*LSU Health Research Café Seminar Series*

# Crafting the Research Strategy

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09 December 2025

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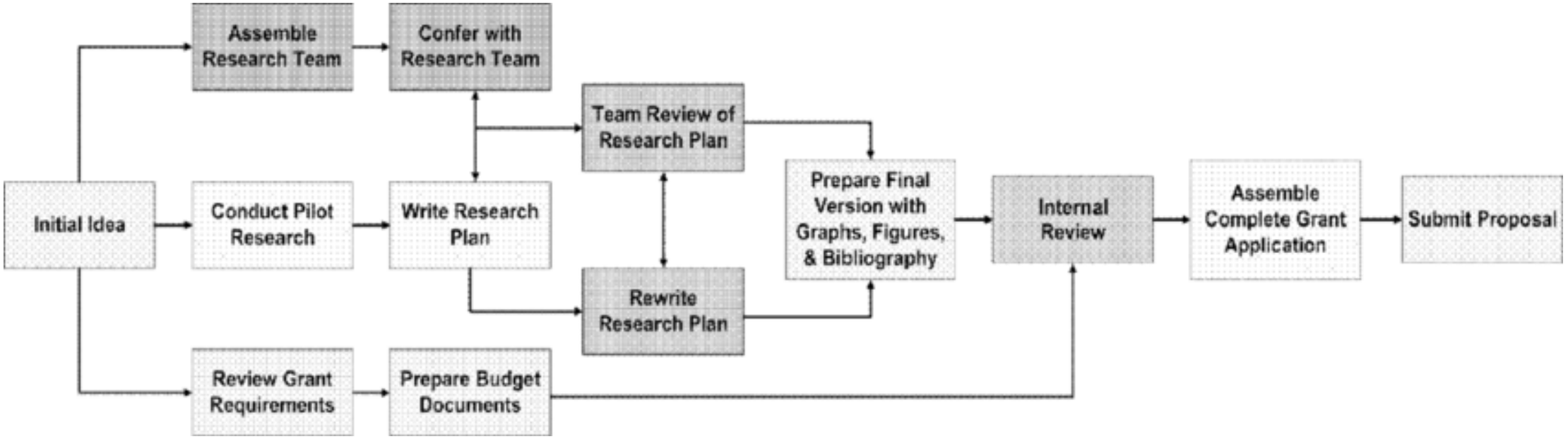
# NIH Grant Writing Team & Timeline

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# NIH Definition of Scientific Rigor

The **strict application of the scientific method to ensure unbiased, well-controlled experimental design, methodology, analysis, interpretation, and reporting of results**, leading to robust, reproducible findings that advance science responsibly.

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# Supporting Fairness and Originality in NIH Research Applications

**Notice Number:**
NOT-OD-25-132

## Key Dates

**Release Date:** July 17, 2025

## Related Announcements

- **July 23, 2018** – NIH/AHRQ Application Submission/Resubmission Policy. See Notice NOT-OD-18-197.

## Issued by

NATIONAL INSTITUTES OF HEALTH (NIH)

## Purpose

NIH is providing guidance to researchers on the appropriate usage of artificial intelligence (AI) to maintain the fairness and originality of NIH's research application process. NIH is also instituting a new policy limiting the number of applications that NIH will consider per Principal Investigator per calendar year.

**Background**

NIH has recently observed instances of Principal Investigators submitting large numbers of applications, some of which may have been generated with AI tools. While AI may be a helpful tool in reducing the burden of preparing applications, the rapid submission of large numbers of research applications from a single Principal Investigator may unfairly strain NIH's application review processes. The percentage of applications from Principal Investigators submitting an average of more than six applications per year is relatively low; however, there is evidence that the use of AI tools has enabled Principal Investigators to submit more than 40 distinct applications in a single application submission round.

NIH will continue to employ the latest technology in detection of AI-generated content to identify AI generated applications, but it is imperative that all NIH research applications are consistent with the NIH Grants Policy Statement (GPS) Section 2.1.2's expectation that institutions and affiliated research teams propose original ideas for funding. AI tools may be appropriate to assist in application preparation for limited aspects or in specific circumstances, but researchers should be aware that using AI comes with its own risks. AI use may result in plagiarism, fabricated citations, or other kinds of research misconduct. As a reminder, NIH oversees research misconduct investigations and acts on non-compliance (see GPS Section 4.1.27).

**Policy**

NIH will not consider applications that are either substantially developed by AI, or contain sections substantially developed by AI, to be original ideas of applicants. If the detection of AI is identified post award, NIH may refer the matter to the Office of Research Integrity to determine whether there is research misconduct while simultaneously taking enforcement actions including but not limited to disallowing costs, withholding future awards, wholly or in part suspending the grant, and possible termination.

