Adult Changes in Thought (ACT) Research Program Ancillary Study Policy and Procedures[1]

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Definitions of Key Terms

[1] Parts of this policy are adapted with permission from the Women's Health Initiative Ancillary Study Policy

Ancillary Study: encompasses research funded with a grant other than the U19 to analyze existing ACT data (secondary data analysis), curate new data sources not previously used in ACT, or collect new ACT data.

Scholarly work: an abstract submitted to a professional conference/meeting; a manuscript submitted to a scientific journal; or similar (academic thesis, etc.) resulting from an analysis or synthesis of data

ACT Investigator: researcher funded by the ACT U19 grant

Internal ACT investigator: ACT investigator located/employed at KPWHRI (data remain behind the firewall)

External ACT investigator: ACT investigator not located at KPWHRI (data leave the KP firewall)

Ancillary Investigator: researcher using data outside of the ACT U19 (e.g., ACT AIR, ACT EYE)

Internal request: request from an ACT investigator (either internal or external investigator)

External request: request from someone who is not an ACT investigator

ACT Data Repository: broadly defined as all data related to ACT research participants. At a high level, data sources that make up the ACT Data Repository include data collected directly by the ACT study, such as self-reported risk factor data, cognitive testing data, and research diagnoses produced by the ACT study team in the course of work directly with participants. Beyond these, the ACT Data Repository includes:

- Data derived from biospecimens
- Data from ancillary studies and data derived from samples/investigations from ancillary studies
- Data from clinical care at KPWA or other institutions
- Data that can be linked to ACT participants

Feasibility Study: exploratory work that includes examination of available data to gauge whether ACT data are a good fit for a research question

Prep-to-Research Query: exploratory use of ACT Data utilizing the ACT Data Query Tool, and includes connection to an Ancillary Study request

Rapid Review: in exceptional circumstances, a process will be utilized in which the ACT U19 leadership agree to review a proposal on an accelerated timeline

Data Use Agreement: a written contract used to govern the transfer of ACT Program research data between organizations, in this case, between KPWHRI and an external data requestor/recipient

Collaborative Research Agreement: ACT U19-specific form that sets forth terms and conditions under which ACT will disclose the Data Set or Data Tables to the Data Recipient

Abbreviations

ACT Adult Changes in Thought Study

AS Ancillary Study

ASRC ACT Ancillary Study Review Committee

Admin Core Administrative Core

EHR Electronic Health Record

KPWHRI Kaiser Permanente Washington Health Research Institute

LOS Letter of Support

MPI Multiple Principal Investigator

NIA National Institutes of Aging

PHI Protected Health Information

PI Principal Investigator

UW University of Washington

P&P Committee Proposals and Publications Committee

1. Overview

Adult Changes in Thought (ACT) Ancillary Studies (AS) are funded with separate grant(s) or other mechanism(s) outside the ACT U19 grant and thus typically require support from non-ACT U19 funds. All AS proposals that involve collecting new data or reprocessing existing data must include budgeting for funds to cover processing and storing data in ACT Data Repository housed at the Kaiser Permanente Washington Health Research Institute (KPWHRI) and/or the University of Washington (UW).

There are three types of AS: Type 1 (secondary analysis of existing ACT data), Type 2 (new use of biospecimens, raw scan data, or EHR data fields), and Type 3 (collection of new data from ACT participants). Details about each type of AS, the AS application and approval process follow.

For all types of AS described herein, investigators who are unaffiliated with ACT should work with one or more participating ACT investigator(s) on preparing the AS proposal. For Type 2 and Type 3 AS, investigators who are unaffiliated with ACT must include at least one ACT investigator on the grant. In cases where the proposed AS will require any ongoing data needs or collaboration, including but not limited to studies proposing new data collection in the ACT cohort, a subcontract with KPWHRI will also be required, and the lead of the proposed AS must identify a KPWHRI site PI to collaborate and lead KPWHRI-related data activities. If available and appropriate, the ACT investigator and KPWHRI collaborator can be the same individual.

In order to receive a Letter of Support (LOS) from ACT, all applicable approvals described herein must be obtained. Without an approved AS application, no LOS can be endorsed by or explicitly mention ACT or ACT resources.

Data requests stemming from an approved and funded AS must be approved in order to receive ACT data, and are covered by the ACT Proposals and Publications (P&P) Policy and Procedures. The processes involved are not described in detail here. Please refer to the P&P Policy linked above or to the ACT website “Work with Us” page for more information.

2. Types of Ancillary Studies

All types of AS are research funded with a grant(s) other than the ACT U19 to either analyze existing ACT data (secondary data analysis), curate new data sources not previously used in ACT, or collect new ACT data. Each type of AS described here may also include activities for the lower numbered type(s). That is, a Type 2 AS study may include the activities described under Type 1, and Type 3 may include activities described under Type 1 or Type 2.

