C O N F I D E N T I A L

Autoimmunity Centers of Excellence

Protocol ARA08

Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA)

Non-IND

Version 3.0: 01MAY2020

Sponsor: Division of Allergy, Immunology, and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)

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Protocol Number: ARA08	**Version Number/Date: v3.0 01MAY2020**
Protocol Title: Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA)	
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PROTOCOL SYNOPSIS

Title of the Protocol: Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA)

ACE Protocol Number: ARA08

Protocol Chair(s): Dr. Kevin Deane, MD, PhD

Sponsor: DAIT/NIAID/NIH

Objectives:
The primary objective is to determine the efficacy of a 12-month course of hydroxychloroquine (HCQ) to prevent the development of clinically-apparent rheumatoid arthritis (RA) (as defined in Section 2.1, *Primary Objective)* at 36 months in subjects at high-risk for future RA due to high titer elevations of anti-cyclic citrullinated peptide-3 (anti-CCP3) (≥ 40 units) but who are without a history or clinical findings of inflammatory arthritis (IA) at Baseline.

Secondary objectives include:

1. To evaluate the safety of a 12-month course of HCQ in subjects who are at high-risk for development of RA.
2. To evaluate the impact of HCQ on development of clinically-apparent RA (as defined in Section 2.1, *Primary Objective*) in high-risk subjects 12 months after initiation of study treatment.
3. To evaluate the impact of HCQ on development of IA that may or may not meet criteria for RA in high-risk subjects 12 months after initiation of study treatment.
4. To evaluate the impact of a 12-month course of HCQ on the timing of development of clinically-apparent RA over the entire study period.
5. To evaluate the impact of a 12-month course of HCQ on the timing of development of IA, that may or may not meet criteria for RA, over the entire study period.
6. To explore the relationship between baseline and evolving symptoms[1], risk factors[2] and the development of future clinically-apparent RA and response to HCQ.
7. To evaluate the relationship between treatment with HCQ and amelioration of symptoms[1] of RA, and potential delay in onset of symptoms.
8. To explore underlying immune responses over time in the early natural history of RA development and in response to HCQ therapy through measurement of a variety of biomarkers.

Study Arms:

- Hydroxychloroquine: These subjects will receive 200 - 400 mg of HCQ (1-2 pills), based upon ideal body weight (IBW) at Screening, daily for 12 months.
- Placebo: These subjects will receive 1-2 pills of placebo (based upon IBW at Screening) daily for 12 months.

Study Design: This is a phase 2 multi-center, randomized, placebo-controlled, double-blind, parallel group 36-month clinical trial to evaluate the effectiveness and safety of intervention with a 12-month course of HCQ to prevent the future onset of clinically-apparent RA (See definition in Section 2.1, *Primary Objective*). At screening, study subjects will be without IA, but will be at high-risk for developing future RA within the trial period as indicated by elevated anti-CCP3 antibodies that are ≥40 units (that is a level ≥2 times the normal cut-off of ≥20 units). Two-hundred eligible subjects will be randomized in a 1:1 ratio to receive either self-administered HCQ or placebo.

Subjects will provide informed consent prior to any Pre-Screening or screening procedures. Subjects who are

[1] Baseline RA symptoms include self-reported joint pain, stiffness, and swelling, and overall fatigue.
[2] Risk factors include but are not limited to age, sex, genetic factors, socio-economic status, education, tobacco exposure, medications and medical hormone use, and dietary factors.

Title of the Protocol: Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA)

found to be eligible after the screening evaluation will return for a Baseline/Randomization visit within 30 days of the initial screening visit. Subject eligibility will be confirmed prior to randomization. Eligible subjects will be randomized to receive either 200 - 400 mg (1-2 pills) of HCQ or 1-2 pills of placebo daily for 12 months based upon IBW at Screening. The weight-based dosing regimen for the study is outlined in Section 5.2, *Dosage Regimen*. Subjects will return to the study site for planned evaluations at Week 6, 12, 24, 36, and 52 (End of Treatment), and Months 18, 24, 30, and 36 (End of Study). During these study visits, subjects will have a joint exam and a physical examination. Study personnel will record the subject's interval medical history, assess adverse events, and collect samples for safety and mechanistic assessments (see Tables 6.1 & 6.2, *Schedule of Events*). Information on demographics (including socio-economic status and education), and other factors that may influence autoimmunity (e.g. tobacco exposure, hormonal status and exposures) may also be collected.

Site coordinators will call subjects at Week 18, 30, and 42 and at Month 15, 21, 27, and 33 to answer subject questions, update contact information, and to assess AEs/reactions, study drug dosing and pregnancy status (during the treatment period), and joint symptoms. If a subject indicates that he/she is experiencing joint symptoms suggestive of RA (that include new or worsening joint pain, stiffness or swelling since the prior study visit), or symptoms suggestive of an AE, the subject will be asked to return to the study site as soon as possible.

Visits and assessments for subjects who develop RA, IA with erosions, or who become pregnant prior to the Month 36 visits will be different from subjects who never develop RA. Details of these assessments may be found in protocol sections 6.5.9, *Evaluations Triggered by a Swollen Joint,* 6.5.10, *Procedures for Subjects Diagnosed with Inflammatory Arthritis or Rheumatoid Arthritis by an Outside Physician,* and 6.5.11, *Special Considerations for Pregnant Subjects*.

Endpoints:

The primary efficacy endpoint is the development of clinically-apparent RA by 36 months, where clinically-apparent RA is defined in Section 2.1, *Primary Objective*.

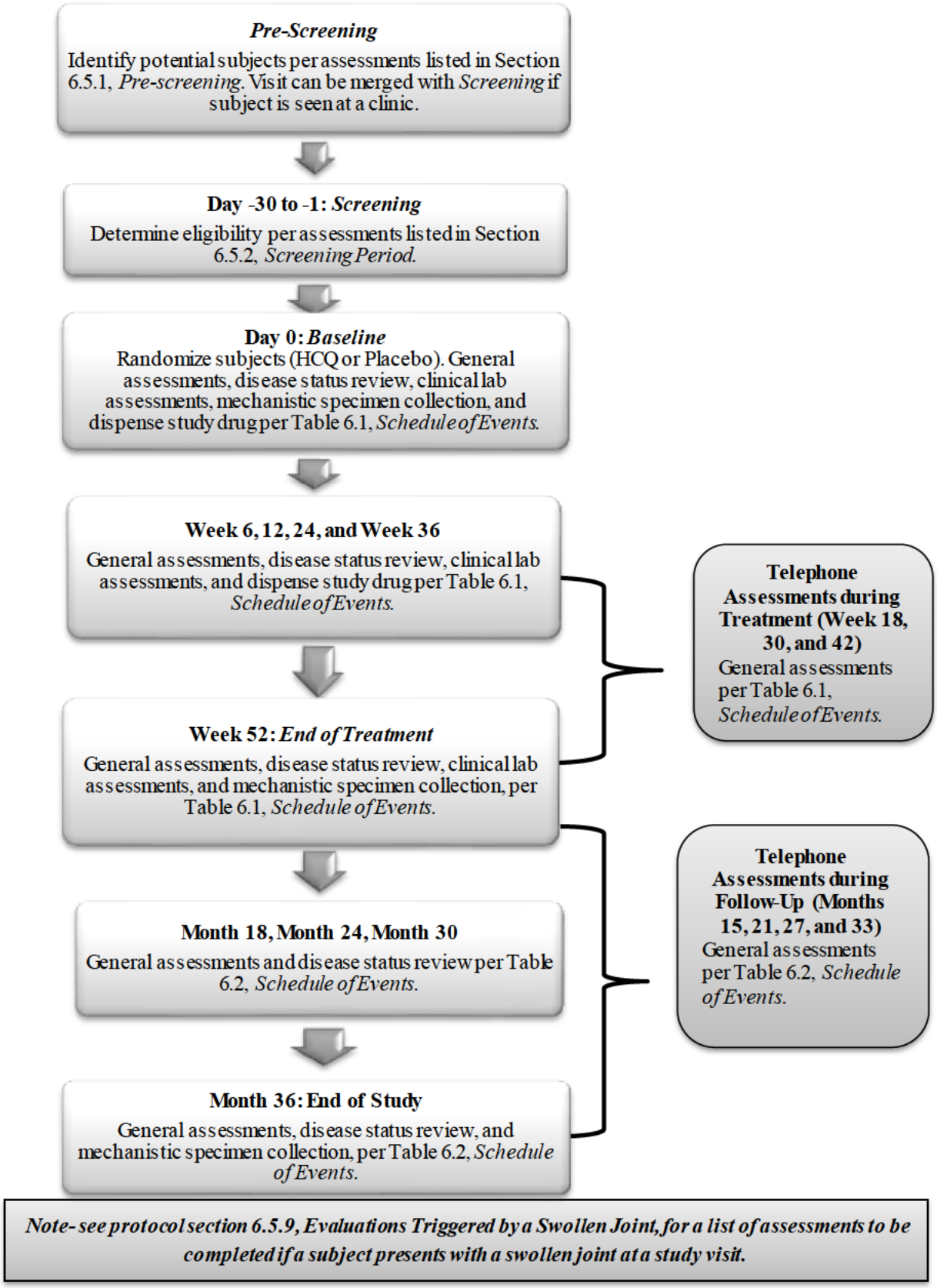
Secondary efficacy and safety endpoints are described in Sections 3.3.1, *Secondary Efficacy Endpoints,* and 3.3.2, *Secondary Safety Endpoints.*

Sample Size: 200 eligible subjects will be randomized in a 1:1 ratio.

Data Analyses: For the primary analysis, we are interested in demonstrating a long-term impact of a 1-year course of HCQ treatment on preventing the development of clinically-apparent RA (defined in Section 2.1, *Primary Objective*) in high-risk subjects. As such, rather than comparing full survival curves between treatment arms, the sample size for this study was selected to achieve sufficient power to compare survival curves at a fixed point 3 years after initiating treatment with HCQ.

All secondary analyses will be conducted in an exploratory fashion with p-values and confidence intervals presented as descriptive statistics with no adjustments for multiple comparisons. Tests will be two-sided and interval estimates will be generated at the 95% confidence level.

FLOW DIAGRAM OF PROTOCOL



ABBREVIATIONS

ACE	Autoimmunity Centers of Excellence
ACPAs	Antibodies to Citrullinated Protein Antigens
ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
Anti-CCP	Anti-Cyclic Citrullinated Peptide
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
AST	Aspartate Aminotransferase
CDAI	Clinical Disease Activity Index
CFR	Code of Federal Regulations
CNS	Central Nervous System
CRP	C-Reactive Protein
DAIT	Division of Allergy, Immunology, and Transplantation
DAS28-CRP	Disease Activity Score (28 joints) – C reactive protein
DHHS	Department of Health and Human Services
DMARDS	Disease-Modifying Antirheumatic Drugs
DNA	Deoxyribose Nucleic Acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ESR	Erythrocyte Sedimentation Rates
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FDR	First Degree Relative
G-6-PD	Glucose-6-phosphate Dehydrogenase
GCP	Good Clinical Practice
HCQ	Hydroxychloroquine
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HTN	Hypertension
hs-CRP	High-Sensitivity C-Reactive Protein
IA	Inflammatory Arthritis
IBW	Ideal Body Weight
ICH	International Conference on Harmonization
IgM	Immunoglobulin M
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISF	Investigator's Study Files
ITT	Intention-to-Treat or Intent-to-Treat

IV	Intravenous
KM	Kaplan-Meier
LEF	Leflunomide
LLN	Lower Limit of Normal
MCPs	Metacarpophalangeal Joints
MDHAQ	Multi-dimensional Health Assessment Questionnaire
MHC	Major Histocompatibility Complex
mITT	Modified Intent-to-Treat
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSAIDS	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OHRP	Office of Human Research Protection
PBMC	Peripheral Blood Mononuclear Cells
PI	Principal Investigator
PP	Per Protocol
PPV	Positive Predictive Value
PR	Palindromic Rheumatism
PRO	Patient Reported Outcomes
PROMIS	Patient-reported Outcomes Measurement Information System
RA	Rheumatoid Arthritis
RAIN	Rheumatoid Arthritis Investigator Network
RAPID-3	Routine Assessment of Patient Index Data 3
RF	Rheumatoid Factor
RhoFED	Rho Federal Systems Division, Inc.
RNA	Ribonucleic Acid
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SDAI	Simplified Disease Activity Index
SD	Spectral Domain
SE	Shared Epitope
SERA	Studies of the Etiology of Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
SP	Safety Population
SSZ	Sulfasalazine
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cells

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1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

This clinical trial will evaluate a novel screening and treatment approach for the large-scale prevention in individuals who are at high-risk of developing future clinically-apparent RA. The success of this trial will represent a substantial shift in the way that we can approach RA, with a new emphasis on prevention rather than solely on treatment of clinically-apparent disease – much like the focus in clinical practice today is on prevention of cardiovascular disease rather than solely treating its consequences. Additionally, the natural history and mechanism-based studies that will be performed as part of this trial, or be possible at a future date using materials collected during this study, will provide us with unique insights into the biology of early RA development that may further our understanding of this disease and perhaps guide additional preventive therapies. Finally, the infrastructure that will be developed as part of this trial, screening very large numbers of individuals and identifying those at significant risk of development of clinically-apparent RA, will enable the implementation of future studies of the development and prevention of RA.

