

# **FRAMINGHAM HEART STUDY PERIPHERAL ARTERIAL TONE (PAT) MANUAL**

FHS PAT Manual prepared by:  
Moirá M. Pryde, MA and Emelia J. Benjamin, MD, ScM

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# Framingham Heart Study Peripheral Arterial Tone (PAT) Manual

## PAT Acquisition Funding

### Grants Supporting the PAT research:

#### 1. Vascular Function in the Framingham Third Generation

PI, Emelia J. Benjamin, MD, ScM

Agency: NHLBI

Type: **RO1 HL70100**

Period: 5/01/02–3/31/07 (extension)

Specific Aims: To study the epidemiology and prognosis of noninvasive vascular function in the community:

#### 2. Endothelial Vasomotor Function in the Framingham Heart Study

PI: Emelia J. Benjamin, MD, ScM

Agency: NHLBI

Type: **1R01 HL60040**

Period: 12/15/98 - 11/30/03

Specific Aims: To examine the distribution & prognosis of endothelial vasomotor function in the FHS third generation.

#### 3. ENDO-PAT research at the Framingham Heart Study.

PI: Emelia J. Benjamin, MD, ScM

Agency: Itamar Medical; <http://www.itamar-medical.com>

Type: Industry unrestricted research grant.

Period: 2003-2009

Please note that Itamar Medical has given a series of unrestricted research grants to Boston University to conduct PAT related research. The grants were to perform analyses of the epidemiology, genetics and prognosis of peripheral arterial tonometry (PAT) digital vascular function. In addition, Itamar Medical did donate the PAT equipment and measurements to the Framingham Heart Study. The grants do subscribe to the NHLBI guidelines for third party funding (<http://www.nhlbi.nih.gov/funding/policies/thirdparty.htm>). The unrestricted research grants have been approved by the Framingham Heart Study Executive Committee. The grants have been reported to the National Heart Lung and Blood Institute, and have been reported to the Framingham Heart Study's Outside Safety Monitoring Board.

# **Framingham Heart Study Peripheral Arterial Tone (PAT) Manual**

## **Introduction to PAT**

The Framingham Heart Study is an observational study designed to identify the relations between risk factors, genetics, cardiovascular disease, and other health conditions over three generations. The purpose of the Framingham study is to 1) investigate factors related to the development of heart and blood vessel diseases, lung and blood diseases; and 2) to examine the relations of genetic variants to the risks of developing these diseases and health conditions.

Vascular dysfunction is a key step in the development of atherosclerosis. Impaired peripheral vasodilator function measured non-invasively has been associated with cardiovascular risk factors and the development of clinical cardiovascular disease. Assessment of digital vasodilator responses using a fingertip peripheral arterial tonometry (PAT) device is a novel measure of vascular function. The baseline digital pulse amplitude is a measure of local arterial tone in the fingertip. The PAT ratio records post-ischemic arterial responsiveness to reactive hyperemia produced by a cuff occlusion in the forearm.

The Framingham Third Generation 1<sup>st</sup> examination cycle included an assessment of digital vascular function using PAT in a subset of 1957 participants. We developed a measure to describe the hyperemic response (the PAT ratio) that is the natural logarithm of the ratio of: the ratio of the post-cuff release to baseline pulse amplitude in the hyperemic finger and the corresponding ratio in the control fingertip. We observed that the relation of the PAT ratio to cardiovascular risk factors was maximized in the 90-120 second interval following cuff release. We identified multiple cardiovascular risk factors that relate to the baseline and hyperemic PAT response. It is hoped that the Framingham PAT resource will advance our understanding of the early development of vascular changes that predispose to the future development of cardiovascular disease.

### **Duration of test:**

The PAT examination takes approximately 15 minutes

Preparation time: 2 minutes

Scanning time: 10 minutes, 2 minutes pre occlusion, 5 minute occlusion, and 3 minutes post occlusion.

Entering information and completing forms: 2 minutes

### **Equipment**

Two Endo\_PAT 2000 (Itamar Medcial Cat. No. OM1695002

Endo\_PAT software CD version 2to run equipment

Two Laptops to run software.

