Revised 7/27/2017

MoTrPAC Ancillary Studies Policy

Overall Principles

The Molecular Transducers of Physical Activity Consortium (MoTrPAC) study is designed to discover and perform preliminary characterization of the range of molecular transducers (the 'molecular map') that underlie the effects of physical activity in humans. To make the best possible use of this resource, MoTrPAC encourages investigators to develop ancillary studies (AS) in conjunction with the MoTrPAC study and to involve other investigators, within and outside of MoTrPAC, in this process. Towards this end, we have developed an interactive AS approval process that facilitates the development of AS and also assures the compatibility of the proposed AS with the resources, efficient execution and mission of the overall MoTrPAC program.

MoTrPAC is composed of 7 clinical centers (6 adult and 1 pediatric center), seven Chemical Analysis Sites (CAS), three Preclinical Animal Sites (PAS), a Consortium Coordinating Center (CCC) to manage clinical study operations and implementation, and a Bioinformatics Center (BIC) to process and integrate data and metadata into a centralized publically accessible MoTrPAC database and develop associated tools for analysis of these data.

In order to assure that an AS does not negatively impact the success of the overall MoTrPAC study, all AS proposals must be approved by the MoTrPAC Steering Committee prior to submission to a funding agency/organization and before implementation. To obtain approval for submission, proposals will be reviewed by the Ancillary Study Committee (ASC) and upon approval, forwarded to the MoTrPAC Steering Committee and the MoTrPAC Data and Safety Monitoring Board (DSMB) for evaluation and final approval. Upon obtaining final approval, the AS investigators will receive a letter of support from the MoTrPAC ASC for inclusion in their grant application.

Definition of an Ancillary Study (AS)

In MoTrPAC, an AS involves collection of data from or about MoTrPAC human participants or rodents using procedures or measurements that are not included in the original core protocol. AS fall broadly into two categories: 1) Studies that involve any contact with MoTrPAC study participants or direct access to MoTrPAC study rodents, including collection of additional data, collection of additional biospecimens, use of any study resources (i.e., physiologic test results, etc.), or use of any participant personal health information (PHI) for purposes above and beyond those set forth in the parent MoTrPAC protocol; and 2) studies that do not involve MoTrPAC study participant contact or direct access to MoTrPAC study rodents, but that do create new data, i.e., propose to utilize existing data for secondary data analyses, additional measurements on stored or archived biospecimens, or other non-clinical resources), or studies performed outside of MoTrPAC on additional subjects or rodents that follow MoTrPAC protocols and add additional data to the MoTrPAC resource.

Evaluation of Ancillary Studies

All AS will be evaluated for their potential impact on the objectives, performance, or planned study group analyses and reports (as applicable) of the MoTrPAC study. An AS must not interfere with or duplicate the MoTrPAC objectives or place unreasonable or undue burden on MoTrPAC participants and/or resources. An AS must not interfere with the recruitment or retention of participants or impose substantial burden on participants of the overall MoTrPAC study. Also, an AS must not

impose substantial burden on MoTrPAC study staff. While the primary evaluation of the AS involves the assessment of burden on the MoTrPAC study, the AS must also be of sufficient scientific merit, require the unique characteristics of the MoTrPAC cohort, and contribute to the aim of examining a broad range of research questions.

The AS will also be evaluated for allocation of appropriate resources to any MoTrPAC component that will experience an increase in workload as a result of the AS. This will often include staff at the clinical centers, PAS, the CCC for its role in coordinating the AS, and the BIC for its role in managing, integrating and disseminating data generated by the AS.

The AS will also be expected to deposit data in the MoTrPAC Bioinformatics resource, as is done by all MoTrPAC consortium members, and to meet the resource sharing guidelines set forth in the MoTrPAC RFAs, and included in Appendix B.

An AS is expected to be of high scientific merit and translational relevance and no AS will be allowed that:

- ☐ Causes a deviation from the MoTrPAC protocol that could interfere with accomplishing the main study or affects the main MoTrPAC protocol in a way that may interfere with the planned analyses of the MoTrPAC study results,
- ☐ Adversely affects participant cooperation or participation,
- ☐ Creates a significant diversion of the MoTrPAC resources at the clinical centers, at the coordinating center, at the Bioinformatics Core, or at any other level, or
- ☐ Otherwise compromises the scientific integrity or execution of the MoTrPAC program.