1.1 Description and Epidemiology of Disease

Rheumatoid arthritis is a systemic autoimmune inflammatory disease that affects ~1% of the population, making it one of the most common chronic autoimmune diseases [1]. It affects women more often than men in a ratio of ~3 to 1, and the average age of onset is ~50 years old. In terms of clinical manifestations, RA primarily affects the joints, with small joints being the primary joints involved (Figure 1.1); however, multiple other systems including respiratory tract (e.g. interstitial lung disease), cardiovascular system (e.g. myocardial infarction) and bones (e.g. osteoporosis) can be affected [2-6].

The overall effects of RA lead to substantial morbidity in terms of joint pain and damage due to destructive arthritis, decreased quality of life, as well as increased mortality compared to age-matched non-RA populations [7-9]. In particular, because the average age of onset of RA is ~50 years-old, people affected by RA are often in their prime working years, further increasing the adverse impact of RA on society. As a result of this as well as the expensive therapies that are commonly needed to manage the disease, RA leads to substantial financial costs, with estimates of >$30 billion annual total health costs in the United States alone [10].

While improving pharmacologic therapies and treatment strategies for RA, including early aggressive therapy have led to improved outcomes [11] (discussed in Section 1.1.7, *Current Treatment for RA*), for the great majority of patients with RA the disease is chronic and requires life-long therapy. Specifically, in analyses of 871 subjects with RA followed in clinical practice, Prince and colleagues found only 45% met criteria for disease remission, and even when remission was reached it was often short-lived (<1 year) [12]. In addition, for many patients with RA, therapy with a single agent is inadequate to control the disease and therefore multiple agents are required, which increases the costs of treatment. In particular, the addition of a biologic therapy, which is necessary in 30-40% of patients with established disease, can lead to medication costs alone of over $1000 per month [13]. Additionally, therapies for RA are associated with a range of toxicities that require frequent monitoring and include, but are not limited, to infection, organ injury (e.g. hepatitis) and gastrointestinal effects [14, 15]. Therefore, strategies to prevent

RA prior to its onset may lead to substantial improvements in the public health impact of this disease.

1.1.1 Clinical pathophysiology of RA and measurement of disease activity

The hallmark of RA is synovial inflammation/synovitis that leads to joint destruction. To the patient, this inflammation is characterized by joint pain, stiffness and swelling, which can all contribute to a loss of function and decreased quality of life. In addition, the systemic inflammation associated with RA leads to effects such as fatigue and malaise, which can also have a major impact on overall well-being in patients with RA [16-18]. On physical examination, this inflammatory arthritis (IA) is characterized by joint swelling (both from synovial hypertrophy as well as joint effusions), tenderness and warmth, and, potentially, deformity and loss of range of motion (Figure 1.1).

In clinical management of RA, disease activity can be assessed by measuring the number of tender and swollen joints on examination, systemic measures of inflammation such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as by assessing a patient's self-reported symptoms of pain, fatigue and overall well-being [19-21]. Validated measures to assess disease activity include instruments such as the Disease Activity Score (DAS) that includes assessment of tender and swollen joints, inflammatory markers (ESR or CRP), and a patient's report of global health. Other validated measures that are used to assess RA disease activity include the Modified Multi-Dimensional Health Assessment Questionnaire (MDHAQ), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI) [22-24]. Importantly, measures of disease activity are now considered essential aspects of managing RA as part of 'treat to target' strategies where clinicians treat RA to meet a goal of low disease activity as measured by a validated instrument [25]. No single instrument has been deemed superior in the measurement of RA disease activity; however, the most commonly used measures include the MDHAQ, the DAS that includes a 28 or 44 joint count, the CDAI, and the measurement of the CRP.

Radiographically, the classic finding of RA is erosive disease, as demonstrated in Figure 1.2. Erosions are seen in a substantial proportion of patients with RA, and are part of the diagnostic criteria for RA (see footnote for Table 1.1). Additionally, erosions are indicative of more severe disease process. Importantly, erosions and associated joint destruction are now believed to develop within a few months after the onset of RA and because of that, as discussed in Section 1.1.7, *Current Treatment for RA*, treatment strategies for RA are now designed to control synovial inflammation prior to the development of erosions in order to preserve long-term joint integrity and function [26-30].

1.1.2 Autoantibodies and measures of inflammation in RA

Autoantibodies are an important component of both the pathophysiology and diagnosis of RA. Numerous autoantibodies have been identified in RA; however, two autoantibody systems have the highest prevalence as well as the highest specificity for RA. The first, rheumatoid factor, can be tested through several modalities including nephelometry as well as enzyme-linked immunosorbent assay (ELISA) testing for specific isotypes, with ELISA testing for the immunoglobulin (Ig) M-RF being one of the most commonly used means to assess RF positivity.

The other autoantibody system is antibodies to citrullinated protein antigens (ACPAs). There are several commercially-available methods to test ACPAs, but the most common is the anti-CCP antibody test, which now has several generations (CCP, CCP2, CCP3 and CCP3.1)[31].

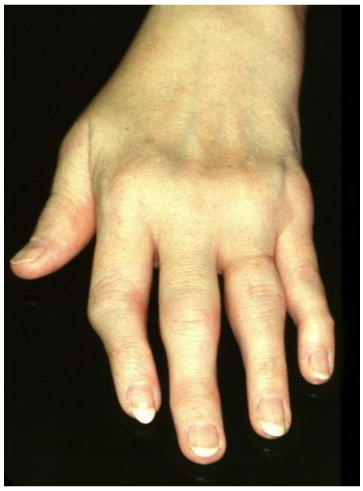

Figure 1.1. Active rheumatoid arthritis with visible swelling across multiple metacarpal phalangeal joints (c) 2014 American College of Rheumatology. Used with permission.

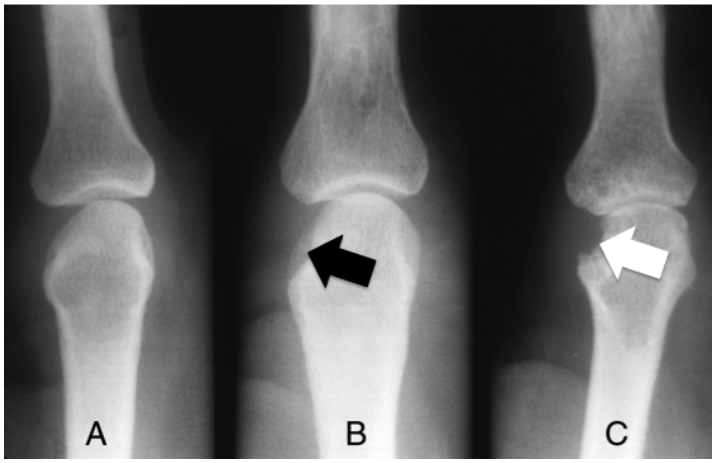

Figure 1.2 Destructive bony erosion in RA. The image on the left demonstrates fairly normal appearing bone around the joint. However, over time, a large erosion has developed (Arrow, C). These types of erosions are associated with joint deformity and loss of function. (c) 2014 American College of Rheumatology. Used with permission.

1.1.2.1 **Biology of RF and ACPAs**

Rheumatoid factor is an autoantibody that targets the Fc portion of another antibody; it is often an IgM isotype, although IgA and IgG isotypes are also seen in RA. In terms of pathophysiology of RA, RF has been implicated in the formation of immune complexes that can initiate as well as propagate synovitis. Citrulline is a post-translationally modified version of arginine, and citrulline and its flanking sequences are targeted by ACPAs [32-34]. In RA, there are a number of citrullinated proteins that are targeted by ACPAs including vimentin, filaggrin, fibrinogen and collagen among others. In animal studies, the presence of ACPAs amplifies experimental arthritis [35]. In addition, studies have demonstrated that ACPAs participate in immune complex formation in RA, as well as directly targeting structures within the joint [34, 36-39]. ACPAs have also been demonstrated to contribute to joint damage in RA by activating osteoclasts [40, 41]. Additional details regarding the role of RF and ACPAs in the pathogenesis of RA are discussed in Section 1.1.5, *Natural history of RA: Focus on preclinical disease development*.

1.1.2.2 **Diagnostic accuracy of RF and ACPAs**

Rheumatoid factor and/or ACPAs are present in ~60-80% of patients with RA, and if present, the disease is labeled 'seropositive RA' (for additional discussion see Section 1.1.3, *Classification of RA*). In particular, in a number of studies, the sensitivity of RF for RA has ranged from 60-80%, with specificities of ~60-80%. The anti-CCP tests (which are one of the most well-studied

versions of ACPAs in RA) are also ~60-80% sensitive for RA; however, their specificity is much greater than RF for RA, with most studies finding that elevations of anti-CCP of a variety of generations (e.g. CCP2, CCP3) are >95% specific for RA [31, 42]. In addition, for both RF and ACPAs, higher levels of autoantibodies (e.g. >2-3 times the normal cut-off values) have greater specificity for disease.

1.1.2.3 **Seropositivity and RA severity**

Identification of RF and/or ACPA positivity in RA assists with the classification/diagnosis of a patient with IA; in addition, determining autoantibody positivity helps with the prediction of disease severity. In particular, seropositive RA is generally thought to be more severe and persistent than seronegative RA [43-46], and emerging data suggest that positivity for anti-CCP imparts the highest risk for more severe RA [47-51]. As such, identification and treatment of seropositive RA is currently a major focus of the rheumatologic community and therefore preventive approaches that target seropositive RA will likely have the greatest positive impact.

1.1.2.4 **Inflammatory markers and RA**

Both local and systemic inflammations are present in RA. Multiple tests have been used to assess systemic inflammation in RA including ESR and CRP, white blood cell counts and total immunoglobulins, and specific cytokines and chemokines [52, 53]. In clinical practice, the measures most commonly used are the CRP and ESR, and elevations of these markers in RA have been associated with poor outcomes including need for joint replacement and increased mortality [4, 9, 54, 55]. These tests are readily available in most clinical laboratories, have been well-studied as good outcome measures in RA, and in particular, the CRP is quite stable in stored blood specimens [53]. Most of the validated disease activity measures for RA, such as the DAS, have been developed to include CRP or ESR testing [24]. Finally, as discussed in Section 1.1.3, *Classification of RA,* the 2010 Classification criteria for RA also include CRP and/or ESR testing. As such, CRP and ESR form an integral part of assessment in RA. In particular, the version of CRP called 'high-sensitivity CRP' is particularly useful for assessment of inflammation in RA and in particular research-related studies because of its stability in stored samples, and its improved ability over standard CRP to measure small changes in levels [56].

1.1.3 **Classification of RA**

Rheumatoid arthritis is diagnosed when a patient presents with the signs and symptoms that meet classification criteria for disease with these symptoms including presence and duration of joint pain, stiffness and swelling, and signs including tenderness and swelling on examination as well as imaging and blood test findings that include autoantibodies and inflammatory markers such as ESR and CRP.

There are now 2 sets of classification criteria established for RA: the 1987 American College of Rheumatology (ACR) criteria [57], and the 2010 ACR/European League Against Rheumatism (EULAR) criteria [58]. These 2 sets of criteria are presented in Table 1.1. As mentioned above, for the majority (~60-80%) of patients, RA is characterized by the presence of autoantibodies RF and/or ACPAs; if one or both of these autoantibodies are present, RA is termed 'seropositive' disease [42].

Notably, the 2010 criteria were developed in large part to allow for an earlier diagnosis and subsequent treatment of RA as compared to the 1987 criteria. Follow-up studies on these criteria have shown that indeed the 2010 criteria classify patients with RA earlier than do the 1987 criteria [59-61]. As such, the 2010 criteria have emerged as the primary criteria for use in patients with early IA and are therefore deemed most appropriate to use to define the primary endpoint in a prevention trial for RA. In addition, while the presence of erosions are not included in the main 2010 criteria largely due to the belief that erosions may not be present in early RA, if erosions are present in the setting of other features of disease, the 2010 Criteria suggest that patients should be considered to have RA [62].

Table 1.1. Comparison of the 1987 ACR RA and 2010 ACR/EULAR RA Classification Criteria

1987 ACR Classification Criteria	2010 ACR/EULAR Classification Criteria[62]	
1) Morning stiffness >1 hour 2) Arthritis of ≥3 joint areas 3) Hand arthritis 4) Symmetric arthritis 5) Nodules 6) Elevation of rheumatoid factor 7) Radiographic changes Findings 1-4 must be present for ≥6 weeks. 4/7 criteria must be satisfied to meet the definition of RA. Arthritis must be observed by a physician.	Who should be tested? Patients with ≥1 swollen joint consistent with synovitis not better explained by another disease. If the patient meets these initial criteria with a score of ≥6/10 they can be classified as having 'definite RA': **A. Joint involvement***	
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (at least 1 small)	5
	B. Serology (at least 1 test needed)	
	Negative RF and ACPA	0
	Low positive RF or ACPA	2
	High positive RF or ACPA**	3
	C. Acute-phase reactants (at least 1 test needed)	
	Normal CRP and ESR	0
	Abnormal CRP or ESR	1
	D. Duration of symptoms	
	<6 weeks	0
	≥6 weeks	1

* Joint involvement refers to any *swollen* or *tender* joint on examination. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. "Large joints "refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** High positive is equivalent to >3 times the upper limit of normal based on the reference range of the laboratory that assesses the biomarker.

