Official Title:	DNA Methylation in Polymyalgia Rheumatica (PMR)
NCT number:	07748195
Document Type:	Study Protocol
Date of the Document:	04/02/2026

Dartmouth Health

HRP-503

TEMPLATE PROTOCOL

INSTRUCTIONS

- *Use HRP-503 - TEMPLATE PROTOCOL when the DH IRB is the Reviewing IRB for this study.*
- *If a question does not apply to your study, **do not delete it**; instead, indicate it is not applicable.*
- *For submission of a protocol specific to a participating Site as part of a Multi-Site Study or when another IRB is the Reviewing IRB, use HRP-508 – TEMPLATE - SITE SUPPLEMENT*
- *Keep an electronic copy of this document. If changes affect the IRB determination, you must modify this copy and submit the changes to the IRB.*

1. BASIC INFORMATION

Protocol Title	DNA Methylation in Polymyalgia Rheumatica (PMR)
Principal Investigator Name	Vivekanand Tiwari, MD
Academic Appointment/Title	Assistant Professor of Medicine
Department	Medicine
Telephone Number	(603) 650- 8622
Email Address	Vivekanand.Tiwari@hitchcock.org

▶ *DH Policy "Principal Investigator Eligibility" (Policy ID 26012) outlines who may be a PI. By listing the individual above as PI, it is attested that this individual may serve as PI on a DH research study.*

VERSION NUMBER/DATE: Click or tap here to enter text.

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

FUNDING: *If the activity is funded, complete the following matrix. This funding may be internal, external, federal, non-federal, or a mixture of funding sources. Add additional matrices for each unique funding source. Reminder: This information must match the information you provide on the funding page of the eIRB application.*

Type of Funding:	☐ Gift ☒ Internal Funding (e.g., from a department) ☐ Federal Funding (e.g., NIH) ☐ Non-Federal Funding (e.g., pharmaceutical company) ☐ Other, specify: Click or tap here to enter text.
▶ *Don't forget to also complete the eIRB SmartForm section, "Funding"*	
If federally funded, please complete the information below.	
Funding Agency[i]:	DH Foundation
Sponsored Research ID#:	N/A
Does the grant indicate that covered activities will include Human Research? (Yes / No / Unknown)	Yes
PI listed on the award	Vivekanand Tiwari, MD
The institution that was awarded direct funding (i.e., "direct awardee")	DH
Prime Award Recipient	Vivekanand Tiwari, MD
Sub-Award Recipients	
▶ *As noted, if multiple funds support this activity, copy the above table and paste it here.*	

2. STUDY SUMMARY	
Protocol Information	**Description**
Study Design	**prospective observational ex vivo cohort study** investigating immune cell dynamics in patients with polymyalgia rheumatica during steroid treatment using methylation cytometry
Primary Objective	To characterize longitudinal changes in immune cell composition in patients with polymyalgia rheumatica (PMR) during corticosteroid treatment and disease relapse using methylation cytometry
Secondary Objective(s)	N/A
Research Intervention(s)/ Investigational Agent(s)	Blood

IND/IDE #	N/A
Study Population	Patients coming to the PMR clinic at Rheumatology, 5C, at DHMC. Healthy volunteers recruited from the community.
Sample Size	50 PMR patients and 25 healthy volunteers
Study Duration for Individual Participants	~20 minutes, as part of the standard of care visits for the patient. PMR patients can expect to be on the study for a maximum of 6 months. Healthy volunteers will be recruited for a one-time visit where blood will be collected, ~10 minutes.
Study Specific Abbreviations/ Definitions	PMR = Polymyalgia Rheumatica SOC = standard of Care

Is this study considered a clinical trial? ☐ Yes ☒ No

- *See DH policy "Registration and Results Reporting of Clinical Research on Clinicaltrials.gov" (22264)*
- *Reference the following decision tool for guidance on determining whether your study is a clinical trial - https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials/ct-decision*
- *If your study is a clinical trial, there are additional requirements. Please reference the following DH policies:*

DH policy "Clinical Research Documentation and Data Capture" (4856)

DH policy "Registration and Results Reporting of Clinical Research on Clinicaltrials.gov Procedure" (22264)

3. OBJECTIVES

3.1 *Describe the purpose, specific aims, or objectives.*

This study aims to characterize immune system alterations in patients with polymyalgia rheumatica (PMR) and identify molecular and cellular markers that predict corticosteroid response and risk of relapse. We will compare immune cell profiles of treated PMR patients with healthy controls, track longitudinal changes in immune composition during prednisone tapering, and assess the role of CD4/CD8 memory T cells, Tregs, and NK cells. Using DNA methylation cytometry, we will quantify glucocorticoid responsiveness through the Glucocorticoid Methylation Index (GCMI) and Neutrophil Dexamethasone Methylation Index (NDMI), evaluating their potential to predict disease relapse and guide personalized treatment strategies.

3.2 *State the hypotheses to be tested.*

We hypothesize that patients with PMR will exhibit distinct immune cell profiles compared to age- and sex-matched healthy controls, despite clinical quiescence on prednisone

We hypothesize that steroid-induced DNA methylation changes, especially in neutrophils, can serve as pharmacodynamic biomarkers that better reflect individual responsiveness to glucocorticoids and help identify patients at higher risk of relapse.

We hypothesize that, compared to healthy controls, even at a stable treatment dose (≥10 mg prednisone), patients with PMR will show disease-specific immune cell composition.

We hypothesize that a) methylation shifts in CD4 and CD8 memory T cells correlate with disease activity and steroid tapering; b) Treg dysfunction (FOXP3 methylation) is associated with increased inflammation and poor steroid response; c) methylation patterns in NK cells suggest a role in PMR's immune regulation and inflammation control.

We hypothesize that GCMI and NDMI reflect molecular glucocorticoid responsiveness and vary with prednisone tapering.

We hypothesize that low GCMI/NDMI during tapering predicts relapse and surpasses conventional markers like ESR.

3.3 *A description of the type/design of the trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose-escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design)*

Not applicable, this is not a clinical trial study. This is an investigator-initiated study.

4. SCHOLARLY BACKGROUND & RATIONALE FOR THE SCIENTIFIC STUDY/RESEARCH

4.1 *Provide the scholarly background for the research based on the existing literature and how it will add to existing knowledge. Also include any gaps in current knowledge that the research will fill, as well as any relevant preliminary data. Be sure to provide a complete bibliography of all citations used.*

Polymyalgia rheumatica (PMR) is a corticosteroid-responsive inflammatory disease characterized by systemic inflammation, muscle pain, and stiffness involving the shoulder and pelvic girdle. Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease in adults over 50, and a lifetime risk of 2.4% for women and 1.7% for men.[1] The incidence is highest in individuals of Northern European descent, ranging from 41 to 113 per 100,000 persons aged 50 years or older, and is 2–3 times more common in women. PMR is closely associated with giant cell arteritis (GCA), with 16–21% of PMR patients developing GCA, which can result in severe complications such as vision loss.[2] Corticosteroids, prednisone in particular, are the mainstay of PMR treatment, often initiated at 12.5-25mg and gradually tapered by 1mg per month. Despite the effectiveness of glucocorticoids, relapse is common, and tapering strategies remain empirical due to a lack of reliable immune biomarkers.[3]

Our multiple retrospective studies have shown a long duration of treatment with corticosteroids in this patient population: Only 18.4% of patients were off prednisone at one year, and only 43% eventually discontinued prednisone at the end of two years.[4,5] Many patients who are able to come off steroids eventually end up resuming steroids due to frequent relapses of the disease and paucity of alternative regimens. Prolonged treatment with corticosteroids results in significant treatment-related toxicities such as osteoporosis, fragility fractures, osteonecrosis, cataracts, glaucoma, and metabolic disorders, including diabetes.[6] Additionally, the economic burden associated with the prolonged treatment of PMR patients is substantial and is associated with significantly increased healthcare utilization, including outpatient services and laboratory testing, compared to matched controls.[7] The goal of this project is to elucidate the immune profiles in patients with PMR and identify immunologic predictors of treatment response.

Current Gaps in Knowledge: Despite these advances, the exact triggers for immune activation, the specific antigens involved, and the mechanisms underlying disease relapses and glucocorticoid resistance remain unclear. Significant gaps remain regarding the roles of CD8+ T cells and natural killer (NK) cells in the development of polymyalgia rheumatica (PMR), particularly in comparison to the more established involvement of CD4+ T cells and regulatory T cells (Tregs). While CD4+ effector-memory T cells, particularly Th1 and Th17 subsets, are known to be key drivers of periarticular inflammation in PMR, and impairment of Tregs is linked to the loss of immune regulation, the role of CD8+ T cells is less clear. Some studies have reported reduced peripheral CD8+ T cell counts in active PMR, while others have shown that CD8+ T cells in PMR can display activation markers and produce inflammatory cytokines.[11,12] Their activation status often correlates with disease activity and response to therapy. The significance of these findings—whether CD8+ T cells are pathogenic, regulatory, or merely bystanders—remains unresolved. For NK cells, the available literature is even more limited. Although innate immune activation is a hallmark of PMR, including increased activity of monocytes and neutrophils, the specific role of NK cells in disease initiation or maintenance remains unclear.[8] Some evidence indicates altered frequencies or activation states of innate-like T cells (including MAIT and γδ T cells)[13], but direct data on classical NK cell involvement are lacking. Overall, the mechanisms by which CD8+ T cells and NK cells might interact with established CD4+ T cell and Treg pathways, or contribute to tissue inflammation and clinical relapse, are poorly understood and represent important areas for future research.