The MoTrPAC strongly encourages AS originating from the broader research community of investigators not currently involved in MoTrPAC. However we note that proposals that involve MoTrPAC components, will also likely have current MoTrPAC investigators involved. In such cases, it would be useful, to facilitate modification and communication during the evaluation process, and ongoing coordination, integration and execution of the AS, that **the AS identifies a MoTrPAC sponsoring co-investigator who is one of the 35 principal investigators of the MoTrPAC program**. All communication with the MoTrPAC ASC, CCC, BIC, participating clinical centers, PAS, CAS, and the MoTrPAC study group will be conducted with the AS PI as well as with a sponsoring MoTrPAC co-investigator if one is identified.

Funding Requirements

It is expected that most AS will require additional funding. MoTrPAC will not provide funds for AS. In particular, no MoTrPAC funds will be provided for additional clinical center activities, Preclinical Animal Sites, the CCC, bioinformatics center, or chemical analysis sites or services in support of an AS. If funds are needed to support the proposed AS, the investigator must explore other avenues, such as submission of a research grant application or use of other sources of funds (i.e., NIH, institutional, foundation, industry, etc.). The anticipated source of funds must always be identified, starting with the initial preliminary concept proposal. AS applications must obtain approval from the ASC and the Steering Committee prior to submission to a funding agency.

In assessing the acceptability of an AS proposal, the ASC and Steering Committee will be concerned with both the explicit and the hidden costs to MoTrPAC incurred by the proposal (e.g., costs to the Consortium Coordinating Center for coordinating the additional data

collection, costs to clinical centers for notification of any alert values/results, as applicable). The PI of the AS should provide evidence that adequate support for carrying out these functions is available at his/her institution; if not, the CCC will conduct the activities required using resources that must be included in the AS budget. (See, "MoTrPAC Reimbursement Costs" for details of the general policy for charges in providing investigators with MoTrPAC data, Attachment A).

Industry-sponsored Ancillary Studies

Proposals for industry-sponsored AS are evaluated in accordance with the MoTrPAC procedures used for all other AS. As in all AS, conduct of industry-sponsored AS must comply with all existing MoTrPAC and NIH practices and guidelines. This includes the stipulation that all data relevant to the AS must be submitted and shared with the Bioinformatics Core. Data from AS must also be submitted to NIH repositories, as applicable (See Appendix B).

In addition, for industry-sponsored AS, it is the responsibility of the AS PI to work with the CCC, other MoTrPAC components, and the NIH sponsors to obtain agreement with the industry sponsor describing how all data, biospecimens, and results will be used and how all publications will be developed. All industry studies will be conducted under auspices of appropriate Data Use Agreements and Materials Transfer Agreements and details about ownership of Intellectual Property as negotiated by study leadership.

Participation by Clinical Centers

For proposals involving participant contact, each clinical center PI will determine whether or not their center will participate in a proposed AS. Depending on the scope of work proposed, all clinical centers may not be required to participate. It is expected that the AS PI(s) and sponsoring MoTrPAC investigators will contact and engage with other MoTrPAC PIs about participating. It is not the responsibility of the ASC to engage MoTrPAC investigators or other entities on behalf of the AS investigators.

Clinical center PIs who wish to participate in the AS should be given the opportunity to review and critique the proposal before it is submitted to the ASC. The ASC will consider AS submissions proposing participation of one or a few centers, if they can have adequate sample sizes (and potentially lower costs) and that exclusion of MoTrPAC sites is adequately justified. In such cases, consultation only with participating center PIs will be required prior to submission. The ASC and Steering Committee may request broader participation. Any funding sought for AS should include a budget appropriate for each of the centers that have agreed to participate in the study, as well as for the CCC/BIC, as applicable.

Application Review Process

The ASC has established a stepwise system of proposal, review, and approval. The system is designed to avoid needless up-front effort by investigators for proposals that are rejected.

It is strongly recommended that the AS PI(s) allow at least two months prior to funding submission deadline for the review of the preliminary proposal by the MoTrPAC.

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The steps for evaluation of an AS are:

