

Operator's Manual OLYMPIC COOL-CAP®



PRECAUTION

Read and be familiar with this manual before installing, operating, or servicing this device. To ensure operator, technician, and infant safety, use only as specified in this manual.

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Olympic Cool-Cap Operator's Manual, 60010-OMA-EN1107Q

United States Patent No. 6,612,453

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Caution: United States Federal Law restricts this device to sale by or on the order of a physician.

The hospital/facility is responsible for ensuring that all personnel who operate or maintain this device are trained in its operation and safe use, and to maintain training records of attendance and evidence of understanding.

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Section

1

Overview

This manual provides the necessary information to assemble, operate, and maintain the Olympic Cool-Cap®. The operating instructions in this manual are intended for use under the direction of a licensed physician and by practitioners who have been trained in the use of Cool-Cap. The assembly instructions in this manual are intended for use by qualified service technicians.

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 by 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* of the following:
- Hypotonia
 - Abnormal reflexes, including oculomotor or pupillary 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 activity (score of 2 or 3) *or* seizures.



- 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 can change over time. The aEEG/CFM reading may be run as long as needed to meet criteria C. Eligibility for treatment is based on the worst aEEG recorded.

The aEEG/CFM score is determined as follows:

- 1a. **Normal:** Lower margin of the 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 the band of aEEG activity above 5 μV ; sleep-wake cycle absent. (Cool only if seizures are present.)
2. **Moderately abnormal:** Upper margin of the band of aEEG activity above 10 μV and lower margin below 5 μV .
3. **Severely abnormal:** Upper margin of the 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*.

For details, see *aEEG/CFM Equipment* and *aEEG/CFM Score* on page 1-3.

Contraindications

Contraindications for using the Cool-Cap system include:

- Imperforate anus
- Evidence of head trauma or skull fracture causing major intracranial hemorrhage
- Birth weight of less than 1,800 g

Warnings and Precautions

For all warnings and precautions associated with the use of Cool-Cap, see Section 3, *Warnings and Precautions* on page 3-1.

* Whenever possible, treatment should be started *as early as possible* (based on animal data).

Training

The hospital/facility is responsible for ensuring that all personnel who operate or maintain this device are trained in its operation and safe use, and to maintain training records of attendance and evidence of understanding.

Properly trained individuals have been through in-service training (either by Olympic Medical or local trained personnel) and are familiar with the contents of this manual.

Additional Clinical Information

Initiation of Cooling

Defer all non-critical investigations that can be performed later in the first 24 hours until after cooling has been started. Cooling should be started within six hours of birth; whenever possible, treatment should be started *as early as possible* (based on animal data).

aEEG/CFM Equipment

The following aEEG/CFM equipment can be used to establish clinical evidence of HIE for criteria C: the Olympic Lectromed CFM 5330, which was used in the Cool-Cap clinical trial, or the Olympic CFM 6000, which is substantially equivalent to the Olympic Lectromed CFM 5330.

aEEG/CFM Score

The aEEG/CFM score is determined as described in *Indications for Use* (criteria C) on page 1-2. Examples of normal (1a), mildly abnormal (1b), moderately abnormal (2), severely abnormal (3), and seizures (S) are provided in the following figures. For more information on determining CFM scores, refer to the *Olympic CFM 6000 Clinical Guide*.

Figure 1.1 Normal (1a)

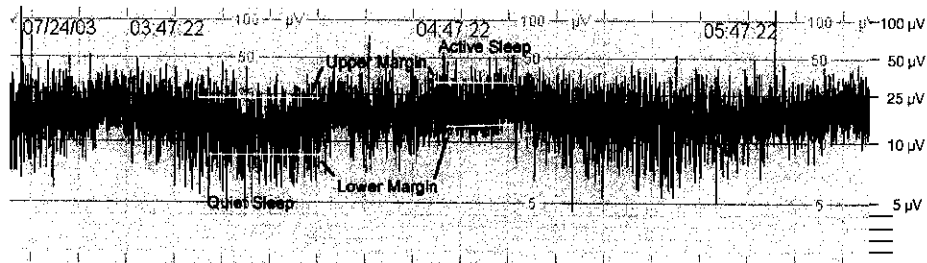


Figure 1.2 Mildly abnormal (1b)

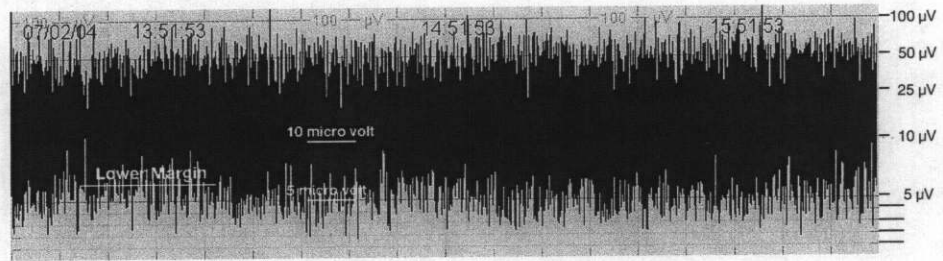


Figure 1.3 Moderately abnormal (2)

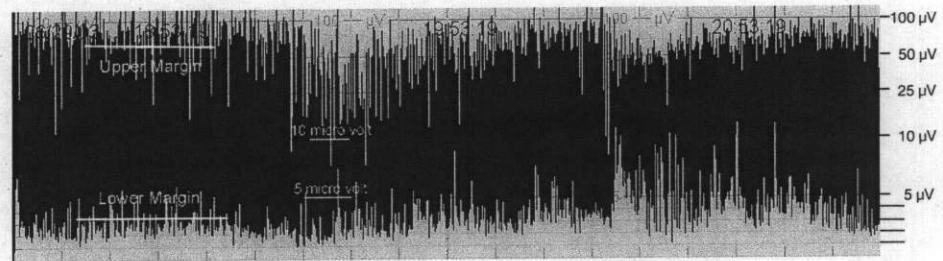


Figure 1.4 Severely abnormal (3)

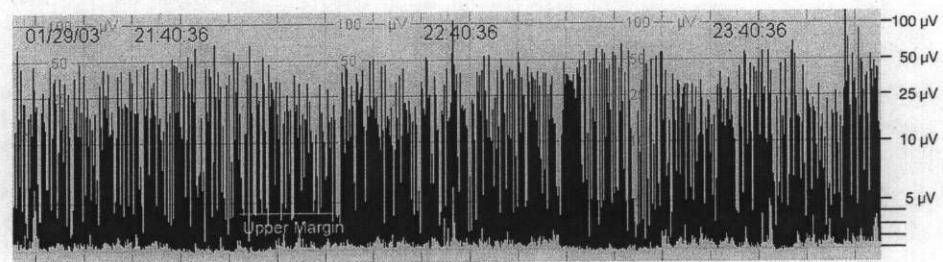
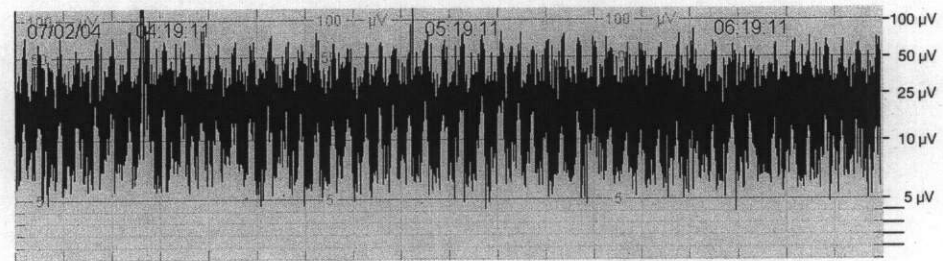
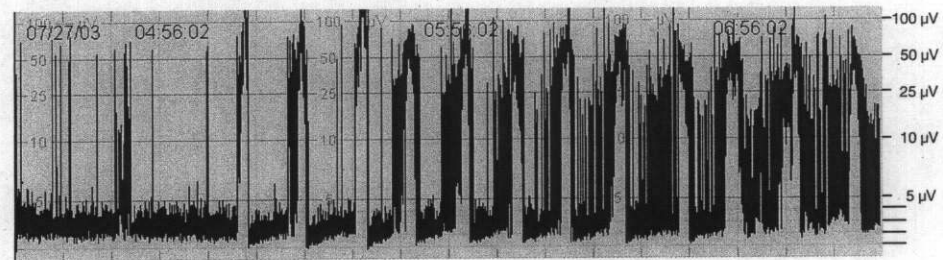





Figure 1.5 Seizures (S)



Conventions

The following conventions are used in this manual.

