Military Aviator Cancer Study (MACS)
Polices & Procedures
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TABLE OF CONTENTS

1. Background 2
1.1. The Military Aviator Cancer Study (MACS) 2
1.2. Phase 2 2
2. MACS Serum Resource Descriptions 3
2.1. Serum Specimens 3
3. Policies for Access to MACS Biospecimens and Data 3
4. MACS Application and Review Procedures 4
5. MACS Proposal Evaluation Criteria and Considerations 5
5.1. Scientific and Technical Merit 5
5.1.1. Overall Study Design 5
5.1.2. Statistical Methods 5
5.2. MACS Programmatic Considerations 6
5.2.1. Collaboration & Coordination 6
5.2.2. Balancing Current & Future Needs 6
5.2.3. Longitudinal Samples 6
6. MACS Management Infrastructure 6
6.1. MACS Steering Committee 6
6.2. MACS Phase 2 Data Access Committee 7
6.3. Study Management and Tracking 7
7. MACS Appeal Process 7
8. MACS Policy on Addenda 7
9. MACS Data Return and Data Sharing Policy 8

1. Background

1.1. The Military Aviator Cancer Study (MACS)

The Military Aviator Cancer Study (MACS) aims to evaluate cancer incidence and mortality rates among military fixed-wing aviators (aircrew) and aviation support personnel (ground crew). The Defense Health Agency's Armed Forces Health Surveillance Division carried out this study in two parts between July 2021 and March 2024.

Phase 1 of the "Study of Incidence of Cancer Diagnosis and Mortality Among Military Aviator and Aviation Support Personnel" was a retrospective cohort study performed to determine whether there was a higher incidence of cancer among Military Aviator and aviation support personnel than in the general U.S. population. Military health records and cancer data were examined for 156,050 aircrew and 737,891 groundcrew; the records were compared to the U.S. population using the Surveillance, Epidemiology, and End Results Program (SEER) as a reference population. Phase 1 of the study was conducted in two parts. Part 1A included only DoD cancer data and evaluated all aircrew and groundcrew. Part 1B included VA and state registry cancer data in addition to DoD data. However, Part 1B was restricted to 138,505 aircrew and 659,825 groundcrew because individuals with a home of record for a state that did not have cancer registry data included in the study were excluded.

1.2. Phase 2

The Phase 2 study is required to investigate and identify the occupational and environmental risk factors contributing to elevated cancer rates in military aviator and aviation support personnel. Phase 2 uses data from various sources and includes the availability of serum specimens.

The goal of this study is to investigate military exposures and risk factors related to cancer incidence, including:

1. **Toxic and hazardous exposures** —carcinogenic toxins and hazardous materials associated with military flight operations from shipboard or land-based facilities, such as fuels, fumes, and other liquids.
2. **Operating environments** —environments where covered individuals may have been exposed to ionizing radiation (from high-altitude flight) or nonionizing radiation (from airborne, ground, or shipboard radars, and electromagnetic fields).
3. **Service-related factors** —individual duty stations, dates of service, aircraft flown, and additional duties (e.g., Landing Safety Officer, Catapult and Arresting Gear Officer, Air Liaison Officer, Tactical Air Control Party, or roles in aircraft maintenance, supply, logistics, fuels, or transportation) that could have elevated cancer risk.
4. **High-risk duty locations or roles** —service locations or specific duties correlated with higher incidences of cancer.
5. **Non-aviation exposures** — Evaluate additional military-related exposures, including burn pits or toxins found in water, soil, bases, or housing.

Application materials and all other relevant MACS documents are posted on the Cancer Data Access System (CDAS) website (https://cdas.cancer.gov/). Information on the specimens is also available on that website.

2. MACS Serum Resource Descriptions

2.1. Serum Specimens

The Department of Defense Serum Repository (DoDSR) was established in 1989 to house serum remaining after the mandatory Human Immunodeficiency Virus (HIV) screening which began in 1985. To date, over 74 million serum specimens have been collected on 12 million service members. The DoDSR is considered as the largest of its kind in the world. At present, over 6 million serum specimens across the 893,941 service members have been collected for individuals in the MACS. The DoD's policies regarding HIV screening and rescreening have changed over time, with varying guidelines across the military services. A major milestone occurred in 2004, when a uniform HIV testing policy was established, mandating testing every two years for service members.