Power adaptor

Power cable

Hokanson E20 Rapid Cuff Inflation System

### **Supplies**

#### **Software updates**

Pneumatic Finger probes

Pneumatic Tubing

Anchores

Latex (free) gloves

Timer

Hokanson Rapid Version Straight Cuff (SC10D)

Hokanson Footswitch for E20 (o1600)

## Framingham Heart Study Peripheral Arterial Tone (PAT) Manual

### FHS PERIPHERAL ARTERIAL TONE (PAT) PROTOCOL

1. Switch on Endo-PAT device
2. Attach probes to the ends of the tubes that lead from the Endo-PAT device.
3. Attach blue “anchors”/circular dividers to clips on tubes of Endo\_PAT device
4. Switch on Laptop
  - Select PAT
  - Select New Patient
  - Enter patient information: Initials, ID and PATographer ID.
5. Set timer to 5 minutes.
6. Switch on the Hokanson blood pressure machines and set inflation level to 250mm/HG
7. Greet participant and ask PAT questions from the Vascular Testing logbook
8. If answers to any of the first three questions is yes, do not do the test and record reason. If no proceed.
9. Record the remainder of the required information on the laptop:
  - Enter Age
  - Enter Systolic and Diastolic Blood pressure
  - In Remark Box 2, enter room temperature.
  - Enter okay and deflate probes by pressing the red arrow at the top of the screen on the left hand side.
  - In Remark Box 1, enter “LN”, if participant's nails extend the fingers by more than 5mm
10. Explain test to participant and ask if participant would like to proceed, explaining that we can stop the test at any time. (See script)
11. If participant does not want to do the test, record on log sheets.
12. If participant want to try test, place cuff on right forearm of participant just below the elbow.
13. Press OK on laptop to record participant information and deflate probes by pressing the deflation button on the top left hand corner of the screen, if you have not already done so. Place the probes into the arm rest and ask participant to gently place the index fingers (or other selected fingers) into the probes. Do not use injured fingers. Any finger can be used except the thumb. Use parallel fingers. Place the blue anchors on the fingers next to the probes, making a kink free loop that is not too tight and not too slack. The tubes should lead distally away from the hand.
14. Check fingers to ensure that nothing is touching the probes. If participant has short fingers and the anchor is resting on the probe, replace the anchor with one that has been trimmed around the edges. Alternatively, the anchor can be placed on an alternate finger and the finger next to the probe can be separated using a small piece of gauze or other soft padding.
15. Inflate probes by pressing black arrow on laptop at top of screen on left hand side and then go into “standby mode” by pressing the yellow button that will light up to the right of the black arrow soon after the probes have been inflated.
16. Remove fingers from rests and place forearm on arm rests with palms flat and the fingers suspended over the edge, ensuring that the rest is not touching the probes. Fingers should be relaxed and nothing should be touching the fingers or the probes.
17. When data looks good on the laptop screen, press the green GO button at the top of the screen next to the standby button to begin monitoring the volume of the pulse pressure.
18. After 2 minutes, simultaneously press the pedal to inflate the cuff and press the timer to start timing the five minute occlusion period.
19. Ensure inflation is at 250mm/HG
20. Ensure that participant is comfortable and ask if pressure is okay.
21. Just before deflation time, remind participant to keep fingers still for the remainder of the test.

## **Framingham Heart Study Peripheral Arterial Tone (PAT) Manual**

22. The timer will sound after 5 minutes at which time you must press the pedal to deflate the cuff and reset the timer.
23. Remove air pipe that connects Hokanson and the cuff.
24. Turn off machines
25. After the 3 minute post occlusion period has ended, hit the red stop button at top of screen on laptop
26. Remove finger probes, dividers and cuff.
27. If participant would like to stop the test. Immediately disconnect all equipment and record reason on log sheets and in adverse reaction logbook.

