Simple Letter of Agreement

between

U.S. Food and Drug Administration

and

University of Rochester

for the

Telemetric and Holter ECG Warehouse Program

I. PURPOSE

This Simple Letter of Agreement (SLA) documents the parameters and conditions for use of information shared within the Telemetric and Holter ECG Warehouse Program (THEW); a working group consisting of staff members of the Food and Drug Administration (FDA), the University of Rochester (UR), scientific societies and institutes, consortia such as the Cardiac Safety Research Consortium (CSRC), as well as other public and private partners. This Agreement is executed between FDA and UR hereafter referred to individually as a "Party" and collectively as the "Parties." This Agreement is deemed effective on the date of the last Party to sign (Effective Date) and will remain in effect for a period of up to three years.

II. BACKGROUND

In March of 2004, the U.S. Food and Drug Administration (FDA) released a white paper entitled "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products."[1] This report called for research to develop and validate new tools and methods for testing new medicines on the "critical path" from the laboratory to the patients. The purpose of this initiative is to identify and solve common issues relating to classes of medical products in order to help FDA succeed in its mission to protect and promote the public health. In its second report, FDA identified issues that seemed to be easily addressable in an "opportunities list" that target specific areas for improvement. One of the recurring themes of the Opportunities List[2] is cardiac safety.

Sudden cardiac arrest (SCA) is the leading cause of death in the United States, resulting in over 450,000 deaths per year. Some causes of SCA are related to adverse interactions of drugs in patients who are predisposed to lethal cardiac arrhythmias, or by action of the drugs themselves. FDA currently requires extensive "thorough QT" studies to determine the proarrhythmic risk associated with new compounds, but requires new tools to evaluate this risk in the course of regulatory review. Additionally, devices are currently capable of detecting proarrhythmic risk in extreme cases, but lack the capability to discern the fine gradations that may identify a patient at risk. These limitations contribute to increased regulatory burden and clinical burden and cost associated with some therapies.

The THEW program represents a unique collaborative opportunity for FDA and UR to develop technologies related to the analysis and the understanding of the electrical activity of the heart. Specifically the THEW will facilitate the development of novel algorithms for identification of proarrhythmic potential of new compounds. The THEW program is built on the expertise of the Heart Research Follow-up Program (HRFUP) and will lead to the creation of an international repository for continuous ECG recordings. The HRFUP at the University of Rochester Medical Center (URMC, NY) has a long history of clinical research activities including extensive experience in the design,

---

[1] "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

[2] "Critical Path Opportunities Report," http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf

conduct, and analysis of world-wide, multicenter, clinical research studies ranging from 100-3,500 subjects. URMC is one of the leading centers for the design and implementation of successful clinical trials such as MADIT I and MADIT II. Simultaneously, the HRFUP has extensive experience in the development of ECG technologies that are validated and further developed under NIH/EPA awards and private funding. UR has extensive research experience in quantitative analysis of ventricular repolarization involving animals, normal subjects, patients with genetic (Long QT Syndrome) and acquired (coronary disease and hypertension) cardiac disorders, and in patients exposed to drugs that affect the QT/U waves of the ECG.

III. GOALS FOR THE THEW PROGRAM:

The overarching goal of the THEW is to provide access to continuous electrocardiographic data to for-profit and not-for-profit organizations for the design and validation of analytic methods to advance the field of quantitative electrocardiography with a strong focus on cardiac safety.

To promote cross-fertilization of scientific knowledge, resources and ideas that will advance the field of quantitative electrocardiography and to meet the aforementioned goal, the THEW will strive to:

- Develop specific projects to implement and to grow the repository of ECG information in the THEW;
- Facilitate scientific projects toward the development, testing and validation of ECG-related technologies and platforms;
- Leverage expertise and resources toward the implementation of collaborative projects among FDA, UR, and other public and private stakeholders;
- Identify, develop and evaluate new electrocardiographic markers of cardiovascular risk related to management of patient care and evaluation of new molecular entities;
- As appropriate, incorporate scientific findings from the THEW into the premarket evaluation process for electrocardiographic devices and associated methodologies, and into the total product life cycle.