1. Investigators submit a preliminary concept proposal (3-5 pages) to the MoTrPAC Ancillary Studies Committee through the MoTrPAC 'sponsoring' investigator of the applicant group, if one is identified, or by emailing the proposal to the Committee coordinator (See Appendix A for detailed instruction). Applications should be uploaded to the MoTrPAC website along with a letter signed by the PI on behalf of all collaborating investigators in which they agree to abide by the policies for AS herein described, including those regarding data sharing and publication or presentation of results.
   The ASC liaison (project manager at the CCC) will review the preliminary concept proposal for appropriate contact information and a description of any anticipated burden to the MoTrPAC study and, if acceptable, notify the ASC chairs that the preliminary concept proposal is ready for distribution through the MoTrPAC website. Submitting investigators will be asked to complete these sections if submissions do not contain this information.
2. The ASC chair, co-chair or an assigned committee member acts as liaison between the submitting PI, the sponsoring MoTrPAC investigator and the ASC.
3. The AS liaison will work with the PI and the MoTrPAC sponsoring investigator to address proposal modifications, if needed.
4. The review process includes evaluation by the ASC, acceptance by the MoTrPAC steering committee and, when appropriate, review by the MoTrPAC Data and Safety Monitoring Board (DSMB). The ASC will provide written reviews of AS proposals.
5. Acceptance of the final revised proposal by MoTrPAC will be made with the understanding that no changes in resource demands or allocation of funding to MoTrPAC components can be made in the final proposal without approval of a revised proposal by MoTrPAC.
6. Final proposals that are approved by the Ancillary Studies and Steering Committees will receive a standard letter of approval signed by the committee chairs that may be submitted to the designated funding agency.

Proposals Not Undergoing Peer Review:

For proposals submitted to the NIH or another funding organization utilizing NIH-like peer review of applications, scientific review will be assessed through the regular NIH/NIH-like peer review system. For applications that will utilize internal funding and/or will not be subjected to peer review, the ASC may recommend a more in-depth review of the application. This in- depth review will be conducted by at least two reviewers with appropriate subject-matter expertise. Reviewers may be selected from within the MoTrPAC consortium or from non-MoTrPAC members with relevant expertise. Reviewer expertise may include, but is not limited to, the scientific area(s) of the proposed AS, analytical/statistical procedures, clinical study design practices, and/or relevant methodological procedures.

Overlapping/Competing Proposals

If an AS proposal meets the test of non-interference with MoTrPAC, it may still overlap and/or compete with other proposed AS for limited additional participant or staff time and/or biological resources (e.g., blood or tissue samples). To maximize efficiency, the Ancillary Studies Committee may recommend that similar and potentially competing proposals be combined and/or revised to avoid duplication. A key objective of the Ancillary Studies and Steering Committees will be to avoid redundancy across AS. The ASC will not divulge any specific information about an AS proposal during the proposal/submission process, but rather will work with AS investigators prior to project

implementation to avoid overlap and redundancy. The ASC reserves the right to mutually inform AS applicants that another independent investigator has submitted a similar proposal and to distribute contact information to relevant AS investigators. The AS proposals itself will be treated as a privileged, confidential communication and its contents will not be shared.

Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC) Approval

All AS must receive all necessary approvals from IRBs or IACUCs at the individual institutions involved, and specific to IRBs and human studies, in conjunction with a central MoTrPAC IRB. Documentation of IRB or IACUC approval is required to be submitted to the MoTrPAC CCC before an AS can be initiated in conjunction with MoTrPAC. Investigators requesting the use of additional measures or protocols should be aware that they will likely be required to work with the MoTrPAC central IRB, and that the central IRB may charge a fee for the review of such materials.

Confidentiality

Confidentiality of individually identifiable data about MoTrPAC participants must be assured. MoTrPAC provides no assurances that AS will be able to identify or contact participants in the future, particularly after MoTrPAC ends.

Timeline for Submitting Ancillary Study Proposals

AS proposals should be submitted to the ASC at least two months before the external funding grant submission deadline to help ensure approval letters can be provided for timely submission of external grant applications.

Monitoring

The MoTrPAC Ancillary Studies Committee will work under the CCC who will track and record the progress of any approved AS. Central monitoring is needed to ensure that the composite impact of the total number of active studies does not have unforeseen consequences. Monitoring will include evaluating the burden on participants and MoTrPAC staff, as well as the use of irreplaceable MoTrPAC resources such as stored biospecimens. Investigators with approved AS must inform the Ancillary Studies Committee Chair and CCC of the outcome of each funding application. Unsuccessful applications may only be re-submitted or submitted to alternate funding agencies after Ancillary Studies Committee review and approval of amended applications. All presentations and publications must follow the MoTrPAC Publications and Presentations Policy.

Provision of Data to Ancillary Study Investigative Teams

The release of any MoTrPAC data from the BIC or CCC to an AS investigator(s) is subject to the rules regarding release of data defined in the MoTrPAC Publications Policy. The BIC and/or CCC will establish a projected cost for data they are asked to provide to the investigator(s) and notify her/him of the charges. Data collected by the AS must be provided electronically to the MoTrPAC BIC for integration into the main database. The BIC will determine reasonable charges for data integration into the main study database to be incurred by the AS investigators. In return, AS investigators receive an analysis file containing their data and approved data from the main study. The AS PI is given the first opportunity to analyze, present, and publish data collected for the specific aims of the AS.

