ACT Ancillary Study Policy

Definition & Overview[1]

In ACT, an Ancillary Study (AS) is defined as any work that uses or collects data from ACT participants and has funding separate from the ACT U-19.

For all types of AS described below, investigators who are unaffiliated with ACT must work with one or more participating ACT investigator(s) on preparing the grant proposal and 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 Kaiser Permanente Washington Health Research Institute (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 and KPWHRI collaborator can be the same individual.

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

Any manuscripts for publication that are produced from an approved and funded AS must be reviewed and approved by the ACT P&P Committee prior to submitting for publication. (See instructions at https://actagingresearch.org/collaboration/p-p_committee)

There are three primary types of AS:

Type 1: Investigator is seeking external funding to analyze existing, previously curated ACT data. This type of AS includes a single data request and 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 subcontract with KPWHRI is required for this type of AS, though a one-time data processing fee may apply. Review and approval typically takes 2-3 months.

Type 2: Investigator is seeking external funding for use of raw, un-curated ACT data such as imaging scans, biospecimens, accelerometer data, or creation of new variables from the Electronic Health Record (EHR) and/or there will be other ongoing data processing, analytic and/or project management needs requiring a subcontract with KPWHRI. Approval typically takes 3-4 months.

Type 3: Investigator is seeking external funding to collect new data from the ACT cohort or undertake any participant-facing research activity. Approval typically takes 6 months.

Each type of AS may also include activities for the lower numbered type(s). That is, a Type 2 study may include the activities described under Type 1, and Type 3 may include activities described under Type 1 or Type 2.

Additional details about each type of AS, how to apply, and the approval process are provided below.

Type 1: Secondary data analysis

This type of AS obtains funding to do a secondary analysis of existing, previously curated ACT data or records. Included data may come from biennial or annual visits, standardly derived MRI or autopsy data, summary accelerometer measures, and/or medical record data. No new data can be collected in this type of

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

AS, and no biospecimens can be requested. Studies proposing to use medical records data that have not previously been extracted for prior ACT investigations may NOT be included here and 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, a one-time data processing fee may apply.

Application and Approval Process for Type 1 AS

Investigators wishing to write a grant for funding to analyze ACT data must submit a *ACT Ancillary Study Application Form* to the kpwa.actproposals@kp.org. Type 1 AS proposals will first undergo a brief review by the ACT Administrative Core to assess whether requested resources align with a Type 1 request. If Administrative Core approves the proposal to proceed as a Type 1 AS, the AS application form will be forwarded to the ACT Proposals and Publications (P&P) Committee for review and approval prior to submitting the grant to funding agencies. These studies are generally treated like other data requests or manuscript proposals; details may be found in the ACT P&P Policy, here: https://actagingresearch.org/collaboration/p-p_committee. If the Admin Core determines that the described study is not consistent with a Type 1 request, feedback and specific instructions will be provided to the project lead and the application will follow either a Type 2 or 3 review process, as applicable.

Once a Type 1 AS has been approved by both the Admin Core and P&P Committee, any required Letters of Support for the grant submission may be requested from ACT.

If funded, all analyses/manuscripts resulting from the grant will require individual Data Request Forms (https://actagingresearch.org/collaboration/work-with-us-1)to be completed and reviewed by the P&P Committee.

Type 2: New processing of scans, biospecimens, or other raw data sources; creation of new derived data; or ongoing analytic support

This type of study is similar to a secondary data analysis, except that it also includes using existing ACT data in a new way, including extracting new data from the EHR, raw accelerometer data, new readings of raw imaging scans, use of stored biospecimens, and/or ongoing analytic support from ACT for any other reason. The new readings of imaging scans may be accomplished by transferring raw images to the AS PI or through the AS providing funding for additional reading/processing to be done by ACT investigators or staff. Studies that only intend to analyze existing derived scan or autopsy data are included in the first category of AS described above. Type 2 AS require completion of an *ACT Ancillary Study Application Form* and are subject to additional levels of review as outlined below.

Access to raw imaging scans

This type of AS only applies to investigators who want to reprocess raw MRI scans. All AS using raw MRI scans must involve the lead of the ACT Neuroimaging Core. Information about contacting this investigator can be found on the ACT website. In proposals where the MRI data are not linked to any other ACT data, requesters will work directly with the lead investigator of the ACT Neuroimaging Core and will follow their procedures. Such proposals are not reviewed by the ACT P&P Committee and do not need to follow the procedures outlined below. Proposals where MRI scan data are linked to other ACT data must follow the procedures in this section.

AS that involve use of raw MRI scans typically require a subcontract with KPWHRI due to work required to prepare scans for sharing.

Access to Neuropathology Specimens or Stored Blood

In proposals where neuropathology specimens are not linked to any other ACT data, requesters will work directly with the lead investigator of the ACT Neuropathology Core and will follow their procedures. Such proposals are not reviewed by the ACT P&P Committee and do not need to follow the procedures outlined below.

