

Summary of Safety and Effectiveness Data

I. General Information

Device Generic Names: Infant Cooling Cap

Device Trade Name: Olympic Cool-Cap®

Applicant's Name and Address: Olympic Medical Corp.
5900 First Ave. South
Seattle, WA 98108

Premarket Approval (PMA) Number: P040025

Date of Panel Recommendation: June 17, 2005

Date of Notice of Approval to the Applicant: December 20, 2006

II. Indications for Use

The Olympic Cool-Cap is indicated for use in full-term infants with clinical evidence of moderate to severe hypoxic-ischemic encephalopathy (HIE)*. Cool-Cap provides selective head cooling with mild systemic hypothermia to prevent or reduce the severity of neurologic injury associated with HIE.

*Clinical evidence of moderate to severe HIE is defined as meeting criteria A, B, and C below:

- A. Infant at greater than or equal to 36 weeks gestational age (GA) and *at least one* of the following:
- Apgar score less than or equal to 5 at 10 minutes after birth.
 - Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth.
 - Acidosis defined as either umbilical cord pH or any arterial pH within 60 minutes of birth less than 7.00.
 - Base Deficit greater than or equal to 16 mmol/L in umbilical cord blood sample *or* any blood sample within 60 minutes of birth (i.e., arterial or venous blood).
- B. Infant with moderate to severe encephalopathy consisting of altered state of consciousness (as shown by lethargy, stupor or coma) and *at least one*

SSED P040025 (Olympic Cool-Cap®)

of the following:

- Hypotonia
- Abnormal reflexes, including oculomotor or papillary abnormalities
- Absent or weak suck
- Clinical seizures

If the infant is paralyzed, assume an abnormal evaluation for criteria B and proceed to criteria C.

- C. Infant has an amplitude-integrated electroencephalogram/cerebral function monitor (aEEG/CFM) recording of at least 20 minutes duration that shows *either* moderately/severely abnormal aEEG background (score of 2 or 3) *or* seizures.

Note: The aEEG/CFM should be performed after one hour of age and should not be performed within 30 minutes following intravenous (IV) anticonvulsant therapy as this may cause suppression of EEG activity.

The aEEG/CFM score is determined as follows:

- 1a. Normal: Lower margin of band of aEEG activity above 7.5 microVolts (μV); sleep-wake cycle present. (Cool only if seizures are present)
- 1b. Mildly abnormal: Lower margin of band of aEEG activity above 5 μV ; sleep-wake cycles absent. (Cool only if seizures are present)
2. Moderately abnormal: Upper margin of band of aEEG activity above 10 μV and lower margin below 5 μV .
3. Severely abnormal: Upper margin of band of aEEG activity below 10 μV and lower margin below 5 μV .
- S. Seizures: Seizures on the aEEG are characterized by a sudden increase in voltage accompanied by narrowing of the band of aEEG activity and followed by a brief period of suppression.

If all three criteria are met, cooling should be started within six hours of birth.

SSED P040025 (Olympic Cool-Cap[®])

III. Contraindications

- Imperforate anus
- Evidence of head trauma or skull fracture causing major intracranial hemorrhage
- < 1,800 g birth weight

IV. Warnings and Precautions

The warnings and precautions can be found in the Olympic Cool-Cap[®] “Physician Implant Manual” and “Physician Lead Manual”.

V. Device Description

The Olympic Cool-Cap[®] provides selective head cooling with mild systemic hypothermia by cooling the head while providing radiant warmth to the remainder of the body. The Olympic Cool-Cap[®] maintains water flow through the fitted cap and maintains the cap water at an operator-specified temperature. The device monitors and displays physiological temperatures (including the rectal temperature); the operator uses the rectal temperature reading as a guide to adjust the cap water temperature. The goal is to adjust the cap water appropriately in order to maintain the infant’s rectal temperature at $34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ ($34.0 - 35.0^{\circ}\text{C}$).

The Olympic Cool-Cap[®] allows the operator to adjust the cap temperature within $\pm 0.1^{\circ}\text{C}$. The operator is responsible for monitoring the infant’s rectal temperature and adjusting the cap temperature to keep the rectal temperature within the target range. The device is designed to work with a radiant warmer to maintain the infant’s core temperature, as indicated by the rectal temperature, within the target range of $34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ ($34.0 - 35.0^{\circ}\text{C}$).

The Olympic Cool-Cap[®] consists of the following main components:

Cooling Unit

The portion of the Olympic Cool-Cap[®] responsible for controlling the cap’s water temperature and for pumping water through the Water Cap. Thermoelectric solid-state devices are attached to an aluminum heat-transfer block with serpentine water channels. When power is applied to the thermoelectric devices, the heat-transfer block is cooled and the water circulating through this block is also cooled. The temperature of the water entering and leaving the heat-transfer block is monitored. Power to the thermoelectric modules is controlled to obtain a target temperature that is the average of the cap inflow and outflow temperatures. This

SSED P040025 (Olympic Cool-Cap[®])

average temperature has been shown to accurately represent the temperature at the cap.