Table 1.1 Conventions

Convention	Description
Button	This character style represents buttons and controls that the operator can touch or press.
 NOTE	Notes provide additional information to clarify a point in the text.
 PRECAUTION	Precautions indicate situations that, if not avoided, could result in minor to moderate injury to the infant or operator, or damage to the equipment or other property. Precautions may also be used to alert against unsafe practices, including the special care necessary for the safe and effective use of the device and the care necessary to avoid damage to the device that may occur as a result of use or misuse.
 WARNING	Warnings indicate situations that, if not avoided, could result in serious injury or death to the infant or operator. Warnings may also describe potential serious adverse reactions and safety hazards to the infant.

Symbols

The following symbols are used on the Cool-Cap system, its accessories, and packaging.

Table 1.2 Icons and symbols








































Symbol	Definition	Symbol	Definition
	Alarm Solid – low priority Flashing – medium priority		Mains power OFF
	Alternating current (ac) voltage		Mains power ON
	Atmospheric pressure		Manufacturer
	Attention, dangerous voltage		Mouse port
	Attention, consult instructions for use; caution		Network port (Ethernet)
	Audio (for alarms)	N	Neutral (neutral conductor)
	Audio paused (for alarms)		Nonionizing electromagnetic radiation
	Authorized representative		Output (OUT main hose connection)
	Consult instructions for use; follow operating instructions		Protective earth (ground)

Table 1.2 Icons and symbols, continued

Symbol	Definition	Symbol	Definition
	Consult maintenance instructions (refer to the <i>Olympic Cool-Cap Service Manual</i>)		Reference number (reorder number)
	Direct current (dc) voltage	SN	Serial number
	Do not reuse (single use only)		Shipping
	Drain (water)	STERILE H₂O	Sterile water only
	Equipotential ground		Storage
	Fill (water)		Temperature limitation (low/high)
	Fuse		Temperature sensor, optional Note: Optional temperature sensor, such as esophageal, nasopharyngeal
	Humidity, condensing		Temperature sensor, skin/scalp
	Input (IN main hose connection)		Temperature sensor, rectal
	Serial in/out port		TempHeart®
	Keyboard port		Type B applied part
LATEX	Latex free		Type BF applied part
L	Line (hot conductor)		USB port

System Overview

Introduction

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 $34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ ($34.0^{\circ}\text{C} - 35.0^{\circ}\text{C}$).

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 $34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ ($34.0^{\circ}\text{C} - 35.0^{\circ}\text{C}$).

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

- Control unit
- Cooling unit
- Temperature sensor module and temperature sensors
- Cooling cap set
- Remaining accessories

Radiant Warmer

A commercially available radiant warmer is to be used with the Olympic Cool-Cap®.

The Cool-Cap System: Control and Cooling Units

Touch Screen

The touch-screen user interface:

- Displays infant data for use in monitoring infant condition.
- Allows user interaction with the system via buttons, drop-down lists, and other touch-screen controls.

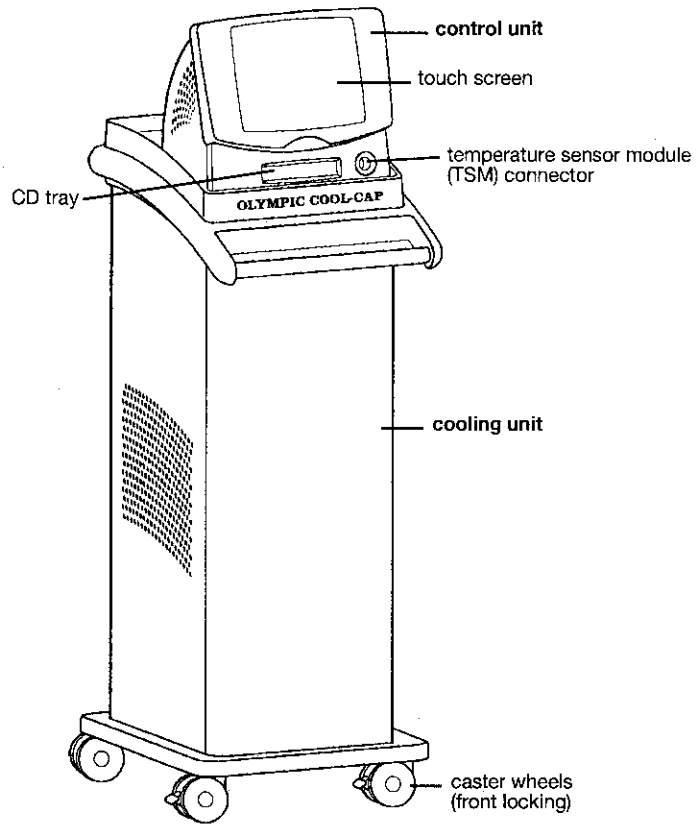
CD Tray

Provides access for updating and installing Cool-Cap software.

Temperature Sensor Module Connector

The temperature sensor module (TSM) plugs into this connector (see *Temperature Sensor Module* on page 1-10).

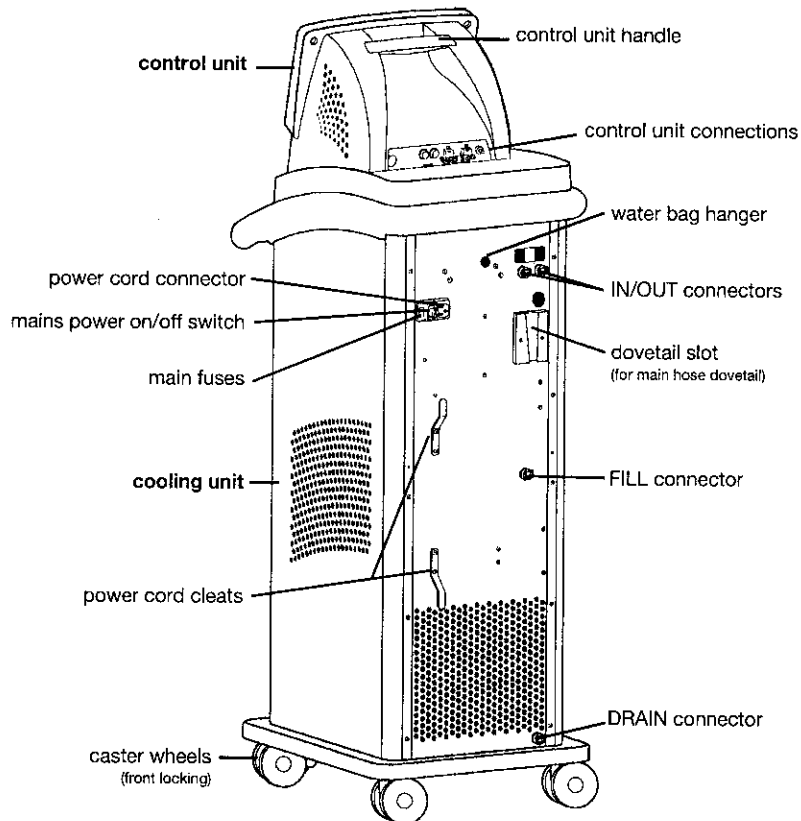
Figure 1.6 Front, Olympic Cool-Cap®



Locking Caster Wheels

When the two front caster wheels are locked, the cooling unit remains in place; when unlocked, the wheels allow the device to be easily moved.

Figure 1.7 Back, Olympic Cool-Cap®



Control Unit Handle

Allows for the control unit to be picked up off of the cooling unit for cleaning and repositioning.

Control Unit Connections

The following connections, listed left-to-right, are on the back of the control unit:

- **Main Connector:** Connects the control unit to the cooling unit (base).
- **Serial In/Out Port†**
- **Keyboard Port‡**
- **Mouse Port†**
- **USB Port†** (see the USB port caution on page 3-5)
- **Network/Ethernet Port†**
- **Equipotential Ground**

† Ports available but not currently active. Do not connect cables during treatment; see precautions on page 3-2.

‡ The keyboard port is only used for service.

Power Connection and Switch

The hospital-grade power cord plugs into the power connection on the back of the cooling unit. Next to the power connection is the mains power switch, which is used to turn the Cool-Cap system **On** (I) or **Off** (O). The main fuses are also located in this area.