DNA methylation cytometry is a novel DNA-based cell typing technology that can quantify changes in blood immune cells. The methylation cytometry approach allows for an in-depth insight into 12 immune cell populations (and over 50 immune profile variables) that is not feasible with standard clinical labs. It is both far more affordable and less labor-intensive than flow cytometry, as well as much less logistically complex because it is DNA-based and does not require intact cell membranes.[14] Blood can be collected as part of the standard-of-care draw and immediately frozen for later use. DNA methylation analysis is a novel approach to understanding the immunologic underpinnings of PMR pathogenesis and treatment.

Preliminary Data: In our pilot prospective study, funded by the Scholarship Enhancement in Academic Medicine (SEAM) grant from the Department of Medicine at Dartmouth Hitchcock Medical Center (DHMC), we employed DNA-methylation cytometry to quantify changes in blood immune cells in patients with PMR. Our study revealed substantial DNA methylation changes in CD4 and CD8 memory T cells in response to steroid treatment, highlighting the dynamic behavior of antigen-experienced immune populations in PMR **(Figure 1)**.

Additionally, observed methylation trends in regulatory T cells and natural killer (NK) cells point to their potential involvement in modulating disease progression and immune regulation.

The current proposal expands on the findings of our pilot study and addresses a critical knowledge gap in assessing immunologic biomarkers for PMR treatment response. **The project directly addresses the Hitchcock Foundation's mission by targeting a highly vulnerable population of older patients at increased risk of complications due to long-term corticosteroid therapy. It aligns with Pilot research grant funding goals by encouraging meaningful research at Dartmouth Hitchcock Medical Center.**

4.2 ***For Investigator-Initiated Trial (IIT) studies that involve an investigational product, where an IND (drug, biologic) submission to the FDA may be possible ,*** *provide the rationale for using the investigational drug for the research study. Include background information on the science that supports the use of the investigational drug and/or the research study.*

If this is not applicable, state "N/A"

N/A, this study does not involve an investigational drug.

5. PRE-CLINICAL DATA

► ***Complete this section ONLY*** *for Investigator-Initiated Trial (IIT) studies that involve an investigational product, where an IND (drug or biologic) or IDE (device) submission to the FDA may be possible.*

5.1 *Provide a brief summary of previous human experience with the drug(s) with reference to the literature or other INDs if pertinent. There may not be any previous human experience if the drug is completely new or if it is first-in-human (FIH). Preclinical animal and/or laboratory experience should be described.*

Toxicology: Includes information on the toxicological effects of the drug in animals and in vitro. For detailed guidance related to content of this section, refer to FDA Guidance for Pharmacology/Toxicology.

N/A

5.2 *Provide (1) a description of the pharmacological effects and the mechanisms of action of the drug in animals and (2) information on the absorption, distribution, metabolism, and excretion of the investigational product. For detailed guidance related to the content of this section, refer to FDA Guidance for Pharmacology/Toxicology.*

N/A

5.3 *Provide a summary of the toxicology effects of the products in animals. For detailed guidance related to the content of this section, refer to FDA Guidance for Pharmacology/Toxicology.*

N/A

5.4 *Per regulation 21 CFR 312.23(a)(8)(b)(iii), all nonclinical laboratory studies subject to good laboratory practice (GLP) regulations under Part 58 must contain a statement that the study was conducted in compliance with the GLP regulations. If the non-clinical study was not conducted under GLP, provide a brief statement explaining the noncompliance.*

N/A

6. STUDY ENDPOINTS

6.1 *Describe the primary and secondary study endpoints.*

The primary endpoint is changes in peripheral blood immune cell composition in PMR patients during corticosteroid treatment and tapering, measured by DNA methylation cytometry. Secondary endpoints include differences from healthy controls, associations between immune or epigenetic markers (GCMI and NDMI) and clinical response or relapse, and correlations with steroid tapering outcomes. Safety endpoints include adverse events from blood draws and monitoring for PMR flares or steroid-related complications.

6.2 *Describe any primary or secondary safety endpoints.*

Safety will be monitored through adverse events, serious adverse events, and clinical or laboratory indicators of glucocorticoid-related effects. Disease activity will be assessed to identify flares or relapse. Participants will end study participation upon completion of the taper, achievement of sustained disease remission, or relapse requiring return to standard-of-care therapy. All safety findings, relapses, and protocol deviations will be documented and reported according to IRB and regulatory requirements.

7. PROTOCOL PROCEDURES

7.1 *Provide a general overview of the procedures that study participants will undergo. If complex, you may also wish to use HRP-509 – TEMPLATE – STUDY SCHEMA EXAMPLES to clarify the text below further. If used, upload to the eIRB section 'Local Site Documents", item 3, and indicate below to reference this document.*

► *It is not an IRB requirement to use this template; however, it may help the IRB better understand the study design and procedures, and the IRB might request it for this purpose.*

Participants will be eligible for enrollment if they are taking **prednisone at a dose of 10 mg or higher**. Upon enrollment, participants will follow a **protocol-defined prednisone taper**. For doses above 10 mg, prednisone will be reduced by **2.5 mg every two weeks** until 10 mg is reached. Once at 10 mg, the taper will continue by **1 mg every two weeks** until discontinuation or remission of disease.
Blood draws will occur at **enrollment**, at approximately **3 months** (timing may vary depending on starting dose), and again at either **disease relapse or successful taper/remission**. Participants will discontinue study participation upon completing the taper, achieving sustained remission, or experiencing a relapse that requires return to standard-of-care prednisone therapy. All clinical data, laboratory results, and adverse events will be documented and reported per IRB and regulatory requirements.

7.2 *Describe the measures taken to minimize/avoid bias, including randomization and blinding.*

This open-label, single-arm study does not involve randomization or blinding. To minimize bias, objective measures such as inflammatory markers (ESR, CRP) and laboratory tests will be used to assess disease activity. Standardized procedures, visit schedules, and protocol-defined assessments for adverse events, taper adherence, and clinical evaluations will ensure consistent data collection across participants. Reliance on objective endpoints and uniform study procedures will reduce measurement and reporting bias.

7.3 *Describe the strategies to monitor the participant's adherence to treatment, if applicable.*

Monitoring will happen at standard of care visits in the PMR clinic.

8. STANDARD OF CARE VS. RESEARCH

► *The HRP-103 – INVESTIGATOR MANUAL provides an overview of the standard of care versus research.*

8.1 *Identify any procedures conducted under this protocol that participants will undergo as a direct result of participation in this study. These are procedures performed for research purposes only; as a consequence of involvement in this research, procedures occurring more frequently than the standard of care or randomization to different standards of care, for example.*

Procedures performed specifically for this study, include the **protocol-defined prednisone taper** and **scheduled blood draws**. Blood samples will be collected at **enrollment, approximately 3 months (timing may vary depending on starting dose), and at either disease relapse or successful taper/remission**.

The prednisone taper schedule, is as follows:

Enrollment will start with patients who are clinically stable on ≥10 mg or higher.
Every study participant with a PMR diagnosis will follow the schedule below (schedule depends on starting dosage):

For participants who are enrolled in the study and are taking a > 10mg dose of prednisone, they will decrease the dose by 2.5 mg every 14 days (2 weeks) until a 10 mg dosage is reached. After which participants will decrease by 1 mg every 14 days (2 weeks) until discontinuation of prednisone or a relapse in disease activity occurs meaning pain and stiffness in the joints of the body along with elevated inflammatory markers in the blood.

For participants who are enrolled in the study and are taking a 10mg dose of prednisone will decrease the dose by 1mg every 14 days (2 weeks) until discontinuation of prednisone or a relapse in disease activity occurs meaning pain and stiffness in the joints of the body along with elevated inflammatory markers in the blood.

For other PMR diagnosed individuals who wish to not participate in the study, the care they seek and the taper would not be any different to that of a study participant.

8.2 *According to national standards (or DH practice if different from national standards), list the protocol procedures the participants will undergo as part of their routine clinical care (regardless of their participation in the research).*

- **Initial Consultation:** The specialist will review your history, discuss the specific reasons for the referral, and ask about your symptoms in detail.
- **Physical Exam:** A focused exam on the area of concern will be conducted (e.g., PMR-related symptoms, including muscle tenderness, stiffness, range of motion, vital signs)
- **Plan Formulation:** The specialist will offer a diagnosis, order targeted tests (blood work, imaging), or initiate treatment, such as medication or lifestyle changes.
- **Follow-Up Plan:** You will discuss next steps, which may include a follow-up appointment to review test results or a referral for further specialized testing

8.3 *Identify whether there is a use of a placebo condition.*

No use of a placebo condition.