Once specimens are collected, they are transported to the nearest medical facility laboratory for processing. They are then refrigerated and shipped to the designated HIV testing center. After testing, the residual amount of serum is placed in a tube, frozen, and transferred to AFHSD for storage at -30° C. If a vial is selected for a subsequent study, it is thawed and allocated into 0.5mL aliquot vials. The vial is then labeled and refrozen.

3. Policies for Access to MACS Biospecimens and Data

The MACS serum specimen resources are available to the scientific community. Access to serum samples and data is based on a peer review process. Details of the application and review process are described in the next section (The MACS Application and Review Procedures). Adherence to the following policies are required to obtain access.

- Once a study is approved, a project summary will be displayed on the web site.
- Data are non-transferable unless prior authorization has been granted.
- No attempt will be made to identify or contact patients or physicians.
- No claims of ownership of the data and/or serum samples will be made. Approved access is not considered an endorsement of the research activities.
- You must provide your institution and its location.
- Investigators are required to submit an annual progress report
- All publications must include the following acknowledgement:

  "The authors thank the Armed Forces Health Surveillance Division (AFHSD) and the National Cancer Institute (NCI) for access to the Military Aviator Cancer Study Phase 2 data set and

specimens in the DoD serum repository. The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by AFHSD or NCI." Additional acknowledgements of the specific state cancer registries will be required and will be communicated upon delivery of the data if it contains state cancer information.

If your project does not use serum specimens you may omit “and specimens in the DoD serum repository”,

- Data Only projects must renew their access to the data yearly, when the project is closed all copies and versions of data must be destroyed.

- NCI may terminate this project or suspend access to the data at any time if the institution or approved users are not compliant with the data use policies.

- Only data and specimens for Phase 2 of the MACS are available to be requested.

- Recipients of MACS serum samples and data are required to sign and abide by an NCI Data Transfer Agreement (DTA). To execute the DTA you must identify a Signing Official at your institution.

- .5mL is the maximum amount of specimen that may be requested for any given time point.

- A maximum amount of 4 specimens from an individual service member may be requested, with no more than one .5mL specimen from any given time point.

- Serum samples may not be shipped internationally; they must remain in the United States.

- Sample processing and shipping will be done at the AFHSD.

- The standard AFHSD serum specimen processing fees are waived for all approved studies. This is because studies will be required to contribute their findings to Phase 2 of the MACS.

- Laboratory analyses shall be conducted in a blinded fashion. The linking of laboratory data with the corresponding individual data shall only be performed by the NCI MACS team, and only after generation of the biospecimen assay data. Analytic datasets will then be sent to the investigator who generated the data.

- In accordance with NIH policies on data sharing, upon completion and publication of the study, laboratory data and final study results, with an accompanying data dictionary, shall be made available to the broader scientific community.

4. MACS Application and Review Procedures

The goal of the MACS application and review process is to ensure fair, equitable access to MACS resources based on scientific merit and alignment with phase 2 priorities. Preliminary applications for access to the MACS data and serum specimens are accepted on a rolling basis. Upon receipt, proposals are reviewed for feasibility by MACS Staff. The purpose of this initial

review is to ensure sample availability and concordance with MACS scientific objectives and priorities. Please note, if you would like a letter confirming availability of specimens for a grant application, you must submit your request at least a month in advance.

Upon approval of the preliminary application, the IRB application you plan to submit must be reviewed and approved by the MACS review panel. IRB proposals must be submitted to the MACS review panel through CDAS prior to the deadline to be reviewed in the current cycle. They are reviewed by the MACS Review Panel for scientific merit and alignment with phase 2 priorities. The MACS Review Panel makes the final decisions. Final decisions are communicated in writing to the applicants along with reviewers' written critiques. The current turnaround time for panel reviews will be quarterly.

