OrganOx® *metra*®
INSTRUCTIONS FOR USE

Contents

Abbreviations

GUI	Graphical User Interface
HTK	Histidine-tryptophan-ketoglutarate solution
IVC	Inferior Vena Cava
K^+	Potassium
ml/h	Millilitres per Hour
mmHg	Millimetres of Mercury (Pressure)
mg/dl	Milligram per Decilitre
NaCl	Sodium Chloride
pCO_2	Partial Pressure of Carbon Dioxide
pH	Measure of the molar concentration of Hydrogen ions in the solution
pO_2	Partial Pressure of Oxygen
PRC	Packed Red Blood Cells
UW	University of Wisconsin solution

Section One: General Introduction

Introduction

The OrganOx® *metra*®, also referred to as OrganOx *metra* throughout this manual, is a transportable medical device intended for normothermic perfusion of donor transplant livers for up to 24 hours.

Read this manual carefully before operating the device, if you have any further questions, please contact the OrganOx toll-free customer support number at 855-ORGANOX (855-674-2669).

 *WARNING: The OrganOx metra has been designed for use as a liver preservation device it must not be used for any other organs.*

 *WARNING: The OrganOx metra has not been certified for Air Transport.*

Indication and Contraindications

The OrganOx® *metra*® is a transportable device intended to be used to sustain donor livers destined for transplantation in a functioning state for a total preservation time of up to 12 hours.

The OrganOx® metra® device is suitable for liver grafts from donors after brain death (DBD), or liver grafts from donors after circulatory death (DCD) ≤40 years old, with ≤20 mins of functional warm ischemic time (time from donor systolic blood pressure <50 mmHg), and macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

The OrganOx® metra® device should not be used for:

- Living donor livers
- Livers intended for split transplant
- Livers with moderate or severe traumatic injury

Cybersecurity

 *WARNING: The OrganOx metra is protected against attack, damage or unauthorized access. The software on the device cannot be altered by the user or any unauthorized parties either directly or remotely. Modification to the software or hardware of the device is only to be undertaken by authorized parties with access to the locked enclosure. Any unauthorized modification of the installed software will initiate a failsafe condition preventing code execution during runtime. In this condition the device will not start.*

Skills, Training and Knowledge Requirements

The user population has been defined by OrganOx Ltd as appropriately trained liver transplant surgeons and transplant technicians.

THE ORGANOX *METRA* IS ONLY INTENDED FOR USE BY SUITABLY TRAINED MEDICAL PERSONNEL. FULL TRAINING ON THE INSTALLATION AND USE OF THE DEVICE WILL BE GIVEN BY ORGANOX LTD PRIOR TO THE FIRST PROCEDURE.

BEFORE YOU SET UP OR OPERATE THE ORGANOX *METRA*, IT IS ESSENTIAL THAT YOU HAVE ATTENDED ONE OF THE ORGANOX TRAINING COURSES AND HAVE BEEN CERTIFIED IN THE USE OF THE DEVICE, CERTIFICATES WILL BE ISSUED BY ORGANOX LTD FOLLOWING SUCCESSFUL TRAINING. IT IS ALSO IMPORTANT THAT YOU HAVE READ AND UNDERSTOOD THIS INSTRUCTION MANUAL. TO ARRANGE TRAINING OR RE-TRAINING PLEASE CONTACT ORGANOX AT 855-ORGANOX (855-674-2669)

IT REMAINS THE SURGEON'S AND SURGICAL TEAMS' RESPONSIBILITY TO DECIDE WHETHER A LIVER PRESERVED ON THE ORGANOX *METRA* IS SUITABLE FOR TRANSPLANT INTO A RECIPIENT.

The following section outlines the steps involved in the operation of the OrganOx *metra* in the recovery and perfusion of a donor liver.

Each use of the OrganOx *metra* requires:

1. The OrganOx *metra* Retained Unit
2. An OrganOx *metra* Disposable Set
3. Perfusion Solutions
4. Leuko-reduced packed red blood cells
5. Terumo CDI®540 calibrator; gas bottles and shunt sensor

 *CAUTION: The OrganOx metra Disposable Set is supplied in a cardboard box and comprises sterile components.*

 *CAUTION: DO NOT forget to take the Terumo Calibrator Unit with you each time you use the OrganOx metra.*

 *CAUTION: It is the responsibility of the retrieval team to ensure all of the Perfusion Solutions required are sourced and taken to each organ retrieval.*

Cleaning, Packaging of the Retained Unit

 *CAUTION: The OrganOx metra is a fragile medical device and must be handled with care both with and without a liver on board. The device weighs greater than 165 pounds. It should only be lifted from its trolley provided that a minimum of three (3) suitable people are available*

 *CAUTION: Do not clean whilst the device is connected to a power supply*

 *CAUTION: Do not clean whilst the device is turned on*

 *CAUTION: Do not allow cleaning fluid to enter the rear panel electrical connectors, the ventilation holes or the battery area*

 *CAUTION: Do not fully immerse the device*

 *WARNING: The operator must wear surgical gloves whilst operating this device*

The reusable OrganOx *metra* components include a Retained Unit set on a trolley with a removable hard cover. It is important that each of these device components be thoroughly cleaned prior to the first and each subsequent use.

The Retained Unit, trolley and exterior of the removable hard cover should be inspected for damage and cleaned before entering the operating theatre. If there are any signs of damage, the device should not be used, and any damage should be reported to OrganOx at 855-ORGANOX (855-674-2669).

The cleaning is then achieved using CaviWipes® (https://www.metrex.com/en-us) or similar cleaning product containing the active ingredients 17.2% Isopropanol and 0.28% Diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride.

Component Cleaning:

- Using a CaviWipe®, wipe up and down over the contaminated area 10 times.
- Fold the ClaviWipe® in half.
- Wipe left and right over the contaminated area 10 times.
- When cleaning the grooves and joints, repeat the cleaning procedure with an additional two fresh wipes.
- Inspect the device components with a magnifying glass (5-10x), and if not visibly clean, repeat cleaning procedure with one or more fresh wipes.
- Once visibly clean, leave the device to fully dry at room temperature.

If difficulty is encountered in obtaining visibly clean component surfaces, the use of a small toothbrush-style cleaning brush is recommended to facilitate the cleaning of these areas.

SECTION OF THE RETAINED UNIT/TROLLEY	RELATED AREA
Tower Top Surface	Pivot end and recess for blood bag prop Corner crevices and screw heads in/around the water inlet area
Right hand side of the tower	Inside the bile pinch valve and sensor Where the tower meets the base
Right hand side of the base plate	In the IVC flow sensor cannula holder and lid connection point
Back of the tower	Gaps around the Terumo monitor Edges of the tower back door

Left hand side of tower	Lip around the water inlet area
Front of the tower	Syringe driver main screw thread and holding recesses Slot on the glucose level knob Recessed rim of the blood pump
Terumo sensor and lead	Plastic joints Rear of sensor Connection between lead and sensor
Pressure sensor connectors	Connection to OrganOx *metra*
Bottom skirting	Inside cover clips Inside the sockets
Mains inlet panel	Around the mains inlet switch Inside the mains inlet IEC socket
Handrail and trolley	Rotating clasps on trolley and device Crevices and gaps on the trolley wheels

PACKAGING OF THE ORGANOX *METRA* DISPOSABLE SET

The Disposable Set is single-use, pre-sterilized and packaged as a complete set. If there is visible damage, the set should not be used and any damage should be reported to OrganOx, at 855-ORGANOX (855-674-2669).

LIFTING THE RETAINED UNIT

WARNING: THIS DEVICE WEIGHS GREATER THAN 165 POUNDS AND NECESSITATES A THREE (3) PERSON LIFT. SEEK FURTHER ASSISTANCE FOR LOADING IF NECESSARY.

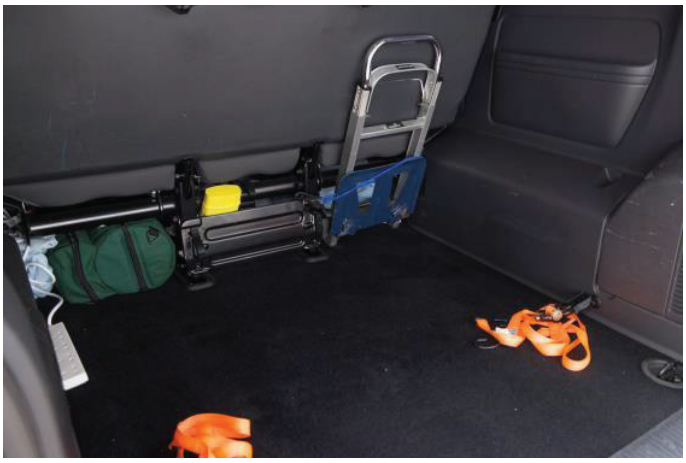
You can protect yourself from injury by following correct lifting principles:

- Bend from your knees, not your back
- Keep your feet wide to provide a stable base
- Keep breathing
- Keep the object close to your body
- Do not twist your back whilst carrying the load
- Bend from your knees to lower the object down

Always first detach the Retained Unit from its trolley by unfastening the two metal clasps counterclockwise before lifting.

SECURING THE ORGANOX *METRA* DURING TRANSIT

Position the device with or without the trolley in the center of the van/medical vehicle. If it is possible for the device to slide or topple during transit, it will need to be secured before transit. Check that all of the anchoring points are accessible.



Place one strap around the handrail, ensuring that it tucks against one of the vertical pillars on the handrail to prevent sliding. Secure the hook to the anchoring point and pull tight to secure.

WARNING: *Do not secure a strap over the top of the hard cover*

If either a mains or a DC power charging point is available in the vehicle, connect as follows:

WARNING: Ensure the socket outlet is easily accessible at all times in case of an emergency.

WARNING: The unit is a Class I product and must be connected to an earthed mains socket.

WARNING: Unless mains power is provided, power connection during transport will extend the life of the batteries during operation but no charging will be taking place.

POWER MANAGEMENT AND INTERNAL BATTERY LIFETIME

The OrganOx *metra* has an internal battery pack which will power all the machine's functions for at least 2 hours while no mains supply is available (for example transfer between vehicles and operating rooms). For maximum battery life the machine should be plugged into a mains power source whenever possible to recharge the batteries. OrganOx recommends that vehicles being used regularly for transport of the machine are fitted with a suitable inverter to allow for mains power during the period of transport between donor and transplant hospitals.

1. Charging the OrganOx *metra*

The OrganOx *metra* should be plugged into a mains power outlet whenever possible. This will maintain the battery charge at the highest possible level.

To ensure the batteries are being charged, the mains lead must be plugged into a suitable outlet, and the green mains power switch on the power inlet panel must be in the "on position" and illuminated as below.

When the machine is running on mains power the battery indicator LED will be unlit and the "mains plug" icon will appear in the top-right corner of the GUI display.

When the machine is running on battery alone, the Battery LED will be illuminated and the mains plug icon does not show.

The OrganOx *metra* will initially charge to >95% in less than 10 hours, but it will take a further 24 hours to achieve maximum charge of typically 98%. As a general rule, each hour of running time on batteries requires a charge time of 3-4 hours.

If after 48 hours of charging the indicated maximum charge is less than 95%, contact a Service Engineer at 855-ORGANOX (855-674-2669).

2. Battery Charge Capacity Indicator and Warnings

Battery level warnings are given at various remaining charge capacities as shown below:

Remaining Capacity	Audible Alarm	Machine functions	Action to reinstate machine function
50%	Pulsed	All functions active	N/A
30%	Pulsed	Display off temperature control off	Press display on/off button
20%	Pulsed	Oxygen concentrator	Plug into mains outlet and run until battery level is >30%
10%	None	Machine turns off, must plug into mains to turn back on	Plug into mains outlet and turn on green mains switch

Air will be delivered to the oxygenator at all times until the batteries are fully depleted, ensuring that the organ is always oxygenated while the blood pump is still running.

Note that any audible alarm can be silenced at any time by pressing the “silence alarm” button on the perfusion or power keypads.

Below 30% battery capacity the GUI screen will automatically turn off to conserve power. The Battery Low lights will illuminate on both membrane keypads. The GUI display can be turned back on temporarily in this “power save” state by pressing the display on/off button on the power keypad. This allows the user to periodically monitor perfusion parameters displayed on the GUI.

EMERGENCY STOP (E-STOP)

The OrganOx *metra* is fitted with an E-Stop button. When pressed the E-Stop will immediately shutdown the device and should only be only be used in an emergency. To restore power to the device, rotate the E-Stop button clockwise and press the OrganOx *metra* power-up button.

Section Two: Device Components, Accessories and Supplies

The OrganOx *metra* Retained Unit is removed from storage and taken by the Retrieval Team to the donor hospital. To accompany this device, the Retrieval Team should take a Disposable Set and the perfusion solutions together with three (3) units of leuko-reduced packed red blood cells (PRC) matched to the donor blood group, three (3) bottles of 500 ml 5% human albumin and all the additional equipment and solutions needed for the liver retrieval including, ice, saline, cold perfusion solution and surgical instruments.

DISPOSABLE SET

The OrganOx *metra* is intended to transport and maintain donor livers prior to transplantation and is indicated for use for up to 24 hours. All components of the Disposable Set have been assessed and found to hold no biological risk. The Disposable Set contains the following sub-sets:

- **OrganOx *metra* Perfusionist Pack:** This pack contains all accessories necessary for priming of the disposable set, including: administration sets (2x) for priming the circuit with leuko-reduced packed red blood cell (pRBC) and human albumin 30 ml syringes (4x) for use on the OrganOx *metra* syringe pump to infuse epoprostenol prostacyclin , bile salts, insulin and heparin, a 50 ml syringe for preparation of the bile salt solution, a syringe filter adapter for preparation of the bile salt solution and microbial filters (2x) for preparation of the epoprostenol prostacyclin and bile salt solutions.
- A Terumo in-line blood gas analyzer sensor used for measurement of pH, pCO_2, pO_2 and labeled with the original Terumo labeling is also provided separate to this pack due to its short shelf life.
- Bile salts
- **OrganOx *metra* Surgeons Pack:** This pack contains the cannulae for insertion into the liver prior to connection to the OrganOx *metra* Retained Unit. These cannulae are color coded as follows:
    - Blue for the IVC
    - Red for the Hepatic Artery which does not contain a pre-connected connector (provided separately)
    - Yellow for Portal Vein
    - Note that there is no color coding for the bile duct cannula but there are three different sizes: 12CH/Fr, 15CH/Fr, 18CH/Fr
    - A sterile 30 ml syringe for use when connecting the liver to the set to avoid air entrainment
    - An administration set for priming the cannulae with human albumin prior to connection to the perfusion circuit
- **OrganOx *metra Liver Perfusion Set:*** The set is packaged within a single large bag supplied below the Perfusionist and Surgeon Packs. It contains a single plastic cartridge on which the oxygenator, blood pump head, pressure sensors, blood lines and infusion lines are pre-assembled, and which is pre-connected to a surrogate organ Y-piece within the liver bowl to enable priming of the complete perfusion set before connecting the liver. The lid for the liver bowl is contained within a separate bag within this pack and is rested on top of the liver bowl.

-  *CAUTION: do not lift or remove the lid until the moment of liver connection, as it protects the sterility of the inside of the liver bowl.*

  A cold liver perfusion assembly is taped to the bottom of the liver bowl, and can be easily accessed for use when removing the liver from the circuit or in case of malfunction or other emergency that requires rapid cold-flushing of the organ. Sterile drapes are also included.

RETAINED UNIT

The OrganOx *metra* normothermic perfusion device incorporates a centrifugal pump, an oxygenator, oxygen concentrator, heat exchanger, reservoir, flow probes, pressure sensors, infusions and blood gas analyzer together with tubing and connector components. The device is comprised of three (3) main components

- A reusable Retained Unit which contains software and hardware
- Single use Disposable Set
- Sodium Taurocholate

In addition, perfusion solutions are required but not supplied as follows:

PERFUSION SOLUTIONS

The OrganOx perfusion system is based on the principle that all the perfusion solutions, additives and leuko-reduced packed red blood cells must be removed from the organ prior to transplant. Therefore, following the completion of the perfusion, the perfusion solutions are flushed out of the organ in accordance with local transplantation practice.

For a complete list of solutions and infusions approved for use with the OrganOx *metra* refer to Appendix Two.

The perfusion solutions comprise the following components:

- Bolus solutions to be used on priming the OrganOx *metra*
  - Calcium gluconate
  - Heparin
  - Antibiotic – e.g. Cefuroxime

- Maintenance infusion solutions provided during the perfusion:
  - Epoprostenol prostacyclin
  - Bile salts
  - Insulin
  - Heparin
  - Nutrition – (CLINIMIX E®) amino acids plus electrolytes
  - Sodium bicarbonate can be added if required during the perfusion

Because the leuko-reduced packed red blood cells (3 units) used on the OrganOx *metra* device are co-administered with human albumin (1 x 500 ml), prior to loading the liver onto the

OrganOx *metra* the liver must be flushed with 2 x 500 ml of human albumin in order to remove any pre-existing preservation solution.

WARNING: The perfusion solutions include components (such as human albumin, cefuroxime) which could cause hypersensitivity reaction in patients. Physicians should consult individual drug labeling and be alert to treat possible reactions.

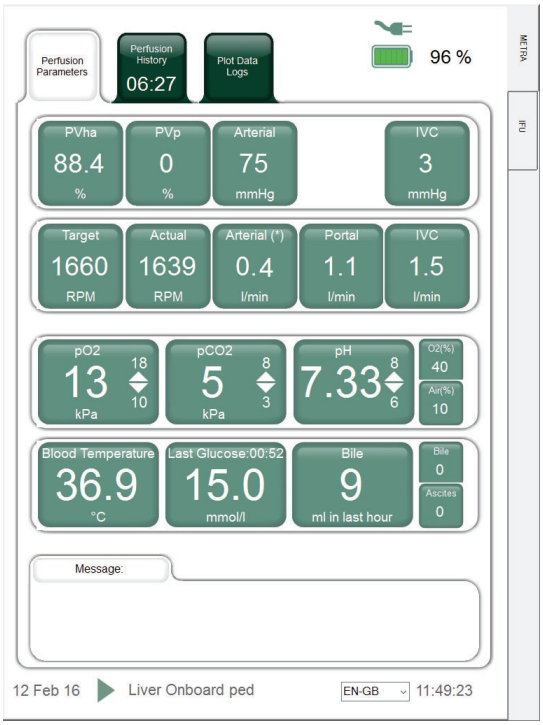
SOFTWARE

Once the liver is placed on the device, the operation is fully automated with the exception of the manual glucose measurement. A graphical user interface (GUI) system displays several perfusion parameters during the operation:

- Flow rates: Arterial, Portal, Inferior Vena Cava (IVC), all in L/min
- Pressures: Arterial, Portal, Inferior Vena Cava (IVC), all in mmHg
- Blood gases: pO_2, pCO_2, in kPa or mmHg (units can be changed by touching the GUI)
- pH
- Blood temperature (°C)
- Glucose in mg/dl or mmol/L (units can be changed by touching the GUI)
- Bile production (ml/h)

Operators are also able to view the complete Instructions for Use and a Set-Up Checklist on screen by using icons indicated on the screen shot below.

The software on the device is an independently validated system compliant with EN 62304 and 21CFR part 11 (version IAR SAM7/SAM9 SAFERTOS®).



Section Three: Instructions For Use

WARNING: THIS EQUIPMENT MUST NOT BE MODIFIED EXCEPT BY AN AUTHORIZED ORGANOX REPRESENTATIVE, APPROPRIATE INSPECTION AND TESTING MUST BE CONDUCTED TO ENSURE CONTINUED SAFE USE OF THE DEVICE

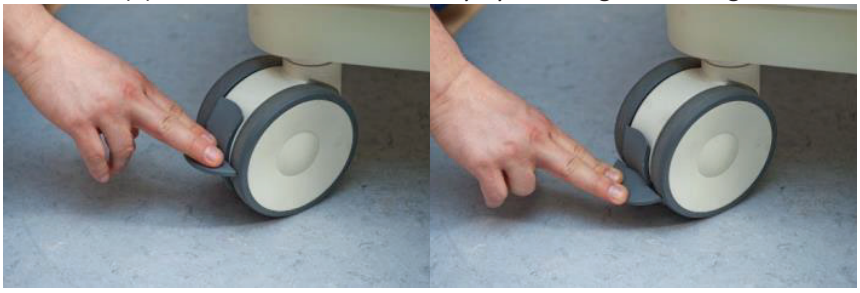
WARNING: THE DEVICE MUST ONLY BE USED BY FULLY TRAINED, PROFESSIONAL PERSONNEL

WARNING: WHEN THE UNIT IS BEING RUN FOR EXTENDED PERIODS (OVER AN HOUR) IN WARM ENVIRONMENTS (AMBIENT GREATER THAN 25°C), THEN THE COVER SHOULD NOT BE FITTED

DEVICE SET UP

1. Wheel the OrganOx *metra* close to a sturdy surface or trolley in the Operating Room (OR) that provides you with a comfortable working height.

2. Lock all four (4) wheels on the device trolley by lowering the locking latch



3. Release all four (4) metallic clasps that secure the cover to the OrganOx *metra* by turning them counterclockwise and lift the cover from the device.

4. Release the two (2) metallic clasps that fasten the OrganOx *metra* to the trolley by turning them counterclockwise.

5. Using three (3) people, two (2) positioned at the tower end of the OrganOx *metra* and one (1) at the liver bowl end, lift the device using the hand rail onto the working surface. Lock all four (4) wheels on the bottom of the device by lowering the locking hatch.

WARNING: THIS DEVICE WEIGHS GREATER THAN 165 POUNDS AND NECESSITATES A THREE (3) PERSON LIFT. SEEK FURTHER ASSISTANCE FOR LOADING IF NECESSARY. Ensure the bench is flat and can support the weight of the device.

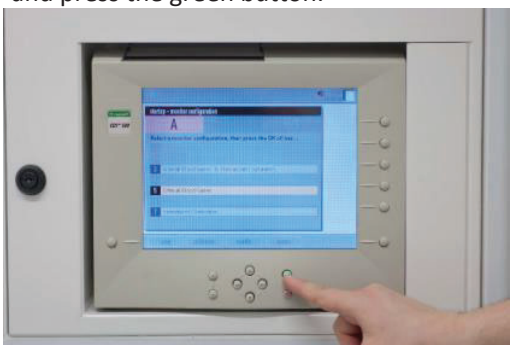
6. Lift the mains cap, connect the OrganOx *metra* to mains power and turn on mains power switch.

WARNING: Ensure socket outlet is easily accessible at all times in case of emergency

WARNING: The unit is a Class I product and must be connected to an earthed mains socket

7. Swing the transparent cap and press the OrganOx *metra* power-up button. Following a 30 second power-up sequence, the GUI displays on the top right corner both the available battery power and a plug symbol indicating successful mains charging.

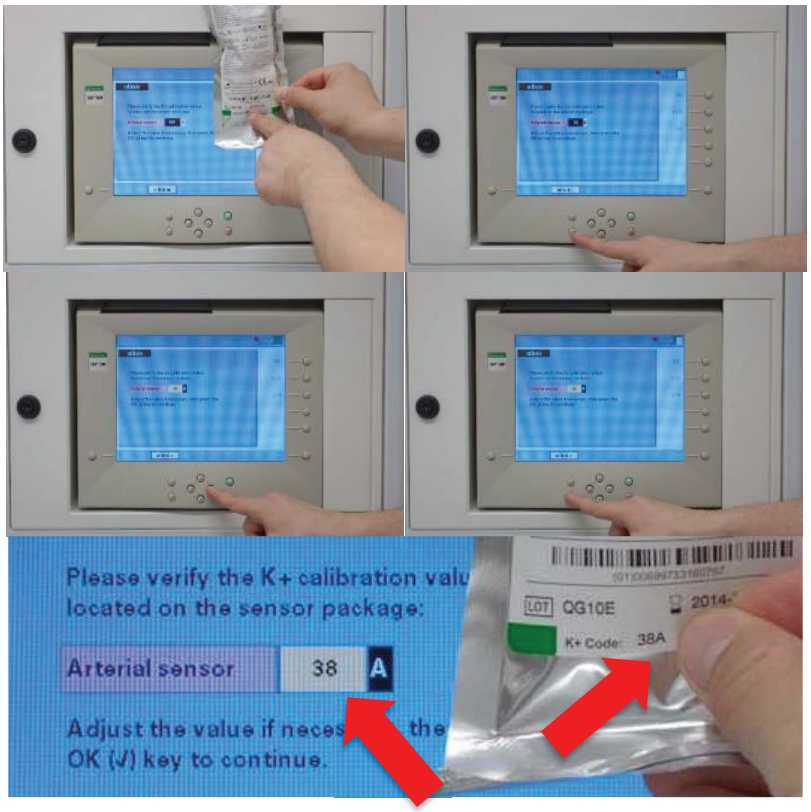
8. On the Terumo CDI®500 monitor situated on the rear face of the OrganOx *metra*, select 'arterial blood gases' and press the green button.