Proposals where neuropathology specimens are linked to other ACT data must follow the procedures in this section.

All AS using ACT stored blood or pathology specimens ("biospecimen") must also involve the director of the blood repository or lead investigator of the ACT Neuropathology Core for purposes of data coordination and/or coordination of specimen transfer.

Access to biospecimens for AS is managed by the P&P Committee through the application process described below. Guidelines pertaining to sample volume limits have been put in place in order to conserve valuable biospecimens and are listed on our website (*to be added soon*). Parsimonious use of specimen is an important consideration in review of AS proposals.

The P&P Committee & Neuropathology Core will consider proposals requesting sample volumes larger than the posted guidelines. To be approved for higher amounts, scientific justification must be included in the proposal, and a copy of the assay procedure(s) provided. Biospecimen volumes approved by the P&P Committee at the time of application will be reevaluated at the time of funding and may be revised to meet current technology.

Please note that sample volume requests must include any necessary 'dead volume' padding.
To ensure that ACT biospecimens are being used for investigation of the most current and relevant hypotheses, approval for each AS involving biospecimens will be in effect for 30 months from the date of the approval letter from the P&P committee. ACT will not support funding submissions past 21 months as they are unlikely to result in funding by the 30th month expiration date. If a PI does not secure funding but would still like to pursue the study, they are welcome to re-apply to the P&P Committee for approval.

Biospecimens must not be used for any purpose other than what they were approved for. If a PI wishes to use residual specimens for additional assays, approval must be granted by the P&P Committee. ACT does not accept unused portions of biospecimens back into the biorepository.

Application and Approval Process for Type 2 AS

To initiate the review process, investigators must complete the *ACT Ancillary Studies Application Form,* in consultation with the ACT collaborating investigator or KPWHRI site PI. Once submitted, AS proposals will be forwarded to the appropriate review committees, described below. Review and approval will generally follow the order listed below, but may occasionally vary given scheduling and project-specific needs.

All of the approvals listed here must be received prior to grant submission.

1. Administrative Core Review: The Administrative Core reviews the proposal for feasibility and potential burden on ACT resources (programmers, analysts, MRI and Neuropathology staff, etc.), as well as availability of ACT data (beyond the scans or biospecimen) to meet the proposal objectives.

2. ACT Ancillary Study Review Committee (ASRC) Review. The ASRC reviews Type 2 AS proposals for:

   - Scientific rigor
   - Alignment with ACT U19 research objectives
   - Non-duplication with existing ACT research
   - Feasibility, specimen availability, and importance of the proposed research

When an AS proposal requesting linked ACT and neuropathology specimen data is approved by the ACT Administrative Core and EC, the project lead must then complete a separate Tissue Request Form to be submitted directly to UW Neuropathology/the ACT Neuropathology Core, which stewards all ACT Neuropathology specimens. Review of biospecimen studies involves assessing feasibility (i.e., availability of requested specimen by outcome category), efficient use of specimen, impact on the biorepository, quality control matters, and compatibility with the current portfolio of ACT core biospecimen studies and approved AS.

Once all reviews are completed, Administrative Core will contact the PI and either give them the go-ahead to submit their grant application, ask for revisions, or decline the proposal. Once a Type 2 AS has been approved by both the Admin Core and ACT ASRC, any required Letters of Support for the grant submission may be requested from ACT.

If funded, all analyses/manuscripts resulting from the grant will require individual Data Request Forms to be completed and reviewed by the P&P Committee.

Modification of Approved Type 2 Ancillary Studies

Any proposed changes to the design of an approved AS, including changes in sample size, biomarkers, or use of specimens (including use of residual specimen), must be approved by the Executive Committee. Modifications involving an increase in sample size greater than 10% and/or a change in specific aims are required to go through the full review process again. To be considered in the study's funding submission, AS PIs need to allow sufficient time for review of the requested modifications before funding submission deadlines.

Type 3: New data collection or curation

The third type of AS is studies that involve collecting new data from ACT participants and/or any other activity requiring revised or additional consent from ACT participants. This type of AS undergoes a deeper review process; ACT participants are elderly, and adding to participant burden through new primary data collection is approved only rarely. Investigators wishing to submit a grant proposal that involves collecting new data from ACT participants must first complete the *ACT Ancillary Studies Application Form*. All such proposals must include an ACT investigator and a site PI from KPWHRI (can be same individual if appropriate) who will participate in 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 ACT AS Application form. This form must be approved by the ACT U19 Administrative Core and the ACT Steering Committee prior to being submitted for funding. **This multi-layered review process will take approximately 6 months. As such, proposals for this type of AS should be initiated well in advance of any applicable funding deadlines.**

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 leaving the study early is unlikely to be approved.

Review criteria:

- Scientific merit
- Burden on ACT participants
- Requires the unique characteristics of ACT participants
- Does not negatively impact ACT main objectives
- Adequate staff and funding resources available to complete proposed work

In addition, an informal review by the *ACT U19 National Institutes of Aging (NIA) Program Officers* will take place for all Type 3 AS to ensure that participant burden is reasonable and that there is no conflict with established ACT objectives.