8.4 *Clarify whether participating in this study will prevent or delay the standard of care.*

Participating in this study will not prevent or delay any standard of care.

8.5 *If relevant, describe the alternative procedures or courses of treatment that may benefit participants.*

N/A

8.6 *Describe any medication(s) or treatment(s) that are allowed (including concomitant and rescue medication) and those that are not allowed before and/or during the study, if applicable.*

Any and all medications and treatments can be taken during the course of being a participant in the study.

9. SPECIFIC STUDY FEATURES

Dartmouth Health

► *For ANY of the below items, consider using HRP-505 – TEMPLATE - DATA AND MATERIAL LISTING, found in the eIRB Library. If used, upload to the eIRB section 'Local Site Documents", item 3, and reference this document in each item.*

9.1 *Will any genetic analyses be conducted in this study?*

☐ Yes – specify the type of analyses: *Click or tap here to enter text.*

☐ No

► *Genetic analysis encompasses a variety of techniques and methods used to study genes and their functions. Genetic analyses may also include RNA.*

► *Studies that conduct genetic analyses may require additional information in the study's informed consent form. See HRP-502 - TEMPLATE CONSENT DOCUMENT for suggested language.*

► *See New Hampshire statute § 141-H:2, which limits the type of genetic testing and requires the individual's informed consent. Specifically, this statute applies to germline genetics only and does not include somatic or infectious genetics. More information may also be found here - https://synergy.dartmouth.edu/wp-content/uploads/2024/11/Understanding-NH-Title-X-Final-v.1.pdf*

9.2 *Will the research involve the use of a 3rd party application?*

☐ Yes – specify the 3rd party application: *Click or tap here to enter text.*

☒ No

► *Use of a 3rd party application that DH has not approved may require review by RIDGe. See the DH Research Informatics and Data Governance (RIDGe) website for more information on activities that require RIDGe review.*

► *If using a 3rd party application that DH has not approved, there is specific language in the DH IRB informed consent form template that is required.*

9.3. *Will any sensitive information be collected for studies conducted at DH? For example, substance use disorder (SUD) treatment (specify if from a SUD clinic), research use of HIV or genetics data (i.e, germline genetics only; not somatic or infectious genetics), business confidential data, psychiatry/psychology/mental health records, sexually transmitted disease treatment, or social security numbers?*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

► *New Hampshire statutes require the individual's consent to use sensitive information.*

► *See the DH Research Informatics and Data Governance (RIDGe) website for more information on activities requiring RIDGe review, including the collection of sensitive information.*

9.4 *Will any Center for Medicaid or Medicare (CMS) data be accessed, obtained, or used?*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

► *DH has limited storage options for CMS data. Please contact The Dartmouth Institute (TDI) for guidance.*

9.5 *Indicate if the study will involve <u>using</u> biohazards in a DH or College research laboratory. Examples include (but are not limited to) cells, tissues, recombinant or synthetic nucleic acids, toxins, or infectious agents (e.g., bacteria, viruses, and fungi). This does not include assays performed in clinical laboratories.*

☒ Yes – specify: whole blood samples will be handled following biosafety protocols.

☒ No

► *The PI of the laboratory submits new projects or modifications to their IBC registration on BioRAFT (https://dartmouth.bioraft.com [dartmouth.bioraft.com]). Some new projects may be covered under existing approvals, such as for core facilities. Contact the Biosafety Officer at biosafety@dartmouth.edu if the lab does not have an IBC registration. Note that the lab PI is not necessarily the PI of the IRB protocol.*

► *Also, see DH Policy, "Institutional Biosafety Policy" (ID 20055) - https://dh.navexone.com/content/dotNet/documents/?docid=32105&anonymous=true*

9.6 *Indicate if the study involves the administration of recombinant or synthetic nucleic acids into human participants. Examples include (but are not limited to): engineered or genetically modified viruses/bacteria/cells, viral vectors, transfected cells, plasmids, mRNA vaccines.*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

► *Email clinical protocol and investigator's brochure to biosafety@dartmouth.edu. The Biosafety Officer will request additional information after confirming that IBC-CGT review is required. Note that the IBC-CGT differs from the IBC above and does not use the BioRAFT system.*

9.7 *Will any Class 3 or Class 4 lasers be used in this study?*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

► *See DH Policy, "Laser Safety Policy" (ID 4513) - https://dh.navexone.com/content/dotNet/documents/?docid=43326&app=pt&source=browse*

9.8 *Will any x-ray imaging, radiopharmaceuticals, external beam, or brachytherapy, whether standard of care or not, be included in this study?*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

► *See DH policy, "Review of Research Studies Using Radiation - Radiation Safety" (ID 25337) - https://dh.navexone.com/content/dotNet/documents/?docid=47294*

9.9 *Will any Artificial Intelligence (AI) be developed/used in this study?*

☐ Yes - see below

☒ No

If you indicated "Yes", please include the following information below:

- *The name of the technology and model(s). If under development, indicate as such.*
- *Current status of the technology (developed in a separate protocol; currently marketed in the U.S.; will be modified or will be used for a purpose different from what it was initially designed, cleared, or approved for; is investigational but works as a component to a U.S. legally marketed device.*
- *Stage of development in the study: Stage 1 (training, proof of concept, training of the model, may include secondary analysis); Stage 2 (pilot testing/validation, training of the model, may include secondary analysis; Stage 3 (real-world testing and deployment, establishes /verifies safety, device performance, benefits, effectiveness, may be deployed in a live environment*

AI will not be used in this study

10. INTERVENTION/INVESTIGATIONAL AGENT

10.1 *If the research involves a drug, biologic, or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on participants and be used only by authorized investigators.*

► *This only applies to a drug, biologic, or device under investigation, whether FDA approved/cleared. See HRP-103 – INVESTIGATOR MANUAL for more information.*

This study does not involve a drug, biologic, or device

10.2 *Complete one (or both) of the following forms and upload them to the eIRB section 'Drugs' and/or 'Devices'.*

- *If using an investigational drug/biologic, complete HRP-504b - TEMPLATE - Protocol Supplement - Drugs & Biologics*
- *If using an investigational device, complete HRP-504c - TEMPLATE - Protocol Supplement - Devices*

► *The DH Biomedical Engineering Department must clear all research protocols involving devices at DH. Contact Engineering Services, Location: B2L2, (603) 650-7150, D-H internal: 5-7150*

► *All research protocols involving investigational drugs or biologics at DHMC must utilize the Research Pharmacy for storing, dispensing, and controlling the investigational drug, whether for inpatient or outpatient use. For more information about the Research Pharmacy, contact them at investigational.pharmacy@hitchcock.org), DH Policy 2091.*

► *Studies that involve an IND or IDE require monitoring by the DH Research Quality and Safety team and use of 21 CFR Part 11 compliant systems, e.g., eREG and e-consent software (if used).*

► *Refer to the HRP-103 – INVESTIGATOR MANUAL for information about when the FDA is required to be contacted when there is a modification to an existing IND or IDE.*

11. DATA AND BIOSPECIMEN/OTHER MATERIAL BANKING

11.1 *If data or biospecimens/other material will be banked for future use, describe where they will be stored, how long they will be stored, how they will be accessed, and who will have access to them.*

The specimens will be de-identified and banked in a locked freezer within a locked laboratory space for future analyses. Subject records and biological samples will receive a unique code in place of information that can be used to identify them (name, address, and DOB). Samples for this study will be handled by the CRC and processed, methylation cytometry by the CORE here at Dartmouth, and stored in the laboratory space of the Skopelja-Gardner lab. Only Dr. Skopelja-Gardner and members of her laboratory will have access to this freezer space. Data will be stored in the laboratory computer (606E Borwell office) that is password protected, on a secure network, and can be accessed only by Dr. Skopelja-Gardner and lab personnel. Specimens and data will be stored for ~3 years after the publication of any results obtained from this study.

