express return label, to permit the return of device to BMD.

Reported malfunctions will be investigated and reported under 21 CFR part 803 by BMD if necessary, and in a manner consistent with the policies and procedures BMD uses for its commercially available devices. The site may be contacted to provide additional information to allow BMD to conduct a thorough investigation.

The Investigator will record any device deficiencies, defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance; includes device malfunctions, use errors and inadequate labeling, in the CRF. A device deficiency has occurred if an investigational device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction or defects. Device deficiencies also include use errors and inadequate labeling. This applies to:

- devices used on the subject; or

- devices in which the package was opened, but the device was not used on the subject; or
- devices with which fever control was attempted, but the device did not remain on the subject.

If the device deficiency was associated with an AE, the reporting provisions for AEs, ADEs, SAEs, SADEs and USADEs as outlined in Section 7 above apply. All device deficiencies will be recorded on the "Device Deficiency" CRF.

The Investigator is responsible for reporting device failures occurring with devices used in the standard care fever control group to the appropriate manufacturer.

9. RISK/BENEFIT ANALYSIS

There are well established standard care methods to control fever in neurocritical patients including anti-pyretic medications and external cooling methods such as fans, ice packs, and cooling blankets. Patients with fever, those treated with external cooling methods, and those treated with the Arctic Sun 5000 System may be at risk for shivering and associated adverse events. As such, prevention and/or control of shivering has been considered and incorporated into study procedures.

The Arctic Sun 5000 Temperature management System and the ArcticGel Pads utilized in this study have 510(k) clearance from the U.S. FDA, are CE marked and will be used in accordance with the indications of the labeling in effect during the study.

Subjects randomized to the fever prevention group may have a higher risk of skin irritation/injury compared to those in the standard care group due to direct skin contact with the cooling surface of the ArcticGel Pads.

Regardless of which group the subject is randomized to, they will receive treatment to control fever. Devices used for this purpose will be used in a manner consistent with their Instructions for Use/Operator's Manual. Study procedures do not pose any additional potential risk to the health, safety or welfare of the subject over and above treatment for their primary diagnosis and fever.

Evidence from limited investigations suggests that fever control may be associated with better outcomes. It is impossible to determine what, if any benefit enrolled subjects may gain by participating in this study. While patients enrolled in this study may not directly benefit from study procedures, the information gained may benefit future patients.

The risks and potential benefits associated with the study procedures will be described in full to the subject or their proxy by the Investigator during the informed consent process.

10. STATISTICAL METHODS

This section describes the planned statistical analyses for this study. A detailed Statistical Analysis Plan (SAP) will be completed and placed on file prior to the database lock. The SAP will contain a comprehensive explanation of the methodology used in the statistical analyses described below.

10.1. Sample Size Considerations

The study sample size is primarily driven by the key secondary endpoint, and the study is powered for both the primary endpoint and the key secondary endpoint. The test of the key secondary endpoint is conditional on the success of the test of the primary endpoint.

The key secondary endpoint is neurologic outcomes assessed by the modified Rankin Scale (mRS). In additional to its standard scale, the 6-category mRS outcome score will also be dichotomized as a binary outcome (scores of 0 to 3 for success and scores of 4 to 6 for failure). Sample size is estimated based on the dichotomized binary outcome with the assumed FP success rate of 50% and the SC success rate of 40%. A sample size of 1000 subjects (500 in each group) will provide an 88% power by a two-group chi-square test at two-sided α=0.05 (nQuery 7.0). Given such a sample size, the analysis based on the standard scale may be slightly more powerful. Both analyses, either using the original standard scale or dichotomized scale, will be performed for mRS in this study.

Assuming a 15% attrition rate, the total sample size of randomized subjects is 1,176, with a 1:1 ratio to the FP and SC group (588 subjects in each of the group).

The primary endpoint of fever burden will be analyzed at the interim when 588 subjects (half of the planned sample size of 1,176 subjects) have completed the 3-month visit. Since fever burden does not follow normal distribution, Wilcoxon rank-sum tests will be used to analyze the data and the sample size estimation will be based on such test as well. In the SC group, the proportion of patients who develop fever and therefore show positive fever burden is estimated at 40%. In the FP group, it is expected that few will have positive fever burden; using a conservative assumption, we estimate 10% of subjects will show a positive fever burden. Under such assumptions, the probability that fever burden in the SC group is higher than in the FP group is 65% (nQuery 7.0 Assistant). Consequently, the test of the primary endpoint will have more than 99% power to show a statistically significant difference between the two groups with 500 subjects (nQuery 7.0).

10.1.1. Sample Size Re-estimation

An interim analysis will be conducted when the first 588 subjects (half of the planned sample size) have completed the 3-month visit (including subjects who

were discontinued early from the study), at which time the primary analysis will be performed to evaluate the treatment effect in fever burden. The key secondary endpoint of modified Rankin Scale will be evaluated as well for futility and sample size re-estimation. If recommended by the Data Monitoring Committee (DMC) and deemed appropriate, the sample size may increase up to double the planned sample size (up to 2,000 evaluable subjects). The overall study characteristics will be displayed by simulation as further described in section 10.5.

10.2. Analysis Population(s)

Enrolled: The enrolled subjects consist of all subjects who sign the informed consent.

Intent-to-Treat (ITT): This is the population of all subjects who have been consented and randomized.

As Treated (AT): This is the ITT population but based on the actual treatment received, not based on randomized, if there are patients who received the wrong treatment.

Per Protocol (PP): This population is defined as all subjects in the ITT who do not have any major protocol deviation. Major protocol deviations include major inclusion/exclusion deviations or other major protocol deviations, as will be defined in the statistical analysis plan.

All efficacy analyses including the primary and key secondary endpoints will be primarily based on the ITT population. Analysis of the AT and PP populations will also be performed on the primary and key secondary endpoints as sensitivity analyses. The safety analyses will be performed on the AT population using the as-treated principle, i.e., subjects will be analyzed based on the actual treatment they receive instead of the randomized treatment.

10.3. Study Endpoints

10.3.1. Primary Efficacy Endpoint

The primary endpoint is the daily average fever burden (°C-hour). Each patient's daily average fever burden will be calculated as the patient's total fever burden divided by the total number of hours the patient was in the acute phase and then multiplied by 24 hours (Total fever burden/(total hour) ×24 hour). Total fever burden is defined as the area under the temperature curve (AUC) during the acute observation period that is above

37.9°C. The acute phase is 336 hours or total hours from randomization to discharge/deemed medically ready for discharge from the intensive care unit, whichever comes first. Although the Arctic Sun System records the patient's temperature every minute, to compare the treatment groups consistently, calculation of fever burden will be based on as based on hourly temperature data.

10.3.2. Key Secondary Efficacy Endpoint

A key objective of this study is to determine whether fever prevention with the Arctic Sun 5000 Temperature Management System improves outcomes in moderate/severe brain-injured patients compared with standard care. Improved outcomes will be assessed using the endpoint of modified Rankin Scale (mRS) assessed at month 3 (6-category mRS outcome scores; mRS score 5 and 6 combined together). Note that mRS score 0-5 are directly collected at month 3; mRS will be scored 6 if subject died before the 3-month visit.

10.3.3. Other Secondary Efficacy Endpoints

Other secondary endpoints will include; but not be limited to:

- Neurologic outcome measures
    - Modified Rankin Scale measured at 6- and 12-months
    - National Institutes of Health Stroke Scale measured at 3- and 6-months
    - Barthel Index measured at 3- and 6-months
    - Glasgow Outcome Scale Extended measured at 3- and 6-months
    - Montreal Cognitive Assessment measured at 3- and 6-months
- Intensive Care Unit length of stay
- ICU Delirium
- Use of mechanical ventilation
- Hospital length of stay
- Mortality [7-day (or hospital discharge), 3-, 6-, and 12-month]

10.3.4. Safety Endpoints

The safety endpoints will include major adverse events (MAEs), the overall incidence of adverse events (AEs), the incidence of infection, and the incidence of shivering.

10.4. Statistical Analysis

10.4.1. Primary Efficacy Endpoint Analysis

The primary endpoint is daily average fever burden and will be evaluated by the following hypothesis:

H_0: The median of the daily average fever burden of FP treatment group is the same as that of SC treatment group.
H_1: The median of the daily average fever burden of FP treatment group is lower than that of SC treatment group.

10.4.1.1. Primary Analysis

The primary analysis will be conducted at the study interim. Only when statistical significance is achieved at 0.05 level (i.e. p-value $\leq$0.05), will the study continue to its full sample size to evaluate other study endpoints. Otherwise, the study will stop for futility.

Since fever burden is not normally distributed, the daily average fever burden in the two treatment groups will be compared using a van Elteren test, which is a direct extension of the Wilcoxon rank-sum tests, with stratification on patient diagnosis (ICH, AIS or SAH). Superiority of FP will be demonstrated if the p-value from the two-sided test is less than 0.05, and the median value of the FP group is less than SC group.

10.4.1.2. Supportive Analysis

A dichotomized variable (positive fever burden versus no fever burden) will be analyzed by Cochran-Mental-Haenszel (CMH) with patient diagnosis (IS, ICH, or SAH) as stratification factor.

The daily average fever burden will also be analyzed using a two-sample t-test (un-adjusted analysis). Exploratory analysis using an ANOVA model may also be conducted with other potential confounding factors included in the model.

The total fever burden may also be analyzed similarly as the daily average fever burden.

10.4.1.3. Poolability Analysis by Investigational Sites

The sites with less than 10 randomized subjects will be sorted by site number and pooled by order to form one or more combined site(s) with at least 10 randomized subjects.

The poolability of the investigational sites on the primary endpoint will be tested using a ranked ANOVA model. The daily average fever burden will be ranked first and the ranks will be fitted with an ANOVA model with treatment, sites, and treatment and site interaction as factors. If the p-value for the interaction test is <0.15, it will be considered evidence of a statistically significant interaction effect, and additional analyses will be performed to explore the differences among the investigation sites to assess potential causes and whether or not they are clinically meaningful.

10.4.1.4. Subgroup Analysis

The primary endpoint will be explored in the following subgroups:

- Gender
- Age (<70, ≥70)
- Patient diagnosis (ICH, AIS or SAH)
- Injury severity (high or low, where high score includes NIHSS ≥ 17, ICH Score ≥3, or WFNS ≥ 4 for IS, ICH, and SAH patients respectively, and low score includes NIHSS < 17, ICH Score ≤2 , or WFNS ≤ 3 for IS, ICH, and SAH patients respectively)
- Acetaminophen use (antipyretic)

10.4.1.5. Handling of Missing Data

Minimal missing data are expected for this endpoint. The analysis will be based on evaluable subjects. A multiple imputation method will be used to evaluate the missing data.

10.4.2. Key Secondary Efficacy Endpoint Analysis

The key secondary endpoint is the 6-category mRS outcome score and will be evaluated by the following hypothesis:

H_0: The median of mRS at month 3 in the FP treatment group is the same as that in the SC treatment group.
H_1: The median of mRS at month 3 in the FP treatment group is lower than that in the SC treatment group.

10.4.2.1. Primary Analysis

The analysis will be performed at the full planned sample size, or the re-estimated sample size, when all subjects finish the 3-month follow-up visit. A “shift analysis” will be employed to analyze the 6-category

mRS outcome scales. This is essentially a van Elteren test (a particular form of Cochran-Mantel-Haenszel (CMH) test), with stratification on patient diagnosis (ICH, IS or SAH).[31] Superiority of FP will be demonstrated if the p-value from the two-sided test is less than 0.05, and the median value of the FP group is less than SC group.

10.4.2.2. Supportive Analysis

Additionally, the 6-category mRS outcome scores will be analyzed using a proportional odds model that includes treatment and patient diagnosis (ICH, AIS or SAH) as factors in the model. Odds ratio and its 95% confidence interval will be estimated and reported.

The mRS will also be dichotomized as a binary outcome and analyzed using two definitions of success. In the first analysis, scores of 0 to 3 for success and scores of 4 to 6 for failure will be used; in the second, scores of 0 to 2 for success and 3 to 6 for failure will be used. The mRS success rate at month 3will be analyzed by the Cochran-Mantel-Haenszel (CMH) test with stratification on patient diagnosis (ICH, IS or SAH).

The mRS scores at 6-month will be analyzed similarly for the 6-category scores and the dichotomized binary outcome.

10.4.2.3. Poolability Analysis by Investigational Sites

The sites with less than 10 randomized subjects will be sorted by site number and pooled by order to form one or more combined site(s) with at least 10 randomized subjects.

The poolability of the investigational sites on the key secondary endpoints will be tested using a logistic regression model using the full 6-category range of the mRS as response with treatment, sites, and treatment and site interaction as factors. If the p-value for the interaction test is <0.15, it will be considered evidence of a statistically significant interaction effect, and additional analyses will be performed to explore the differences among the investigation sites to assess potential causes and whether or not they are clinically meaningful.

10.4.2.4. Subgroup Analysis

The key secondary endpoint will be explored in the following subgroups:

- Gender
- Age (<70, ≥70)

• Patient diagnosis (ICH, AIS or SAH)
• Injury severity (high or low, where high score includes NIHSS ≥ 17, ICH Score ≥3, or WFNS ≥ 4 for IS, ICH, and SAH patients respectively, and low score includes NIHSS < 17, ICH Score ≤2, or WFNS ≤ 3 for IS, ICH, and SAH patients respectively)
• Acetaminophen use (antipyretic)

10.4.2.5. Handling of Missing Data

Study endpoints may be missing due to withdrawal of consent, investigator's decision, or lost to follow-up. As long as the missing data is unrelated to the study intervention and the observed and unobserved data, limiting the analysis to those subjects who contribute endpoints produces unbiased estimates of the event rates.

The reason for missing data for all subjects will be reported. In addition, the worst-case analysis (if in FP then score of 6; if in SC then score of 0 will be assigned to the missing mRS) and tipping point analysis will be performed to assess the sensitivity of the main analysis. A multiple imputation method will be used to evaluate the missing data.

10.4.3. Secondary Efficacy Endpoint Analysis

For analysis of binary variables in secondary endpoints, the two-group chi-square test will be used. For analysis of continuous variables in secondary endpoints, the two-sample t-test will be used. For time to event variables, Kaplan-Meier survival analysis will be used.

10.4.4. Safety Endpoint Analysis

Summaries of all AEs by treatment arm will include:

- The number (n) and percentage (%) of patients with at least 1 event by System Organ Class (SOC) and Preferred Terms (PT)
- Event by intensity (severe, moderate, mild), presented by SOC and PT
- Event by relationship to treatment or procedure (related, not related), presented by SOC and PT
- Serious adverse event presented by SOC and PT

MAE and incidence of shivering will be listed and summarized by treatment arm.

10.4.5. Multiplicity Control

The primary endpoint and the key secondary endpoint will be tested in hierarchical fashion according to the following sequence.

1. The primary endpoint, the daily average fever burden, will be tested at two-sided alpha=0.05 when half of the planned sample size complete the 3-month assessment.

2. Conditional on success of the primary endpoint, the key secondary endpoint, the mRS scores, will be tested at two-sided alpha=0.05 at the full planned sample size or the re-estimated sample size.

All other secondary endpoints will be for exploratory purposes and not adjusted for multiplicity and reported with unadjusted nominal p-values.

10.5. Interim Analysis

10.5.1. Administration of the Interim Analysis

An independent data monitoring committee (DMC) will be assembled which will be composed of medical experts with experience in treating subjects with stroke and a statistician, all of whom are not otherwise involved in any other aspects of the conduct of the study. The DMC will review safety data on an ongoing basis including adverse events. During the course of the study, the DMC will review the efficacy data in accordance with the guidelines for the pre-planned interim analyses. An independent statistician will provide data analyses support to DMC.

The interim analysis will be performed when half of the planned sample size subjects have completed the 3-month visit. A two-step decision will be made at the interim based on the following decision criteria:

1) futility decision based on the primary endpoint; and,
2) futility or sample size increase decision on the key secondary endpoint.

The study can only stop because of futility; there will be no stopping of the study due to strong result in effectiveness. If the result of the primary endpoint is a success, an interim study report will be produced for regulatory submission. The study will continue unless futility is shown for the key secondary endpoint.

For the analysis of the primary endpoint of fever burden, the primary analysis is at the interim, which will be performed by the independent statistician. The statistician will also work with a regulatory affairs specialist (independent of clinical study team) to produce an interim study report for regulatory submission. The interim study report will not include analysis of the secondary endpoints. All of the interim results will be blinded to any personnel at the investigational sites and any Bard personnel who are involved with the conduct of the study.