If after the panel review the MACS review panel requires clarifications to the IRB proposal the applicant has one year to respond to these clarifications. Failure to respond will result in the application being withdrawn. The applicant may apply again in a later round but will be expected to respond to the clarifications at that time.

Upon approval of the IRB application by the MACS Panel Review Board, it may be submitted to your institution's IRB board or Human Subjects Research Determination. The outcome of that review must be uploaded on CDAS to be fully approved.

5. MACS Proposal Evaluation Criteria and Considerations

Due to the exhaustible nature of the serum specimens, stringent evaluation criteria apply to the selection of proposal applications. In addition to the overall scientific and technical merits, a research proposal must demonstrate the need and suitability to use MACS specimens and be in alignment with the research goals of Phase 2. A strong justification must be provided for each type of data being requested to access the data.

The sections below describe in more detail some of the specific requirements that are of particular importance.

5.1. Scientific and Technical Merit

5.1.1. Overall Study Design

Study design must be consistent with Phase 2 aims, including appropriate choice of study subjects, data requests, assays, statistical methods, study power, and must address potential confounders and biases.

5.1.2. Statistical Methods

Applications should include an analytic plan and a statistical methods section. It is also recommended that a biostatistician be included as a co-investigator. They should also include a proposed sample size and provide the estimated statistical power for the analysis. For studies with a large number of analytes, statistical adjustment for multiple comparisons must be used.

5.2. MACS Programmatic Considerations

5.2.1. Collaboration & Coordination

Investigators not familiar with MACS data or the DoDSR are particularly encouraged to seek collaborations or feedback. Duplicate or highly similar efforts are not supported in general. Investigators with similar ideas and approaches are usually asked to develop a collaborative project.

Programmatic and logistic coordination may be beneficial when multiple studies are ongoing and addressing related scientific questions. An example is studies that focus on the same cancer, and can use the same sampling plan and a core dataset. Use of a common sample and data set facilitates direct comparison or integration of data across studies. In addition, it is often necessary to coordinate among multiple studies so that the samples can be selected at once, saving labor cost.

5.2.2. Balancing Current & Future Needs

Management of the DoDSR serum sample resource requires judicious balancing of the need to further the phase 2 goals in the short-term *versus* preserving samples for unforeseen future uses. The MACS leadership takes stewardship of the resource seriously, and decision rules have been established to assure maintenance of critical levels of the samples for future studies for all study subjects. To ensure that serum specimens will not be wasted, investigators must provide detailed justifications for the amount of samples requested. Investigators should provide the estimated number of samples needed for each assay or laboratory method.

5.2.3. Longitudinal Samples

Longitudinal serum samples are available from the DoDSR. investigators who propose to use longitudinal samples must provide justification as to why longitudinal samples are required in order to address the research questions. Additionally, no more than four samples per service member may be requested in any given application and only one from each time point.

6. MACS Management Infrastructure

The Murtha Cancer Center, Armed Forces Health Services Division (AFHSD), National Institute for Occupational Safety and Health (NIOSH), and the NCI Division of Cancer Prevention (DCP) collaborate in the joint management of the MACS Phase 2 program. All divisions are committed to supporting the MACS infrastructure, providing extensive capabilities in serum specimens management and tracking, as well as scientific coordination, administration and strategic planning.

6.1. MACS Steering Committee

Guidance and oversight of the management of the MACS is carried out by the MACS Steering Committee (SC), comprised of AFHSD/DOD, NIOSH, and the DCP. The SC develops management policies and procedures, provides oversight and direction to the day-to-day management of the studies, and resolves conflicts over management and policy issues.

6.2. MACS Phase 2 Data Access Committee

The MACS Phase 2 Data Access Committee is responsible for the review of proposals submitted to the MACS program. The panel is comprised of members from the Murtha Cancer Center, AFHSD, NIOSH, and NCI who have expertise in biologically based epidemiologic cohort studies. If needed, *ad hoc* reviewers may also be chosen for specialized areas of expertise. The Panel makes recommendations based on scientific and technical merits of each proposal.