Control Unit

The portion of the Olympic Cool-Cap[®] responsible for displaying temperatures and providing user control buttons. The user interacts with the screen by touch (i.e., it is a touch-screen). The Control Unit also sends appropriate commands to, and obtains data from, both the Cooling Unit and the Temperature Sensor Module to provide overall control of the system.

The user primarily monitors the infant's rectal temperature using the built-in temperature measurement/display circuitry to determine the level of cooling being achieved. The user may also monitor skin (abdominal) and scalp (fontanel) temperatures. The user adjusts the cap target temperature to produce appropriate cooling in the infant (i.e. obtaining a target rectal temperature of $34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$). The unit sounds an alarm when the rectal temperature is above or below the target range.

Temperature Sensor Module

Component with input from five Temperature Sensors and output to Control Unit.

Temperature Sensors

The Olympic Cool-Cap[®] uses YSI Series 4000 medical temperature sensors. The temperature sensors used to obtain temperature measurements from the scalp/fontanel and abdomen/skin are YSI 4499. The sensors are capable of an accuracy of $\pm 0.1^{\circ}\text{C}$ from 25° to 45°C . The radiant warmth sensor is a commercially available temperature sensor that is used to give a qualitative reading of the amount of radiant warmth reaching the infant. The radiant warmth sensor is not in contact with the infant.

Water Cap

Polyurethane water-filled cap placed in direct contact with infant's scalp for effective heat conduction.

Water Cap Retainer

Blue fabric cap made of Spandex responsible for holding the Water Cap firmly to the infant's scalp.

Insulating Cap

Polyester fleece with metallized polyester outer surface placed over the Water Cap Retainer and meant to provide insulation from radiant warmth.

SSED P040025 (Olympic Cool-Cap[®])

Radiant Warmer

Although not provided as part of the Olympic Cool-Cap[®], the device is used in conjunction with a standard, commercially available radiant warmer. The radiant warmer is directed at the infant's torso and adjusted to maintain 100% output. The infant's head is shielded from the radiant warmer.

VI. Alternative Practices and Procedures

There are no approved alternative treatments for HIE. Support and treatment of symptoms are the current standard-of-care for HIE and include maintaining metabolic and respiratory parameters within the normal range as well as treating seizures with anticonvulsants.

VII. Marketing History

The Olympic Cool-Cap[®] has not been marked in the U.S. or any foreign country.

VIII. Potential Adverse Effects of the Device on Health

A total of 25 sites enrolled 235 patients in the clinical trial. One patient was withdrawn from the study due to inadequate consent, resulting in a total patient count of 234. There was no statistically significant difference in the rates of any of the serious adverse events (AEs). There was also no statistically significant difference in the rates of 16 of the 18 types of anticipated AEs. Two anticipated AEs did, however, occur more frequently in the cooled group: minor cardiac arrhythmias and "other" AEs (most of which were scalp edema). Please refer to page 13 of Section X for more detail.

IX. Summary of Preclinical Studies

Biocompatibility Tests

The water cap is constructed of medical-grade polyurethane. In addition to documentation provided by the polyurethane manufacturer, biocompatibility tests were performed by NAMSA in 1998 for the cap liner. Based on its contact with the infant's scalp, the cap is categorized as a surface device (skin) with prolonged contact (72 hours). Therefore, in accordance with ISO 10993-1 and FDA Blue Book Memorandum #G95-1 standards, the following tests were performed on the cap material: Cytotoxicity, Sensitization, and Irritation. Test results showed no evidence of cytotoxicity, sensitization or irritation. Tests for extractables were also performed. All testing results met the USP requirements.

Electrical Safety Tests

The following were tested in accordance with IEC 60601-1 (1998): Electrical shock hazards, Mechanical hazards, Excessive temperature, Hazardous output,

SSED P040025 (Olympic Cool-Cap[®])

and abnormal operation and fault conditions. All testing results met the IEC 60601-1 (1998) requirements.

Electromagnetic Immunity (EMI) and Compatibility (EMC) Tests

The Cool-Cap[®] was determined to meet the requirements of IEC 60601-1-2 (2nd Edition, 2001) “Medical Electrical Equipment: Part 1 General Requirements for Safety”.

Packaging

Vibration testing was performed in accordance with ASTM D4169 – Schedule A, ALII and results met all requirements.