AS data generally need to be released to and integrated into the main study database in a manner and timeline followed by all MoTrPAC consortium centers. Data from AS will be subject to the same NIH public data release guidelines as the parent study. It is the responsibility of the AS PI to state in advance in writing to the Steering Committee any special circumstances that would mitigate against these guidelines for data sharing. Reasonable and justified requests for limiting Steering Committee access to the data will be considered.

Publications and Presentations

Proposals must be submitted for all publications, presentations, and abstracts from an AS for review and approval by the Publications Committee prior to submission or presentation, in accordance with the general rules for publications and presentations.

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Appendix A

MoTrPAC ANCILLARY STUDY Proposal Template

(Date)

The following areas are to be addressed in the proposal. The proposal is limited to 5 pages or less (using 11 point font). Submit your proposal to Michael Stancil, Coordinating Center Liasion to Ancillary Studies Committee Email: mstancil@ufl.edu

NOTE: The submission is to be received at least 2 months in advance of any planned grant submission deadline. Submissions received <2 months in advance are not guaranteed to be reviewed and a decision made prior to the grant submission deadline.

Detailed instructions and outline of AS Proposal:

Page 1 (Face Page):

- Date:
- Title of Ancillary Study:
- Principal Investigator:
  - Institution:
  - Address:
  - E-mail Address:
  - Phone Number:
- MoTrPAC sponsoring PI (if any) who is a Co-Investigator on this Project:
- Additional Co-Investigators and E-mail Addresses:
- Project Title
- Project Duration
- Summary Budget Information (Annual and Total)
- Source(s) of proposed project funding
- Anticipated date of submission for approved projects

Page 2 (Summary and Rationale):

- Abstract (30 lines per NIH format)
- Rationale for Linking to MoTrPAC (20 lines)

Page 3 (Specific Aims/Hypotheses)

Page 4-8 (Research Strategy)

- Significance and Scientific Premise
- Innovation
- Approach and Methods:
  - Existing data that will be requested
  - If requesting biological samples (stored blood, tissue samples), details on the number of samples, time periods requested, amount of sample, and details on how the samples will be used
  - New data generated by the research
  - Sample size and power justification
- State how the project will enhance the MoTrPAC mission

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Page 9 (Study Burden and Plans to Mitigate the Burden through Budget and Other Strategies)
Details of how the proposed study and budget will result in no additional costs to MoTrPAC with specific reference to:

- Participants
- Clinic Staff
- Study Staff
- Bioinformatic Database data processing and/or dissemination
- Clinical coordinating center

Additional Information:

- NIH Biosketch for PI and coinvestigators
- Letter of Agreement from MoTrPAC sponsoring site(s)
- Completed the MoTrPAC Ancillary Study Data & Safety Monitoring Form
- Assurance that project will be submitted by the anticipated date
- Statement of intention to include all data in the MoTrPAC repository
- Statement of intention to cite the MoTrPAC support in all presentations and publications

Bibliography

Revised 7/27/2017

Appendix B

Resource sharing guidelines from MoTrPAC RFAs (e.g. RFA-RM-15-010)

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan. Data from the MoTrPAC are expected to be handled so as to increase the value of the significant public investment in the creation and operation of the Consortium. Consistent with achieving the goals of the program, NIH expects that all project datasets will be widely shared with the scientific community via existing databases such as dbGaP and/or via the Bioinformatics Center for the promotion of additional research, while carefully observing standards of participant privacy, confidentiality, and secure management of health information. Information such as new analytical methods and metabolic, proteomic, and transcriptomic data are expected to be made available through the Bioinformatics Center or via an open access section of a database [such as the Human Metabolome Database (HMDB) or the Scripps Metabolite and Tandem MS Database (METLIN)], other public web sites, and publication in the scientific literature. Cloud-based access to the data and associated informatics elements will be expected to be made widely available, first within the Consortium, and subsequently within the general scientific community. All funded elements are expected to participate in achieving high data quality, making the data available publicly in a timely and accessible manner, and analyzing this rich and valuable dataset. All applicants should name a responsible individual as contact for data sharing both within and outside the Consortium, and clearly identify support requested for data sharing.
- Resources generated by the MoTrPAC are also expected to be widely shared with the Consortium and the broader scientific community for research. The Steering Committee will develop and implement Consortium-wide approaches for resource deposition and use, including submission to national repositories as appropriate. Resources include human and animal biospecimens, instrumentation and assays, special standards, protocols, bioinformatics tools, and animal models.