NOTE: Patients with erosive disease typical of rheumatoid arthritis with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA.

1.1.4 Risk factors for RA

The exact etiology of RA is currently unknown; however, multiple genetic and environmental risk factors have been associated with disease. In particular, specific gene sequences contained within the Major Histocompatibility Complex (MHC), which are in aggregate termed the shared

epitope (SE), are strongly associated with RA with odds ratios across multiple studies of approximately 8 [63]. In addition, multiple other gene polymorphisms have been associated with RA, although none is as powerful as the association of the SE [64].

There are also numerous environmental exposures associated with increased risk for RA, with the strongest of these being exposure to tobacco smoke, although multiple other factors have been associated with risk for RA including dietary factors, hormone and contraceptive use, menstrual factors, pregnancies, and breast feeding (reviewed in [65]). There are also potentially protective factors such as statin use, alcohol intake, or fatty fish consumption, as well as the use of omega-3 fatty acid-containing and other types of supplements [66-69]. Furthermore, there is emerging evidence that RA-related autoimmunity may be related to mucosal inflammation and microbial influences [70, 71]. However, at this time the role of genetic and environmental factors in either the prediction of future RA or as modifiable risk factors is unclear. As such, relevant factors will be assessed but not included as part of inclusion/exclusion criteria or considered as targets for prevention at this time, although this will be an area of future interest.

1.1.5 Natural history of RA: Focus on preclinical disease development

RA becomes clinically apparent when an individual develops the symptoms of joint disease, and is subsequently identified as having synovitis classifiable as RA by a health care provider. However, over the past several decades it has emerged from a number of studies that for the majority of individuals who develop seropositive RA, systemic RA-related autoimmunity is present on average for 3-5 years prior to the first clinically detectable arthritis [72-78]. This period of time of detectable autoimmunity prior to the development of clinically-apparent RA is currently termed the 'preclinical' period of RA development (reviewed in [79, 80]), and a number of studies describing this period are listed in Table 1.2.

Table 1.2. Studies of RA-related autoantibodies and other biomarkers prior to the onset of clinically-apparent RA.

Study	Biomarkers	Findings
Silman et al 1992 [81]	RF	Average incidence of RA 8 per 1000 person-years in first degree relatives (FDRs); highest rate in FDRs with RF+: 34.8 per 1000 person-years
Rantapaa-Dahlqvist et al 2003 [76]	RF, anti-CCP	Retrospective case/control study; positivity for anti-CCP with or without concomitant RF positivity with a PPV for future RA of >82% for future RA.
Nielen et al 2004 [77]	RF-IgM, anti-CCP	Retrospective case/control study; combinations of RF and/or anti-CCP positivity with PPV up to 100% for RA diagnosis within 5 years.
Deane et al 2010[82]	RF and anti-CCP and multiple cytokines, chemokines and CRP	Retrospective case/control study; anti-CCP and/or 2 or more RF isotypes >96% specific for future RA; anti-CCP2 levels >2x the normal cut-off 92% specific for RA onset within 3 years.
van de Stadt et al 2011[83]	Anti-CCP, 5 specific ACPAs and RF	Retrospective case/control study; subjects with greater numbers of ACPAs have higher risk of developing clinically-apparent IA; high-titer anti-CCP associated with greater array of specific ACPAs
Sokolove et al 2012[84]	Multiple ACPA tests as well as cytokines and chemokines	Retrospective case/control study; in early preclinical RA there are few reactivities to citrullinated proteins; however as the time of clinically-apparent RA approaches, the number of ACPAs increases, along with the number of abnormal cytokines and chemokines.

Table 1.2. Studies of RA-related autoantibodies and other biomarkers prior to the onset of clinically-apparent RA.

Study	Biomarkers	Findings
Bos et al 2010[85]	Anti-CCP and RF	Prospective study; 27% of subjects with anti-CCP positivity developed IA after a median of 11 months of follow-up; rates of development of RA of 50% in ~12 months were seen in patients with higher anti-CCP titers.
Beck et al 2013[86]	Anti-CCP and RF	Prospective study; 47 subjects identified in a health-fair with CCP positivity in absence of IA; 18/47 (38%) developed IA all within 36 months of follow-up. Specifically, in subjects with CCP3 levels >2x normal, 70% developed RA within 36 months.

Abbreviations: RA=rheumatoid arthritis; RF=rheumatoid factor; anti-CCP=anti-cyclic citrullinated peptide antibody; ACPA=antibodies to citrullinated protein antigens; PPV=positive predictive value; FDR = first degree relative; IgM = immunoglobulin M; CRP = c-reactive protein; IA = inflammatory arthritis

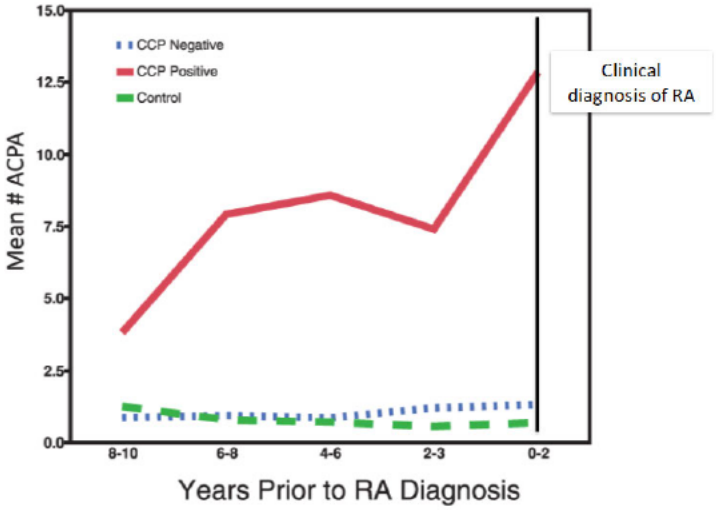

Figure 1.3 Preclinical expansion of antibodies to citrullinated proteins. The mean number of autoantibodies expands from ~2.5 8-10 years prior to RA, to ~12.5 at the time of onset of clinically-apparent RA.

In particular, based on several studies that have assessed autoimmune responses to citrullinated proteins in preclinical RA, it appears that in the earliest phase of autoimmunity, there are reactivities to just a few citrullinated antigens, and that over time the number of citrullinated antigens recognized by autoantibodies increases [84, 87]. An example of this is presented in Figure 1.3, where, using an array that can test for numerous autoantibody reactivities to individual citrullinated antigens, Sokolove and colleagues have demonstrated that preclinical RA is characterized by initially few ACPAs that expands as the time of appearance of clinically-apparent RA approaches [84, 88].

Based on these as well as other studies, the natural history of preclinical seropositive RA and its transition to clinically-apparent disease is outlined in Figures 1.4 and 1.5. In this model of RA development, the earliest phase of preclinical RA is characterized by limited autoantibody responses in terms of numbers of antigens targeted as well as lower levels of these autoantibodies. Over time, the levels as well as the numbers of autoantibodies increase. This is demonstrated by increasing numbers of citrullinated antigens that are targeted (epitope spreading), as well as the development of both RF and ACPAs. Importantly, this expansion of epitopes is paralleled by increased titers in the commercial anti-CCP tests; as such a rising titer of anti-CCP can be used as a surrogate for epitope spreading [84].

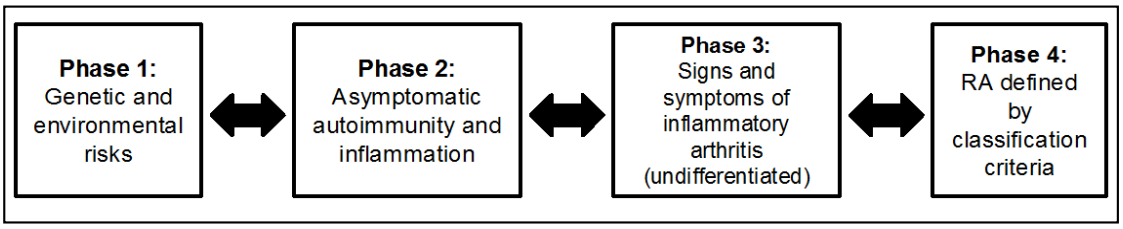

Figure 1.4 Phases of development of RA. In this model of RA development, disease begins with genetic and environmental risks (Phase 1), followed by autoimmunity and inflammation (Phase 2), with eventual progression to symptomatic and clinically-apparent inflammatory arthritis (Phase 3) that ultimately can be classified as RA by established classification criteria (Phase 4).

The precise mechanisms that drive a transition from circulating autoimmunity in absence of clinically-apparent synovitis to clinically-apparent synovitis are not yet known. However, studies of early synovitis in RA as well as synovial tissue samples from subjects with autoantibody positivity in the absence of otherwise clinically-apparent synovitis suggest that immune complex deposition and other immune targeting that may lead to infiltration of inflammatory cells are likely the factors that initiate synovitis in RA [89]. Importantly, this model of RA development strongly suggests that a preclinical intervention with an immunomodulatory agent that could decrease autoantibody expansion and epitope spreading, and inflammation in preclinical RA, as well as perhaps lead to long-lasting normalization of immune responses, could ultimately lead to decreased transition from asymptomatic autoimmunity to clinically-apparent RA (Figure 1.5), These concepts form the basis of this clinical trial for the prevention of RA.

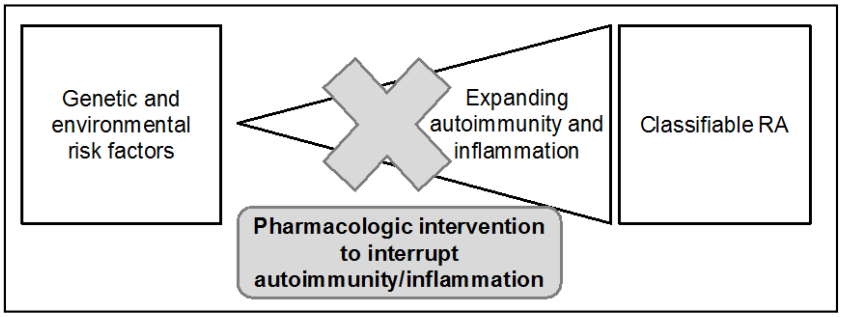

Figure 1.5 Preventive approach to RA. Pharmacologic interruption of the expansion of autoimmunity in preclinical RA could lead to abrogation of progression to clinically-apparent RA.

1.1.6 Prediction of future RA in individuals without current inflammatory arthritis

Autoantibody testing in preclinical RA has led to a greater understanding of the pathogenesis of disease development. In addition, autoantibody testing can be used in preclinical RA to predict the likelihood as well as timing of future RA in individuals who are currently without IA (Table 1.2).

Importantly, while both RF and ACPAs (including anti-CCP testing) are predictive of future disease, anti-CCP testing has emerged as the test with the highest positive predictive value (PPV) for future onset of RA. This has been demonstrated in multiple retrospective case-control studies where anti-CCP positivity consistently demonstrates PPVs for future RA of >90% (Table 1.2). As mentioned above, there are several types of anti-CCP testing clinically available including anti-CCP2, anti-CCP3, and anti-CCP3.1, all of which have high specificity (>90%) for RA in patients with established inflammatory arthritis [90]. As for data regarding specificity for future RA using the anti-CCP3 test, using a set of samples from a cohort of 83 United States Armed Forces personnel, who ultimately developed RA and 83 matched controls, anti-CCP3 levels of ≥2 times the normal cut-off of ≥20 units (or ≥40 units) was 99% specific for future RA (manuscript in preparation by Deane KD et al). As such, testing for anti-CCP3 and in particular using a cut-off level that is ≥2 times the normal cut-off level in individuals without current IA is highly predictive of future development of RA.

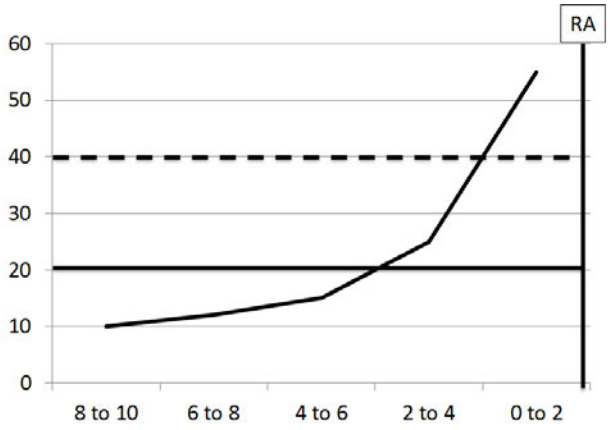

Figure 1.6 CCP3 levels rise in preclinical RA. In serum samples obtained from military subjects prior to the onset of RA, median levels (solid black line) of anti-CCP3 increase as the time of diagnosis approaches. The horizontal black line represents the normal cut-off level for anti-CCP3 positivity (≥20 units). Importantly, anti-CCP3 levels that are ≥2 time the normal cut-off level (or ≥40 units indicated by the dotted black line) are typically found within 5 years of diagnosis (Kevin Deane, Manuscript in Development).