11.2 *List the data to be stored or associated with each biospecimen/other material.*

► *If the list is lengthy, consider using HRP-505 – TEMPLATE - DATA AND MATERIAL LISTING, found in the eIRB Library. If used, upload to the eIRB section 'Local Site Documents", item 3, and indicate below to reference this document.*

Medication- prednisone or equivalent

office visit notes that allow for evaluation on how to participants are doing on the taper at their clinic visit(s)

lab work values of the standard of care. CBC, CMP/BMP, ESR, CRP will be looked at to help determine how to participant is doing with the medication taper

11.3 *Describe the procedures to release data or biospecimens/other material, including the process to request a release, approvals required for release, who can obtain data or biospecimens/other material, and the data to be provided with biospecimens/other material.*

The providers and the research coordinator will have access to data

12. SHARING OF RESULTS WITH PARTICIPANTS OR OTHERS

► *For studies taking place at DH, all imaging must have a DH radiologist interpret imaging exams and ensure unexpected actionable findings are conveyed to ordering providers promptly. See DH policy "Required Review of Imaging Exams Performed for Human Subjects Research Protocols" (#25166). Note that different DH locations may have different processes.*

Refer to the following for additional considerations on the return of results to study participants:

- *SACHRP Recommendations, "Return of Individual Results", 2016*

- *National Academies of Sciences, Engineering, and Medicine, "Returning Individual Research Results to Participants: Guidance for a New Research Paradigm". The National Academies Press 2018*
- *Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University, "MRCT Center Recommendations Document for Returning Individual Results", 2017*
- *Jarvik et al., "Return of genomic results to research participants: The floor, the ceiling, and the choices in between". American Journal of Human Genetics 94(6): 818-826. 2014*

12.1 *Describe whether results (study results or individual participant results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with participants or others (e.g., the participant's primary care physicians), and if so, describe how it will be shared.*

Results of the research testing will not be shared with the participants

12.2 *Describe the validity of the result to be returned. For example, is the result from a device or assay that has regulatory approval from the Food and Drug Administration (FDA) or from a lab that has certification under the Clinical Laboratory Improvement Amendment (CLIA) from the Centers for Medicare and Medicaid Services (CMS)?*

Results of the research testing will not be shared with the participants

12.3 *Choose the reason why the result is to be returned (choose all that apply):*

☐ Clinically actionable: Established therapeutic or preventive interventions or other available actions have the potential to change the clinical course of the disease/condition or lead to an improved health outcome.

☐ Urgent: If not treated or addressed quickly, the results pose life-threatening or severe health consequences.

☐ Valid: The results are analytically and clinically valid. Analytic validity indicates how accurately and reliably the test measures a certain criterion, such as a genotype of interest. Clinical validity refers to the accuracy of predicting a clinical outcome.

☐ Feasible: The return of results can be reasonably accomplished without compromising the research. Feasibility is determined by multiple factors, including the potential for causing bias, the resources available to communicate the results effectively and appropriately, and other challenges, costs, and burdens. For example, returning results to a low-income, transient population with mental health disorders may not be feasible if the study does not have the significant resources that would be required to put an appropriate plan in place.

☒ Other – describe: results of the research testing will not be shared with the participants

13. STUDY TIMELINES

13.1 *Describe the duration of an individual participant's participation in the study.*

Duration on the study is dependent on the starting dosage of prednisone of each participant. If a participant is clinically stable at a dosage of 15mg of prednisone, and follow the taper schedule of 2.5mg every 2 weeks until 10mg then 1 mg every 2 weeks, they will be on the study for 169 days (~6 months). If a participant is clinically stable at a dosage of 10mg of prednisone, and follow the taper schedule of 1 mg every 2 weeks, they will be on the study for 154 days (~5 months).

The duration of the study participants depends on the starting dosage of prednisone, with the inclusion for the study being on a dosage of 10mg or greater.

13.2 *Describe the duration anticipated to enroll all study participants.*

In the pilot study, it took three months for the majority of the patients to be recruited to the study. The same timeline is anticipated for this study.

13.3 *Describe the estimated date for the investigators to complete this study (complete primary analyses).*

January 2027 is the estimated date for the investigators to complete primary analyses.

14. INCLUSION AND EXCLUSION CRITERIA

14.1 *Describe the criteria that define who will be included or excluded from your final study sample.*

The CRC, will screen patients scheduled in the PMR clinic the Friday in advance to identify potential eligible participants. Eligibility will be confirmed during the visit, and interested patients will be introduced to the study and provided with informed consent before enrollment to ensure compliance with ethical guidelines.

Using the inclusion/exclusion criteria.

Inclusion:

Anyone ≥50-89 years old

Taking ≥10mg of prednisone or prednisone equivalent at time of enrollment with a stable disease

normal ESR and CRP (inflammation markers) which would indicate presence of inflammation or not

- ***CRP:*** *<1.0 mg/dL*
  (some labs report in mg/L → normal is usually <3 mg/L)
- **ESR:**
- **Men ≥50 years:** 0–20 mm/hr
- **Women ≥50 years:** 0–30 mm/hr

Have a PMR diagnosis

Able to provide written consent

Exclusion:

History of concomitant Giant cell arteritis (GCA)

any other rheumatological disorders like lupus, arthritis (psoriatic, osteo), scleroderma, sjogrens

Active malignancy- presence of tumor by imaging or labs

Infection- infection can cause increased levels of innate immune cells making it difficult to differentiate between disease and infection

recent surgery- within the past 6 months

14.2 *Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the below populations as participants in your research unless you indicate this in your inclusion criteria.)*

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant persons*
- *Prisoners*

The above special populations will not be included in this research study.

15. SPECIAL POPULATIONS

15.1 *Will your research involve the following populations? (Check all that apply)*

☐ Children/minors

☐ Pregnant persons

☐ Fetuses

☐ Prisoners

☐ Participants with impaired decision-making capacity

☐ Non-English speaking

☐ Illiterate or low-literacy

☐ Visual or hearing impairments *(i.e., those whose impairment might impact the informed consent process)*

☐ Those with a status relationship with the PI, such as students or employees.

☒ None of the above

▶ *If any special population was chosen, complete HRP-504d - TEMPLATE - Protocol Supplement - Special Populations and upload to the eIRB section, "Local Site Documents," item 3.*

▶ *See DH "Surrogate Health Care Decision Making Policy: How to Identify a Health Care Agent under an Advance Directive or Other Surrogate for Patients Lacking Capacity; Understanding the Authority of an Agent or Other Surrogate Decision Maker Policy ID:16389" if including those with impaired decision-making capacity.*

▶ *Refer to HRP-013 - SOP - LARs, Children, and Guardians, found in the eIRB Library. Note that NH has particular restrictions on the use of LAR for clinical trials or experimental treatments. Specifically, the Durable Power of Attorney (DPOA) for Healthcare document must specifically permit clinical trial participation.*

16. NUMBER OF PARTICIPANTS

16.1 *Indicate the total number of participants accrued at DH sites, by location and name.*

According to a previous estimate, we treated 540 patients with PMR at the DHMC Rheumatology Clinic between 2019 and 2021. This pilot study will **prospectively enroll 50 PMR patients and 25 age matched healthy volunteers** (over 50 years of age, both male and female)

16.2 *If applicable, distinguish between the number of participants expected to be enrolled and screened and the number of participants needed to complete the research procedures (i.e., the number of participants excluding screen failures).*

The total number of participants needed is 75, 50 PMR diagnoses and 25 age matched healthy volunteers.

17. RECRUITMENT METHODS

▶ *DH researchers should use materials provided by DH ORO Marketing, found here - https://one.hitchcock.org/intranet/education-research/office-of-research-operations/recruitment_marketing_toolkit*

17.1 *Describe when, where, and how potential participants will be recruited. If applicable, describe procedures for oral or written communication with the prospective participant or legally authorized representative that will be done for purposes of screening, recruiting, or determining eligibility.*

Potential participants will be recruited from patients scheduled to be seen in the PMR clinic at the DH PMR clinic in 5C. Prior to clinic visits, the Clinical Research Coordinator (CRC) will review clinic schedules and the medical record, as permitted, to pre-screen for basic eligibility criteria. This review will be limited to the minimum information necessary to determine potential eligibility. Potentially eligible patients will be identified to their treating provider, who will briefly introduce the study during the clinical visit to assess interest and willingness to learn more. At this and all subsequent points of contact, it will be clearly stated that participation is completely

voluntary and will not affect the patient's clinical care, relationship with their providers, or access to services. If the patient expresses interest, the provider will inform the patient that a CRC will speak with them. The CRC will then meet with the patient in a private clinic setting to explain the study, answer questions, and confirm eligibility. The voluntary nature of participation will be emphasized, and patients will be informed they may decline or withdraw at any time without penalty. The informed consent process will be conducted orally by the CRC in a private setting. The CRC will review all required consent elements, allow time for questions, and confirm the participant's understanding and voluntary agreement before any study procedures are performed. Documentation of oral consent will be completed per IRB and institutional policy. All recruitment and screening interactions will occur in person in a private clinical space to protect confidentiality.

► *Potential participants identified through medical records or clinical settings should first be contacted by individuals known to them, e.g., their primary care providers. This also pertains to contacting potential participants through MyDH messaging.*

17.2 *Describe the source of the participants*

Rheumatology, 5C and the PMR clinic that happens once a week on Monday.

17.3 *Describe the methods that will be used to identify potential participants. If applicable, describe procedures for accessing records or stored identifiable biospecimens/other material for screening, recruiting, or determining eligibility.*

The research coordinator will screen Drs. Tiwari and Rigby schedule, in eDH, for patients who meet the study criteria for enrollment. Once a potential patient is identified to fitting the study enrollment criteria, the provider will help determine, during the visit, if the patient is a good candidate to enroll.

17.4 *Will you access the DH medical record to screen for potential participants?*

☒ Yes – see below

☐ No

► *If you will be accessing the DH medical record to screen for patients only and you will not be obtaining HIPAA Authorization to do so from each potential study participant (this is most likely the case), complete HRP-504a - TEMPLATE - Protocol Supplement – Waivers (Section 2, Recruitment) and upload to the eIRB section, "Local Site Documents," item 3.*

► *See the DH Research Informatics and Data Governance (RIDGe) website for more information on activities that require RIDGe review, including manual chart review.*

17.5 *If accessing the DH medical record, how will you do so? (Choose all that apply)*

☒ Manual chart review – see below.