IV. INFORMATION SHARING AND INTELLECTUAL PROPERTY

To achieve the goals of the THEW, and specifically, to facilitate the advancement of quantitative electrocardiography, to collaborate on the oversight, management or conduct of basic and applied research relating to the THEW, FDA and UR have agreed to share information and expertise under a Confidentiality Disclosure Agreement (CDA) executed May 20, 2008, between the Parties. There is no expectation that FDA will share confidential, proprietary or submission-related information under this SLA or the CDA.

FDA understands that some employees of UR have ongoing relationships with regulated industry. FDA also understands that UR has put in place a Conflict of Interest Management Plan to manage potential conflicts of interest, and as outlined in Appendix 2.

"Invention" refers to any subject matter and discovery patentable or otherwise protected under Title 35 of the United States Code. "THEW Inventions" are Inventions conceived or first reduced to practice in the conduct of any THEW project. "Intellectual Property" is defined by the Parties as patents, patent applications, know-how, trade secrets, copyrights and computer programs and algorithms. Rights to Inventions or Intellectual Property developed under THEW will be addressed in separate project-specific development and implementation agreements among the Parties. Inventorship will be governed by U.S. law. In the case of sole Inventorship of THEW Inventions, ownership will be governed by the policies of the employer of the Invention. In the case of joint Inventorship, ownership of Inventions will be governed by the policies of the employer of each inventor. Licenses for THEW Inventions made under a Federal grant or contract, will be subject to the Bayh-Dole Act.

V. RESOURCES

The Parties envision the THEW Program as a public-private partnership. The terms for support will be set forth in the specific written agreements for each project.

VI. GENERAL PROVISIONS

1. Nothing in this SLA alters the statutory authorities or obligations of FDA. This SLA is intended to facilitate collaborative efforts between the Parties in the areas of quantitative electrocardiography, cardiac safety and public health.

2. Proprietary and/or nonpublic information will not be disclosed under this SLA, unless such disclosure is governed by appropriate, separate, written CDA, and to the extent such disclosure is permitted by Federal law.

3. The roles and responsibilities of FDA staff, designated as Federal Liaisons under the THEW, will be governed by applicable federal law and as outlined in Appendix 3.

4. It is understood that, although the Parties have mutual interests, there may be opportunities for independent collaborations and activities outside the scope of this SLA, but which are within the scope of the Parties' respective missions. As such, the Parties may, as appropriate, enter into independent negotiations and agreements with prospective partner/s without any effect on this SLA.

5. Rights to Inventions or Intellectual Property developed under THEW will be addressed in separate written agreements between the Parties. To the extent there is FDA participation in any projects related to development of any regulated product, Invention or Intellectual Property developed under the THEW Program,

such activities will be governed by applicable Federal law. Any regulated product developed under the THEW will be evaluated through normal regulatory mechanisms and processes and appropriate recusal/s for FDA staff will be implemented.

6. Additional staff related to the Parties and who are involved with the activities of the THEW, shall acknowledge the terms of this SLA and shall sign the "Acknowledgement of the Simple Letter Agreement of the THEW" in Appendix 1 of this SLA

7. Any notice or other communication required or permitted under this SLA shall be in writing and will be deemed effective on the date it is received by the receiving Party.

VII. TERM, TERMINATION AND MODIFICATIONS

1. This SLA constitutes the entire agreement between the Parties and to the matters herein. There are no representations, warranties, agreements, or understandings, expressed or implied, written or oral, among the Parties relating to the subject matter of this SLA that are not fully expressed herein.

2. This SLA may be modified only upon the mutual written consent of the Parties. No oral statement by any person shall be interpreted as modifying or otherwise affecting the terms of this SLA.

3. This SLA, when accepted by the Parties, will remain in effect for three (3) calendar years from the Effective Date, unless modified or terminated.

4. Either Party to this SLA may terminate their participation in the THEW Program by written notice at any time, with or without cause, and without incurring any liability or obligation. Such written notice shall be given by the terminating Party to the other Party at least 60 days prior to the date of actual termination.