2.1 Type 1 AS: Secondary data analysis

In a Type 1 AS, an investigator is seeking external funding to analyze existing, previously curated ACT data or records. This type of AS does not involve any new data collection; reprocessing of ACT data, scans, or specimens; or any additional ongoing data processing or analytic needs (e.g., proposals to link ACT data to new external data sources). No biospecimens are requested. Included data may come from biennial or annual visits, standardly derived MRI or autopsy data, summary accelerometer measures, and/or medical record data.

Note that studies proposing to use medical records data that have not previously been extracted for prior ACT investigations would be considered a Type 2 “new derived data” request.

Type 1 AS will generally require only a single data request from standard elements in the ACT Data

Repository and will not have ongoing support needs from ACT (e.g., programming or analytic support, project management, etc.). While no ongoing subcontract with KPWHRI is typically required for this type of AS, processing fees may apply. Review and approval of Type 1 AS typically takes 2-3 months.

2.2 Type 2 AS: New processing of ACT data; or ongoing analytic support

In a Type 2 AS, an investigator is seeking external funding for use of raw, un-curated, or not-previously generated ACT data and/or there will be other ongoing data processing, analytic and/or project management needs requiring a subcontract with KPWHRI.

This type of AS is similar to a secondary data analysis in that it makes use of data that have already been collected from ACT participants. However, it differs from a Type 1 AS because it proposes using existing ACT data in a new way, including extracting new data from the Electronic Health Record (EHR), readings of raw imaging scans, raw accelerometer data, use of stored biospecimens, and/or ongoing analytic support from ACT for any other reason. Note that AS that only intend to analyze existing derived imaging or autopsy data are considered Type 1. Review and approval of Type 2 AS typically takes 3-4 months.

2.2.1 Type 2 AS: Proposals requesting raw imaging scans

Sharing of derived metrics from clinical and research imaging scans follows standard data sharing procedures for Type 1 AS. New readings of imaging scans or derivation of different metrics may be accomplished by transferring raw images to the AS PI or by providing funding through the AS for additional reading/processing to be done by ACT investigators or staff. All AS using raw MRI scans (i.e., for reprocessing) should involve consultation with the lead investigator or member of the ACT Neuroimaging Core.

2.2.2 Type 2 AS: Proposals requesting biospecimens including neuropathology tissue, stored plasma or DNA

Biospecimens obtained from ACT participants are a finite resource. For all types of biospecimen requests, ACT prioritizes original investigations that both leverage the strengths of the ACT cohort and that have potential to enrich ACT repository data resources. ACT typically discourages requests for sharing biospecimens for proposed pilot studies, replication studies, methods development or studies involving a single biomarker.

Parsimonious use of specimens is an important consideration in review of AS proposals. Sample limits exist in order to conserve valuable biospecimens. ACT will consider proposals requesting larger biospecimen quantities. However, to be approved for higher amounts, scientific justification must be included in the proposal, and a copy of the assay procedure(s) provided. Biospecimen quantities approved at the time of application will be reevaluated at the time of funding and may be revised to meet current technology requirements.

Biospecimens must not be used for any purpose other than for what they were approved. If a PI wishes to use residual specimens for additional assays, approval must be sought and granted. ACT does not accept the return of biospecimens.

Samples will be sent to investigators upon securing funding and execution of the subaward.

- **Plasma or DNA**

All AS requesting stored plasma or DNA will be reviewed by ACT including Biorepository leadership. A subaward is required to cover cost of sample processing and shipping. Standard aliquot sizes are 0.25 mL.

- **Neuropathology tissue**

All AS using ACT neuropathology specimens must involve the ACT Neuropathology Core for purposes of data coordination and/or coordination of specimen transfer. The ACT Neuropathology Core has their own procedures to follow, including submitting the UW Neuropathology Core Resource Request Form.

In proposals where neuropathology specimens **are linked** other ACT repository data, investigators should complete and submit an ACT Ancillary Study Application for review by ACT.

In proposals where neuropathology specimens are **not linked** to any other ACT repository data, requesters will work directly with ACT Neuropathology Core. Such proposals are not reviewed by ACT; investigators **do not** need to submit an ACT Ancillary Study Application and **do not** need to follow procedures described in this Policy.

2.3 Type 3 AS: New data collection

In a Type 3 AS, an investigator is seeking external funding to collect new data from ACT participants or to undertake any additional participant-facing research activity. As such, Type 3 AS require additional IRB approval and a separate or additional informed consent from ACT participants. Any AS protocols involving recruitment of ACT participants must clearly state that participation in the AS is a separate activity that will not affect participation in ACT.