In addition to predicting the overall likelihood of RA development, autoantibodies, and in particular anti-CCP can be used to predict the timing of future onset of RA – an important concept when considering a clinical trial of limited temporal duration. Supporting this, in multiple studies, anti-CCP positivity is first identified on average 3-5 years prior to the clinical onset of RA [76-78, 91]; therefore, if anti-CCP is positive, as discussed above it is highly specific for the future onset of RA, as well as highly indicative of RA within a 5-year time period. In addition, higher levels of autoantibody typically develop closer to the time of clinical appearance of RA (Figure 1.6). In particular, in a prospective study of subjects who were positive for anti-CCP in the absence of inflammation at baseline, van de Stadt and colleagues demonstrated that anti-CCP levels >3 times the normal cut-off level were the strongest predictive factor for development of future RA with a 2-3 year period [92]. Bos and colleagues have also shown that ~30% of subjects with anti-CCP2 positivity developed RA within ~3 years; in addition, subjects with the highest levels of anti-CCP2 had the highest rates of progression (>50%) to RA [85]. In addition, Beck and colleagues have identified in prospective follow-up of individuals identified with anti-CCP2 or anti-CCP3 positivity in absence of IA through health-fair screening that anti-CCP2 levels of >2-3 times the normal cut-off level were associated with a 70% PPV of development of RA within 3 years [86]. Furthermore, Demoruelle and colleagues have demonstrated that anti-CCP2 levels >2 times the normal cut-off level had a 55% PPV for the onset of clinically-apparent RA within 2 years [31], with additional unpublished analyses identifying that an elevation of anti-CCP3 ≥2 times the normal cut-off had a PPV of ~60% for future RA within 3 years. Finally, in a natural history study of initially arthritis-free FDRs of family members with RA, Ramos-Remus

and colleagues found that in individuals who were anti-CCP2 positive at any level (and RF negative) had a PPV of 58.3% for future onset of RA [90]. In addition, they found that over 50% of subjects who were positive for anti-CCP (+) at their baseline visit developed RA within 3 years.

In sum, anti-CCP positive at any level, and in particular anti-CCP3 levels of ≥2 times the normal cut-off level (or ≥ 40 units) are both highly predictive of future RA development, as well as highly predictive of RA development within a 3-year time interval. Specifically, we believe that the above data support that an anti-CCP3 level of ≥2 times the normal cut-off will exhibit a >50% PPV for RA within 3 years.

1.1.7 Current Treatment for RA

Current treatments for RA are instituted once a patient has developed the clinically-apparent signs and symptoms of RA. These treatments include a wide variety of immunomodulatory therapies including HCQ, sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF), as well as biologic therapies including tumor necrosis factor (TNF) inhibitors, B cell depleting therapies (e.g. rituximab), interleukin (IL)-1 (e.g. anakinra), and IL-6 inhibition (e.g. tocilizumab), and co-stimulation modulation (e.g. abatacept). Overall, over the past two decades the expanding number and types of drugs available for RA have greatly improved clinical outcomes in disease. Importantly, there are established and emerging data that treatments initiated soon after the clinical appearance of RA (within 3-6 months of the onset of symptoms) lead to improved long-term outcomes. Several studies regarding these findings are presented in Table 1.3.

Table 1.3. Examples of studies supporting that early treatment of RA results in improved outcomes

Anderson et al, 2000 [91]	Meta-analysis demonstrating that RA patients with a shorter disease duration respond better to similar therapies as compared to patients with longer-term disease.
Mottonen et al, 2002 [92]	Delay of initiation of RA therapy by 4 months after the onset of symptoms decreased the ability for a single drug to induce remission in early RA.
Cush, 2007 [27]	Review article that summarizes data from subanalyses of several trials of biologic therapies in RA. Shows that early treatment (<2-3 years of disease duration) results in improved outcomes compared to treatment initiated in disease of 2 years duration.
van der Woude et al, 2009 [93]	Data from two large early arthritis cohorts demonstrated that sustained, disease modifying antirheumatic drug (DMARD)-free remission of RA was significantly associated with shorter duration of symptoms of IA at time of initiation of therapy.
van der Linden, et al 2010 [94]	In an early arthritis cohort, assessment and treatment of RA within 3 months of symptom onset was associated with increased chance of DMARD-free remission and less joint destruction.

Particularly, in some studies, early therapy has been shown to increase rates of drug-free remission, with this early period being termed a 'window of opportunity' to treat and prevent long-term adverse outcomes in RA [26, 27, 95]. In addition, Barra and colleagues identified several patients with early IA/RA who, after presenting with early clinically-apparent arthritis and institution of therapy, had disappearance of RF and ACPAs as well as resolution of their arthritis [96].

The mechanisms for improved outcomes associated with earlier therapy are not yet clear, although there are some speculations. It may be that early therapy suppresses inflammation before the immune system has had time to develop permanent alterations in cellular processes that could drive inflammation. For example, in the setting of longstanding inflammation, synovial fibroblasts in RA may undergo epigenetic changes that make them less amenable to 'turn off' their production of damaging enzymes, and early treatment may prevent those changes from occurring [97-101]. In addition, as discussed in Section 1.1.5, *Natural history of RA: Focus on preclinical disease development*, epitope spreading is an important feature in the early evolution of RA, and may in fact be crucial to the transition from asymptomatic autoimmunity to clinically-apparent disease; as such, early treatment may reduce inflammation and also epitope spreading and therefore lead to less wide-spread tissue damage [84, 102, 103]. In addition, it may be that early pharmacologic immunomodulation may allow for endogenous regulatory mechanisms to counter the development of autoimmunity and restore tolerance [104, 105].

However, while the expanding therapeutic armamentarium for RA as well as the finding that earlier institution of therapy leads to improved long-term outcomes has been encouraging to the field, for the majority of patients and even those who are treated soon after the onset of their RA symptoms, the disease requires life-long systemic immunotherapy. In particular, as previously mentioned, the study by Prince and colleagues demonstrated that <50% of patients with RA who are followed in routine clinical practice achieve remission by defined criteria; furthermore, even if remission was reached, it typically lasted <1 year [12]. As such, immunologic therapy even initiated soon after the onset of clinically-apparent disease is unlikely to treat disease in a sufficient proportion of subjects to avoid the adverse health impacts and high cost of RA; therefore, preventive approaches hold great promise to reduce the significant adverse impact of RA on public health.

Importantly, despite the failure to reach remission in the majority of patients with RA seen in routine clinical practice, the benefits of early therapy in RA support the notion that therapy instituted even prior to the clinical appearance of synovitis has a strong chance to abrogate immune responses and halt the progression to clinically-apparent RA. Early therapy may even potentially lead to a permanent 'reset' of the immune system where even after an immunomodulatory intervention is stopped; disease does not progress, or may even regress. Moreover, while it is not known whether or not immunomodulatory or other interventions in the early phases of autoimmune disease in absence of clinically-apparent organ toxicity (e.g. synovitis) could lead to long-lasting drug-free improvements in autoimmunity, several observations discussed in more detail below support the premise that the intervention proposed in this trial will have lasting benefit.

Natural history studies of preclinical RA that include control subjects have demonstrated that control subjects who do not go on to develop RA can have elevations of RA-related autoantibodies yet not progress to disease. Specifically, in longitudinal studies of military subjects, it was noted that ~8-10% of healthy controls were positive for one or more RA-related autoantibodies, including several with anti-CCP positivity, yet did not develop RA [76-78]. Furthermore, some of these individuals were noted to have disappearance of their elevated levels of autoantibodies[106]. The factors associated with this lack of progression to disease and in some cases disappearance of autoantibodies is not yet known; however, these findings support the

idea that autoimmunity may be especially modifiable in very early disease and prior to the clinical appearance of significant organ injury.

Studies of palindromic rheumatism (PR), a disease process that has been described as a form of very early RA and even preclinical RA, support the potential benefit of very early immunomodulatory therapy, and in particular therapy with HCQ, for preventing future RA [107-114]. An observational study by Gonzalez-Lopez and colleagues of patients with PR, identified that the use of HCQ (or the similar agent chloroquine) halted the progression to classifiable RA (1987 criteria) in 44/64 (~69%) of subjects; furthermore, in comparison to observational controls, use of antimalarials led to a nearly 3-fold decrease in progression to persistent disease[112]. In addition, in a case-series by Hanonen and colleagues, 7/15 (~47%) of patients with PR treated with HCQ had complete disease remission [114]. James and colleagues also found that HCQ use prior to the fulfillment of full diagnostic criteria for systemic lupus erythematous (SLE) led to a delay in progression to classifiable SLE as well as a decreased number of SLE-related autoantibodies [115]. While these data are from an uncontrolled study, and HCQ was begun after the first clinical manifestations of SLE, they suggest that HCQ may interfere with epitope spreading – a mechanism that could also potentially be important in blocking the transition to clinically-apparent RA.

Overall, these findings have led to the central hypothesis of this clinical trial that instituting disease-modifying therapy, and in particular HCQ (see Section 1.5.1, *Rationale for the Treatment Arm*), in preclinical disease will lead to a durable decrease of autoimmunity and prevention of disease.

1.2 Study Plan

This study is a randomized (1:1), double-blinded, placebo-controlled, phase 2, multicenter trial to evaluate the efficacy and safety of hydroxychloroquine (HCQ) in the prevention of future onset of clinically-apparent rheumatoid arthritis (RA).

The study will randomize 200 subjects who are at high-risk for future development of classifiable RA although currently without a diagnosis of IA or findings of RA-like synovitis. These subjects will be selected because of the presence of elevations of the RA-related autoantibody anti-CCP3 that are greater than or equal to 2 times the normal cut-off level (i.e. anti-CCP3 $\geq$ 40 units), a biomarker status that is highly specific for future RA (>90%), and also indicative of the imminent onset of clinically-apparent disease. These subjects will be recruited through several mechanisms, including a large-scale, well-established cohort of first degree relatives (FDRs) of patients with RA, established large-scale community-based screening efforts, and through rheumatology clinics where anti-CCP (+) subjects without IA are regularly evaluated as part of referral processes. In total, these populations represent subjects in whom this type of screening and treatment approach for the prevention of clinically-apparent RA could readily be applied in a "real-world" fashion.

Subjects will be treated daily with HCQ (or placebo) for the initial 12 months after enrollment, then drug will be stopped and the subjects followed for an additional 24 months for a total trial duration of 36 months.

The primary endpoint will be the development of "clinically-apparent RA" defined using the 2010 ACR/ EULAR criteria (See Section 2.1, *Primary Objective*). Analyses will focus on the rates of clinically-apparent RA between subject groups at 36 months in order to test the central

hypothesis that a 12-month intervention with HCQ will result in durable decreased rates in progression to RA in individuals at high-risk for future RA.

As discussed in more detail above, the rationale for conducting this trial derives from multiple studies demonstrating that RA-related biomarkers are elevated prior to the initial appearance of the IA that is characteristic of this disease [73, 74, 76-79, 81, 82, 116]. Importantly, during the early period of RA development, it appears that the expansion of RA-related autoimmunity measured by increases in autoantibody titers, epitope spreading and increased general inflammation are crucial aspects of the mechanism of transition from asymptomatic autoimmunity to clinically-apparent IA [76, 102, 117, 118]. There are also growing data supporting that early treatment of RA leads to improved long-term outcomes, including increased rates of drug-free remission [119, 120]. Together, these findings suggest that an intervention with an immunomodulatory agent in individuals who in the preclinical period of RA development should interrupt the evolution and expansion of autoimmunity, leading to prevention of future onset of clinically-apparent RA. Furthermore, the highly specific nature of the autoantibody inclusion criteria (anti-CCP3 ≥2 times the normal cut-off) for this study allows for their use in accurate identification of subjects who are at high-risk for near-term development of future RA.

1.3 Clinical Studies of Hydroxychloroquine in RA

1.3.1 Hydroxychloroquine Background

Historically, HCQ was identified after it was noted that individuals who chewed the bark of the cinchona tree had improved outcomes from malaria. Based on this observation, HCQ was originally developed and used as an antimalarial. However, over time HCQ has had recognized benefits in autoimmune disorders including RA and SLE [121]

1.3.2 Current Licensing of Hydroxychloroquine

HCQ is currently FDA approved for suppressive treatment and treatment of acute attacks of malaria due to Plasmodium vivax, P. malariae, P. ovale and susceptible strains of P. falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus and RA.

1.3.3 Other Diseases in Which Hydroxychloroquine Use Has Been Described

Other diseases (rheumatic or otherwise) for which HCQ use has been described include Behcet's disease, Sjögren's Syndrome, sarcoidosis, Lyme disease, Q fever, dermatomyositis, in combination therapy for certain cancers, urticarial syndromes and coagulopathies including the antiphospholipid antibody syndrome [121].