VIII. CONTACTS

Notices or formal communications pursuant to this SLA shall be sent in writing by personal delivery, overnight delivery, facsimile telecommunication with confirmatory receipt, or certified or registered mail, return receipt requested, to the following contact for each Party:

For FDA:

Wendy R. Sanhai, Ph.D.
Senior Scientific Advisor
Office of the Commissioner, FDA
5600 Fishers Lane, Suite 14 B-45, HZ-1
Rockville, MD. 20857

Phone: (301) 827-7867, Fax (301) 443-9718
Email: wendy.sanhai@fda.hhs.gov

With a copy to:

Benjamin C. Eloff, Ph.D.
Biomedical Engineer
Cardiac Electrophysiology and Monitoring Branch
Division of Cardiovascular Devices
Center for Devices and Radiological Health, FDA
9200 Corporate Boulevard, HFZ-450
Rockville, MD 20850
Phone: (240) 276-4058, Fax: (240) 276-4002
Email: benjamin.eloff@fda.hhs.gov

For UR:

Gail Norris
Director, Office of Technology Transfer & Senior Counsel
University of Rochester Medical Center
518 Hylan Bldg, Rochester, NY 14627
Rochester, NY, 14642
Phone: (585) 275-2758, Fax:
Email: gnorris@admin.Rochester.edu

With a copy to:

Jean-Philippe Couderc, PhD
Research Associate Professor of Medicine/Electrical and Computer Engineering
Heart Research Follow-Up Program - Cardiology Department
University of Rochester Medical Center
601 Elmwood Avenue, Box 653
Rochester, NY 14642
Phone: (585) 275 1096, Fax: (585) 273 5283
Email: jean-philippe.couderc@heart.rochester.edu

The Parties shall notify each other of any change of address or change of named contact by written notice. All notices shall be effective upon date of receipt.

Signatures begin on the following page

Authorized Signatures of Responsible Parties

We, the undersigned, agree to abide by the terms and conditions of this Agreement

APPROVED AND ACCEPTED FOR THE FDA

---------- Date 5/22/08

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
U.S Food and Drug Administration

CONCURRING FOR THE CENTER FOR DRUG EVALUATION AND RESEARCH

---------- Date 5/27/08

Norman Stockbridge, MD, PhD
Director Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

APPROVED AND ACCEPTED FOR THE UNIVERSITY OF ROCHESTER

---------- Date 29 May 2008

Gunta Liders
Director of the Office of Research and Project Administration
University of Rochester

Appendix 1

Acknowledgement of the Simple Letter Agreement of the THEW

As a member/participant of the Telemetric and Holter ECG Warehouse (THEW), I have read and understand the terms as described in this Simple Letter Agreement.

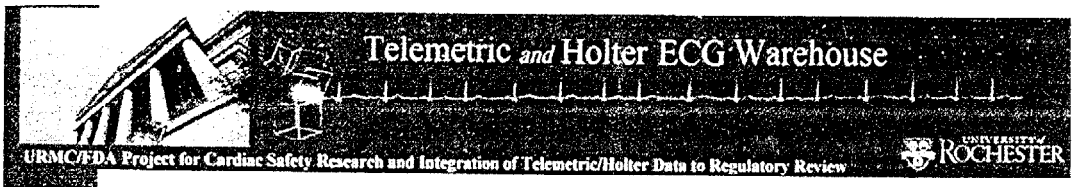
Name: _____

Title: _____

Organization: _____

_____

Date: _____



The Telemetric and Holter ECG Warehouse
University of Rochester Medical Center
601 Elmwood Ave., Box 653
Rochester, NY 14642, USA
THEW@ heart.rochester.edu
Phone 585-275-3445
Fax 585-273-5283

Tuesday, February 19, 2008

Wendy R. Sanhai, Ph.D.
Senior Scientific Advisor
Office of the Commissioner, FDA
5600 Fishers Lane, Suite 14-B45
Rockville, MD 20857

Dear Wendy,

This letter describes the various relationships between and among Dr. Jean-Philippe Couderc, the University of Rochester Medical Center and iCardiac Technologies Inc. and the University's actions taken to appropriately manage any potential conflicts of interest that could be perceived to arise out of these relationships.