NIH will only accept six new, renewal, resubmission, or revision applications from an individual Principal Investigator/Program Director or Multiple Principal Investigator for all council rounds in a calendar year. This policy applies to all activity codes except T activity codes and R13 Conference Grant Applications. Based on recent data, this limit will affect a relatively small number of Principal Investigators while enabling the NIH to maintain consistently high-quality grant application review and appropriately steward taxpayer dollars.

**Effective Date**

This policy is effective for applications submitted to the September 25, 2025, receipt date and beyond.

## Inquiries

Please direct all inquiries to:

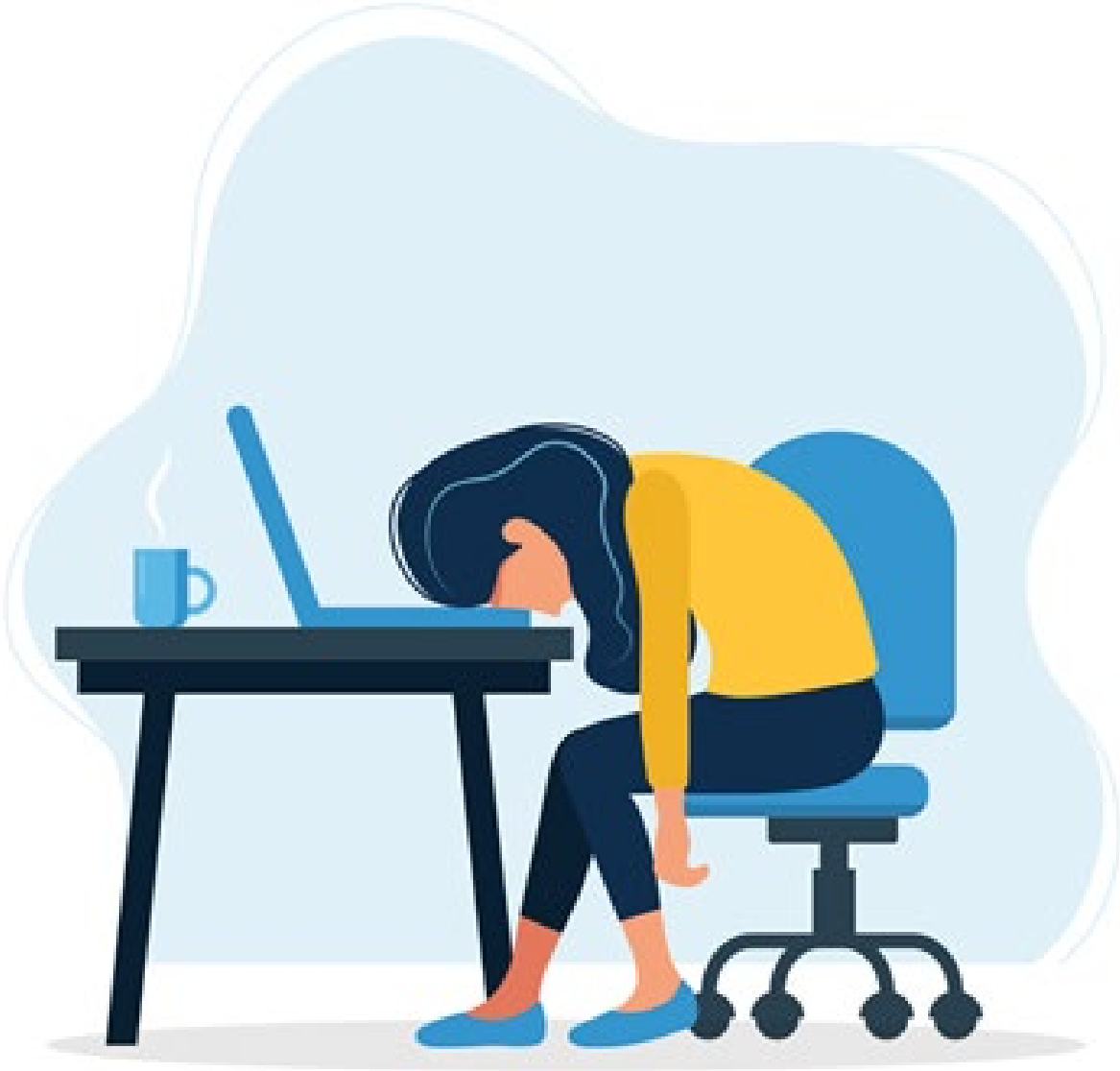
NIH Office of Science Policy:
SciencePolicy@od.nih.gov

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

## Policy

NIH **will not consider** applications that are either substantially developed by AI, or **contain sections substantially developed by AI**, to be original ideas of applicants.