## **Framingham Heart Study Peripheral Arterial Tone (PAT) Manual**

### **FHS Peripheral Arterial Tone (PAT) Script**

- The next test is a vascular test. This test looks at the health of the lining of the small vessels. To do this test we place finger probes on a finger of each hand to measure the volume of the pulse pressure. Here are the probes. (Show participant the finger probes) We also place a blood pressure cuff on your forearm that is going to be very tight for 5 minutes, tighter than a regular blood pressure cuff.
- Are you okay with that? (If yes)
- You would like to try the test? (If yes)
- If you feel that it is too uncomfortable when the cuff is inflated, please let me know. We can stop the test at any time.
- Now I will explain the entire test to you. I have placed the probes in the arm rests and I would like you to gently place your index fingers into the probes. I am now going to inflate the probes to attach them to your fingers. (Inflate the probes and start recording on standby.)
- Now I'd like you to rest your arms on the arm rests with your palms flat and your fingers suspended over the edge. I am now placing dividers on your fingers, which help to keep your fingers from resting on the probes. We try to keep everything away from the probes and that way we get a better signal. Are you comfortable? Would you like a blanket? (When everything is in place start recording)
- I am now recording the volume of the pulse pressure in your fingers. I do this for two minutes and then I inflate the cuff. When the cuff is inflated it comes up suddenly and it is very tight. We keep it like that for 5 minutes and because the blood flow is restricted, it is normal for you to feel numbness and tingling in your arm and hand, as well as pressure from the cuff. When I deflate the cuff, you will feel the blood come back into your fingers with more pressure. We continue to record the increased volume in the pulse pressure for 3 minutes. The test takes ten minutes and we ask that you try to keep your fingers as still as possible during the test.
- I will give you warning before I inflate the cuff and then you can let me know if it is too uncomfortable for you. If it is too uncomfortable, we can stop the test immediately. Just let me know at any time.

#### **Just before inflation time:**

- It is time to inflate the cuff. On the count of 3, I will inflate the cuff. 1 2 3. (Inflate cuff pressing timer and cuff inflation pedal simultaneously)
- How is that pressure? (*If okay*)
- Would you like to continue the test? (*If non committal or showing signs of discomfort*).
- Would you like me to stop the test? (If indicated, STOP test immediately, and thank participant for trying the test.) If participant wants to continue
- If you have a change of mind, we can stop the test at any time. Just let me know and I will stop the test immediately.

#### **Just before deflation time:**

- It is time to deflate the cuff now. Please continue to keep your fingers still for the last 3 minutes.

#### **When test ends:**

- The test is over now. What did you think of the test? Do you have any questions or concerns? Thank you (Remove probes and cuff)

# **Framingham Heart Study Peripheral Arterial Tone (PAT) Manual**

## **Reference List**

1. Hamburg NM, Keyes MJ, Larson MG, Vasan RS, Schnabel R, Pryde MM, Mitchell GF, Sheffy J, Vita JA, Benjamin EJ. *Circulation*. 2008 May 13;117(19):2428-30. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study.
2. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D. *Am J Epidemiol*. 2007 Jun 1;165(11):1328-35. Epub 2007 Mar 19 The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination.



# ***APPENDIX I***

## ***Endo PAT FDA Approval***

# FACSIMILE

**To:** ITAMAR MEDICAL LIMITED

**F.A.O:** ORI LUBIN

**FROM:** DAVID GALE

**FAX No:** 00 972 8627-5588

**DATE:** 15 JANUARY 2003

**REF:** DAG/STX 1488

**PAGE(S)** 1 of 1

**CC:** CLIENT FILE

**SUBJECT:** ENDO\_PAT 2000

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PLEASE TELEPHONE 0161 928 8924 IF YOU HAVE NOT RECEIVED THIS FAX IN ITS ENTIRETY

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Dear Mr Lubin

I am pleased to confirm that the additional response that you forwarded following the review of the technical documents for the above device were considered to be satisfactory and that you can proceed to CE mark the device with our Notified Body number for endothelial dysfunction testing.

Best regards

For and on behalf of

**AMTAC Certification Services Ltd**

David Gale  
Director

---

**AMTAC CERTIFICATION SERVICES LIMITED**

NORMAN ROAD • BROADHEATH • ALTRINCHAM • CHESHIRE • WA14 4EP • UNITED KINGDOM

TELEPHONE: +44 (0)161 928 8924 • FAX: +44 (0)161 927 7359 • EMAIL: [acsl@amtac.co.uk](mailto:acsl@amtac.co.uk) • WEB: [www.amtac.co.uk](http://www.amtac.co.uk)

*Amtac Certification Services Limited*

**AMTAC MEDIQA**



# *Certificate of Registration*

**ISO 9001: 2000 and ISO 13485: 2003**

*This is to certify that*

**Company: ITAMAR MEDICAL LTD**  
**Situated at: P O Box 12006, 1<sup>st</sup> Floor 2 Ha'eshel Street**  
**Caesarea Ind Park South, Caesarea, Israel**

**has demonstrated compliance of their Quality System to the requirements of**  
**ISO 9001: 2000 and ISO 13485: 2003 for the**  
**Design, Manufacture and Inspection of**