The University of Rochester has recently received a $40M grant from the NIH to create the Center for Translational Research. One of the objectives of this Center is to promote the translation of scientific discoveries into practical applications to improve human health. A path to this goal might require commercialization of the technologies developed in our academic center. In this process, the University has ensured that such path would not create opportunities for unmanaged conflict of interests that would jeopardize its reputation.

For instance, the technology developed by Dr. Couderc had very limited use to patients until we have transferred it to a company: iCardiac Technologies Inc. This company has licensed from the University certain technologies developed in Dr. Couderc's research laboratory. Dr. Couderc is the primary inventor/author of those technologies. iCardiac is a company servicing pharmaceutical companies and Contract Research Organizations by providing ECG-based metrics and data analysis. In addition to his interest as an inventor/author of the licensed technologies, Dr. Couderc is currently a consultant for this company and serves as Chief Technology Officer counseling the company in the development of ECG technologies.

The University of Rochester and Dr. Couderc have put in place a Conflict of Interest Management Plan to ensure that Dr. Couderc's interest in iCardiac is managed in a way that ensures that his research and related work for the University is not inappropriately influenced by his outside interests. The University's Conflict of Interest policy can be accessed at http://www.rochester.edu/ORPA/policies/coipolicy.pdf. As required by our policy, real or perceived conflicts of interest will be reduced, managed or eliminated. Conflicts that the Dean agrees can be managed require a written conflict of interest management plan that is co-signed by both the Dean and the faculty member. Among the management strategies implemented in Dr. Couderc's Plan are:

- Full disclosure by Dr. Couderc of his financial interests in iCardiac in grants, publications and presentations that relate to novel advanced ECG-based biomarkers or improved methods for measuring standard ECG-based biomarkers;
- Full disclosure by Dr. Couderc of his financial interests to students, postdocs, and lab personnel;
- Submission of manuscripts to the Dean of the School of Medicine and Dentistry for determination whether and independent scientific review is warranted;
- At the discretion of the Dean, the appointment of an ad hoc oversight committee to monitor the sponsored projects;
- Routing of work plans for any iCardiac sponsored testing or research through Dr. Couderc's Chair and the AVP for Research Administration to ensure appropriateness of the work statements and use of University resources;
- Prohibition on the use of University resources for iCardiac purposes other than for defined sponsored programs;
- Periodic reporting to the Dean on any changes to Dr. Couderc's sponsored funding or financial interests;
- Reporting to NIH on the managements of this potential financial conflict of interest.

This measure has been taken in order to ensure that the action of the URMC employees following the level of ethics required by the University.

Today, iCardiac is part of the seven companies that have committed to financially support the THEW project. iCardiac will not receive any benefit or advantage as a supporter of the THEW project other than those equally afforded to all other company supporters of the THEW project.

The THEW will function under a "cost center" structure. This structure fits to not-for-profit organization regulation and thus the fees required to users of the warehouse will be estimated based on the expenses to develop and maintain the THEW activities. This costing structure will be in accordance with OMB Circular A-21 costing for specialized service facilities and will not discriminate against federally supported activities.

Please let us know if you have questions.

Sincerely,

Jean-Philippe Couderc, PhD
Res. Associate Professor of Medicine and Electrical Engineering.
PI of the Telemetric and Holter Warehouse Project
University of Rochester Medical Center

Gunta Liders
Director of the Office of Research and Project Administration (ORPA)
University of Rochester Medical Center

Gail Norris
Director of the Office of Technology Transfer Office
VP & University Counsel
University of Rochester Medical Center

Roles and Responsibilities for FDA Employees Interacting with an Outside Organization under a PPP