Remember who your audience is.



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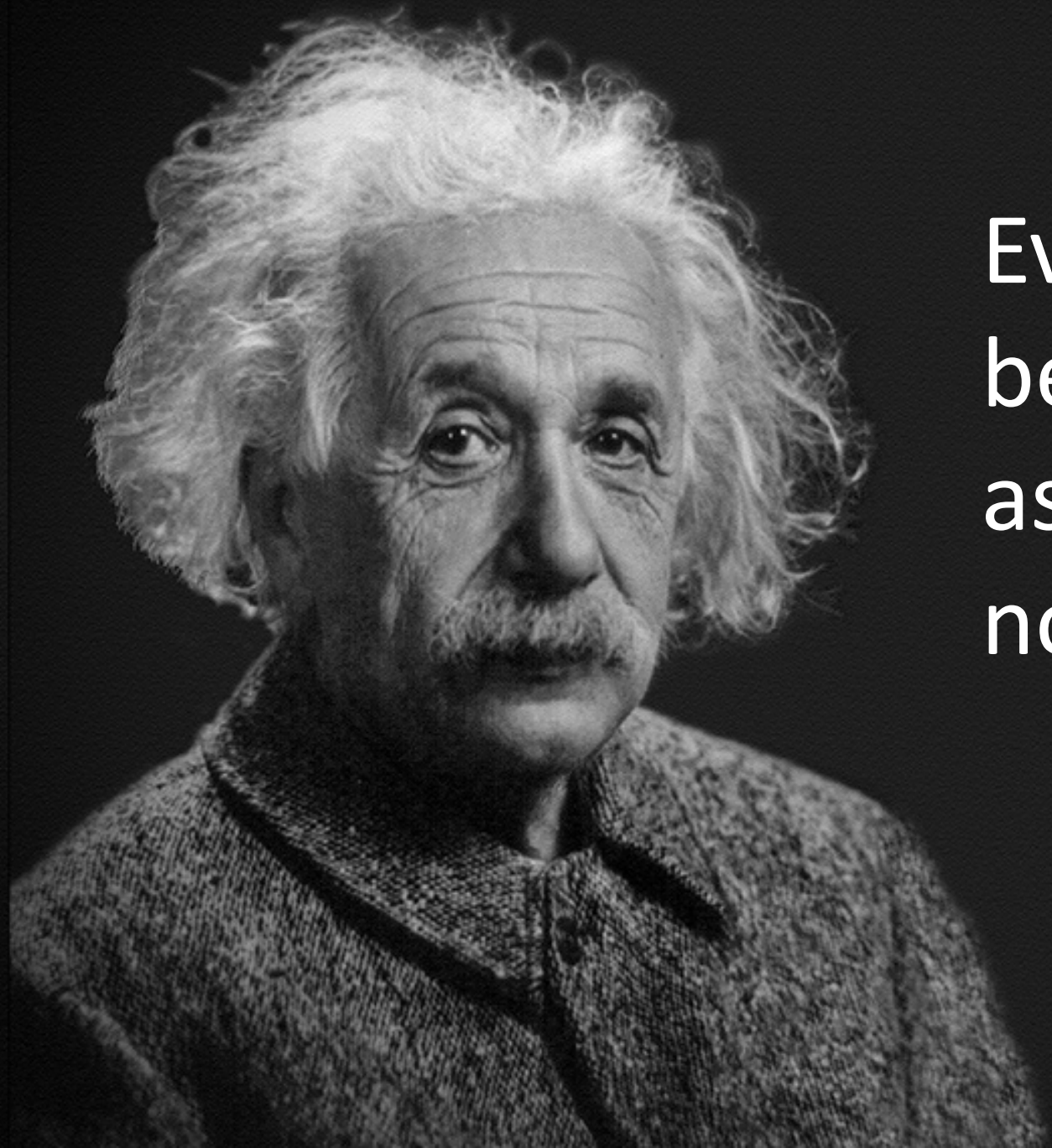

Everything should be made as simple as possible, but not simpler.