9. On the Terumo CDI®500 monitor, use the left arrow ' < ' button to select 'calibration' (highlighted in yellow) and press the green button.

10. Remove the Terumo CDI®510H sensor, which is enclosed in a self-contained aluminum foil package, from the individual box.

11. Read the K+ calibration value from the bottom of the label on the sensor and enter this number on the Terumo CDI®500 using the '+' and '-' buttons.



12. Press the green button on the Terumo CDI®500 to obtain the following screen:

13. Uncoil the Terumo head cable from the OrganOx *metra* device as shown:

14. Verify the gas bottle expiration dates for both gas A and gas B

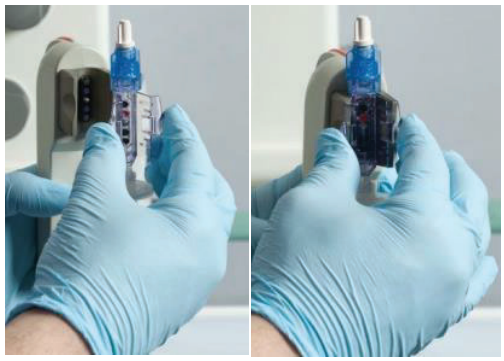
15. Connect the Terumo calibrator cable to the calibrator port on the OrganOx *metra*, ensuring that the red dots line up.

16. FROM THIS POINT FORWARD, WEAR GLOVES AND A SURGICAL CAP AT ALL TIMES

WARNING: Use aseptic procedures including surgical gloves. The perfusion circuit and cannulae are provided pre-sterilized. To minimize the potential for infection of the liver (and its eventual recipient), aseptic procedures must be used whenever handling the liver and whenever opening the perfusion circuit. Aseptic procedures include the use of sterile field, gown, gloves, and instruments and aseptic management of IV tubing, as would be typical in surgical and nursing practice.

17. **Open** the aluminum foil package and carefully remove the CDI®510H sensor.

18. Pick up the Terumo sensor head and, with the large blue venting luer to the top, gently squeeze the CDI®510H sensor and push into head until it clicks into place.



19. Remove the bottom blue luer cap on the CDI®510H sensor, leaving the white filter in place. Fully loosen the top large blue venting luer, without removing the white cap.

20. Install the Terumo cable head into either hub in the calibrator as shown, pushing it in until it clicks into place.

21. Press the green button on the Terumo CDI®500: sensor calibration begins and will last approximately ten (10) minutes, as indicated by the progress bar.

22. Whilst the Terumo CDI®510H sensor is being calibrated, prepare the bolus and infusion solutions as follows

For a complete list of solutions approved for use with the OrganOx *metra* refer to Appendix Two.

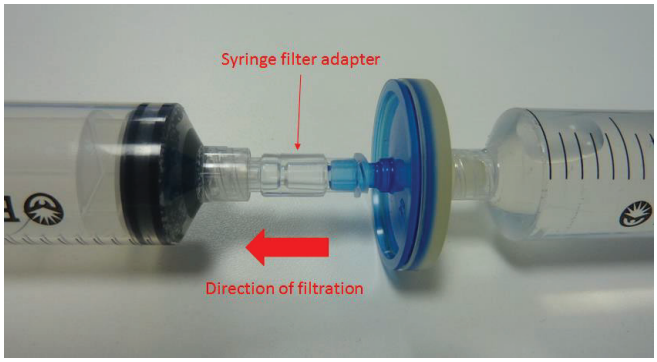
BOLUS (*use ANY available STERILE syringes*)

a. Antibiotics: reconstitute the entire vial (750mg) of cefuroxime with 10 ml of 0.9% NaCl solution and draw into a syringe.
   Note :If using 1.5 g of cefuroxime, inject 20 ml sodium chloride for injection into the vial of 1.5 g cefuroxime and allow to mix. Aspirate 10 ml and inject this into the reservoir of the OrganOx metra. Discard the remaining 10 ml. This will give 750 mg of cefuroxime.
b. Heparin: draw 2 ml of 5,000 u/ml solution (10,000 units) into a syringe.
c. 10% Calcium gluconate: draw 10 ml into a syringe.

INFUSIONS (***use STERILE 30 ml syringes provided in Perfusionist Pack***)

a. Bile salts: draw 30 ml of 0.9% NaCl solution into the 50 ml syringe provided, inject into vial containing 5.6 g of Sodium Taurocholate, shake well until powder has dissolved. Invert the vial and carefully draw back the solution into same syringe. Connect this syringe to
   - The microbial filter
   - The syringe filter adapter
   - 30 ml syringe

   Push the solution through the filter into the second syringe.



b. If using, epoprostenol prostacyclin: Draw 10 ml of glycine buffer (epoprostenol prostacyclin diluent) and add it to the 0.5 mg vial of epoprostenol prostacyclin. USING THE SECOND MICROBIAL FILTER PROVIDED, draw 5 ml out of the vial containing epoprostenol prostacyclin and the glycine buffer into the 30 ml syringe provided, and draw a further 25 ml of 0.9 % NaCl.
   If using, Veletri®: Use a sterile 30 ml syringe provided in the perfusionist pack. Draw 10 ml sterile 0.9% sodium chloride and add to the vial of Veletri®. Using one of the microbial filters provided in the perfusionist pack, draw 5 ml from the vial containing Veletri® and 0.9% sodium chloride into the 30 ml syringe provided. Draw up a further 25 ml of 0.9% sodium chloride, this will make the total volume in the syringe 30 ml.

c. Heparin: Draw 5 ml of 5,000 u/ml solution (25,000 units) of heparin and 25 ml of 0.9 % NaCl
d. Insulin: draw 2 ml of 100u/ml Actrapid (200 units) of and 28 ml of 0.9 % NaCl

23. Store all bolus and infusion syringes in a cool place whilst carrying out steps 23-51.

WARNING: The perfusion solutions include components (such as human albumin and cefuroxime) which could cause hypersensitivity reaction in patients. Physicians should consult individual drug labeling and be alert to treat possible reactions. Needles and sharps should be handled with care, and handling kept to a minimum.

24. Once the Terumo CDI®510H sensor calibration is complete, follow instructions on the Terumo CDI®500 screen, namely:

a. Close the large blue venting luer, ensuring that it is fully tightened
b. Remove the cable-head from calibrator. Coil the cable around the white cable-head mount on the OrganOx *metra* and slot the cable-head onto mount
c. Unplug the calibrator cable from calibrator port

25. Press the green button on the Terumo CDI®500 monitor, then select 'Operate' by using the > arrow and press the green button again. Ensure that both the Terumo CDI®500 monitor and the OrganOx *metra* GUI now display pO2, pCO2, pH and temperature values and that error messages 170 and 190 have now cleared from the OrganOx *metra* GUI, with only messages 140 and 150 remaining.

26. Remove the OrganOx *metra* Liver Perfusion Set from the OrganOx *metra* Liver Perfusion Circuit Pack and remove from packaging by tearing along the white lining.

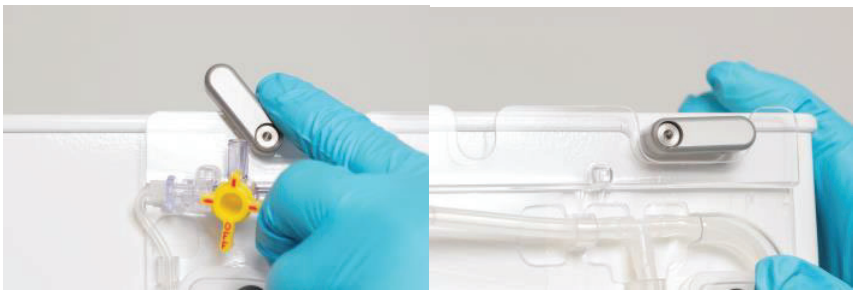
WARNING: Do not drop or pull the liver bowl and the circuit. Discard liver bowl and disposable circuit if dropped.

WARNING: The Disposable Circuit including the liver bowl are supplied sterile and should not be reused or re-sterilized.

27. Place the folded Disposable Set on the Retained Unit as shown, with the plastic ledge on the liver bowl facing the mounting bracket on the OrganOx *metra*. Remove the red-labeled tape protecting the base of the liver bowl.

28. Gently unfold the cartridge tray and place on front panel, <u>ensuring that the bottom part locates in the long groove at the base of panel</u> (Note: the liver bowl lid is packed separately above bowl and should <u>not</u> be unpacked or moved at this stage).

29. Slip the cartridge tray over the proportional pinch valves and clip into place using the two (2) rotating levers at the top of the panel.



30. Engage the liver bowl in the bracket on side of the device and swing the locking pin over it.

31. Stretch the reservoir inlet tube and insert in the upper proportional pinch valve.

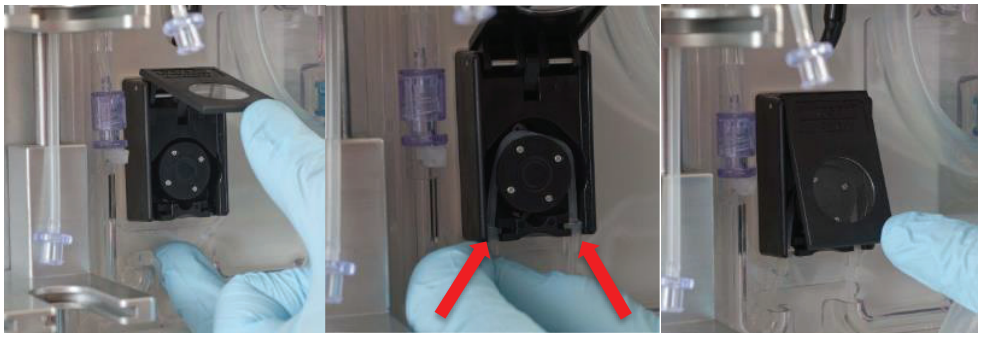
32. Pull the reservoir outlet tubing into place, carefully aligning the markings either side of the proportional pinch valve. Stretch the tubing and slide into the pinch valve.

WARNING: The connectors could potentially be a pinch hazard, care should be taken.

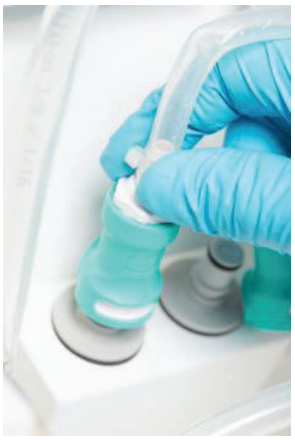
33. Attach the oxygenator gas inlet female CPC connector (green color) to the male panel mount CPC connector just above the portal flow sensor.

34. Open the portal flow sensor (on the reservoir outlet) by pressing the button to the left of the sensor. Slightly wet a gloved finger with water and run through the inner surface of the sensor and over the reservoir outlet tubing. Insert the tubing into sensor and close the door.

35. Open the door to the nutrient roller pump and mount the nutrient tubing over the hub ensuring it is located in place with the two locating tabs in place. Close the door.

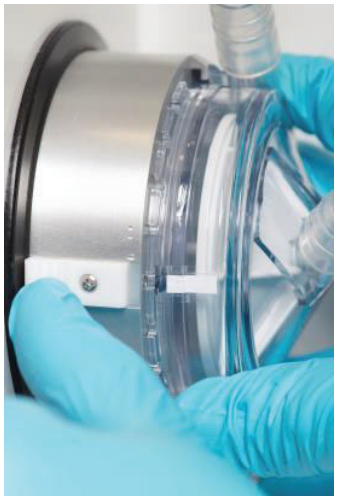


36. Connect the front oxygenator water inlet female CPC connector onto the left-hand male panel mount connector.

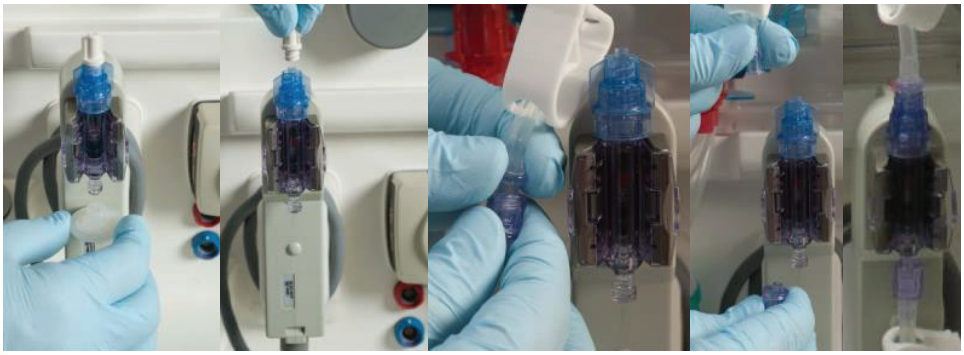


37. Repeat with the rear water outlet female CPC connector which fits on the right-hand male panel mount connector.

38. Locate the centrifugal pump drive head into the magnetic pump drive ensuring the white marking on pump head is aligned with the white clip on the pump casing. Check for kinking in the line from the pump head outlet to the oxygenator inlet. Remove kinks if necessary by rotating the tubing on the oxygenator inlet.

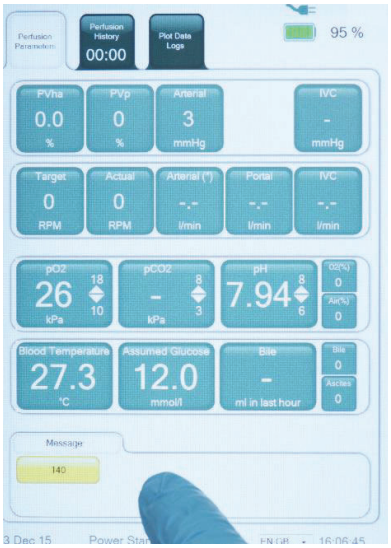


39. Carefully remove the top white cap and bottom white filter from the Terumo CDI®510H sensor, taking care not to touch the open ends. Disconnect the luer lock connection on blood gas analyzer bypass line and connect to top and bottom of Terumo sensor. Ensure that the white plastic Roberts Clamps either side of the sensor remain open.

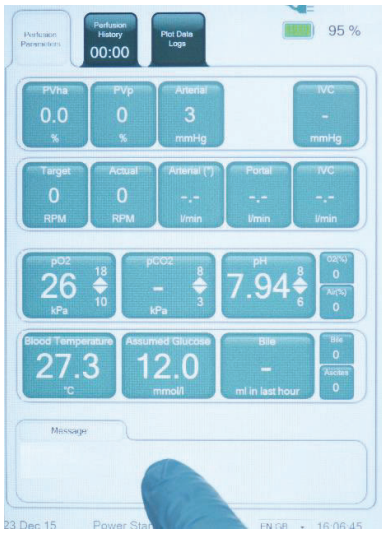


WARNING: Ensure the user is wearing surgical gloves during the operation and set up of the OrganOx metra

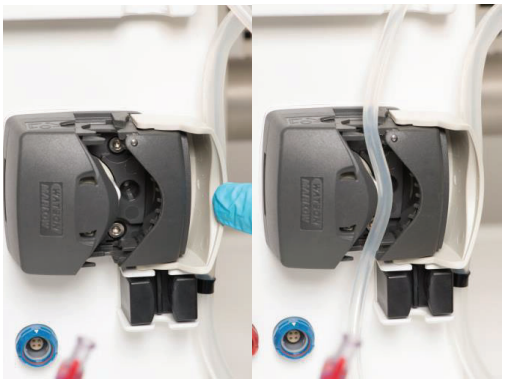
40. Connect the red arterial pressure sensor to the upper pressure port (also marked red). Ensure striations on the male connector face upwards and push in until a clicking sound is heard. Safe connection is confirmed by the disappearance of error message 150 from the OrganOx *metra* GUI.



41. Connect the blue IVC pressure sensor to the lower pressure port (also marked blue). Ensure striations on male connector face upwards and push in until a clicking sound is heard. Safe connection is confirmed by the disappearance of error message 140 from the OrganOx *metra* GUI.



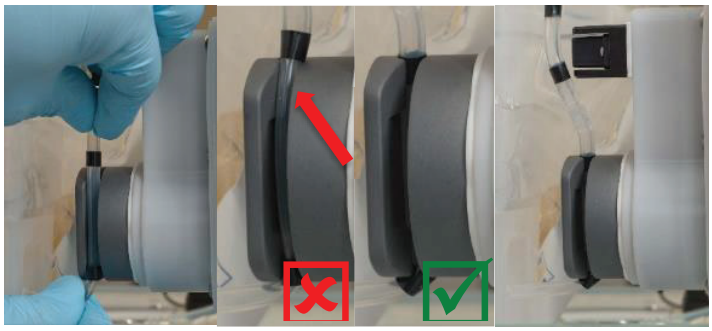
42. Open the door to the ascites pump (ensuring it is fully open). Insert the peristaltic tubing (without markings) into pump, ensuring it lies within the V-grooves, and shut the door.



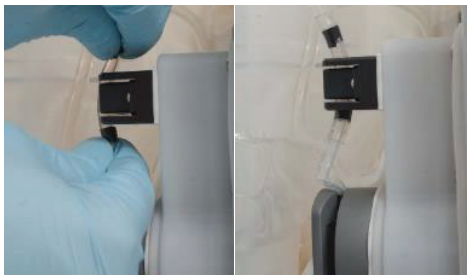
WARNING: this is a pinch hazard; care should be taken when closing the door.

43. Slightly wet a gloved finger with water and wet the outer surface of the ascites level line between the two black markings. Line up markings on the ascites level line with the optical level sensor and insert the tubing into sensor. Ensure that there are no kinks on the ascites line and that it lies flat as shown.

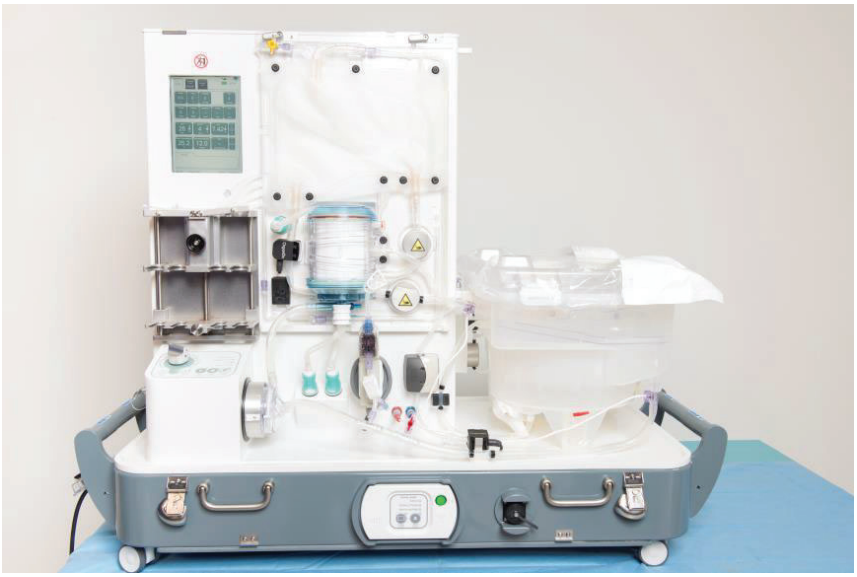
44. Align the lower two markings on the bile drainage line with the bile pinch valve, stretch the tube and insert into the valve ensuring that it is fully located in place.



45. Align the upper two (2) markings with the bile level sensor and insert into sensor.



The OrganOx *metra* is now ready for priming:

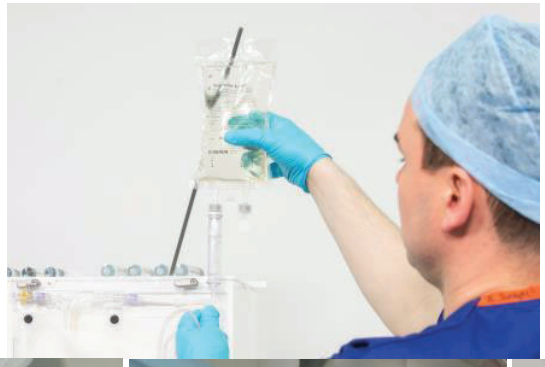


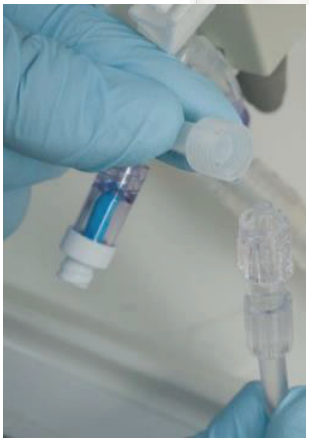
PRIMING

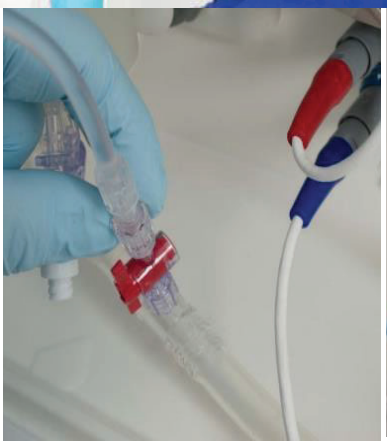
WARNING: The perfusion solutions include components (such as human albumin and cefuroxime) which could cause hypersensitivity reaction in patients. Physicians should consult individual drug labeling and be alert to treat possible reactions.

46. Lift the priming pole on top of the OrganOx *metra*.

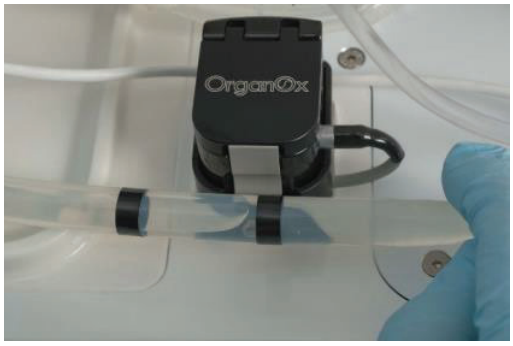
47. Using the administration sets in the Perfusionist Pack, spike one bottle (1 x 500 ml) of *human albumin*. Prime the line, remove the protective cap from the luer-lock end and connect to the OrganOx *metra* priming port, allowing it to fill the disposable circuit under gravity. One bottle of *human albumin* will enable priming of the circuit up to the lower third of the reservoir. Ensure that the unit is disconnected before any air is entrained into the circuit.







48. During priming, ensure that no air is trapped in the tubing or the centrifugal pump head. If air is trapped in the tubing, slope upwards towards liver bowl and allow air to rise towards the oxygenator. If air is visible in the pump head, remove the pump head, allowing air to escape towards the oxygenator, and re-position, ensuring white markings are aligned.



49. During priming, once the *human albumin* rises to a level higher than the oxygenator, close the venting port on the oxygenator by rotating the white tap away from the front panel to the final position shown below.

50. The *human albumin* bottle will be close to empty once the level reaches the lower third of the reservoir. Turn the 2-way tap on the priming port to a horizontal position to avoid air entrainment and close the roller clamp.

51. Press start on the OrganOx *metra* control panel. The fluid will be circulated through the disposable set.

52. Check all connections for kinks or leaks ensuring the device remains in 'Preparation Mode' during this period.

53. The pressure in the circuit should then be raised to a level experienced during perfusion.

54. Intermittently occlude both arterial (red) and portal (blue) lines exiting the oxygenator for three (3) seconds and release for three (3) seconds – repeating this five (5) times whilst in preparation mode. This will momentarily raise the pressure in the oxygenator.