Recruiting and Consenting ACT Participants to Ancillary Studies

Generally speaking, any ACT participant may be recruited for an approved AS. Type 3 AS require a separate Informed Consent document and IRB approval. Any AS involving recruitment of ACT participants must clearly state that participation in the AS is a separate activity that will not affect a person's participation in ACT.

Application and Approval Process for Type 3 AS

To initiate the review process, investigators must complete the *ACT Ancillary Studies Application Form.* Once submitted, AS proposals will be forwarded to the appropriate review committees, described below. Review and approval will generally follow the order listed below but may occasionally vary given scheduling and project-specific needs.

All of the approvals listed here must be received prior to grant submission.

1. ACT Administrative Core. The Admin Core reviews each Type 3 AS proposal to assess for adequacy of budgetary and staffing resources among the ACT team and at KPWHRI. The Admin Core will provide guidance on feasibility and needed adjustments to the budget, staffing, or scope of the proposed work.

2. ACT Steering Committee. The Steering Committee reviews each Type 3 AS proposal, assessing participant burden against ACT priorities and policy and operational criteria. While in-depth, NIH-style review is not the primary purpose of this review process, the Steering Committee provides a general scientific appraisal of all Type 3 AS.

If the Steering Committee and/or Admin Core do not approve a proposal, the PI will receive detailed feedback and may be invited to resubmit the proposal with a response addressing the reviewers' concerns.

3. External Review. Studies involving separate informed consent and/or additional participant burden must also be discussed and informally reviewed by the ACT U19 NIA Program Officers. If an *NIA Program Officer* review is needed, it is facilitated by the ACT Multiple Principal Investigators (MPIs). The *NIA Program Officer* review is less formal than the Steering Committee review but serves as a second, independent review of the proposal for the criteria outlined above.

When a Type 3 AS is approved by the Steering Committee and Admin Core, an Admin Core representative will inform the P&P Committee of the approval for tracking purposes. Once a Type 3 AS has been approved by the Admin Core, ACT Steering Committee, and appropriate external reviewers, any required Letters of Support for the grant submission may be requested from ACT. If funded, all analyses/manuscripts resulting from said grant will require individual Data Request Forms to be completed and reviewed by the P&P Committee.

Modification of Approved Ancillary Studies

Any proposed changes to the design of an approved AS, including changes in sample size, must be approved by the Steering Committee and Admin Core. 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 are 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.

POLICIES THAT APPLY TO ALL ANCILLARY STUDY TYPES

Funding for Ancillary Studies

All AS require funding from non-ACT contract funds (i.e., funded via a separate grant or other mechanism outside the current ACT U-19 mechanism). All AS proposals that involve collecting new data or reprocessing existing data must include funds for processing and storing the data in ACT Data Repository housed at the Kaiser Permanente Washington Health Research Institute (KPWHRI) and/or the University of Washington, as well as site PI leadership at applicable locations.

Analysis and Data Ownership

Upon study funding, the AS PI will sign a Data and Materials Transfer and Use Agreement (DMTUA; 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.

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 for review and will be incorporated into the ACT Data Repository. For studies testing ACT biospecimen, the test results must be submitted to the lead investigator of the relevant ACT Core (e.g., MRI, Neuropathology) before the AS PI is granted access to the ACT dataset.

Publications from AS

Manuscript proposals arising from any of the three types of AS must be approved by the P&P Committee. Such proposals will follow the Data Request procedures outlined on the P&P Committee page of the ACT website.

For all studies, ACT requires that the following be submitted to the ACT Data & Analysis Core at the time of the primary publication from the study: a final analytical dataset that includes data generated from the AS, a data dictionary, a one-page summary of the results, and updated PI contact information.

One year after the study's funding end date and after notifying the study's PI, ACT may release data generated by the AS to qualified scientific investigators requesting access through established ACT procedures. ACT will encourage the scientific investigators requesting access to collaborate in analyses and publications with the PI who generated the data.

Studies with Industry Involvement

ACT data are not available for any for-profit purposes. However, it is potentially possible that an individual working for a for-profit entity might want to use ACT data for a research, non-profit-related reason. If so, that person can contact ACT to inquire whether the proposed use fits within ACT approved uses.

Annual Progress Report – Type 2 and Type 3 AS Only

The PI of each Type 2 or Type 3 AS is expected to submit a written progress report to the ACT Steering Committee and P&P Committee annually. This report should include the following information for activity in the preceding 12 months:

- Scientific progress toward study aims
- 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

Publications and Presentations

Publications resulting from an AS must follow the policies described in the ACT Publications and Presentations (P&P) Policy, which is available on our website: https://actagingresearch.org/collaboration/p-p_committee. All publications and presentations involving ACT study data are to be submitted to the ACT P&P Committee for approval prior to submission to the target journal. Proposals and analysis plans for manuscripts and abstracts that will report findings from AS must be reviewed by ACT P&P.