Research Strategy, the prolonged and increasingly interdependent evolution of the analytical subsystems has produced a methodological environment in which the reviewer must continuously navigate multiple overlapping domains of uncertainty, each of which imposes in… …n the most routine …ms of evaluation; and although preli… …the ca… …ayers of conditional dependen… …within the current architecture gen… …ent i… …that necessitate repeated … …calibration, thereby inducing a form… …cognitive … …tha… …each subsequent inter… …pass. ***The extent to which these recursive rec… …bration … …au… …bute to methodologic… … remains both substantial and insufficiently characterized, p… …ependent variance i… …with unresolved edge-case anomalies, producing a series of su… …agate nonline… …downstream workflows, further amplifying the interpretive loa… …*** …ed to accom… …stoc… …tributional irregularities forces the analytical pipeline t… …ar… …ing … …n of heu… …rrections th… …technically defensible, nonetheless generate a… …nstable… …ent… …; a… …ese corrective i… …umulate, the reviewer is confronted wi… …of *internal… …sis… …ally ambiguous* reas… …ot only obscures the direct cau… …the system but als… …npl… …ment with established NI… …n criteria. This dynamic … …ingly pronounced whe… …vio… …ilized parameters begin drift… …se to micro-fluctu… …d by secondary modules att… …ing… …olve latent conflicts among parti… …ping dataset… …ucing a recursive analytic cycle… …whi… …terpretive clarity is systematically er… …con… …tion of prior uncertainties. *As the a… …ytic… …environment becomes progressively more… …must expend disproportionate cognitive energy… …disentangling the conceptual, procedural, ana… …ocks embedded within the methodological appa…atu… …all while navigating a document that—by virt… …tified formatting, compressed structure, and scarc…y … …visual relief—demands extended periods of… …that compound the already substantial mental bu…de… …inherent in evaluating complex scientifi… …rching conceptual framework guiding this Resear… Strategy, the prolonged and increa… …ender… …of the analytical subsystems has produced… methodological environment in … …wer must … …ly navigate multiple overlapping domains… …ncertainty, each of which im… …al interpretive bu… …complicate even the most routine form… …valuation; and although pr… …s have indicated nomi… …ments in throughput, the *cascading l… …conditional dependen… …within the current architectu… …e recurrent interpretive ambiguitie… …ssitate repeated … …oration, thereby inducing a form… …ive fatigue that escalates wit…

… pass. ***The extent to which these recursive recalibration reg… …ntribute to …ological opa… …ins both substantial and insufficiently characterized, particul… …ext-dependent variance interacts with… …edge-case anomalies, producing a series of … …s that propagate nonlinearly through downstre… …further amplifying the interpreti… …*** …e persistent need to accommodate stochastic distributiona… …ities force… the analytical … …panding collection of heuristic corrections that, though technicall… …y unstable inferential terrain; and as these corrective measures accumulate, the revie… …e lattice of *internally consistent yet externally ambiguous* reasoning that not only obscures the direct causal structure of the system but also complicates alignment with established NIH evaluation criteria. *This dynamic becomes increasingly pronounced when previously stabilized parameters begin drifting in response to micro-fluctuations introduced by secondary modules attempting to*

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# Factors that Increase Reading Fatigue

- Dense text with minimal spacing
- Serif fonts
- Full justification
- No headings or subheadings
- No paragraph breaks
- Limited white space
- Jargon, acronyms, abbreviations
- Long sentences
- Tightly wrapped text around figures
- Excessive italics, underlining, or bold
- Passive voice (overuse)
- Frequent parentheticals
- Rapid topic shifting
- Repetitiveness
- Poor logical organization
- Inconsistent terminology
- Abrupt transitions

**Hardest → Easiest:**
*Italics → Underlined → Bold*

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# NIH Reviewer-Fatigue Diagnostic Tool

1. Does the text exceed 80 characters per line?
2. Are paragraphs longer than 8–10 lines?
3. Is there inconsistent or visually noisy formatting?
4. Does the document lack clear section hierarchy?
5. Are figures/tables crammed with no spacing?
6. Do sentences exceed 30 words?
7. Does jargon require constant rereading?
8. Does the layout cause noticeable scanning strain?

# Simplified Review Framework

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# Five regulatory criteria reorganized into three factors

## For due dates before Jan 25, 2025

(all considered in overall impact score)

- **Significance** - scored
- **Investigator(s)** - scored
- **Innovation** - scored
- **Approach** - scored
- **Environment** - scored

## For due dates on/after Jan 25, 2025

- **Factor 1 : Importance of the Research**
  - Significance, Innovation
  - Scored 1 - 9
- **Factor 2 : Rigor and Feasibility**
  - Approach (also includes Inclusion and Clinical Trial (CT) Study Timeline )
  - Scored 1 - 9
- **Factor 3 : Expertise and Resources**
  - Investigators, Environment
  - Evaluated as appropriate or gaps identified; gaps require explanation
  - Considered in overall impact; no individual score

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## Additional Review Criteria (can affect overall score)

**Additional Review Criteria Before Jan 25, 2025**

- Human Subject (HS) Protections (for HS and CT)
- Vertebrate Animal Protections
- Biohazards
- Resubmission/Renewal/Revisions
- Study Timeline (for CT only)*
- Inclusion of Women, Minorities, and Individuals across the lifespan (for HS and CT)*