55. The device should remain in 'Preparation Mode' during these checks. Should the device enter 'Liver on board' mode, wait until the testing has finished before exiting this mode.

56. Following the series of intermittent occlusions of the portal and arterial lines, use a dry paper towel to check all connectors and luer taps outside the liver bowl; inspect the paper towel for any signs of fluid.

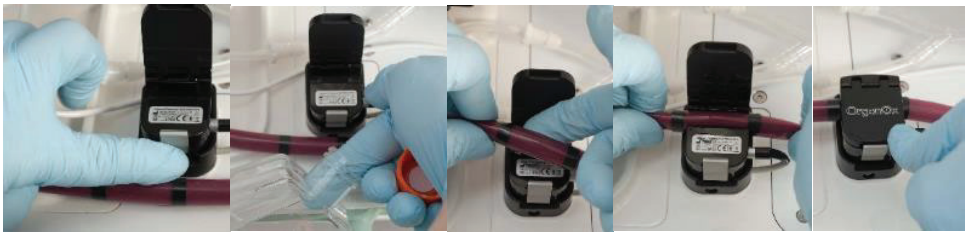
57. Tubing within the liver bowl should be visually checked for leaks; it is not necessary to remove the liver bowl lid to perform these checks, thus maintaining the sterility of the liver bowl.

58. Following completion of the leak check press the "stop perfusion" button. Then press the "eject cartridge" button twice within three (3) seconds to open the pinch valves.

59. Verify that you have three (3) units of leuko-reduced packed red blood cells of the **correct blood type matching that of the donor.** Carefully remove the spike from the empty bottle of *human albumin* and spike the first unit of leuko-reduced packed red blood cells, ensuring that the spike is fully pushed in. Open blue roller clamp on line and two-way tap on priming port, and hang unit from priming pole, gently squeezing. Repeat the procedure for the remaining two units of leuko-reduced packed red blood cells, then turn off the two-way tap on priming port, disconnect the administration line and discard.

    The reservoir should be more than ¾ full and approximately at the fill level, by the end of the priming phase: if this is not the case, use part of an additional bottle of *human albumin* to top up the fluid level.

60. Once priming is complete, open the IVC flow sensor (located on the base of the Retained Unit) by pressing the button to the front of the sensor. Slightly wet a gloved finger with water and run through the inner surface of the sensor and over the reservoir outlet tubing. Insert tubing into the sensor, and close the door.

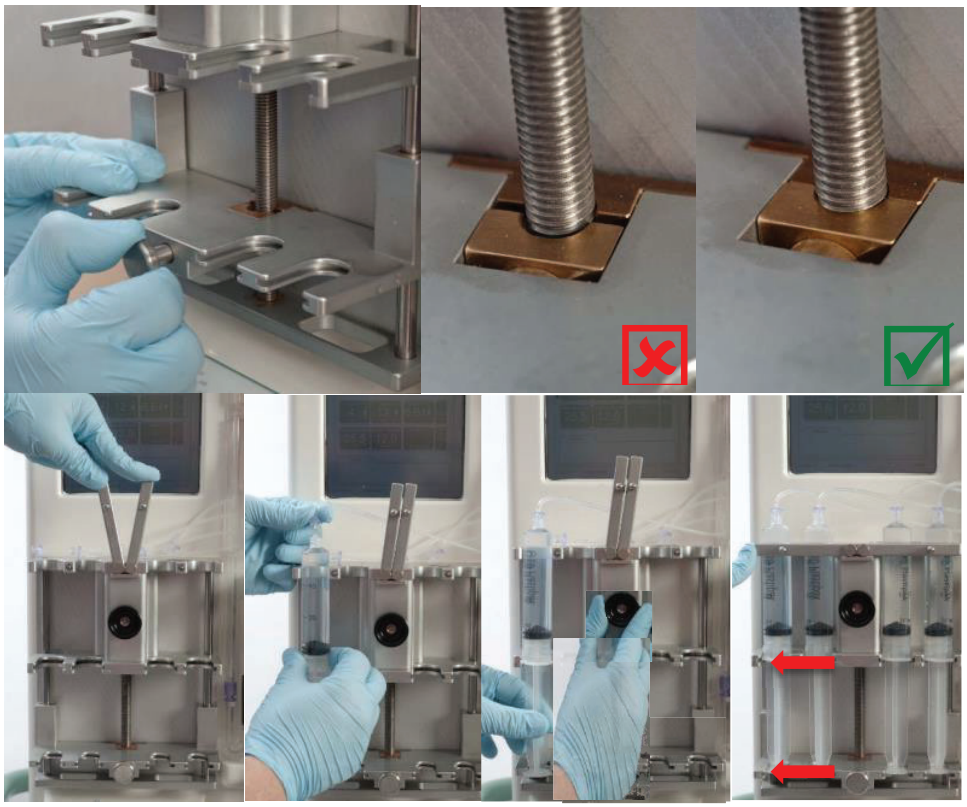


61. Inject all three (3) bolus infusions (first cefuroxime, then calcium gluconate, then heparin) through the three-way tap on the top of the reservoir as shown. Make sure to turn the three-way tap so that 'OFF' is to the left prior to injection, to prevent leakage into the nutrition line.

62. Follow the instructions for use on the CLINIMIX E® bag, ensuring that the peel seam is broken in order for the glucose and amino acid solutions to mix. Then hang the bag to the side of the OrganOx *metra* tower above the liver bowl and insert the nutrition line spike into infusion port (indicated by a white cap on the CLINIMIX E®).

63. Introduce each of the four infusion solution syringes (bile salts, heparin, insulin, epoprostenol prostacyclin) prepared during step 0 into each of the syringe pump drives as follows:
    a. Fully lower the syringe pump drive by pulling on metallic knob and pushing downwards. Upon releasing, ensure that the drive fully engages the lead screw as shown.
    b. Lift the metallic levers.
    c. Connect the first syringe to the longest infusion line.
    d. Engage syringe lip into leftmost syringe pump groove.
    e. Adjust height of syringe pump drive by turning the black knob until the edge of the syringe plunger lines up with the slit on the syringe pump drive.
    f. Push the syringe inwards to ensure that both the barrel and the plunger lips are fully engaged in the syringe pump.

g. Insert the remaining 3 syringes, using the longest infusion line for the leftmost syringe.
h. The order of syringes and solutions in the syringe pump is unimportant.



64. Once priming of the circuit is complete, expel any residual air from the top of the reservoir bag by gentle compression, and then close the yellow three-way tap on top of the reservoir to air as shown.

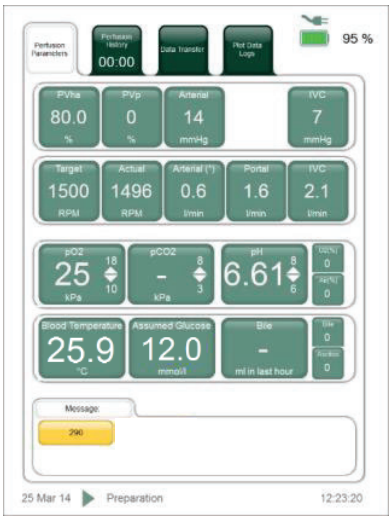
CAUTION: If a pressure build up is detected within the reservoir bag which cannot be relieved by expelling the air as shown above, it is likely that the system has been over filled. Where this is the case drain a little of the fluid from the system through the priming port until there is a small gap between the top of the fluid and the top of the reservoir. Then expel the air as described above. Make sure that the final fluid volume fills the bag to at least ¾ full.

65. Turn the black knob clockwise on syringe pump to prime infusion lines, clearing any air to the reservoir. NOTE: The knob does not turn counterclockwise to avoid any contamination.

The OrganOx *metra* is now ready for preparation and liver connection

PREPARATION AND LIVER CONNECTION

66. Press ▶ on the control panel below the syringe pump. The GUI displays a target pump speed of 1500 RPM and blood begins to flow. If message 290 appears then the water reservoir on top of the Retained Unit should be topped up with deionized water.



CAUTION - OrganOx recommends that the water reservoir should be filled with 0.22µm filtered, deionized water, which will prevent the insertion of mycobacteria into a system of total volume 500 ml.

67. Unscrew the cap at the top of the tower, add water until the message 290 clears, and close the cap. Make sure **not to overfill** by checking that level does not exceed the threaded part of the filler cap.

CAUTION – *The water in the thermo-control unit should be replaced in its entirety at least once every 3 months via drainage port, situated underneath the device. This will be carried out by the OrganOx service engineer during regularly scheduled maintenance visits, ensuring both adhere to cleaning instructions and the establishment of regular cleaning schedules.*

68. Once the temperature displayed on the OrganOx *metra* screen exceeds 36.5°C, check the pH of the perfusate (the fluid inside the perfusion circuit). If the pH is below 7.3, use a syringe to inject sodium bicarbonate solution via the injection port on the reservoir as needed to achieve a pH in the range 7.3-7.4. Typically, 20-30 ml of bicarbonate will be required. It is recommended to add an initial 20 ml, followed by up to two additional injections of 10 ml, if necessary. 10-15 minutes should be allowed between injections to ensure equilibration of pH and displaying of an up-to-date value. Ensure the three-way tap is closed to air following injection.

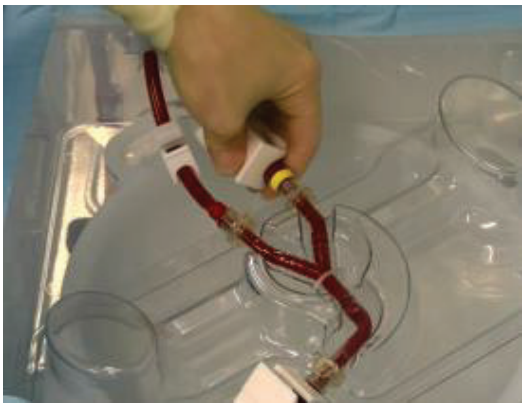
69. Once the temperature displayed on the OrganOx *metra* screen exceeds 36.5°C and the pH exceeds 7.3, organ connection can take place. **Cannulation must only be carried out using the cannulae supplied as part of the OrganOx *metra* Surgeon Pack (included in each OrganOx *metra* disposable set) as per standard training.**

70. Press ⏹ on the control panel and lift the liver bowl lid (still in its original packaging) from off the liver bowl.

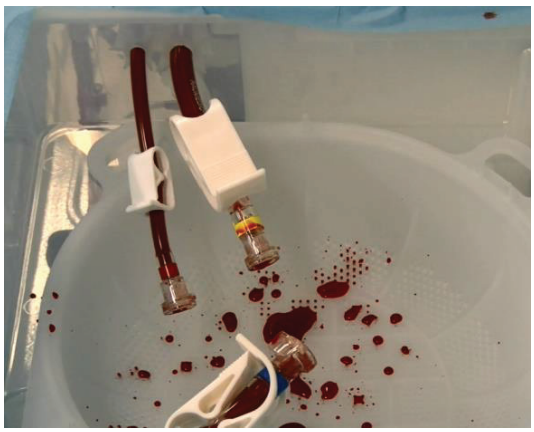
⚠ *WARNING: Ensure the user is wearing sterile surgical gloves before accessing the interior of the liver bowl.*

NOTE THAT THE ORGAN CANNULAE AND THE Y-CONNECTORS ARE COLOR CODED TO ENSURE CORRECT CONNECTION.

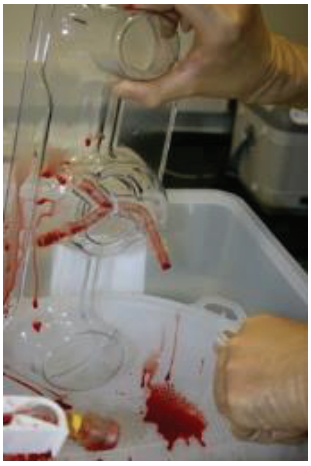
71. Close all the three (3) white Roberts clamps inside liver bowl so that all lines are completely occluded. The clamps should be closed as close as possible to the quick-disconnect fittings.



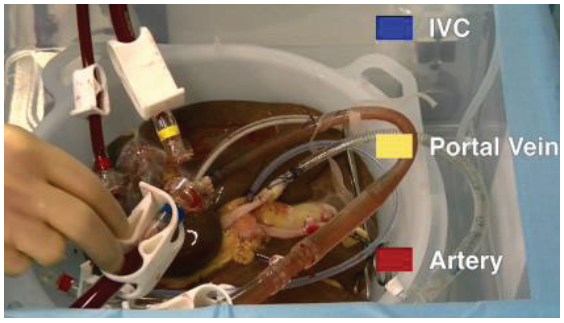
72. Disconnect each of the three quick-disconnect fittings in turn by pressing the plastic tab and pulling the 'female' collar away from the 'male' fitting.



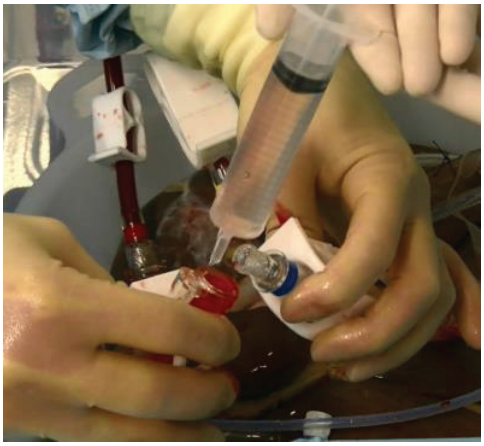
73. Drain any blood trapped in “Y shunt” inside the bowl before discarding the Y shunt.



74. Position the cannulated organ inside the sling in the liver container, ensuring that the liver lobes and vessels are not twisted. Adjust the sling position so that cannulae exit the organ near the rear left corner of the organ container.



75. Hold the IVC cannula (blue marking) and the IVC line (blue marking) as shown. Using the syringe provided, a second operator should then fill both the male and female connectors to the rim with cold perfusion fluid, whilst two connectors are coupled to avoid any air entrainment.

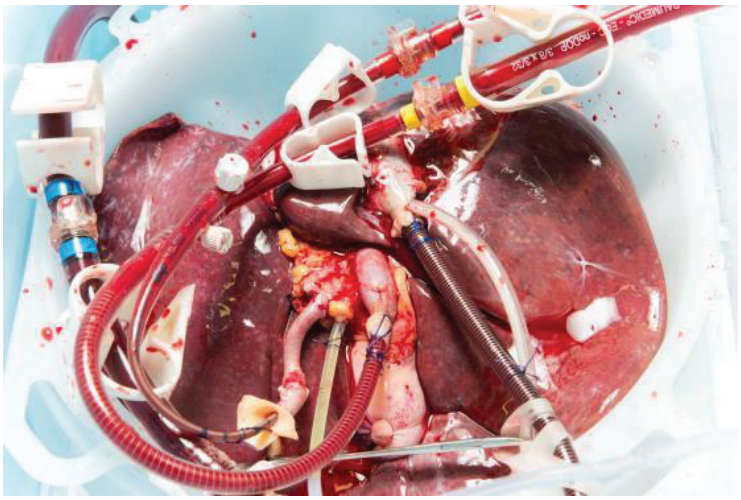


WARNING: Avoiding entrapment of air.

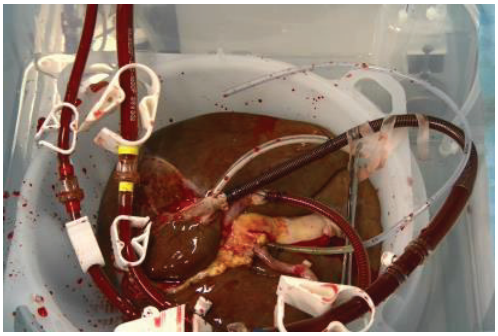
76. Repeat the process for the portal and hepatic artery lines and cannulae.

77. Cut the bile cannula to length and connect it to the bile drainage port on the liver bowl.

78. Fully release **ALL SIX (6)** white Roberts clamps within liver bowl and ensure that there are no visible kinks or twists in the lines or liver lobes.



79. Press ▶. The liver should instantly start perfusing throughout, whilst the perfusate temperature on the OrganOx *metra* GUI should gradually rise again to 37°C.



WARNING: Check for regions of poor perfusion and adjust the position of the liver lobes and vessels as necessary.

80. 15 minutes after connection, Message 100 appears requesting a glucose input value. Take a blood sample from the sampling port on the blood gas analyzer bypass line and obtain a measurement of blood glucose using a suitable device available (eg a fingerstick glucose strip monitor or equivalent). Enter this value by first rotating the metallic knob on the OrganOx *metra* control panel to the correct value and then by pressing 'Glucose set dial'. Ensure that the correct value (to within 9mg/dl) is displayed on the GUI.

WARNING: This procedure will have to be repeated at intervals not exceeding four (4) hours, as indicated by the 'Last Glucose' timer, otherwise an alarm will sound.

81. Once satisfactory perfusion has been achieved throughout the organ, unwrap the liver bowl lid and seal the liver bowl by clipping the lid on. **Ensure that the bile cannula is not kinked by the lid.**

WARNING: Do not open the Liver Bowl Lid again until you are ready to Transplant the organ

82. Always place and secure the hard cover before transporting the OrganOx *metra*. Switch off the mains power to the unit at the mains switch (next to the mains inlet socket) and disconnect the mains lead. The unit will automatically switch to battery power. Ensure the socket covers are down.

83. Using a recommended minimum of three (3) people, move the OrganOx *metra* onto its trolley, and reposition the hard cover over the device, locking all clasps through a clockwise rotation.

84. The OrganOx *metra* and on-board organ are now ready for transport.

85. When transporting the OrganOx *metra*, ensure that the mains lead, trolley, and Terumo calibrator are also transported with the unit. Refer to the section **Securing the OrganOx metra During Transit** starting on page 6 for detailed instructions on how to load and secure the device for transit.

LIVER DISCONNECTION (NO MORE THAN 24 HOURS FROM START OF PERFUSION)

86. Transport the OrganOx *metra* to an Operating Room and remove the hard cover.

87. To disconnect the organ from the device, press  "Stop Perfusion".

88. Fully close **ALL SIX (6)** white Roberts clamps within the liver bowl and disconnect the quick-release fittings on the arterial, portal and IVC lines.

89. Remove the cold perfusion set from beneath the liver bowl and connect the spike from the cold organ flushing solution in accordance with local practice.

90. Connect the arterial and portal cannulae connectors to the cold perfusion set (provided with each OrganOx *metra* disposable set), fully open all three (3) white Roberts clamps, and following the completion of the perfusion, the perfusate is flushed out of the organ with HTK solution (or the preferred preservation solution of the implanting center), allowing effluent to drain into the OrganOx *metra* liver bowl via the open IVC cannula.

CARTRIDGE REMOVAL AND DISPOSAL

91. Once the organ has been removed from the OrganOx *metra,* the Disposable Set should be removed from the Retained Unit.

92. Press the "remove cartridge" button on the control panel twice within three (3) seconds.

93. Disconnect the bile pinch valve and bile sensor.

94. Remove the tubing from the ascites pump and the ascites sensor.

95. Disconnect the red pressure sensor.

96. Disconnect the blue pressure sensor.

97. Open the IVC flow sensor and remove the tubing.

98. Disengage the pump head from the pump drive.

99. Disconnect the oxygenator water lines.

100. Remove the Terumo sensor from blood gas analyzer head.

101. Disconnect the oxygenator gas inlet line.

102. Remove the nutrient line from small roller pump.

103. Open the portal flow sensor and remove tubing.

104. Disengage the tubing from both proportional pinch valves.

105. Remove the syringes from syringe pump.

106. Unclip the cartridge from perfusionist panel.

107. Fold the perfusionist panel over the liver bowl and discard as clinical waste.

FOLLOWING THE REMOVAL OF THE ORGANOX METRA LIVER PERFUSION CIRCUIT, THE RETAINED UNIT SHOULD BE CLEANED, WIPED DRY AND STORED IN A SUITABLE DRY CLEAN ENVIRONMENT (REFER TO SECTION ONE (1) ON DEVICE CLEANING). THE SPENT DISPOSABLE SET SHOULD BE DRAINED AND DISPOSED OF USING LOCAL PROCEDURES FOR CLINICAL WASTE.

WHILST IN STORAGE MAINS POWER SHOULD BE SUPPLIED TO THE BATTERIES TO ENSURE THE DEVICE IS READY FOR THE NEXT USE

REMOTE SCREEN VIEWING VIA A WI-FI CONNECTED DEVICE

The Wi-Fi facility is a convenience that enables operators to have better access to the messages and the reported state of the machine. The OrganOx *metra* can be operating in transit for several hours and access to the OrganOx *metra* can be restricted. The device can be in the back of an ambulance, for example, with the operator in the front seat. The Wi-Fi addition will allow the operator to keep a constant check on the device by using a smartphone or similar device, without having to stop the vehicle to examine the GUI screen. This is particularly pertinent if there is a warning message from the device. The operator can see the message on a hand-held device and decide if the OrganOx *metra* needs immediate attention or otherwise.

The OrganOx *metra* will connect to any Wi-Fi enabled device with an internet browser, such as a smartphone, tablet or PC and the expected range is approximately 30 feet.

Loss of the Wi-Fi facility has no impact on the operation of the OrganOx *metra* device but if the OrganOx *metra* GUI cannot be viewed remotely, it will be necessary to periodically examine the GUI screen directly. This may require periodically stopping the transport vehicle.

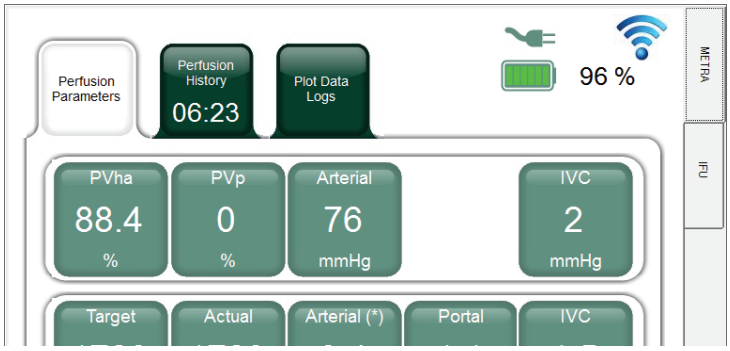
ENABLING WI-FI OPERATION

To enable the Wi-Fi connection to an external device, press the green button on the switch panel shown below.

Note: If Wi-Fi is not required, such as during flight transport, the green button should be pressed to disable Wi-Fi operation.

The position of the Wi-Fi on/off button

The GUI screen will show the Wi-Fi icon in the top-right corner of the screen when the OrganOx *metra* is ready for a Wi-Fi connection (see below).



Example GUI screen with Wi-Fi icon

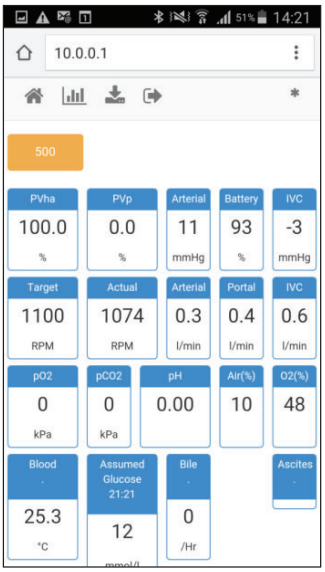
The OrganOx *metra* will operate as a Wi-Fi hotspot with a name 'METRAXXXX', where XXXX is the serial number of the OrganOx *metra*. The network password is '20002000'. Up to five devices can be connected to the OrganOx *metra* Wi-Fi at any one time.

To connect to an external device, go to 'Network Connections' on the connecting device and select the OrganOx *metra* hotspot. Enter the password when requested.

Using the internet browser on the connecting device, enter the web address '10.0.0.1'. The connecting device should display a screen similar to the screenshot below:

The metraOnline login screen

Select the required language. The display should be shown similar to the screenshot below:



Example of metraOnline live data screen

Note: The glucose, pO_2 and pCO_2 units displayed on the screen can be changed from mmol/L and kPa to mg/dl and mmHg respectively by tapping the value on the display.