Power Cord Cleats

Wrap the power cord around the cord cleats when the system is not in use.

Water Bag Hanger

Supports the 1-liter bag of sterile water on the back of the cooling unit.

Dovetail Slot

Point of attachment for the main hose:

- **On the cooling unit:** Slide the dovetail tab on the main hose into the dovetail slot to secure the main hose to the cooling unit. Connect the main hose to the IN/OUT connectors after securing the dovetail slot.
- **On the main hose support:** Slide the dovetail tab on the main hose into one of the six dovetail slots to secure the main hose to the main hose support (see Figure 5.8 on page 5-9).

IN/OUT Connectors

Point of entry/exit for the water through the main hose. When the main hose is connected and cooling is in progress, the cooled water circulates from the cooling unit to the main hose (blue connector) to the cap connector tube (blue) to the water cap, then back through the cap connector tube (red) through the main hose into the cooling unit (red connector).

FILL Connector

Point of entry for the sterile water to enter the cooling unit. Connect the 1-liter bag of sterile water to this connector via the spiked fill tube.

DRAIN Connector

After treatment is complete, drain the system by attaching the water bag and spiked fill tube to this connector (see *Shutdown Procedure* on page 5-27).

Accessories Overview

Temperature Connections

The temperature connections are used to monitor physiological and environmental temperatures during treatment.

Temperature Sensor Module

The temperature sensor module (TSM) relays temperatures from the temperature sensors to the control unit. During treatment, these temperatures are displayed on the screen.

Module Clip

The module clip attaches the TSM to the infant's bedding. This helps prevent the temperature sensors from being pulled out of place.

Figure 1.8 Temperature Sensor Module (TSM), with module clip

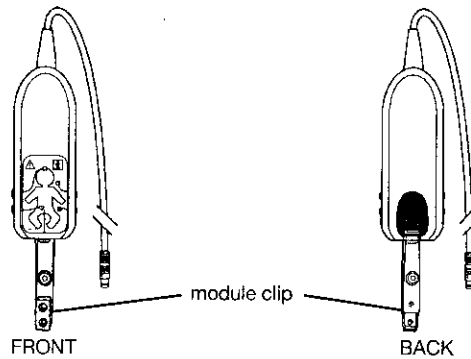
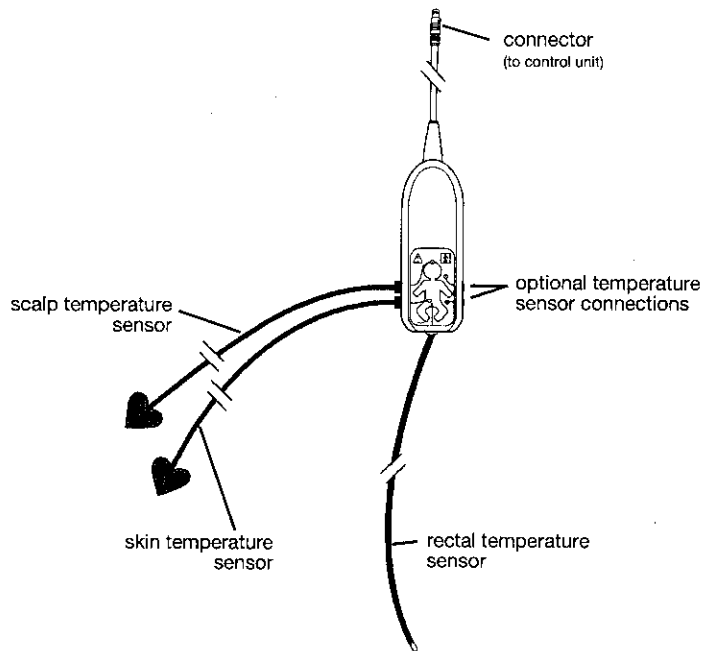






Figure 1.9 TSM, with sensors connected




 **Rectal Temperature Sensor**
The rectal sensor monitors the infant's rectal temperature; the goal is to maintain the rectal temperature at $34.5 \pm 0.5^\circ\text{C}$.

 **Skin/Scalp Temperature Sensors**
The skin sensor monitors the infant's skin (abdominal) temperature; the scalp sensor monitors the infant's scalp (fontanel) temperature.

 **NOTE** Position the scalp temperature sensor's TempHeart® so that the wires come out over the forehead.

 **Optional Temperature Sensors**
Optional sensors: esophageal, nasopharyngeal, or other

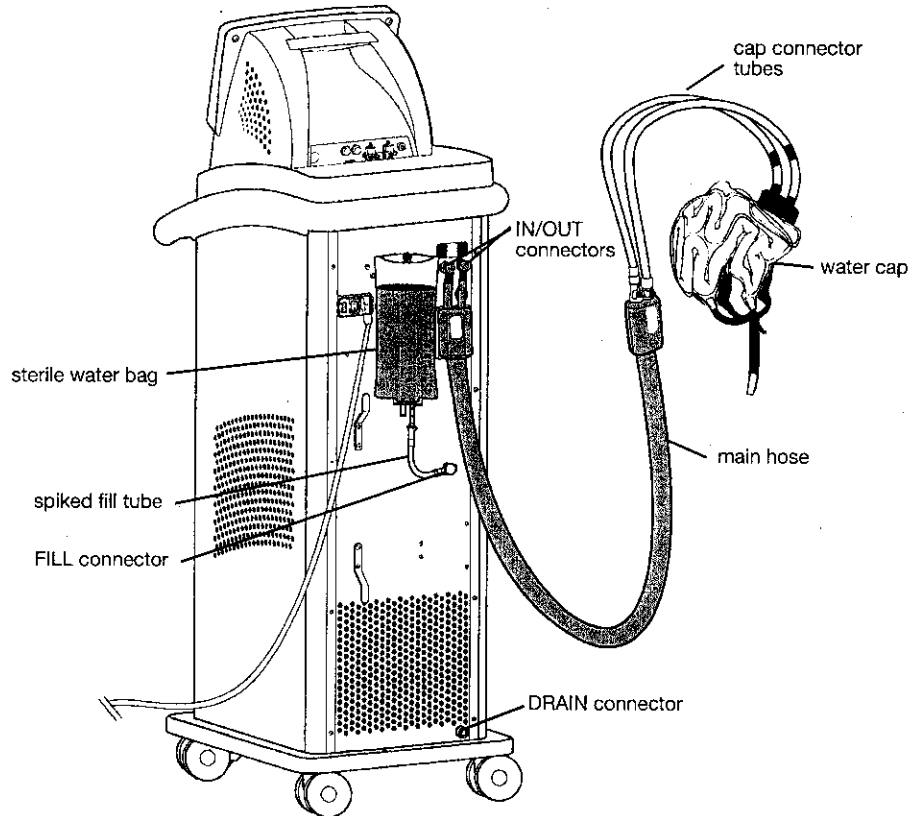
 PRECAUTION	<p>Only use YSI 4400 series compatible temperature sensors with this device. The optional sensors must be a YSI 4400 series medical temperature sensor or equivalent, and must have a demonstrated accuracy of $\pm 0.1^\circ\text{C}$ in the range of 25–45°C (i.e., equivalent to the accuracy of all temperature sensors provided by Olympic Medical with the Cool-Cap system).</p>
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45

Water Connections

During cooling treatment, the water connections cycle cooled water from the cooling unit to the water cap, which is on the infant's head.

Figure 1.10 Water connections—Cool-Cap accessories



Spiked Fill Tube

This reusable tube connects the 1-liter sterile water bag to the FILL connector on the cooling unit during treatment. After treatment is complete, the spiked fill tube is used to drain water from the cooling unit back into the water bag via the DRAIN connector.

Main Hose

This reusable hose connects the cooling unit (via the IN/OUT connectors) to the cap connector tubes. It is insulated to help keep the circulating water cool.

Cap Connector Tubes

These reusable tubes connect the main hose to the water cap. After treatment, the cap tubes are used to vent the water system during draining.

Water Cap

This disposable cap circulates cooled water over the infant's head. Its chin strap secures it in place.

Cooling Cap Set

The water cap circulates cooled water over the infant's head. The water cap retainer holds the water cap securely in place against the infant's head to assure maximum surface area contact between the water cap and the infant's scalp. The insulating cap reflects infrared heat away from the water cap (see Figure 1.11). The caps are available in three sizes: small, medium, and large; see Table 5.2 on page 5-9 for more information.