**Revised Additional Review Criteria**

- Human Subject Protections (for HS and CT)
- Vertebrate Animal Protections
- Biohazards
- Resubmission/Renewal/Revisions

*Incorporated into Factor 2

## Additional Review Considerations (no effect on overall score)

**Additional Review Considerations Before Jan 25, 2025**

- Applications from Foreign Organizations†
- Select Agent Research†
- Resource Sharing Plans†
- Authentication of Key Biological and/or Chemical Resources
- Budget and Period of Support

- Authentication of Key Biological and/or Chemical Resources
- Budget and Period of Support

†Review shifted to NIH staff

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# Pre-2025 Research Strategy

**Significance**

**Innovation**

**Approach**

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# 2025 Research Strategy?

**Significance & Innovation**

**Approach**

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# 2025 Research Strategy

**Importance of the Research**

**Rigor and Feasibility**

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# 2025 Research Strategy

**Should it be done?**

**Will it be done well?**

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# 2025 Research Strategy

**Significance & Innovation**

- The Problem & Critical Barrier
- The Rigor of Prior Research
- Innovation
- Impact Statement

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# What to do with Innovation?

| INNOVATION |
| --- |
| First 'proof-of-concept' clinical trial to test precision medicine GRAS strategies to reduce senescent T cells. |
| Uses feature selection to discover bacteria and metabolite levels that may be most predictive of senescent T cell levels. |
| Mixed-methods assessment of GRAS-specific mechanisms that contribute to changes in outcome variables. |
| Employs diverse, multi-domain input data to inform AI predictive algorithms. |
| Uses a *comprehensive* battery of metrics to assess biological aging. (senescent cell absolute quantification, senescence-associated secretory phenotype (SASP), frailty measures, & epigenetic clocks) |
| While precision medicine has improved oncology care,[132] its application to age-related conditions is new.[133] |

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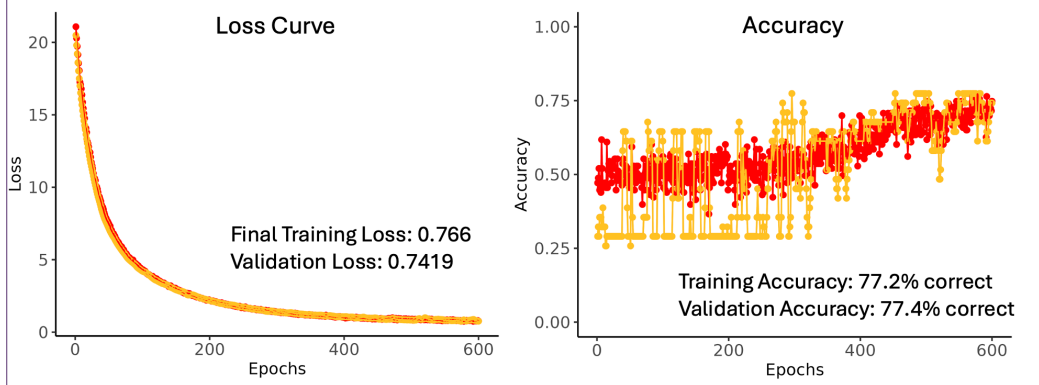
# Preliminary Data

## Scientific Foundation

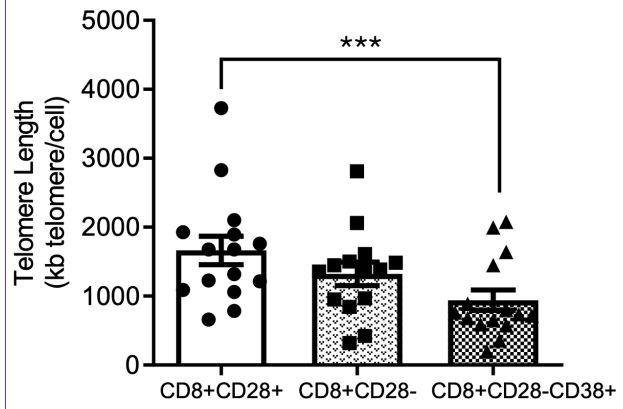
**Figure 2:** Proof-of-Principle Demonstration of ANN Prediction of Senescent CD8 T Cell Prevalence




Loss curves measure the difference between the predicted and actual values with lower values during progressive iterations of the ANN model. Lower values are desirable. Accuracy measures how often a machine learning model correctly predicts the outcome. # correct predictions ÷ total # of predictions.

