

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, 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 List² 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 THEW facilitates the development of novel methods and technologies for the identification of proarrhythmic potential of new compounds. The THEW program is hosted by the Center for Quantitative Electrocardiography and Cardiac Safety built on the expertise of the Heart Research Follow-up Program (HRFUP) and has led to the creation of an international repository for continuous ECG recordings.

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

In 2008, the HRFUP and a list of private companies including ECG equipment companies, contract research organizations (CROs) and pharmaceutical companies have enabled the inception of the THEW (www.thew-project.org). This initiative was designed to provide access to continuous electrocardiographic data (Holter and standard resting ECGs) to for-profit and not-for-profit organizations/entities for the design and validation of analytic methods to advance the field of quantitative electrocardiography with a strong focus on cardiac safety. In 2010, the THEW received a multi-million dollar award from the National Heart, Lung and Blood Institute (NHLBI) to further develop its infrastructure through the development of the Center for Quantitative Electrocardiography and Cardiac Safety. Today, the THEW and the center are actively involved in the development of research related to ECG technologies with a strong emphasize on the analysis of continuous electrocardiogram and telemetric systems. The initiative received a multi-million dollar grant from the National Heart, Lung and Blood Institute (NHLBI) to support this initiative. Currently, the THEW includes 12 databases of continuous ECG recordings with various length and technical specifications. These recordings are fully digital and fully annotated. The THEW includes data from healthy individuals exposed to cardiac and non-cardiac drugs, patients with congenital long QT syndrome, post-myocardial patients and patients with coronary artery disease, and patients with an acute coronary syndrome.

The scientific network defined by the members of our initiative has reached an international recognition. The current list of the THEW members contains organizations scattered across the North America, Europe, Asia and Australia, including 21 universities and 14 for-profit companies. Use of THEW data has resulted in 18 peer-reviewed publications, and numerous presentations at international scientific conferences, including a dedicated symposium at Computing in Cardiology, 2010. Tools and techniques developed and tested on THEW data are being incorporated into the design of analytical algorithms for use in medical devices and the evaluation of ECGs from patients enrolled in thorough QT studies.

III. GOALS FOR THE THEW PROGRAM:

The objective of the Telemetric and Holter ECG Warehouse (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, THEW will strive to:

- Develop specific projects to implement and to grow the repository of ECG information in the THEW;
- Foster scientific collaborative projects for the development, the testing and the validation of ECG-related technologies ;

- Facilitate collaborative discussions and leverage for resources for the implementation of joint projects among FDA, UR, and other public and private stakeholders;
- Develop, identify 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.
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IV. INFORMATION SHARING

FDA and UR have agreed to share information under a Confidentiality Disclosure Agreement (CDA) executed May 20, 2008 as outlined in this SLA for the sole purpose of advancing the goals of the THEW Program and facilitating the advancement of quantitative electrocardiography, and in the context of this purpose, to collaborate on the oversight, management or conduct of basic and applied research relating to the respective public health missions of FDA and UR.

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. (Appendix 2) The THEW program shall remain an academic research enterprise. All interactions with regulated industry shall be treated equally with no preferences shown to any one entity.

“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 a 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 cooperative efforts between the Parties in the area of quantitative electrocardiography.
2. Proprietary and/or nonpublic information will not be disclosed under this SLA, unless such disclosure is governed by appropriate, separate, written Confidentiality Disclosure Agreements (CDAs), and to the extent such disclosure is permitted by Federal law.
3. The roles and responsibilities of Federal Liaisons assigned under this SLA will be governed by applicable federal law 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 development and implementation agreements between the Parties. To the extent there is FDA participation in any projects related to development of any product, invention or property developed under the THEW Program, such activities will be governed by applicable Federal law.
6. 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: Janet Woodcock, M.D.
Director
CDER/FDA
Bldg 51, Rm 6133
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: (301) 796-5400
Email: janet.woodcock@fda.hhs.gov

With copies to: Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
CDER/FDA
Bldg 22, Rm 4168
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: (301) 796-2240, Fax (301) 796-9841
Email: norman.stockbridge@fda.hhs.gov

Mr. Devi Kozeli
Project Manager
Division of Cardiovascular and Renal Products
CDER/FDA
Bldg 22, Rm 4183
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: (301) 796-1128, Fax (301) 796-9841
Email: devi.kozeli@fda.hhs.gov

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

With a copy to: Jean-Philippe Couderc, PhD
Associate Professor of Medicine/Electrical and Computer
Engineering
Center for Quantitative Electrocardiography and Cardiac Safety
HRFUP- 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 CDER


----- Date 6/23/11

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

APPROVED AND ACCEPTED FOR THE UNIVERSITY OF ROCHESTER

----- Date -----
Gunta Lidars
Director of the Office of Research and Project Administration
University of Rochester

Appendix 1

Acknowledgement of Simple Letter Agreement of THEW

As a member of the Telemetric and Holter ECG Warehouse (THEW), I have received and understand the conditions for information sharing of this program as described in this associated Simple Letter Agreement.

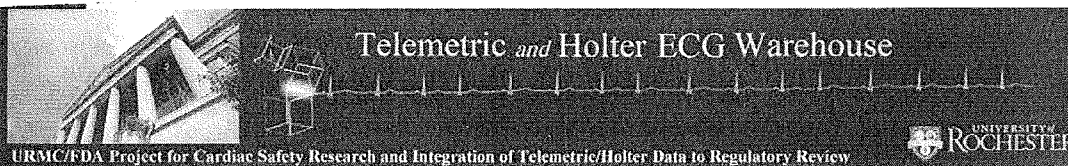
Name: _____

Title: _____

Organization: _____

Date: _____

Appendix 2



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:

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- 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.

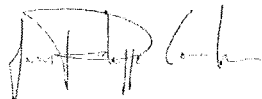
This measure has been taken in order to ensure that the action of the URMC employees following the level of ethics required by the University.

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.

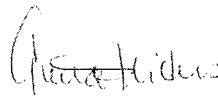
The THEW will function under a "cost center" structure. This structure fits to not-for-profit organization regulation and thus the fees required to users of the warehouse will be estimated based on the expenses to develop and maintain the THEW activities. This costing structure will be in accordance 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 Lidars
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 Title 18 U.S.C. section 208, of 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

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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.