☐ Use of the DH Analytics Institute

☐ Other – specify: *Click or tap here to enter text.*

► *Manual chart review done without the DH Analytics Institute must meet specific criteria. See the DH Research Informatics and Data Governance (RIDGe) website for more information*

17.6 *Who will access the DH medical record? List the person or persons who will conduct the manual chart review.*

Research Coordinator and the providers

► *Manual chart review must be conducted by a DH member of the study team, as identified in the eIRB and protocol, who already has access to eDH. See the DH Research Informatics and Data Governance (RIDGe) website for more information*

17.7 *How will you identify the right patients?*

The Clinical Research Coordinator (CRC) will conduct pre-screening of patients prior to PMR clinic visits to identify potentially eligible participants. A list of eligible patients, per the inclusion/exclusion criteria, will be provided to the clinical providers, who will confirm the eligibility during the visit. If determined eligible, the provider will introduce the study to these patients during their visit to assess interest and willingness to participate. If a patient expresses interest, the provider will briefly mention that the CRC will discuss the study in detail. The CRC will then meet with the patient to review the study, answer questions, and complete the informed consent process. For patients who consent to participate, the CRC will accompany them to complete the required blood collection per protocol.

17.8 *What data will be abstracted from the medical record?*

► *If the list is lengthy, consider using HRP-505 – TEMPLATE - DATA AND MATERIAL LISTING, found in the eIRB Library. If used, upload to the eIRB section 'Local Site Documents", item 3, and indicate below to reference this document.*

Age, sex, diagnosis, patient history, treatment, consultations, labs

► *HIPAA requires that only the minimum necessary PHI be used unless the PHI is used for treatment or unless the use or disclosure is made subject to a written authorization (including a research authorization). Thus, the minimum necessary standard requires researchers to limit their access to PHI to only what is needed to accomplish the research initiative and the intended purpose of the use and disclosure of PHI.*

17.9 *Will any biospecimens/other material be procured or received to determine eligibility?*

► *If the list is lengthy, consider using HRP-505 – TEMPLATE - DATA AND MATERIAL LISTING, found in the eIRB Library. If used, upload to the eIRB section 'Local Site Documents", item 3, and indicate below to reference this document.*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

17.10 *Will any tools be utilized for study recruitment, including those that use Artificial Intelligence (AI)?*

☐ Yes – go to next question.

☒ No

17.11 *Specify if you will use any tools for recruitment:*

☐ TriNetX: *A global health research network and real-world data platform that connects healthcare organizations, pharmaceutical companies, and researchers to facilitate clinical research and drug development, with particular focus on clinical trial accrual and opportunities.*

☐ Epic Cosmos*: Epic Systems' de-identified database that aggregates electronic health record data from Epic's network of healthcare organizations, has three access options: SlicerDicer, Data Scientist, and Data Architect.*

☐ Deep-6: *Deep-6 uses AI and Natural Language Processing (NLP) to provide patient matches for clinical trials*

☐ OMOP: *The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) transforms electronic health record data into a standardized format, enabling collaborative research across institutions.*

☐ EPIC Tools - specify: *Click or tap here to enter text.*

☐ MyDH portal messaging

☒ Other - specify: *recruitment of a participant would come day of when communication with the provider would take place via eDH messaging.*

► *Use of these tools may require RIDGe review. See the DH Research Informatics and Data Governance (RIDGe) website for more information*

17.12 *Will you use an outside firm to assist with recruitment?*

☐ Yes – specify: *Click or tap here to enter text.*

☒ No

► *This Institution prohibits payments to professionals in exchange for referrals of potential participants ("finder's fees") and payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")*

17.13 *Describe materials that will be used to recruit participants. (Attach copies of these documents in the eIRB section Local Site Documents, item 2.)*

No additional materials will be used to recruit participants

18. WITHDRAWAL OF PARTICIPANTS

18.1 *Describe anticipated circumstances under which participants will be withdrawn from the research without their consent.*

The PI does not anticipate any circumstances under which participants will be withdrawn from the research without their consent.

18.2 *Describe any procedures for orderly termination.*

No procedures are in place.

18.3 *Describe procedures that will be followed when participants withdraw from the research, including partial withdrawal from procedures with continued data collection. Include the type and timing of the data to be collected for withdrawn/discontinued participants, including the process by which the data are handled, in accordance with applicable regulatory requirements*

The PI does not anticipate any circumstances where a participant may wish to withdraw since this study only requires a very short term in-person participation. However, if after data collection a participant contacts the PI wishing to not be included in any data analysis/publication, their data will be withdrawn from analysis. As soon as a participant informs the PI they wish to withdraw, a notation will be made in the compliance binder, and their data will not be analyzed upon data analysis.

18.4 *Indicate whether and how participants will be replaced.*

Continue recruitment

18.5 *Describe how you will follow up with participants who have discontinued the use of the investigational product, if applicable.*

This study will not use an investigational product

19. RISKS TO PARTICIPANTS

19.1 *Identify the reasonably foreseeable risks, discomforts, hazards, or inconveniences associated with the participant's participation in the research. Include, as useful for the IRB's consideration, a description of the risks' probability, magnitude, duration, and reversibility. Consider physical, psychological, social, legal, and economic risks.*

Blood sample collection: Potential bruise (a black and blue mark) or pain where the blood sample is taken. There is also a small risk of infection, lightheadedness, and/or fainting.

Risk of Loss of Privacy: All effort will be made to protect participants' personal data and information that is collected, shared and used for the purposes of this study. The risk of accidental disclosure is very low. Information will be provided to the participant outlining what information is being collected, and under what conditions the information will be shared or used. The results of this study may be published.

Publications will not use name or identify the participants personally. These will relate to the results of the whole study and not any individual subject.
19.2 ***If this study involves an investigational drug***, *list any risks of particular severity or seriousness anticipated based on the toxicological data in animals or prior human studies with the investigational drug (or related drugs of the same chemical class).*
This study will not use an investigational product
19.3 *If applicable, indicate which procedures may have risks to the participants that are currently unforeseeable.*
Not applicable. There are no unforeseeable risks.
19.4 *If applicable, indicate which procedures may have risks to an embryo or fetus should the participant be or become pregnant.*
There is no risk to an embryo or fetus.
19.5 *If applicable, describe risks to others who are not participants.*
There are no risks to others who are not participants.
20. POTENTIAL BENEFIT TO PARTICIPANTS AND OTHERS
20.1 *Describe the potential benefits individual participants may experience from the research. Include, as may be helpful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits. Please see the next question if there is no anticipated direct benefit to the participant.*
There are no benefits from taking part in this research. No benefits to others from taking part in this research can be guaranteed.
20.2 *Indicate if there is no direct benefit. Do not include benefits to society or others.*
There is no direct benefit
20.3 *Describe the anticipated benefit(s) to society and others expected from this research.*

Anticipated benefits include new knowledge on how to identify patterns that could help doctors predict which patients are responding well to steroids and who might be at higher risk of relapse.

21. DATA MANAGEMENT AND CONFIDENTIALITY

▶ *Refer to the DH Data Classification Policy (Policy ID 10084) for classifying and controlling DH Enterprise Data.*

21.1 *Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.*

Specimens will be picked up by the research coordinator who is part of the Dr. Skopelja-Gardner lab from the phlebotomy lab, 3L, and transported directly to the Skopelja-Gardner lab. The sample will be labeled with a study ID. The coordinator has completed all necessary CITI trainings along with training of the protocol.

21.2 *Describe any procedures used for quality control of collected data.*

Data quality will be ensured through standardized data collection procedures, routine review for accuracy and completeness, and secure, access-restricted data storage.

21.3 *Select the identifiability of the data and/or biospecimens/other material when first collected:*

☐ **Anonymous** (identifiers were never collected)
☒ **De-identified** (identifiers may have been collected but have been stripped/removed/destroyed before receipt)
☐ **Coded** (identifying information has been linked to a code, and there is a key that connects the code to the individual)
☐ **Identifiable** (contains direct identifiers)

21.4 *Identify who holds/has access to the key to the code:*

The study coordinator has access

21.5 *Select the identifiability of the data and/or biospecimens/other material when stored:*

☐ **Anonymous** (identifiers were never collected)
☒ **De-identified** (identifiers may have been collected but have been stripped/removed/destroyed before receipt)
☐ **Coded** (identifying information has been linked to a code, and there is a key that connects the code to the individual)
☐ **Identifiable** (contains direct identifiers)

▶ *DH offers a de-identification service for all images; see - Imaging De-ID Request Form*

21.6 *Describe the procedures for maintaining confidentiality.*

Participant confidentiality will be maintained by limiting access to study data to authorized personnel and storing all data in secure, password-protected systems. Identifiable information will be separated from study data whenever possible and handled in accordance with institutional policies.