## Technical Feasibility

**Figure 5:** Telomere Length Differs by CD8+ T Cell Phenotype




Human PBMCs were flow sorted into CD8+ populations and telomere length estimated by qPCR. ***$p$ = 0.015

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# Approach

- Overview
- For Each Aim:
  - Introduction (Rationale & Hypothesis)
  - Experimental Design
  - Analysis / Statistical Considerations
  - Expected Outcomes
  - Potential Problems / Alternative Approaches
- Timeline / Benchmarks
- Future Steps

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# Aims-Based Figure

Generate Genome-wide Polygenic Scores for 10 Diseases with Major Health Importance

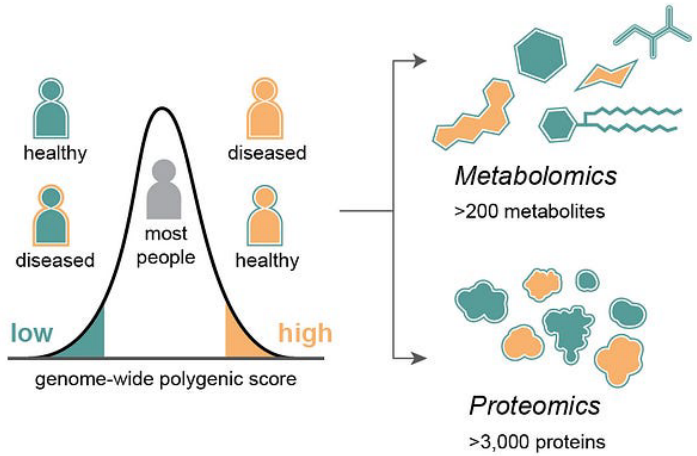
***Cardiometabolic***
*Heart attack*
*Type 2 diabetes*
*Obesity*
*Kidney disease*

***Neurodegenerative***
*Amyotrophic Lateral Sclerosis*
*Parkinson's Disease*
*Alzheimer's Disease*

***Psychiatric***
*Schizophrenia*
*Major depression*
*Attention Deficit Disorder*

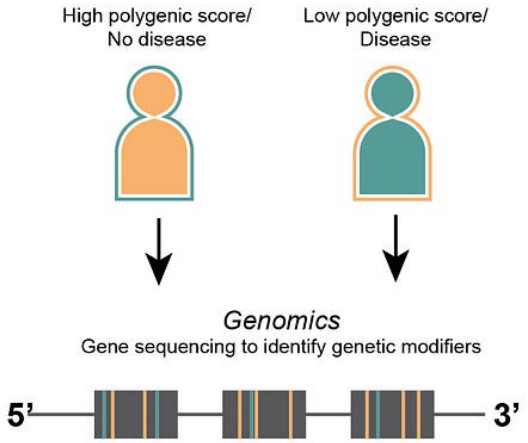
***Aim 1:***
***Molecular signatures of inherited susceptibility***

*Extremes of polygenic score distributions*




***Aim 2:***
***Identify rare protective genetic mutations***

*Polygenic score to enrich for large effect mutations*

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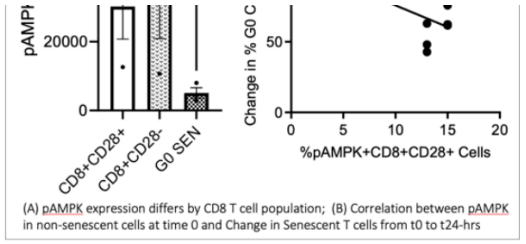
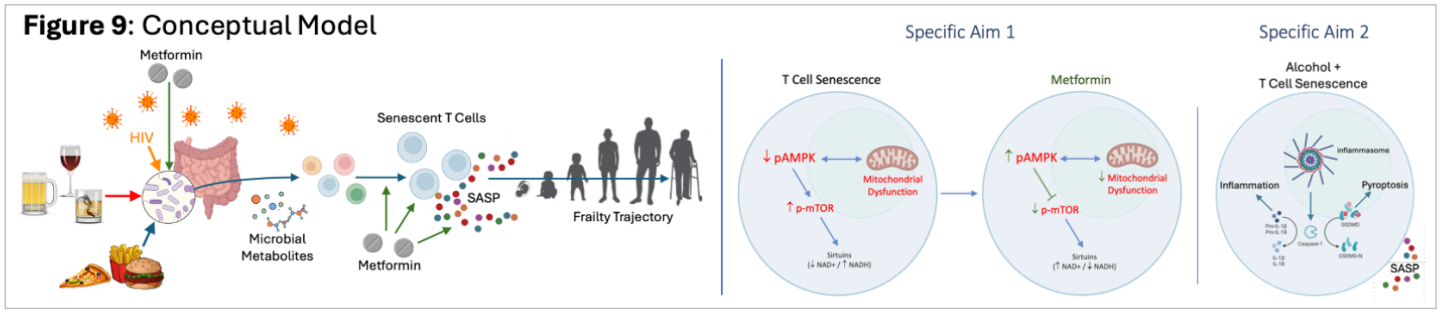
# Conceptual Model