Device Validation Testing

Due to design differences between the commercial device and the actual device used in the clinical investigation validation testing was performed to demonstrate that the differences between the two devices will not affect the safety and effectiveness of the device. None of the key functional components of the device (i.e., cooling hardware, water circulation, cap design, and cooling system control algorithms) were changed in the commercial version of the device but due to advances in technology and the obsolescence of the device microprocessor, the commercial configuration of the Olympic Cool-Cap[®] was updated. The main change was to the software control system which included improvements to the user interface to include a full-colored graphic display to allow for display of temperature trend graphs, instructional photographs, user prompts, and touch screen control buttons. The original design incorporated a seven-segment light emitting diode (LED) display, push buttons, and a printed study manual (note that a printed manual is also available with the commercial version of the device). A Pentium style microprocessor replaced the trial device’s NEC V25 microcontroller and the custom embedded operating system was replaced with Linux.

- Assessment Test

The purpose is for NICU-based clinicians to assess the graphical user interface, software controls, and software-based wizards developed for the commercial device. This test was performed with five NICU personnel, with prior direct experience using, or coordinating use of, the clinical trial configuration of Cool-Cap, on the control module. The test participants reviewed the graphical user interface, software controls and software based wizards (setup, rewarming and shutdown). All test participants completed an 8-page test questionnaire. Subjects responded to questions regarding the following: First screen impressions, Setup Wizard, Main Screen, Rewarming, and Shutdown Wizard. Test participants were also asked to compare the user interface for the commercial configuration of Cool-Cap to that of the clinical

SSED P040025 (Olympic Cool-Cap[®])

trial configuration. All test participants concluded that the proposed commercial device is easier to use than the clinical trial device.

- Preliminary Validation Test

A usability / pre-validation test on the user interface of the new commercial configuration of the Olympic Cool-Cap® was performed on seven subjects with prior direct experience using, or coordinating use of, the clinical trial configuration of Cool-Cap: 1 neonatologist, 1 neonatal nurse, 2 nurse coordinators, 1 clinical trial coordinator, 1 PICU nurse and 1 respiratory therapist/research. Six subjects were involved in the clinical investigation and had experience with the investigational device design. Two of the subjects completed operator's manual validation and five completed label validation. In general, the pre-validation test confirmed that the prototype software is user-friendly, the wizards/functions are easily learnable, and the product meets the users' needs.

- Validation Test

A usability / validation test was performed on a production unit of the proposed commercial configuration of the Olympic Cool-Cap®. A total of three NICU nurses were tested at the offices of Olympic Medical. This test had the following purposes:

- To confirm that the final software is user-friendly and the wizards/functions are easily learnable
- To confirm that the product meets the users' needs
- To confirm that users can use the device to:
 - o Circulate temperature-controlled water through a patient-applied cap
 - o Adjust the cap water temperature
 - o Display cap and physiological temperatures
- To confirm that users can administer hypothermia treatment with effectiveness, efficiency, and satisfaction in a specified context of use

The users had some type of clinical experience but, no prior experience with Cool-Cap. Methods used for this validation test included:

- *User testing* of realistic, representative tasks (i.e., *context analysis*)
- *Questionnaire* response to obtain direct feedback
- *Observation* of user testing with documentation of user actions, observer comments, assists provided by observers, and descriptions of user errors

The test environment was a conference room at Olympic Medical. In addition to the Cool-Cap device, a radiant warmer was present as well as some sort of bed (such as a Bili-Bassinet). The baby was simulated with a baby doll and,

SSED P040025 (Olympic Cool-Cap®)

during a portion of the validation test, background NICU sounds were provided via a tape-recording in order to compare Cool-Cap's auditory alarms. Overall, the usability / validation test confirmed that the final software is user-friendly, the wizards/functions are easily learnable, and the product meets the users' needs.

Animal Studies

The Cool-Cap was tested in piglets by a group of researchers in Bristol, England. These data demonstrated that it was possible to use the device to cool the brain more than the body (Thorenson et al., 2001), and to maintain this gradient for a 24-hour period, while keeping the core temperature mildly hypothermic (Tooley et al., 2002). Furthermore, brain measurements were made in the striatum, demonstrating that selective head cooling can effectively cool deep brain structures, such as the basal ganglia, as well as the cortex. These studies confirmed clinical observations that it was possible to establish a temperature gradient between the deep brain structures and the body, when using a cooling cap and warming the body with an overhead heater (Thorenson et al., 2001). Selective head cooling did not result in either skin injury or superficial brain hemorrhage (Tooley et al., 2002). These studies further demonstrated that this selective head cooling procedure safely improved outcome following a 45-minute global hypoxic-ischemic insult in the piglet model (Tooley et al., 2003).

X. Summary of Clinical Studies

The objectives of this clinical study were to determine whether treatment of moderate to severe HIE in full term infants with head cooling and mild systemic hypothermia can produce meaningful improvements in neurodevelopmental outcome and survival rates at 18 months of age and to confirm the safety of prolonged head cooling with mild systemic hypothermia in full term newborn infants with moderate to severe HIE. Patient's meeting all of the following inclusion and exclusion criteria were included in the study.