1.4 Known and Potential Risks and Benefits of Hydroxychloroquine

1.4.1 Known and Potential Benefits of Hydroxychloroquine in RA and Other Diseases

Multiple studies have demonstrated that HCQ alone or in combination with other immunomodulatory therapies improves the clinical signs and symptoms of RA [122-134]. Specific examples include the **H**ydroxychloroquine in **E**arly **R**heumatoid **A**rthritis (HERA) study, a 36-week randomized, blinded study of HCQ compared to placebo in 120 patients with RA of < 2 years duration, that demonstrated that HCQ use at up to 400 mg/day was associated with >50% improvement in a composite joint index that included joint tenderness, swelling and stiffness [131]. Intriguingly, after 3 years of follow-up after the initiation of the HERA study, the investigators noted that delay of 9 months in institution of HCQ in these subjects was associated with worse composite measure of pain and physical function [135]; these findings suggest that even as monotherapy, early institution of HCQ led to improved long-term outcomes and support its use in a prevention trial.

In addition, in a 6-month randomized, blinded study of HCQ compared to placebo in 126 patients with RA of <5 years duration, Clark and colleagues demonstrated that HCQ at 400 mg/day was associated with >50% improvement in measure of joint inflammation in 71% of treated subjects [127]. HCQ has also been shown to be effective when used in combination with other therapies. In particular, the **R**heumatoid **A**rthritis: **C**omparison of **A**ctive **T**herapies in Patients With Active Disease Despite Methotrexate Therapy (RACAT) trial, adding HCQ and sulfasalazine to patients who had failed monotherapy with MTX resulted in improved clinical outcomes, and in particular these improvements were similar to those seen in patients taking combination therapy with MTX and the biologic agent etanercept [136].

HCQ has also been shown in multiple studies in SLE to allow for control of active disease as well as reduce the incidence of new flares [115, 121, 122, 128, 137-139]. In particular, in one human study, HCQ administered soon after the first onset of symptoms of SLE appeared to decrease the development of autoantibodies over time as well as decrease and delay future clinical manifestations of disease [115]. HCQ also appears to decrease cytokine production in dendritic cells from patients with SLE in response to Toll-like receptor agonists, a potential mechanism of reduction of antigen presentation and expansion of autoimmunity [140].

HCQ has also been demonstrated to have specific effects on the development of autoimmunity. This has been shown in many animal studies where use of HCQ blunts or halts immune activation related to a variety of inflammatory/autoimmune diseases including experimental arthritis, antiphospholipid antibody syndrome [141], and SLE [142, 143]. In particular, in animal models, HCQ administered early in the development of disease can have strong effects showing the abrogating/halting of inflammation and autoimmunity. In addition, based on data from both animal and human studies, HCQ appears to decrease endothelial activation and risk of thrombosis and other tissue injury in the antiphospholipid antibody syndrome [141, 144, 145]. Furthermore, as discussed above, in humans, HCQ use has been associated with decreased number of autoantibodies in SLE [115] and alteration/down regulation of antigen presentation and cellular activation [121, 122, 146-150] – factors which are likely to be important in the progression and expansion of RA-related autoimmunity prior to the onset of IA.

In sum, evidence from human clinical trials and animal studies strongly suggest that the use of HCQ in the preclinical period of RA development should lead to abrogation of the immune response and prevention of development of clinically-apparent disease.

1.4.2 Known and Potential Risks of Hydroxychloroquine

1.4.2.1 Ocular Toxicity

An important potential adverse effect of HCQ is ocular toxicity that can take many forms but is most commonly retinal injury. However, this effect is rare (<1%, [139]), particularly when subjects are dosed appropriately and do not have underlying renal or hepatic disease that may alter the pharmacokinetics of HCQ. Wolfe and colleagues studied ~4000 patients with RA and SLE and found confirmed retinal toxicity in <1% of treated patients, especially those treated for <5 years [151]. A newer study has found higher rates of presumed HCQ-related toxicity using more sensitive examination techniques including spectral domain optical coherence tomography (SD-OCT) in patients using doses of HCQ >5 mg/kg/day based on actual body weight and in those using HCQ for >5 years; even within this newer study, the overall the rate of toxicity appears to be low (<1%) within the first year of therapy[152].The current (2016) recommendations for retinopathy screening with HCQ use as put forward by the American Academy of Ophthalmology include a baseline funduscopic exam within the first year of HCQ use, with additional testing to include visual field and SD OCT testing if maculopathy is present, and then annual screening after 5 years of use[153].

A more detailed description of potential ocular toxicities is included below:

- *Ciliary body*: Disturbance of accommodation with symptoms of blurred vision. This reaction is dose-related and reversible with cessation of therapy.
- *Cornea*: Transient edema, punctate to lineal opacities, decreased corneal sensitivity. The corneal changes, with or without accompanying symptoms (blurred vision, halos around lights, photophobia), are fairly common, but reversible. Corneal deposits may appear as early as three weeks following initiation of therapy. The incidence of corneal changes and visual side effects appears to be considerably lower with hydroxychloroquine than with chloroquine.
- *Retina: Macula*: Edema, atrophy, abnormal pigmentation (mild pigment stippling to a "bull's-eye" appearance), loss of foveal reflex, increased macular recovery time following exposure to a bright light (photo-stress test), elevated retinal threshold to red light in macular, paramacular, and peripheral retinal areas. Cases of maculopathies and macular degeneration have been reported and may be irreversible [154, 155]. Other fundus changes include optic disc pallor and atrophy, attenuation of retinal arterioles, fine granular pigmentary disturbances in the peripheral retina and prominent choroidal patterns in advanced stage.
- *Visual field defects*: Pericentral or paracentral scotoma, central scotoma with decreased visual acuity, rarely field constriction, abnormal color vision. The most common visual symptoms attributed to the retinopathy are: reading and seeing difficulties (words, letters, or parts of objects missing), photophobia, and blurred distance vision, missing or blacked out areas in the central or peripheral visual field, light flashes and streaks. Retinopathy appears to be dose related and has occurred within several months (rarely) to several years

of daily therapy; a small number of cases have been reported several years after antimalarial drug therapy was discontinued. It has not been noted during prolonged use of weekly doses of the 4-aminoquinoline compounds for suppression of malaria. Patients with retinal changes may have visual symptoms or may be asymptomatic (with or without visual field changes). Rarely scotomatous vision or field defects may occur without obvious retinal change. Retinopathy may progress even after the drug is discontinued. In a number of patients, early retinopathy (macular pigmentation sometimes with central field defects) diminished or regressed completely after therapy was discontinued. If allowed to develop, there may be a risk of progression even after treatment withdrawal [154, 155]. Paracentral scotoma to red targets (sometimes called "premaculopathy") is indicative of early retinal dysfunction that is usually reversible with cessation of therapy. A small number of cases of retinal changes have been reported as occurring in patients who received only HCQ. These usually consisted of alteration in retinal pigmentation that was detected on periodic ophthalmologic examination; visual field defects were also present in some instances. A case of delayed retinopathy has been reported with loss of vision starting one year after administration of hydroxychloroquine had been discontinued.

1.4.2.2 **Additional Toxicities**

The list below contains potential AEs related to HCQ according to package inserts [154, 155], and listed in order of most common to least common:

- **Gastrointestinal Reactions:** Anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.
- **Dermatologic Reactions:** Rash, pruritius, bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema multiforme, erythema annulare centrifugum, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and exfoliative dermatitis).
- **Central Nervous System (CNS) Reactions:** Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia, and suicidal behavior
- **Neuromuscular Reactions:** Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction.
- **Hematologic Reactions:** Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, anemia, thrombocytopenia (hemolysis in subjects with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency).
- **Allergic Reactions**: Urticaria, angioedema and bronchospasm have been reported.
- **Risks to Pregnant Women**: Hydroxychloroquine crosses the placenta and should be avoided during pregnancy. 4-aminoquinolines, such as hydroxychloroquine, in therapeutic doses have been associated with damage to the central nervous system (including ototoxicity, retinal hemorrhages, and abnormal retinal pigmentation) in the fetus[154].
- **Miscellaneous Reactions**: Weight loss, lassitude, exacerbation or precipitation of porphyria, hypoglycemia, and nonlight-sensitive psoriasis have been reported.

Cardiomyopathy has been rarely reported with daily dosages of HCQ that exceed the recommended dosing levels, or in patients with compromised renal or hepatic function. Interactions with other drugs including oral hypoglycemic agents and digoxin may occur. Dose adjustments may be required.

1.5 Rationale for Study Design

1.5.1 Rationale for the Treatment Arm

Hydroxychloroquine has been selected as the immunomodulatory agent for this study for the following reasons listed below. Of note, as discussed above, there are numerous genetic and environmental risk factors for RA, and it is intriguing to consider risk factor modification as an approach to RA prevention. Indeed, an observational study suggests that smoking cessation may decrease future risk for RA[156]. However, to date there has not been convincing data that risk factor modification in a prospective manner is beneficial for disease prevention. As such, environmental exposures will be assessed in this study, and we will recommend that subjects who participate in the trial stop using tobacco products, but these factors will not otherwise be addressed for modification as part of the preventive strategy. Instead, modification of immune responses and prevention of RA will be approached through the use of HCQ, with rationale for the choice of HCQ as follows:

1. Hydroxychloroquine has been shown in multiple clinical trials to be efficacious in improving the signs and symptoms of active RA as monotherapy and combination therapy [121, 127, 131]. In particular and as discussed above, monotherapy of HCQ has been associated with >50% improvement in symptoms and in number of swollen joints in several placebo-controlled studies [157-159]. Furthermore, HCQ has been demonstrated to be particularly effective in early classifiable RA, a clinical condition that likely approximates the preclinical period of disease development [129].
2. Several studies have shown that HCQ use slows or halts the progression to persistently active RA in patients with palindromic rheumatism [110, 112, 113], and may decrease the production of autoantibodies in SLE, as well as delay the onset of full disease classification once early symptoms have developed [115]. Specifically, an observational study by Gonzalez-Lopez and colleagues of patients with palindromic rheumatism, identified that the use of HCQ (or the similar agent chloroquine) halted the progression to classifiable RA (1987 criteria) in 44/64 (~69%) of subjects; furthermore, in comparison to observational controls, use of antimalarials led to a nearly 3-fold decrease in progression to persistent disease[112]. In addition, in a case-series by Hanonen and colleagues, 7/15 (~47%) of patients with PR treated with HCQ had complete disease remission [114].
3. The growing understanding of the mechanisms of HCQ in abrogating the immune response further supports its use in preventing future RA in high-risk individuals. In particular, HCQ has been shown to decrease cellular activation including hindering of antigen presentation to CD4 (+) T cells [122], actions that may lead to decreased autoantibody production. Also, growing evidence suggests that HCQ modulates Toll-like receptor function, leading to decreased inflammatory responses to immune complexes, decreased antigen presentation by dendritic and other antigen presenting cells, and decreased activation of the innate immune system that may lead to improvement of

autoimmune and inflammatory processes especially if initiated early in natural history of disease [122, 148].

4. Hydroxychloroquine is already a Food and Drug Administration (FDA)-approved agent for active RA, and widely used in clinical practice. Therefore, in real-world applications, this medication could be used easily to prevent RA in high-risk populations. Furthermore, from unpublished interviews with ~50 rheumatologists, HCQ would be an agent that ~85% would be comfortable prescribing as a preventive therapy for RA based on issues that include cost, safety, tolerability, and monitoring needs.
5. While there are multiple agents that are effective in RA (e.g. MTX, SSZ, biologic therapies), the overall safety and tolerability of HCQ makes it an excellent choice for prevention of RA in large-scale interventions if it is indeed effective in preventing future RA. Importantly, from unpublished data in interviews of approximately 40 at-risk subjects followed in a natural history study of RA, 80% of subjects reported that they would be willing to take a medication with the safety and tolerability profile of orally-administered HCQ, although <30% were willing to undergo a more invasive or perceived potentially toxic therapy such as an MTX or injection. In addition, in published work from Finckh et al, first-degree relatives of patients with RA were willing to undergo a preventive intervention (including medication) if their risk for future RA was 30% or greater within the next 5 years [160].
6. The cost of HCQ is relatively low compared to other immunomodulatory agents. As such, if this trial is successful, the cost-effectiveness of HCQ in RA prevention will be more readily demonstrated.
7. Hydroxychloroquine has the potential to impart broad benefits to a variety of health conditions. These include reduced risk for thrombosis, improved cardiovascular disease events, diabetes and hypertension [161].

1.5.2 Rationale for Duration of HCQ Treatment and Post-Treatment Follow-up

Subjects will be enrolled in the trial for three years, with drug/placebo treatment for the first year, and post-drug follow-up for the last two years.

The rationale for a three-year trial is that this time frame will allow for sufficient numbers of subjects reaching the primary endpoint (classifiable RA) to allow for robust evaluation of the efficacy of HCQ to prevent RA even after cessation of therapy.

The optimal duration of HCQ treatment for the prevention of RA is currently unknown; however, there are several factors that have led to the selection of this duration of therapy:

1. While there are very limited data regarding the duration of pharmacologic therapy to prevent RA, in a study by Bos and colleagues of autoantibody positive individual without IA, 2 doses of intramuscular corticosteroids failed to reduce progression to clinically-apparent IA [162]. In the PRAIRI study (Prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease), a single dose of rituximab delayed the onset of RA by approximately 12 months compared to placebo; however, it did not prevent RA when compared to placebo [163]. As such, using an agent for a longer duration is likely necessary to prevent future RA.