plans to test metformin in the CBA/SIV NHP model. Metformin has many effects that may contribute to senoprotection including activating AMPK, optimizing mitochondrial function, and altering the microbiota.[68, 74-76] AMPK is a nutrient sensor and regulator of cellular energy homeostasis, and activation of AMPK protects against the development of senescence.[62-64] **Figure 8** shows that pAMPK is lower in G0 senescent T cells (NS) and that higher pAMPK inversely correlates with the development of senescent T cells (p=0.012).



(A) pAMPK expression differs by CD8 T cell population; (B) Correlation between pAMPK in non-senescent cells at time 0 and Change in Senescent T cells from t0 to t24-hrs




***Premise & Conceptual Model***: The data presented above along with the published literature support a *model of accelerated aging in PWH that correlates with LAE, which we believe is due to the cumulative effects of active alcohol use on T cell senescence. This is exaggerated in individuals with chronic viral stimulation and poor nutrition*. Our data further suggest that the intestinal microbiota mediate these relationships. We propose that alcohol-induced senescent cells may then contribute to organ dysfunction, frailty, and geriatric comorbidities by maintaining a chronic inflammatory state by the release of SASP mediators. We propose that mitigating this pathogenesis pathway by normalization of nutrient sensing (e.g., AMPK activation) and mitochondrial homeostasis by metformin will attenuate alcohol-related frailty in PWH by decreasing cellular senescence.

# Introduction (for Each Aim)

The *objective* of this aim is ….

To attain this objective, we will test our *working hypothesis* that….

The *rationale* for this aim is that….

Our *approach* to testing the working hypotheses….

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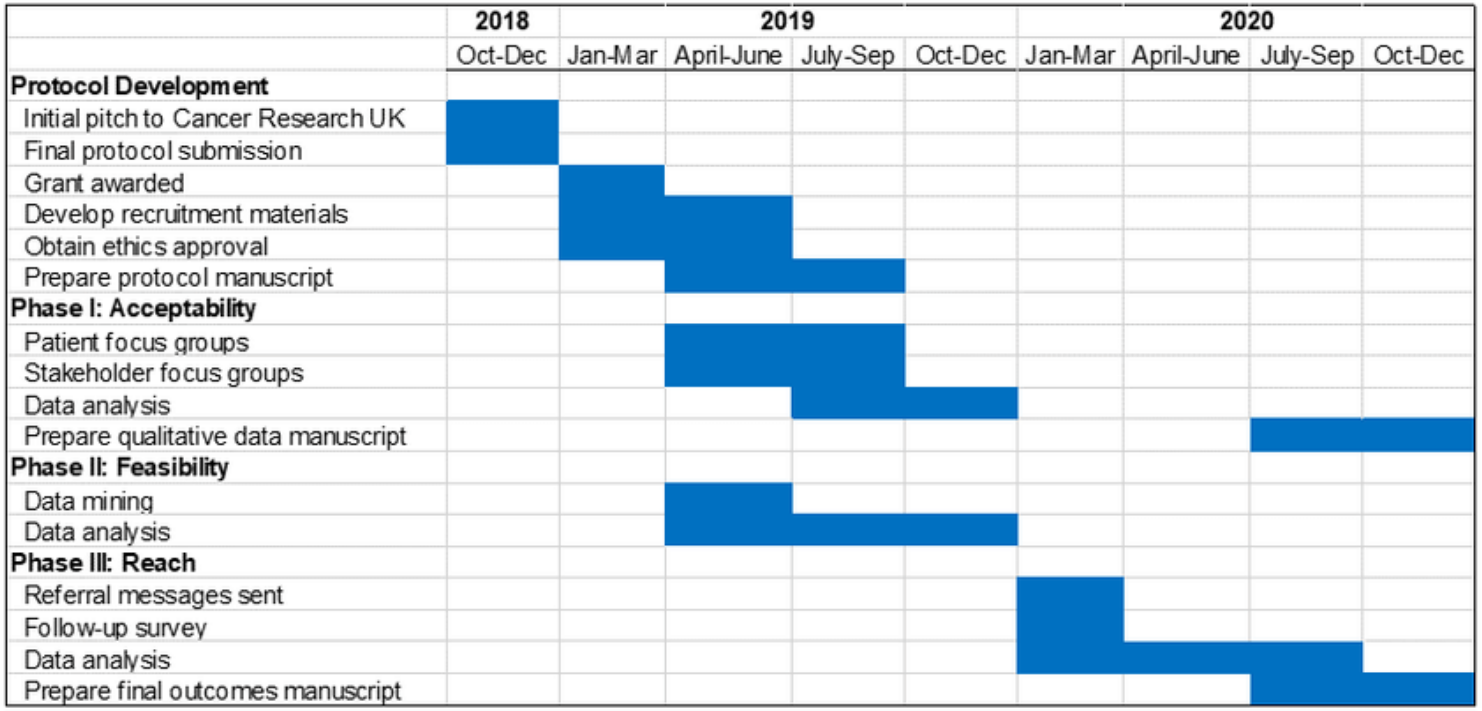