Section Four: Safety Requirements

Device Disposal Instructions

The expended Disposable Set should be disposed of in accordance with the local hospital clinical waste management policy

If the OrganOx *metra* Retained Unit is found to be faulty, notify OrganOx and arrangements will be made to return the device or for a designated OrganOx Ltd representative to service or collect the device as necessary

All waste solutions i.e. bile must be disposed of as clinical waste in accordance with local hospital policies

It is essential that all personnel who operate the OrganOx *metra* have read and understand this manual before operating the device. All personnel should follow all warnings and precautions outlined below, for their safety and the safety of those around them. In this manual, definitions apply for all WARNINGS and CAUTION statements

WARNING: any operation, procedure etc., which if not observed may cause harm to personnel or patient

CAUTION: any operation, procedure etc., which if not observed may cause harm to the equipment

Warnings

1) The device must only be used by trained medical professionals.

2) The parameter values displayed on the OrganOx *metra* GUI are intended as an aid for the clinical user and should not be used as a diagnostic tool. Use standard precautions and good clinical practice when performing any medical procedures. It is the operating transplant surgeon's decision to transplant the liver following storage on the OrganOx *metra* device. The device should not be a replacement for current medical and transplant practices.

3) The equipment must not be modified by any unauthorized person. If this equipment is modified by any unauthorized person all warranties are invalidated.

4) Following maintenance and modification, appropriate inspection and testing must be conducted to ensure continued safe use of the equipment

5) Use aseptic procedures when handling the disposable circuit
The OrganOx *metra Liver Perfusion Circuit Pack is supplied pre-sterilized by the manufacturer. To minimize the risk of infection to the liver and the recipient, aseptic technique must be used when handling liver and when opening the disposable circuits. Aseptic procedures include the use of a sterile field, gloves, gown and instruments, as would be typical in surgical and nursing practice.*

6) Use current medical practices and precautions with the liver
The liver may carry undetected pathogens from the donor. Use proper aseptic precautions as indicated above, when handling the liver.

7) The OrganOx *metra* should be checked before each perfusion procedure.
Visually check the device for overall integrity and transport-worthiness before each use. Do not use if parts are loose or cracked or broken or liquid is leaking.

8) Do not reuse or re-sterilize the disposable circuit
The disposable circuit is supplied pre-sterilized using ethylene oxide gas, and is intended for single-use. After use it should be disposed of in accordance with local guidelines for biomedical waste.

9) Do not open the back of the Retained Unit to service it:
Shock hazard. There are no user serviceable components in this device.

10) Use only grounded electrical connections
This unit is a Class I product and must be connected to an earthed mains socket

11) Use only OrganOx approved accessories

12) Do not attempt to change any lithium button cell batteries in the GUI, call a Service Engineer or return to OrganOx or its agents for any embedded PC problems

13) Do not remove or open the liver bowl lid once a liver is attached until the liver is ready to be placed into the device.

14) This device has not been validated for air transportation

15) The device has not been tested in an oxygen rich environment

16) The disposable set device contains phthalates

17) This equipment/system may cause radio interference or may disrupt the operation of nearby equipment. It may be necessary to take mitigation measures, such as reorienting or relocating the OrganOx *metra* System.

18) This equipment is intended for use in a professional healthcare facilities and Special Healthcare – (Vehicular Use). The equipment is not intended to be used in a domestic or residential environment.

19) Particular precaution must be considered during use of strong emission sources such as High Frequency surgical equipment and similar so that e.g. the HF-cables are not routed on or near the device. If in doubt, contact OrganOx Ltd.

20) Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should not be used closer than 12 inches to any part of the OrganOx *metra*, including cables recommended by the manufacturer. Otherwise degradation of the performance of this equipment could result.

21) The OrganOx *metra* is protected against attack, damage or unauthorized access. The software on the device cannot be altered by the user or any unauthorized parties either directly or remotely. Modification to the software or hardware of the device is only to be undertaken by authorized parties with access to the locked enclosure. Any unauthorized modification of the installed software will initiate a failsafe condition preventing code execution during runtime. In this condition the device will not start.

22) The relationship between the bile production rate and liver viability has not been experimentally or clinically confirmed, and as such, the bile production rate value should not be used to assess liver viability.

CAUTIONS

1) Read the instructions carefully

2) Use good clinical judgment

3) Secure the device before transportation (Refer to Section One)

4) All OrganOx *metra* disposables are single use only
The Disposable Set is supplied pre-sterilized using ethylene oxide gas and is intended for single-use. After use it should be disposed of in accordance with local guidelines for biomedical waste

5) Keep the device upright during transportation, avoid direct sunlight and hot and cold extremes

6) Make sure power supplies/battery levels are sufficient for the intended travelling time. When fully charged, the batteries will run the OrganOx *metra* for at least two (2) hours

7) Make sure that the disposable perfusion circuit is properly connected

8) Connect the system to the electric supplies according to labeling
Ensure the socket outlet is easily accessible at all times in case of an emergency

9) Use precaution when lifting (Refer to Section One)
This device weighs greater than 165 pounds and necessitates a three (3) person lift. Seek further assistance for loading if necessary.

10) If a pressure build up is detected within the reservoir bag which cannot be relieved by expelling the air as shown above, it is likely that the system has been over filled. Where this is the case drain a little of the fluid from the system through the priming port until there is a 40mm gap between the top of the fluid and the top of the reservoir. Then expel the air as described above. Make sure that the final fluid volume fills the bag to at least ¾ full.

11) OrganOx recommends that the water reservoir should be filled with 0.22µm filtered, deionized water, which will prevent the insertion of mycobacteria into a system of total volume 500 ml.

12) The water in the thermo-control unit should be replaced in its entirety at least once every 3 months via drainage port, situated underneath the device. This will be carried out by the OrganOx service engineer during regularly scheduled maintenance visits, ensuring both adhere to cleaning instructions and the establishment of regular cleaning schedules.

EMC Information

Precautions to consider related to EMC and other interference according to sub-clause 6.8.2 a) in Amendment 2 to IEC 60601-1

The device complies with the EMC requirements according to IEC 60601-1-2:2014

The essential performance of the machine was maintained in all modes and in all intended environments of operation. The actual acceptance criteria assessed during for the Equipment Under Test (EUT) was as follows:

With respect to: Continuous Phenomena – Radiated RF Immunity, Conducted RF Immunity, Power Frequency Magnetic Field Immunity

Liver On Board Mode - The equipment shall continue to operate as intended during and after the test. During the test there shall be no variations in the displayed values for blood temperature, arterial pressure, the rpm of the blood pump motor and of the blood glucose measurement. The parameters displayed within the GUI window of the EUT should also be displayed correctly on both the laptop and the tablet with both of these devices showing the heartbeat indicator in the top right-hand corner. There shall be no visual and/or audible error messages during the test.

Preparation Mode - The equipment shall continue to operate as intended during and after the test. The parameters displayed within the GUI window of the EUT should also be displayed correctly on both the laptop and the tablet with both of these devices showing the heartbeat indicator in the top right-hand corner. There shall be no visual and/or audible error messages during the test.

With respect to: Transient Phenomena – ESD, Electrical Fast Burst Transient Immunity, Surge Immunity, Power Line Voltage Dips and Interrupts

Liver On Board Mode - The equipment shall continue to operate as intended after the test. During the test there is allowed to be variations in the reading displayed for blood temperature, arterial pressure, the rpm of the blood pump motor and the reading of the blood glucose level provided all of these values return to their original values on completion of the test. Variations in all of these values are also permitted within the replicated GUI display on the support laptop and tablet provided that these too can also self-recover and return to the original displayed values. Error messages are permitted provided the EUT can self-recover on completion of the test and they disappear from the EUT's display.

Preparation Mode - The equipment shall continue to operate as intended after the test. During the test there is allowed to be variations in all of the values within the replicated GUI

display on the support laptop and tablet provided that these can self-recover and return to the original displayed values. Error messages are permitted provided the EUT can self-recover on completion of the test and they disappear from the EUT's display.

With respect to: Transient Phenomena – Power Line Voltage Dips and Interrupts

Liver On Board Mode - The equipment shall continue to operate as intended after the test. During the test complete loss of all of the parameter values displayed within the GUI display and conversely within the replicated displays on the support laptop and tablet provided these values self-recover after the test or the function of the EUT can be restored by user intervention. Error messages are permitted provided the EUT self recovers or they can be fixed via user intervention.

Preparation Mode - The equipment shall continue to operate as intended after the test. During the test complete loss of all of the parameter values displayed within the GUI display and conversely within the replicated displays on the support laptop and tablet provided these values self-recover after the test or the function of the EUT can be restored by user intervention. Error messages are permitted provided the EUT self recovers or they can be fixed via user intervention.

External equipment intended for connection to signal input, signal output or other connectors shall comply with relevant IEC standard (e.g. IEC 60950 for IT equipment and the IEC 60601 series for medical electrical equipment). In addition, all such combinations – *systems* – shall comply with the standard IEC 60601-1-1, *Safety requirements for medical electrical systems.* Equipment not complying with IEC 60601-1 shall be kept outside the patient environment, as defined in the standard (at least 1.5 m from the patient or the patient support).

Any person who connects external equipment to signal input, signal output or other connectors has formed a system and is therefore responsible for the system to comply with the requirements of IEC 60601-1-1. If in doubt, contact OrganOx Ltd at 855-ORGANOX (855-674-2669).

The device complies with the EMC requirements according to IEC 60601-1-2:2014 when connected with external cables with the following specification:

Type		Description	Outdoor cable Y/N	Test Length	Max installation length
1	3 core unscreened	Mains cable for AC powered mode only	N	1.0m	1.0m
2	CAT5e STP	Ethernet Cable	N	3.0m	3.0m
3	2 core unscreened	DC power cable (for 12VDC charge mode only)	N	1.0m	1.0m

EMC TABLES

Guidance and Manufacturers declaration – electromagnetic emissions for all equipment and systems.

<table>
<tr><th colspan="3">The OrganOx metra is intended for use in the electromagnetic environment specified below. The customer or user of the OrganOx metra assures that it is used in such an environment.</th></tr>
<tr><th>Emissions test</th><th>Compliance</th><th>Electromagnetic environment guidance</th></tr>
<tr><td>EN6100-3-2:2006+A2:2009</td><td>Class A</td><td rowspan="4">The OrganOx metra is intended for use in a professional healthcare facilities and Special Healthcare – (Vehicular Use). The equipment is not intended to be used in a domestic or residential environment.</td></tr>
<tr><td>Radiated emissions
EN55011:2009+A1 2010</td><td>Class A</td></tr>
<tr><td>Conducted emissions
EN55011:2009+A1 2010</td><td>Class A</td></tr>
<tr><td>Conducted emissions
EN55022:2010 using CISPR 25 Line Impedance Stabilisation Network (LISN) as per EN 301489 in battery charging mode</td><td>Class B</td></tr>
<tr><td>Mains harmonic emissions
EN61000-3-2:2006 + A2:2009</td><td>Class A</td><td rowspan="2">The OrganOx metra is suitable for use in all establishments other than domestic and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.</td></tr>
<tr><td>Mains voltage fluctuations and flicker
EN61000-3-3:2013</td><td>Complies</td></tr>
<tr><td>CFR 47:2013 Part 15.107 and 15.109</td><td>Class A</td><td>The OrganOx metra uses Wi-Fi for local area communication. Wi-Fi can be disabled in accordance with p. 46 of this document (FCC number YXA-WU106AM).</td></tr>
</table>

EMC TABLES – PART TWO

Guidance and Manufacturer's declaration – electromagnetic emissions for all equipment and systems.

The OrganOx *metra* is intended for use in the electromagnetic environment specified below. The customer or user of the OrganOx *metra* assures that it is used in such an environment.			
Immunity test	**Test Level**	**Compliance Level**	**Electromagnetic environment guidance**
Electrostatic Discharge (ESD) EN61000-4-2:2009	±8kV – contact discharge ± 15kV – air discharge	8kV – contact discharge ≥ 15kV – air discharge	Floors should be wood, concrete or ceramic with synthetic material; the relative humidity should be at least 30%.
Radiated Immunity EN61000-4-3:2006+A2:2010	3 V/m 80MHz–2.7GHz – Frequency range 10V/m –voltage	3V/m 80MHz–2.7GHz - Frequency range 10V/m – test voltage	Portable and mobile RF communication equipment should be used no closer to any part of the OrganOx *metra,* including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. **Recommended separation distance:** d = 1.2 √*P* d = 1.2 √*P* 80MHz to 800 MHz d = 2.3 √*P* 800MHz to 2.5GHz Where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and *d* is the recommended separation distance in metres (m). Field strength from fixed RF transmitters as determined by an electromagnetic site survey 'should be less than the compliance level in each frequency range' (over the frequency range 150kHz to 80 MHz, field strength shall not exceed 3 V/m).
Electrical fast transient/burst EN61000-4-4:2012	±2kV for ac supply lines and ±1kV for signal lines	±2kV for ac supply lines and ±1kV for signal lines	Mains power quality shall be of a typical commercial or hospital environment.
Surge IEC61000-4-5:2006	±2kV for Common mode ±1kV for Differential mode	±2kV for Common mode ±1kV for Differential mode	
Conducted RF EN61000-4-6:2009 (Per IEC 60601-1-2 Ed. 4)	3 Vrms 150kHz – 80MHz	3 Vrms	Portable and mobile RF communication equipment should be used no closer to any part of the OrganOx *metra,* including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. **Recommended separation distance:** d = 1.2 √*P* d = 1.2 √*P* 80MHz to 800 MHz d = 2.3 √*P* 800MHz to 2.5GHz Where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and *d* is the recommended separation distance in metres (m).

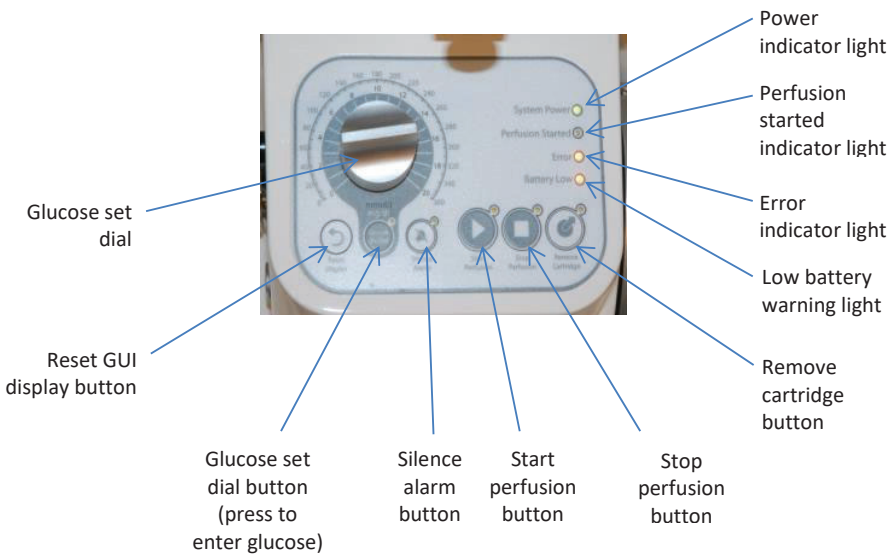
			Field strength from fixed RF transmitters as determined by an electromagnetic site survey 'should be less than the compliance level in each frequency range' (over the frequency range 150kHz to 80 MHz, field strength shall not exceed 3 V/m). Interference may occur in the vicinity of equipment marked with the following symbol: 
Power frequency (50/60Hz) magnetic field EN61000-4-8:2010	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines EN61000-4-11:2004	100% reduction for 10 ms/half cycle 30% reduction for 500 ms/25 cycles 100% reduction for 20 ms/1 cycle 100% interruption for 5s	100% reduction for 10 ms/half cycle 30% reduction for 500 ms/25 cycles 100% reduction for 20 ms/1 cycle 100% interruption for 5 s	Mains power quality shall be of a typical commercial or hospital environment.
Conducted transient immunity ISO 7637-2:2011	compliant	Pulse severity level I/II	Final measurements were made in an indoor semi-anechoic EMC chamber and therefore were not influenced by external atmospheric and climatic conditions, such as rainfall.
Conducted transient emissions ISO 7637-2:2011	compliant	LISN 5 µH/50Ω	Final measurements were made in an indoor semi-anechoic EMC chamber and therefore were not influenced by external atmospheric and climatic conditions, such as rainfall.
Magnetic immunity AIM 7351731 ISO 14223 ISO 14443-3 (Type A) ISO 14443-4 (Type B) ISO 18000-3 (Mode 1) ISO 18000-3 (Mode 3)	 134.2kHz / 65 A/m 13.56 MHz / 7.5 A/m 13.56 MHz / 7.5 A/m 13.56 MHz / 5 A/m 13.56 MHz / 12 A/m	 134.2kHz / 65 A/m 13.56 MHz / 7.5 A/m 13.56 MHz / 7.5 A/m 13.56 MHz / 5 A/m 13.56 MHz / 12 A/m	No effect observed / Essential functions maintained
Radiated RF immunity AIM 7351731 ISO 18000-7 ISO 18000-63 (Type C) ISO 18000-4 (Mode 1)	 433.92 MHz / 3 V/m 860-960 MHz in 1% increments / 54 V/m 2.45 GHz / 54 V/m	 433.92 MHz / 3 V/m 860-960 MHz in 1% increments / 54 V/m 2.45 GHz / 54 V/m	 No effect observed / Essential functions maintained WiFi communication lost, no other effect observed WiFi not required for device functionality, information only WiFi communication lost, no other effect observed WiFi not required for device functionality, information only

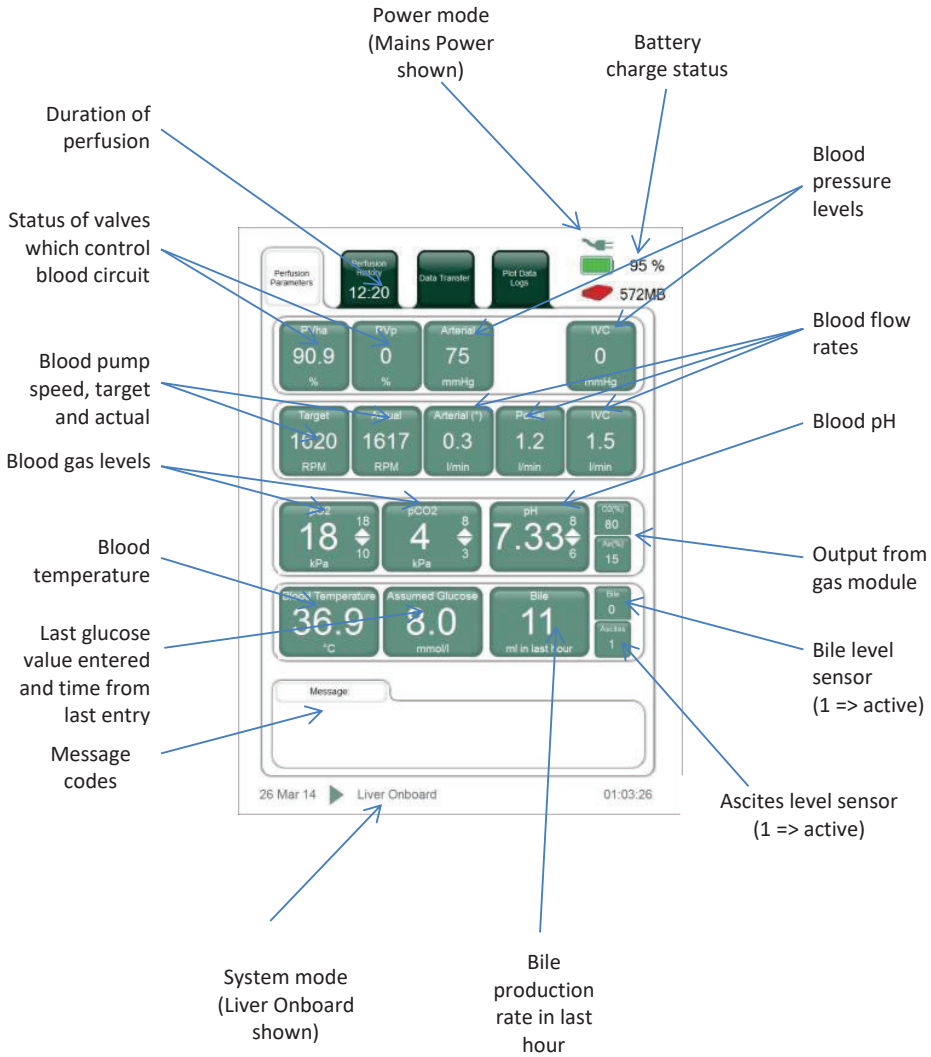
Four faces of the EUT were tested for each of the frequencies listed below:

Test Frequency (MHz)	Modulation	Test Level (V/m)
385	Pulse Modulation18 Hz	27
450	FM 5 kHz Deviation, 1 kHz sine wave	28
710	Pulse Modulation 217 Hz	9
745	Pulse Modulation 217 Hz	9
780	Pulse Modulation 217 Hz	9
810	Pulse Modulation 18 Hz	28
870	Pulse Modulation 18 Hz	28
930	Pulse Modulation 18 Hz	28
1720	Pulse Modulation 217 Hz	28
1845	Pulse Modulation 217 Hz	28
1970	Pulse Modulation 217 Hz	28
2450	Pulse Modulation 217 Hz	28
5240	Pulse Modulation 217 Hz	9
5500	Pulse Modulation 217 Hz	9
5785	Pulse Modulation 217 Hz	9

Radiated Immunity to RF Wireless Communications as per EN61000-4-3:2006+A2:2010

USER CONTROLS





Section Five: Technical Specifications

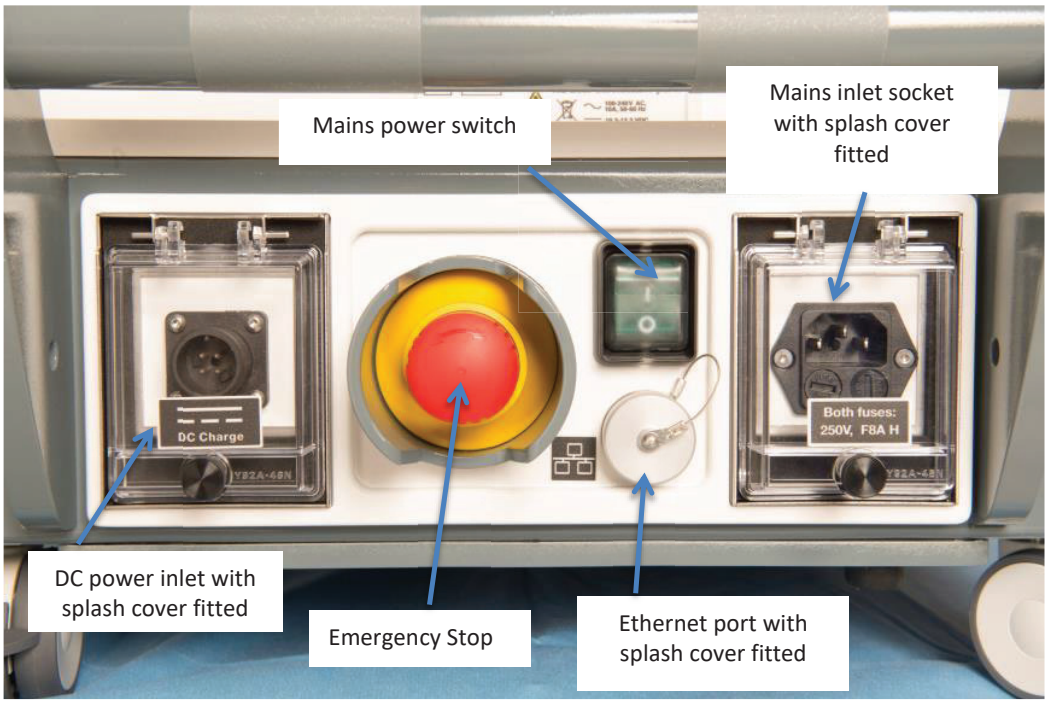
Parameter	Operating	Transit	Storage
Temperature (Retained Unit)	15 to 30°C	15 to 30°C continuous 0 to 50 °C for limited periods, when outside the range 15 to 30°C, exposure time (t) is calculated by ΔT x t = 150 °C.minutes. Where ΔT is the size of the excursion outside of the range 15 to 30°C. (E.g. 10 mins at 0 °C, 15 mins at 5 °C or 7.5 mins at 50 °C.)	0 to 40°C
Temperature (Disposable Set)	15 to 30°C	15 to 30°C continuous 0 to 50 °C for limited periods, when outside the range 15 to 30°C, exposure time (t) is calculated by ΔT x t = 150 °C.minutes. Where ΔT is the size of the excursion outside of the range 15 to 30°C. (E.g. 10 mins at 0 °C, 15 mins at 5 °C or 7.5 mins at 50 °C.)	15 to 25°C
Atmospheric pressure	750 to 1050 mbar	750 to 1050 mbar	750 to 1050 mbar
Relative Humidity	15 – 85% non-condensing	15 – 85% non-condensing	15 – 85% non-condensing

Supply Rating			
Electrical rating AC	100-240 VAC, 10A, 50-60 Hz		
Electrical rating DC	10.3 – 13.3 VDC, 10A		
Ingress Protection Rating	IP44		
Product life (Retained unit and Trolley)	24 hours		
Shelf life (Disposable Set)	12 months		
Shelf life (Retained Unit and trolley)	2 years		
Dimensions (with the trolley and hard cover)			
Height (Inches)	Length (Inches)	Depth (Inches)	Weight (lbs)
44	20	42	209
Dimensions (without the trolley and hard cover)			
Height (Inches)	Length (Inches)	Depth (Inches)	Weight (lbs)
43	19	36	165
Dimensions (Disposable Set)			
Height (Inches)	Length (Inches)	Depth (Inches)	Weight (lbs)
18.5	24.5	17.75	18

WIRELESS ADAPTER SPECIFICATION

Standards	IEEE 802.11n, IEEE 802.11g, IEEE 802.11b
Wireless Signal Rates With Automatic Fallback	11n: Up to 150Mbps (Dynamic) 11g: Up to 54Mbps (Dynamic) 11b: Up to 11Mbps (Dynamic)
Frequency Range	2.4-2.4835GHz
Wireless Transmit Power	18dBm(MAX)
Modulation Type	DBPSK,DQPSK,CCK, OFDM
Receiver Sensitivity	135M: -68dBm@10% PER 54M: -68dBm@10% PER 11M: -85dBm@8% PER
Work Mode	Ad-Hoc Infrastructure
Wireless Security	64/128 bit WEP WPA/WPA2, WPA-PSK/WPA2-PSK (TKIP/AES)

DEVICE CONNECTION



WARNING: Only OrganOx-approved terminals are to be connected to the Ethernet port.