Inclusion Criteria

The infant was assessed sequentially by criteria A, B and C listed below:

- A. Infants ≥ 36 weeks gestation admitted to the NICU with ONE of the following:
- Apgar score of < 5 at 10 minutes after birth
 - Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
 - Acidosis defined as either umbilical cord pH or any arterial pH within 60 minutes of birth < 7.00

SSED P040025 (Olympic Cool-Cap[®])

- Base Deficit \geq 16 mmol/L in umbilical cord blood sample or any blood sample within 60 minutes of birth (arterial or venous blood)

If the infant met criteria A then they were assessed for neurological abnormality (by certified study personnel):

- B. Moderate to severe encephalopathy consisting of altered state of consciousness *and* at least one or more of lethargy, stupor or coma, hypotonia, abnormal reflexes including oculomotor or pupillary abnormalities, an absent or weak suck or clinical seizures, as recorded by study personnel.

If the infant met criteria A & B then they were assessed by aEEG (read by certified study personnel):

- C. At least 20 minutes duration of amplitude integrated EEG recording that shows abnormal background aEEG activity or seizures (see Appendix A). The aEEG may be performed from one hour of age. If subsequently an abnormal aEEG is recorded before 5.5 hours of age, the infant would then become eligible for enrollment. The aEEG should not be performed within 30 min of IV anticonvulsant therapy as this may cause suppression of EEG activity. In particular, high dose prophylactic anticonvulsant therapy (e.g., $>20\text{mg/kg}$ phenobarbitone) should not be given prior to performing the aEEG.

Interpretation of amplitude integrate EEG (aEEG):

The aEEG was interpreted using the following quantitative voltage criteria:

- 1a. Normal: Lower margin of band of aEEG activity above $7.5 \mu\text{V}$; sleep - wake cycle present.
- 1b. Mildly abnormal: Lower margin of band of aEEG activity above $5\mu\text{V}$; sleep- wake cycles absent.
2. Moderately abnormal: Upper margin of band of aEEG activity above $10 \mu\text{V}$ and lower margin below $5 \mu\text{V}$.
3. Severely abnormal: Upper margin of band of aEEG activity below $10 \mu\text{V}$ and lower margin below $5 \mu\text{V}$.

Seizures on the aEEG were characterized by a sudden increase in voltage accompanied by narrowing of the band of aEEG activity and followed by a brief period of suppression.

Exclusion Criteria

- Infants expected to be >5.5 hours of age at the time of randomization.
- Prophylactic administration of high dose anticonvulsants (eg. >20mg/kg phenobarbitone). After trial entry phenobarbitone or other anticonvulsant therapy may be given as clinically indicated to treat seizures (see *co-treatment* below).
- Major congenital abnormalities, such as diaphragmatic hernia requiring ventilation, or congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis.
- Imperforate anus (since this would prevent rectal temperature recordings).
- Evidence of head trauma or skull fracture causing major intracranial hemorrhage.
- Infants <1,800 g birth weight.
- Head circumference < (mean-2SD) for gestation if birth weight and length are > (mean-2SD).
- Infants “in extremis” (those infants for whom no other additional intensive management will be offered in the judgment of the attending neonatologist). Record in detail reason for exclusion.
- Unavailability of essential equipment (e.g., cooler, aEEG).
- Planned concurrent participation in other experimental treatments.

Study Design

The trial was an international multi-center, prospective, randomized, controlled study. The outcome measure of severe neurodevelopmental disability was assessed by a blinded independent observer.

In summary, within six hours of birth, and after inclusion/exclusion criteria were met and informed consent was obtained, infants were randomized to either a non-cooled control group treated with standard of care and with a rectal temperature maintained at $37 \pm 0.5^{\circ}\text{C}$ or to a treatment group for head cooling with mild systemic hypothermia (i.e., the rectal temperature at the target range of $34.5 \pm 0.5^{\circ}\text{C}$).

For those infants randomized to head cooling, a water-circulating cooling cap was fitted around the infant’s scalp to cool the head and an overhead radiant warmer was set at 100%. The core rectal temperature of the infant was controlled by adjusting the cap water temperature to maintain the rectal temperature at the target range of $34.5 \pm 0.5^{\circ}\text{C}$. The infant’s rectal, nasopharyngeal, scalp (fontanel) and skin (abdominal) temperatures were continuously monitored along with metabolic, cardiovascular, pulmonary and coagulation status. Cooling was

SSED P040025 (Olympic Cool-Cap[®])

maintained for 72 hours, followed by slow rewarming (with the goal of raising the rectal temperature by 0.5°C/hour) to 37 ± 0.2°C.