21.7 *Where and how will data or biospecimens/other material be stored?*

Biospecimens will be de-identified using a unique study ID. The study coordinator will maintain the key in a secure location. Samples will be stored in −80°C freezers with access limited to authorized laboratory personnel. Physical study documents, including informed consent forms, will be maintained by the study coordinator in a locked office.

► *See the DH Research Informatics and Data Governance (RIDGe) website for more information on permitted places to store DH data.*

21.8 *How long will the data or biospecimens/other material be stored?*

Data and biospecimens will be stored for 3 years after publication.

► *See DH policies "Record Retention Policy – Sponsored Program Uniform Guidance (#12759)" and "Health Record Retention Policy (#20413)" for information that might apply to your research study.*

21.9 *Will data or biospecimens/other material be transferred to another site from your site?*

☐ Yes – specify where: Click or tap here to enter text.
☒ No

► *Note that another 'site' might be a performance site, sponsor, CRO, or other collaborator in this study.*

► *Data transfer will most likely require a data use agreement. Biospecimen/other material transfer will most likely require a material transfer agreement. For assistance, contact the DH Clinical Trials Office. The DUA and/or MTA may be included in the agreement or sub-award if the 'other site' is a collaborator or sponsor.*

21.10 *Specify the direction of transfer.*

☐ Data/biospecimen/other material will transfer to the other site only.

☐ Data/biospecimen/other material will transfer from the other site only.

☐ Data/biospecimen/other material will transfer to and from the other site.

☒ No data/biospecimen/other material transfer

21.11 *Will any data be submitted to a national repository (e.g., dbGaP, GEO, other)?*

☐ Yes – specify where: Click or tap here to enter text.

☒ No

► *Submission of data to a national repository may require institutional certification and specific language in the study's informed consent form.*

21.12 *Who is responsible for collecting or transmitting the data or biospecimens/other material?*

The study coordinator

21.13 *How will data and biospecimens/other material be transported?*

Biospecimens will be transported using institution-approved procedures in secure, labeled containers and will be identified only by study ID. Electronic data will be transferred through secure, password-protected, institution-approved systems accessible only to authorized study personnel

21.14 *Who will have access to the data or biospecimens/other material for DH sites?*

☒ DH affiliate (Paymaster from DHMC (MHMH) or DH Clinics)
☐ Other DH affiliates (DH Hospitals other than DHMC or DH Clinics)
☐ Dartmouth College affiliate
☐ Researchers from other institutions. List name/affiliation: Click or tap here to enter text.
☐ Not applicable, not a DH site.

22. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

► *This section is required when research involves more than Minimal Risk to participants.*

► *Minimal risk is defined as a risk where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Minimal risk research is typically reviewed as the Exempt review level (see HRP-312 - WORKSHEET - Exemption Determination) or the Expedited review level (see HRP-313 - WORKSHEET - Expedited Review).*

► ***IMPORTANT!*** *If this study is being conducted under an IND or IDE, it is the responsibility of the Sponsor (entity/person responsible for the initiation and management of the clinical trial, i.e., IND/IDE holder) to report certain adverse events or unanticipated problems to the FDA.*

- *The Sponsor is required to report qualifying adverse events as an IND Safety Report or IDE Unexpected Adverse Device Effect (UADE) Report.*
- *Reporting Process: Adverse events may be submitted on FDA Form 3500A or in a narrative format and attached to the Safety Report with a Cover Letter. IND/IDE Safety Reports will be compiled and submitted to FDA on the Sponsor's behalf. Contact the RQS Research Regulatory Affairs Specialist as soon as possible if a safety event occurs.*

22.1 *Describe the plan to periodically evaluate the data collected regarding harms and benefits to determine whether participants remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.*

Research personnel will meet periodically, over the course of the study, to go over study status, findings, and next steps.
22.2 *What data are reviewed, including safety data, untoward events, and efficacy data?*
This study is an investigator-initiated study.
22.3 *How will the safety information be collected (e.g., with case report forms, at study visits, by telephone calls with participants)?*
At study visits
22.4 *The frequency of data collection, including when safety data collection starts.*
Safety data collection starts at time of consenting. Data will be collected at pre-defined time points, at enrollment, at 5 mg of prednisone or prednisone equivalent dosing, or at time of relapse or successful discontinuation of prednisone.
22.5 *Who will review the data?*
The PI and study coordinator will review the data
22.6 *The frequency or periodicity of review of cumulative data.*
Quarterly
22.7 *Describe the procedures for obtaining reports of and for recording and reporting adverse events.*
Adverse events (AEs) will be collected through participant report, study visits, and clinical/laboratory assessments, and documented with severity and relatedness. Serious adverse events (SAEs) will be reported to the IRB per regulatory requirements. All events will be recorded in the study database and followed until resolution or stabilization.
22.8 *The statistical tests used for analyzing the safety data to determine whether harm is occurring.*
There are no tests used for analyzing the safety data to determine whether harm is occurring
22.9 *Any conditions that trigger an immediate suspension of the research*.
There are no conditions that would trigger an immediate suspension of the research
22.10 *Describe the type and duration of the follow-up of participants after adverse events and other events such as pregnancies.*

Participants with adverse events will be followed through clinic visits, phone contact, or medical record review until resolution or stabilization. Serious adverse events and other reportable events, including pregnancy, will be followed to outcome and documented per IRB and regulatory requirements.

23. STATISTICAL ANALYSES

23.1 *Describe the statistical methods to be employed, including timing and purpose of any planned interim analysis(ses), and the statistical criteria for the stopping of the study.*

Aim 1a: For comparison with healthy individuals, we will leverage age- and sex-matched control participants who will provide a single baseline blood sample. Immune profiles from these controls will be compared cross-sectionally to baseline samples from PMR patients using linear regression adjusted for age and sex. This will help us identify disease-specific immune alterations independent of steroid tapering.

Aim 1b: We will use linear mixed-effects models to assess longitudinal changes in immune cell composition over time in PMR patients during steroid tapering. These models will include timepoint, steroid dose, and clinical outcome (relapse vs. sustained response) as fixed effects, with random intercepts for each subject to account for repeated measures. The key impact of interest will be the interaction between time and clinical outcome, which will indicate whether immune cell trajectories—such as increases in CD4 memory T cells or decreases in T regulatory cells (Tregs)—differ between patients who relapse and those who remain in remission. We will also use logistic regression to evaluate whether early shifts in immune cell composition (e.g., between 10 mg and 5 mg prednisone) are predictive of subsequent relapse. Additionally, time-to-event models can be used to examine the associations between immune features and the time to relapse. All analyses will follow a pre-specified statistical plan aligned with our hypotheses.

Aim 2: To evaluate the relationship between epigenetic steroid response markers (GCMI and NDMI) and clinical outcomes, we will use longitudinal mixed-effects models to assess within-subject changes in GCMI and NDMI values over time across different stages of steroid tapering. These models will account for repeated measures and varying follow-up durations across individuals. We will include fixed effects for time point, clinical status (responders vs. relapsers), and relevant covariates, such as age, sex, and baseline inflammatory markers, with a random intercept for each subject. To determine whether GCMI or NDMI at specific time points predicts future relapse, we will use logistic regression, modeling relapse (yes/no) as the dependent variable and GCMI or NDMI values at prior time points as predictors. We will also perform receiver operating characteristic (ROC) curve analysis to evaluate the sensitivity and specificity of GCMI and NDMI thresholds in identifying patients at risk for relapse. All analyses will be conducted using standard statistical software such as R or Stata, with significance set at $p < 0.05$.

23.2 *Provide a brief sample size calculation or description of sample size calculation. Include methods and assumptions such as loss to follow-up, anticipated evaluability rate, power, and clinical justification, as appropriate.*

This pilot study will **prospectively enroll 50 PMR patients** (over 50 years of age, both male and female) with well-controlled disease (absence of pain and stiffness in

the shoulders, hips, or both, with normal ESR and CRP (inflammation markers) characterized by

- ***CRP:*** *<1.0 mg/dL*
  (some labs report in mg/L → normal is usually <3 mg/L)
- **ESR:**
- **Men ≥50 years:** 0–20 mm/hr
- **Women ≥50 years:** 0–30 mm/hr

which would indicate presence of inflammation or not

on a stable dose of 10 mg or higher prednisone or its equivalent for at least two weeks. Additionally, **25 age matched healthy volunteers will be recruited for a one-time study visit to collect blood**. The target number of patients can be achieved within the Hitchcock Foundation's timeline, as we see an average of 15-20 patients with PMR per week. Notably, we successfully recruited the majority of the patients with PMR in our pilot study within the first three months.

24. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

24.1 *Describe the measures that will be implemented to safeguard the privacy interests of participants. "Privacy interest" refers to an individual's desire to control with whom they engage and the personal information they share.*

Participants' privacy interests will be safeguarded by limiting access to identifiable information and controlling when and how personal information is collected and shared. Only authorized study personnel will interact with participants and collect data necessary to conduct the study. Identifiable information will be collected only when required and will not be shared outside the research team. Study procedures will be conducted in a manner that minimizes inadvertent disclosure of participation or personal information, and participants may decline to answer any questions they are not comfortable with.