Section Six: Troubleshooting

Most of the problems encountered will be easily solved. The first thing to check when troubleshooting the system is to make sure the power supply is available. If the power light comes on but the device still does not work, check the following table for probable causes and actions:

Trouble	Probable Cause	Action
No power	Mains power not connected and batteries flat	Connect mains power lead and switch on at rocker switch. If power does not return, switch off unit, remove mains power lead and check/replace fuses as described in the Servicing (Section Seven) If problem persists, contact OrganOx at 855-ORGANOX (855-674-2669)
Alarms	See table below	See table below
Display blank or missing or incorrect display elements at power-on	Software or display PC error	Press the display Reset button on the control panel. If problem persists, contact OrganOx at 855-ORGANOX (855-674-2669)
Liquid leaks from inside unit	Leak in water heating circuit	Switch off unit and disconnect mains power lead. Contact OrganOx at 855-ORGANOX (855-674-2669)
Power on, but buttons are unresponsive	An unresolved fault is preventing the system from starting	Check the fault codes in the table below
No flow reading displayed on display (i.e. displayed as '--')	Poor coupling between flow sensor and tube	Apply gel or water to outside of tubing, where it fits inside the flow sensor.

The device has alarms that are sounded when a fault condition occurs. The device can recover from many of these faults and perfusion will automatically resume. Check the following list of fault messages, possible causes and recommended actions to determine how to respond if the device alarm sounds.

The device has alarms that are classified into medium and low priority. If there is at least one medium priority fault condition the error indicator light will flash, and an audible alarm will sound at regular intervals. If fault conditions are only low priority the error indicator light will be permanently on with no audible alarm. Medium priority error message codes are shown with an asterisk next to them on the GUI display.

The device can recover from many of these faults and perfusion will automatically resume. Check the following list of fault messages, possible causes and recommended actions to determine how to respond if the device alarm sounds.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
50	MED	Measured blood temperature > 41°C	Ambient temperature too high	Remove OrganOx *metra* cover and/or move device to a cooler environment IMMEDIATELY.
			Blood gas analyzer not operational	Check that blood gas analyzer (BGA) is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. Contact Service Engineer if problem persists.
			Water not circulating through heater and oxygenator	Check that both water connections to oxygenator are fully engaged and have no kinks. Contact Service Engineer if problem persists.
60*	MED	Measured blood temperature > 41°C for more than 10 minutes	Blood gas analyzer temperature sensor or water heater malfunction.	Stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ.
80*†	MED	Low battery	No external power source	Connect to an external power source. Note that temperature control and oxygenation will be automatically shut down once alarm sounds.
			Battery nearing end-of-life.	Ensure battery is fully charged before device used again. Contact Service Engineer if rapid discharge problem persists.
90*†	MED	Empty battery – system has stopped	Battery empty. No external power source.	URGENTLY connect to an external power source and re-start the perfusion or re-start the device as necessary. If no power source available, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ.
100	LOW	Glucose update required	No glucose value has been entered for 4 hours or more	Measure blood glucose and enter value.
110	LOW	Less than 2 hours of perfusion remaining.	Perfusion has exceeded 22 hours with a maximum allowed period of 24 hours.	Remove liver from device as per IFU by 24 hours.
120	LOW	Temperature within electronics enclosure > 60°C	Excessive heat production or reduced heat dissipation within device.	Ensure blood temperature remains physiological. Remove outer hardcover and/or move device to cooler environment. If problem persists contact Service Engineer.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
130	MED	Temperature within electronics enclosure is > 70°C – system has stopped	Excessive heat production or reduced heat dissipation within device.	Ensure blood temperature remains physiological. URGENTLY remove outer hardcover and/or move device to cooler environment. Re-start the perfusion or re-start the device as necessary. If problem persists contact Service Engineer.
140*†	MED	No IVC pressure detected	IVC pressure sensor is not connected	Check that IVC pressure sensor is connected. Disconnect and reconnect IVC sensor according to IFU.
			IVC pressure sensor is faulty	If liver not connected, replace disposable set (do not attempt to replace sensor). If liver connected, stop perfusion and remove liver from device using cold perfusion. If problem persists with different disposable set, contact Service Engineer.
150*†	MED	No Arterial pressure detected	Arterial pressure sensor is not connected	Check that arterial pressure sensor is connected. Disconnect and reconnect IVC sensor according to IFU.
			Arterial pressure sensor is faulty	If liver not connected, replace disposable set (do not attempt to replace sensor). If liver connected, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. If problem persists with different disposable set, contact Service Engineer.
170*†	MED	No blood temperature measurement detected	Blood gas analyzer not operational	Check that blood gas analyzer (BGA) is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. Contact Service Engineer if problem persists.
			Blood gas analysis sensor is faulty	Replace blood gas analysis sensor as per IFU. If problem persists, stop perfusion and remove liver from device using cold perfusion It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
180*‡	LOW	interface board (IFB) timeout / no replies / IFB cyclic redundancy check (CRC) error	Hardware fault	Fault will normally self-resolve. Check the following on the OrganOx *metra* GUI over a period of 5 minutes to ensure that it has: 1) Temperature is controlled to 37C; 2) pO_2 and pCO_2 values remain within the normal range indicated; 3) Blood pump target RPM and actual RPM are within 100 RPM and IVC flow is non-zero. If this is not the case, power down and restart the OrganOx *metra* as per IFU. If error still persists with liver on board, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
190*‡	MED	Terumo timeout / no replies Terumo CRC error	Blood gas analyzer not operational	Check that blood gas analyzer (BGA) is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. Contact Service Engineer if problem persists.
			Hardware fault	Attempt to power down and restart the OrganOx *metra* as per IFU. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
200*‡	MED	Blood Pump Error	Hardware fault	Attempt to power down and restart the OrganOx *metra* as per IFU. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
220*‡	MED	Upper proportional pinch valve error	Hardware fault	Attempt to power down and restart the OrganOx *metra* as per IFU. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
230*‡	MED	Lower proportional pinch valve error	Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
240‡	MED	Portal flow sensor error: system cannot detect air bubbles	Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion. Contact Service Engineer. It is the surgeon's discretion whether to transplant this organ.
250‡	MED	IVC flow sensor error	Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
260	MED	Battery monitor error - no battery level available	Hardware fault	Urgently connect device to an external power supply (note - no warning will be given of empty battery). Contact Service Engineer.
270	MED	Syringes need replacement	Occluded tubing	Check all four syringe lines for occlusions. If problem persists, contact Service Engineer.
			Syringes empty	Replace syringes with syringes filled with freshly prepared solutions, as per IFU. Inform Service Engineer.
280	MED	High water temperature	Water not circulating through heater and oxygenator	Check that both water inlet and outlet connects to oxygenator are fully engaged and have no kinks. Contact Service Engineer if problem persists.
			Blood gas analyzer providing erroneous blood temperature information.	Check installation of blood gas analyzer (BGA) sensor. Check that BGA is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. Contact Service Engineer if problem persists.
			Ambient temperature too high	Move device to a cooler environment.
290†	MED	Low water reservoir	Not enough water in reservoir	Check and re-fill water reservoir
			System tilted to expose level sensor	Level the system as soon as practicable
			Possible leak in water circulation system	Check for leaks and re-fill water reservoir as necessary. Contact Service Engineer if problem persists.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
300	LOW	Ascites pump running continuously	Excessive fluid leakage from liver	Check surgical integrity of liver and take necessary action.
			Malfunction of ascites recirculation system.	Check ascites level sensorCorrect fitting of ascites recirculation line through pump. Contact Service Engineer if problem persists.
310	MED	Ascites pump never running	Malfunction of ascites recirculation system.	Check whether fluid has accumulated in liver bowl, and if so check ascites level sensor. Contact Service Engineer if problem persists.
			Hardware fault	Contact Service Engineer.
320	MED	No water temperature measurement detected	Hardware fault	Attempt to power down and restart the OrganOx *metra*. Check that blood temperature remains physiological. If not, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
330*	MED	Frequently empty blood reservoir	Excessive fluid in liver bowl	Check surgical integrity of liver and take necessary action. Check that IVC drainage is occurring and reposition cannula if necessary. Check functioning of ascites recirculation system. If issue persists, add *human albumin* to replenish reservoir.
340†	MED	Clinimix® pump error	Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists and liver already on board, deliver nutrition manually as per the IFU. Contact Service Engineer.
350†	MED	Bile pinch valve error	Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists and liver already on board, remove bile tubing from bile pinch valve - bile will now drain freely into bile collection compartment and bile production will no longer be automatically measured. Contact Service Engineer.
360	MED	Excessive blood/water temperature difference.	Blood gas analyzer providing erroneous blood temperature information. Or the Terumo sensor is not fully engaged.	Check installation of blood gas analyzer (BGA) sensor. Check that the Terumo sensor is correctly fitted and is clicked into place. Check that BGA is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. If the problem persists remove the liver using the rapid retrieval technique and contact Service Engineer if problem persists.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
			Ambient temperature too high	Remove hard cover and/or move device to a cooler environment.
			Water not circulating through heater and oxygenator	Check that both water inlet and outlet connects to oxygenator are fully engaged and have no kinks. If water not circulating, power the OrganOx *metra* down and restart as per IFU. Contact Service Engineer if problem persists.
370	MED	Low portal vein flow	Portal tubing kinked, Roberts clamp not open, or poor cannula placement.	Re-wet portal flow sensor. Ensure Roberts clamp on portal line within liver bowl is fully open and check portal line for kinks. If issue persists, reposition portal cannula.
			Empty reservoir	Check whether fluid has accumulated in liver bowl, and if so check ascites level sensor and pump. Add *human albumin* solution to replenish reservoir if necessary. Contact Service Engineer if problem persists.
			Lower pinch valve malfunction	Press 'Stop Perfusion', then 'Remove Cartridge' twice to fully open pinch valve, then 'Start Perfusion'. If problem persists, power down and restart the OrganOx *metra* as per IFU. If problem still persists with liver on board, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ.
380	MED	Low IVC flow	IVC tubing kinked, Roberts clamp not open, or poor cannula placement.	Ensure Roberts clamp on IVC line within liver bowl is fully open and check IVC line for kinks. If issue persists, reposition IVC cannula.
			Hardware fault	Check whether IVC pressure <2mm Hg with liver on board. If not, press 'Stop Perfusion', then 'Start Perfusion'. If problem persists, power down and restart the OrganOx *metra* as per IFU. If problem still persists with liver on board, stop perfusion and remove liver using cold perfusion. It is the surgeon's discretion whether to transplant this organ.
390	MED	Low hepatic artery flow	Arterial tubing kinked, Roberts clamp not open, or poor cannula placement.	Ensure Roberts clamp on arterial line within liver bowl is fully open and check arterial line for kinks. If issue persists, reposition arterial cannula.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
			Upper pinch valve malfunction	Press 'Stop Perfusion', then 'Remove Cartridge' twice to fully open pinch valve, then 'Start Perfusion'. If problem persists, power down and restart the OrganOx *metra* as per IFU. If problem persists with liver on board, stop perfusion and remove liver using cold perfusion. It is the surgeon's discretion whether to transplant this organ.
			Hardware fault	Press 'Stop Perfusion', then 'Start Perfusion'. If problem persists, power down and restart the OrganOx *metra* as per IFU. If problem still persists with liver on board, stop perfusion and remove liver using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact service engineer.
400	MED	Low blood temperature	Water not circulating through heater and oxygenator	Check that both water inlet and outlet connections to the oxygenator are fully engaged and have no kinks. Contact Service Engineer if problem persists.
			Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
410*	MED	Low blood oxygen levels	Oxygenator gas port not connected	Check that gas line into oxygenator is fully engaged and has no kinks. Contact Service Engineer if problem persists.
			Blood not circulating through blood gas analyzer bypass line	Check that the Roberts clamps on the blood gas analyzer bypass line are fully open, that the Terumo sensor is connected and that there are no kinks or obstructions on the line.
			Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion. It is the surgeon's discretion whether to transplant this organ. Contact Service Engineer.
430	MED	Unable to determine power source	Hardware fault	Urgently connect device to an external power supply (note - no warning will be given of empty battery). Contact Service Engineer.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
450	LOW	Measured blood temperature > 38°C	Ambient temperature too high	Remove the OrganOx *metra* cover and/or move device to a cooler environment as soon as possible.
			Blood gas analyzer not operational	Check that blood gas analyzer (BGA) is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. Contact Service Engineer if problem persists.
			Water not circulating through heater and oxygenator	Check that both water connections to oxygenator are fully engaged and have no kinks. Contact Service Engineer if problem persists.
460	LOW	Measured tower temperature < 5°C	Ambient temperature too low	Move device to a warmer environment as soon as possible. Contact Service Engineer if problem persists.
470	LOW	Oxygen Concentrator Failure	Hardware fault	Stop perfusion and attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion. Contact Service Engineer if problem persists.
480	LOW	High blood oxygen levels measured continuously for more than 3 minutes	Blood not circulating through BGA bypass line	Contact Service Engineer if problem persists.
490	LOW	High blood carbon dioxide levels measured continuously for more than 3 minutes	No gas flow into oxygenator	Check that the oxygenator gas inlet Colder Products Company (CPC) connector is fully engaged into the male panel mount CPC connector just above the portal flow sensor. Check that the BGA sensor is correctly fitted and is clicked in place. Check that the Roberts clamps on the BGA bypass line are fully open. Check that BGA is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. Attempt to power down and restart the OrganOx *metra.* If problem persists, stop perfusion and remove liver from device using cold perfusion. Contact Service Engineer if problem persists.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
500	LOW	Low blood carbon dioxide levels measured continuously for more than 3 minutes	Blood not circulating through BGA bypass line BGA not operational Hardware fault	Check that the Roberts clamps on the BGA bypass line are fully open, that the Terumo sensor is connected and that there are no kinks or obstructions on the line. Check that the BGA sensor is correctly fitted and is clicked in place. Check that BGA is in 'Operate' mode and that data displayed on BGA matches data on the OrganOx *metra* GUI. If not, power the OrganOx *metra* down and restart as per IFU. If problem persists, stop perfusion and remove liver from device using cold perfusion. Contact Service Engineer if problem persists.
510	LOW	Arterial blood pressure in excess of 100 mmHg for more than 3 minutes	Arterial tubing kinked, Roberts clamp not open, or poor cannula placement Upper pinch valve malfunction Hardware fault	Press 'Stop Perfusion' and then 'Start Perfusion'. If problem persists, power down and restart the OrganOx *metra* as per IFU. If problem persists, stop perfusion and remove liver from device using cold perfusion. Contact Service Engineer if problem persists.
520	LOW	Power Board Fault	Hardware fault	Attempt to power down and restart the OrganOx *metra*. If problem persists, stop perfusion and remove liver from device using cold perfusion, it is at the discretion of the transplanting surgeon if this organ is transplanted. Contact Service Engineer if problem persists.
10xx*	LOW	Internal software fault	An unexpected software condition has occurred	Re-start system (stop, switch off and on, start). Report failure to OrganOx, and provide log files for analysis
2060	LOW	Critical fault reported	Measured blood temperature exceeded 41°C for more than 10 minutes at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2080	LOW	Critical fault reported	Low battery potentially led to temperature control and oxygenation being shut down	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2090	LOW	Critical fault reported	Empty battery led to system stopping	Refer to 'Plot Data Logs' tab for detailed perfusion history.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
2140	LOW	Critical fault reported	No IVC pressure measurement was detected for more than 10s at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2150	LOW	Critical fault reported	No arterial pressure measurement was detected for more than 10s at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2170	LOW	Critical fault reported	No blood temperature measurement was detected for more than 10s at some point during the perfusion.	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2180	LOW	Critical fault reported	An Interface Board (IFB) error occurred for more than 5s at some point during the perfusion.	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2190	LOW	Critical fault reported	No measurements could be retrieved from the Terumo blood gas analyzer for more than 5s at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2200	LOW	Critical fault reported	A blood pump error occurred at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2210	LOW	Critical fault reported	An air compressor error occurred at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2220	LOW	Critical fault reported	An upper proportional pinch valve error occurred at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2230	LOW	Critical fault reported	A lower proportional pinch valve error occurred at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.

Message Code	Priority	Meaning	Possible Cause(s)	Action(s)
2330	LOW	Critical fault reported	The reservoir was frequently empty over the course of 30 minutes or more at some point during the perfusion	Refer to 'Plot Data Logs' tab for detailed perfusion history.
2410	LOW	Critical fault reported	Low blood oxygen levels were measured continuously for several minutes at some point during the perfusion.	Refer to 'Plot Data Logs' tab for detailed perfusion history.

† This fault will prevent the system from starting; unless a perfusion has already been started (a liver has been detected)
‡ This fault will prevent the system from starting
* This fault will lead to the generation of a related persistent four-digit message code

Section Seven: Maintenance and Repair

Storage

Clean the Retained Unit according to the instructions on page two before storing. The Retained Unit should be stored in a dry location out of direct sunlight. The Retained Unit will function normally if stored between 0°C and 40°C and 65% to 85% RH.

Prior to use, the Disposable Set should be stored in a dry location out of direct sunlight.

Servicing

Note: OrganOx Ltd will provide circuit diagrams, component part lists, descriptions, calibration instructions to assist service personnel in parts repair.

There are no device components that can be replaced during use of the OrganOx *metra*.

The only user serviceable parts on the device are the mains inlet fuses, which are located just below the mains inlet socket. To access the fuses, first switch the unit off and disconnect the mains lead and trickle charge lead, if being used. Unscrew the fuse holders with a flat-bladed screwdriver and replace both fuses. Both fuses are identical and are: 250V, F8A H, 5 x 20mm.

There are no other user serviceable parts on this device. In the event of any malfunction, the users should immediately contact OrganOx Ltd at 855-ORGANOX (855-674-2669).

Service intervals for the equipment and internal battery packs refer to the Service Manual Instructions for preventative inspection, calibration, maintenance and its frequency refer to the Service Manual.

Routine Maintenance

Water in the thermo-control unit should be replaced in its entirety at least once every 3 months via drainage port, situated underneath the device.

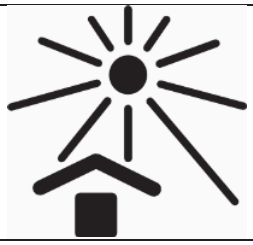
Maintenance and Repair - For Service Personnel Only

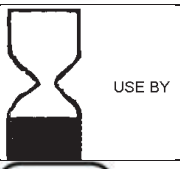
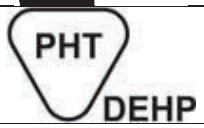
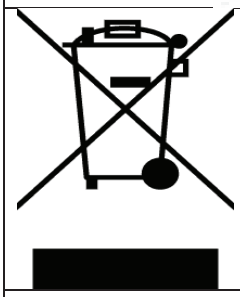
Battery pack replacement should be performed by trained service engineers only.

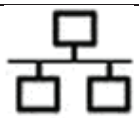
Shipment

For return to OrganOx, the device should be shipped with specialized agents who are experienced in the transportation of heavy, expensive medical equipment. For further information contact OrganOx at 855-ORGANOX (855-674-2669).

Appendix One: Glossary of Symbols

SYMBOL	USED FOR
	Warning or Caution
	FCC Declaration of Conformity
	MET Certification Mark
	European CE Mark
	Refer to instruction manual/ booklet
	Date of manufacture
	Serial number
	Catalogue Number
	Single Use - Do not reuse
	Do not re-sterilize
	Keep away from sunlight

	**Keep dry**
	**Temperature limit** The upper and lower limits will be displayed
	**Use by date**
	**Contains Phthalates**
	**Contains natural rubber latex**
REF	**Catalog Number**
	**Lot Number**
	**Sterilized by ethylene Oxide**
	**Manufacturer**
	**WEEE disposal requirements,** **Symbol indicating "Not for general waste." For European Union (EU) States.**
IP44	**Ingress Protection rating**
	**Pinch hazard**

	**Do not use If packaging is damaged**
	**No user serviceable parts**
	**Lift correctly**
	**No pushing**
	**Windows 7 Embedded**
	**High Voltage/Electric Shock warning**
	**USB Port**
	**Ethernet Port**
	**DC Charge**
	**Calibrator Port**

Appendix Two: Approved Perfusion Solutions

*All solutions used for the OrganOx metra must be **FDA approved products** with the same concentration and volume as the table noted below.*

Product	Concentration	Volume/mass
CLINIMIX E® 5/25 CLINIMIX E® 5/20	E 5/25 E 5/20	1000 ml/2000 ml
Cefuroxime	N/A	750mg 1.5 g (follow instructions for dilution to 750mg)
Sodium Heparin	5,000U/ml	5 ml
Calcium gluconate	10%	10 ml
Sodium bicarbonate	8.4%	100 ml
Epoprostenol sodium	N/A	0.5mg
Insulin	100U/ml	10 ml
Human albumin	5%	500 ml
Leuko-reduced packed red blood cells (pRBC) *(donor matched)*	N/A	1 unit
Sodium chloride	0.9%	250 ml
Hospital standard cold flush solution (e.g. HTK, UW)	2000 ml	2000 ml
Sodium Taurocholate (bile salts) (OrganOx provided)	5.6g	N/A

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Appendix Three: OrganOx *metra* US IDE Study (WP01)

A. OrganOx *metra* US IDE Study (WP01)

Study Design

The US IDE Study was a multicenter, open label, randomized (1:1), controlled trial comparing the efficacy of OrganOx *metra* (NMP) with SCS in human liver transplantation. Subjects were enrolled between October 9, 2016 and February 3, 2020 across 14 sites. The data for this PMA reflected data collected through the final database lock on July 1, 2021 and included 267 enrolled subjects, 266 transplanted livers (136 in the NMP arm and 130 in the SCS arm), and 383 randomized livers.