Although panel members are allowed to submit a MACS application, or to be a co-investigator on a MACS application during their term, they must recuse themselves from evaluating or discussing these applications. They are required to acknowledge any potential conflict of interest as soon as they are aware of such.

6.3. Study Management and Tracking

Contract support coordinates the MACS application and review processes including the MACS panel review meeting, and monitors progress and tracks status of all approved studies. Contractor also provides support for day-to-day data and serum specimens management actives, and the post-approval sample requisition process.

The Cancer Data Access System (CDAS) is developed and maintained by a contractor. All completed and on-going studies are stored in CDAS, including proposal abstracts and annual progress status. Prospective investigators can search for past and current research activities that may be related to proposed studies, thereby avoiding duplicate effort. The MACS proposal review process is also managed and tracked by this database system.

7. MACS Appeal Process

If an applicant has concerns about an MACS Panel review and wishes to appeal the review outcome, he/she must submit a formal appeal letter within 30 days of the date on the final decision letter. An appeal letter must describe specific issues with the review. Appeals based solely on differences of scientific opinion will not be accepted. The MACS Steering Committee will conduct the initial review and will make the final decision. There are three possible outcomes: 1) the appeal has merit and the application is approved, with or without certain conditions; 2) the appeal has merit and the application will be re-reviewed in the next round; and 3) the appeal has no merit and is rejected. The outcome of an appeal is final and cannot be appealed again.

8. MACS Policy on Addenda

Certain circumstances may merit an addendum request to an approved on-going MACS study. The addendum process is intended, in general, for small scale extension of an existing MACS project. These can include requesting a larger subset of subjects, a different marker, or additional variables. Requests of no more than 10% of the original request, either sample size or amount of the materials, are considered suitable for an addendum. Requests larger than 10% of the original approved requests, or limited expansion of scientific scope or aims, may be considered on a case-by-case basis by the MACS Steering Committee.

Addenda that substantially expand the scope of the project—for example, examining a different class of markers, a different technology of assessment, or a different endpoint, will not be approved. These require a new application. The steering committee will make final decisions to accept or deny addendum requests.

9. MACS Data Return and Data Sharing Policy

When investigators generate new biomarker data using MACS serum specimens, these data must be shared with MACS and, ultimately, with the broader research community. To help ensure this occurs, MACS ships only blinded specimens for biomarker analyses. To unblind specimens (and receive other participant data), investigators must submit their biomarker data (and relevant data dictionaries) to MACS. These data are kept confidential by MACS until the investigators publish their results or 18 months have passed since unblinding—whichever occurs first. After this period, other qualified researchers may request access by submitting a proposal to MACS and receiving approval. If investigators wish to extend the 18-month confidentiality period, they must submit a strong written justification and obtain approval from MACS.

In publications, there must be a statement informing the community of the name(s) of the data repository where the data has been deposited into (e.g MACS CDAS or CDRC) and the associated accession number for data retrieval (e.g. MACS ID).

Below is the list of data elements and other information that must be submitted to MACS.

Assay Data: for each sample provide the following:

1. Sample ID (provided by MACS)
2. Marker name(s) (include full protein name, gene symbol and aliases so that there is no ambiguity in the marker identity)
3. Marker measurement(s) (specify unit of measurement, assay batch number)
4. Name of the assay platform
5. Date and time assay performed
6. Reagent lot/batch number
7. Instrument(s) and calibration
8. Any QC data on the MACS samples (as an example, PH level)
9. All other QC data
10. Missing value indicator and reason(s) for the missing value
11. If applicable, case/control predictions

Descriptive information

1. Name of the laboratory that performed the assay measurements
2. Name of the Principal Investigator responsible for the data submitted/Owner of the data
3. Study ID (MACS XXXX-XXXXX) and title
4. Technical description of the assay platform(s)
5. Detailed assay protocol, including specimen preparation method
6. Description of method for normalization of marker measurements if applicable