Patient Assessment

The primary outcome was the combined rate of mortality at 18 months of age and severe neurodevelopmental disability in survivors. The presence of any one of the following constitutes severe neurodevelopmental disability: (a) Gross Motor Function (GMF) impairment level 3-5, (b) Bayley mental scale (MDI) <70, (c) bilateral cortical visual impairment.

At 18 months, patients completed the study with the following assessments: neurodevelopmental exam, measurements of head circumference, weight and length, psychometric testing with Bayley-II, audiology assessment, and ophthalmology examination. All exams were performed by qualified personnel who were masked to the treatment. A socio-economic status questionnaire was also administered.

Six-month follow-up visits were conducted to help cohort retention in the study. Data collected at this visit included head circumference, weight and length measurements and reasons for any referral to therapy. Some patients were also referred to therapy if deemed appropriate by the evaluating physician.

Demographic Data

A total of 25 sites enrolled 235 patients in the clinical trial. One patient was withdrawn from the study due to inadequate consent, resulting in a total patient count of 234. Of these 234 patients, 75% (176/234) were enrolled at U.S. sites and 25% (58/234) were enrolled internationally. The international enrollees were distributed as follows: 11% (26/234) from England, 9% (21/234) from Canada, and 5% (11/234) from New Zealand. See Table **Error! Reference source not found.** for a breakdown of the patient enrollment distribution by site.

As seen in Table 1, baseline patient characteristics were generally well balanced. Due to a decision to stratify the treatment randomization by participating site only and the generally small number of patients enrolled per site, imbalance in patient population occurred in the case of Apgar score at five minutes after birth and aEEG background (both had more severely affected infants in the cooled group).

Table 1 – Baseline characteristics of all enrolled infants

	Cooled (n=116)		Control (n=118)		Total (n=234)	
Gestational Age (weeks)						
Mean (Std. Dev.)	38.9	(1.6)	39.1	(1.4)	39.0	(1.5)
Birth Weight (g)						
Mean (Std. Dev.)	3399	(663)	3504	(625)	3452	(645)
Birth Length (cm)						
Mean (Std. Dev.)	50.8	(3.5)	51.5	(3.0)	51.2	(3.2)
Head Circumference (cm)						
Mean (Std. Dev.)	34.6	(1.8)	35.0	(1.9)	34.8	(1.8)
Gender						
Female	52	45%	60	51%	112	48%
Male	64	55%	58	49%	122	52%
Apgar at 5 minutes*						
0 – 3	88	77%	77	68%	165	72%
4 – 6	25	22%	31	27%	56	24%
7 – 10	2	2%	6	5%	8	3%
Assisted Ventilation Pre-randomization						
No	0	0%	0	0%	0	0%
Yes	116	100%	118	100%	234	100%
Pre-randomization aEEG Background:						
Normal/Mildly Abnormal	7	6%	9	8%	16	7%
Moderately Abnormal	63	54%	76	64%	139	59%
Severely Abnormal	40	37%	31	28%	74	32%
Unclassifiable**	4	3%	1	1%	5	2%
Pre-randomization aEEG: Presence of Seizure						
No	48	41%	43	36%	91	39%
Yes	68	59%	75	64%	143	61%

SSED P040025 (Olympic Cool-Cap®)

Age at Randomization (hours)						
Median (range)	4.8	(2.6-6.0)	4.7	(2.1-6.1)	4.8	(2.1-6.1)
> 2 – 4	29	25%	24	20%	53	23%
> 4 – 6	86	74%	92	78%	178	76%
> 6	1	1%	2	2%	3	1%

* data available for 229 patients

** all unclassifiable aEEGs were eligible for the trial due to the presence of seizures

Data Analysis and Results

A. Safety

Since all except one of the anticipated Adverse Events (AEs) (evidence of skin breakdown due to pressure of cooling cap; see Table 2) could be consequences of hypoxia-ischemia, detailed statistical testing was essential to determine whether cooling could be a contributing factor. Two-sided p values < 0.05 are considered statistically significant. Note that the study was not designed to detect a statistically significant difference with respect to some rare adverse events.

As shown in Table 2, there was no statistically significant difference in the rates of any of the serious AEs. There was also no statistically significant difference in the rates of 16 of the 18 types of anticipated AEs. Two anticipated AEs did, however, occur more frequently in the cooled group: minor cardiac arrhythmias and “other” AEs (most of which were scalp edema).

Although minor cardiac arrhythmias occurred more frequently in the cooled infants, this was not unexpected since mild sinus bradycardia is known to be associated with hypothermia, and all episodes resolved with proper therapy. None of the cooled infants experienced a major cardiac arrhythmia.