10.5.2. Statistical Approach for Control of Alpha and other Consideration

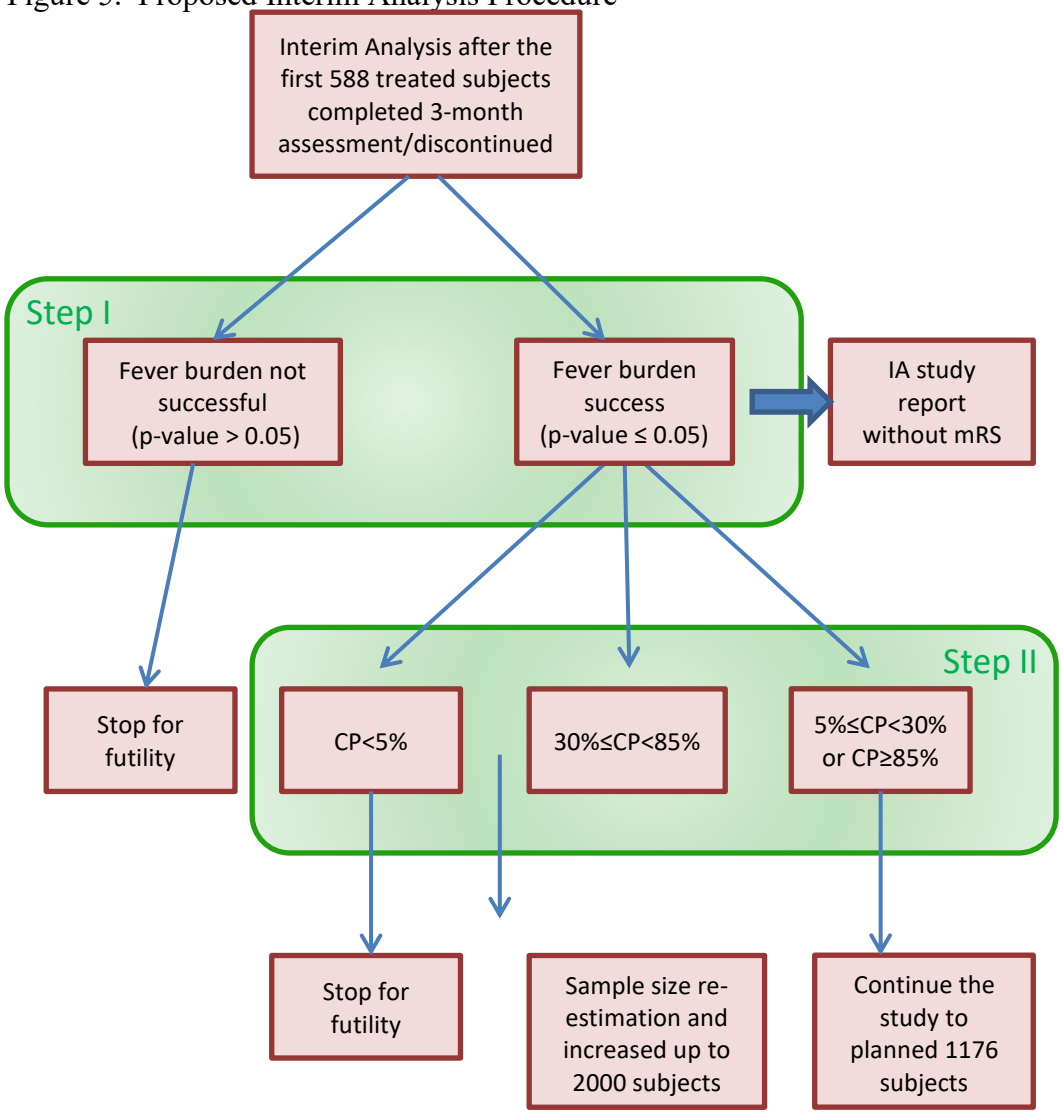
It is well known that adaptive design with sample size re-estimation can increase the power of the study but may cause inflation of type 1 error rate. On the other hand, futility analysis may decrease the power of the study and reduce the type 1 error rate. The proposed study design includes both features in the interim analysis for the key secondary endpoint of mRS. It is important to evaluate the impact on study power and type 1 error rate.

The rules of the two-step decision to be made at the interim are described below (See Figure 5 for illustration):

1. If the primary analysis of fever burden is not successful (p-value > 0.05), then the study will stop for futility; otherwise, an interim study report will be produced without any data for the key secondary endpoint of mRS , and the study will continue or stop based on the step 2 decision.

2. If the primary analysis of fever burden is successful, the futility and sample size re-estimation decision will be evaluated based on the dichotomized binary mRS outcome (scores of 0 to 3 for success and scores of 4 to 6 for failure) using the conditional power (CP) calculated under the current trend: If CP is less than 5%, the study will stop for futility; if the CP is between 5% and 30% or greater than 85%, the study will be finished at planned sample size (1000 subjects); if the CP is between 30% and 85%, the sample size will be re-estimated based on the observed effect at IA (current trend). If the re-estimated sample size is greater than 2000 evaluable subjects, the final sample size will be capped at 2000 evaluable subjects.

Figure 5. Proposed Interim Analysis Procedure



Note: CP is the conditional power under current trend on the key secondary binary endpoint (mRS scores of 0 to 3 for success and scores of 4 to 6 for failure).

$$CP_{\hat{\theta}} = 1 - \Phi\left(\frac{z_{\alpha/2} - E_{\hat{\theta}}\{B(1)|B(t)=b\}}{\sqrt{1-t}}\right) = 1 - \Phi\left(\frac{z_{\alpha/2} - \hat{\theta}}{\sqrt{1-t}}\right)$$

Where the B-value and $\hat{\theta}$ are defined following Proschan, et al:[32] assume the success rate for the FP is p_T, and for the SC is p_C. At the interim, treatment difference $\hat{\delta}_1 = \hat{p}_T - \hat{p}_C$, with the standard error $SE_{\hat{p}_T - \hat{p}_C} = \{\hat{p}_T(1 - \hat{p}_T)/N_T + \hat{p}_C(1-\hat{p}_C)/N_C\}^{1/2}$. Then test statistics $(t) = \frac{\hat{p}_T - \hat{p}_C}{SE_{\hat{p}_T - \hat{p}_C}}$, and the empirical estimate $\hat{\theta} = \frac{B(t)}{t} = \frac{Z(t)}{\sqrt{t}}$ (t=1/2).

A simulation study was performed to evaluate the operating characteristics. The study was simulated under null hypothesis ($p_C = 40\%$, and $p_T = 40\%$) and under alternative hypothesis ($p_C = 40\%$, and $p_T = 50\%$), respectively, with 1000 subjects (500 in treatment arm and 500 in control arm). At the interim, the CP was calculated, and the decision was made based on Figure 5. For each simulation, at the end of the study, the two treatment arms were compared by a chi-square test at two-sided α=0.05. Based on 10000 simulations, the overall type 1 error for this study is 2.1%, which is well under control (<5%), and the overall study power is 90.8%.

Trial operating characteristics

	Futility at IA	Probability of Sample Size increased	Reject Null
Under Null Hypothesis ($p_C = 40\%$, and $p_T = 40\%$)	73.3%	9.6%	2.1%
Under Alternative Hypothesis ($p_C = 40\%$, and $p_T = 50\%$)	4.8%	24.4%	90.8%

11. CASE REPORT FORMS

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation. All clinical study data will be recorded in the CRFs provided to the investigational site.

12. ADMINISTRATIVE REQUIREMENTS

This study will be conducted in accordance with Good Clinical Practice (GCP); the principles of the Declaration of Helsinki; applicable requirements of the USA Code of Federal Regulations (CFR); applicable requirements of the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the study is conducted in the EU; and any specific national, regional and local regulations if the study is conducted elsewhere.

12.1. Publication Policy

A Publications Committee will be established to define and manage publications emanating from this study.

12.2. Investigator Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of the protocol, including the protection of human subjects. Other site personnel must

have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects.

The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training. Federal databases will be searched to ensure that the Investigator and/or the site are not prohibited from engaging in federally Sponsored clinical research.

The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

12.3. Investigator Training

Prior to the start of the study, up to two (2) investigators from each participating site will undergo a mandatory study training that will be designed to cover aspects of the use of the study devices and the requirements of this protocol. The training is designed to ensure safe and effective use of the study devices and enhance protocol adherence.

12.4. Regulatory and Ethical Considerations

The Sponsor will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

12.4.1. Institutional Review Board or Ethics Committee Approval

Before commencement of the study, the Investigator must provide Sponsor with written documentation of IRB/EC approval. (The sponsor may obtain approval from a leading or central IRB/EC in certain countries, depending on local requirements.) This approval must refer to the Informed Consent Form and the study by both the title and the protocol number assigned by Sponsor. The Investigator, if a member of the IRB/EC, is not to participate in the approval decision for this study. This non-participation should be noted in the approval letter, if possible. Any additional requirements of the IRB/EC or national, regional or local regulations will be followed.

No device supplies, if applicable, will be shipped to the Investigator until the IRB/EC approval has been supplied to Sponsor and all relevant agreements have been executed.

If required by national, regional or local regulations, the IRB/EC must give written renewal of the original approval at least annually to continue the study. A copy of the written renewal must be provided to Sponsor.

12.4.2. Informed Consent

Prior to screening or the procedure, the Investigator must explain to each subject (or the subject's legally authorized representative) the nature of the study, its purpose, expected duration, and the benefits and risks of study participation. After this explanation and before entering screening or the study, the subject (or legally authorized representative) must voluntarily sign and date the appropriate IRB/EC-approved Informed Consent form.

12.5. Protocol Adherence and Amendment

The study will be conducted as described in this protocol. Investigators are not permitted to deviate from this protocol except to protect the patient's rights, safety or well-being. Any deviations from this protocol must be documented by the Investigator. If an emergency situation arises in which the rights, safety or well-being of a subject may require immediate alternative intervention, the Investigator should act in the best interests of the subject. Sponsor and the site's IRB/EC must be notified immediately if this occurs. This should be followed with written confirmation that describes the emergency action and outcomes to Sponsor and the IRB/EC within 10 working days. Protocol deviations will be reviewed during monitoring visits; as appropriate, investigators will be required to identify corrective and preventive actions to prevent further deviations. An investigator may be disqualified from the study for repeated and/or egregious protocol deviations.

This protocol may be amended as necessary by the Sponsor. Any protocol amendments will be documented via an incremented version of this protocol (with the relevant revision history) and a "was/is" comparison table to highlight the protocol changes. Amendments to the protocol must undergo the same approval process by the Sponsor, investigators, ethics committees and regulatory authorities as the original protocol.

12.6. Data Collection

The Investigator is responsible for completely and accurately recording study data in the appropriate sections of the CRFs provided by Sponsor. The CRFs must be signed by the Investigator or by his/her authorized person as designated in a note to file.

The monitor will ensure the quality of data recording at each investigational site by comparison to supporting source documents during periodic site visits. Adherence to proper recording of information as well as assuring that corrections are being made will also be addressed during these periodic visits.

The site is responsible for downloading data from the Arctic Sun 5000 console and uploading to a site-specific email address. Data files should be uploaded as soon as possible after the case is completed.

12.7. Measures to Control Bias

For this study, several measures are being used to control or reduce potential bias. Those measures include, but are not limited to the following:

- Subject randomization;
- Personnel performing follow-up neurologic assessments at 3-, 6-, and 12-month visits blinded to treatment assignment;
- Statistical analysis plan;
- Use of an independent statistician to conduct the planned interim analysis; and,
- Use of a Data Monitoring Committee for the planned interim analysis.

12.8. Communications with the Sponsor

Although the Investigator and his/her staff may have contact with other key individuals at Sponsor throughout the course of the study, all communications regarding conduct of the study must be channeled through the assigned clinical research associate or the project manager designated on the cover page of this protocol.

12.9. Required Documentation

At a minimum, the following documentation must be received by the Sponsor prior to study commencement:

- CVs for the principal Investigator and sub-Investigators;
- Signed Financial Disclosure Statement;
- Signed Clinical Study Agreement;
- Fully executed Confidentiality/Nondisclosure Agreement for Investigator and Sub-Investigators;
- Signed “Agreement to Participate” (page ii of this protocol);
- Written approval from the IRB/EC of both the protocol and informed consent form;
- IRB/EC Assurance of Compliance Form or equivalent.

13. SITE MONITORING

The study monitors are designated as agents of the Sponsor and are assigned to oversee the conduct and progress of the study and to be the principal communication link between Sponsor and Investigator.

The study monitors will be involved in Investigator selection and training, assurance of IRB/EC approvals, and periodic on-site inspection and monitoring of sites and records, to ensure continued compliance with the protocol and adequacy of the Investigator and the facility to carry out the study. In addition, the monitor will verify that the device is being used in accordance with the protocol.

The monitor will perform several types of site visits during the course of the study. In all cases, the study monitor will provide a written summary of the visit, including necessary follow-up items, to the Investigator and Sponsor.

13.1. Study Initiation Visit

Before the study begins, the study monitor will visit the site. The purpose of this visit is to review with the Investigator and staff the provisions and proper conduct of the clinical evaluation. This includes a detailed review of the protocol and CRFs with instructions as to their completion, as well as reviewing regulations pertaining to the conduct of the clinical study. Arrangements for timely and accurate reporting of clinical data and relevant medical events will be established as well as ensuring safe and secure storage for the study devices. Additionally, device training will be provided to the research staff as well as bedside nurses caring for study subjects.

The study monitor will:

- confirm that the ICF to be used is the one approved by the IRB/EC
- verify that all necessary documents are on file at the site; and
- confirm that there are provisions to continue and maintain all documents and records throughout the study as required by good clinical practice regulations.

13.2. Ongoing Monitoring Visits

The study monitor will maintain personal contact with the Investigator and staff throughout the study by telephone, e-mail, fax, mail, and on-site visits. Monitoring will begin after the first subjects are enrolled and continue until the study is completed. This monitoring will assure continued protocol compliance, adequate subject enrollment, accurate data reporting (including the comparison of CRFs with subject records), device accountability, and continued IRB/EC acceptance of the study. The study monitor will evaluate and summarize the results of each visit in written reports, identifying any ongoing data problems with any study site and

specifying recommendations for resolution of noted deficiencies. A formal monitoring plan will describe the planned extent of source data verification.

13.3. Final Monitoring Visit

At the completion of the study, the study monitor will conduct a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, confirm that the Investigator's files are accurate and complete, review the record retention requirements with the Investigator, and assure that all applicable requirements for closure of the study are met. The actions and observations made at this visit will be recorded and filed.

14. TERMINATION OF STUDY

Sponsor reserves the right to suspend enrollment or terminate the study at any time as set forth in the Clinical Study Agreement. Written notice will be submitted to the Investigator in advance of such termination.

Sponsor may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements.

Sponsor may request that site personnel undergo training on the protocol and clinical research requirements during the study.

15. REPORTING REQUIREMENTS

The Investigator must promptly report to Sponsor any withdrawal of Institutional Review Board (IRB) or Ethics Committee (EC) approval at the site. Additional reporting requirements of the Investigator include:

- Reporting to the IRB/EC of all Informed Consent violations.
- Reporting to Sponsor of any SAEs, SADEs USADEs or device deficiencies that could have led to a SADE, as outlined in this protocol.

16. RECORD RETENTION

The Investigator shall retain all study records for a period of at least 2 years after the date on which the investigation is terminated or completed or as required by local laws/regulations, whichever is longer. All Investigators will be notified by the Sponsor when the record retention period has ended. The Investigator may withdraw from the responsibility to maintain records for the period required and transfer custody of the

records to any other person who will accept responsibility for retaining them. Notice of a transfer shall be given to Sponsor no later than 10 working days after transfer occurs.

17. AUDIT/INSPECTIONS

The investigational sites may also be subject to quality assurance audit by personnel of the Sponsor (and its affiliates) and the Sponsor's study contractor personnel, as well as by IRB/ECs and regulatory authorities. It is important that the Principal Investigator and the relevant investigational site personnel are available during the audits and that sufficient time is devoted to the process.

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19. APPENDICES

19.1. Modified Rankin Scale

Modified Rankin Scale	Structured Interview
5=Severe disability: bedridden, incontinent, and requiring constant nursing care and attention	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver. Question: Does the person require constant care?
4=Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.	4=Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?
3=Moderate disability; requiring some help, but able to walk without assistance.	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?
2=Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?
1=No significant disability despite symptoms; able to carry out all usual duties and activities.	1=No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?
0=No symptoms at all.	0=No symptoms at all; no limitations and no symptoms.