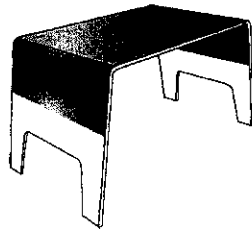
Figure 1.11 Complete cap set



Heat Shield

This plastic shield is placed over the infant's head to reflect heat from the radiant warmer and keep the infant's head cool.

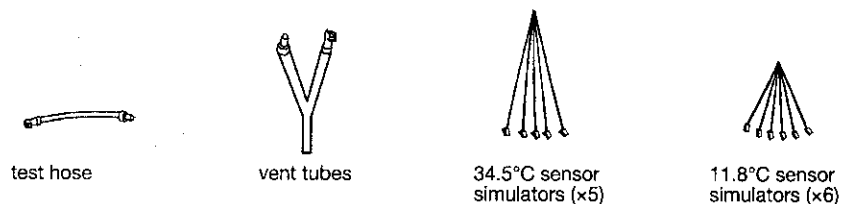
Figure 1.12 Heat shield



Test Kit

The test kit includes two sets of sensors that simulate temperatures (11.8°C and 34.5°C) and a test hose. For instructions on using the test kit, see *Testing the Cool-Cap System* on page 4-4.

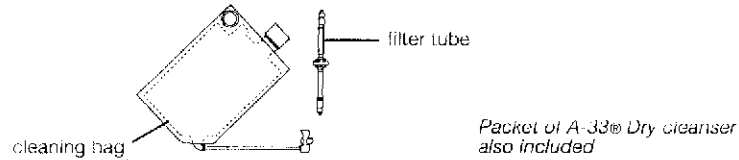
Figure 1.13 Test Kit



Cleaning Kit

The cleaning kit includes a cleaning bag, filter tube, and a packet of A-33® Dry cleanser. For instructions on performing the annual cleaning flush, refer to the *Olympic Cool-Cap Service Manual*.

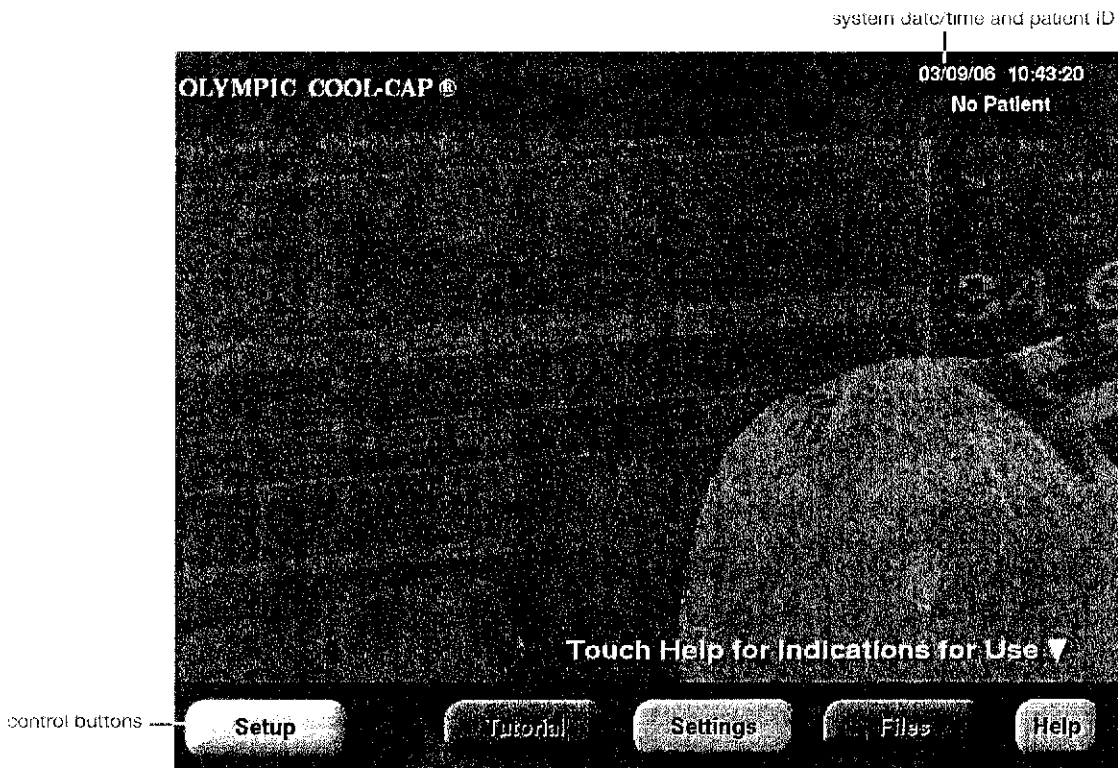
Figure 1.14 Cleaning Kit



User Interface: Touch Screens

Start Screen

Figure 1.15 Start screen



Patient Status and System Date/Time





Displays the patient ID (no patient) and the current date and time.

Control Buttons

The primary navigational buttons are described below. Additional information, including tips on using the Cool-Cap software, are included in the online help system; touch **Help** to access the topics.

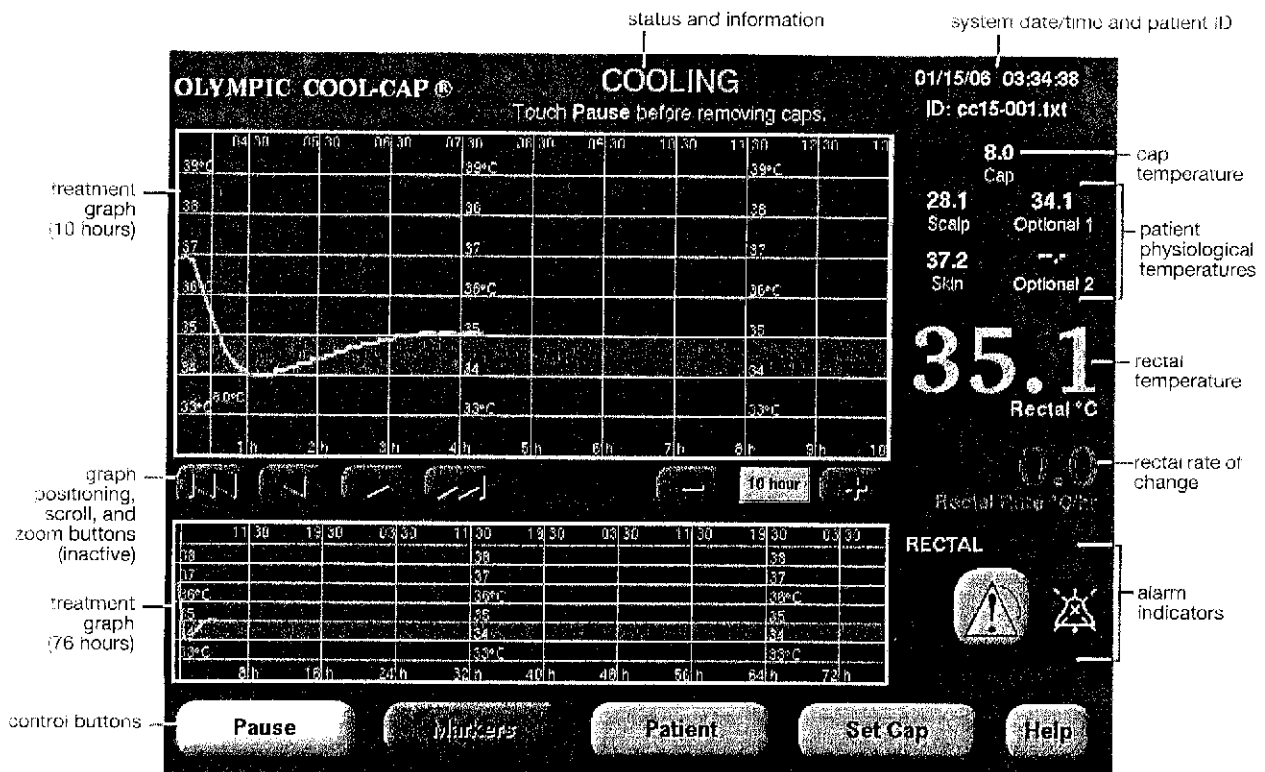


Touch **Setup** to begin a new cooling treatment and access the setup wizard (see *Instructional Wizard Pages* on page 1-18).