The primary endpoint in this study was severity of immediate graft injury as measured by early allograft dysfunction (EAD). The hypothesis was written as follows:

H_0: $EAD_{NMP} \geq EAD_{SCS}$
H_A: $EAD_{NMP} < EAD_{SCS}$,

where EAD is a binary outcome defined by the presence of one of the following 3 outcomes:

1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant
2. International normalized ratio ≥ 1.6 at day 7 post-transplant
3. ALT or AST > 2000 IU/L within the first 7 days post-transplant

A one-sided significance level of $\alpha = 0.025$ was used to test the primary endpoint; therefore, if the hypothesis test results in a one-sided p-value that is less than 0.025, the study would be considered a success. The sample size estimate was based on a one-sided significance level of 0.025 and power of 90%. The final sample size of 266 transplanted livers was derived based on these assumptions. No formal hypothesis testing was done for the secondary endpoints.

Donor livers were randomly assigned to NMP or SCS with 1:1 allocation as per a computer-generated randomization schedule using variable block randomization using the following stratification factors: participating (recipient) center and donor type (DBD or DCD). The randomization schedule was created by the study statistician and the size of the randomization blocks were known only to the study statistician and the Data Safety Monitoring Board (DSMB) statistician. A core laboratory was utilized to perform pathology evaluation of the study liver biopsies. The core laboratory histopathologists were blinded to randomization assignment, primary endpoints, and primary and secondary outcome results by randomization group. OrganOx representatives were blinded to primary endpoints and primary and secondary outcome results by randomization group. Local investigators were blinded to primary and secondary outcome results by randomization group.

With respect to safety evaluation, this study was conducted with robust safety oversight as all adverse events collected through follow-up were reviewed by an independent Medical Monitor. A Clinical Events Committee (CEC) adjudicated the most critical adverse events, and a DSMB reviewed aggregate safety data.

1. Clinical Inclusion and Exclusion Criteria

Randomization in the OrganOx US clinical study was limited to livers that met the following inclusion criteria:

1. DBD donor aged 40 years or greater
2. DCD donor aged 16 years or greater
3. Liver allograft from donation after brain death (DBD) or donation after circulatory death (DCD) donors

Enrollment in the OrganOx US clinical study was limited to subjects (recipients) that met the following inclusion criteria:

1. Subject is 18 years of age or greater
2. Subject is registered as an active recipient on the UNOS waiting list for liver transplantation
3. Subject, or legally authorized representative, is able and willing to give informed consent and HIPAA authorization
4. Subject is able and willing to comply with all study requirements (in the opinion of the Investigator)

Randomization of livers was not permitted in the OrganOx US clinical study if they met any of the following exclusion criteria:

1. Living donor liver
2. Liver intended for split transplant
3. Liver which Investigator is unwilling to randomize to either arm

Subjects were not permitted to enroll in the OrganOx US clinical study if they met any of the following exclusion criteria:

1. Subject requiring all of the following at the time of transplantation:
    a. Oxygen therapy via a ventilator/respirator
    b. Inotropic support
    c. Renal replacement therapy
2. Subject has acute/fulminant liver failure (UNOS status 1A)
3. Subject undergoing simultaneous transplantation of more than one organ (e.g., liver and kidney)
4. Subject is pregnant (as confirmed by urine or serum pregnancy test) or nursing
5. Concurrent enrollment in another clinical trial. Subjects enrolled in clinical trials or registries where only measurements and/or samples are taken (NO TEST DEVICE or TEST DRUG USED) are allowed to participate.

2. Follow-up Schedule

All transplanted subjects were assessed daily (Days 1-7) and Day 10 by their clinical team and managed according to standard local protocols during their post-transplant inpatient stay.

Subjects were scheduled to return for follow-up examinations at the following post-transplant timepoints:

- Day 30 (± 7 days)
- Month 3 (± 14 days)
- Month 6 (± 14 days)
- Month 12 (±30 days)

Preoperatively, information on donor and recipient demographics was collected along with the EQ-5D quality of life questionnaire. Postoperatively, the objective parameters measured during the study included biochemical assessments in addition to assessments for primary non-function, graft survival, subject survival, resource use, safety outcomes, readmissions, and renal replacement therapy requirement. The EQ-5D quality of life questionnaire was also completed at the Month 6 follow-up. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The pre-specified primary endpoint was:

To compare the effect of NMP to SCS in preventing preservation-related graft injury based on severity of immediate graft injury as measured by early allograft dysfunction (EAD) during days 1-7.

The primary endpoint analysis was performed on all transplanted subjects.). The study hypothesis was:

H_0: $EAD_{NMP} \geq EAD_{SCS}$
H_A: $EAD_{NMP} < EAD_{SCS}$,

where EAD is a binary outcome defined by the presence of one of the following 3 outcomes:

1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant
2. International normalized ratio ≥ 1.6 at day 7 post-transplant
3. ALT or AST > 2000 IU/L within the first 7 days post-transplant

A one-sided significance level of $\alpha = 0.025$ was used to test the primary endpoint; therefore, if the hypothesis test results in a one-sided p-value that is less than 0.025, the study would be considered a success.

The pre-specified secondary endpoints are listed below and were compared between NMP and SCS arms. No formal hypothesis testing was done for the secondary endpoints.

- Primary non-function rates: irreversible graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation.
- Graft survival rates at 30 days, 3 months, and 6 months following transplantation.
- Subject survival rates at 30 days, 3 months, and 6 months following transplantation.
- Assessment of mean arterial pressure (MAP) pre- and post-reperfusion and requirement for vasopressor use.
- Bilirubin, GGT, ALT, AST, ALP, and INR at days 1-7, day 30, month 3, and month 6 post-transplant.

- Lactate at days 1-7 while the subject is in ICU.
- Analysis of post-reperfusion biopsies of Ischemia Reperfusion Injury (IRI).
- Incidence of biliary investigations and/or interventions between 7 days and 6 months post-transplant.
- Incidence of livers randomized but not transplanted and reasons for not-transplanting.
- Incidence of one or more of the following per randomized liver: (i) EAD; (ii) discard (non-transplant) of a retrieved liver; (iii) primary non-function.
- Assessment of logistical and healthcare costs (length of stay in ICU and hospital) and quality of life measures

Accountability of PMA Cohort

Fifteen (15) investigative sites were initiated during the study. As detailed in Figure 1, a total of 383 livers were randomized into either the NMP group (n=192) or SCS group (n=191). Table 1 provides the detailed breakdown of subject disposition by randomization group and donor type along with the reason for study exit of livers that did not proceed to transplant. There were 267 enrolled subjects with 266 transplanted livers (136 in the NMP arm and 130 in the SCS arm).

At the time of the database lock, of the 267 subjects enrolled in the IDE study, 91.0% (243/267) subjects are available for analysis at the completion of the Month 12 post-transplant visit, the final Month 12 visit occurred on February 19, 2021. The dataset included data for all eligible subjects through the Month 12 follow-up visit. 99.6% of subjects that were not exited from the study before Month 12 completed their Month 12 follow-up visit. Of enrolled subjects, 89.7% (122/136) of the NMP subjects and 92.4% (121/131) of the SCS subjects completed the Month 12 follow-up visit. The remaining Month 12 visits in each arm were not completed as the subjects were exited from the study prior to the Month 12 follow-up visit.

- Fourteen (14) of the investigative sites enrolled a total of 267 subjects.
    - One (1) enrolling site (Site #105) elected to discontinue participation during the study after enrolling two (2) subjects andwas closed following completion of subject follow-up. Both subjects enrolled at that site were exited from the study following completion of their Month 12 visit.
- One (1) site (Site #107) screened subjects throughout the study, but did not enroll any subjects, and is therefore excluded fromthe enrollment table below.

The flowchart in Figure 1 provides the data for final analysis for the ITT population. There were a total of 116 randomized livers that were excluded from the study (56 NMP, 60 SCS). Of these livers:

- Ninety (90) livers were deemed not suitable for retrieval for transplant by the study investigators (40 NMP, 50 SCS). Of these ninety (90) livers:
    - Eighty-six (86) livers were not procured (38 NMP, 48 SCS). Details are provided below:

- Forty-six (46) livers where the donor did not proceed (DCD donor did not proceed to donation or prolonged warm ischemic time, outside of local criteria for liver transplantation) (20 NMP, 26 SCS)
- Twenty-one (21) livers due to donor liver quality (cirrhosis/fibrosis/steatosis) (9 NMP, 12 SCS)
- Fourteen (14) livers due to other reasons (5 NMP, 9 SCS)
- Two (2) livers due to injury to the hepatic artery (1 NMP, 1 SCS)
- One (1) liver due to injury to the IVC/parenchymal damage (1 NMP, 0 SCS)
- One (1) liver due to abnormal lesion within the liver (1 NMP, 0 SCS)
- One (1) liver due to donor problem (1 NMP, 0 SCS)

  - Two (2) livers were procured for research purposes (1 NMP, 1 SCS).
  - Two (2) livers were procured and transplanted outside of the study (1 NMP, 1 SCS).

Of the remaining twenty-six (26) livers that were excluded from the study:

- Eight (8) livers were excluded because the subject was not medically suitable (eligible) on the day to proceed with the transplant (5 NMP, 3 SCS)
- Five (5) livers were discarded following retrieval, prior to transport (2 NMP, 3 SCS):
- Three (3) livers were discarded following transport (3 NMP, 0 SCS):
- Two (2) livers were excluded because the subject was withdrawn by the investigator (2 NMP, 0 SCS) due to cardiac issues (1 NMP) and heart arrhythmia (1 NMP)
- Two (2) livers were excluded because the subject withdrew consent (1 NMP, 1 SCS)
- Six (6) livers were excluded for other reasons (3 NMP, 3 SCS). Details are as follows:

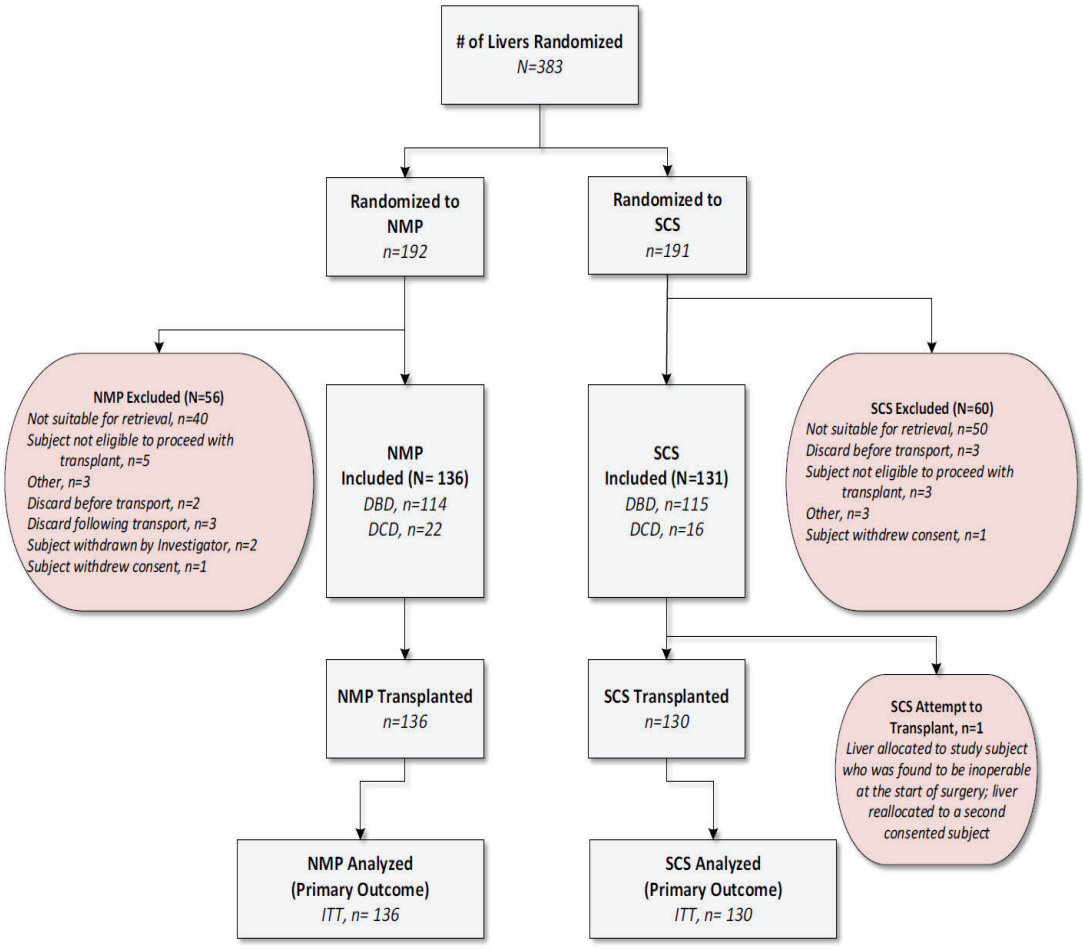

Figure 1 – Study Accountability Flow

Table 1: Subject Disposition by Randomized Group and Donor Type

	Overall		DBD		DCD	
	NMP	SCS	NMP	SCS	NMP	SCS
Randomized	192	191	143	144	49	47
Enrolled (knife-to-skin contact)	136	131	114	115	22	16
If enrolled, donor type						
DBD	114	115	114	115	0	0
DCD	22	16	0	0	22	16
Not Enrolled (no knife-to-skin contact)	56	60	29	29	27	31
Reason for study exit						
Liver not Suitable for Retrieval	40	50	15	22	25	28
Liver Discarded Before Transport	2	3	1	2	1	1
Liver Discarded Following Transport	3	0	3	0	0	0
Subject was not Eligible to Proceed withTransplant	5	3	4	3	1	0
Subject Withdrew Consent	1	1	1	0	0	1
Subject Withdrawn by Investigator	2	0	2	0	0	0
Other	3	3	3	2	0	1
Transplanted	136	130	114	114	22	16
If transplanted, Per-Protocol analysis group						
NMP*	133	0	113	0	20	0
SCS	0	130	0	114	0	16
If transplanted, As-Treated analysis group						
NMP*	133	2	113	1	20	1
SCS	0	130	0	114	0	16
Re-allocated	0	1	0	1	0	0

*One subject (AGBX122) was excluded from the analysis due to exclusion criteria being met. Two additional subjects(AEJX212, AELD404) were excluded due to being transported using Static Cold Storage.

The primary analysis was performed on all subjects in the intent-to-treat (ITT) population. Per the protocol and SAP, additional sensitivity analyses included:

1. Analysis of donor type crossovers per the corrected donor type
2. Analysis of preservation type where any livers randomized to the NMP arm, but unable to be preserved on the machine and therefore preserved using SCS, were analyzed in the SCS arm
3. Multiple imputation for EAD status that is unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD
4. Per Protocol analysis
   For item 1 in the list above, there were no transplanted livers where the donor type was corrected and considered a crossover, therefore no results are presented.

   Following is a summary of the populations analyzed:

   - The ITT population includes all transplanted subjects (a subject with reperfusion of a donor liver) and analyzes them in the groups to which the liver was randomly assigned, irrespective of whether the assigned method of preservation was actually used.
   - The Per-Protocol population includes all transplanted subjects who were followed according to the protocol procedures with no major deviations.
     - One (1) subject (Subject 08-021/Liver AGBX122) was excluded from the Per-Protocol analysis due to exclusion criteria being met.
     - Two (2) subjects (Subject 13-003/Liver AEJX212 and Subject 06-019/Liver AELD404) were excluded from the Per-Protocol analysis as they were randomized to NMP but were unable to be placed on the device and instead were transported using SCS.
   - The As-Treated population includes all transplanted subjects and analyzes them in the treatment groups corresponding to the method of preservation that was actually used.
     - One (1) subject (Subject 08-021/Liver AGBX122) was excluded from the As-Treated analysis due to exclusion criteria being met.
     - Two (2) subjects (Subject 13-003/Liver AEJX212 and Subject 06-019/Liver AELD404) were included in the SCS arm in the As-Treated analysis because they received livers that were randomized to NMP but were unable to be placed on the device and instead were transported using SCS.

   There were three (3) subjects (Subject 08-017/Liver AFJX183, Subject 03-049/Liver AGJY324, and Subject 09-002/Liver AECG396) identified as having elevated day 7 INR values due to therapeutic anticoagulation. Day 7 INR values for these three (3) subjects were therefore considered missing for all analyses, and imputed to determine EAD status.

Study Population Demographics and Baseline Parameters

Table 2 summarizes baseline demographics of the 266 donors (136 NMP, 130 SCS) with attempted transplants. There were no noteworthy differences in the donor demographics between the NMP and SCS groups.

Table 2: Donor Demographics with Attempted Transplant

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Age (years)						
N	136	130	114	114	22	16
Mean ± SD	53.1 ± 12.9	52.5 ± 11.5	56.5 ± 9.3	54.4 ± 9.7	35.6 ± 15.2	38.7 ± 14.4
Median	54.0	52.0	56.0	53.0	30.5	37.0
Range (Min, Max)	(18.0, 80.0)	(20.0, 79.0)	(40.0, 80.0)	(40.0, 79.0)	(18.0, 66.0)	(20.0, 61.0)
IQR	47.0, 60.0	45.0, 60.0	49.0, 62.0	47.0, 61.0	22.0, 47.0	27.0, 50.0
Male	45.6% (62/136)	52.3% (68/130)	43.0% (49/114)	50.9% (58/114)	59.1% (13/22)	62.5% (10/16)
Female	54.4% (74/136)	47.7% (62/130)	57.0% (65/114)	49.1% (56/114)	40.9% (9/22)	37.5% (6/16)
Race						
American Indian or Alaskan Native	0.7% (1/136)	0.8% (1/130)	0.0% (0/114)	0.9% (1/114)	4.5% (1/22)	0.0% (0/16)
Asian	0.0% (0/136)	0.8% (1/130)	0.0% (0/114)	0.9% (1/114)	0.0% (0/22)	0.0% (0/16)
Black or African American	18.4% (25/136)	20.8% (27/130)	21.1% (24/114)	23.7% (27/114)	4.5% (1/22)	0.0% (0/16)
Native Hawaiian or other Pacific Islander	0.0% (0/136)	0.0% (0/130)	0.0% (0/114)	0.0% (0/114)	0.0% (0/22)	0.0% (0/16)
White	77.9% (106/136)	75.4% (98/130)	76.3% (87/114)	73.7% (84/114)	86.4% (19/22)	87.5% (14/16)
Other	2.9% (4/136)	2.3% (3/130)	2.6% (3/114)	0.9% (1/114)	4.5% (1/22)	12.5% (2/16)
Ethnicity						
Hispanic or Latino	23.1% (9/39)	25.0% (10/40)	24.2% (8/33)	21.6% (8/37)	16.7% (1/6)	66.7% (2/3)
Not Hispanic or Latino	76.9% (30/39)	75.0% (30/40)	75.8% (25/33)	78.4% (29/37)	83.3% (5/6)	33.3% (1/3)
Diabetes	18.0% (24/133)	11.8% (15/127)	20.7% (23/111)	13.5% (15/111)	4.5% (1/22)	0.0% (0/16)
Smoker	52.7% (69/131)	47.2% (60/127)	53.2% (58/109)	45.9% (51/111)	50.0% (11/22)	56.3% (9/16)
History of Heavy Alcohol Use	19.5% (26/133)	22.8% (29/127)	21.4% (24/112)	23.4% (26/111)	9.5% (2/21)	18.8% (3/16)
History of Illicit Drug Use	35.1% (47/134)	41.3% (52/126)	33.0% (37/112)	40.5% (45/111)	45.5% (10/22)	46.7% (7/15)
Body Mass Index (BMI) (kg/m^2)						
N	136	130	114	114	22	16
Mean ± SD	30.2 ± 7.9	29.4 ± 6.9	30.5 ± 8.4	29.8 ± 6.9	28.9 ± 5.1	26.6 ± 6.3
Median	29.2	28.3	29.2	28.5	29.3	25.3
Range (Min, Max)	(18.2, 80.7)	(17.3, 51.0)	(18.2, 80.7)	(17.8, 51.0)	(20.7, 37.8)	(17.3, 44.9)
IQR	25.6, 33.8	24.5, 32.6	25.6, 34.6	25.1, 33.1	25.9, 32.6	23.0, 28.0
Diagnosis of Hepatitis C Virus (HCV)	8.1% (11/136)	3.8% (5/130)	8.8% (10/114)	3.5% (4/114)	4.5% (1/22)	6.3% (1/16)
Diagnosis of Hepatocellular Carcinoma (HCC)	0.0% (0/136)	0.0% (0/130)	0.0% (0/114)	0.0% (0/114)	0.0% (0/22)	0.0% (0/16)

Denominator includes all donors that have a demographics assessment date
Data reported as 'unknown' are considered as missing

Table 3 summarizes baseline characteristics of the donors with attempted transplants. There were no major differences in cause of death or mean DRI between the randomization arms.

Table 3: Donor Baseline Characteristics with Attempted Transplant

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Cause of Death						
Cerebrovascular Accident (CVA)	37.5% (51/136)	44.6% (58/130)	40.4% (46/114)	47.4% (54/114)	22.7% (5/22)	25.0% (4/16)
Hypoxia	2.2% (3/136)	1.5% (2/130)	0.9% (1/114)	1.8% (2/114)	9.1% (2/22)	0.0% (0/16)
Trauma	15.4% (21/136)	15.4% (20/130)	14.0% (16/114)	13.2% (15/114)	22.7% (5/22)	31.3% (5/16)
Anoxia	40.4% (55/136)	34.6% (45/130)	41.2% (47/114)	35.1% (40/114)	36.4% (8/22)	31.3% (5/16)
Other	4.4% (6/136)	3.8% (5/130)	3.5% (4/114)	2.6% (3/114)	9.1% (2/22)	12.5% (2/16)
Donor Risk Index (DRI)						
N	136	130	114	114	22	16
Mean ± SD	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	1.9 ± 0.4	1.9 ± 0.5
Median	1.6	1.6	1.5	1.6	1.9	1.7
Range (Min, Max)	(1.1, 2.8)	(1.0, 3.1)	(1.1, 2.4)	(1.0, 2.3)	(1.4, 2.8)	(1.4, 3.1)
IQR	1.4, 1.8	1.4, 1.8	1.3, 1.8	1.4, 1.8	1.5, 2.1	1.6, 2.0

Table 4 summarizes the baseline demographics of the 267 enrolled subjects (136 NMP, 131 SCS). There were no notable differences in the subject demographics between the NMP and SCS groups.