19.2. Glasgow Coma Scale

ACTIVITY	SCALE	SCORE
Eye Opening Non To pain To speech Spontaneous	 1 = Even to supra-orbital pressure 2 = Pain from sternum/limb/supra-orbital pressure 3 = Non-specific response, not necessarily to command 4 = Eyes open, not necessarily aware	
Motor Response None Extension Flexor Response Withdrawal Localizes pain Obeys commands	 1 = To any pain; limbs remain flaccid 2 = Shoulder adducted and shoulder and forearm internally rotated 3 = Withdrawal response or assumption of hemiplegic posture 4 = Arm withdraws to pain, shoulder abducts 5 = Arm attempts to remove supra-orbital/chest pressure 6 = Follows simple commands	
Verbal Response None Incomprehensible Inappropriate Confused Oriented	 1 = No verbalization of any type 2 = Moans/groans, no speech 3 = Intelligible, no sustained sentences 4 = Converses but confused, disoriented 5 = Converses and oriented	
TOTAL (3-15)		

Predicted Verbal Glasgow Coma Scale for Intubated Patients

	GCS Eye Score			
GCS Motor	1	2	3	4
1	1	1	1	2
2	1	2	2	2
3	2	2	3	3
4	2	3	3	4
5	3	3	4	4
6	3	4	4	5

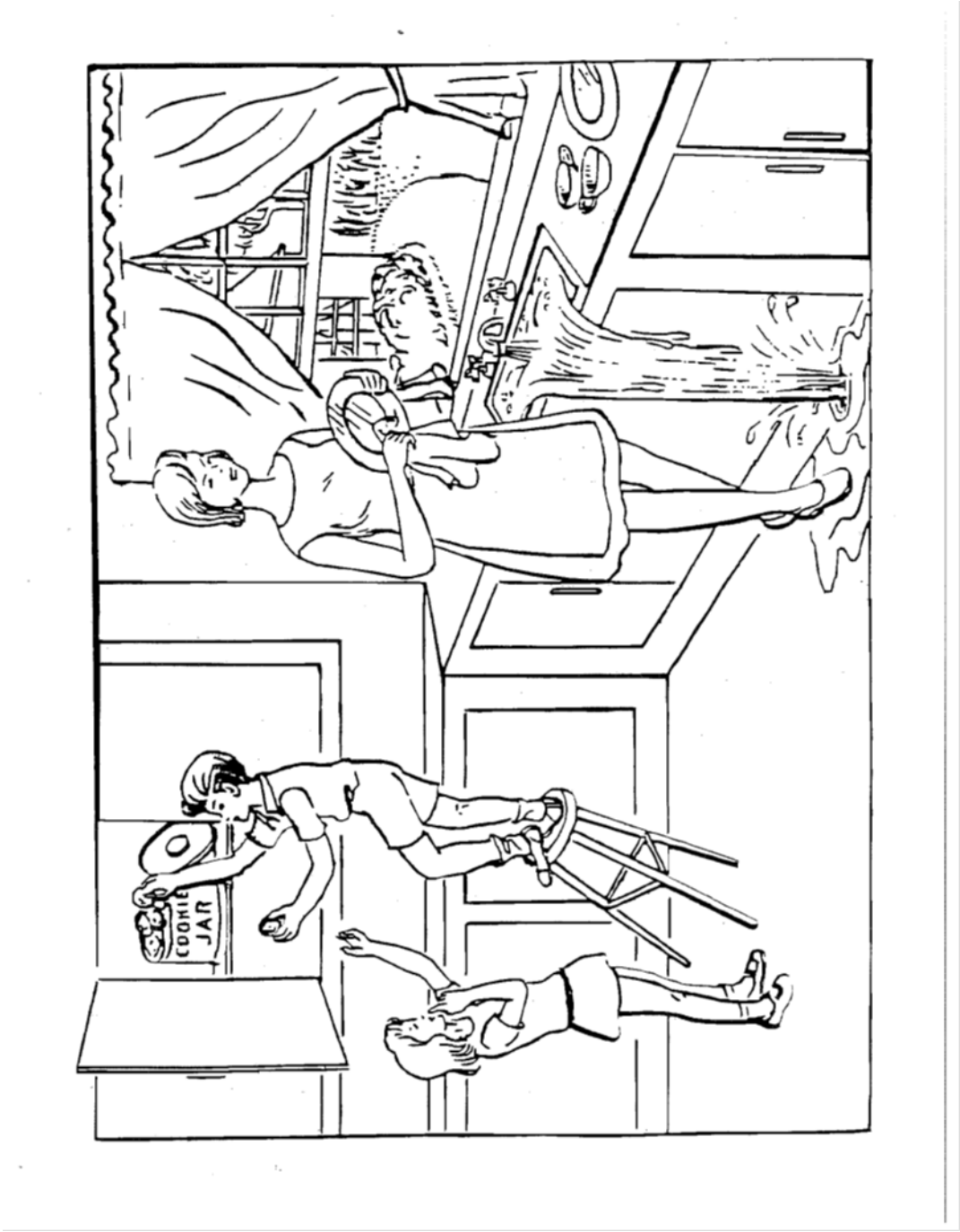
19.3. National Institutes of Health Stroke Scale

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	

testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.		
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm	

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____	
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of	

the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain:_____	
11. Extinction and Inattention: Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	



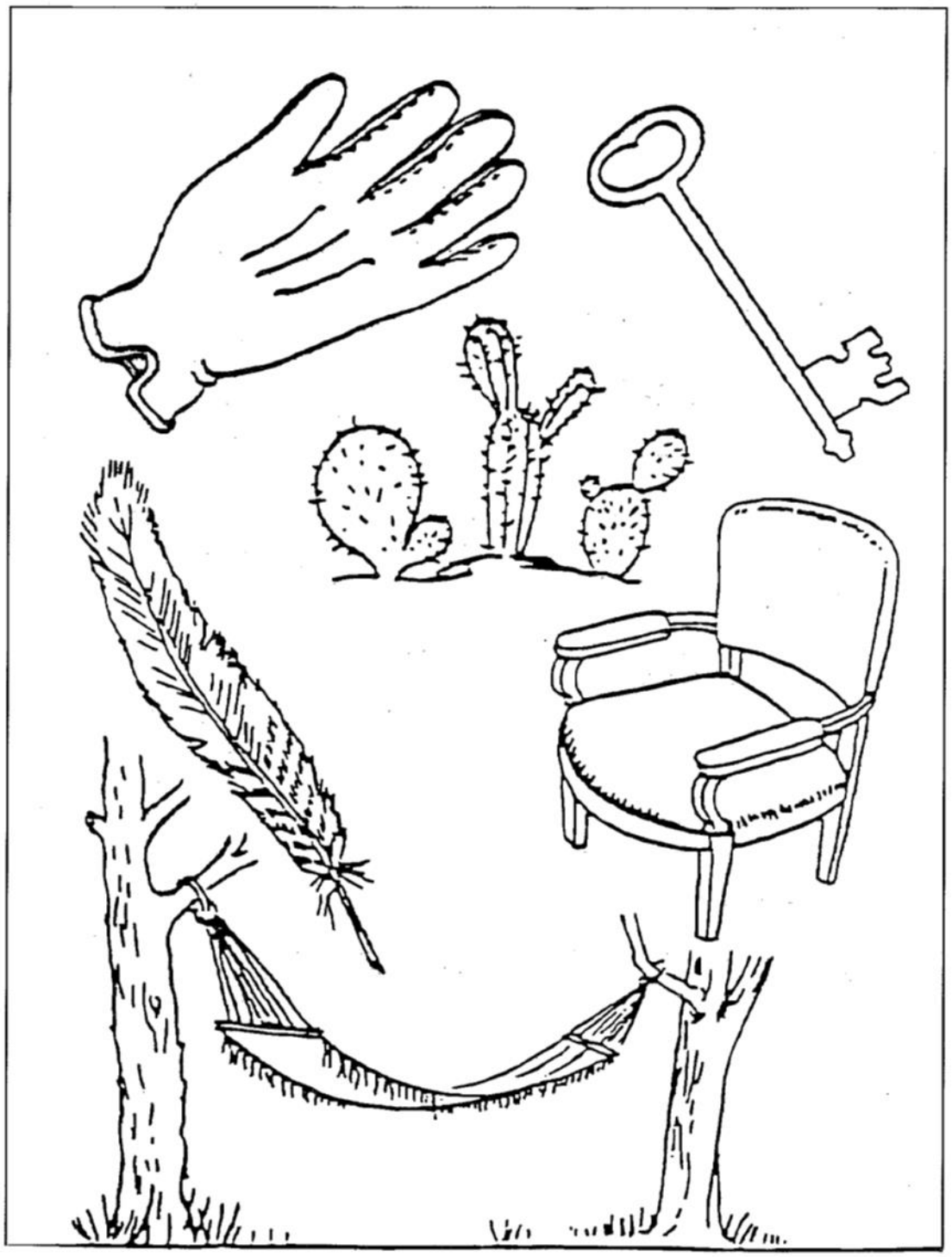
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

NIHSS Scoring

Scale Item	Coma	Difficult or Confused	Tips
1a LOC Responsiveness	2 - for some movement 3 - Flaccid or no movement	0 - if awake, alert	Can usually tell score by greeting
1b LOC Questions	2	1 - ET tube, trauma, severe dysarthria; 2 - Aphasia,stupor, confusion	Score initial response; pt may write answers.
1c LOC Commands	2	2 - if unable to understand or follow the commands	You are not testing grip strength. May pantomime if pt doesn't respond to command; ok if impaired by weakness
2 Best Gaze	0 if normal eye movement noted	0 if patient able to track your movements	Coma - hold eyes open and turn head side-to-side. Confused - Make eye contact and move to other side of bed
3 Visual	0 if blinks to visual threat 3 if no blink in any field 3 if blind due to any cause	0 if blinks to visual threat 3 if no blink in any field 3 if blind due to any cause	Three ways to test - finger counting, finger movement or threat; test in 4 quads of each eye separately
4 Facial Palsy	3	If patient is verbal, observe for facial droop. If confused and nonverbal, use noxious stimulation to elicit grimace	Check NLF in advance; score 1 for minor asymmetry on smiling; score 2 major for asymmetry of smile; score 3 for absence of movement in upper **and** lower face
5a, 5b Motor arm	3 for no effort against gravity 4 for no movement at all	If unable to follow directions, use observation to score. Is the patient using the arm?	**UN**testable only with amputation or fusion.
6a, 6b Motor leg	3 for no effort against gravity 4 for no movement at all	If unable to follow directions, use observation to score. Is the patient moving the leg?	**UN**testable only with amputation or fusion.
7 Limb ataxia	0	0 if unable to follow directions	Absent if paralyzed or unable to understand. **UN**testable only with amputation or fusion
8 Sensory	2	Use pinprick and observe patient's reactions if patient unable to cooperate	Ask pt, "can you feel this, can you feel this, and does it feel the same on each side"; (do not ask if sharper/duller)
9 Best Language	3	Choose score for stupor/limited cooperation: 2 - listener carries burden of communication; 3 - garbled or mute AND not following commands	Best language and COMPREHENSION; describe scene, name objects and read phrases. If blind, place object in hand and have patient describe
10 Dysarthria	2	1 - Difficult to understand (regardless of cause), 2 - speech not understandable, garbled	Listen to their words; if they can't read - have them repeat words or listen to the words they do say **UN**testable only with physical barrier
11 Extinction and Inattention	0	Score only if present	Looking for lack of awareness with double tactile/visual stimulation
Reminders:	a. Perform and score in numerical order.	b. Accept first response. c. Do not coach.	

19.4. World Federation of Neurological Societies Grading Scale for Subarachnoid Hemorrhage

GRADE	Glasgow Coma Scale	Motor Deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Absent or Present
V	6-3	Absent or Present

19.5. Intracerebral Hemorrhage Score

Test/Scale/Finding	Score
Glasgow Coma Score • 3 – 4 • 5 – 12 • 13 - 15	 +2 +1 0
Age ≥80 years	+1
ICH Volume ≥30ml	+1
Intraventricular Hemorrhage	+1
Infratentorial Origin of Hemorrhage	+1
TOTAL SCORE	

19.6. Intensive Care Delirium Screening Checklist

- Score your patient over the entire shift. Components don't all need to be present at the same time.
- Components #1 through #4 require a focused bedside patient assessment. This cannot be completed when the patient is deeply sedated or comatose (i.e., SAS = 1; RASS =-4 or -5).
- Components #5 through #8 are based on observations throughout the entire shift. Information from the prior 24 hours (i.e., from 1-2 nursing shifts) should be obtained for components #7 and #8.

Give a score of 1 to each of the 8 items below if the patient clearly meets the criteria defined in the scoring instructions.

ASSESSMENT	SCORING INSTRUCTIONS		SCORE
1.Altered Level of Consciousness*	• Deep sedation/coma over entire shift [SAS=1, 2; RASS= -4,-5] • Agitation [SAS = 5, 6, or 7; RASS= 1-4] at any point • Normal wakefulness [SAS = 4; RASS = 0] over the entire shift • Light sedation: no recent sedatives [SAS = 3; RASS= -1, -2, -3] • Light sedation: recent sedatives [SAS = 3; RASS= -1, -2, -3]	Not assessable = 1 point = 0 points = 1 point = 0 points	
2.Inattention	• Difficulty following instructions or • Easily distracted by external stimuli or • Difficulty in shifting focus (Does the patient follow you with their eyes?)	1 Point if any present	
3.Disorientation	• Mistake in time, place, person (Does the patient recognize their caregiver?) (Does the patient know what kind of place they are in?)	1 Point for any abnormality	
4.Hallucination/ delusions/ psychosis	• Unequivocal manifestation of hallucinations or of behavior probably due to hallucinations (e.g., catching non-existent object) • Delusions • Gross impairment in reality testing (Is the patient inappropriately afraid of the people or things around them?)	1 Point for any	
5.Psychomotor agitation or retardation	• Hyperactivity requiring additional sedatives or restraints in order to control potential dangerousness (e.g. pulling out IV lines, hitting staff) • Hypoactive or clinically noticeable psychomotor slowing or retardation	1 Point if any are present	
6.Inappropriate speech or mood	• Inappropriate, disorganized or incoherent speech • Inappropriate mood or display of emotion related to events or situation (Is the patient apathetic, or inappropriately demanding?)	1 Point if any are present	
7.Sleep wake/cycle disturbance	• Sleeping less than 4 hours at night or • Waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment) or • Sleeping during most of day	1 Point if any are present	
8.Symptom fluctuation (1 Point if present)	• Fluctuation of any of the above items over a 24 hour period (e.g., from one shift to another).	1 Point if present	
TOTAL SCORE (0-8/8):			

19.7. Barthel Index

Guidelines

a. The index should be used as a record of what a patient does, not as a record of what a patient could do.
b. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
c. The need for supervision renders the patient not independent.
d. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
e. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
f. Middle categories imply that the patient supplies over 50 per cent of the effort.
g. Use of aids to be independent is allowed.

ACTIVITY	SCORE
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	
BATHING 0 = dependent 5 = independent (or in shower)	
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	
TOILET USE 0 = dependent 5 = needs some help, but can do something alone	

10 = independent (on and off, dressing, wiping)	
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, >50 yards 10 = walks with help of one person (verbal or physical) >50 yards 15 = independent (may use any aid; e.g., cane) >50 yards	
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	
TOTAL (0–100)	

19.8. Glasgow Outcome Scale Extended

DESCRIPTION	SCORE
Dead	1
Vegetative State (VS)	2
Lower Severe Disability (Lower SD)	3
Upper Severe Disability (Upper SD)	4
Lower Moderate Disability (Lower MD)	5
Upper Moderate Disability (Upper MD)	6
Lower Good Recovery (Lower GR)	7
Upper Good Recovery (Upper GR)	8

Structured Interview for GOS-E

Consciousness:

1. Is the head-injured person able to obey simple commands or say any words?

_____Yes _____No (VS)

Note: anyone who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with
nursing staff and/or other caretakers. Confirmation of VS requires full assessment.

Independence at Home:

2a. Is the assistance of another person at home essential every day for some activities of daily living?

_____Yes _____No If no, go to 3

Note: for a NO answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding and should be capable of being left alone overnight.

2b. Do they need frequent help of someone to be around at home most of the time?

_____Yes (Lower SD) _____No (Upper SD)

Note: for a NO answer they should be able to look after themselves at home up to eight hours during the day if necessary, though they need not actually look after themselves

2c. Was the patient independent at home before the injury?

_____Yes _____No

Independence Outside Home:

3a. Are they able to shop without assistance?