24.2 *Describe what steps you will take to make the participants feel at ease with the research situation regarding the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort but the sense of intrusiveness a participant might experience in response to questions, examinations, and procedures.*

Participants will be informed in advance about the nature of the questions and study procedures during the consent process, including what information will be requested and why it is necessary. Study staff will emphasize that participation is voluntary and that participants may skip any questions or withdraw at any time without penalty. Questions will be limited to those essential to the research aims and asked in a respectful, nonjudgmental manner. Study procedures will be conducted by trained research personnel who will allow time for questions and address any concerns to help participants feel comfortable and respected throughout the research process.

24.3 *Indicate how the research team is permitted to access any sources of information about the participants. This refers to whether the study team has the necessary level of permission to access sensitive data, such as information from medical records.*

Recruitment will occur through a limited review of provider clinic schedules and associated medical records to identify potentially eligible participants. This pre-screening activity will be conducted by authorized study personnel and is permitted under the institution's RIDGe agreement. Only the minimum necessary information will be accessed to assess eligibility. No contact with potential participants will occur, and no identifiable information will be recorded or retained for research purposes until informed consent (and HIPAA authorization, if applicable) has been obtained. Access to medical records will be limited to study personnel listed on the IRB protocol and conducted in accordance with institutional policies and applicable regulations.

25. PUBLICATION

25.1 *The publication and authorship policies should be described in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. Please refer to your specific contract, grant, and/or Clinical Trials Agreements. If details of the publication policy are described in the study's MOP, refer to it here. If not applicable to this study, state "N/A"*

The PI, Vivekanand Tiwari, will be the first author with co-authors coming from the hospital and college. These individuals are, Dr. William Rigby and Sladjana Skopelja-Gardner, PhD.

26. COMPENSATION FOR RESEARCH-RELATED INJURY

26.1 *If the research poses more than minimal risk to participants, please choose the available compensation for a research-related injury.*

► *Refer to the DH IRB informed consent form template (HRP-502 – TEMPLATE CONSENT DOCUMENT or the HRP-820 - FORM - DH Institutional Requirements and Local Context Concerns for the text of each option.*

☒ Standard Statement

☐ Alternate Statement #1 – Use if Sponsor requests MMSEA 111 Language

☐ Alternate Statement #2 – Use for studies of COVID-19 countermeasures that are covered by the PREP Act Declaration

☐ Alternate Statement #3 – Use for studies where the Sponsor chooses to remain silent, and/or the Sponsor is the NIH

27. ECONOMIC BURDEN TO PARTICIPANTS

27.1 *Describe any costs participants may be responsible for because of participation in the research, e.g., fuel, parking, and childcare.*

No additional costs will be incurred by participants, as all research visits and procedures will coincide with standard-of-care clinical visits.

28. COMPENSATION

28.1 *Describe the payment method (e.g., cash, check, gift cards) and include how much money will be provided, for what activities, and when (timing) compensation will be provided. If no compensation will be provided, state that here in this section and skip to the next section.*

No compensation will be provided

28.2 *If special populations are involved, explain the following (if applicable): For pediatric participants, please specify who will be paid (the minor or their parent/guardian). For incapacitated adults,* indicate whether payment will be made to the participant or the *LAR.*

No compensation will be provided

28.3 *Describe how compensation will be prorated if there are multiple research activities or a participant withdraws from the study before finishing.*

No compensation will be provided

28.4 *Describe any reimbursement that might be provided (e.g., travel expenses such as hotel or mileage), as applicable, and the process for reimbursement (e.g., collection of receipt).*

No compensation will be provided

29. CONSENT PROCESS

▶ *Refer to DH policy "Informed Consent Process for Research Studies Policy—Research Operations" (28975) regarding who may provide consent and other important information.*

▶ *Refer to HRP-090 - SOP - Informed Consent Process for Research, found in the eIRB Library.*

29.1 *Will you obtain consent from participants to participate in this study?*

☒ Yes – *Continue*

☐ No - *Complete HRP-504a - TEMPLATE - Protocol Supplement – Waivers (Section 1). Upload this form to the eIRB section, "Local Site Documents," item 3.*

29.2 *Where does the consent process take place?*

During the PMR clinic in the exam room(s)

29.3 *Is there a waiting period between informing the prospective participant and obtaining their consent? Describe.*

All discussion around the study will happen at the same time

29.4 *Is there a process in place to ensure ongoing consent? Describe.*

Yes. Ongoing consent will be maintained by reminding participants throughout the study that participation is voluntary and that they may withdraw at any time without penalty.

29.5 *Explain how you will ensure that enough time is devoted to the consent process. (e.g., not seeking consent right before surgery, or taking more time to explain complex concepts with those who have a low reading ability)*

Sufficient time will be devoted to the consent process by conducting consent discussions in a non-rushed setting and allowing participants adequate time to review the consent form, ask questions, and consider participation. Study staff will tailor explanations to the participant's level of understanding and provide additional time as needed to ensure comprehension before consent is obtained.

29.6 *Steps taken to minimize the possibility of coercion or undue influence.*

To minimize the possibility of coercion or undue influence, participants will be informed that participation is entirely voluntary and that their decision will not affect their medical care or relationship with their provider. Consent will be obtained by trained study personnel, and participants will be given adequate time to decide whether to participate without pressure.

29.7 *Steps taken to ensure the participant's understanding.*

Participants' understanding will be ensured by clearly explaining study procedures, risks, and benefits in plain language, encouraging questions, and confirming comprehension before obtaining consent. Additional time and explanations will be provided as needed.

► *Refer to DH Policy "Documenting Decision-Making Capacity, Health Care Agents, Surrogate Decision Makers, and Advance Care Planning in eD-H v.1" (16391)*

► *Refer to HRP-090 - SOP - Informed Consent Process for Research, found in the eIRB Library.*

29.8 *If the study is accessing DH HIPAA PHI, indicate whether you will obtain HIPAA Authorization.*

☒ Yes

☐ No – *See below.*

► *If you will not obtain HIPAA Authorization, complete HRP-504a - TEMPLATE - Protocol Supplement – Waivers (Section 2). Upload this form to the eIRB section, "Local Site Documents," item 3.*

30. HUMANITARIAN USE DEVICE (HUD)

30.1 *For HUD uses, describe how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use*.

HUD will not be used in this study

31. PROCESS TO DOCUMENT CONSENT IN WRITING

31.1 *Indicate whether you will follow HRP-091 - SOP - Written Documentation of Consent. If not, describe whether and how the participant's consent will be documented in writing.*

☒ Yes
☐ No – *See below.*

▶ *If you will not obtain consent documentation, complete HRP-504a - TEMPLATE - Protocol Supplement – Waivers (Section 1). Upload this form to the eIRB section, "Local Site Documents," item 3.*
▶ *Refer to HRP-091 - SOP - Written Documentation of Consent, found in the eIRB Library.*

32. SETTING

32.1 *Identify where the DH study team will perform research procedures.*

☒ Dartmouth Hitchcock Medical Center	☐ Merrimack Clinic
☐ Dartmouth Cancer Center	☐ Milford Clinic
☐ Lebanon Clinic	☐ South Vermont Clinic
☐ Heater Road Clinic	☐ Bennington Clinic
☐ Lyme Clinic	☐ Manchester Center Clinic
☐ Outpatient Surgery Clinic	☐ Wilmington, VT Clinic
☐ Bedford Clinic	☐ Keene Clinic
☐ Concord Clinic	☐ St. Johnsbury (DCC North) Clinic
☐ Manchester Clinic	☐ Other location(s), Specify: *Click or tap here to enter text.*
☐ Nashua Clinic	
☐ Hudson Clinic	

32.2 *Describe the composition and involvement of any community advisory board, if applicable.*

Not applicable

32.3 *For research conducted outside of the organization and its affiliates, describe:*
- *Site-specific regulations or customs that affect research conducted outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Research will be conducted inside of DH