**PAT - PERIPHERAL ARTERIAL TONOMETER**

**Signed for and on behalf of ACSL**

**Director:**

**Original Issue Date: 20<sup>th</sup> January 2004**  
**Date Re-Issued: 12<sup>th</sup> February 2004**  
**Certificate No: 316A**



**"AMTAC Mediqa" is a trade name of AMTAC Certification Services Limited**  
**Valid until 20<sup>th</sup> January 2009 subject to continued compliance demonstrated at periodic surveillance and 3 yearly re-assessment**



# itamar

Itamar Medical Ltd.  
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Fax: +972-4-627 5598  
In U.S. 1-800-206-6952  
[www.itamar-medical.com](http://www.itamar-medical.com)

Itamar Medical Ltd

October 29, 2002

## **Endo PAT 2000 device**

The Endo PAT 2000 device manufactured by Itamar Medical Ltd is exactly the same device as the ETT PAT 2000, which has already passed safety and EMC testing and has CE 0473 clearance.

The Endo PAT 2000 differs only in the clinical application for which it is used and in the measurement procedure. Instead of the patient performing an exercise stress procedure as in the case of the ETT PAT 2000, with the Endo PAT 2000 the patient undergoes a reactive hyperemia procedure.

The system of the Endo PAT 2000 also differs from the ETT PAT 2000 system in the PC compatible display and analysis software.

The Endo PAT 2000 is a low risk device. It was tested in feasibility studies and accomplished good results without any adverse events or any patient discomfort.

Itamar Medical Ltd have started the process for CE clearance to the Endo PAT 2000.

Yours truly,

Ori Lubin

QA & Regulatory Affairs Manager



Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

NOV 12 2003

Itamar Medical, Ltd.  
c/o Dorit Winitz, Ph.D.  
Project Manager  
Push-med Ltd.  
117 Ahuzah Street  
Ra'anana 43373  
ISRAEL

Re: K032519

Trade Name: Endo PAT 2000  
Regulation Number: 21 CFR 870.1425  
Regulation Name: Programmable Diagnostic Computer  
Regulatory Class: Class II (two)  
Product Code: DQK  
Dated: August 13, 2003  
Received: August 15, 2003

Dear Dr. Winitz:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to other additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 398. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Page 2 – Dorit Winitz, Ph.D.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050. This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4646. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>

Sincerely yours,



for Bram D. Zuckerman, M.D.  
Director  
Division of Cardiovascular Devices  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

## INDICATIONS FOR USE STATEMENT

510(k) Number (if K032519  
known): \_\_\_\_\_

Device Name: Endo PAT 2000

**Indications for Use:** The Endo-PAT2000 device is a non-invasive device, intended for use as a diagnostic aid in the detection of coronary artery Endothelial Dysfunction (positive or negative) using a reactive hyperemia procedure.

The Endo-PAT2000 has been shown to be predictive of coronary artery Endothelial Dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The device is intended to be used in a hospital or clinic environment by competent health professionals

The Endo-PAT2000 device is not intended for use as a screening test in the general patient population. It is intended to supplement, not substitute, the physician's decision-making process. It should be used in conjunction with knowledge of the patient's history and other clinical findings.

(PLEASE DO NOT WRITE BELOW THIS LINE -CONTINUE ON ANOTHER PAGE IF  
NEEDED)

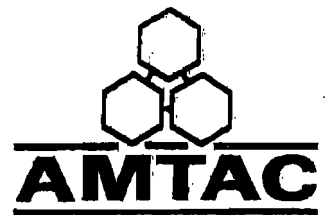
Concurrence of CDRH, Office of Device Evaluation (ODE)

*[Signature]*  
(Division Sign-Off)

510(k) Number Division of Cardiovascular Devices

510(k) Number K032519

Prescription Use \_\_\_\_\_ OR \_\_\_\_\_ Over the Counter  
Use \_\_\_\_\_



**ATTACHMENT TO CERTIFICATE No: 316A**  
**Original Issue Date: 11<sup>th</sup> March 2003**  
**Date Re-issued: 31<sup>st</sup> December 2003**

PAT<sup>TM</sup> – Site PAT 200

PAT<sup>TM</sup> – PAT 1000 RD

PAT<sup>TM</sup> – ETT PAT 2000

PAT<sup>TM</sup> – Watch PAT 100

PAT<sup>TM</sup> – ENDO PAT 2000

Signature: D. A. S. S. S.