2. In clinical trials of HCQ in patients with active RA, a duration of therapy of 12 months is considered to be sufficient to determine if it will have a clinical effect. As such, 12 months duration will likely provide adequate exposure to the drug to identify a biologic effect.
3. While HCQ use is generally considered safe, there is a potential for toxicity especially with prolonged use. Given that the overall benefits of HCQ in the prevention of RA are as of yet unknown, 1 year of therapy will limit risk until more information regarding its benefit can be gained.
4. Subjects who are at risk for future RA reported that taking a therapy for 1 year was acceptable (manuscript in development by Deane KD et al); however, a longer duration of therapy may result in decreased compliance. In addition, studies in other conditions where a drug was used to treat a relatively asymptomatic condition such as hypertension (HTN) prolonged drug use led to increasing rates of non-compliance over time [164]. As such, 1 year of therapy will likely maximize adherence to therapy and provide the most robust data regarding drug effect.
5. The trial design specifies that HCQ will be given for 1 year, and subjects will be followed for an additional 2 years. This approach will allow for analyses to determine if the effect of HCQ on decreasing progression to RA is apparent while subjects are on drug, and wanes when subjects are off drug. These results will inform the design of future studies.

1.5.3 Rationale for the Control Arm

In order to determine the therapeutic effect of treatment with HCQ in subjects for the prevention of the onset of RA, the response of subjects receiving HCQ will be compared to the response of subjects receiving placebo. The use of a control arm will additionally provide data for evaluation of safety of HCQ in this subject population as well as natural history data regarding the evolution of RA-related autoimmunity in preclinical disease.

1.5.4 Rationale for the Inclusion Criteria

The goal of the inclusion criteria is to identify subjects that are at high-risk for developing IA and clinically-apparent RA within 3 years. As discussed above, there are numerous genetic and environmental risk factors for RA; however, while it is intriguing to consider genetic and environmental factors in the prediction of RA, there is not clear data to date that evaluating genetic and environmental factors adds substantial predictive power to future RA beyond that of anti-CCP positivity. In particular, Bos et al. demonstrated that within anti-CCP positive subjects, the presence of the SE was not associated with increased risk for progression to RA [85]. As such, genetic factors including the presence of the SE as well as environmental exposures will be assessed in this study, although these factors will not be used in the development of inclusion/exclusion criteria.

1.5.5 Rationale for the Exclusion Criteria

The goal of the exclusion criteria is to ensure that subjects who have already developed RA-like synovitis are excluded from the study. Subjects are also excluded to minimize the potential that they will receive immunomodulating therapy for conditions other than RA that could affect the

outcomes of the study. In addition, subjects are excluded to ensure safety as well as to ensure a homogenous study population.

1.5.6 Rationale for Mechanistic Studies

The mechanistic studies will provide insights into the immunobiology of early RA that should further the understanding of disease development and potentially lead to additional types of preventative approaches for RA, including targeted biologic/small molecule therapeutics and potentially antigen-specific tolerance induction.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Primary Objective

To determine the efficacy of a 12-month course of HCQ to prevent the development of clinically-apparent RA at 36 months in subjects at high-risk for future RA due to high titer elevations of anti-CCP3 (≥ 40 units) but who are without a history or clinical findings of IA at Baseline.

For this study, clinically-apparent RA will be defined using the 2010 ACR/EULAR Classification Criteria as either:

(1) A score of ≥ 6 defining "definite RA" or

(2) A joint examination consistent with RA-like synovitis with ≥ 1 erosion identified via x-ray imaging of the hands, wrists, and feet.

2.2 Secondary Objectives

Secondary objectives for the study include:

1. To evaluate the safety of a 12-month course of HCQ in subjects who are at high-risk for development of RA.
2. To evaluate the impact of HCQ on development of clinically-apparent RA (as defined above in Section 2.1, *Primary Objective*) in high-risk subjects 12 months after initiation of study treatment.
3. To evaluate the impact of HCQ on development of IA, that may or may not meet criteria for RA, in high-risk subjects 12 months after initiation of study treatment.
4. To evaluate the impact of a 12-month course of HCQ on the timing of development of clinically-apparent RA (as defined above in Section 2.1, *Primary Objective*) over the entire study period.
5. To evaluate the impact of a 12-month course of HCQ on the timing of development of IA, that may or may not meet criteria for RA, over the entire study period.
6. To explore the relationship between baseline and evolving symptoms[3], risk factors[4] and the development of future clinically-apparent RA and response to HCQ.

[3] Baseline RA symptoms include self-reported joint pain, stiffness, and swelling, and overall fatigue.

7. To evaluate the relationship between treatment with HCQ and amelioration of symptoms[3] of RA, and potential delay in onset of symptoms.
8. To explore underlying immune responses over time in the early natural history of RA development and in response to HCQ therapy through measurement of a variety of biomarkers.

3 STUDY DESIGN

3.1 Description of Study Design

This is a phase 2 multicenter, randomized, placebo-controlled, double-blind, parallel-group, 36-month clinical trial to evaluate the effectiveness and safety of intervention with a 12-month course of HCQ to prevent the future onset of clinically-apparent RA (see definition in Section 2.1, *Primary Objective*). At screening, study subjects will be without IA but will be at high-risk for developing future RA within the trial period as indicated by elevated anti-CCP3 antibodies that are ≥40 units (that is a level ≥2 times the normal cut-off of ≥20 units). Two hundred eligible subjects will be randomized in a 1:1 ratio to receive either self-administered HCQ or placebo.

Subjects will provide informed consent prior to any Pre-Screening or Screening procedures. Subjects who are found to be eligible after the screening evaluation will return for a Baseline/Randomization visit within 30 days of the initial screening visit. Subject eligibility will be confirmed prior to randomization. Eligible subjects will be randomized to receive either 200 - 400 mg of HCQ or placebo daily for 12 months based upon ideal body weight (IBW) at Screening. The weight-based dosing regimen for the study is outlined in Section 5.2, *Dosage Regimen*.

Subjects will return to the study site for planned evaluations at Weeks 6, 12, 24, 36, and 52 (End of Treatment), and Months 18, 24, 30, and 36 (End of Study). During these study visits, subjects will have a joint exam and a physical examination. Study personnel will record the subject's interval medical history, assess AEs, and collect samples for safety and mechanistic assessments (see Tables 6.1 and 6.2, *Schedule of Events,* for specific assessment schedule). Information on demographics (including socio-economic status and education), and other factors that may influence autoimmunity (e.g. tobacco exposure, hormonal status and exposures) will also be collected.

Site coordinators will also call subjects at Week 18, 30, and 42, and at Month 15, 21, 27, and 33 to answer subject questions, update contact information, and to assess AEs/reactions, study drug dosing and pregnancy status (during the treatment period), and joint symptoms,. If a subject indicates that he/she is experiencing joint symptoms suggestive of RA (that include new or worsening joint pain, stiffness or swelling since the prior study visit) or symptoms suggestive of an AE, the subject will be asked to return to the study site for evaluation via an unscheduled visit as soon as possible. Visits and assessments for subjects who develop RA, IA with erosions, or who become pregnant prior to the Month 36 visit will be different from subjects who never develop these conditions. Details of these assessments may be found in protocol sections 6.5.9, *Evaluations Triggered by a Swollen Joint,* 6.5.10, *Procedures for Subjects Diagnosed with*

[4] Risk factors include but are not limited to age, sex, genetic factors, socio-economic status, education, tobacco exposure, medications and medical hormone use, and dietary factors.

Inflammatory Arthritis or Rheumatoid Arthritis by an Outside Physician, and 6.5.11, *Special Considerations for Pregnant Subjects*.

Subject use of non-immunomodulatory agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS), and herbal supplements are allowed. DMARDS, systemic corticosteroids, and biologic therapies are prohibited during study participation as outlined in Section 5.6, *Prohibited Medications.*

After completing the screening period, the expected duration of study participation for each subject is 36 months.

The enrollment period is projected to be approximately 24 months from the opening of the first 75% of study sites.

3.1.1 Stratification, Randomization, and Blinding

Subjects will be randomized in a 1:1 ratio to either HCQ or placebo. As some study sites may only randomize a few subjects, an adaptive randomization procedure based on Pocock and Simon[165] minimization concepts will be used to increase the likelihood of balance between treatment arms on key factors associated with progression to clinically-apparent RA. The key factors will include smoker status (smoker vs. non-smoker), study site, and method of recruitment (i.e. FDR, general population, or clinic screening. For additional detail on recruitment strategies, see Section 4.3, *Strategies for Recruitment and Retention*).

To maintain the study blind, the appearance of the study treatments, HCQ and placebo, and their packaging will be identical. Clinical staff will be blinded to the treatment assignments until completion of the study with the exception of an unblinded pharmacist. In addition, clinical staff members, including the investigators, will not have access to any mechanistic data, and mechanistic laboratory staff will not have access to any clinical results until completion of the study.

An individual's treatment assignment will only be unblinded if the subject experiences a suspected adverse reaction that is serious and unexpected (see Section 7.2.2, *Adverse Reaction and Suspected Adverse Reaction* and Section 7.2.3, *Unexpected Adverse Reaction*) or other protocol-specific event(s) determined by DAIT/NIAID to warrant unblinding.

3.1.1.1 Subject Completion and Replacement

A subject is considered to have completed the study if he/she has completed the Month 36 visit. Subjects who withdraw from the study prior to receiving drug will not be counted towards the target accrual of 200 subjects. Eligible subjects receiving at least one dose of study drug will count towards target accrual.

3.2 Description of Primary Endpoint

The primary efficacy endpoint is the development of clinically-apparent RA by 36 months, where clinically-apparent RA is defined in Section 2.1, *Primary Objective*.

3.3 Description of Secondary Endpoints

3.3.1 Secondary Efficacy Endpoints

1. Time to development of clinically-apparent RA as defined in Section 2.1, *Primary Objective*.
2. Time to development of a swollen joint(s) that is (are) consistent with RA-like synovitis.
3. Development of clinically-apparent RA by 12 months, where clinically-apparent RA is defined in Section 2.1, *Primary Objective*.
4. Development of a swollen joint(s) that is (are) consistent with RA-like synovitis by 12 months, where synovitis is determined by joint exam.
5. Trends in disease activity during the treatment period (i.e. Baseline through Week 52) will be evaluated over time using multiple indices:
    - Physician assessed tender joint count
    - Physician assessed swollen joint count
    - DAS28-CRP score
    - Clinical Disease Activity Index (CDAI)
    - Routine Assessment of Patient Index Data 3 (RAPID-3)
6. Trends in disease activity during the post-treatment follow-up period (Week 52 through Month 36) will be evaluated over time using multiple indices (as noted in above).
7. Trends in patient self-reported evaluations of joint pain, stiffness and swelling will be evaluated over the treatment period (i.e. Baseline through Week 52). The following endpoints are of interest:
    - Total number of painful joints
    - Total number of stiff joints
    - Total number of swollen joints
    - Number of painful joints in the hands, in the wrists, in the feet
    - Number of stiff joints in the hands, in the wrists, in the feet
    - Number of swollen joints in the hands , in the wrists, in the feet
8. Trends in patient self-reported evaluations of joint pain, stiffness and swelling will be evaluated over the post-treatment follow-up period (Week 52 through Month 36). See specific endpoints noted above.
9. Trends in patient-reported outcomes (PRO) for physical, mental and social health (collected via NIH Patient-reported Outcomes Measurement Information System (PROMIS) instrument Profile 29 v2.0) will be evaluated over the treatment period (i.e. Baseline through Week 52).

10. Trends in PRO for physical, mental and social health will be evaluated over the post-treatment follow-up period (Week 52 through Month 36).

3.3.2 Secondary Safety Endpoints

Safety for individual subjects will be monitored by assessing AEs and serious adverse events (SAEs) and measuring hematology and clinical chemistry parameters at scheduled visits and unscheduled visits (as needed) throughout the trial. Safety events that might cause discontinuation of treatment for an individual or trigger a safety review of the study by the Data and Safety Monitoring Board (DSMB) are described in Sections 5.8.1, *Study Treatment Discontinuation* and 5.8.3, *Safety Stopping Guidance*, respectively.

Safety analyses are described more fully in Section 8.3.2, *Safety Analysis*, but the following endpoint is of particular interest in describing the safety profile of HCQ for prevention of RA:

- The proportion of subjects in each arm experiencing a Grade 3 or higher AE according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) system.

3.3.3 Secondary Mechanistic Endpoints

1. Levels of anti-CCP3 over time
2. Levels of IgM-RF over time
3. Levels of hsCRP over time
4. Gain/Loss of autoantibody reactivity to citrullinated protein as measured by ACPA array.
5. Expansion/contraction of inflammation as measured by a multiplex cytokine and chemokine array.

4 SELECTION OF SUBJECTS

Written informed consent must be obtained prior to the subject undergoing any study-related procedure, including screening tests.