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# What goes at the end of the Research Strategy?

## The Future

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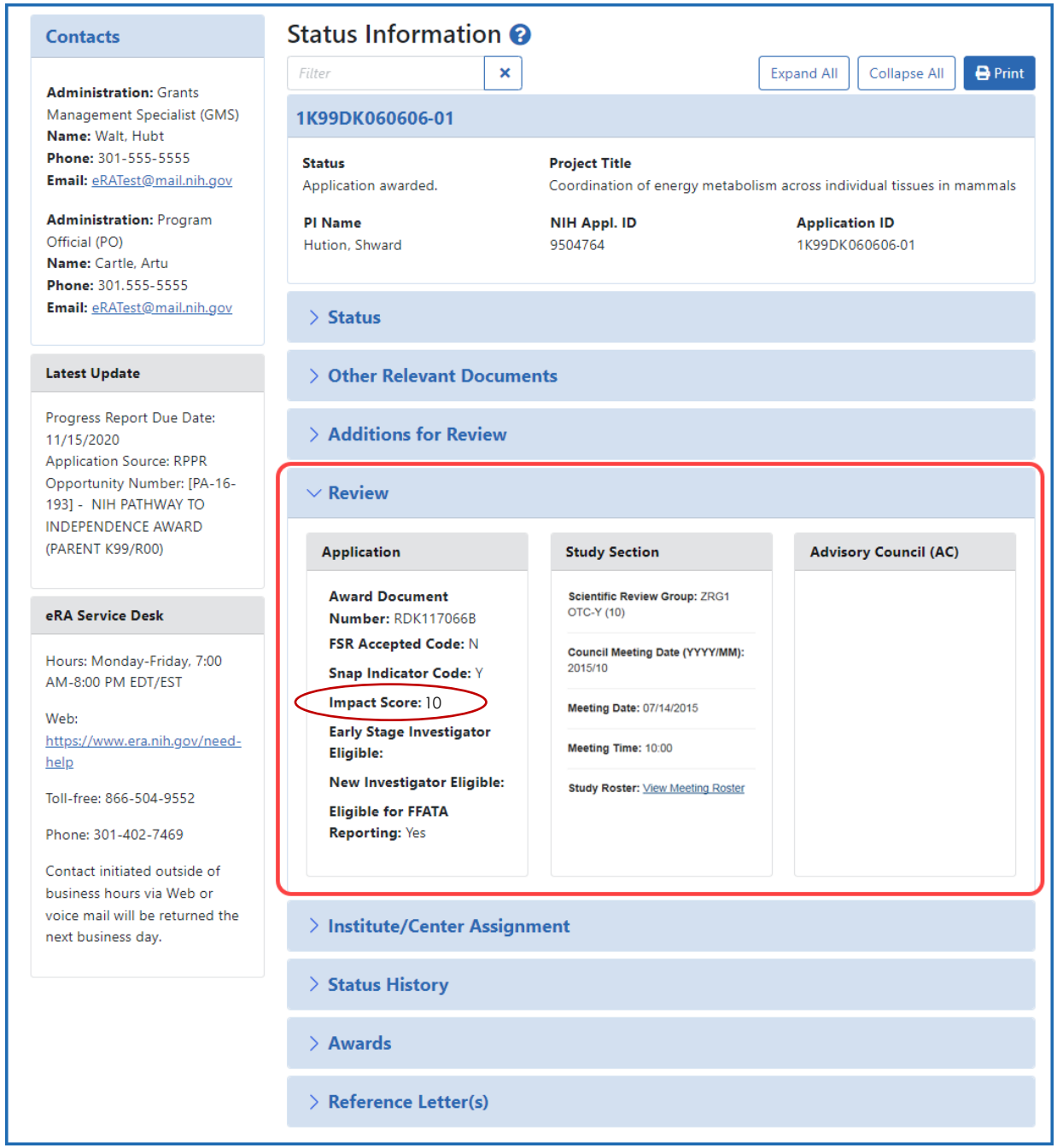


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