33. RESOURCES AVAILABLE

33.1 *Justify the feasibility of recruiting the required number of suitable participants within the agreed recruitment period. For example, how many potential participants do you have access to? What percentage of those potential participants do you need to recruit?*
According to a previous estimate, we treated 540 patients with PMR at the DHMC Rheumatology Clinic between 2019 and 2021. This pilot study will prospectively enroll 50 PMR patients (over 50 years of age, both male and female) with well-controlled disease (absence of pain and stiffness in the shoulders, hips, or both, with normal ESR and CRP) on a stable dose of 10 mg or higher prednisone or its equivalent for at least two weeks. Additionally, 25 age matched healthy volunteers will be recruited for a one-time study visit for a blood draw. The target number of patients can be achieved within the Hitchcock Foundation's timeline, as we see an average of 15-20 patients with PMR per week. Notably, we successfully recruited the majority of the patients with PMR in our pilot study within the first three months.
33.2 *Describe how your facilities can accommodate this research (e.g., do you have the proper space, equipment, and other essential items).*
Dr. Skopelja-Gardner's laboratory space (650 sq feet) is located on the 6th floor of the Borwell Research Building at the Dartmouth Hitchcock Medical Center, within the Department of Microbiology and Immunology at the DartmouthMedical School. Additional shared space on the floor houses several freezers (1 x -20C, 2 x -80C) and 100sqft cold room. The lab is fully equipped with standard items including balances, three large centrifuges, four small benchtop centrifuges, one 6ft and one 3ft cell culture cabinet, water baths, additional freezer (-20C) and fridges (3), 2 C02 incubators, gel systems equipment. Lab office space is next to the laboratory, allowing for efficiency. The PI's laboratory has all the resources and equipment to perform the proposed studies, as well as access for free to Immunology and Microbiology equipment on the 6th floor of Borwell. These include: 2 bacterial and 3 CO2incubators, a bacterial shaker, bacterial and TC centrifuges and microfuges (Beckman Coulter), an inverted microscope, a Nanodrop spectrophotometer (ThermoFischer), cryopro storage unit and MilliQ water, a cold room, dark room, ice machine, qPCR instrument (Bio-Rad), high speed centrifuge (Sorvall RC2B), fluorescence plate reader (BioTek Synergy), ELISA reader (Epoch, BioTek), electrophoresis instruments (Bio-Rad), gel and Western blot imager, chemiluminescence imager (Syngene G-Box system), Tyler Research UV-2 irradiation and dosimetry system.
33.3 *Describe the availability of medical or psychological resources that participants might need due to an anticipated consequence of human research (e.g., looking at the risks/harms that might occur for this research, are resources available should a risk/harm arise).*
None anticipated

33.4 *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

All study personnel will receive training on the study protocol, procedures, and their specific roles before participating. This includes reviewing the consent process, data collection methods, and participant safety measures. Ongoing oversight, regular team meetings, and documentation of training will ensure that all personnel remain informed and adhere to the protocol throughout the study.

34. MULTI-SITE AND COLLABORATIVE RESEARCH

34.1 *Will this study involve multi-site or collaborative research?*

☐ Yes – *See below and continue to 34.2*
☒ No

► *The term "multi-site project" is used to describe a subset of cooperative non-exempt human research where the same research procedures (i.e., the "same protocol") are conducted at two or more U.S. research sites under the control of a participating investigator at each site.*

A multi-site project typically involves a lead site (lead PI) that manages the administrative functions of the project in addition to conducting the same research procedures as the participating sites. A multi-site project could be a clinical trial, an observational study, or a basic clinical research study.

► *A "cooperative" (or "collaborative") project involves two or more U.S. research sites where each site is conducting a different part of a research protocol under the direction/control of the lead PI. An example would be a non-exempt study where DH is the lead site and conducts the interaction or intervention with human participants, but an external institution or collaborator performs the data analysis. A collaborative project may take place at a single site or multiple sites. The key takeaway is that a collaborative project involves individuals from more than one institution.*

► *Under NIH and Common Rule sIRB guidelines, both multi-site and cooperative research projects may: 1) require the use of a single IRB for oversight, 2) have a lead site/PI who receives the grant or contract from a sponsor and then establishes a subaward or subcontract to each participating site, 3) require authorization ("reliance") agreements to establish the contractual terms for IRB oversight and project management.*

► *If this study involves multiple sites (i.e., non-DH institutions; whether multi-site or collaborative), and if the DH IRB will act as the Reviewing IRB for those sites, and activities occur at those sites, the creation of a "pSite" will be required if the study has been determined to be non-exempt by the DH IRB office. For a consultation on including non-DH individuals in your research, email IRB@Hitchcock.org with the subject line "Reliance Consultation Service". A DH IRB Reliance Team member will be in touch once the information is received. Do not assume that the DH IRB will serve as the Reviewing IRB for non-DH affiliates.*

34.2 *Select all that apply:*

☐ DH is an enrolling site
☐ DH PI serves as the lead PI
☐ DH will serve as the coordinating center

☐ DH will serve as the data coordinating center

34.3 *Will those from other institutions work at DH on this study only (e.g., **no activity taking place at their home institution**)?*

☐ Yes – see next question.
☒ No – go to 34.5

34.4 *List the other institutions that will be working **at** DH on this study. Then refer to the text box below.*

Not applicable

► *If study activities will only be taking place at DH, complete the HRP-220 - FORM - Non-DH Study Staff Form by listing those from the other institutions, and upload to the eIRB Section, Local Study Team Members, item 2.* ***YOU DO NOT NEED TO COMPLETE THE REST OF THIS SECTION IF NO ACTIVITY WILL BE TAKING PLACE AT THE OTHER SITES.***

34.5 *List the other sites that are involved in this research.*

Not applicable

► **If the DH site is the lead site and requesting that the DH IRB provide IRB review for the other sites, complete the items below.**

► *For each site, a pSite should be created in the eIRB submission if the site activities involve any of the below activities. See HRP-103 – INVESTIGATOR MANUAL for instructions on creating a pSite.*

34.6 *What activities are taking place at the other sites? Check all that apply for each site. If there are more sites, copy and paste for each new site.*

Site 1: Dartmouth Hitchcock Medical Center

☒ Consenting study participants
☒ Intervening/Interacting with study participants
☒ Collecting, obtaining, and/or analyzing identifiable data
☐ Other, specify:

Site 2: <Insert name of site>

☐ Consenting study participants
☐ Intervening/Interacting with study participants
☐ Collecting, obtaining, and/or analyzing identifiable data
☐ Other, specify:

Site 3: <Insert name of site>

☐ Consenting study participants
☐ Intervening/Interacting with study participants
☐ Collecting, obtaining, and/or analyzing identifiable data

☐ Other, specify:

34.7 *Outline the steps to ensure that collaborating sites obtain IRB approval documents promptly, including the protocol, informed consent forms, and approved study modifications.*

► *DH IRB approval must be secured before distributing study documents to study sites.*

There are no collaborating sites for this study.

34.8 *Describe the data management systems that ensure the integrity of the data while protecting the privacy and confidentiality of personal information.*

Study data will be stored in secure, password-protected electronic systems accessible only to authorized study personnel. Identifiable information will be coded, and the key linking codes to participants will be kept separately by the study coordinator. Data entry will include quality checks to ensure accuracy and completeness, and all electronic systems comply with institutional security policies and HIPAA regulations to protect privacy and confidentiality.

34.9 *Explain the secure process for transmitting and storing data to the coordinating center/other sites.*

Data will be stored at only one center, Dartmouth Health.

34.10 *Will the data sent to the coordinating center or among sites include any personally identifiable information?*

☐ Yes
☒ No
☐ Not applicable

34.11 *If "Yes," explain the methods to reduce the risk of disclosing personally identifiable information and safeguarding participants' confidentiality.*

Research is happening at one institution

34.12 *Will personally identifiable information be shared with any central laboratory or investigator for central review?*

☐ Yes
☒ No

☐ Not applicable

34.13 *If "Yes," please justify and confirm that the consent document informs the participant about this disclosure.*

Not applicable

34.14 *What provisions are in place for managing interim results? Explain how often the data will be analyzed and how frequently these results will be reported to the DH IRB. Describe the process for ensuring adherence to stopping rules (including participant-specific rules) that significantly affect the rights or welfare of research participants.*

Interim data will be reviewed quarterly by the study team to monitor safety, efficacy, and participant welfare.

34.15 *How will adverse events and unforeseen issues related to risks for participants or others be reported, reviewed, and managed? Please provide details on the processes for the prompt review of reports, the individuals responsible for notifying regulatory authorities, and the methods for distributing information to study sites.*

Any adverse events or unforeseen issues related to participant risks will be promptly documented and reported to the study team. Study personnel will immediately notify the principal investigator (PI), who is responsible for assessing the event and determining whether it meets criteria for reporting to regulatory authorities, including the IRB. Serious or unexpected events will be reported according to institutional and regulatory timelines. The PI will also ensure that relevant information is communicated to all study sites and staff through secure channels, such as email or the study's electronic reporting system, along with guidance on any necessary actions to protect participants. All reports and reviews will be maintained in the study records.

35. ANCILLARY REVIEWS / APPROVALS

► *The Principal Investigator is responsible for ensuring all institutional requirements and aspects of local context are covered. For research at DH, refer to HRP-309 - WORKSHEET - Ancillary Review Matrix, found in the eIRB Library.*

[i] The following activities conducted or supported by the Department of Defense (DOD) are NOT research involving human subjects: Activities carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease

in Service members and other mission essential personnel under force health protection programs of the Department of Defense, including health surveillance pursuant to section 1074f of Reference (g) and the use of medical products consistent with DoD Instruction 6200.02. Authorized health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment. Activities performed for the sole purpose of medical quality assurance consistent with 10 USC 1102 and DoDD 6025.13. Activities performed solely for an OT&E project where the activities and project meet the definition of OT&E as defined in 10 USC 139(a)(2)(A). Activities performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units, including such activities as occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information. Activities, including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of Government officials responsible for the operation or oversight of the program being evaluated and are not intended for generalized use beyond such program. Survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by DoDD 5240.01.