4.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment into the study:

1. Able and willing to give written informed consent and comply with requirements of the study.
2. Age ≥18 years-old at the Screening Visit.
3. Elevation of anti-CCP3 ≥40 units at Screening.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria are ineligible to participate in the study:

1. Medical history or current evidence of IA (any type) and/or rheumatic disease and immunologic diseases that may be associated with IA. These diseases include but are not limited to RA, SLE, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and reactive arthritis), inflammatory bowel disease (including Crohn's and ulcerative colitis), Sjögren's syndrome, scleroderma, polymyalgia rheumatica and vasculitis. Patients with mild/moderate crystalline arthropathies do not need to be excluded.
2. Prior or current systemic treatment with DMARDs, immunomodulatory agents, or glucocorticoids for IA or other rheumatic or immunologic diseases. See Section 5.6, *Prohibited Medications*, for a list of excluded medications.
3. Tetracycline class antibiotic use for autoimmune conditions, taken within 12 months prior to Screening. *Note: If a tetracycline class antibiotic is used for non-autoimmune conditions, it should be stopped at Day 0/ Randomization visit.*
4. Systemic corticosteroid use for non-IA conditions taken 28 days prior to Screening.
5. A history of a chronic condition that in the opinion of the investigator is highly likely to require therapy with systemic corticosteroids (oral, intramuscular (IM) or intravenous (IV)) within the study period including but not limited to severe asthma and severe crystalline arthropathy.
6. More than 3 local corticosteroid injections, including but not limited to intra-articular, epidural, and intra-bursal injections, during the 3 months prior to randomization.
7. Women who are pregnant, breastfeeding or desire to become pregnant and/or breast feed within the duration of the 12-month treatment phase of the study.
8. Women of childbearing potential not using or agreeing to use adequate birth control measures (e.g., total abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization, Depo-Provera, or hormonal implants) during the treatment phase of the study.
9. Functional status of NY Heart Association (NYHA) Class III or higher (see Section 15.4, *NYHA Classification*) at the screening visit.
10. Medical history of cardiomyopathy, congestive heart failure, or significant cardiac conduction disorders. Cases of surgically corrected conduction disorders with no cardiac damage, no recurrence, and no need for medication may be eligible.
11. Medical history of chronic liver disease.
12. Medical history of psoriasis (due to potential for increased risk for flare of skin disease) or porphyria.
13. Medical history or serologic evidence at Screening of chronic infections including, but not limited to, human immunodeficiency virus (HIV), hepatitis B, and untreated hepatitis C.
    - *Note: A subject who is Hepatitis C antibody positive will be eligible to participate in the study if he/she is negative for viral load at Screening or has documentation of treatment and negative hepatitis C viral load at least 12 weeks post- treatment.*
14. History of malignancy within the last 5 years, except for treated basal or squamous cell carcinoma, treated cervical dysplasia, or treated in situ cervical cancer Grade I.
15. A history of alcohol or substance abuse within 1 year of randomization.
16. Ideal or actual body weight ≤24.4 kg (see Table 5.1 in Section 5.2, *Dosage Regimen*) at Screening.

17. Any of the following laboratory abnormalities at the Screening visit:
    - Serum creatinine clearance < 50 ml/min (as calculated by the Cockcroft-Gault formula)
    - Alanine Aminotransferase (ALT) > 2x the upper limit of normal (ULN)
    - Aspartate Aminotransferase (AST) > 2x the upper limit of normal (ULN)
    - Total white blood count (WBC) < 3.0 x 10^9/L
    - Platelet count ≤ 150 x10^9/L
    - Hemoglobin < 11 g/dL
    - Absolute Neutrophil Count (ANC) < 2.0 x 10^9/L
18. Evidence of significant retinal disease upon eye examination during the screening period that in the opinion of the examiner would make identification of potential future retinal toxicity from HCQ difficult to evaluate. *Note: Retinal exam results may be applied to evaluations of subject eligibility for up to 6 months after the initial retinal exam.*
19. The physician may exclude, for any reason, any subject he/she does not believe would be a good study candidate.

4.2.1 Co-enrollment Guidelines

Subjects may be in observational registries or cohorts as long as the combined blood draw totals do not exceed the limits of NIH or the local institutional review boards. If a subject elects to participate in any other sort of study or clinical trial, the subject may be withdrawn at the discretion of the NIH/NIAID/DAIT.

4.3 Strategies for Recruitment and Retention

Subjects with elevated anti-CCP levels that meet assay positivity criteria will be identified for this trial through three general approaches that will include the following:

- Pre-screening FDRs of patients with RA.
- Health-fair, biobank, or other population-based pre-screening.
- Identification in rheumatology clinics of subjects with ACPA positivity in the absence of IA.

Overall, these three subject pools provide a sampling of the types of subjects for whom this preventative approach would be applicable in a real-world fashion at the completion of a successful trial. Anticipated recruitment for each pool is discussed in the following subsections.

4.3.1 FDRs of probands with RA

For this prevention trial, FDRs will be targeted for screening, because of their higher rates of positivity for RA-related autoimmunity, and higher risk for incident RA when compared to the general population (estimated 3-9 fold increased risk) [166]. Importantly, FDRs also represent a population that several participating study sites are familiar with in terms of identification and recruitment for studies of the history of RA as part of the Studies of the Etiology of Rheumatoid Arthritis (SERA) Project [167]. For the SERA project, FDRs without IA/RA are followed prospectively to study the natural history of RA [168].

For this clinical trial, probands will be identified and contacted via letter or in clinic. The study will be explained to the probands, and the proband will then communicate study information to their FDRs. These FDRs will then contact study personnel if they are interested in being evaluated for participation in the study. FDRs may also be recruited through distribution of flyers or other study promotional materials. Once the FDRs have contacted the site and have been consented, the FDRs will be evaluated using a brief questionnaire that assesses if they have a prior diagnosis of RA, and tested for anti-CCP. No physician evaluation will be needed at this initial Pre-Screening. FDRs meeting the biomarker inclusion criteria and who do not have RA based on their questionnaire responses will be invited back for a study screening visit, and invited to enroll if they meet study entry criteria.

Based on published data and pilot analyses in the SERA project, the focus for recruitment will be on FDRs of probands with seropositive RA, which will maximize the identification of FDRs who are most likely to meet inclusion criteria. **To avoid possible issues of familial correlation, our strong preference is to randomize only 1 FDR per family. Subjects will be asked about participation of immediate family members during the consent process. However, recognizing operational barriers to accurately track family membership and our suspicion that multiples per family will be a rare occurrence, multiple FDRs per family may be randomized.** With this approach, based on data from evaluations of ~2,500 FDRs to date at several of the sites that will be participating in this trial , it is projected that ~2% of FDRs pre-screened will be eligible for this study. Based on a pilot feasibility study, we conservatively estimate that ~40% of eligible FDRs will agree to participate in this trial (See Section 1.5.1 *Rationale for the Treatment Arm*, bullet 5).

4.3.2 Health-Fair, Biobank, or Population-based Pre-Screening

Subjects who are candidates for this trial may be identified through population-based screening activities such as testing for CCP at a health-fair or other similar setting. For example, since 2008, under the direction of Kevin Deane, the University of Colorado has collaborated with the Colorado-based "9Health Fair", so named because of its early association with a local television station broadcast on Channel 9 [169], to evaluate over 10,000 individuals for undiagnosed RA or risk for future RA based on CCP positivity. Through these efforts, 160 (~1.8%) individuals with a CCP test ≥2x normal in absence of IA have been identified demonstrating that this method can be effective to identify individuals who are at high-risk for future RA.

For this clinical trial, it is projected that ~ 8-10,000 subjects will be evaluated at health-fairs that include the Colorado-based 9Health Fair, as well as health-fairs at other study sites. The procedure for initial evaluation will entail a brief questionnaire that assesses if they have a prior diagnosis of RA, and blood testing for anti-CCP. Subjects meeting the biomarker criteria for the study and who do not have RA based on their questionnaire responses will be invited back for a study screening visit, and invited to enroll if they meet study entry criteria.

4.3.3 Rheumatology Clinics

Individuals who are anti-CCP positive in the absence of IA (with testing typically performed by primary care providers for evaluation of non-inflammatory musculoskeletal pain) are evaluated regularly and with increasing frequency in rheumatology clinics, raising an important clinical

issue regarding how to manage these patients, and potentially prevent them from developing clinically-apparent RA. Importantly, in discussion with multiple clinicians these patients are on occasion being treated with HCQ if they have symptoms that are interpreted as related to RA, even in absence of IA. Therefore, formalizing the benefit of this therapy could lead to a significantly improvement in clinical care.

Briefly, these subjects will be identified through IRB-approved means including screening clinic registries and medical records, and making practitioners aware of this clinical trial. Individuals meeting inclusion criteria will be approached for trial screening and enrollment.

5 TREATMENT OF SUBJECTS

5.1 Description of Study Product

5.1.1 Product Description

HCQ is a non-biologic antimalarial drug that is used as a DMARD with the chemical configuration of 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino] ethanol sulfate (1:1). This colorless, crystalline solid is soluble in water to at least 20 percent and has the following inactive ingredients: Dibasic calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 400, Polysorbate 80, corn starch, and titanium dioxide[155].

Placebo will be a solid compound consisting of fast-flo lactose (39%, 136.5mg/tablet), Avicel (PH102, NF, 60%, 210mg/tablet), and Magnesium Stearate (NF, 1%, 3.5mg/tablet).

Both the HCQ and placebo will be encapsulated in a blue, opaque, hard gelatin capsule. Any void space will be filled with microcrystalline cellulose. The HCQ and placebo tablets will appear identical. More information for the HCQ product used in this study can be found at http://www.prasco.com/our-products.html (search hydroxychloroquine).

5.1.2 Packaging and Labeling of Study Product

HCQ 200 mg tablets (or placebo) will be packaged in a single, light-resistant bottle with a 50 pill supply per bottle.

The label will include conditions for storage, a unique bottle ID, and other pertinent information such as Sponsor, expiration date, and caution statement. Neither HCQ nor placebo should be used after the expiration date unless a written notification of an expiration date extension is provided by the manufacturer.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the pills or bottles, it should not be used. The study drug in question should be quarantined at the study site and the problem immediately reported to DAIT/NIAID or their representative.

5.1.3 Storage and Handling of Study Product

The study Site Principal Investigator and site pharmacist are responsible for the appropriate storage of study drug at the site. HCQ and placebo must be stored at room temperature, between 59 and 86°F (15 and 30°C), in a tightly closed, light resistant bottle[155].

5.1.4 Study Product Accountability

Both the investigational drug that is used during the course of the study, as well as any remaining unused investigational drug, must be accounted for on a drug accountability record provided or approved by the study sponsor or its designee. This documentation must include complete, accurate recording of shipment receipt(s), dispensing, and returns of the study product as required by the ARA08 protocol and applicable law. A copy of all completed drug accountability records must be placed in the Investigator's Study Files (ISF) after the closure of the study, once study treatment assignments are unblinded to clinical staff, and a copy sent to the study sponsor or its designee. Study product must be used only in accordance with the ARA08 protocol and for no other purpose, and is non-transferable to any party other than the sponsor/manufacturer; with no modification, replication, or other engineering derivative undertaken.

All bottles of study product that were not dispensed need to be returned to the distribution vendor. Bottles of study product that are dispensed, must be returned to the site pharmacy and may be sent back to the distribution vendor, or may be destroyed onsite, after a confirmatory pill count is completed (see the ARA08 Investigational Product Dispensing and Administration Manual.).

5.2 Dosage Regimen

Subjects participating in this study will be randomized to receive 200 – 400 mg/day (1-2 pills) of either active HCQ or 1-2 pills of placebo for 12 months with dosing based upon Screening IBW as outlined in Table 5.1.

Table 5.1. Weight-based dosing regimen for HCQ (and placebo)

Weight (kilograms based on IBW*)	Number of pills**
≤ 24.4 kg (ideal or actual body weight)	Excluded from trial
> 24.4 - < 47 kg	1 pill daily
≥ 47 kg	2 pills daily

*IBW based on the following calculation:

- Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet, or subtract 1kg for every inch under 5 feet.
- Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet, or subtract 1kg for every inch under 5 feet.

Each 200 mg HCQ pill contains 155 mg of active drug. These dosing regimens are designed to not exceed a dose of 6.6 mg/kg/day of active drug. In subjects ≥ 47 kg, 2 pills daily = 310 mg/day of active drug. This dose may be lower than 6.6 mg/kg/day; however, given 2 pills daily is used commonly in clinical practice and is a dosing regimen that is comfortable for most rheumatology practitioners. We will not exceed 2 pills daily for this study.

For some individuals, this dose may be somewhat higher than the 2016 recommendation of the American Academy of Ophthalmology which has recommended that doses of <5 mg/kg/day of actual body weight be used to avoid eye toxicity [153]. For this study we will be using the weight-based dosing regimen noted above because prior studies that have demonstrated the efficacy of HCQ in rheumatic disease have used a HCQ dose of ≤ 6.5 mg/kg/day based on ideal body weight. In addition, the rates of eye toxicity from HCQ within the first year of therapy at doses ≤ 6.5 mg/kg/day are <1%.