Original Issue Date: 11<sup>th</sup> March 2003

Date Re-issued: 31<sup>st</sup> December 2003



**ITAMAR MEDICAL LIMITED - PRODUCT SCHEDULE**  
**TO BE USED WITH CERTIFICATE NUMBER 316CE**

PAT<sup>TM</sup> - Site PAT 200

PAT<sup>TM</sup> - PAT 1000 RD

PAT<sup>TM</sup> - ETT PAT 2000

PAT<sup>TM</sup> - Watch PAT 100

PAT<sup>TM</sup> - ENDO PAT 2000

Original Issue Date: 16<sup>th</sup> October 1998      Signature: .....

Date Re-Issued: 29<sup>th</sup> January 2003

NOV 12 2003

510(K) SUMMARY

**ITAMAR MEDICAL**

510(k) Number K032519

p.1/3

**Applicant's Name:**

Itamar Medical Ltd.  
2 Haeshel St., P.O.Box 3579  
Caesarea 38900, Israel  
Tel + 972 4 6177000  
Fax + 972 4 6275598  
e-mail: itamar-medical.com

**Contact Person:**

Dorit Winitz, Ph. D.  
Push-Med Ltd.  
117, Ahuza St., Ra'ananna 43373, Israel  
Tel: (972) 9 771-8130  
Fax: (972) 9 771-8131  
e-mail: dorit@push-med.com

**Date Prepared:**

August 2003

**Trade Name:**

Endo PAT 2000

**Classification Name:**

Programmable Diagnostic Computer

**Classification:**

**Product Code:** 74 DQK  
**Regulation No:** 870.1425  
**Class:** II  
**Panel:** Cardiovascular

**Predicate Device:**

- PAT 1000 RD (Itamar Medical Ltd.), cleared under K001852
- Standard Procedures used for Endothelial Dysfunction evaluation:
  - The Intra-coronary Acetylcholine (Ach) Challenge method ("Gold Standard")
  - The method of Flow Mediated Dilation (FMD) response to reactive hyperemia of the brachial artery

**Performance Standards:**

No performance standards have been established for such a device under Section 514 of the Federal Food, Drug, and Cosmetic Act. However, the Endo PAT 2000 complies with the following voluntary standards:

-IEC 60601-1:1988+A1:1991+A2:1995

-IEC 60601-1-2:1993

**Intended Use / Indications for Use:**

The Endo PAT 2000 device is a non-invasive device, intended for use as a diagnostic aid in the detection of coronary artery Endothelial Dysfunction (positive or negative) using a reactive hyperemia procedure.

The Endo PAT 2000 has been shown to be predictive of coronary artery Endothelial Dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The device is intended to be used in a hospital or clinic environment by competent health professionals

The Endo PAT 2000 device is not intended for use as a screening test in the general patient population. It is intended to supplement, not substitute, the physician's decision-making process. It should be used in conjunction with knowledge of the patient's history and other clinical findings.

**Device Description:**

The Endo PAT 2000 consists of a main control unit, finger probes and tubing and a software package. The Endo PAT 2000 main control unit is connected to two independent, thimble-shaped, finger mountable probes via two air-conducting tubes. A standard PC or Laptop is connected to the Endo PAT 2000 main control unit for on line display and archiving of device recordings and off line analysis. The output of the Endo PAT 2000 probe are pressure fluctuations sensed at its distal compartment induced by the volume changes of the pulsating digital arteries.

The Endo PAT 2000 system consists of two separate platforms connected by RS-232 channels:

- A PC platform running the custom "Endo PAT 2000 application program"
- An Endo PAT 2000 Main Control Unit with a micro-controller (8257) running a custom embedded program

#### **Clinical Study:**

The safety and effectiveness of the Endo PAT 2000 as an aiding tool in the diagnosis of coronary artery Endothelial Dysfunction were evaluated versus a Gold Standard for Endothelial Dysfunction evaluation, the Intracoronary Acetylcholine (Ach) Challenge method.

The reference method is an Intra-coronary procedure, which incorporates measurements of endothelium-dependent and endothelium-independent coronary flow reserve, calculated as the percentage change in coronary blood flow (CBF) and coronary artery diameter (CAD) in response to the Ach challenge.