-  Inactive button.
-  Touch **Settings** to set the system date/time.
-  Inactive button.
-  Touch **Help** to access indications for use, contact information (emergency telephone number), the software version installed on the device, and help topics.

Main Screen

Figure 1.16 Main screen, cooling treatment



Patient ID and System Date/Time






Displays the infant identification, if entered, and the current date and time.

Control Buttons

The primary navigational buttons are described below. Additional information, including tips on using the Cool-Cap software, are included in the online help system; touch **Help** to access the topics.



When the system is cooling, touch **Pause** to maintain the internal system temperature and disable the alarms when the caps need to be temporarily removed for scalp checks and other medical treatments. (See Resume, below.)

-  **Resume** When the system is paused, touch **Resume** to exit the paused state. **Resume** is only available when the system is paused.
-  **Markers** Inactive button.
-  **Patient** Touch **Patient** to access a window that includes:
 - Infant data, clinical data, and notes
 - Labelling for the optional sensors
 - Emergency shutdown with choices to enter the rewarm or shutdown wizards or to power down
-  **Set Cap** Touch **Set Cap** to open a window that is used to adjust the desired cap temperature by $\pm 0.1^{\circ}\text{C}$.
-  **Help** Touch **Help** to access indications for use, contact information (e.g., emergency help line), the software version installed on the device, and help topics.

Status and Information

The status area shows the current status of the system (e.g., cooling, pause, rewarm) and provides informational messages (e.g., touch **Resume** to continue).

Temperature Graphs

The temperature graphs chart the rectal temperature of the infant. The top graph shows the most current 10 hours, while the bottom graph shows the full treatment period (i.e., 72-hour cooling and four-hour rewarm). The highlighted area (target zone) allows the user to quickly identify if the temperature is in the target range of $34 \pm 0.5^{\circ}\text{C}$.

Graph Positioning and Scroll Buttons

Inactive buttons.

Graph Zoom Buttons

Inactive buttons.

Patient Physiological Temperatures and Rate of Change

The infant temperature area shows the temperatures obtained from the temperature sensors in degrees Celsius ($^{\circ}\text{C}$). These include:

- **Rectal $^{\circ}\text{C}$:** Temperature from the rectal temperature sensor
- **Rate $^{\circ}\text{C}/\text{h}$:** Rate of increase or decrease of the infant's rectal temperature in degrees Celsius per hour
- **Skin $^{\circ}\text{C}$:** Temperature from the skin (abdominal) temperature sensor
- **Scalp $^{\circ}\text{C}$:** Temperature from the scalp (fontanel) temperature sensor
- **Optional 1 and Optional 2 $^{\circ}\text{C}$:** Temperatures from the optional** temperature sensors (for additional information, see *Temperature Sensor Module* on page 1-10). The displayed temperatures correspond to the sensors connected to the ① and ② connections on the TSM.

** Optional sensors: esophageal, nasopharyngeal, or other appropriate temperature sensor.

Cap Temperature

The water cap temperature displays in degrees Celsius (°C). The cap temperature is derived from the temperatures of the water coming in to and going out of the cooling unit via the main hose. Cap temperature is the average of IN and OUT.

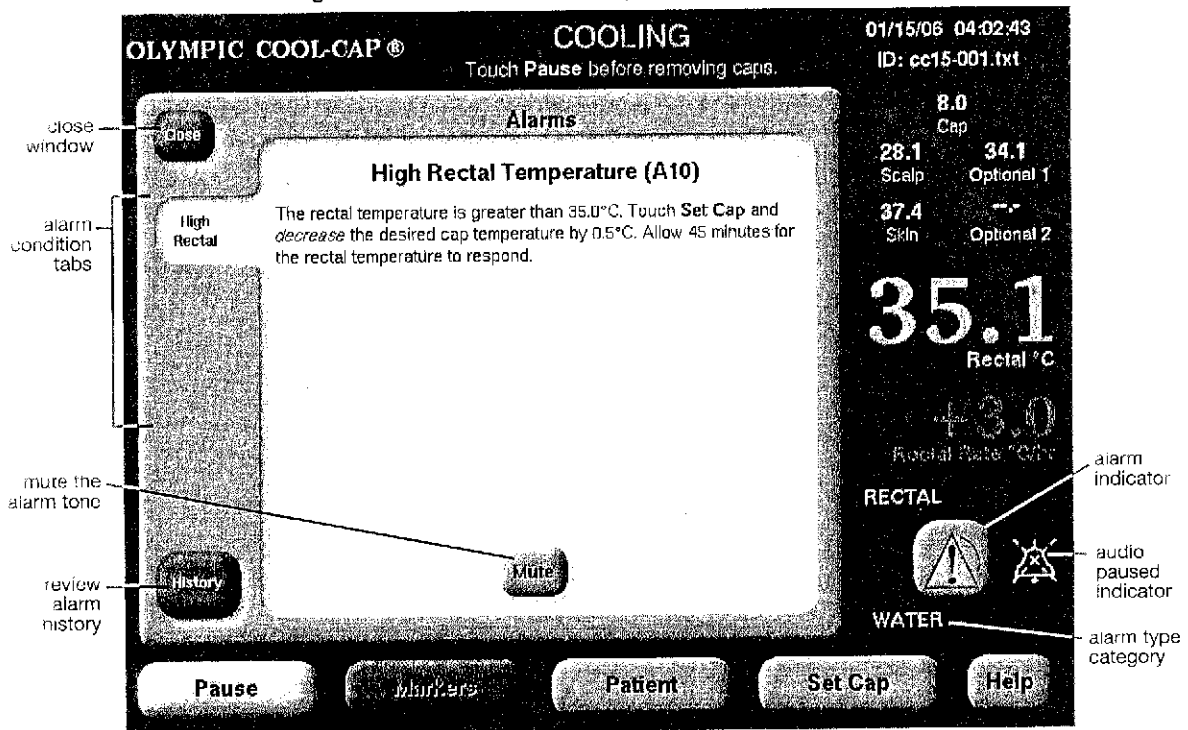
To change the cap temperature, see *Adjusting the Cap Temperature* on page 5-17.

Alarm Indicators

The alarm icons display when an alarm condition is active. Touch the alarm button (⚠) to open the alarm window (see Figure 1.17). A non-flashing alarm indicator indicates a low-priority alarm; flashing indicates a medium-priority alarm. The type of alarm category (rectal, water, cap, other) displays above and below the alarm indicator.

To silence the alarm, touch **Mute**; the audio paused symbol (🔇) displays on the main screen, indicating that the alarm is temporarily silenced.

Figure 1.17 Alarm window, example

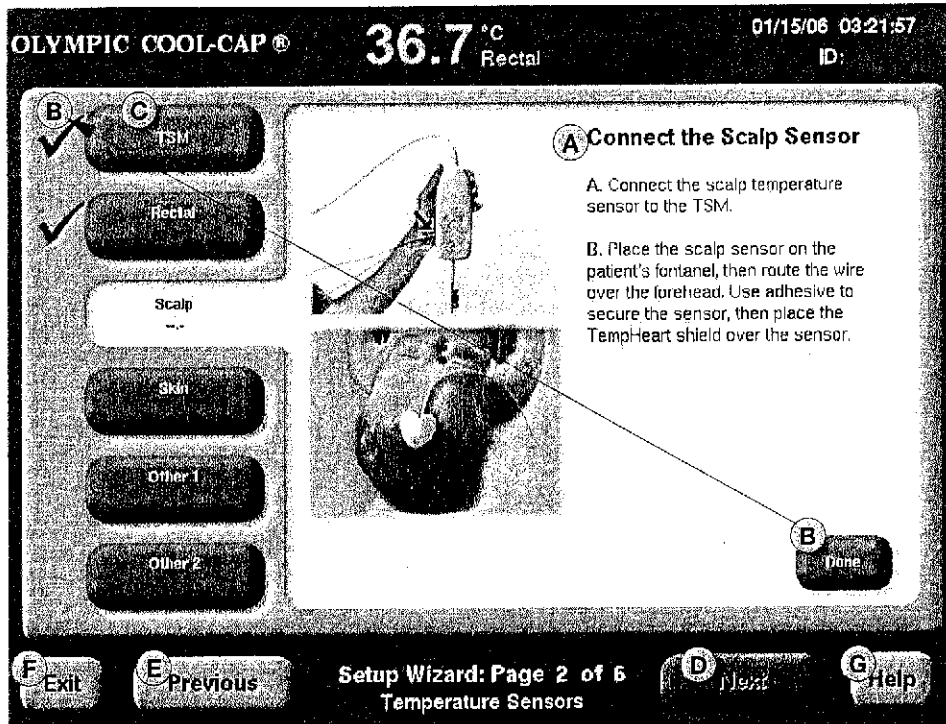


Instructional Wizard Pages

Wizards provide on-screen instructions for setting up cooling treatment, preparing for rewarm treatment, and shutting down the system.