Table 4: Subject Demographics by Donor Type and Randomization Arm

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Age (years)						
N	136	131	114	115	22	16
Mean ± SD	57.4 ± 10.5	57.2 ± 10.6	57.7 ± 10.4	57.8 ± 10.5	55.8 ± 11.3	52.6 ± 10.3
Median	59.0	60.0	59.5	60.0	58.0	55.0
Range (Min, Max)	(20.0, 76.0)	(21.0, 77.0)	(21.0, 76.0)	(21.0, 77.0)	(20.0, 73.0)	(37.0, 67.0)
IQR	54.0, 64.0	52.0, 65.0	54.0, 64.0	53.0, 65.0	53.0, 62.0	42.0, 59.0
Male	68.4% (93/136)	63.4% (83/131)	69.3% (79/114)	66.1% (76/115)	63.6% (14/22)	43.8% (7/16)
Female	31.6% (43/136)	36.6% (48/131)	30.7% (35/114)	33.9% (39/115)	36.4% (8/22)	56.3% (9/16)
Race						
American Indian or Alaskan Native	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Asian	0.0% (0/136)	0.8% (1/131)	0.0% (0/114)	0.9% (1/115)	0.0% (0/22)	0.0% (0/16)
Black or African American	3.7% (5/136)	6.9% (9/131)	3.5% (4/114)	7.0% (8/115)	4.5% (1/22)	6.3% (1/16)

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Native Hawaiian or other Pacific Islander	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
White	93.4% (127/136)	90.8% (119/131)	93.0% (106/114)	90.4% (104/115)	95.5% (21/22)	93.8% (15/16)
Other	2.9% (4/136)	0.8% (1/131)	3.5% (4/114)	0.9% (1/115)	0.0% (0/22)	0.0% (0/16)
Ethnicity						
Hispanic or Latino	11.0% (15/136)	9.9% (13/131)	11.4% (13/114)	9.6% (11/115)	9.1% (2/22)	12.5% (2/16)
Not Hispanic or Latino	89.0% (121/136)	90.1% (118/131)	88.6% (101/114)	90.4% (104/115)	90.9% (20/22)	87.5% (14/16)
Etiology of Liver Disease/ Indication for Liver Transplant*						
Hepatocellular Disease	81.6% (111/136)	85.5% (112/131)	83.3% (95/114)	87.8% (101/115)	72.7% (16/22)	68.8% (11/16)
Cholestatic Liver Disease	8.1% (11/136)	6.9% (9/131)	6.1% (7/114)	7.0% (8/115)	18.2% (4/22)	6.3% (1/16)
Vascular Disease	0.7% (1/136)	0.0% (0/131)	0.9% (1/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Metabolic disorder and metabolic liver disease	5.1% (7/136)	6.1% (8/131)	5.3% (6/114)	5.2% (6/115)	4.5% (1/22)	12.5% (2/16)
Primary Hepatocellular carcinoma	31.6% (43/136)	29.8% (39/131)	35.1% (40/114)	29.6% (34/115)	13.6% (3/22)	31.3% (5/16)
Toxic reactions	0.0% (0/136)	1.5% (2/131)	0.0% (0/114)	0.9% (1/115)	0.0% (0/22)	6.3% (1/16)
Trauma	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Other	11.0% (15/136)	12.2% (16/131)	8.8% (10/114)	10.4% (12/115)	22.7% (5/22)	25.0% (4/16)
Body Mass Index (BMI) (kg/m^2)						
N	136	131	114	115	22	16
Mean ± SD	29.2 ± 5.7	29.5 ± 6.0	29.4 ± 5.8	29.8 ± 5.8	27.8 ± 4.9	27.7 ± 7.5
Median	28.3	28.9	28.7	29.1	26.6	26.4
Range (Min, Max)	(18.5, 49.3)	(16.8, 49.5)	(18.5, 49.3)	(16.8, 49.5)	(21.8, 41.4)	(18.7, 47.4)
IQR	25.4, 32.0	25.4, 33.0	25.6, 32.1	25.6, 33.2	24.9, 30.3	22.1, 31.5
Smoker	31.9% (43/135)	26.2% (34/130)	32.7% (37/113)	25.4% (29/114)	27.3% (6/22)	31.3% (5/16)
History of Heavy Alcohol Use	37.1% (49/132)	33.1% (43/130)	38.7% (43/111)	31.6% (36/114)	28.6% (6/21)	43.8% (7/16)
Re-transplant	0.7% (1/136)	1.5% (2/131)	0.9% (1/114)	1.7% (2/115)	0.0% (0/22)	0.0% (0/16)
If re-transplant, cause of failure of previous liver transplant*						
Primary graft non-function	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Hepatic artery thrombosis	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Chronic rejection	0.0% (0/136)	1.5% (2/131)	0.0% (0/114)	1.7% (2/115)	0.0% (0/22)	0.0% (0/16)

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Ischemic type biliary lesions after donation after cardiac death	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Recurrent non-neoplastic disease causing late graft failure	0.0% (0/136)	0.0% (0/131)	0.0% (0/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Recurrence of original liver disease	0.7% (1/136)	0.0% (0/131)	0.9% (1/114)	0.0% (0/115)	0.0% (0/22)	0.0% (0/16)
Other	0.0% (0/136)	0.8% (1/131)	0.0% (0/114)	0.9% (1/115)	0.0% (0/22)	0.0% (0/16)

*Multiple responses are possible for 1 subject
† Denominator includes all subjects that have a demographics assessment date
Data reported as 'unknown' are considered as missing

Table 5 summarizes preservation times for NMP and SCS livers. The mean total preservation time using the As Treated population was 75% longer in the NMP arm of the study compared to the SCS arm (NMP 553.8 ± 115.9 minutes; SCS 316.9 ± 94.1 minutes).

Table 5: NMP and SCS Preservation Times (As-Treated Analysis)

	Overall		DBD		DCD	
Measure	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Cold Ischemia Time (minutes)[1]						
N	134	132	113	115	21	17
Mean ± SD	134.9 ± 35.7	316.9 ± 94.1	130.3 ± 35.2	315.3 ± 95.8	159.9 ± 27.8	328.0 ± 82.8
Median	133.5	303.0	126.0	303.0	156.0	315.0
Range (Min, Max)	(24.0, 229.0)	(143.0, 623.0)	(24.0, 229.0)	(143.0, 623.0)	(122.0, 228.0)	(211.0, 505.0)
IQR	111.0, 157.0	246.0, 370.5	108.0, 153.0	243.0, 368.0	141.0, 172.0	269.0, 395.0
Time on Pump (minutes) - NMP[2]						
N	133	-	112	-	21	-
Mean ± SD	356.2 ± 105.9		349.9 ± 103.7		389.8 ± 113.6	
Median	323.0		322.0		363.0	
Range (Min, Max)	(196.0, 701.0)		(196.0, 701.0)		(256.0, 616.0)	
IQR	269.0, 421.0		262.5, 403.0		297.0, 482.0	
Total Preservation Time (minutes)[3]						
N	134	132	113	115	21	17
Mean ± SD	553.8 ± 115.9	316.9 ± 94.1	543.0 ± 110.0	315.3 ± 95.8	611.5 ± 132.2	328.0 ± 82.8
Median	523.0	303.0	517.0	303.0	577.0	315.0
Range (Min, Max)	(365.0, 890.0)	(143.0, 623.0)	(365.0, 890.0)	(143.0, 623.0)	(439.0, 872.0)	(211.0, 505.0)
IQR	466.0, 617.0	246.0, 370.5	463.0, 594.0	243.0, 368.0	522.0, 676.0	269.0, 395.0

	Overall		DBD		DCD	
Measure	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Functional Warm Ischemia Time (minutes)[4]						
N	20	17	-	-	20	17
Mean ± SD	12.3 ± 4.9	11.4 ± 3.6			12.3 ± 4.9	11.4 ± 3.6
Median	12.5	11.0			12.5	11.0
Range (Min, Max)	(3.0, 22.0)	(7.0, 19.0)			(3.0, 22.0)	(7.0, 19.0)
IQR	9.5, 14.5	9.0, 14.0			9.5, 14.5	9.0, 14.0

[1]Cold ischemia time (NMP) is calculated as time from aortic cold perfusion to initiation of NMP for the DCD arm and time of cross clamp to initiation of NMP for the DBD arm.
[1]Cold ischemia time (SCS) is calculated as time from aortic cold perfusion to portal reperfusion for the DCD arm and time from cross clamp to portal reperfusion for the DBD arm.
[2]Time on pump (NMP) is calculated as time from initiation of NMP to cessation of NMP.
[3]Total preservation time is calculated as time from cross clamp to portal reperfusion in the DBD arm and time from aortic cold perfusion to portal reperfusion in the DCD arm.
[4]Functional warm ischemia time (minutes) is calculated for DCD donors only as onset time of systolic blood pressure falling below 50mmHg (SBP < 50 mmHg) to earlier of time of start of aortic cold perfusion or time of start of portal cold perfusion.

Table 6 shows procedural details for the NMP and SCS groups**.** The mean total operative time was similar between the groups (NMP 350.2 minutes; SCS 345.5 minutes). The increased mean anastomotic time reported for NMP livers (NMP 60.2 ± 22.3 vs. SCS 38.5 ± 19.2) was not due to an increase in operative time. The increased time was due to inclusion of the cold flush time following cessation of NMP in the calculation of anastomotic time, which is not required for SCS livers.

Of note is the reduction in the occurrence of post-reperfusion syndrome in the NMP arm of the study (NMP 5.9%; SCS 14.6%).

Table 6: Summary of Liver Procedures

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
Total Operative Time (mins.)						
N	136	131	114	115	22	16
Mean ± SD	350.2 ± 110.1	345.5 ± 112.5	345.1 ± 107.9	342.8 ± 107.4	376.6 ± 119.8	365.3 ± 146.6
Median	332.5	326.0	328.0	324.0	381.5	381.0
Range (Min, Max)	(133.0, 670.0)	(104.0, 788.0)	(133.0, 670.0)	(104.0, 651.0)	(175.0, 588.0)	(160.0, 788.0)
IQR	277.0, 405.5	267.0, 409.0	277.0, 401.0	267.0, 408.0	281.0, 481.0	262.0, 429.0
Anastomotic time (secondary warm ischemia)[1] (mins.)						
N	132	129	110	113	22	16
Mean ± SD	60.2 ± 22.3	38.5 ± 19.2	60.1 ± 22.7	38.7 ± 19.5	60.2 ± 20.5	37.4 ± 17.2
Median	57.0	33.0	57.0	33.0	55.5	33.5
Range (Min, Max)	(22.0, 138.0)	(5.0, 129.0)	(22.0, 138.0)	(5.0, 129.0)	(28.0, 100.0)	(10.0, 64.0)

	Overall		DBD		DCD	
Characteristic	**NMP**	**SCS**	**NMP**	**SCS**	**NMP**	**SCS**
IQR	43.0, 73.0	26.0, 46.0	42.0, 72.0	26.0, 43.0	47.0, 75.0	24.0, 50.0
Occurrence of post-reperfusion syndrome [2]	5.9% (8/136)	14.6% (19/130)	4.4% (5/114)	14.0% (16/114)	13.6% (3/22)	18.8% (3/16)
Use of vasopressors prior to and after reperfusion	97.4% (114/117)	99.1% (108/109)	96.9% (95/98)	98.9% (93/94)	100.0% (19/19)	100.0% (15/15)
Intraoperative transfusion of blood and blood products	79.4% (108/136)	84.6% (110/130)	78.1% (89/114)	83.3% (95/114)	86.4% (19/22)	93.8% (15/16)

[1]Defined as time between removal of organ from ice (SCS) or perfusion device (NMP) to organ reperfusion (whichever is first of portal or arterial)
[2]Defined as a decrease in mean arterial pressure (MAP) of more than 30% from the baseline value for more than one minute during the first five minutes after reperfusion

Safety and Effectiveness Results

Safety Results

Table 7 below provides a summary of the serious adverse events (SAEs) that occurred in ≥ 1% of subjects by randomization arm. A detailed listing of all reported AEs including events resulting in death is provided in the clinical study report. There were 275 SAEs in 95 subjects in the NMP arm and 244 SAEs in 93 subjects in the SCS arm.

Table 7: SAEs by System and Specific Codes that Occurred in ≥ 1% of Subjects

	NMP n(%)		SCS n(%)	
Safety Event Type	**Patients (N = 136)**	**Events (N = 275)**	**Patients (N = 131)**	**Events (N = 244)**
Hepatic	39 (28.7)	68 (24.7)	37 (28.2)	47 (19.3)
Biliary stricture (anastomotic)	17 (12.5)	20 (7.3)	7 (5.3)	7 (2.9)
Rejection	8 (5.9)	9 (3.3)	16 (12.2)	17 (7.0)
Graft dysfunction	14 (10.3)	14 (5.1)	6 (4.6)	7 (2.9)
Bile leak	3 (2.2)	3 (1.1)	4 (3.1)	4 (1.6)
Cholangitis	5 (3.7)	5 (1.8)	2 (1.5)	2 (0.8)
Other	4 (2.9)	5 (1.8)	3 (2.3)	3 (1.2)
Biliary other	3 (2.2)	3 (1.1)	2 (1.5)	2 (0.8)
Hepatic artery thrombosis	4 (2.9)	4 (1.5)	1 (0.8)	1 (0.4)
Ischemic cholangiopathy	2 (1.5)	2 (0.7)	1 (0.8)	3 (1.2)
Bleeding Complications	15 (11.0)	16 (5.8)	24 (18.3)	26 (10.7)
Bleeding – transfusion required	8 (5.9)	8 (2.9)	12 (9.2)	12 (4.9)
Bleeding requiring reoperation	3 (2.2)	3 (1.1)	11 (8.4)	11 (4.5)
Infection	20 (14.7)	24 (8.7)	17 (13.0)	19 (7.8)
Blood	11 (8.1)	14 (5.1)	6 (4.6)	6 (2.5)
Gastrointestinal	5 (3.7)	5 (1.8)	3 (2.3)	3 (1.2)
Abdominal	2 (1.5)	2 (0.7)	5 (3.8)	5 (2.0)

Safety Event Type	NMP n(%)		SCS n(%)	
	Patients (N = 136)	Events (N = 275)	Patients (N = 131)	Events (N = 244)
Other	1 (0.7)	1 (0.4)	3 (2.3)	3 (1.2)
Respiratory	15 (11.0)	16 (5.8)	20 (15.3)	26 (10.7)
Acute Respiratory Failure	6 (4.4)	6 (2.2)	8 (6.1)	8 (3.3)
Other	4 (2.9)	4 (1.5)	7 (5.3)	7 (2.9)
Pneumonia	2 (1.5)	2 (0.7)	6 (4.6)	6 (2.5)
Pulmonary Edema	1 (0.7)	2 (0.7)	2 (1.5)	2 (0.8)
Cardiovascular	17 (12.5)	26 (9.5)	17 (13.0)	19 (7.8)
Other	5 (3.7)	5 (1.8)	5 (3.8)	5 (2.0)
Myocardial infarction	2 (1.5)	2 (0.7)	5 (3.8)	5 (2.0)
Congestive heart failure	5 (3.7)	6 (2.2)	1 (0.8)	1 (0.4)
Hypotension	2 (1.5)	2 (0.7)	4 (3.1)	4 (1.6)
Arrhythmias	3 (2.2)	4 (1.5)	2 (1.5)	2 (0.8)
Tachycardia	3 (2.2)	3 (1.1)	1 (0.8)	1 (0.4)
Gastrointestinal	20 (14.7)	28 (10.2)	10 (7.6)	13 (5.3)
Other	6 (4.4)	9 (3.3)	4 (3.1)	5 (2.0)
Nausea/vomiting	8 (5.9)	8 (2.9)	1 (0.8)	2 (0.8)
GI Bleeding	5 (3.7)	5 (1.8)	3 (2.3)	3 (1.2)
Diarrhea	5 (3.7)	5 (1.8)	2 (1.5)	2 (0.8)
Genitourinary	15 (11.0)	20 (7.3)	15 (11.5)	15 (6.1)
Renal dysfunction/Acute Kidney Injury	11 (8.1)	13 (4.7)	15 (11.5)	15 (6.1)
Other	5 (3.7)	6 (2.2)	0 (0.0)	0 (0.0)
Other systemic disease/event	15 (11.0)	19 (6.9)	11 (8.4)	14 (5.7)
Other	9 (6.6)	9 (3.3)	2 (1.5)	2 (0.8)
Surgery – planned/elective	5 (3.7)	5 (1.8)	4 (3.1)	4 (1.6)
Pain (beyond anticipated pain post-surgery)	2 (1.5)	2 (0.7)	6 (4.6)	6 (2.5)
Surgery – emergency	3 (2.2)	3 (1.1)	2 (1.5)	2 (0.8)
Hematology	11 (8.1)	12 (4.4)	15 (11.5)	16 (6.6)
Anemia	2 (1.5)	2 (0.7)	6 (4.6)	6 (2.5)
Leukopenia	3 (2.2)	3 (1.1)	5 (3.8)	5 (2.0)
Malignancy	1 (0.7)	1 (0.4)	3 (2.3)	3 (1.2)
Other	3 (2.2)	4 (1.5)	1 (0.8)	1 (0.4)
Fluid Collection	11 (8.1)	14 (5.1)	9 (6.9)	11 (4.5)
Ascites	4 (2.9)	6 (2.2)	2 (1.5)	3 (1.2)
Pleural effusion	2 (1.5)	2 (0.7)	3 (2.3)	3 (1.2)
Abdominal collection	2 (1.5)	3 (1.1)	2 (1.5)	2 (0.8)
Extremities edema	2 (1.5)	2 (0.7)	1 (0.8)	1 (0.4)
Other	1 (0.7)	1 (0.4)	2 (1.5)	2 (0.8)

Safety Event Type	NMP n(%)		SCS n(%)	
	Patients (N = 136)	Events (N = 275)	Patients (N = 131)	Events (N = 244)
Neurology/Psychiatry	9 (6.6)	11 (4.0)	8 (6.1)	9 (3.7)
Altered mental status	4 (2.9)	4 (1.5)	3 (2.3)	4 (1.6)
Seizure	1 (0.7)	2 (0.7)	3 (2.3)	3 (1.2)
Stroke/TIA	3 (2.2)	3 (1.1)	0 (0.0)	0 (0.0)
Musculoskeletal	9 (6.6)	9 (3.3)	7 (5.3)	7 (2.9)
Other	8 (5.9)	8 (2.9)	7 (5.3)	7 (2.9)
Electrolyte abnormality	3 (2.2)	3 (1.1)	10 (7.6)	11 (4.5)
Hyperkalemia	3 (2.2)	3 (1.1)	8 (6.1)	9 (3.7)
Early Allograft Dysfunction	6 (4.4)	6 (2.2)	4 (3.1)	4 (1.6)
ALT or AST > 2000 IU/L	5 (3.7)	5 (1.8)	4 (3.1)	4 (1.6)
Dermatologic	3 (2.2)	3 (1.1)	3 (2.3)	3 (1.2)
Other	3 (2.2)	3 (1.1)	1 (0.8)	1 (0.4)
Endocrinology	0 (0.0)	0 (0.0)	3 (2.3)	3 (1.2)
Hyperglycemia	0 (0.0)	0 (0.0)	3 (2.3)	3 (1.2)
TOTAL	95 (69.9)	275 (100.0)	93 (71.0)	244 (100.0)

Number of events in specific codes may not add up to the number of events for the corresponding system code since only system and specific codes that occurred in ≥ 1% of subjects were presented.

Table 8 provides information on reported liver incidents and device deficiencies by donor type. Device deficiencies include device failures, device malfunctions, and user errors. There were a total of two (2) liver incidents (due to livers discarded following transport) and fourteen (14) device malfunctions in the study. There were no device failures or user errors reported during the study. None of the liver incidents or device deficiencies resulted in a subject adverse event.

Table 8: Liver Incidents and Device Deficiencies by Donor Type

	Overall # events (# subjects)		DBD # events (# subjects)		DCD # events (# subjects)	
Event	NMP	SCS	NMP	SCS	NMP	SCS
Liver Incident	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Device Failure (NMP Only)	0 (0)	-	0 (0)	-	0 (0)	-
Device Malfunction (NMP Only)	14 (14)	-	10 (10)	-	4 (4)	-
Use Error (NMP Only)	0 (0)	-	0 (0)	-	0 (0)	-

Table 9 presents the SAEs by randomization group at the study follow-up visits. There were no notable differences in the incidence of SAEs between the two randomization arms overall. There were no UADEs reported in this study.

Table 9: SAEs per Randomization Group at Study Timepoints

	Discharge # events (# subjects)			30 Days # events (# subjects)			3 Months # events (# subjects)			6 Months # events (# subjects)			12 Months # events (# subjects)			Overall # events (# subjects)		
	ALL	NMP	SCS	ALL	NMP	SCS	ALL	NMP	SCS	ALL	NMP	SCS	ALL	NMP	SCS	ALL	NMP	SCS
Serious Adverse Event	203 (115)	101 (58)	102 (57)	69 (52)	37 (30)	32 (22)	99 (59)	52 (30)	47 (29)	67 (47)	45 (30)	22 (17)	81 (53)	40 (25)	41 (28)	519 (188)	275 (95)	244 (93)
Serious Adverse Event (Procedure-related)[1]	190 (110)	95 (56)	95 (54)	59 (46)	30 (25)	29 (21)	82 (53)	43 (27)	39 (26)	49 (34)	32 (22)	17 (12)	62 (38)	32 (18)	30 (20)	442 (174)	232 (87)	210 (87)
Serious Adverse Event (Device-related)[2]	38 (28)	38 (28)	-	8 (8)	8 (8)	-	13 (9)	13 (9)	-	12 (10)	12 (10)	-	9 (5)	9 (5)	-	80 (47)	80 (47)	-

[1]Procedure-related events include those events categorized as either probably not, possibly, probably, or definitely related to the procedure.
[2]Device-related events include those events categorized as either probably not, possibly, probably, or definitely related to the device.
Discharge events include events occuring on or prior to discharge or events where a discharge date was not reported
30 Day events include events occuring after discharge and on or before 30-day visit window close
3 Month events include events occuring after 30-day visit window close and on or before 3-month visit window close
6 Month events include events occuring after 3-month visit window close and on or before 6-month visit window close
12 Month events include events occuring after 6-month visit window close and on or before 12-month visit window close

Anastomotic biliary strictures: In December 2018, OrganOx began to share best practice for bile duct cannulation with surgeons during in-person and remote support: this related to the use of a different (monofilament) material in place of silk, ensuring that the correct tube size was matched to each bile duct, and that this was inserted the correct depth within the bile duct. Subjects with anastomotic biliary strictures for both the NMP and SCS arms are presented for the As-Treated analysis population based on these enhanced training dates using a tertile analysis in Table 10. The rate of subjects with anastomotic biliary strictures reduced in the NMP arm over time demonstrating continued improvement during the study with enhanced training and guidance on best practices contributing to the improvement.

Table 10: Enhanced Training Analysis – Anastomotic Biliary Strictures (As-Treated)

	Tertile 1 and 2		Tertile 3	
	NMP[1]	SCS	NMP[1]	SCS
Number of transplanted subjects	90	89	42	43
At risk at 12 months[2]	68	75	35	42
Subjects with events	15	8	3	0
Cumulative Incidence[3]	17.7%	9.2%	7.5%	0.0%
Standard error	4.2%	3.1%	4.2%	0.0%

	Tertile 1 and 2		Tertile 3	
	NMP[1]	SCS	NMP[1]	SCS
95% CI	(11.0%, 27.7%)	(4.7%, 17.6%)	(2.5%, 21.6%)	(0.0%, 0.0%)

[1]Surgeons of two NMP subjects (Liver IDs: AFED332, AFLJ403) did not have a training date reported. Subject AFED332 had a transplant that occurred prior to Enhanced Training 2 and experienced a biliary stricture, therefore is included in the transplanted subjects in Tertiles 1 and 2. Subject AFLJ403 had a transplant that occurred after Enhanced Training 2 and did not experience a biliary stricture. Due to transplant timing, they are unable to be included in the transplanted subjects (would fall in either Tertile 2 or 3).
[2]Number of subjects at risk at the beginning of 12 months visit windows (335 days from procedure).
[3]Estimates made at scheduled visit days (365 days from procedure).
Tertile 1 and 2: Transplant performed before the completion of Enhanced Training 1 and/or Enhanced Training 2
Tertile 3: Transplant performed after the completion of both Enhanced Training 1 and Enhanced Training 2

Safety Results Summary

The analysis of safety was based on the ITT cohort of 136 NMP and 131 SCS enrolled subjects. All adverse events reported for a subject, regardless of the duration of time in the study, are included through a subjects exit from the site. If a cohort other than ITT was presented, this is noted in the title of the table.

- The rates of SAEs were comparable between arms throughout the duration of the study, suggesting the safe use of the *metra* device.
- The incidence of subjects with biliary investigations was comparable between the arms (12.6% NMP; 13.4% SCS). The incidence of subjects with biliary interventions was comparable between the arms (9.4% NMP; 8.7 SCS); however, there was a marked numerical reduction in the DCD cohort, acknowledging that the sample size for this group is smaller (19.0% NMP; 28.6% SCS).
- Twelve-month graft survival rates were 97.0% and 97.7% in the NMP and SCS arms, respectively. 2019 OPTN/SRTR data show national graft survival rates with SCS at 12-months post-transplant as 91.1%. The graft survival data in both arms of this trial compare favorably with the national average.
- Twelve-month subject survival rates were 92.5% and 96.6% in the NMP and SCS arms, respectively. 2019 OPTN/SRTR data show national subject survival rates with SCS at 12-months post-transplant as 92.6%. This data indicates that subject survival using the OrganOx *metra* device was in line with the national average.
- Rates of reported device malfunctions were low and there were no instances of Adverse Events or graft loss due to device malfunction. No increased risk or additional risks were observed in donor organs or recipients as a result of these reported malfunctions.
- There were no safety signals observed in patient mortality, graft survival, or Serious Adverse Events, and reported events were those typically experienced following liver transplantation.