_____Yes _____No (Upper SD)

Note: this includes being able to plan what to buy, take care of money themselves and behave appropriately in public. They need not normally shop, but must be able to do so.

3b. Were they able to shop without assistance before?

_____Yes _____No

4a. Are they able to travel locally without assistance?

_____Yes _____No (Upper SD)

Note: they may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b. Were they able to travel locally without assistance before the injury?

_____Yes _____No

Work:

5a. Are they currently able to work (or look after others at home) to their previous capacity?

_____Yes If yes, go to 6 _____No

5b. How restricted are they?

a. Reduced work capacity? _____ a (Upper MD)

b. Able to work only in a sheltered workshop or non-competitive job or currently unable to work? _____ b (Lower MD)

5c. Does the level of restriction represent a change in respect to the pre-trauma situation?

_____Yes _____No

Social and Leisure Activities:

6a. Are they able to resume regular social and leisure activities outside home?

_____Yes If yes, go to 7 _____No

Note: they need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation, then this is also considered a disability.

6b. What is the extent of restriction on their social and leisure activities?

a. Participate a bit less: at least half as often as before injury _____ a (Lower GR)

b. Participate much less: less than half as often _____ b (Upper MD)

c. Unable to participate: rarely, if ever, take part _____ c (Lower MD)

6c. Does the extent of restriction in regular social and leisure activities outside home represent a change in respect or pre-trauma

_____Yes _____No

Family and Friendships:

7a. Has there been family or friendship disruption due to psychological problems?

_____Yes _____No If no, go to 8

Note: typical post-traumatic personality changes are: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression and unreasonable or childish behavior.

7b. What has been the extent of disruption or strain?

a. Occasional - less than weekly _____a (Lower GR)

b. Frequent - once a week or more, but not tolerable _____ b (Upper MD)

c. Constant - daily and intolerable _____ c (Lower MD)

7c. Does the level of disruption or strain represent a change in respect to pre-trauma situation?

_____Yes _____No

Note: if there were some problems before injury, but these have become markedly worse since the injury then answer yes to question

Return to Normal Life:

8a. Are there any other current problems relating to the injury which affect daily life?

_____Yes (Lower GR) _____No (Upper GR)

Note: other typical problems reported after head injury: headaches, dizziness, sensitivity to noise or light, slowness, memory failures and concentration problems.

8b. If similar problems were present before the injury, have these become markedly worse?

_____Yes _____No

9. What is the most important factor in outcome?

_____ a. Effects of head injury
_____ b. Effects of illness or injury to another part of the body
_____ c. A mixture of these

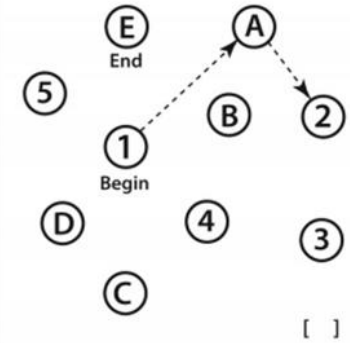
Note: Extended GOS grades are shown beside responses on the assessment form.
The overall rating is based on the lowest outcome category indicated.
Areas in which there has been no change with respect to the pre-trauma situation are ignored when the overall rating is made.

19.9. Montreal Cognitive Assessment

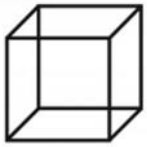
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

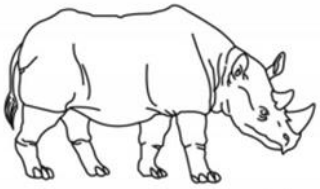


Draw CLOCK (Ten past eleven) (3 points)

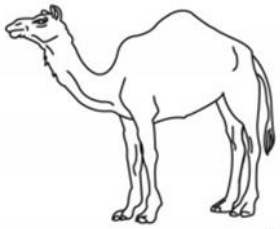
[ ] [ ] [ ] __/5
Contour Numbers Hands

NAMING

[ ]



[ ]



[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30 TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

19.10. Instructions for Use

ARCTIC SUN® 5000

TARGETED TEMPERATURE MANAGEMENT

OPERATOR'S MANUAL

Medivance®

Chapter 1 – Getting Started

Indications for Use

The Arctic Sun Temperature Management System is intended for monitoring and controlling patient temperature.

Warnings and Cautions

Warnings

- Do not use the Arctic Sun in the presence of flammable agents because an explosion and/or fire may result.
- Do not use high frequency surgical instruments or endocardial catheters while the Arctic Sun is in use.
- There is a risk of electrical shock and hazardous moving parts. There are no user serviceable parts inside. Do not remove covers. Refer servicing to qualified personnel.
- Power cord has a hospital grade plug. Grounding reliability can only be achieved when connected to an equivalent receptacle marked "hospital use" or "hospital grade".
- When using the Arctic Sun, note that all other thermal conductive systems, such as water blankets and water gels, in use while warming or cooling with the Arctic Sun may actually alter or interfere with patient temperature control.
- Do not place ArcticGel Pads over transdermal medication patches as warming can increase drug delivery, resulting in possible harm to the patient.

Cautions

- This product is to be used by or under the supervision of trained, qualified medical personnel.
- Federal law (USA) restricts this device to sale, by or on the order of a physician.
- Use only distilled or sterile water. The use of other fluids will damage the Arctic Sun system.
- When moving the Arctic Sun always use the handle to lift the controller over an obstacle to avoid over balancing.
- The patient's bed surface should be located between 30 and 60 inches (75 cm and 150 cm) above the floor to ensure proper flow and minimize risk of leaks.
- The clinician is responsible to determine the appropriateness of custom parameters. When the system is powered off, all changes to parameters will revert to the default unless the new settings have been saved as new defaults in the Advanced Setup screen. For small patients (≤30 kg) it is recommended to use the following settings: Water Temperature High Limit ≤40°C (104°F); Water Temperature Low Limit ≥10°C (64.4 °F); Control Strategy =2.
- The operator must continuously monitor patient temperature when using Manual Control and adjust the temperature of the water flowing through the pads accordingly. Patient temperature will not be controlled by the Arctic Sun in Manual Control.
- Due to the system's high efficiency, Manual Control is not recommended for long duration use. The operator is advised to use the automatic therapy modes (e.g. Control Patient, Cool Patient, Rewarm Patient) for automatic patient temperature monitoring and control.
- The Arctic Sun will monitor and control patient core temperature based on the temperature probe attached to the system. The clinician is responsible for correctly placing the temperature probe and verifying the accuracy and placement of the patient probe at the start of the procedure.
- Medivance recommends measuring patient temperature from a second site to verify patient temperature. Medivance recommends the use of a second patient temperature probe connected to the Arctic Sun Temperature 2 input as it provides continuous monitoring and safety alarm features. Alternatively, patient temperature may be verified periodically with independent instrumentation.
- The displayed temperature graph is for general information purposes only and is not intended to replace standard medical record documentation for use in therapy decisions.
- Patient temperature will not be controlled and alarms are not enabled in Stop Mode. Patient temperature may increase or decrease with the Arctic Sun in Stop Mode.
- Carefully observe the system for air leaks before and during use. If the pads fail to prime or a significant continuous air leak is observed in the pad return line, check connections. If needed, replace the leaking pad. Leakage may result in lower flow rates and potentially decrease the performance of the system.
- The Arctic Sun Temperature Management System is for use only with the ArcticGel Pads.
- The ArcticGel Pads are only for use with the Arctic Sun Temperature Management Systems.
- The ArcticGel Pads are non-sterile for single patient use. Do not reprocess or sterilize. If used in a sterile environment, pads should be placed according to the physician's request, either prior to the sterile preparation or sterile draping. ArcticGel Pads should not be placed on a sterile field.
- Use pads immediately after opening. Do not store pads once the kit has been opened.
- Do not place ArcticGel Pads™ on skin that has signs of ulceration, burns, hives, or rash.
- While there are no known allergies to hydrogel materials, caution should be exercised with any patient who has a history of skin allergies or sensitivities.
- Do not allow circulating water to contaminate the sterile field when patient lines are disconnected.
- The water content of the hydrogel affects the pad's adhesion to the skin and conductivity, and therefore, the efficiency of controlling patient temperature. Periodically check that pads remain moist and adherent. Replace pads when the hydrogel no longer uniformly adheres to the skin. Replacing pads at least every 5 days is recommended.
- Do not puncture the ArcticGel Pads with sharp objects. Punctures will result in air entering the fluid pathway and may reduce performance.
- If accessible, examine the patient's skin under the ArcticGel Pads often, especially those at higher risk of skin injury. Skin injury may occur as a cumulative result of pressure, time and temperature. Do not place bean bag or other firm positioning devices under the ArcticGel Pads. Do not place positioning devices under the pad manifolds or patient lines.
- The rate of temperature change and potentially the final achievable patient temperature is affected by many factors. Treatment application, monitoring and results are the responsibility of the attending physician. If the patient does not reach target temperature in a reasonable time or the patient is not able to be maintained at the target temperature, the skin may be exposed to low or high water temperatures for an extended period of time which may increase the risk for skin injury. Ensure that pad sizing / coverage and custom parameter settings are correct for the patient and treatment goals, environmental factors such as excessively hot rooms, heat lamps, and heated nebulizers are eliminated, water flow is greater than or equal to 2.3 liters per minute, a patient temperature probe is in the correct place, and patient shivering is controlled. Otherwise, consider increasing minimum water temperature, modifying target temperature to an attainable setting, or discontinuing treatment.
- Due to underlying medical or physiological conditions, some patients are more susceptible to skin damage from pressure and heat or cold. Patients at risk include those with poor tissue perfusion or poor skin integrity due to diabetes, peripheral vascular disease, poor nutritional status, steroid use or high dose vasopressor therapy. If warranted, use pressure relieving or pressure reducing devices under the patient to protect from skin injury.
- Do not allow urine, antibacterial solutions or other agents to pool underneath the ArcticGel Pads. Urine and antibacterial agents can absorb into the pad hydrogel and cause chemical injury and loss of pad adhesion. Replace pads immediately if these fluids come into contact with the hydrogel.
- Do not place ArcticGel Pads over an electrosurgical grounding pad. The combination of heat sources may result in skin burns.
- If needed, place defibrillation pads between the ArcticGel pads and the patient's skin.
- Carefully remove ArcticGel Pads from the patient's skin at the comple-

tion of use. Discard used ArcticGel Pads in accordance with hospital procedures for medical waste.

- The USB data port is to be used only with a standalone USB flash drive. Do not connect to another mains powered device during patient treatment.
- Users should not use cleaning or decontamination methods different from those recommended by the manufacturer without first checking with the manufacturer that the proposed methods will not damage the equipment. Do not use bleach (sodium hypochlorite) as it may damage the system.
- Medivance will not be responsible for patient safety or equipment performance if the procedures to operate, maintain, modify or service the Medivance Arctic Sun are other than those specified by Medivance. Anyone performing the procedures must be appropriately trained and qualified.

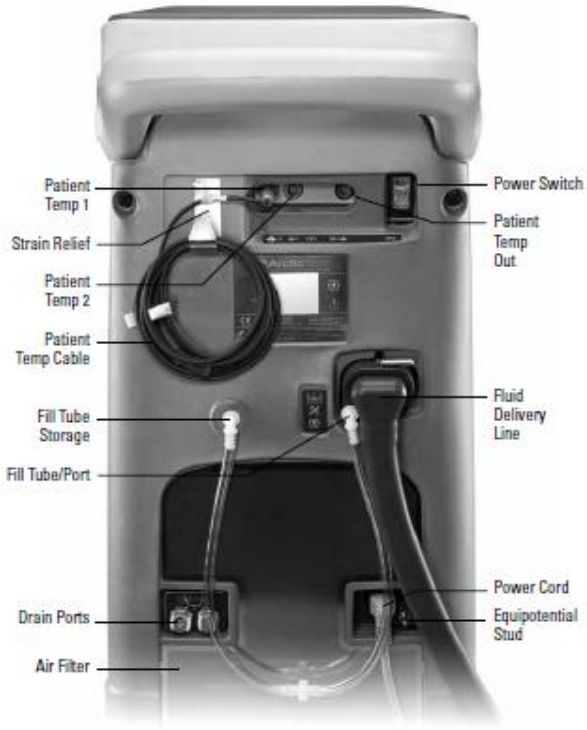
System Setup

Unpack

1) Unpack the Arctic Sun Control Module and accessories.
2) Allow the control module to remain upright for at least 2 hours prior to completing the installation and setup procedure in order to allow the chiller oil to settle. Damage to the chiller compressor may result otherwise.

Connections

1) Use only Medivance cables and accessories with the Arctic Sun Control Module. Connect the Fluid Delivery Line, Patient Temp 1 cable, Patient Temp 2 cable (optional) and Fill Tube to the back of the control module.
2) Plug the Power Cord into the wall outlet. Position Arctic Sun so that access to the power cord is not restricted.



Power On

1) Turn the power ON by activating the Power Switch.
2) The control module will automatically go through a brief self-test of the independent safety alarm.
3) A New User Training module option is available from the start up screen.

4) When the self-test is complete, the **Patient Therapy Selection** screen will appear on the control panel.

Fill Reservoir

1) Fill the reservoir with sterile or distilled water only.
2) Four liters of water will be required to fill the reservoir at initial installation.
3) Add one vial of Arctic Sun Cleaning Solution to the sterile or distilled water.
4) From the **Patient Therapy Selection** screen, press either the **Normothermia** or **Hypothermia** button, under the New Patient heading.
5) From the **Hypothermia** or **Normothermia** therapy screen, press the **Fill Reservoir** button.
6) The **Fill Reservoir** screen will appear. Follow the directions on the screen.

Functional Verification
Perform the following functional verification procedure after initial setup and installation of the control module.

1) Power **On** the control module
2) From the **Patient Therapy Selection** screen, press the **Hypothermia** button to display the **Hypothermia** therapy screen.
3) From the **Hypothermia** therapy screen, press the **Manual Control** button to open the **Manual Control** window.
4) Use the Up and Down arrows to set the **Manual Control** water target temperature to 40°C and the duration to 30 minutes.

5) Press the **Start** button to initiate **Manual Control**. Allow at least 3 minutes for the system to stabilize.
6) Monitor the flow rate and water temperature in the **System** status area on the **Hypothermia** therapy screen.
7) Verify that the flow rate reaches at least 1.5 liters/minute.
8) Verify that the water temperature increases to 30°C.
9) Press the **Stop** button.
10) Set the Manual Control water target temperature to 4°C and the duration to 30 minutes.
11) Press the **Start** button to initiate **Manual Control**.
12) Monitor the flow rate and water temperature in the **System** status area of the **Hypothermia** therapy screen. Verify that the water temperature drops to 6°C.
13) Press the **Stop** button to stop **Manual Control**
14) Press the **Cancel** button to close the **Manual Control** window
15) Power **Off** the control module.

Chapter 2 – Patient Therapy

Place ArcticGel Pads
Read the Instructions for Use that accompany the ArcticGel Pads. Examine each pad for damage prior to placement.

Connect ArcticGel Pads
Orient the blue and white colors on the pad line connector and Fluid Delivery Line. While holding the pad line tubing, insert the clear pad line connector into the Fluid Delivery Line manifold. Do not press or squeeze the wings when connecting. The connector will click into place.

Temperature Probe Placement
Patient temperature control with the Arctic Sun requires patient temperature feedback provided by an indwelling patient temperature probe connected to the Patient Temperature 1 connector on the back of the Control Module. Any commercially-available Yellow Springs Instrument 400 Series (YSI 400) compatible patient temperature probe can be connected to the Arctic Sun. Refer to the manufacturer's Instructions for Use for the specific indications and temperature probe placement.

Patient Therapy Selection
Use the **Patient Therapy Selection** screen to initiate a **New Patient**, **Continue a Current Patient**, or access the **Advanced Setup** screen.

New Patient - Normothermia
Select **Normothermia** if the therapy goal is to maintain a patient temperature at a pre-defined target temperature for an indefinite period of time. Press the **Normothermia** button to display the **Normothermia** therapy screen.

New Patient - Hypothermia
Select **Hypothermia** to reduce and maintain a patient temperature at a set target temperature for a defined period of time, then slowly re-warm the patient at a controlled re-warming rate. Press the **Hypothermia** button to display the **Hypothermia** therapy screen.

Current Patient
The **Continue Current Patient** button and the date and time that the current therapy was paused will display on the **Patient Therapy Selection** screen if a patient therapy was paused within the past 6 hours.

Press the **Continue Current Patient** button to resume a paused patient therapy.