Scalp edema also occurred in 21% (23/112) of the cooled infants. All except for three (87%, or 20/23) of the edema cases were of mild to moderate severity; the remaining three were severe. All 23 cases of scalp edema resolved prior to or after completion of cooling treatment with either no action, massage, changing position, or cap adjustment.

SSED P040025 (Olympic Cool-Cap®)

Table 2 – Analysis of device safety based on occurrence of adverse events (n=230; entire 234 population excluding four patients randomized to cooling but not cooled)

AE Code	Adverse Event	Cooled (n=112)		Control (n=118)		Fisher's exact P value
Major Adverse Events						
01	Major cardiac arrhythmia	0	0%	0	0%	----
02	Major venous thrombosis	0	0%	2	2%	0.50
03	Severe hypotension despite full support	3	3%	3	3%	1.00
04	Unanticipated serious adverse event	1	1%	0	0%	0.49
Other Anticipated Adverse Events						
05	Cardiac arrhythmia (not reaching code 01)	10	9%	1	1%	0.004*
06	Hypotension (not reaching code 03)	62	55%	61	52%	0.60
07	Coagulopathy	21	19%	17	14%	0.38
08	Prolonged coagulation times	56	50%	50	42%	0.29
09	Abnormal renal function	73	65%	83	70%	0.48
10	Hyponatremia	49	44%	46	39%	0.50
11	Hypokalemia	71	63%	73	62%	0.89
12	Bone marrow depression	36	32%	26	22%	0.10
13	Elevated liver enzyme levels	42	38%	62	53%	0.02*
14	Metabolic acidosis	22	20%	27	23%	0.63
15	Respiratory distress	94	84%	92	78%	0.31
16	Systemic infection	1	1%	2	2%	1.00
17	Hemoconcentration	3	3%	1	1%	0.36
18	Hypoglycemia	14	13%	20	17%	0.36
19	Hypocalcemia	49	44%	51	43%	1.00
20	Skin breakdown due to cooling cap pressure	0	0%	0	0%	----
21	Difficulties in temperature control	36	32%	27	23%	0.14
22	Other:	51	46%	26	22%	0.0003*
	Scalp edema (subset of Other)	23	21%	1	1%	<0.0001*

* Statistically significant finding (p < 0.05)

There was no evidence that mortality rates (see Table 3) differed between the two study groups (p=0.48). Mortality rates were 33% (36/108) in the cooled group and 38% (42/110) in the control group.

SSED P040025 (Olympic Cool-Cap®)

Table 3 – Mortality rates for enrolled population (n=234)

	Cooled (n=116)		Control (n=118)		Total (n=234)	
	N	%	N	%	N	%
Survival Status						
Alive	73	63%	71*	60%	144	62%
Dead	36	31%	42	36%	78	33%
Unknown	7	6%	5	4%	12	5%

* Three control infants that had incomplete data for evaluation were alive at 18-months

As shown in Table 4, the majority of the deaths (53/78 or 68%) occurred within seven days after randomization. Deaths during this time period included 26 in the control group (26/78, or 33%) and 27 in the cooled group (27/78, or 35%). Although not statistically significant, there was an increased number of deaths in the cooled group on Day 4 following 3 days of cooling treatment (Cooled 11 vs. Control 2). This may represent the physician and family decision to complete the full period of cooling before withdrawing care.

Table 4 – Distribution of infants deaths as a function of time (n=78)

Time Period	Cooled (n=108)	Control (n=110)
Total during the first 8 days (day 0-7)	27	26
Days 0-3	15	19
Days 4-5	11	2
Days 6-7	1	5
Total during the first 2 months (<60 days)	32	37
Total during the first 18 months (total trial deaths)	36	42