All Type 3 AS proposals must include an ACT investigator and a site PI from KPWHRI (can be same individual if appropriate) who will collaborate with AS investigators for the study. A subcontract with KPWHRI to cover needed staff and collaborator effort will be required. It is recommended that the requesting investigator work with the ACT investigator and KPWHRI collaborator to complete the AS application.

Type 3 AS undergo a more extensive review process. ACT participants are older adults and adding to the participant burden through new primary data collection is approved only rarely. Maintaining the integrity of ACT, retaining and protecting study participants, and adhering to ACT protocols are of paramount importance; any proposed AS that would interfere with ACT procedures, involve unreasonable participant burden, or possibly lead to participants withdrawing from the study is unlikely to be approved.

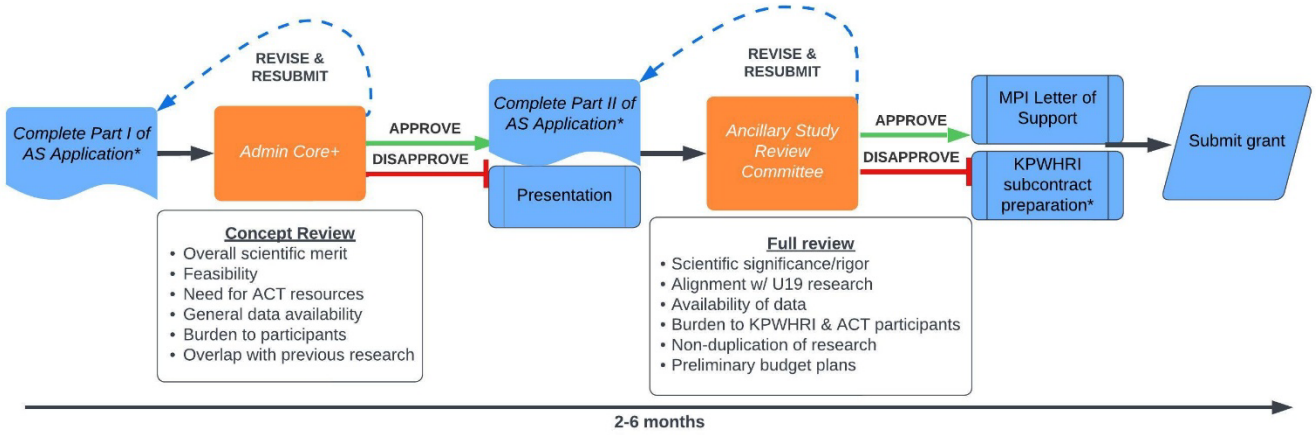
In addition, an informal review by the ACT U19 National Institutes of Aging (NIA) Program Officers may take place for Type 3 AS to ensure that participant burden is reasonable and that there is no conflict with established ACT objectives. As such, review and approval of Type 3 AS typically takes 6 months.

3. Application Procedure

Applications for ACT AS involve a two-stage proposal process. PIs/AS lead researchers first complete Part I of the Ancillary Study Application and submit it for concept review by the ACT Administrative (Admin) Core. Once researchers are notified of proposal concept approval, they then complete Part II of the Ancillary Study Application and submit it for full proposal review by the Ancillary Study Review Committee (ASRC). Researchers will be scheduled to provide a presentation of their proposed study to the ASRC after the proposed AS has been approved by the Admin Core.

4. Review Process

Review of AS proposals follows the process shown in the Figure.



**Collaborating with an KPWHRI ACT investigator is required for a Type 2 or 3 AS and suggested for a Type 1 AS*
+If the AS will involve proposed use of ACT biospecimens, review may involve the leadership of the ACT Biorepository or ACT Neuropathology Core

The first stage of review is for the proposal concept and is conducted by the Admin Core based on Part I of the AS Application. The Admin Core evaluates the proposal for:

- Overall scientific merit
- Feasibility
- Need for ACT resources (programmers, analysts, MRI and Neuropathology staff, etc.)
- General data availability (including scans or biospecimens)
- Burden to participants
- Similarity to previous research

Admin Core review decisions include approve, revise and resubmit, or disapprove. If the Admin Core approves the proposal in concept, the PI/project lead will be informed and prompted to complete Part II of the AS Application Form and scheduled to present at an upcoming ASRC meeting.