Therapy Screens

Normothermia Therapy Screen

Hypothermia Therapy Screen

The following information is displayed and functions are available from the **Normothermia** and **Hypothermia** therapy screens.

A Cool Patient window (Hypothermia screen)
Control Patient window (Normothermia screen)
B Rewarm Patient window (Hypothermia screen)
C Patient Monitoring area
D Patient Temperature
E Patient Temperature 2 (if enabled)
F Patient Temperature Trend Indicator
G System Monitoring area
H Water Temperature
I Water Flow Rate
J Reservoir Water Level
K Therapy Graph
L Manual Control button (if enabled)
M Empty Pads button
N Fill Reservoir button
O Therapy Selection / Screen Lock button
P Temperature Units button (if enabled)
Q Stop button
R Help button

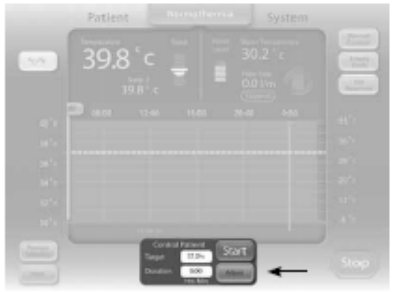
Initiate Normothermia (Control Patient)

Normothermia therapy is initiated and managed, and patient temperature is automatically controlled to a set target temperature from the **Control Patient** window in the **Normothermia** therapy screen. The **Control Patient** window displays the patient target temperature and the duration since the initiation of normothermia therapy.

To initiate Normothermia therapy:

1) From the **Patient Therapy Selection** screen, press the **Normothermia** button to display the **Normothermia** therapy screen.

2) The default patient target temperature will display in the **Control Patient** window.



3) To modify the patient target temperature, press the **Adjust** button to display the **Control Patient-Adjust** window.

4) **Control Patient** To: Use the Up and Down arrows to set the desired patient target temperature to control the patient.
5) Press the **Save** button to save the new settings and close the **Control Patient-Adjust** window
6) Press **Start**, in the **Control Patient** window to initiate therapy. You will hear a tone and then a voice stating "Therapy Started". Additionally, the **Control Patient** window and the Arctic Sun icon will blink, indicating that therapy is in progress.

Initiate Hypothermia (Cool Patient and Rewarm Patient)

Hypothermia therapy is initiated and managed, and patient temperature is automatically controlled to a set target temperature from the **Cool Patient** and **Rewarm Patient** windows in the **Hypothermia** therapy screen.

The **Cool Patient** window displays the cooling phase patient target temperature and the length of time remaining in the cooling phase of the **Hypothermia** therapy.

The **Rewarm Patient** window displays the rewarming phase patient target temperature and the length of time remaining in the rewarming phase of the **Hypothermia** therapy.

To initiate hypothermia therapy:

From the **Patient Therapy Selection** screen, press the **Hypothermia** button to display the **Hypothermia** therapy screen.

1. Cool Patient Settings

- The default patient target temperature and duration will display in the **Cool Patient** window.

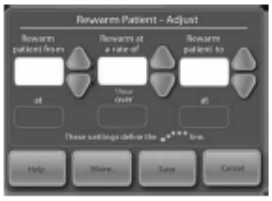
- To modify the patient target temperature and duration, press the **Adjust** button to display the **Cool Patient-Adjust** window.

- **Cool Patient To:** Use the Up and Down arrows on the left side to set the desired patient target temperature to cool the patient
- **Cool Patient For:** Use the Up and Down arrows on the right side to set the cooling duration to cool the patient before rewarming begins.
- Press the **Save** button to save the new settings and close the **Cool Patient-Adjust** window

2. Rewarm Patient Settings

- The default patient target temperature and duration will display in the **Rewarm Patient** window.

- To change the rewarming phase patient target temperature and rewarming rate, press the **Adjust** button in the **Rewarm Patient** window to display the **Rewarm Patient-Adjust** screen. Use the Up and Down arrows on the left side to set the desired final patient target temperature.



- **Rewarm Patient To:** Use the Up and Down arrows on the right side to set the desired final patient target temperature.
- **Rewarm at a Rate of:** Use the Up and Down arrows in the center of the screen to set the rewarming rate.
- **Rewarm Patient From:** When cooling a patient, adjustment of the **Rewarm Patient From** setting on the left side of the screen is disabled and defaults to the **Cool Patient** target temperature.
- When rewarming a patient, the **Rewarm Patient From** adjustment is enabled and the value can be modified. The **Rewarm Patient From** setting is the temperature to which the system is currently controlling the patient. The **Rewarm Patient From** temperature will automatically increase as the rewarming process continues. This feature allows the rewarming procedure to be optimized by allowing complete control of the rewarming ramp.

- Using the **Rewarm Patient From** temperature, the **Rewarm Patient To** temperature and the rewarming rate settings, the system will calculate and display the rewarming duration and the date/time at which the the patient will reach the final rewarming target temperature.
- Press the **Save** button to save the new settings and close the **Rewarm Patient-Adjust** window.

3. Initiate Patient Cooling

- Press **Start**, in the **Cool Patient** window to initiate therapy. You will hear a tone and then a voice stating "Therapy Started". Additionally, the **Cool Patient** window and the Arctic Sun icon will blink, indicating that therapy is in progress.

4. Initiate Patient Rewarming

- Upon completion of the cooling phase, there are two options for initiation of patient rewarming, either Automatically or Manually, depending on the **Rewarming Begins** setting in **Hypothermia Settings**.
- If **Rewarming Begins** is set to **Automatically**, the rewarming process starts automatically when the **Cool Patient** therapy is complete and the duration reaches zero.
- If **Rewarming Begins** is set to **Manually**, the rewarming process starts when the **Start** button is pressed in the **Rewarm Patient** window. The cooling process will continue until the **Rewarm Patient Start** button is pressed. An **Alert** will occur when the **Cool Patient** duration reaches zero.

End Therapy

- From the **Normothermia** therapy or **Hypothermia** therapy screen, press the **Stop** button to terminate water circulation to the pads.
- Press the **Empty Pads** button, and follow the instructions to purge the pads of water.
- Disconnect the pads from the Fluid Delivery Line.
- Slowly and carefully remove pads from the patient skin.
- Discard the used pads in accordance with hospital procedures for medical waste.
- Press the power switch **Off**.

If power is lost while the power switch is in the On position, an audible alert will be issued until it is switched Off. This alerts the user that the treatment may have been accidentally stopped.

Chapter 3 – Normothermia Settings

Normothermia Settings

Use the **Normothermia Settings** screen to view the current settings and modify the settings for the following parameters. To modify any parameter setting, press the **Adjust** button to the right of the parameter.

Normothermia Settings screen parameters:

Therapy Settings

- Timer Begins

Water Temperature Settings

- Pre-Condition Water
- Manual Control
- High Water Limit
- Low Water Limit

Patient Temperature Settings

- High Patient Alert
- Low Patient Alert
- Control Strategy

Display Settings

- Temperature Units
- Temperature Units Adjust
- Patient Temp 2
- Speaker Volume

To access the Normothermia Settings screen:

1) Press **Adjust** on the **Control Patient** window.
2) Press the **More** button on the **Control Patient Adjust** window.
3) The **Normothermia Settings** screen will be displayed.

4) To save the new settings as the current patient therapy settings, press the **Close** button. For instructions on saving the settings as the system defaults, see **Advanced Setup**.

Chapter 4 – Hypothermia Settings

Hypothermia Settings

Use the **Hypothermia Settings** screen to view the current settings and modify the settings for the following parameters. To modify any parameter setting, press the **Adjust** button to the right of the parameter.

Hypothermia Settings screen parameters:

Therapy Settings
- Cooling Begins
- Rewarming Begins

Water Temperature Settings
- Pre-Condition Water
- Manual Control
- High Water Limit
- Low Water Limit

Patient Temperature Settings
- High Patient Alert
- Low Patient Alert
- Control Strategy

Display Settings
- Temperature Units
- Temperature Units Adjust
- Patient Temp 2
- Speaker Volume

To access the Hypothermia Settings screen:
1) Press **Adjust** on the **Cool Patient** window or the **Rewarm Patient** window.
2) Press the **More** button on the **Cool Patient Adjust** window or **Rewarm Patient Adjust** window.
3) The **Hypothermia Settings** screen will be displayed.

4) To save the new settings as the current patient therapy settings, press the **Close** button. For instructions on saving the settings as the system defaults, see **Advanced Setup**.

Chapter 5 – Advanced Setup

Use the **Advanced Setup** screen to view the current settings and modify the settings for the following parameters. To modify any parameter setting, press the **Adjust** button to the right of the parameter.

Location / Time Settings
- Language
- Number Format
- Current Time
- Date Format
- Current Date

The following functions can be initiated from the Advanced Setup screen.
- Download Patient Data
- Calibration
- Total Drain
- Save All Settings As Default

Additionally, the following information can be viewed in the Advanced Setup screen.
- Software Versions
- Last Calibration date
- Next calibration due

To access the Advanced Setup screen:
1) Press **Advanced Setup** button on the **Patient Therapy Selection** screen.
2) The **Advanced Setup** screen will be displayed.

Chapter 6 – Alarms and Alerts

The Arctic Sun safety system continually monitors the state of the device and the patient, and issues alarms or alerts to notify the user of conditions that may interfere with patient safety or system performance.

There are two types of conditions: **Alarms** and **Alerts**.

An Alarm notifies the user that a condition that may potentially pose an unsafe situation with respect to the patient or the device. An Alarm is a High Priority condition that requires immediate operator response.

An Alert informs the user about patient and device status without interrupting the procedure. An Alert is a Medium Priority condition that requires prompt operator response.

Alarms

An Alarm is denoted by an audio signal that repeats every 10 seconds until the Alarm is cleared. The Alarm screen will appear that displays the alarm number, alarm title, a description of the problem or conditions that triggered the alarm, and solutions and instructions for troubleshooting and resolving the alarm condition. If certain Alarm conditions are not acknowledged by the operator within 2 minutes, a Reminder tone will sound. All Alarm settings are maintained in the event of a mains power interruption.

Main Safety Alarms

While there are multiple alarms and safety features in the Arctic Sun, there are five main safety alarms that will place the device into Stop mode until the condition is addressed.

Alarm	Specification
High Patient Temperature	39.5 °C (103.1 °F)
Low Patient Temperature	31.0 °C (87.8 °F)
High Water Temperature	42.5 °C / 44 °C (108.5 °F / 111.2 °F)
Low Water Temperature	3.0 °C / 3.5 °C (37.4 °F / 38.3 °F)
System Self-Test Failure	At device power ON

Each time the Arctic Sun is powered On, a system self test for the independent safety alarm is automatically run. This test stimulates a "water high temperature" fault situation on both the primary and secondary water temperature sensors. Both the primary and secondary safety systems must respond to the fault and be verified by the opposing safety system. If either safety systems do not respond appropriately either an alarm 80 or 81 will be issued. Contact Medivance Customer Support.

Non-Recoverable Alarms

If an Alarm condition occurs that prevents proper use of the device or proper patient treatment (such as the five main safety alarms discussed above), the system is placed into Stop mode and will not allow therapy to continue. This type of Alarm is known as Non-Recoverable. If this situation occurs, cycle the device power (turn device Off then On). If the alarm recurs contact Medivance Customer Support.

Recoverable Alarms

Other Alarms that temporarily Stop the device until the user is able to correct the cause and clear the Alarm are classified as Recoverable. If the condition that initiated the alarm is not addressed and problem persists, the Alarm will recur.

If a Recoverable Alarm occurs:

1) When an alarm is issued the device is placed into **Stop** mode.
2) Read the displayed instructions.
3) Note the **Alarm** number.
4) Press the **Close** button to clear the alarm.
5) Follow the instructions to correct the alarm condition. Perform the actions in the order listed until the alarm condition is resolved.
6) Once you have cleared the alarm, press the Start button in the therapy window to restart therapy. You will hear a tone and a voice stating "Therapy Started". Additionally, the active therapy window and the Arctic Sun icon will blink.
7) If the condition does not resolve, contact Medivance Customer Support.

Alerts

Alerts are denoted by an audio signal that repeats every 25 seconds. The Alert screen will appear that displays the alert number, alert title, a description of the problem that triggered the alert, and solutions and instructions for troubleshooting and resolving the alert condition.

If an Alert occurs:

1) Read the displayed instructions.
2) Note the Alert number.
3) Press the **Close** button to clear the alert.
4) Follow the instructions to correct the alert condition. Perform the actions in the order listed until the alarm condition is resolved. If the condition does not resolve, contact Medivance Customer Support.

Chapter 7 – Maintenance and Service

Cleaning and Maintenance

Cleaning and Maintenance Routine cleaning and preventive maintenance should be performed on the Arctic Sun control module every 6 months at a minimum. This consists of cleaning the external surfaces, accessories and chiller condenser, inspecting the device, and replenishing the internal cleaning solution that suppresses microorganism growth in the water reservoir and hydraulic circuit.

External Surfaces

- Clean the exterior body of the control module, fluid delivery lines, power cords and temperature cables using a soft cloth and mild detergent or disinfectant according to hospital protocol.

Condenser

- A dirty chiller condenser will significantly reduce the cooling capacity of the control module.
- To clean the condenser, wipe the dust from the exterior grill using a soft cloth. Depending on the quality of your institution's air, periodically remove the back cover and vacuum or brush the condenser fins. At a minimum the condenser fins should be cleaned annually. Maintenance activities should be performed by qualified personnel.

Device Inspection

- Periodically inspect the external areas of the device for damaged, loose or missing parts, and frayed or twisted power cords and cables.
- Discontinue using the device displaying one or more of the above conditions until the problem is corrected and has been verified to be operating correctly.

Replenish Internal Cleaning Solution

Contact Medivance Customer Service to order internal cleaning solution.

To replenish the internal cleaning solution:

1) Drain the reservoir.
   - Turn control module power Off.
   - Attach the drain line to the two drain ports on the back of the control module. Place the end of the drain line into a container. The water will passively drain into the container.
2) Refill the reservoir.
   - From the Hypothermia therapy screen or the Normothermia therapy screen, press the Fill Reservoir button.
   - The Fill Reservoir screen will appear. Follow the directions on the screen.
   - Add one vial of Arctic Sun cleaning solution to the first bottle of distilled or sterile water.
   - The filling process will automatically stop when the reservoir is full. Continue to replace the bottles of sterile or distilled water until the filling process stops.
   - When the Fill Reservoir process is complete, the screen will close.

Software Update

Software updates will be provided from Medivance on a flash drive. Installation of software updates will be performed via the USB port on the front of the control module.

The software update feature will automatically initiate if the control module detects the proper files on a flash drive inserted in the USB port at power On.

To install software update:

1) Insert flash drive provided by Medivance into the USB port.
2) An image of a timer will display while the software update in being installed, and will disappear when the software installation process is completed.
3) After installation, the new software version will display in the **Software Version** field in **Advanced Setup**.

Service

Contact Medivance Customer Support for technical support and customer service instructions to enable appropriately qualified technical personnel to repair those parts of the equipment that Medivance considers repairable.

Calibration

See Arctic Sun 5000 Service Manual for calibration requirements and instructions.

Appendix A: Product Specifications

Technical Description

The Arctic Sun Temperature Management System is a thermoregulatory device that monitors and controls patient temperature within a range of 32°C to 38.5°C (89.6°F to 101.3°F). The Arctic Sun System consists of the Control Module and disposable ArcticGel Pads.

A patient temperature probe connected to the Control Module provides patient temperature feedback to an internal control algorithm which automatically increases or decreases the circulating water temperature to achieve a pre-set patient target temperature determined by the clinician.

The Arctic Sun pulls temperature-controlled water ranging between 4°C and 42°C (39.2°F and 107.6°F) through the ArcticGel Pads at approximately 0.7 liter per minute per pad. This results in heat exchange between the water and the patient.

The Arctic Sun Control Module is a CLASS I mobile device (Type BF, IPX0 and Mode of Operation – Continuous) per classification scheme of IEC 601-1.

The Arctic Sun Control Module meets both the electromagnetic interference and susceptibility requirements of IEC 60601-1, and is compatible with other equipment that also conforms to that standard. There is no known failure mode in the Arctic Sun Control Module associated with electromagnetic interference from other devices. See the Arctic Sun 5000 Service Manual for the full declaration regarding electromagnetic compatibility.

Environmental Conditions

Temperature Range
Operating: .....10°C to 27°C (50°F to 80°F)
Storage: .....-30°C to 50°C (-20°F to 120°F)

At operating temperatures higher than 27°C (80°F), the refrigeration system's cooling capacity and therefore its ability to cool a patient is compromised.