Effectiveness Results

Table 11 shows the results of the primary endpoint for the ITT, Per-Protocol, and As-Treated populations. EAD rates both prior to and following imputation are included, and the 1-sided superiority p-values are presented. Adjustment for participating (recipient) center was pre-specified in the SAP for the primary analysis of the imputed data. However, due to convergence issues, a logistic model that did not adjust for participating (recipient) center was used. In the ITT analysis, the NMP arm had a lower imputed EAD rate than the SCS arm (20.6% and 23.7%, respectively; p-value=0.275). The most pronounced difference in the two arms can be seen in the As-Treated analysis, with NMP and SCS imputed EAD rates of 18.7% and 24.9%, respectively (p=0.115).

Table 11: Early Allograft Dysfunction – ITT, Per-Protocol, and As-Treated Analysis Populations

	NMP*	SCS	Superiority P-value
Primary Endpoint[1]			
Analysis Population	N=136	N=130	
Number of subjects with incomplete EAD information requiring imputation	N=9	N=3	
EAD Prior to Imputation	20.5% (26/127)	22.8% (29/127)	
EAD using imputation[2]	20.6% (14.5%, 28.5%)	23.7% (17.1%, 31.9%)	0.275
Per-Protocol Analysis[3, 4]			
Analysis Population	N=133	N=130	
Number of subjects with incomplete EAD information requiring imputation	N=9	N=3	
EAD Prior to Imputation	18.5% (23/124)	22.8% (29/127)	
EAD using imputation[2]	18.6% (12.7%, 26.4%)	23.8% (17.2%, 31.9%)	0.158
As-Treated Analysis[3, 4]			
Analysis Population	N=133	N=132	
Number of subjects with incomplete EAD information requiring imputation	N=9	N=3	
EAD Prior to Imputation	18.5% (23/124)	24.0% (31/129)	
EAD using imputation[2]	18.7% (12.8%, 26.5%)	24.9% (18.2%, 33.1%)	0.115

*Three subjects (AFJX183, AGJY324, AECG396) were identified as having elevated day 7 INR values due to anticoagulation. Day 7 INR values for these 3 subjects were therefore considered missing, and imputed to determine EAD status.
[1]ITT Population
[2]Multiple imputation was used for subjects with missing lab values that were required to determine EAD status. Imputation was not used to determine EAD status when: i) the subject already had one or more lab values meeting EAD criteria; ii) the subject had been discharged prior to day 7 with lab values below EAD threshold; or iii) the subject had last available INR values and available follow-up INR values below EAD threshold with no reported hospital re-admissions.
[3]One subject (AGBX122) was excluded from the analysis due to exclusion criteria being met.
[4]Two subjects (AEJX212, AELD404) received livers that were randomized to the NMP arm but were not placed on the device and instead were transported using cold storage. These subjects are excluded from the Per-Protocol analysis and included in the SCS arm in the As-Treated analysis.

As an additional sensitivity analysis, EAD was also assessed using multiple imputation to impute missing lab values to determine EAD status for subjects discharged from the hospital prior to day 7 and/or subjects with available early INR values below the EAD threshold. In the primary analysis these subjects were considered not to have EAD. As in the primary analysis, multiple imputation was also used for subjects where EAD status was unable to be confirmed by complete labs or at least one (1)

lab value meeting criteria for EAD. Sensitivity analyses were conducted to demonstrate the impact on primary endpoint results using multiple imputation for EAD status that is unable to be confirmed by complete labs or at least one (1) lab value meeting criteria for EAD. The results of this sensitivity analysis are presented in Table 12. EAD rates using imputation are similar to the ITT analysis in both the NMP and SCS arms (21.4% and 25.6%, respectively; p-value=0.218).

Table 12: Early Allograft Dysfunction – Sensitivity Analysis

	NMP*	SCS	Superiority P-value
Sensitivity Analysis[1]			
Analysis Population	N=136	N=130	
Number of subjects with incomplete EAD information requiring imputation	N=19	N=14	
EAD Prior to Imputation	22.2% (26/117)	25.0% (29/116)	
EAD using imputation[2, 3]	21.4% (15.1%, 29.5%)	25.6% (18.7%, 34.1%)	0.218

*Three subjects (AFJX183, AGJY324, AECG396) were identified as having elevated day 7 INR values due to anticoagulation. Day 7 INR values for these 3 subjects were therefore considered missing, and imputed to determine EAD status.
[1]ITT Population
[2]Multiple imputation was used in the Sensitivity Analysis to impute missing lab values to determine EAD status for subjects discharged from hospital prior to day 7 and/or subjects with available INR values below the EAD threshold. In the Primary Analysis these subjects were considered not to have EAD.
[3]As in the Primary Analysis, multiple imputation was also used for subjects where EAD status is unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.

In addition to the primary endpoint analysis of Early Allograft Dysfunction by randomization arm, results were also summarized by donor type. The EAD rates by donor type and randomization arm are presented in Table 13 for the ITT, Per-Protocol, and As-Treated analysis populations. Differences in EAD rates between the randomization arms is most pronounced in subjects receiving DCD donor livers (As-Treated analysis following imputation: 22.8% NMP vs. 44.6% SCS) than in the subjects receiving DBD donor livers (As-Treated analysis following imputation: 17.9% NMP vs. 22.0% SCS).

Table 13: Early Allograft Dysfunction by Donor Type – ITT, Per-Protocol, and As-Treated Analysis Populations

	DBD		DCD	
	NMP*	SCS	NMP	SCS
Primary Endpoint[1]				
Analysis Population	N=114	N=114	N=22	N=16
Number of subjects with incomplete EAD information requiring imputation	N=8	N=2	N=1	N=1
EAD Prior to Imputation	18.9% (20/106)	20.5% (23/112)	28.6% (6/21)	40.0% (6/15)
EAD using imputation[2]	18.7% (12.5%, 27.2%)	21.3% (14.7%, 29.8%)	30.1% (14.5%, 52.4%)	41.0% (19.8%, 66.0%)
Per-Protocol Analysis[3, 4]				
Analysis Population	N=113	N=114	N=20	N=16
Number of subjects with incomplete EAD information requiring imputation	N=8	N=2	N=1	N=1
EAD Prior to Imputation	18.1% (19/105)	20.5% (23/112)	21.1% (4/19)	40.0% (6/15)

	DBD		DCD	
	NMP*	SCS	NMP	SCS
EAD using imputation[2]	17.9% (11.8%, 26.4%)	21.3% (14.7%, 29.9%)	22.3% (8.8%, 46.2%)	41.1% (19.9%, 66.1%)
As-Treated Analysis[3, 4]				
Analysis Population	N=113	N=115	N=20	N=17
Number of subjects with incomplete EAD information requiring imputation	N=8	N=2	N=1	N=1
EAD Prior to Imputation	18.1% (19/105)	21.2% (24/113)	21.1% (4/19)	43.8% (7/16)
EAD using imputation[2]	17.9% (11.8%, 26.4%)	22.0% (15.3%, 30.5%)	22.8% (9.1%, 46.6%)	44.6% (23.1%, 68.3%)

*Three DBD subjects (AFJX183, AGJY324, AECG396) were identified as having elevated day 7 INR values due to anticoagulation. Day 7 INR values for these 3 subjects were therefore considered missing, and imputed to determine EAD status.
[1]ITT Population
[2]Multiple imputation was used for subjects with missing lab values that were required to determine EAD status. Imputation was not used to determine EAD status when: i) the subject already had one or more lab values meeting EAD criteria; ii) the subject had been discharged prior to day 7 with lab values below EAD threshold; or iii) the subject had last available INR values and available follow-up INR values below EAD threshold with no reported hospital re-admissions.
[3]One DCD subject (AGBX122) was excluded from the analysis due to exclusion criteria being met.
[4]One DBD subject (AEJX212) and one DCD subject (AELD404) received livers that were randomized to the NMP arm but were not placed on the device and instead were transported using cold storage. These subjects are excluded from the Per-Protocol analysis and included in the SCS arm in the As-Treated analysis.

Subgroup Analyses

EAD (unimputed) events were explored across different ranges of Donor Risk Index. Using the observed data, EAD by randomization arm is presented in the DRI quartiles of the study in Table 14. In the lower quartiles of DRI, EAD rates were similar between the randomization arms. The largest difference between the arms was observed in the highest quartile of DRI (19.2% EAD rate in the NMP arm and 33.3% in the SCS arm).

Table 14: Early Allograft Dysfunction by Donor Risk Index

	Donor Risk Index (DRI)							
	DRI ≤ 1.404948		1.404948 < DRI ≤ 1.622325		1.622325 < DRI ≤ 1.870489		DRI > 1.870489	
	NMP	SCS	NMP	SCS	NMP	SCS	NMP	SCS
Early Allograft Dysfunction (EAD)	25.0% (10/40)	25.7% (9/35)	17.6% (6/34)	19.4% (7/36)	18.5% (5/27)	15.6% (5/32)	19.2% (5/26)	33.3% (8/24)

EAD is a binary outcome defined by the presence of one of the following 3 outcomes: 1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant; 2. International normalized ratio ≥ 1.6 at day 7 post-transplant; 3. ALT or AST > 2000 IU/L within the first 7 days post-transplant. Additional clinically justified decision rules were implemented if EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.

An analysis of EAD rates (unimputed) against the observed time on pump was performed for livers in the NMP arm. Table 15 shows EAD rates vs. time on pump tertiles. There was no correlation between time on pump and observed EAD rates.

Table 15: Early Allograft Dysfunction by Time on Pump (NMP arm)

	Time on Pump Tertiles		
	Low (≤288 minutes)	**Intermediate (288 < time on pump ≤381 minutes)**	**High (>381 minutes)**
Early Allograft Dysfunction (EAD)	14.3% (6/42)	26.2% (11/42)	17.5% (7/40)
Chi-square test comparing EAD proportions between time on pump tertiles: p=0.3612 EAD is a binary outcome defined by the presence of one of the following 3 outcomes: 1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant; 2. International normalized ratio ≥ 1.6 at day 7 post-transplant; 3. ALT or AST > 2000 IU/L within the first 7 days post-transplant. Additional clinically justified decision rules were implemented if EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.			

Primary Endpoint Discussion and effect of training

The study's primary analysis was designed around the hypothesis that EAD rates following transplant of livers preserved with NMP would be superior to (lower than) EAD rates following transplant of livers preserved with SCS. The study was designed to demonstrate a reduction in EAD rates from 25% in the SCS arm to 10% in the NMP arm. Although the primary analysis failed to demonstrate this treatment effect in the analyzed populations, the As Treated analysis resulted in EAD rates of 18.7% NMP vs. 24.9% SCS (superiority p-value = 0.115). In subjects with DCD liver transplants for the as treated analysis, there is evidence of a treatment effect (22.8% NMP vs. 44.6% SCS); however, the study was not powered to measure the significance of this effect.

Although the device was designed to be used by transplant teams, nonetheless specific training in its use is essential. Upon the early observation in the study that additional training for optimal liver cannulation technique would be beneficial, between March and May of 2018, OrganOx implemented enhanced surgeon training relating to the use of the device, with a particular focus on cannulation. An intensive program of enhanced training was initiated, comprising further video and on-site training from the OrganOx Clinical Field Specialists. In particular, attention was paid to the technique for the placement and securing of the vascular cannulae. At the same time OrganOx changed the training sign-off such that individual surgeons were required to be certified as trained by the specialists. This contrasted with the previous practice whereby it was the institution that was required to be signed off.

EAD rates (unimputed) for both the NMP and SCS arms are presented for the As-Treated analysis population before and after enhanced surgeon training in Figure 2 and Table 16. EAD rates in the NMP arm decreased after enhanced training (23.5% before enhanced training as compared to 14.1% after enhanced training), while the rates were similar pre- and post-enhanced training in the SCS arm (21.3% before enhanced training and 25.6% after enhanced training). It is notable that the incidence of EAD following these changes was substantially lower than before the enhanced training, whereas the incidence of EAD in the SCS arm showed no such change.

Figure 2: EAD by Pre- and Post-Enhanced Training Completion at Sites (As-Treated)

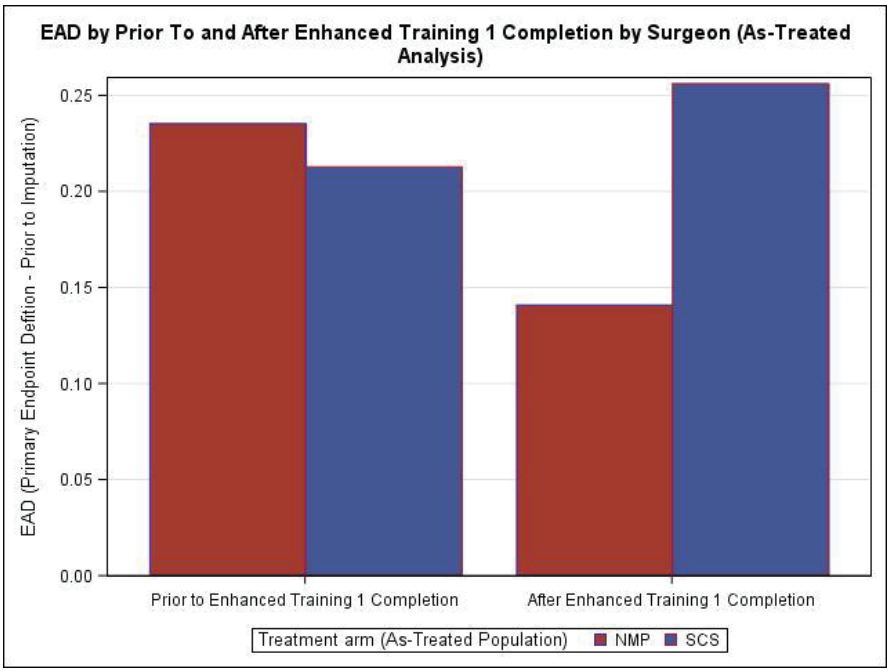

Table 16: Enhanced Training Analysis – Early Allograft Dysfunction (As-Treated)

	Early Allograft Dysfunction (EAD) by Enhanced Training 1 Timing	
Randomization Arm	**Prior to Enhanced Training 1 Completion by Surgeon**	**After Enhanced Training 1 Completion by Surgeon**
NMP[1]	23.5% (12/51)	14.1% (10/71)
SCS[2]	21.3% (10/47)	25.6% (21/82)

EAD is a binary outcome defined by the presence of one of the following 3 outcomes: 1. Serum bilirubin ≥ 10 mg/dL at day 7 post-transplant; 2. International normalized ratio ≥ 1.6 at day 7 post-transplant; 3. ALT or AST > 2000 IU/L within the first 7 days post-transplant.
Additional clinically justified decision rules were implemented if EAD status was unable to be confirmed by complete labs or at least 1 lab value meeting criteria for EAD.
[1]Surgeons of two NMP subjects (Liver IDs: AFED332, AFLJ403) did not have a training date reported. Therefore, these 2 subjects are not included in this analysis. An additional 9 subjects had incomplete EAD information and are not included.
[2]Three subjects had incomplete EAD information and are not included in this analysis.

As demonstrated in Table 17 the rate of anastomotic biliary strictures in the NMP arm demonstrated continued improvement throughout the study; the evidence suggests that enhanced training and guidance on best practices contributed to this improvement. Both of these analyses suggest a 'training' effect.

Table 17: Enhanced Training Analysis – Serious Anastomotic Biliary Strictures (As Treated)

	Serious Biliary Strictures (anastomotic) by Enhanced Training Timing		
Randomization Arm	First Tertile	Second Tertile	Third Tertile
NMP	9	5	1
SCS	1	3	0
Cutoffs between tertiles correspond to the following: First and Second Tertile (March-May 2018): Date that site signed off as completing review of training videos relating to 'backtable and cannulation positioning' and 'liver disconnection and vessel preparation' Second and Third Tertile (08DEC2018): Date OrganOx began to share revised best practice for bile duct cannulation with surgeons during in-person/remote support, including the use of a monofilament suture. The choice of suture material and technique used was discussed with the surgeon and recorded			

US Study Secondary Endpoints

The secondary objectives of the study suggest a benefit from NMP in some parameters (peak AST, peak ALT, reperfusion syndrome, creatinine). The secondary objectives results were:

1. To compare graft and subject survival between NMP and SCS livers
    - Seven (7) graft failures (four (4) in the NMP arm and three (3) in the SCS arm) were reported. Graft failures include PNF, any instances of re-transplant during the follow-up period, and any deaths due to graft failure. Twelve month graft survival rates were 97.0% and 97.7% in the NMP and SCS arms, respectively. 2019 OPTN/SRTR data show national graft survival rates with SCS at 12-months post-transplant as 91.1%. The graft survival data in both arms of this trial compare favorably with the national average.
    - Subject survival rates at twelve months were 92.5% and 96.6% in the NMP and SCS arms, respectively. While there was a numerical difference in the number of deaths between the randomization arms, the timing post-transplant was inconsistent and there were no deaths adjudicated as related to the *metra* device. 2019 OPTN/SRTR data show national subject survival rates with SCS at 12-months post-transplant as 92.6%. The results indicate that subject survival using the OrganOx metra device was in line with the national average.
2. To compare evidence of post-reperfusion syndrome between NMP and SCS livers on transplantation
    - The occurrence of post-reperfusion syndrome decreased from 14.6% in the SCS arm to 5.9% in the NMP arm. While lower rates of post-reperfusion syndrome

were seen in the NMP group compared to the SCS group overall, the difference was most pronounced in DBD livers (4.4% NMP vs. 14.0% SCS).

3. To compare biochemical liver function between NMP and SCS livers

- There were notable differences in the first 7 days post-operatively between the NMP and SCS arms with lower median levels of AST, ALT, and creatinine in the NMP arm.
- All other assessments did not demonstrate a difference between treatment arms.

Table 18: Biochemical Liver Function Assessments: AST, ALT and Creatinine

Biochemical test*	NMP	SCS	p-value**
AST (IU/L)			
Day 1-7 N	162.2 (101.3, 332.8) 136	200.7 (141.4, 349.4) 129	0.032
ALT (IU/L)			
Day 1-7 N	215.9 (113.9, 349.7) 136	268.6 (169.9, 457.9) 129	0.009
Creatinine (mg/dL)			
Day 1-7 N	1.2 (0.9, 1.6) 135	1.4 (1.0, 1.8) 129	0.047

*Median and interquartile range displayed for each treatment group.
**P-value calculated from a Mann-Whitney test

Table 19: Peak AST by Randomization Arm and Donor Type

	Overall				DBD				DCD			
	NMP		SCS		NMP		SCS		NMP		SCS	
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)
Peak AST - Any AST lab(s) available in first 7 days	136	540.3 (453.3, 644.1)	129	722.4 (609.0, 857.0)	114	528.8 (439.1, 636.8)	114	653.7 (548.9, 778.5)	22	604.2 (352.5, 1035.7)	15	1543.8 (904.0, 2636.4)
Peak AST - Day 1 AST available[1]	133	538.1 (450.8, 642.4)	129	722.4 (609.0, 857.0)	112	519.6 (430.8, 626.6)	114	653.7 (548.9, 778.5)	21	649.2 (376.5, 1119.3)	15	1543.8 (904.0, 2636.4)
Peak AST - At least 2 AST labs available[2]	135	540.3 (452.7, 644.8)	129	722.4 (609.0, 857.0)	113	528.6 (438.2, 637.7)	114	653.7 (548.9, 778.5)	22	604.2 (352.5, 1035.7)	15	1543.8 (904.0, 2636.4)

[1]Day 1 is often the peak AST observed
[2]COPE Study used this definition

Table 20: Peak ALT by Randomization Arm and Donor Type

	Overall				DBD				DCD			
	NMP		SCS		NMP		SCS		NMP		SCS	
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)
Peak ALT - Any ALT lab(s) available in first 7 days	136	381.8 (326.4, 446.5)	129	500.9 (432.7, 579.8)	114	374.7 (316.4, 443.7)	114	464.6 (397.4, 543.1)	22	420.6 (270.4, 654.4)	15	887.3 (642.9, 1224.8)
Peak ALT - Day 1 ALT available	133	378.0 (322.9, 442.6)	129	500.9 (432.7, 579.8)	112	368.1 (310.7, 436.0)	114	464.6 (397.4, 543.1)	21	435.8 (275.5, 689.3)	15	887.3 (642.9, 1224.8)
Peak ALT - At least 2 ALT labs available	135	382.1 (326.3, 447.4)	129	500.9 (432.7, 579.8)	113	375.0 (316.2, 444.8)	114	464.6 (397.4, 543.1)	22	420.6 (270.4, 654.4)	15	887.3 (642.9, 1224.8)

4. To compare evidence of ischemia-reperfusion injury between NMP and SCS livers
   - There were no notable differences in the degree of ischemia reperfusion injury between arms.
   - There was a small but notable difference in the proportion of livers with mild/moderate/severe lobular inflammation when comparing the post reperfusion to pre-storage biopsies between the arms. In the NMP arm, there was a 26.5% increase between pre-storage (52.4%) and post-reperfusion (78.9%) biopsies, whereas in the SCS arm there was a 44.7% increase between pre-storage (43.1%) and post-reperfusion (87.8%) biopsies.
5. To compare evidence of biliary complications between NMP and SCS livers
   - Biliary investigations and interventions between Day 7 and Month 6 were slightly lower in the NMP arm.
     - Biliary investigations occurred in 111.0% (14/127) of NMP subjects and 12.7% (16/126) SCS subjects.
     - Biliary interventions were reported for 9.4% (12/127) and 8.7% (11/126) of NMP and SCS subjects, respectively.
6. To assess the feasibility and safety of NMP as a method of organ storage and transportation
   - There was a small difference between arms: thirty-one (31) subjects in the NMP arm and thirty-three (33) subjects in the SCS arm experienced at least one of the following: EAD, discard of a retrieved liver, or primary non-function.
7. To compare organ utilization between NMP and SCS livers
   - There were similar rates of livers randomized but not transplanted in NMP and SCS livers for DBD donors (NMP 20.3%; SCS 20.8%). There were more SCS than NMP livers randomized but not transplanted for DCD donors (NMP 55.1%; SCS 66.0%)

8. To assess the health economic implications of normothermic liver perfusion

    - The median length of ICU stay after transplant was lower in the NMP (two (2) days) compared to the SCS arm (three (3) days). The median total length of hospital stay was the same in both treatment arms (nine (9) days).

Effectiveness Results Summary

The analysis of effectiveness was based on 136 NMP and 130 SCS transplanted subjects. The endpoint included information through 7 days post-transplant; however, the primary analysis was based on imputed data therefore all 266 transplanted subjects were included in the primary analysis for effectiveness. Table 11 also summarizes results relating to the primary endpoint for the per-protocol and as-treated populations. The table also describes EAD prior to imputation to demonstrate consistency between the results.

- There was a trend towards a reduced incidence of EAD. This is seen in the Intention-to-Treat, Per-Protocol, and As-Treated analyses (18.5% NMP; 24.0% SCS – unimputed, As-Treated).
- There was greater benefit demonstrated in the subset of subjects who received higher-risk donor organs, as seen in recipients of both DCD donor organs and organs from higher DRI donors.
- There was a marked effect of enhanced training on reducing the incidence of EAD in the NMP arm following surgeon completion of this training (14.1% NMP; 25.6% SCS).
- All secondary objectives were achieved by comparing NMP to SCS, showing the following benefits of the OrganOx *metra.*
    - There was reduced graft injury as measured by transaminase release (AST, ALT), most notably in recipients of higher-risk donor organs.
    - There was a substantial reduction in the incidence of post-reperfusion syndrome in the NMP arm (a 60% decrease vs. SCS). This is an important, clinically meaningful benefit which may influence the eligibility of patients with more advanced liver disease to gain access to a larger pool of donor livers.
    - There was improved renal function in the early post-operative period with a reduction in the median level of creatinine during the first seven days post-operatively (NMP 1.2 mg/dl; SCS 1.4mg/dl).
    - There was evidence of short to medium term benefit including reduced rates of reoperation due to graft-related complications and acute rejection. This has the potential to lessen the impact to the healthcare system post-transplant with a health economic cost benefit.
    - There was a clinically important difference in the total preservation times between the two arms of the study (mean NMP 9.2 hours; SCS 5.3 hours). The ability to prolong the safe period of preservation (in this case by 75%), without increasing the cold ischemic time has considerable value: it enables organs to be retrieved from a greater distance; allows patients to be admitted for transplant from further afield; and allows the logistics of transplant to be optimized for both the hospital and patient.