Study population included intent to treat patients, who had been referred to the cardiac catheterization laboratory for diagnostic angiography secondary to signs or symptoms of ischemic heart disease and suspected coronary endothelial dysfunction, but who showed no angiographic evidence of obstructive coronary artery disease, and who underwent Intra-Coronary Acetylcholine (Ach) challenge test.

Patients were then evaluated using the Endo PAT 2000, which measures Peripheral Arterial Tone (PAT) changes at the fingertip, to a reactive hyperemia challenge.

Study results demonstrate that the Endo-PAT2000 is safe and effective for its intended use, as a statistical analysis of the study results showed acceptable sensitivity and specificity in a comparative study to a Gold Standard procedure, and no adverse events related to the device were reported.

#### **Substantial Equivalence:**

Itamar Medical Ltd. believes that, based on verification, validations, and safety and performance testing results, the Endo PAT 2000 device is substantially equivalent to its predicate device and to the standard procedures cited above without raising new safety and/or effectiveness issues.

## ***APPENDIX 2***

***Agreement between Itamar and Boston University***



## Boston University Medical Campus

### Office of Research Administration

715 Albany Street, 560  
Boston, Massachusetts  
02118-2526  
617 638-4600

February 3, 2004

Koby Sheffy, Ph.D  
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Web: [www.Itamar-medical.com](http://www.Itamar-medical.com)

RE: Memorandum of Understanding between Itamar Medical Limited and Trustees of Boston University

Dear Dr. Sheffy:

The purpose of this letter is to set forth the terms of the agreement between Itamar Medical Limited (hereinafter referred to as "Itamar") and Trustees of Boston University (on behalf of the Framingham Heart Study) (hereinafter referred to as "Trustees") under which Trustees and the Framingham Heart Study investigators shall study endothelial function in small distal vessels with PAT equipment and software provided by Itamar (hereinafter referred to as "Study").

**Itamar has agreed to donate the materials and software listed below to Trustees for the noninvasive vascular testing station.**

1. Two PAT machines [Endo\_PAT2000] Itamar Medical Cat. No OM1695002
2. Software Endo\_PAT2000 software CD Version 2.0 to run the machines
3. Software update releases
4. Two laptops to run the software
5. Accessories (e.g., 4 pneumatic probe tubing; Serial communication cables; Power adaptor; Power cable)
6. Operation manuals
7. A set of two single use PAT probes and anchors for each Framingham Generation III and Omni Generation II participant to be studied.
8. Ongoing technical support and supplies, should equipment or software problems arise

Itamar understands that the Framingham Heart Study is a nonprofit research institute administered by Boston University and the NHLBI. All data and results generated in the

Itamar understands that the Framingham Heart Study is a nonprofit research institute administered by Boston University and the NHLBI. All data and results generated in the performance of the Study shall be solely and exclusively owned and controlled by Trustees. Trustees and the investigators at the Framingham Heart Study shall be free to publish and present the data and results of the Study.

As the funder of the Study, the NHLBI requires that Itamar and Trustees adhere to the guidelines outlined in the '*Guidelines for Third Party Involvement*' document which is attached hereto as Exhibit A. Some of the guidelines included in Exhibit A are set forth below:

- a. Itamar will have limited participation in the Study under the NHLBI guidelines, which will include the following:
  - i. Developing the protocol and reviewing the Study results prior to submission of a manuscript;
  - ii. Itamar will not be able to control the general design of the Study. While Itamar may have limited access to pooled data [not subject specific data], as determined by the Framingham Heart Study investigators, Itamar will not control the analysis, interpretation or reporting of the results.
  - iii. All PAT data generated during the course of the Study shall be the property of Trustees.
- b. Itamar will have no access to the Study participants' data. The privacy of all Study participants will be maintained in accordance with all applicable laws, rules and regulations.
- c. Itamar will have no access to Study data other than that which forms the basis for published reports or is available to other qualified members of the scientific community, unless agreed to by Trustees.
- d. Itamar must have no commitments with the Trustees or Framingham Heart Study investigators as to intellectual or tangible property or other issues that conflict with PHS policy on grants or contracts (particularly as to reporting, distribution of unique research resources, inventions, or commercialization).
- e. The nature of Itamar's support is listed above. The conditions under which the support is to be provided are clearly stated in this memorandum.
- f. In the event that any adverse events whatsoever shall be sustained by the Study participants as a result of the performance of the Study and/or during its term, the Trustees shall promptly inform Itamar. The Trustees are entitled to immediately cease the continued performance of the Study in the event of a safety concern.