Humidity Range (relative humidity, non-condensing)
Operating:.....5% to 70%
Storage:.....5% to 95%
Atmospheric Pressure Range:.....60 kPa to 110 kPa

Arctic Sun 5000 Specifications

Parameter	Specification
Therapy Modes	Normothermia: Control Patient Hypothermia: Cool Patient, Rewarm Patient
Heater Capacity	2500 BTU/hr / 750 Watts
Circulating Fluid	Distilled or Sterile Water
Reservoir Capacity	3.5 liters
Water Flow Rate	5 liters per minute
Patient Probe Type	YSI 400 Series compatible
Patient Temperature Inputs	Patient Temp 1: control, monitor, alarm Patient Temp 2: monitor, alarm
Patient Temperature Display Range	10°C to 44°C 50°F to 111.2°F 0.1°C / °F increments
Patient Temperature Measurement Accuracy	±0.4°C (10°C to 32°C) ±0.2°C (32°C to 38°C) ±0.4°C (38°C to 44°C) Includes ±°0.1C external probe
Patient Temperature Control Range	32°C to 38.5°C 89.6°F to 101.3°F 0.1 °C/°F increments
Water Temperature Display Range	3°C to 45°C / 37.4°F to 113.0°F
	1 °C/°F increments
Water Temperature Control Range (Manual)	4°C to 42°C / 39.2°F to 107.6°F 0.1 °C/°F increments
High Water Temperature Limit	36°C to 42°C / 96.8°F to 107.6°F 1 °C/°F increments
Low Water Temperature Limit	4°C to 25°C / 39.2°F to 77°F 1 °C/°F increments
Time to heat water from 20°C to 37°C	8 minutes (approximate)
Sound Pressure	Alarm Tone: 70dB to 80dB at 1 meter, repeats every 10 seconds Alert Tone: 63dB to 71dB at 1 meter, repeats every 25 seconds Reminder Tone: 65dB at 3 meters, 0.5 seconds on/20 seconds off
Mains Input	115 VAC, 60 Hz, 11.0 Amp (nominal) 230 VAC, 50 Hz, 5.5 Amp
Leakage Current	<300 µA
Operating Relative Humidity Range	5% to 70% non-condensing
Storage Relative Humidity Range	5% to 95% non-condensing
Operating Temperature Range	10°C to 27°C / 50°F to 80°F
Storage Temperature Range	-30°C to 50°C / -20°F to 120°F
Atmospheric Pressure Range	60 kPa to 110 kPa
Dimensions	Height: 35 inches (89 cm) Width: 14 inches (36 cm) Depth: 18.5 inches (47 cm)
Weight	Empty: 43 kg / 95 lbs ; Filled: 47 kg / 103 lbs

Appendix B: Symbols

The Arctic Sun Control module bears the following symbols:


For the safe and effective use of this device, the operator must consult the accompanying documents prior to use

Identifies European Representative


This symbol adjacent to the patient connections means that the thermal probe connection is a "Defibrillator-Proof, Type BF Applied Part", per standard IEC 60601-1 and affords the degree of patient protection defined in that standard for this type of applied part


Models of the Arctic Sun that bear the ETL Monogram have been Certified for Safety by ETL Intertek in accordance with CAN/CSA C22.2 STD 601.1-M90 and UL STD 6060.1.


Indicates high temperature part or component


Indicates that only sterile or distilled water should be used when filling the Arctic Sun Control Module


Identifies Patient Temperature 1, the patient temperature probe input for monitoring and control


Identifies Patient Temperature 2, the patient temperature probe input for monitoring


Identifies the drain port

Identifies the storage temperature range

Identifies the storage relative humidity range


Indicates electrical hazard


Do not re-use.


Risk of overbalance due to pushing, leaning, resting, etc.

Appendix C: Electromagnetic Compatibility

Medical electrical equipment needs special precautions regarding electromagnetic compatibility. Ensure that the Arctic Sun 5000 is installed and used according to the electromagnetic compatibility information provided. The following are guidance and manufacturer's declarations regarding electromagnetic compatibility for the Arctic Sun Model 5000.

- The use of accessories or cables other than those specified or sold by Medivance is not recommended. Use of unapproved accessories or cables may result in increased emissions or in decreased immunity of the Arctic Sun 5000.
- If the Arctic Sun 5000 is used directly adjacent to or stacked with other equipment, the user should periodically observe the Arctic Sun device to verify it operates normally in that environment.
- Portable and mobile RF communications equipment can affect Medical Electrical Equipment.

1.1 EN/IEC 60601-1-2 Table 1		
Guidance and Manufacturer's Declaration – Electromagnetic Emissions		
The Arctic Sun Model 5000 is intended for use in the electromagnetic environment specified below. The customer or the end user of the Arctic Sun Model 5000 should assure that it is used in such an environment.		
Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions CISPR 11	Group 1	The Arctic Sun Model 5000 uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF emissions CISPR 11	Class A	The Arctic Sun Model 5000 unit is suitable for use in all establishments other than domestic, establishments and those directly connected to the public low-voltage power supply network that supplies buildings for domestic purposes.
Harmonic emissions IEC 61000-3-2	Class A	
Voltage fluctuations/ Flicker emissions IEC 61000-3-3	Complies	

1.2 EN/IEC 60601-1-2 Table 2			
Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The Arctic Sun Model 5000 unit is intended for use in the electromagnetic environment specified below. The customer or the end user of the Arctic Sun Model 5000 unit should assure it is used only in such an environment.			
Immunity Test	IEC60601 test level	Compliance Level	Intended Electromagnetic Environment
Electromagnetic discharge (ESD) IEC 61000-4-2	+- 6kV contact +- 8kV air	+- 6kV contact +- 8kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/burst IEC 61000-4-4	+-2kV for power supply lines +-1kV for input/ output lines	+-2kV for power supply lines +-1kV for input/ output lines	Mains power quality should be that of a typical commercial or hospital environment.
Surge IEC 61000-4-5	+-1kV differential mode (line-line) +-2kV common mode (line-earth)	+-1kV differential mode (line-line) +-2kV common mode (line-earth)	Mains power quality should be that of a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5% UT (>95% dip in UT) for 0.5 cycle 40% UT (60% dip in UT) for 5 cycles 70% UT (30% dip in UT) for 25 cycles <5% UT (>95% dip in UT) for 5 seconds	<5% UT (>95% dip in UT) for 0.5 cycle 40% UT (60% dip in UT) for 5 cycles 70% UT (30% dip in UT) for 25 cycles <5% UT (>95% dip in UT) for 5 seconds	Mains power quality should be that of a typical commercial or hospital environment. If the user of the Arctic Sun Model 5000 unit requires continued operation during power mains interruptions, it is recommended that the Arctic Sun Model 5000 unit be powered from an uninterruptible power supply with sufficient capacity to run the unit for the maximum required time of interruption.
Power frequency (50/60Hz) magnetic field IEC 61000-4-8	3A/m	3 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
Note: UT is the a.c. mains voltage prior to application of the test level.			

1.3 EN/IEC 60601-1-2:2007 Sub-clause 5.2.2.2 Table 4:			
Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The Arctic Sun Model 5000 unit is intended for use in the electromagnetic environment specified below. The customer or the end user of the Arctic Sun Model 5000 unit should assure it is used in such an environment.			
Immunity Test	IEC60601 test level	Compliance Level	Intended Electromagnetic Environment
Conducted RF IEC 61000-4-6 Radiated RF IEC 61000-4-3	3Vrms 150kHz to 80MHz 3V/m 80MHz to 2.5GHz	3Vrms 150kHz to 80MHz 3V/m 80MHz to 2.5GHz	Portable and mobile RF communications equipment should be used no closer to any part of the Arctic Sun Model 5000 unit, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. Recommended separation distance $d = 1.2\sqrt{P}$ $d = 1.2\sqrt{P}$ 80MHz to 800 MHz $d = 2.3\sqrt{P}$ 800MHz to 2.5GHz where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended minimum separation distance in meters (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey[a], should be less than the compliance level in each frequency range.[b] Interference may occur in the vicinity of equipment marked with the following symbol: ((•))
NOTE 1 At 80MHz and 800MHz, the higher frequency range applies NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from objects, structures and people.			
[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the Arctic Sun Model 5000 unit is used exceeds the applicable RF compliance level above, the Arctic Sun Model 5000 unit should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the Arctic Sun Model 5000 unit. [b] Over the frequency range 150kHz to 80MHz, field strengths should be less than 3V/m.			

1.4 EN/IEC 60601-1-2:2007 Sub-clause 5.2.2.2 Table 6:			
Recommended separation distances between portable and mobile RF communications equipment and the Arctic Sun Model 5000 unit			
RF communications equipment can effect medical electrical equipment. The Arctic Sun Model 5000 unit is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the Arctic Sun Model 5000 unit can help prevent electromagnetic interference by maintaining a minimum distance between the portable and mobile RF communications equipment (transmitters) and the Arctic Sun Model 5000 unit as recommended below, according to the maximum output power of the communications equipment.			
Rated maximum output power of transmitter in watts (W)	Separation distance according to frequency of transmitter in meters (m)		
	150kHz to 80MHz $d = 1.2\sqrt{P}$	80MHz to 800MHz $d = 1.2\sqrt{P}$	800MHz to 2.5GHz $d = 2.3\sqrt{P}$
0.01	0.12	0.12	0.23
0.1	.38	.38	.73
1.0	1.2	1.2	2.3
10	3.8	3.8	7.3
100	12	12	23
For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer. NOTE 1 At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies. NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.			

ARCTIC SUN®
TEMPERATURE MANAGEMENT SYSTEM

ARCTICGEL™ Pads

INSTRUCTIONS FOR USE

Medivance

ENGLISH

ArcticGel™ Pads - Instructions for Use

Indications for Use
- The Arctic Sun® Temperature Management System is a thermal regulating system, indicated for monitoring and controlling patient temperature in adult and pediatric patients of all ages.

Contraindications
- There are no known contraindications for the use of a thermoregulatory system.
- Do not place ArcticGel™ Pads on skin that has signs of ulcerations, burns, hives or rash.
- While there are no known allergies to hydrogel materials, caution should be exercised with any patient with a history of skin allergies or sensitivities.

Warning
- Do not place ArcticGel™ Pads over transdermal medication patches as warming can increase drug delivery, resulting in possible harm to the patient.

Cautions
- Federal law restricts this device to sale by or on the order of a physician.
- This product is to be used by or under the supervision of trained, qualified medical personnel.
- The clinician is responsible for determining the appropriateness of use of this device and the user-settable parameters, including water temperature, for each patient. For small patients (≤30 kg) it is recommended to use the following settings: Water Temperature High Limit ≤40°C (104°F); Water Temperature Low Limit ≥10°C (64.4°F); Control Strategy =2. It is recommended to use the Patient Temperature High and Patient Temperature Low alert settings.
- Due to underlying medical or physiological conditions, some patients are more susceptible to skin damage from pressure and heat or cold. Patients at risk include those with poor tissue perfusion or poor skin integrity due to diabetes, peripheral vascular disease, poor nutritional status or steroid or high dose vasopressor therapy. If accessible, examine the patient's skin under the ArcticGel™ Pads often; especially those patients at higher risk of skin injury.
- Skin injury may occur as a cumulative result of pressure, time and temperature. Do not place bean bags or other firm positioning devices under the ArcticGel™ Pads. Do not place any positioning devices under the Pad manifolds or patient lines.
- Do not allow urine, antibacterial solutions or other agents to pool underneath the ArcticGel™ Pads. Urine and antibacterial agents can absorb into the pad hydrogel and cause chemical injury and loss of pad adhesion. Replace pads immediately if these fluids come into contact with the hydrogel.
- Do not place ArcticGel™ Pads directly over an electrosurgical grounding pad. The combination of heat sources may result in skin burns.
- Carefully remove ArcticGel™ Pads from the patient's skin at the completion of use. Aggressive removal or removal of cold pads from the patient's skin may result in skin tears.
- The ArcticGel™ Pads are non-sterile for single patient use only. Do not place pads in the sterile field. If used in a sterile environment, pads should be placed according to the physician's directions, either prior to the sterile preparation or sterile draping.
- Do not reprocess or sterilize.
- Use Pads immediately after opening. Do not store pads in opened pouch.
- Do not allow circulating water to contaminate the field when lines are disconnected.
- The ArcticGel™ Pads should not be punctured with sharp objects. Punctures will result in air entering the fluid pathway and may reduce performance.
- If warranted, use pressure relieving or pressure reducing devices under the patient to protect from skin injury.
- The ArcticGel™ Pads are only for use with an Arctic Sun® Temperature Management System.
- The water content of the hydrogel affects the pad's adhesion to the skin and conductivity, and therefore, the efficiency of controlling patient temperature. Periodically check that pads remain moist and adherent. Replace pads when the hydrogel no longer uniformly adheres to the skin. Replacing pads at least every 5 days is recommended.
- If needed, place defibrillation pads between the ArcticGel™ Pads and the patient's skin.
- Discard used ArcticGel™ Pads in accordance with hospital procedures for medical waste.

Directions for use
1. ArcticGel™ Pads are only for use with an Arctic Sun® Temperature Management System Control Module. See Operators Manual for detailed instructions on system use.
2. Select the proper number, size and style pad for the patient size and clinical indication. However, the rate of temperature change and potentially the final achievable temperature is affected by pad surface area, patient size, pad placement and water temperature range. Best system performance will be achieved by using the maximum number and largest size pads.
3. For patient comfort, the pads may be prewarmed using Water Temperature Control Mode (manual) prior to application.
4. Place the pads on healthy, clean skin only. Remove any creams or lotions from patient's skin before pad application. Remove the release liner from each pad and apply to the appropriate area. The pads may be overlapped or folded adhesive-to-adhesive to achieve proper placement. The pads may be removed and reapplied if necessary. The pad surface must be contacting the skin for optimal energy transfer efficiency. Place pads to allow for full respiratory excursion.
5. Attach the pad's line connectors to the patient line manifolds. Begin circulating water through the pads using either Patient Temperature Control Mode (automatic) or Water Temperature Control Mode (manual). If the pads fail to prime or a significant continuous air leak is observed in the pad return line, check connections, then if needed replace the leaking pad.
6. Once the pads are primed, assure the flow rate displayed on the control panel is greater than 2.3 liters per minute, which is the minimum flow rate for a full pad kit.
7. When finished, empty water from pads. Cold temperature increases the adhesiveness of the hydrogel. For ease of removal, leave pads on the patient for approximately 15 minutes to allow the hydrogel to warm. Slowly remove pads from the patient and discard.

19.11. Guidelines for Treatment of Patients with Ischemic Stroke

Adapted from: Guidelines for Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association (2013)

Classification/Level of Evidence Scheme

- Class I: *Benefit*>>>*Risk*; Procedure/treatment SHOULD be performed/administered
- Class IIa: *Benefit* >> *Risk*; IT IS REASONABLE to perform procedure/administer treatment
- Class IIb: *Benefit*≥*Risk*; Procedure/treatment MAY BE CONSIDERED
- Class III: *No Benefit* OR *Harm*; Procedure/treatment is NOT RECOMMENDED/SHOULD NOT BE PERFORMED

- Evidence Level A: Data derived from multiple randomized clinical trials or meta-analyses
- Evidence Level B: Data derived from a single randomized trial or non-randomized studies
- Evidence Level C: Only consensus opinion of experts, case studies, or standard of care

RECOMMENDATIONS

Emergency Evaluation and Diagnosis of Acute Ischemic Stroke (AIS)

1. An organized protocol for the emergency evaluation of patients with suspected stroke is recommended (Class I; Level of Evidence B). The goal is to complete an evaluation and to begin fibrinolytic treatment within 60 minutes of the patient's arrival in an ED. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is encouraged. Patients with stroke should have a careful clinical assessment, including neurological examination.
2. The use of a stroke rating scale, preferably the NIHSS, is recommended (Class I; Level of Evidence B).
3. A limited number of hematologic, coagulation, and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of intravenous rtPA (Class I; Level of Evidence B).
4. Baseline electrocardiogram assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA (Class I; Level of Evidence B).
5. Baseline troponin assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA (Class I; Level of Evidence C).
6. The usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac, or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of fibrinolysis (Class IIb; Level of Evidence B).