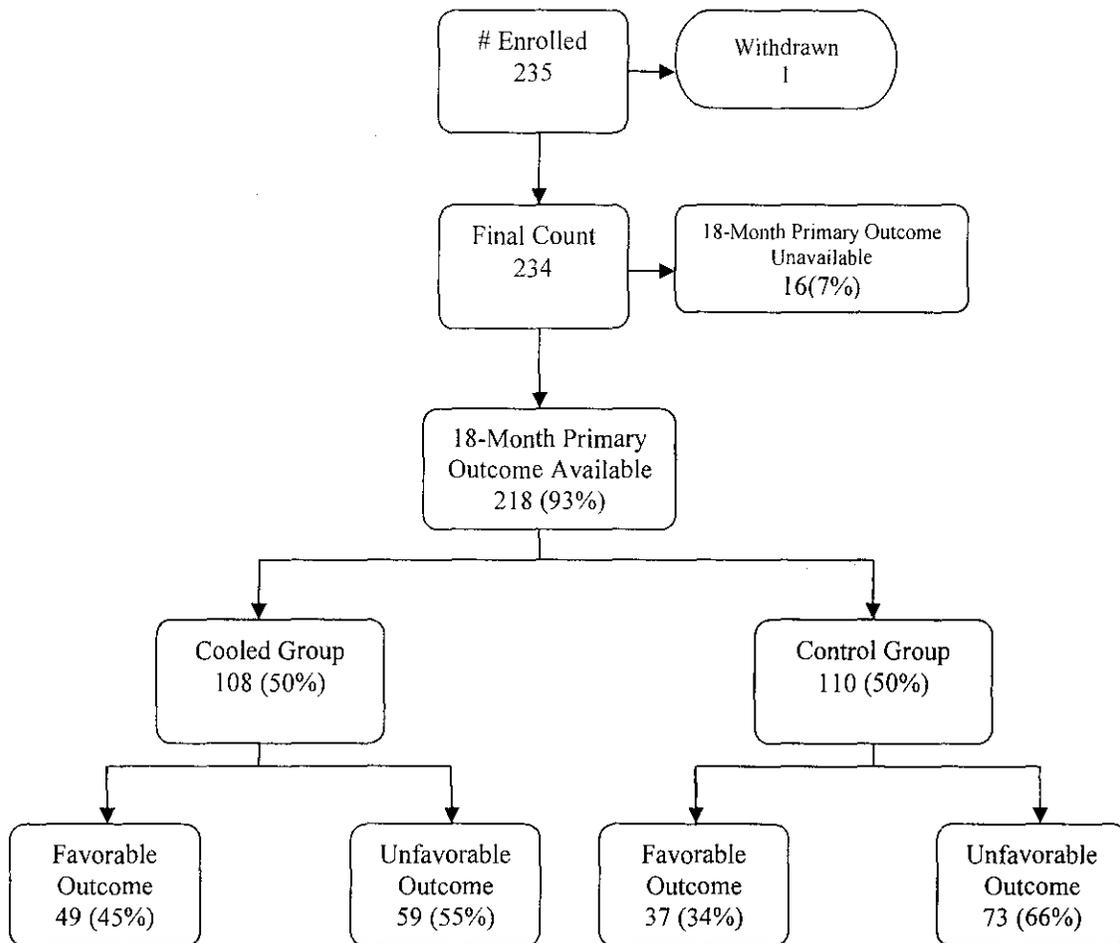
Hypothermia may inhibit the metabolism and clearance of anticonvulsants and one patient in the trial was noted to have elevated clonazepam levels. Another patient in the trial developed seizures on rewarming. Rewarming may unmask seizures that were suppressed during hypothermia. In order to allow for device use while a Premarket Approval (PMA) application was being evaluated by the FDA, a continued access trial was approved on April 1, 2003. In that trial, two patients developed seizures on rewarming. One patient in the continued access trial developed sclerema neonatorum which has been associated with hypothermia.

SSED P040025 (Olympic Cool-Cap®)

B. Effectiveness

As shown in Figure 1, 18-month primary outcome results were available in 93% (218/234) of the patients; primary outcome results were unavailable for 7% (16/234) of the patients. Of the 218 patients, 50% (110/218) were in the control group and 50% (108/218) in the cooled group. Within the control group, 34% (37/110) had a favorable outcome while 45% (49/108) had a favorable outcome in the cooled group. Fisher's exact test showed no statistical significance ($p=0.10$, 95% Confidence Interval (CI) Cooled-Control: 11% [-1%, 25%]).

Figure 1 – Primary outcome (death and severe neurodevelopmental disability in survivors at 18 months of age as defined on page 11 under Patient Assessment) for patients for whom 18-month primary outcome is known (n=218).



SSSD P040025 (Olympic Cool-Cap®)

However, the randomization resulted in a greater proportion of infants with severe aEEG baseline in the cooled group (37% or 40/108) as compared to the control group (28% or 31/110). Logistic regression analysis adjusting for baseline aEEG background, aEEG seizure status, Apgar score, birth weight, gender and age at randomization indicated a treatment effect of statistical significance ($p=0.042$, 95% CI Odds Ratio of Unfavorable Outcome Cooled/Control: 0.53 [0.29, 0.98]).

Device Failures and Replacements

A total of 11 reported device failures were attributed to equipment issues as opposed to operator error or environmental conditions. Five of these were corrected in the field and six were resolved by replacing the equipment.

The most common error (6/11) involved a pinch valve that controlled water flow into the system from the 1-liter bag of sterile water. The valve design was changed in the commercial version of Cool-Cap[®]. Other failures included non-volatile RAM reset (2/11), fan failure (1/11), failed power supply (1/11) and a failed thermistor circuit (1/11). These failures were determined to be random electrical or mechanical component failures.

Only one infant of the 235 enrolled was not treated due to a failure of the equipment. Cooling was delayed until after 6 hours for one other infant due to an equipment issue that was resolved by using their backup system.