As shown in Figure 1.18, the main text area of the wizard screens display photographic and written instructions. The instructions tell the user how to simultaneously prepare the infant and set up the system.

Figure 1.18 Sample wizard page, setup cooling treatment



To navigate the wizard:

- A** ■ Perform the tasks illustrated on the screen.
- B** ■ Touch **Done** to confirm that the tasks are complete, a check mark appears and the next task displays. Continue through each tab on that wizard page.
- C** ■ To preview or review tasks, touch the *vertically placed tabs/buttons*. When finished previewing or reviewing tasks, return to the first tab that has no checkmark (indicating that it hasn't yet been marked as done); once the task is complete, touch **Done**.
- D** ■ When all tasks on the wizard page are complete, **Next** becomes active. Touch **Next** to advance to the next wizard page. **Next** is inactive until all required tasks are marked with the done check mark.
- E** ■ Touch **Previous** to return to the previous wizard page.
- F** ■ Touch **Exit** to quit the wizard.
- G** ■ Touch **Help** to access the on-screen Help topics.

NOTE For additional information on navigating and using the software, touch **Help** and review the on-screen topics.

Clinical Trial Results

The following is a summary of safety and effectiveness data from the Cool-Cap clinical trial. Differences between the clinical trial and commercial configurations of Cool-Cap are described on page 2-8.

Trial Description

The Cool-Cap clinical trial was an international multicenter, prospective, randomized control study. Enrollment occurred July 1999 through January 2002, and follow-up was completed in September 2003. The outcome measure of severe neurodevelopmental disability was assessed by a blinded, independent observer.

In summary, within six hours of birth, after inclusion/exclusion criteria were met and informed consent was obtained, infants were randomized to either a non-cooled control group with rectal temperature maintained at $37.0 \pm 0.5^{\circ}\text{C}$, or to a treatment group for head cooling with mild systemic hypothermia with rectal temperature maintained at $34.0 \pm 0.5^{\circ}\text{C}$.

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 infant's core rectal temperature was maintained at $34.5 \pm 0.5^{\circ}\text{C}$ by adjusting the cap water temperature. The infant's rectal, nasopharyngeal, scalp (fontanel), and skin (abdominal) temperatures were continuously monitored. Also, metabolic, cardiovascular, pulmonary, and coagulation laboratory measurements were assessed at predefined time points. Cooling was maintained for 72 hours, followed by slow rewarming, with the goal of raising the rectal temperature to normal body temperature by 0.5°C per hour.

The trial had two primary research objectives:

- To determine whether treatment of moderate or severe hypoxic-ischemic encephalopathy (HIE) in term infants with head cooling and mild systemic hypothermia could produce meaningful improvement in neurodevelopmental outcome and survival rates at 18 months of age.
- To confirm the safety of prolonged head cooling with mild systemic hypothermia in term newborn infants with moderate or severe HIE.

Study Inclusion/Exclusion Criteria

For inclusion criteria, see *Indications for Use* on page 1-1. Exclusion criteria included the contraindications (see page 1-2) as well as infants who were:

- Greater than 5.5 hours of age at time of randomization.
- Receiving prophylactic administration of high-dose anticonvulsant (since this was considered a concurrent experimental treatment).
- Diagnosed with major congenital abnormalities.
- *In extremis*.
- Diagnosed with microcephaly.
- Participating, or going to participate, in a concurrent experimental treatment(s).

Infant Assessment

Prior to treatment, and as a component of the inclusion criteria, aEEG/CFM recordings were taken and analyzed by qualified personnel. During the 72-hour treatment, cardiovascular, hematologic, metabolic, blood chemistry, and temperature data were recorded.

At 18 months, infants completed the study with the following: neurodevelopmental examination; 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 completed.

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

Study Population

A total of 25 sites enrolled 235 infants in the clinical trial. One infant was withdrawn from the study due to inadequate consent resulting in a total infant count of 234. Of these 234 infants, 75% (176/234) were enrolled at sites in the United States and 25% (58/234) were enrolled internationally. The international enrollees were distributed as follows: 11% (26/234) in England, 9% (21/234) in Canada, and 5% (11/234) in New Zealand.

Baseline infant characteristics were generally well balanced with the exception of Apgar score at five minutes after birth and aEEG/CFM background (both had more severely affected infants in the cooled group).

Safety

Since all except one of the anticipated Adverse Events (AEs) (i.e., evidence of skin breakdown due to pressure of cooling cap; see Table 2.1) could be consequences of hypoxia-ischemia, detailed statistical testing was essential to determine whether cooling could be a contributing factor. Two-sided p values less than 0.05 are considered statistically significant.

The study was not designed to detect a statistically significant difference with respect to some rare adverse events. As shown in Table 2.1, 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. Note, however, that none of the cooled infants experienced a major cardiac arrhythmia.

Scalp edema also 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.

For the AE of elevated liver enzymes, the incidence in cooled infants (38% or 42/112) was lower than that in control infants (53% or 62/118) with statistical significance ($p=0.02$).

Table 2.1 Analysis of device safety based on occurrence of adverse events (n=230; entire 234 population excluding four infants 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

Table 2.1 Analysis of device safety based on occurrence of adverse events, continued (n=230; entire 234 population excluding four infants randomized to cooling but not cooled)

AE Code	Adverse Event	Cooled (n=112)		Control (n=118)		Fisher's Exact p Value
		n	%	n	%	
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*
	■ Head/scalp edema	23	21%	1	1%	<0.0001*
	■ Other AEs, excluding head/scalp edema	28	25%	25	21%	0.53

*Statistically significant finding (p is less than 0.05)

With regard to mortality, as shown in Table 2.2, there was no evidence that the death rates 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.

Table 2.2 Mortality rates for enrolled population (n=234)

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

As shown in Table 2.3, the majority of the deaths (68% or 53/78) occurred within seven days after randomization. Deaths during this time included 26 in the control group (33% or 26/78) and 27 in the cooled group (35% or 27/78). Note, however, that four of the infants in the cooled group were not actually cooled; thus, only 23 infants who received the cooling treatment died within seven days of randomization.

Table 2.3 Distribution of infant 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

Although not statistically significant, there was an increased number of deaths in the cooled group on Days 4–5 following three days of cooling treatment (11 cooled infants and 2 control group infants).

Although not a statistically significant finding, the time of death shifted by several days in the cooled group. This shift is probably a consequence of the unmasked trial of a novel therapy; attending physicians likely delayed withdrawal of care for a few cooled infants until the treatment period had been completed. Perhaps more importantly, this data demonstrates that care can still be withdrawn from infants with profound HIE even if withdrawal is delayed from the first three days to the fourth, or even later, day of life.

Potential adverse events during hypothermia treatment to prevent or reduce the severity of neurologic injury associated with hypoxic-ischemic encephalopathy include the following:

- Mild sinus bradycardia may occur during hypothermia treatment.
- One patient in the trial was noted to have elevated clonazepam levels. Hypothermia may inhibit the metabolism and clearance of anticonvulsants (including phenobarbitone, phenytoin, lidocaine, and the benzodiazepines) potentially prolonging their half-lives; therefore, whenever possible, measure the infant's blood levels and administer repeated doses with caution.
- One 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 Application (PMA) was being evaluated by the FDA, a continued access trial was approved on April 26, 2003. In that trial, two patients developed seizures on rewarming. One patient in the continued access trial developed sclerema neonatorum. Sclerema neonatorum has been associated with hypothermia. Sclerema neonatorum — a generalized swelling and hardening of the skin, which is characterized by stony consistency that is cold and non-pitting — is an uncommon disorder that may be associated with hypothermia. In the rare instance that it may occur, it may be characterized by an abrupt onset that may progress to generalized involvement in four days; however, there are not any reported long-term sequelae from this condition and it usually resolves within two weeks. No specific management has been shown to alter the course of sclerema neonatorum once it has begun and, in particular, at present there is no evidence that rewarming will improve the condition.