Early Diagnosis: Brain and Vascular Imaging

Recommendations for Patients With Acute Cerebral Ischemic Symptoms That Have Not Yet Resolved

1. Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke (Class I; Level of Evidence A). In most instances, NECT will provide the necessary information to make decisions about emergency management.
2. Either NECT or MRI is recommended before intra- venous rtPA administration to exclude ICH (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present (Class I; Level of Evidence A).
3. Intravenous fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodensity) on CT, regardless of their extent (Class I; Level of Evidence A).
4. A noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either intra-arterial fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay intravenous rtPA if indicated (Class I; Level of Evidence A).
5. In intravenous fibrinolysis candidates, the brain imaging study should be interpreted within 45 minutes of patient arrival in the ED by a physician with expertise in reading CT and MRI studies of the brain parenchyma (Class I; Level of Evidence C).
6. CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for intravenous fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making (Class IIb; Level of Evidence B).
7. Frank hypodensity on NECT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one third of the MCA territory, intravenous rtPA treatment should be withheld (Class III; Level of Evidence A).

Recommendations for Patients With Cerebral Ischemic Symptoms That Have Resolved

1. Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIAs (Class I; Level of Evidence A).
2. Noninvasive imaging by means of CTA or MRA of the intracranial vasculature is recommended to exclude the presence of proximal intracranial stenosis and/or occlusion (Class I; Level of Evidence A) and should be obtained when knowledge of intracranial stenoocclusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with non- invasive testing.
3. Patients with transient ischemic neurological symptoms should undergo neuroimaging evaluation within 24 hours of symptom onset or as soon as possible in patients with delayed presentations. MRI, including DWI, is the

preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed (Class I; Level of Evidence B).

General Supportive Care and Treatment of Acute Complications

1. Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours (Class I; Level of Evidence B).
2. Patients who have elevated blood pressure and are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered (Table 1) so that their systolic blood pressure is <185 mm Hg and their diastolic blood pressure is <110 mm Hg (Class I; Level of Evidence B) before fibrinolytic therapy is initiated. If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with intravenous rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after intravenous rtPA treatment.
3. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway (Class I; Level of Evidence C).
4. Supplemental oxygen should be provided to maintain oxygen saturation >94% (Class I; Level of Evidence C).
5. Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Class I; Level of Evidence C).
6. Until other data become available, consensus exists that the previously described blood pressure recommendations should be followed in patients undergoing other acute interventions to recanalize occluded vessels, including intra-arterial fibrinolysis (Class I; Level of Evidence C).
7. In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg (Class I; Level of Evidence C).
8. Hypovolemia should be corrected with intravenous normal saline, and cardiac arrhythmias that might be reducing cardiac output should be corrected (Class I; Level of Evidence C).
9. Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with acute ischemic stroke (Class I; Level of Evidence C). The goal is to achieve normoglycemia.
10. Evidence from one clinical trial indicates that initiation of antihypertensive therapy within 24 hours of stroke is relatively safe. Restarting antihypertensive medications is reasonable after the first 24 hours for patients who have preexisting hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known (Class IIa; Level of Evidence B).
11. No data are available to guide selection of medications for the lowering of blood pressure in the setting of acute ischemic stroke. The antihypertensive medications and doses included in Table 1 are reasonable choices based on general consensus (Class IIa; Level of Evidence C).

12. Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in patients with acute ischemic stroke (Class IIa; Level of Evidence C).
13. The management of arterial hypertension in patients not undergoing reperfusion strategies remains challenging. Data to guide recommendations for treatment are inconclusive or conflicting. Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke. Until more definitive data are available, the benefit of treating arterial hypertension in the setting of acute ischemic stroke is not well established (Class IIb; Level of Evidence C). Patients who have malignant hypertension or other medical indications for aggressive treatment of blood pressure should be treated accordingly.
14. Supplemental oxygen is not recommended in nonhypoxic patients with acute ischemic stroke (Class III; Level of Evidence B).

Intravenous Fibrinolysis

1. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke (Class I; Level of Evidence A). Physicians should review the criteria outlined in Tables 2 and 3 (which are modeled on those used in the NINDS Trial) to determine the eligibility of the patient. A recommended regimen for observation and treatment of patients who receive intravenous rtPA is described in Table 4.
2. In patients eligible for intravenous rtPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival (Class I; Level of Evidence A)
3. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset (Class I; Level of Evidence B). The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients >80 years old, those taking oral anticoagulants regardless of INR, those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the MCA territory, or those with a history of both stroke and diabetes mellitus.
4. Intravenous rtPA is reasonable in patients whose blood pressure can be lowered safely (to below 185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous rtPA (Class I; Level of Evidence B).
5. In patients undergoing fibrinolytic therapy, physicians should be aware of and prepared to emergently treat potential side effects, including bleeding complications and angioedema that may cause partial airway obstruction (Class I; Level of Evidence B).
6. Intravenous rtPA is reasonable in patients with a seizure at the time of onset of stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon (Class IIa; Level of Evidence C).
7. The effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established (Class IIb; Level of Evidence B).

8. The usefulness of intravenous administration of tenecteplase, reteplase, desmoteplase, urokinase, or other fibrinolytic agents and the intravenous administration of ancrod or other defibrinogenating agents is not well established, and they should only be used in the setting of a clinical trial (Class IIb; Level of Evidence B).
9. The effectiveness of intravenous treatment with rtPA is not well established (Class IIb; Level of Evidence C) and requires further study for patients who can be treated in the time period of 3 to 4.5 hours after stroke but have 1 or more of the following exclusion criteria: (1) patients >80 years old, (2) those taking oral anticoagulants, even with INR ≤1.7, (3) those with a baseline NIHSS score >25, or (4) those with a history of both stroke and diabetes mellitus.
10. Use of intravenous fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered, and potential increased risk should be weighed against the anticipated benefits (Class IIb; Level of Evidence C). These circumstances require further study.
11. The intravenous administration of streptokinase for treatment of stroke is not recommended (Class III; Level of Evidence A).
12. The use of intravenous rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, plate- let count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rtPA (Class III; Level of Evidence C). Further study is required.

<u>Endovascular Interventions</u>

1. Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered (Class I; Level of Evidence A).
2. Intra-arterial fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA who are not otherwise candidates for intravenous rtPA (Class I; Level of Evidence B). The optimal dose of intra-arterial rtPA is not well established, and rtPA does not have FDA approval for intra-arterial use.
3. As with intravenous fibrinolytic therapy, reduced time from symptom onset to reperfusion with intra-arterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy (Class I; Level of Evidence B).
4. Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked (Class I; Level of Evidence C).
5. When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci (Class I; Level of Evidence A). The relative effectiveness of the Penumbra System versus stent retrievers is not yet characterized.
6. The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological

fibrinolysis in carefully selected patients (Class IIa; Level of Evidence B). Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in randomized controlled trials to determine the efficacy of such treatments in improving patient out-comes.

7. Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis (Class IIa; Level of Evidence C).
8. Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis. Additional randomized trial data are needed (Class IIb; Level of Evidence B).
9. The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established (Class IIb; Level of Evidence C). These devices should be used in the setting of clinical trials.
10. The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials (Class IIb; Level of Evidence C).
11. The usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients is not well established (Class IIb; Level of Evidence C). Use of these techniques may be considered in certain circumstances, such as in the treatment of acute ischemic stroke resulting from cervical atherosclerosis or dissection (Class IIb; Level of Evidence C). Additional randomized trial data are needed.

Anticoagulants

1. At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with acute ischemic stroke is not well established (Class IIb; Level of Evidence B). These agents should be used in the setting of clinical trials.
2. The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established (Class IIb; Level of Evidence B).
3. Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke, is not recommended for treatment of patients with acute ischemic stroke (Class III; Level of Evidence A).
4. Urgent anticoagulation for the management of non- cerebrovascular conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications (Class III; Level of Evidence A).
5. Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recommended (Class III; Level of Evidence B).

Antiplatelet Agents

1. Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients (Class I; Level of Evidence A).
2. The usefulness of clopidogrel for the treatment of acute ischemic stroke is not well established (Class IIb; Level of Evidence C). Further research testing the usefulness of the emergency administration of clopidogrel in the treatment of patients with acute stroke is required.

3. The efficacy of intravenous tirofiban and eptifibatide is not well established, and these agents should be used only in the setting of clinical trials (Class IIb; Level of Evidence C).
4. Aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including intravenous rtPA (Class III; Level of Evidence B).
5. The administration of other intravenous antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended (Class III; Level of Evidence B). Further research testing the usefulness of emergency administration of these medications as a treatment option in patients with acute ischemic stroke is required.
6. The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of intravenous fibrinolysis is not recommended (Class III; Level of Evidence C).

Volume Expansion, Vasodilators, and Induced Hypertension

1. In exceptional cases with systemic hypotension producing neurological sequelae, a physician may pre- scribe vasopressors to improve cerebral blood flow. If drug-induced hypertension is used, close neurological and cardiac monitoring is recommended (Class I; Level of Evidence C).
2. The administration of high-dose albumin is not well established as a treatment for most patients with acute ischemic stroke until further definitive evidence regarding efficacy becomes available (Class IIb; Level of Evidence B).
3. At present, use of devices to augment cerebral blood flow for the treatment of patients with acute ischemic stroke is not well established (Class IIb; Level of Evidence B). These devices should be used in the setting of clinical trials.
4. The usefulness of drug-induced hypertension in patients with acute ischemic stroke is not well established (Class IIb; Level of Evidence B). Induced hypertension should be performed in the setting of clinical trials.
5. Hemodilution by volume expansion is not recommended for treatment of patients with acute ischemic stroke (Class III; Level of Evidence A).
6. The administration of vasodilatory agents, such as pentoxifylline, is not recommended for treatment of patients with acute ischemic stroke (Class III; Level of Evidence A).

Neuroprotective Agents

1. Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable (Class IIa; Level of Evidence B).
2. The utility of induced hypothermia for the treatment of patients with ischemic stroke is not well established, and further trials are recommended (Class IIb; Level of Evidence B).
3. At present, transcranial near-infrared laser therapy is not well established for the treatment of acute ischemic stroke (Class IIb; Level of Evidence B), and further trials are recommended.
4. At present, no pharmacological agents with putative neuroprotective actions have demonstrated efficacy in improving outcomes after ischemic stroke, and therefore, other neuroprotective agents are not recommended (Class III; Level of Evidence A).
5. Data on the utility of hyperbaric oxygen are inconclusive, and some data imply that the intervention may be harmful. Thus, with the exception of stroke secondary to air embolization, this intervention is not recommended for treatment of patients with acute ischemic stroke (Class III; Level of Evidence B).

Surgical Interventions

1. The usefulness of emergent or urgent CEA when clinical indicators or brain imaging suggests a small infarct core with large territory at risk (e.g., penumbra), compromised by inadequate flow from a critical carotid stenosis or occlusion, or in the case of acute neurological deficit after CEA, in which acute thrombosis of the surgical site is suspected, is not well established (Class IIb; Level of Evidence B).
2. In patients with unstable neurological status (either stroke-in-evolution or crescendo TIA), the efficacy of emergent or urgent CEA is not well established (Class IIb; Level of Evidence B).

General Acute Care After Hospitalization

1. The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation is recommended (Class I; Level of Evidence A).
2. Patients with suspected pneumonia or UTIs should be treated with appropriate antibiotics (Class I; Level of Evidence A).
3. Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent DVT (Class I; Level of Evidence A).
4. The use of standardized stroke care order sets is recommended to improve general management (Class I; Level of Evidence B).
5. Assessment of swallowing before the patient begins eating, drinking, or receiving oral medications is recommended (Class I; Level of Evidence B).
6. Patients who cannot take solid food and liquids orally should receive NG, nasoduodenal, or PEG tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing (Class I; Level of Evidence B).
7. Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended (Class I; Level of Evidence C).
8. Treatment of concomitant medical diseases is recommended (Class I; Level of Evidence C).
9. Early institution of interventions to prevent recurrent stroke is recommended (Class I; Level of Evidence C).
10. The use of aspirin is reasonable for treatment of patients who cannot receive anticoagulants for DVT prophylaxis (Class IIa; Level of Evidence A).
11. In selecting between NG and PEG tube routes of feeding in patients who cannot take solid food or liquids orally, it is reasonable to prefer NG tube feeding until 2 to 3 weeks after stroke onset (Class IIa; Level of Evidence B).
12. The use of intermittent external compression devices is reasonable for treatment of patients who cannot receive anticoagulants (Class IIa; Level of Evidence B).
13. Routine use of nutritional supplements has not been shown to be beneficial (Class III; Level of Evidence B).
14. Routine use of prophylactic antibiotics has not been shown to be beneficial (Class III; Level of Evidence B).
15. Routine placement of indwelling bladder catheters is not recommended because of the associated risk of catheter-associated UTIs (Class III; Level of Evidence C).

Treatment of Acute Neurological Complications

1. Patients with major infarctions are at high risk for complicating brain edema and increased ICP. Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended (Class I; Level of Evidence A). Early transfer of patients at risk for

malignant brain edema to an institution with neurosurgical expertise should be considered.

2. Decompressive surgical evacuation of a space-occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression (Class I; Level of Evidence B).
3. Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially lifesaving (Class I; Level of Evidence B). Advanced patient age and patient/family valuations of achievable outcome states may affect decisions regarding surgery.
4. Recurrent seizures after stroke should be treated in a manner similar to other acute neurological conditions, and antiepileptic agents should be selected by specific patient characteristics (Class I; Level of Evidence B).
5. Placement of a ventricular drain is useful in patients with acute hydrocephalus secondary to ischemic stroke (Class I; Level of Evidence C).
6. Although aggressive medical measures have been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, the usefulness of these measures is not well established (Class IIb; Level of Evidence C).
7. Because of lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) are not recommended for treatment of cerebral edema and increased ICP complicating ischemic stroke (Class III; Level of Evidence A).
8. Prophylactic use of anticonvulsants is not recommended (Class III; Level of Evidence C).

Table 1.
Potential Approaches to Arterial Hypertension in Acute Ischemic Stroke Patients Who Are Candidates for Acute Reperfusion Therapy

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:

- Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time; or
- Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
- Other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate

If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA

Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below180/105 mm Hg:

- Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
- If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg: Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or
- Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h
- If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

BP indicates blood pressure; IV, intravenously; and rtPA, recombinant tissue- type plasminogen activator.

Table 2.
Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset

Inclusion criteria:

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <3 hours before beginning treatment
- Aged ≥18 years

Exclusion criteria:

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to Platelet count <100 000/mm³
- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
- Current use of anticoagulant with INR >1.7 or PT >15 seconds
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration <50 mg/dL (2.7 mmol/L)
- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Relative exclusion criteria:

- Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
    - Only minor or rapidly improving stroke symptoms (clearing spontaneously)
    - Pregnancy
    - Seizure at onset with postictal residual neurological impairments
    - Major surgery or serious trauma within previous 14 days
    - Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
    - Recent acute myocardial infarction (within previous 3 months)

The checklist includes some FDA-approved indications and contraindications for administration of IV rtPA for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.
Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.
In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.
In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm³.
aPTT indicates activated partial thromboplastin time; CT, computed tomography; ECT, ecarin clotting time;FDA, Food and Drug Administration; INR, international normalized ratio; IV, intravenous; PT, partial thromboplastin time; rtPA, recombinant tissue plasminogen activator; and TT, thrombin time.

Table 3.

Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset

Inclusion criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms within 3 to 4.5 hours before beginning treatment

Relative exclusion criteria

- Aged >80 years
- Severe stroke (NIHSS>25)
- Taking an oral anticoagulant regardless of INR
- History of both diabetes and prior ischemic stroke

INR indicates international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and rtPA, recombinant tissue plasminogen activator.

Table 4.
Treatment of Acute Ischemic Stroke: Intravenous Administration of rtPA

- Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 minutes, with 10% of the dose given as a bolus over 1 minute.
- Admit the patient to an intensive care or stroke unit for monitoring.
- If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV rtPA is being administered) and obtain emergent CT scan.
- Measure blood pressure and perform neurological assessments every 15 minutes during and after IV rtPA infusion for 2 hours, then every 30 minutes for 6 hours, then hourly until 24 hours after IV rtPA treatment.
- Increase the frequency of blood pressure measurements if systolic blood pressure is >180 mm Hg or if diastolic blood pressure is >105 mm Hg; administer antihypertensive medications to maintain blood pressure.
- Delay placement of nasogastric tubes, indwelling bladder catheters, or intra- arterial pressure catheters if the patient can be safely managed without them.
- Obtain a follow-up CT or MRI scan at 24 hours after IV rtPA before starting anticoagulants or antiplatelet agents.