**In return for Itamar's donation of the materials and software listed above, Trustees and the Framingham Heart Study investigators**

- i. Will acknowledge the donation of material and software in research presentations and publications.
- ii. On a case by case basis, [to be agreed upon by Dr. Sheffy and Framingham Heart Study investigators] Framingham Heart Study investigators will respond to inquiries about the Itamar materials from scientists.

- iii. Trustees understand that Itamar holds the patent on all the PAT machines that will be used in the Study and the Trustees have NO commercial interest in the equipment. In addition, Trustees will not share Itamar's proprietary or confidential information concerning the PAT machines received from Itamar with any third parties without Itamar's prior written consent, unless required by law.
- iv. Trustees will NOT receive any direct compensation from Itamar as the result of this Study.

Please sign below in your capacity as an authorized representative of Itamar to confirm the agreement of Itamar to the terms listed above.

Thank you.

*Joseph Barabino 2/3/04*  
Joseph Barabino  
Director of Research Administration

Agreed and accepted on behalf of Itamar Medical Ltd.

*CyV*  
Koby Sheffy, Ph.D.

Date: *2/10/2004*

I have read the above terms and on behalf of the Framingham Heart Study investigators I agree to act in compliance with them.

*Emelia J. Benjamin*  
Emelia J. Benjamin, MD, ScM

Date: *2/4/04*



***APPENDIX 3***  
***OSMB Approval***



DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health  
National Heart, Lung, and Blood Institute  
II Rockledge Centre, MSC 7934  
6701 Rockledge Drive  
Bethesda, Maryland 20892-7934

April 11, 2003

Emelia Benjamin, MD, ScM  
Associate Professor of Medicine  
The Framingham Heart Study  
73 Mt. Wayte Avenue  
Framingham, MA 01702-5827

Dear Dr. Benjamin,

The Framingham Heart Study OSMB has recommended approval for your request to use new equipment in the current vascular testing protocol. No concerns were raised, however, one question was asked about whether the donation of the equipment from the manufacturer necessitates an agreement with them concerning ownership of data. I would appreciate your relaying your response to this question through the Project Officer.

Best wishes for success with this new technology.

Sincerely,

A handwritten signature in cursive script, appearing to read "Catherine Loria", is positioned below the "Sincerely," text.

Catherine Loria, PhD  
Executive Secretary  
Framingham Heart Study Monitoring Board  
NHLBI, DECA, EBP

cc: Russell Luepker, M.D. Chair, FHS Monitoring Board  
Paul Sorlie, Ph.D, FHS Project Officer  
Teri Manolio, M.D., Ph.D., Director, Epidemiology and Biometry Program

***APPENDIX 4***  
***FHS PAT Log Book Sheet***


# Vascular Testing

## Exam 8 Framingham Study Vascular Function Participant Worksheet

Keyer 1: \_\_\_\_\_

Keyer 2: \_\_\_\_\_

0 1 9

If yes,  discontinue PAT


**Do you have a latex allergy?** (0=No, 1=Yes, 9=Unknown)

0 1 9

If yes,  discontinue brachial

**Do you have active Raynaud's disease, as manifested by daily attacks of Raynaud's currently blue fingers or ischemic finger ulcers?** (0=No, 1=Yes, 9=Unknown)

0 1 2 3 8 9

If 1(right),  discontinue brachial

If 2(left),  BP on right

**Women Only: Have you had a radical mastectomy on right side?** A radical mastectomy is the removal of the breast, associated lymph nodes, and underlying musculature. Does NOT include lumpectomy or simple mastectomy. (0=No, 1=Yes, right, 2=Yes, left, 3=Yes, both, 8=Male, 9=Unknown)

0 1 9

if yes  
fill 

**Have you had any caffeinated drinks in the last 6 hours?**

(0=No, 1=Yes, 9=Unknown)

\_\_\_\_ How many cups? (99=Unknown)

0 1 9

**Have you eaten anything else including a fat free cereal bar this morning?**

(0=No, 1=Yes, 9=Unknown)

0 1 9

if yes  
fill 

**Have you smoked cigarettes in the last 6 hours?** (0=No, 1=Yes, 9=Unkn)

\_\_\_\_:\_\_\_\_ If yes, how many hours and minutes since your last cigarette?  
(99:99=Unknown)