The second stage of review is for a full proposal review and is conducted by the ASRC based on Parts I and II of the AS Application. The ASRC evaluates the proposal for:

- Scientific significance/rigor
- Alignment w/ U19 research
- Availability of data
- Burden to KPWHRI & participants
- Non-duplication of research
- Preliminary budget plans

ACT ASRC review decisions include approve, revise and resubmit, or disapprove. If the ASRC approves the full proposal, the PI/project lead can proceed with KPWHRI subcontract preparation (if applicable) and may request a LOS from ACT MPIs.

If either the Admin Core or ASRC do not approve a proposal at their respective stages, the PI will receive detailed feedback and may be invited to revise and resubmit the proposal demonstrating that

the revised proposal has addressed concerns identified in the review.

Both the Admin Core and ASRC approvals must be received prior to grant submission. Review of AS proposals are expected to take 2-6 months, with the time correlating with the complexity of the AS proposal (Type 1 requiring less time and Type 3 involving more). As such, AS proposals should be initiated well in advance of any applicable funding deadlines.

ACT AS requesting biospecimens include the additional steps described below.

- **Review of AS requesting plasma or DNA**

Review of AS proposing the use of biospecimens involves assessing feasibility (i.e., availability of requested specimen by outcome category), efficient use of specimen, burden on the biorepository, and compatibility with current portfolio of ACT biospecimen studies and approved AS.

As part of the Admin Core review, Biorepository leadership will confirm specimen availability. ASRC review takes into consideration adequacy/relevance of the assay procedures and parsimonious use of biospecimen. ACT seeks a balance between providing sufficient sample to AS investigators to test stated hypotheses and the important goal of conserving sample for future studies. AS investigators are asked to be explicit regarding their intended assay procedures and willingness to consider analytic approaches having comparable results that require smaller volumes of specimen.

The amount of biospecimen approved for an AS should be considered the maximum amount approved, subject to reduction at the time specimens are pulled should ACT determine that assays require less specimen or less specimen becomes available.

- **Review of AS requesting neuropathology tissue**

For AS proposals involving ACT repository data **linked** with neuropathology tissue, in addition to AS approval by the ACT Admin Core and the ASRC, the project lead must also complete a separate Tissue Request Form to be submitted directly to UW Neuropathology/the ACT Neuropathology Core, which stewards all ACT Neuropathology specimens. The ACT Neuropathology Core assesses the availability of requested specimen by outcome category and efficient use of specimen.

5. Modification of Approved Ancillary Studies

Proposed changes to the design of an approved AS, including changes in sample size, biomarkers, or a change in use of specimens (including use of residual specimen) must be approved by the Admin Core and ASRC. Modifications involving an increase in sample size greater than 10%, a change in specific aims, or that will significantly add to participant and/or ACT staff burden or raise new human subjects issues may be required to go through the entire review process again. To be considered in the study's funding submission, AS PIs need to allow sufficient time (i.e., a minimum of 3 months) for review of the requested modifications before funding submission deadlines.

6. Once an Ancillary Study Has Been Approved: Key points

- **Data Access and Ownership**

Upon receiving AS funding, AS requiring ACT data must request these data from the ACT P&P Committee following ACT P&P Policy and Procedures and using a Data Request and Manuscript Proposal Form. Additionally, the AS PI will sign a Data Use Agreement/Collaborative Research Agreement, Data and Materials Transfer and Use Agreement (or other agreement as deemed appropriate by KPWHRI contract officials) outlining the data and/or biological specimens to be

released to the PI and the relevant ACT policies with which the PI agrees to comply.

Note that except in rare circumstances, data linkages requiring access to Protected Health Information (PHI) beyond a limited dataset must be done by a KPWHRI employee with PHI data remaining behind the KPWHRI firewall.

- **AS-generated data**

Data of any kind generated by an AS (e.g., biospecimen assay results, new computed variables) are required to be submitted to the ACT Data & Analysis Core and will be incorporated into the ACT Data Repository. In addition to a final analytical dataset that includes data generated from the AS, investigators will be asked to provide their programming code and updated PI contact information.

- **Publications and Presentations**

Proposals for scholarly works (abstracts, manuscripts, etc.) and the scholarly works themselves that result from or report findings from an AS must be reviewed and approved by ACT P&P. Investigators must follow the policies described in the ACT P&P Policy and Procedures. All publications and presentations involving ACT study data must have ACT P&P Committee approval prior to submission to the target journal or conference.

- **Annual Progress Report**

PIs of AS are expected to provide a progress report to ACT annually until the project is considered closed. ACT will send team leads a survey querying project activities in the preceding 12 months - including:

- Status of grant (submitted, reviewed, revise & resubmit, funded, with dates etc.)
- Scientific progress toward study aims
- Related data request or manuscript proposals to the P&P Committee
- Status of any manuscripts that are in process or have been published
- Any changes to study timeline
- Any other significant events or activities that have impacted the study