CT indicates computed tomography; IV, intravenous; MRI, magnetic resonance imaging; and rtPA, recombinant tissue plasminogen activator

19.12. Guidelines for Treatment of Patients with the Intracerebral Hemorrhage

Adapted from: Guidelines for the Management of Spontaneous Intracerebral Hemorrhage (ICH): A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association (2010)

Classification/Level of Evidence Scheme

- Class I: *Benefit*>>>*Risk*; Procedure/treatment SHOULD be performed/administered
- Class IIa: *Benefit* >> *Risk*; IT IS REASONABLE to perform procedure/administer treatment
- Class IIb: *Benefit*≥*Risk*; Procedure/treatment MAY BE CONSIDERED
- Class III: *No Benefit* OR *Harm*; Procedure/treatment is NOT RECOMMENDED/SHOULD NOT BE PERFORMED

- Evidence Level A: Data derived from multiple randomized clinical trials or meta-analyses
- Evidence Level B: Data derived from a single randomized trial or non-randomized studies
- Evidence Level C: Only consensus opinion of experts, case studies, or standard of care

RECOMMENDATIONS

Emergency Diagnosis and Assessment of ICH and Its Causes

1. Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH (Class I; Level of Evidence: A).
2. CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion (Class IIb; Level of Evidence: B), and CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography, and magnetic resonance venography can be useful to evaluate for underlying structural lesions, including vascular malformations and tumors when there is clinical or radiological suspicion (Class IIa; Level of Evidence: B).

Medical Treatment for ICH

1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I; Level of Evidence: C).
2. Patients with ICH whose INR is elevated due to OACs should have their warfarin withheld, receive therapy to replace vitamin K– dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence: C).
3. PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP (Class IIa; Level of Evidence: B).
4. rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH (Class III; Level of Evidence: C).

5. Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients. (Class III; Level of Evidence: A). Further research to determine whether any selected group of patients may benefit from this therapy is needed before any recommendation for its use can be made.
6. The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational (Class IIb; Level of Evidence: B).
7. Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings (Class I; Level of Evidence: B).
8. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset (Class IIb; Level of Evidence: B).

Blood Pressure

1. Until ongoing clinical trials of BP intervention for ICH are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence. Current suggested recommendations for target BP in various situations are listed in Table 1 and may be considered (Class IIb; Level of Evidence: C).
2. In patients presenting with a systolic BP of 150 to 220 mm Hg, acute lowering of systolic BP to 140 mm Hg is probably safe (Class IIa; Level of Evidence: B).

Table 1.
Suggested Recommended Guidelines for Treating Elevated BP in Spontaneous ICH

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure >60 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min.

Note that these recommendations are Class C. SBP indicates systolic blood pressure; MAP, mean arterial pressure.

Management and Prevention of Secondary Brain Injury

1. Initial monitoring and management of ICH patients should take place in an intensive care unit with physician and nursing neuroscience intensive care expertise (Class I; Level of Evidence: B).
2. Glucose should be monitored and normoglycemia is recommended (Class I: Level of Evidence: C).

3. Clinical seizures should be treated with antiepileptic drugs (Class I; Level of Evidence: A).
4. Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury (Class IIa; Level of Evidence: B).
5. Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs (Class I; Level of Evidence: C).
6. Prophylactic anticonvulsant medication should not be used (Class III; Level of Evidence: B).

Procedures/Surgery

1. Patients with a GCS score of <8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A cerebral perfusion pressure of 50 to 70 mm Hg may be reasonable to maintain depending on the status of cerebral autoregulation (Class IIb; Level of Evidence: C).
2. Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness (Class IIa; Level of Evidence: B).

Intraventricular Hemorrhage

1. Although intraventricular administration of recombinant tissue-type plasminogen activator in IVH appears to have a fairly low complication rate, efficacy and safety of this treatment is uncertain and is considered investigational (Class IIb; Level of Evidence: B).

Clot Removal

2. For most patients with ICH, the usefulness of surgery is uncertain (Class IIb; Level of Evidence: C). Specific exceptions to this recommendation follow.
3. Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible (Class I; Level of Evidence: B). Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended (Class III; Level of Evidence: C).
4. For patients presenting with lobar clots >30 mL and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb; Level of Evidence: B).
5. The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational (Class IIb; Level of Evidence: B).
6. Although theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding (Class III; Level of Evidence: B).

Outcome Prediction and Withdrawal of Technological Support

1. Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended (Class IIa;

Level of Evidence: B). Patients with preexisting DNR orders are not included in this recommendation. Current methods of prognostication in individual patients early after ICH are likely biased by failure to account for the influence of withdrawal of support and early DNR orders. Patients who are given DNR status at any point should receive all other appropriate medical and surgical interventions unless otherwise explicitly indicated.

Prevention of Recurrent ICH

2. In situations where stratifying a patient's risk of recurrent ICH may affect other management decisions, it is reasonable to consider the following risk factors for recurrence: lobar location of the initial ICH, older age, ongoing anticoagulation, presence of the apolipoprotein E E2 or E4 alleles, and greater number of microbleeds on MRI (Class IIa; Level of Evidence: B).
3. After the acute ICH period, absent medical contra- indications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy (Class I; Level of Evidence: A).
4. After the acute ICH period, a goal target of a normal BP of <140/90 (<130/80 if diabetes or chronic kidney disease) is reasonable (Class IIa; Level of Evidence: B).
5. Avoidance of long-term anticoagulation as treatment for nonvalvular atrial fibrillation is probably recommended after spontaneous lobar ICH because of the relatively high risk of recurrence (Class IIa; Level of Evidence: B).
6. Anticoagulation after nonlobar ICH and antiplatelet therapy after all ICH might be considered, particularly when there are definite indications for these agents (Class IIb; Level of Evidence: B).
7. Avoidance of heavy alcohol use can be beneficial (Class IIa; Level of Evidence: B).
8. There is insufficient data to recommend restrictions on use of statin agents or physical or sexual activity (Class IIb; Level of Evidence: C).

Rehabilitation and Recovery

1. Given the potentially serious nature and complex pattern of evolving disability, it is reasonable that all patients with ICH have access to multidisciplinary rehabilitation (Class IIa; Level of Evidence: B).
2. Where possible, rehabilitation can be beneficial when begun as early as possible and continued in the community as part of a well-coordinated (seamless) program of accelerated hospital discharge and home-based resettlement to promote ongoing recovery (Class IIa; Level of Evidence: B).

19.13. Guidelines for Treatment of Patients With Subarachnoid Hemorrhage

Adapted from: Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage (aSAH); A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association (2012)

Classification/Level of Evidence Scheme

- Class I: *Benefit>>>Risk*; Procedure/treatment SHOULD be performed/administered
- Class IIa: *Benefit >> Risk*; IT IS REASONABLE to perform procedure/administer treatment
- Class IIb: *Benefit≥Risk*; Procedure/treatment MAY BE CONSIDERED
- Class III: *No Benefit* OR *Harm*; Procedure/treatment is NOT RECOMMENDED/SHOULD NOT BE PERFORMED

- Evidence Level A: Data derived from multiple randomized clinical trials or meta-analyses
- Evidence Level B: Data derived from a single randomized trial or non-randomized studies
- Evidence Level C: Only consensus opinion of experts, case studies, or standard of care

Recommendations

Clinical Manifestations and Diagnosis of aSAH

1. aSAH is a medical emergency that is frequently misdiagnosed. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache (Class I; Level of Evidence B).
2. Acute diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture (Class I; Level of Evidence B).
3. CTA may be considered in the workup of aSAH. If an aneurysm is detected by CTA, this study may help guide the decision for type of aneurysm repair, but if CTA is inconclusive, DSA is still recommended (except possibly in the instance of classic perimesencephalic aSAH) (Class IIb; Level of Evidence C).
4. Magnetic resonance imaging (fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences) may be reasonable for the diagnosis of aSAH in patients with a nondiagnostic CT scan, although a negative result does not obviate the need for cerebrospinal fluid analysis (Class IIb; Level of Evidence C)
5. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by a noninvasive angiogram) and for planning treatment (to determine whether an aneurysm is amenable to coiling or to expedite microsurgery) (Class I; Level of Evidence B).

Medical Measures to Prevent Rebleeding After aSAH

1. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (Class I; Level of Evidence B).
2. The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mm Hg is reasonable (Class IIa; Level of Evidence C).
3. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (<72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (Class IIa; Level of Evidence B).

Surgical and Endovascular Methods of Treatment of Ruptured Cerebral Aneurysms

1. Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after aSAH (Class I; Level of Evidence B).
2. Complete obliteration of the aneurysm is recommended whenever possible (Class I; Level of Evidence B).
3. Determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm (Class I; Level of Evidence C).
4. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered (Class I; Level of Evidence B).
5. In the absence of a compelling contraindication, patients who undergo coiling or clipping of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (eg, growing) remnant (Class I; Level of Evidence B).
6. Microsurgical clipping may receive increased consideration in patients presenting with large (>50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling may receive increased consideration in the elderly (>70 years of age), in those presenting with poor-grade (World Federation of Neurological Surgeons classification IV/V) aSAH, and in those with aneurysms of the basilar apex (Class IIb; Level of Evidence C).
7. Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded (Class III; Level of Evidence C).

Anesthetic Management During Surgical and Endovascular Treatment

1. Minimization of the degree and duration of intraoperative hypotension during aneurysm surgery is probably indicated (Class IIa; Level of Evidence B).
2. There are insufficient data on pharmacological strategies and induced hypertension during temporary vessel occlusion to make specific recommendations, but there are instances when their use may be considered reasonable (Class IIb; Level of Evidence C).
3. Induced hypothermia during aneurysm surgery is not routinely recommended but may be a reasonable option in selected cases (Class III; Level of Evidence B).

4. Prevention of intraoperative hyperglycemia during aneurysm surgery is probably indicated (Class IIa; Level of Evidence B).
5. The use of general anesthesia during endovascular treatment of ruptured cerebral aneurysms can be beneficial in selected patients (Class IIa; Level of Evidence C).

Management of Cerebral Vasospasm and Delayed Cerebral Ischemia (DCI) after aSAH

1. Oral nimodipine should be administered to all patients with aSAH (Class I; Level of Evidence A). (It should be noted that this agent has been shown to improve neurological outcomes but not cerebral vasospasm. The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain.)
2. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI (Class I; Level of Evidence B).
3. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended (Class III; Level of Evidence B). (New recommendation)
4. Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm (Class IIa; Level of Evidence B).
5. Perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischemia (Class IIa; Level of Evidence B).
6. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it (Class I; Level of Evidence B).
7. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (Class IIa; Level of Evidence B).

Management of Hydrocephalus Associated With aSAH

1. aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (EVD or lumbar drainage, depending on the clinical scenario) (Class I; Level of Evidence B).
2. aSAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion (Class I; Level of Evidence C).
3. Weaning EVD over >24 hours does not appear to be effective in reducing the need for ventricular shunting (Class III; Level of Evidence B).
4. Routine fenestration of the lamina terminalis is not useful for reducing the rate of shunt-dependent hydrocephalus and therefore should not be routinely performed. (Class III; Level of Evidence B).

Management of Seizures Associated With aSAH

1. The use of prophylactic anticonvulsants may be considered in the immediate post-hemorrhagic period (Class IIb; Level of Evidence B).
2. The routine long-term use of anticonvulsants is not recommended (Class III; Level of Evidence B) but may be considered for patients with known risk factors for delayed seizure disorder, such as prior seizure, intracerebral hematoma, intractable hyper-tension, infarction, or aneurysm at the middle cerebral artery (Class IIb; Level of Evidence B).

Management of Medical Complications Associated With aSAH

1. Administration of large volumes of hypotonic fluids and intravascular volume contraction is not recommended after aSAH (Class III; Level of Evidence B).

2. Monitoring volume status in certain patients with recent aSAH by some combination of central venous pressure, pulmonary wedge pressure, and fluid balance is reasonable, as is treatment of volume con- traction with crystalloid or colloid fluids (Class IIa; Level of Evidence B).
3. Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH (Class IIa; Level of Evidence B).
4. Careful glucose management with strict avoidance of hypoglycemia may be considered as part of the general critical care management of patients with aSAH (Class IIb; Level of Evidence B).
5. The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined (Class IIb; Level of Evidence B).
6. The use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia (Class IIa; Level of Evidence B).
7. Heparin-induced thrombocytopenia and deep venous thrombosis are relatively frequent complications after aSAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms (Class I; Level of Evidence B).

19.14. Guide for Addressing Arctic Sun Water Temperature Below 25°C

Note: The following information is intended to assist the investigator/clinician in assessing an Arctic Sun water temperature ≤25°C. Pictures of the Arctic Sun screen are provided for illustrative purposes only and may not represent what is observed in an actual clinical setting.

Routine Assessment

The Arctic Sun water temperature should be assessed hourly by the bedside nurse to determine if the system is working to cool the patient (water temperature for a normothermic patient is typically 28^0-30^0C). If the water temperature is ≤25^0C this could indicate that the subject is generating heat (fever or shivering).

Assessing Potential Heat Generation

Potential Shivering
If the water temperature is ≤25^0C, assess the patient for signs of shivering. This can be performed by visually assessing the patient for obvious shivering and/or by palpation of the masseter, neck, or chest wall. You may also look for irregularity of the baseline on your limb leads (any of the conductors connected to the electrocardiograph). If shivering is detected or suspected, implement Tier 1 of the shiver control measures, or the next appropriate Tier if shiver control measures have already been implemented. (See section 6.10 of the protocol)

Potential Fever
If shivering is not detected or implementation of shiver control measures do not raise the water temperature (heat still being generated), you should consider a potential source of fever. A fever work-up should be performed including any standard tests or diagnostic procedures performed as standard of care. Empiric antimicrobials should be prescribed according to physician orders and in compliance with institutional guidance. Please refer to Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America for additional recommendations.

Other Potential Sources of Heat
It is possible that heat can be generated from sources other than shivering or fever (e.g., heated ventilator). If the water temperature remains low, check for other sources of heat generation and consider if additional action is necessary.

Supplemental Information

The Arctic Sun® Temperature Management System measures temperature in 0.01°C increments and can internally identify change before it shows on the display screen. The

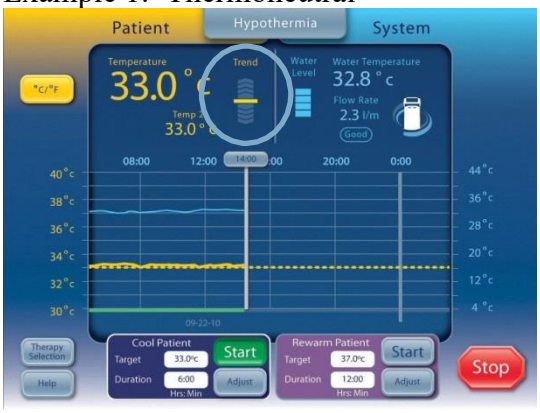
Patient Temperature Trend Indicator reflects the rate of change in the patient's temperature over the previous 5 minutes. When assessing a patient, the clinician may refer to the Patient Temperature Trend Indicator for insight into patient heat generation which may be indicative of shivering or fever generation.

Patient Trend Indicator

The Patient Trend Indicator can be found in the upper center of the display screen. Trends in temperature will be displayed in the following way:

- Center bar- no change or less than 0.25°C change per hour
- One arrow (up or down) - 0.25°C to 0.5°C change per hour
- Two arrows (up or down) - 0.5°C to 0.75°C change per hour
- Three arrows (up or down) - 0.75°C to 2.0°C change per hour
- Four arrows (up or down) - > 2.0°C change per hour

Example 1: Thermoneutral



Example 2: Patient Possibly Generating Heat

19.15. Major Adverse Event Definition Guidance

A. Pneumonia Definition (Modified CDC Definition)

Imaging Test Evidence	Signs/Symptoms/Laboratory
Two or more serial chest imaging test results with at least one of the following: New and persistent OR progressive and persistent • Infiltrate • Consolidation • Cavitation Note: In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging test result is acceptable.	For ANY PATIENT, at least one of the following: • Fever (>38.0°C or >100.4°F) OR Arctic Sun water temperature consistently below 25°C for at least 2 hours despite all efforts to control potential shivering • Leukopenia (≤4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm3) • For adults >70 years old, altered mental status with no other recognized cause And at least two of the following: • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (e.g., O2 desaturations (e.g., PaO2/FiO2 <240), increased oxygen requirements, or increased ventilator demand)

B. Malignant Cerebral Edema Definition

- Neurological deterioration that manifests after the first 8-12 hours after injury as measured by a standardized scale (e.g. NIHSS, GCS)
- Evidence of mass effect or sulcal effacement, which may manifest as progressive midline shift on neuroimaging
- Clinical attribution of deterioration to swelling

C. Sepsis Definition (From: The Third International Consensus Definitions for Sepsis and Septic Shock)

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.