### PAT SCAN

\_\_\_\_/\_\_\_\_/\_\_\_\_

**Date of PAT scan?** (mo/day/yr)

\_\_\_\_

**PAT Sonographer ID**

\_\_\_\_.\_\_\_\_

**Room temperature** (Celsius)

\_\_\_\_

**Mean systolic baseline blood pressure**

\_\_\_\_

**Cuff inflation pressure** (Baseline SBP + 50 or 250)

0 1 2

**Was PAT protocol completed?** (Determined at time of scan or at time of interpreting)

0=No: protocol was not completed i.e. none of 3 parts completed of Baseline, Doppler, Deflation.

1=Yes: protocol was done and completed i.e. all 3 parts completed of Baseline, Doppler, Deflation

2=Yes, Partial: protocol was partially completed i.e. 1 part of 3 completed, 2 of 3 completed of Baseline, Doppler, Deflation

If no (0) or partial (2)



**PAT scan deviations: circle ALL that apply**

1: Subject refusal

2: Subject discomfort

3: Time constraint

4 Equipment problem (if not #5 or #6), specify \_\_\_\_\_

5: Foot pedal problem/cuff sequence problem

6: Doppler problem

7: Other, specify \_\_\_\_\_

## ***APPENDIX 5***

### ***FHS PAT Adverse Events Log Sheet***

## TONOMETRY / PAT / ECHO ADVERSE REACTION LOG

*To be filled out when a test was administered and adverse reaction occurred.\*\**

NAME: \_\_\_\_\_

Fram ID: \_\_\_\_\_

DATE OF CLINIC VISIT: \_\_\_\_ - \_\_\_\_ - \_\_\_\_ (mm/dd/yyyy)

Tech ID: \_\_\_\_\_

For which test is this log being filled out? (please circle one): TONOMETRY / PAT / ECHO

### TONOMETRY / PAT / ECHO TEST - SKIN REACTION - PETECHIAE

*Fill in and circle all that apply*

Abnormality Location	Time Course	Skin Reaction Pain?	Patient Upset?	Prior Occurrence?	Easy Bruising?
Hand	<u>Onset</u>	YES	YES	YES	YES
Forearm	Date: ____ - ____ - ____	NO	NO	NO	NO
Upper arm	Time: ____:____ AM PM	<i>Describe:</i>	<i>Describe:</i>	<i>Describe:</i>	<i>Describe:</i>
<i>Describe:</i>	<u>Offset</u>				
	Date: ____ - ____ - ____				
	Time: ____:____ AM PM				

### OTHER ADVERSE REACTIONS

*Fill in and circle all that apply*

Discomfort / Pain	Other
Date: ____ - ____ - ____	Date: ____ - ____ - ____
<i>Describe:</i>	<i>Describe:</i>

**\*\*Note:** If test was not administered due to adverse reaction, then all information should be recorded in the log book. Adverse reaction is defined by MD/Tech group.

# ***APPENDIX 6***

## ***Data Procedures***

## Peripheral Arterial Tone Process

- ✚ Daily – Technicians:
  - Person responsible: Birgitta Lehman, Shuxia Fan
  - Data is collected to laptop from participants.
  
- ✚ Weekly – I.T.
  - Person responsible: Dan Kupka
  - I.T. copies data from PAT collection machines to PC Workstation (admission1)
  
- ✚ Monthly – I.T.
  - Person responsible: Dan Kupka, Galina Medvedev or John Leary
  - Generate and log to Ingres, a list of Patient ID's for Data Manager & Data entry Staff processing. This log will reflect the data that is burned to CD.
  - Month of data will be burned to CD – two copies.
    - a. Log and send one copy to Israel for analysis and correction.
    - b. Log and send one copy to Iron Mountain for storage
  
- ✚ Israel, Data Management,
  - Person responsible: Dan Kupka, Diane Corey, Moira Pryde, Doctor Sheffy, Sue Blease, Michelle Kupka
  - Corrected data is returned from Israel on CD to I.T.
  - I.T. will generate a list from the CD and log it to Patient for Data Manager & Data entry Staff processing on Ingres.
  - I.T. transfer the CD data in Excel format to Unix System.
  - Data Management runs SAS and builds a data set.
  - Data Management checks it against list of sent ID's
  - Log is printed and added to log book.
  - Send CD to Iron Mountain for storage.