Effectiveness

As shown in Figure 2.1 on page 2-7, 18-month primary outcome results were available in 93% (218/234) of the infants; primary outcome results were unavailable for 7% (16/234) of the infants. Of the 16 infants for whom primary outcome results were unavailable, three control infants and one cooled infant were known to be alive. However, datasets for these four infants were incomplete for primary outcome assessment. This accounts for the difference in number of unknowns for mortality rates (n=12) as compared to primary outcome (n=16).

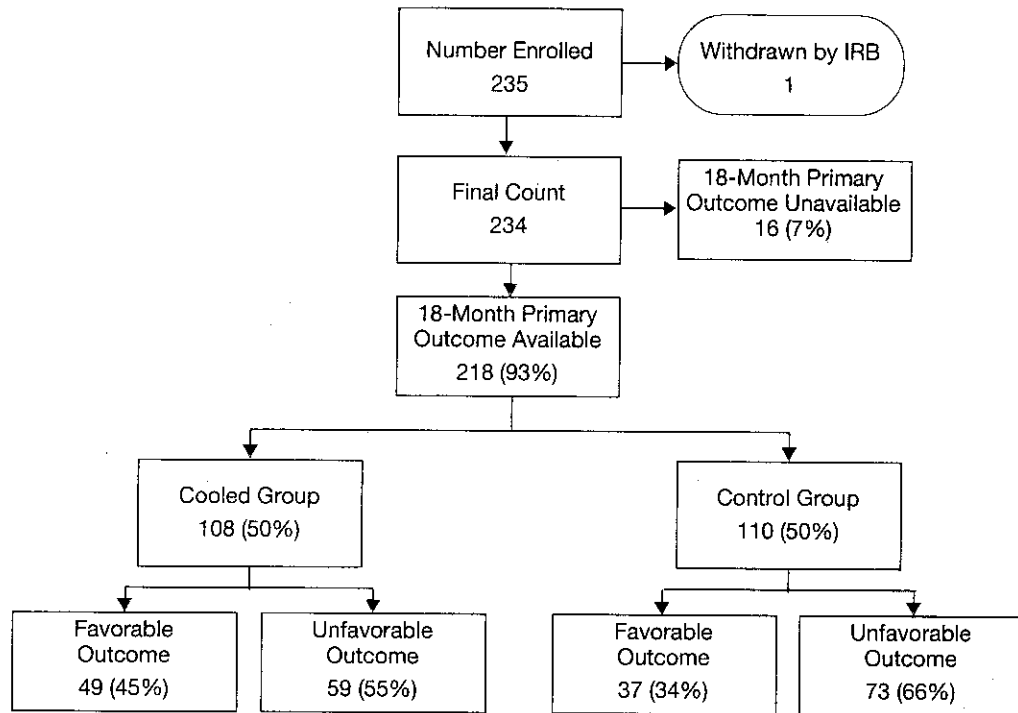
Of the 218 infants, 50% (110/218) were in the control group and 50% (108/218) in the cooled group. The control group had a favorable outcome of 34% (37/110),

while the cooled group had a favorable outcome of 45% (49/108). Fisher's exact test showed no statistical significance ($p=0.10$; 11% difference, 95% confidence interval -1% to 25%).

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). The study protocol included a planned logistic regression analysis. A 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 ($p=0.042$; odds ratio 0.53, 95% confidence interval 0.29-0.98).

Therefore, it was concluded that, in full-term neonates with moderate to severe HIE, selective head cooling with mild systemic hypothermia, when administered with the Olympic Cool-Cap® in the manner described, is associated with a reduction in the combined endpoint of death and severe neurodevelopmental disability.

Figure 2.1 Primary outcome (death and severe neurodevelopmental disability in survivors at 18 months of age) for infants for whom 18-month primary outcome is known ($n=218$)



Fisher's Exact Test for Primary Outcome: $p=0.10$

However,

37% (40/108) of cooled group had a severe aEEG baseline
28% (31/110) of control group had a severe aEEG baseline

So, adjusting for baseline aEEG background, aEEG seizure status,
Apgar score, birth weight, gender, and age at randomization:

Logistic Regression Analysis: $p=0.042$
(statistically significant treatment effect)

Patient Discontinuation and Complaints

Due to the patient population (newborns), patient complaints were not applicable to this clinical study. Eighty-four percent (196/234) of the patients completed the prescribed acute treatment period (72 hours from randomization): 86% (100/116) in the cooled group and 81% (96/118) in the control group. Most of the patients who died following discontinuation of the acute study treatment (64% or 23/36) had death or *in extremis* reported as the reason for treatment discontinuation. This included 7% (8/116) of the cooled group and 13% (15/118) of the control group.

Clinical Device Failures and Replacements

A total of 11 reported failures were attributed to clinical equipment issues as opposed to operator error or environmental conditions. Five of these were corrected in the field; six were resolved by replacing the equipment. Only one infant of the 235 enrolled was not treated due to an equipment failure.

The most common error (55% or 6/11) involved a pinch valve that controlled water flow into the system from the 1-liter bag of sterile water. This problem could generally be resolved in the field. The pinch valve has been eliminated from the new Cool-Cap system. The remaining reported failures were random electrical or mechanical component failures.

Clinical Trial and Commercial Device Configurations

With advances in technology and the obsolescence of a few device components (i.e., the microprocessor), the commercial configuration of Cool-Cap was designed with significant improvements to the user interface (i.e., screen). A full-color graphic display allows temperature trend graphs, instructional photographs, context-appropriate prompts, and touch-screen control buttons. This is a significant improvement over the clinical trial device's seven-segment light-emitting diode (LED) display, push buttons, and printed study manual. Note, however, that the key functional components of the commercial version of Cool-Cap remain unchanged from the clinical trial device: cap design, water flow rate, cooling system (Peltier devices), and cooling control algorithm.

Conclusions

Neonatal HIE is a difficult condition for which there has been no FDA-approved treatment. A significant number of those infants afflicted with moderate to severe HIE have a very poor outcome with death or severe neurodevelopmental disability. Poor outcome is devastating to families, with enormous emotional and economic cost.

There are potential benefits of neuroprotective treatment for HIE but the risks associated with Cool-Cap are minimal. Although mild sinus bradycardia and scalp edema occur in higher frequencies in treated infants, these conditions are not life-threatening. Overall mortality rates were not significantly different in the treated group than in the control group. Furthermore, all deaths were reviewed by

the trial's medical officer and determined to be unrelated to Cool-Cap or to the trial protocol.

Conclusions

Warnings and Precautions



Treatment Parameters:

- Cooling and rewarming outside of the suggested parameters may result in potential unknown adverse effects beyond those discussed in the Warnings and Precautions.

Cooling:

- Hypothermia can inhibit the metabolism and clearance of many anticonvulsants (including phenobarbitone, phenytoin, lidocaine, and the benzodiazepines) potentially prolonging their half-lives; therefore, whenever possible, measure the infant's blood levels and administer repeated doses with caution.
- Hypothermia inhibits antimicrobial activity. It is important to take appropriate cultures and initiate antibiotic treatment even in infants with apparent HIE since the diagnosis can occasionally be confounded by peripartum sepsis.
- Hypothermia has anticoagulant effects. Correct hemorrhagic diathesis (e.g., fresh frozen plasma) before initiating hypothermia.

Over-Cooling:

- At very low temperatures (30–32°C) hypothermia may increase pulmonary hypertension.
- Avoid over-cooling infants, particularly very sick infants. Carefully manage ventilation and other therapies while cooling very sick infants.
- If an infant is markedly overcooled (~32.0°C), they may reduce their peripheral circulation in an attempt to conserve heat. This will reduce the effectiveness of the radiant warmer, thus increasing the problem. Should this occur, remove the cap and carefully rewarm the infant <0.5°C per hour until the infant is within the target range. Then resume cooling using the previous or a slightly higher cap setting.

Rewarming:

- Small, full-term infants weighing under 2.5 kg may require special attention during rewarming. Watch carefully for cardiovascular instability. Treatment of infants less than 1.8 kg is contraindicated.
- Ensure that the infant does not rewarm at more than 0.5°C per hour when re-exposed to the full force of the radiant warmer. Rewarming too quickly can cause vasodilation and hypotension in an unstable infant. Furthermore, animal studies suggest that rewarming too quickly may, in some cases, be associated with seizures.