The activities of all FDA representatives to a Public-Private Partnership (PPP) will abide by Title18 U.S.C. section 208, the criminal conflict of interest statute, which prohibits federal employees from participating in an official matter that affects the financial interest of an outside organization in which the employee serves as officer, director, trustee or employee. The Department of Justice has opined a federal employee can violate section 208 by participating in an official matter that affects the financial interest of an outside organization in which the federal employee serves as officer, director, trustee, or employee even where the federal employee serves as an official duty activity. Therefore, section 208 prohibits federal employees from serving in their official capacity as officer, director, trustee, or employee of an outside organization, unless one of the following options has been satisfied:

- An FDA employee may serve in an official capacity if a federal statute expressly authorizes such service with the organization; or
- An FDA employee may serve in an official capacity if the outside organization releases the individual from all fiduciary obligations. In order for such a release to be effective, it would have to be permitted under applicable state law; or
- An FDA employee may serve in an official capacity if the individual obtains a waiver of the conflict of interest statute under section 208 from the appropriate DHHS official (see link for sample waiver); or
- An FDA employee may serve an organization in a purely private capacity, as an outside activity. An employee who engages in an outside activity as officer, director, trustee, or employee of an organization would have to recuse himself from any official matter that affects the financial interest of the organization. This includes particular matters affecting the organization specifically (such as a grant application or an investigation) as well as particular matters that affect the organization as part of a class of entities (e.g., a new regulation affecting all universities with medical schools). The employee would have to avoid any appearance of using his public office for private gain, and proper clearance must be obtained on Form HHS-520, "Request for Approval of Outside Activity."

In addition to the above factors, supervisors and employees should be aware that when serving as an officer, director, trustee, or employee of an outside organization, liability issues can arise as a result of such service. Where the employee undertakes such service as an outside, private activity, the federal government would have no responsibility for providing legal representation if the employee is a party to a lawsuit stemming from such service, and would not be responsible for satisfying any judgment entered against the employee. Even where an employee has been assigned to such service as an official duty activity, there have been past cases where the Department of Justice has declined to provide legal representation where the employee was a named defendant in a lawsuit stemming from service with an outside organization. To qualify for representation, there must be a determination that it is within the agency's programmatic legal authority to

undertake the proposed activity. The Federal Tort Claims Act (FTCA) constitutes a limited waiver of sovereign immunity regarding claims for money against the United States for injury or loss of property, or personal injury or death caused by the negligent or wrongful act or omission of any employee of the Government while acting within the scope of his office or employment. Determinations of scope of employment are made on a case-by-case basis, are generally fact-specific, and may require consideration of a variety of factors. The results under any particular set of facts, therefore, are not always entirely predictable, and the Department of Justice has the primary role in certifying whether or not a given activity falls within the scope of employment.

Accordingly, where agency managers wants to assign personnel to tasks that would not obviously fit within the regular course and scope of an employee's regular workplace duties (including service as an officer, director, trustee, or employee of an outside organizations), there should be a written determination by a supervisor with authority for making such a determination that the activity supports the Department's authorized activities and is not otherwise prohibited by law or agency policy. Other documentation tools may include Memoranda of Understanding or Agreement, personnel orders, letters of assignment, or other written documents that memorialize the understandings of the agency, the employee, and the receiving outside organization. However, none of these factors are necessarily determinative of whether or not an activity will ultimately be found to have occurred within the scope of employment.

An alternative to serving as an officer, director, trustee, or employee of an outside organization is to assign an employee to serve as a "Federal Liaison" to the organization, which would not implicate section 208 or the above-described liability issues. As a Federal Liaison to a PPP, the employee would be the FDA representative to the organization, and would present and receive information and views on behalf of the Department of Health and Human Services (DHHS) and FDA; but would not hold a position as an officer, director, trustee, or employee of the organization, and would not direct the organization's internal operations. Serving as a Federal Liaison (rather than as an officer, director, trustee, or employee of the organization) is the preferred method of interacting with outside organizations under a PPP.

It is recommended that each component determine whether employees in their FDA Center/Office are serving outside organizations in their official capacity as an officer, director, trustee, or employee. If it is determined that an employee is serving an outside organization as part of his official duties, action should be taken on one of the options listed above.