XI. Conclusions Drawn from the Studies

Risk/Benefit Analysis

Neonatal hypoxic-ischemic encephalopathy is a difficult condition for which there is no FDA approved treatment. A significant number of infants afflicted with moderate or severe HIE have a very poor outcome with death or severe neurodevelopmental disability. Poor outcome is devastating to both patients and families with enormous emotional and economic costs.

The clinical trial has demonstrated that the Olympic Cool-Cap[®] can prevent or reduce the severity of neurologic injury associated with HIE in the studied population and the risks were demonstrated to be acceptable. Although mild sinus bradycardia and scalp edema occur in higher frequencies in treated patients, these were not life-threatening. Mortality rates were also shown to be not significantly different in the treated group than in the control group.

SSSED P040025 (Olympic Cool-Cap[®])

Safety and Effectiveness

The randomized, controlled trial sponsored by Olympic Medical supports that the Olympic Cool-Cap[®], when used in full-term infants ≥ 36 weeks gestation at risk for moderate to severe hypoxic-ischemic encephalopathy (HIE), may safely and effectively prevent or reduce the severity of neurologic injury associated with HIE in the patient population that was studied.. In the population for whom 18-month primary outcome data were known (n=218), after adjusting for randomization differences in the two groups, treatment effect was statistically significant (p=0.042) with favorable outcomes in 34% (37/110) of the control group and 45% (49/108) of the cooled group.

There was no statistically significant difference in the rates of any of the serious AEs. There was also no statistically significant difference in the rates of 16 of the 18 types of anticipated AEs. Two anticipated AEs did, however, occur more frequently in the cooled group: minor cardiac arrhythmias and “other” AEs (most of which were scalp edema). Although minor cardiac arrhythmias occurred more frequently in the cooled infants, this was not unexpected since mild sinus bradycardia is known to be associated with hypothermia. It is important to note that none of the cooled infants experienced a major cardiac arrhythmia. Scalp edema occurred in 21% (23/112) of the cooled infants. All except three (87%, or 20/23) of the edema cases were of mild to moderate severity; the remaining three were severe. However, all 23 cases of scalp edema resolved prior to or after completion of cooling treatment with either no action or massage, changing position, or cap adjustment. Scalp edema is presumably a direct result of thermal effects on capillary permeability and pressure from the cooling cap.

Thus, it may be concluded that selective head cooling with mild systemic hypothermia, as administered with Cool-Cap[®], can safely and effectively prevent or reduce the severity of moderate to severe hypoxic-ischemic encephalopathy when used in infants ≥ 36 weeks gestation.

XII. Panel Recommendations

At an advisory meeting held on June 17, 2005, the Neurological Devices Panel recommended that Olympic Medical Corporation’s PMA for the Olympic Cool-Cap[®] be approved subject to submission to and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

- (1) A registry should be instituted to collect information on real world device usage to track patient outcomes.
- (2) A training and certification process should be required for all users of the

SSED P040025 (Olympic Cool-Cap[®])

device.

- (3) Use of the device should be restricted to the protocol defined patient population.

XIII. CDRH Decision

CDRH concurred with the Panel recommendation of June 17, 2005, and issued a letter to Olympic Medical Corporation, on August 2, 2005 advising that its PMA was approvable subject to the following conditions:

- (1) A registry should be instituted to collect information on real world device usage to track patient outcomes.
- (2) A training and certification process should be required for all users of the device.
- (3) Use of the device should be restricted to the protocol defined patient population.

In an amendment received by FDA on January 26, 2006, Olympic Medical submitted the registry and it was acceptable. In an amendment received by FDA on April 14, 2006 Olympic Medical submitted a copy of the final draft labeling and it was acceptable. The labeling includes a statement that users should undergo in-service training (either by Olympic Medical or local trained personnel) prior to using the device. The applicant's manufacturing facility was inspected on November 2, 2006 and was found to be in compliance with the Quality System Regulation (21 CFR 820). FDA issued an approval order on December 20, 2006.

XIV. Approval Specifications

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

SSED P040025 (Olympic Cool-Cap[®])

XV. References

1. Thoresen,M., Simmonds,M., Satas,S., Tooley,J. & Silver,I.A. Effective selective head cooling during posthypoxic hypothermia in newborn piglets. *Pediatr. Res.* **49**, 594-599 (2001).
2. Tooley,J., Satas,S., Eagle,R., Silver,I.A. & Thoresen,M. Significant selective head cooling can be maintained long-term after global hypoxia ischemia in newborn piglets. *Pediatr.* **109**, 643-649 (2002).
3. Tooley,J.R., Satas,S., Porter,H., Silver,I.A. & Thoresen,M. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. *Ann Neurol.* **53**, 65-72 (2003).