Power, Fuses, and Ports:

- **Electrical shock hazard.** Connect the cooling unit to a properly grounded hospital-grade electrical outlet. For electrical requirements, see page 9-1.
- To avoid electrical shock hazard, turn off the device and unplug the power cord before cleaning the device.
- For protection against fire hazard, replace only with the correct type and rating of fuse.
- To avoid electrical shock hazard, ensure that the cover is securely placed over the USB port connector when not in use, and never touch the connector and infant simultaneously.

General Device Use:

- **Explosion hazard.** Do not use in the presence of flammables (e.g., oxygen, nitrous oxide, anesthetics).



Assembly and Use:

- Read and be familiar with this manual before assembling and operating this device. To ensure operator, technician, and infant safety, use only as specified in this manual.
- This device should only be used by properly trained personnel (see *Training* on page 1-3) and under the direct supervision of a licensed physician.
- Only qualified technicians should assemble, maintain, and service this device.
- Only use Olympic Medical-approved parts with the Cool-Cap system.

Treatment Guidelines:

- Hypothermia treatment should be according to the following protocol:
 - Maintain the rectal temperature within the range of $34.5 \pm 0.5^{\circ}\text{C}$,
 - Maintain cooling treatment for 72 hours, and
 - Active rewarming should not exceed 0.5°C per hour.

Set Up for Infant Monitoring:

- Inspect the Cool-Cap system before each use to ensure proper functioning.
- Keep the caster wheels locked during treatment to prevent the device from pulling on the water and temperature connections.
- Prior to use, check the packaging integrity and shelf life of the accessory temperature sensors per the manufacturer's recommendations.
- Only use YSI 4400 series compatible temperature sensors with this device. The optional sensors must be a YSI 4400 series medical temperature sensor or equivalent, and must have a demonstrated accuracy of $\pm 0.1^{\circ}\text{C}$ in the range of $25\text{--}45^{\circ}\text{C}$ (i.e., equivalent to the accuracy of all temperature sensors provided by Olympic Medical with the Cool-Cap system).
- Only use sterile water in the cooling unit to help prevent corrosion.
- Do not connect cables to the control unit's input/output ports (see *Control Unit Connections* on page 1-9) during treatment. Doing so may result in electromagnetic interference that may interrupt treatment.

Laboratory Considerations:

- Correct all blood gases and pH values for core temperature.

CONT'D



General Infant Care:

- Be aware that the device monitors only the infant's temperature but that multiple factors, in addition to the device, will influence the infant's temperature and condition. Frequent infant assessments should be performed and taken into consideration when making clinical treatment decisions.
- Remove diapers from infants undergoing treatment to allow maximum body exposure to the radiant warmer, and to allow for checks for meconium and/or a dislodged rectal temperature sensor.
- Do not blow or circulate air over the infant. Convection caused by circulating air results in loss of heat from the infant—even if the air is warm.
- Do not initiate oral feeding during the cooling and rewarming processes of treatment.

Potential Adverse Effects of Hypothermia:

- Hypothermia is known to increase oxygen consumption. Therefore, some infants may show a small increase in their oxygen requirement during the induction of hypothermia and require appropriate adjustments.
- Transient hyperglycemia may occur during hypothermic treatment.
- Hypothermia may produce prolongation of the QT interval in infants with bradycardia but should normalize after cooling. Be cautious with other treatments that may further prolong the QT interval (e.g., drugs and electrolytes) and monitor the QT interval until it normalizes.

Considerations for Cap Temperature Adjustments:

- Anticipate changes in temperature due to medication administered; anticonvulsants are likely to lower the rectal temperature and may require an increased cap water temperature. For the first dose of anticonvulsants, always increase the desired cap temperature by 0.5°C at the time of drug administration.
- Full-term infants with a birth weight of less than 2.5 kg and/or infants with cardiac compromise requiring inotrope support may require a higher cap temperature during the initial cool down and should be closely monitored. Make temperature adjustments early to avoid overshooting (i.e., reaching a lower than desired rectal temperature). Treatment of infants less than 1.8 kg is contraindicated.
- When adjusting the desired cap temperature, consider the infant's size, condition, medication, anticipated procedures, and rectal temperature trends, to maintain the rectal temperature in the target range.
- The infant's temperature takes approximately 45 minutes to stabilize after the cap temperature has been adjusted. Allow time for adjustments to take effect to avoid overcompensation. In general, avoid changing the cap temperature by more than 1.0°C at a time.
- Monitor the infant's metabolic rate during treatment. Core temperature will increase in infants who are upset, jittery, or shivering. Core temperature will decrease in infants who are quiet and sleeping. These changes in core temperature may require a change in cap temperature.

CONT'D



Skin Integrity:

- Use the cap set only on unbroken skin, or cover lesions per standard medical practices.
- To avoid interference with cooling or the creation of pressure points, only the scalp temperature sensor and its TempHeart® should be placed under the water cap.
- Remove the cooling cap set every 12 hours and carefully inspect the infant's scalp and any skin in contact with the chin strap for irritative injury that may relate to the cap's use. Infants with hypotension or disseminated intravascular coagulation (DIC) are likely to be at greater risk of scalp injury. Use of a larger cap size during cooling may help reduce scalp edema. In cases of local erythema, it is reasonable to briefly maintain the infant at the target rectal temperature with the cap off to give the scalp a chance to recover before reseating the caps and continuing with head cooling. If the erythema does not resolve, reseat the caps but recheck the scalp after 6 hours, then return to the every 12-hour check. It may sometimes be necessary to loosen the chin strap as edema develops; this may help prevent excess tension on the strap.

Punctures and Leaks:

- If water leaks are present, reseat the leaking component (i.e., cap tubing, main hose, spiked fill tube) or replace the leaking water cap. Never use punctured or damaged water caps, tubing, or hoses.

Pausing Treatment:

- The treatment alarms (i.e., physiological and cap) are inactive, or silenced, when the system is paused. Frequently monitor the infant when alarms are silenced.
- If the cap was removed while the system was paused, before resuming cooling treatment place the:
 - Complete cap set back on the infant's head, and the
 - Heat shield over the infant's head, to the chin level.Failure to correctly place the cap set and heat shield before resuming cooling treatment may result in overheating the infant.

Heat Shield:

- During cooling treatment, the heat shield must be in place to block infrared radiation, which is produced by the radiant warmer, from the infant's head and neck.
- The heat shield must rest evenly and directly on the mattress.
- Do not block the front and back openings of the heat shield.
- Route the cap connector tubes and temperature sensor cables so the heat shield can be removed without disturbing the connections.

Radiant Warmer:

- Do not use the radiant warmer in manual mode as it will make the infant's temperature less stable.
- Do not set the radiant warmer servo temperature above 37.5°C to prevent overheating the infant.
- During rewarm, regularly check the infant's rectal temperature between the 30-minute servo adjustments.

Rewarming:

- Larger infants may require less heat to rewarm or may rewarm faster than 0.5°C per hour, despite the radiant warmer setting. Closely monitor these infants.

CONT'D



PRECAUTION

Shutdown and Clean Up:

- Only technically qualified personnel should perform maintenance procedures.
- To prevent contamination, perform cleanup procedures after each use.
- Drain the system after each use to help prevent corrosion.
- Do not allow cleaning solutions to enter the enclosures as this may damage internal components.
- External surfaces must be wiped clean with a liquid disinfectant that is compatible with plastics. Use of sodium hypochlorite (bleach) may damage the instrument surfaces. Use only mild cleaning detergents; other cleaning agents may damage the exterior of the Cool-Cap system. Dilute cleaning agents according to their label instructions. Use of improper cleaners (e.g., corrosives) will void the warranty.
- Do not reprocess (i.e., gas sterilize, autoclave, pasteurize) the main hose, cap tubing, and spiked fill tube as this may shorten their reusable life.
- Discard the disposable items according to your facility's guidelines. Single-use items are not safe for re-use and must be properly disposed of to prevent a biohazard.

Electromagnetic Interference:

- Use of electrical field radiating equipment may adversely affect the operation of the system; keep electrosurgical cables and communication devices at the recommended distance (see page 9-5).
- Do not connect cables to the control unit's input/output ports (page 1-9) during treatment. Doing so may result in electromagnetic interference that may interrupt treatment.

USB Devices:

- To meet electrical safety requirements, USB line-connected devices used with the Cool-Cap system must meet the requirements of IEC 60601-1. Alternately, if the line-connected device is approved to an appropriate national standard other than 60601-1, a separation device must be used (refer to IEC 60601-1-1).