5.3 Administration of Study Product

5.3.1 Preparation for Administration

Upon subject randomization, the unblinded pharmacist will receive a notification from the randomization system, outlining the subject treatment assignment, Screening IBW, and the number of pills that should be taken each day.

The unblinded pharmacist will apply an auxiliary label to the bottle prior to distribution that indicates how many pills should be taken by the subject each day.

5.3.2 Administration

Study subjects will be instructed to take 1 or 2 pills of study therapy daily based upon their IBW [155].

Subjects will take the first dose of study therapy in clinic at the Baseline visit. The subject will be observed per institutional standards.

Study therapy will be dispensed per the table below:

Table 5.2: Study Therapy Distribution

Subject IBW at Screening	Baseline	Week 6	Week 12	Week 24	Week 36
> 24.4 - < 47 kg	1 bottle	2 bottles	2 bottles	2 bottles	3 bottles
≥ 47kg	2 bottles	3 bottles	4 bottles	4 bottles	6 bottles

5.4 Toxicity Management Plan for Study Product

5.4.1 Prevention of Known Toxicities to Study Product

5.4.1.1 Ocular Toxicity

As outlined in protocol section 1.4.2, *Known and Potential Risks of Hydroxychloroquine*, an important AE associated with HCQ use is ocular toxicity and in particular, retinal injury. The current (2016) recommendations for retinopathy screening for HCQ use as put forward by the American Academy of Ophthalmology include a baseline exam within the first year of HCQ use and then annual screening after 5 years of use[153]. While there are not clear associations

between baseline eye abnormalities and future risk for HCQ-related eye injury [153, 170] , this baseline examination helps to identify underlying problems that may make future identification of HCQ toxicity difficult.

For ARA08, the eye examination will include 3 parts: a) dilated funduscopic examination, b) SD-OCT, and c) 10-2 visual field testing. Of note, the 2016 American Academy of Ophthalmology recommends only a dilated funduscopic evaluation at baseline, and further testing with SD-OCT and visual field testing only if there is evidence of retinal disease on the dilated examination [153]. However, we will perform all three tests to provide maximal understanding of possible retinal disease at baseline.

The study excludes individuals with a history of renal and/or liver disease, limits HCQ use to 12 months or less, and restricts HCQ dosing to ≤ 6.5 mg/kg/day of ideal body weight to minimize toxicities.

We will not repeat an ocular examination after subject randomization as part of the official study protocol. If a subject develops ocular symptoms, the subject will be referred to clinical care. Study therapy will be discontinued if the subject develops ocular symptoms as described in Section 1.4.2, *Known and Potential Risks of Hydroxychloroquine.*

5.4.2 Management of Known Toxicities to Study Product

5.4.2.1 Hematologic Reactions

Subjects in the study will have complete blood counts obtained at Screening, Week 24, and Week 52. If changes suspicious of HCQ-related effects occur, study therapy will be discontinued (see Section 5.8.1, *Study Treatment Discontinuation*).

5.4.2.2 Gastrointestinal Reactions

Gastrointestinal reaction and liver injury will be assessed throughout the subject's participation in the study. (See Section 5.8.1, *Study Treatment Discontinuation*, for criteria for discontinuation of study therapy.)

5.4.2.3 Allergic Reactions

Subjects will be counseled during study enrollment about the possible reactions as outlined in Section 1.4.2.2, *Additional Toxicities*, and will be instructed to stop the study drug immediately if allergic reactions develop, and seek medical attention.

5.4.2.4 Over Dosage

There have been fatal reactions described with overdoses of HCQ and, therefore, individuals that overdose on study product must immediately seek emergency medical attention and inform health care providers of the possibility of ingestion of HCQ. In the event of an overdose, the subject and/or appropriate clinical staff may be unblinded.

5.5 Concurrent Medications and Therapy

Agents such as acetaminophen, NSAIDS and herbal supplements are allowed, although the subject is required to report all of these medications to the study investigators. **Absorption of HCQ can be impaired if taken simultaneously with antacids; a four hour window between drug administrations is recommended.** HCQ has been reported to cause hypoglycemia. It is suggested that subjects taking hypoglycemic agents have their blood sugar monitored and medication doses adjusted as necessary. Additionally, digoxin levels may increase with the administration of HCQ. Dose adjustment may be needed. All such medications are to be recorded in the study documents.

Use of corticosteroids for non-IA conditions is allowed, as follows:

- Systemic corticosteroid use may include short courses defined as ≤ 21 days at doses of ≤ 60 mg daily of prednisone or equivalent for treatment of allergic or infectious conditions (e.g. asthma flare, sinusitis), and must be limited to 2 courses of corticosteroids per year.
- Systemic corticosteroid use within 3 weeks of the Month 36 visit is prohibited.
- Local steroid injections for non-IA conditions are limited to 3 injections within the 3 months prior to Month 36.
- If an intra-articular injection for a non-IA condition occurs within 3 weeks of any visit, the impacted joint will not be assessed at the visit.

5.6 Prohibited Medications

Use of DMARDS, systemic corticosteroids, and biologic therapies, as noted below are prohibited during study participation.

- Any small molecule for the treatment of RA or other immunologic conditions
- Any biologic therapy for the treatment of RA or other immunologic conditions
- Oral, intravenous, intramuscular, or intraarticular systemic corticosteroids for IA
- MTX
- LEF
- Cyclosporine (excluding eye drops)
- Mycophenolic acid
- Cyclophosphamide
- Chlorambucil
- Penicillamine
- Azathioprine or 6-mercaptopurine
- HCQ
- SSZ
- Tofacitinib
- Tacrolimus (excluding topical)

Note: Chronic use of tetracycline class antibiotics is prohibited. Short courses for treatment of acute infection are allowed.

If there are other agents that the study investigator believes may be immunomodulatory, discuss with the protocol team.

5.7 Procedures for Monitoring Subject Compliance

At each visit during the treatment period, subjects must return their drug bottles, and drug/placebo will be assessed by study personnel via pill counts. Accountability of study drug must be done in the presence of the subject in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Accountability of the study drug must be recorded on the drug accountability form.

5.8 Treatment Discontinuation and Subject Withdrawal

5.8.1 Study Treatment Discontinuation

Study treatment will be discontinued permanently for any individual subject under the following conditions:

1. At any time during the study at the request of the subject or subject's guardian.
2. If investigators or NIAID determine that the subject's health, safety, and/or well-being are threatened.
3. If the subject is administered any of the medications outlined in Section 5.6, *Prohibited Medications*, whether the medication is prescribed by a study site investigator or an outside physician. Study drug should be discontinued at the time the study team becomes aware that the subject has started prohibited medications.
4. Study treatment will be discontinued for any subject who experiences any of the following:

    a. Pregnancy
    b. Development of clinically-apparent RA via the 2010 ACR/EULAR Criteria (defined as a score ≥ 6, OR findings consistent with RA-like synovitis paired with ≥ 1 erosion(s) identified by x-ray) at a single study visit.
    c. An AE of Grade 3 or higher by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) that is probably, possibly, or definitely related to HCQ.
    d. Retinal disease consistent with HCQ toxicity as described in Section 1.4.2, *Known and Potential Risks of Hydroxychloroquine.*
    e. Any allergic reaction attributed to study drug (see Section 1.4.2.2, *Additional Toxicities*)
    f. Any of the following persistent lab abnormalities:
    Note: Abnormal lab values meeting a criterion noted below should be confirmed within 4 weeks, prior to discontinuation.
        i. Serum creatinine clearance < 50 ml/min;
        ii. ALT or AST ≥ 3.5x the upper limit of normal (ULN);
        iii. WBC ≤ 2.5 x10^9/L;

iv. Platelet count < 75 x10^9/L;
v. Hemoglobin < 10 g/dL;
vi. ANC < 1.5 x10^9/L

Subjects who discontinue protocol-specified treatment requirements will be treated as medically indicated according to physician discretion.

5.8.1.1 **Procedures for Discontinuation of Protocol-Specified Treatment Requirements**

Whenever possible, subjects who have been discontinued from study treatment should complete all scheduled study visits including all exams, procedures, assessments, and tests for the duration of the study. The HCQ level specimen will be collected at any visit where study therapy is discontinued, provided it was not previously collected. Furthermore, if discontinuation is due to safety concerns, subjects will be given appropriate care under medical supervision beyond the last scheduled study visit, if necessary, until the symptoms of any AE resolve or the subject's condition becomes stable. If the site Principal Investigator (PI) determines that completion of these visits is not clinically appropriate for the subject or if the subject or subject's guardian elects not to complete these visits, the subject will be withdrawn from the study per the guidelines in Section 5.8.2.1, *Procedures for Subject Withdrawal from the Study*.

5.8.2 **Subject Withdrawal from the Study**

When a subject is withdrawn from the study, protocol-specified treatment requirements are discontinued, and study-related visits, exams, procedures, assessments, tests and data collection are terminated. Individual subjects will be withdrawn from the study under the following conditions:

1. The subject or subject's guardian withdraws consent.
2. The investigator or NIAID believes it is in the best interest of the study or the subject.
3. If the subject elects to participate in any other sort of study or clinical trial (excluding observational registries or cohorts), the subject may be withdrawn at the discretion of the DAIT/NIAID/NIH.

5.8.2.1 **Procedures for Subject Withdrawal from the Study**

Subjects who plan to withdraw early from the study regardless of the reason will be asked to consent to annual phone calls to answer inquiries about the development of RA and related information until the subject reaches 3 years past randomization.

Whenever possible, subjects to be withdrawn from the study will be asked to come in for an end-of-study evaluation, which includes all scheduled exams, procedures, and laboratory tests planned for the Month 36 visit. After this end-of-study visit, the site PI (or designated treating physician) may continue to follow the subject to manage clinical care, but no additional study-related data will be collected.

5.8.3 Safety Stopping Guidance

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews or emergency meetings. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger a safety review:

1. Any immediately life threatening event or death that is possibly, probably, or definitely related to HCQ.
2. The number of subjects in the HCQ arm who experience an SAE that is at least possibly related to HCQ during the 12 month treatment period reaches a level listed in Table 5.3
    - The values for the "# of HCQ subjects with an SAE" in Table 5.3 are derived under the assumption that the maximum tolerable risk of an SAE is 10% for subjects in the HCQ arm. If this risk is truly $\leq 10\%$, then the chance of observing the indicated "# of HCQ subjects with an SAE" (or more) is small (i.e. probability ≤ 0.1). As such, hitting this boundary suggests the actual risk may exceed 10%, hence, warranting a closer look at the data.
    - If a DSMB Emergency Safety Review is called due to this rule, and the decision is to continue the study, then the DSMB may also consider how many new SAEs should accrue before a subsequent emergency review will be required.

Table 5.3. Number of SAEs in the HCQ arm that would trigger a DSMB Emergency Safety Review

# of HCQ subjects	≤5	6-11	12-18	19-25	26-32	33-40	41-47	48-55	56-63	64-71	72-79	80-87	88-96	97-100
# of HCQ subjects with an SAE	2	3	4	5	6	7	8	9	10	11	12	13	14	15

For the events noted above, the DSMB chair will review details of the events and decide whether or not the full committee should convene for a DSMB Emergency Safety Review. A halt in enrollment will occur if the DSMB Emergency Safety Review is not completed within 3 weeks. In the event of a temporary halt in enrollment, no new subjects will be consented or start on therapy with HCQ or placebo; subjects already on HCQ or placebo will continue on therapy unless they are the focus of the DSMB review. Subjects in the screening phase of the study may continue to undergo minimal risk procedures (e.g., blood tests), but more than minimal risk procedures should be deferred. Randomization will not occur until the DSMB review is complete. After careful review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

6 ASSESSMENT OF SAFETY AND EFFICACY

6.1 Assessments of Safety

To assess safety in this population, chemistries and hematologies will be evaluated at Screening, and at visits scheduled at Weeks 24, and 52 (End of Treatment). Physical exams and vital sign assessments will be assessed at clinic visits per Tables 6.1 and 6.2, Schedule of Events. These safety evaluations may also be performed at any unscheduled Visits.

Additionally, medical history will be collected at Screening and Baseline. AEs of NCI-CTCAE Grade 2 and above will be recorded at each scheduled visit through Month 18 (see protocol section 7.3.2, *Collection Period*, for additional details). Site coordinators will also collect information regarding AEs during the telephone assessments and during the treatment and follow-up periods. AEs of NCI-CTCAE Grade 3 or greater are of particular interest for safety endpoints.

6.2 Assessments of Efficacy

6.2.1 ACR/EULAR Criteria (2010)

The primary outcome of this trial is the development of clinically-apparent RA (see definition in Section 2.1 *Primary Objective*) based on both clinical examination findings and laboratory testing.

If a subject presents with swollen joint(s) that are consistent with RA-like synovitis, all the items necessary to establish the fulfillment of the 2010 ACR/EULAR criteria will be ascertained (See Table 1.1); however, the laboratory parameters including IgM-RF, CCP and hsCRP will be tested at a central laboratory. Hence, the final determination as to whether or not the subject met criteria for clinically-apparent RA will be delayed (< 21 days). Of note, due to issues regarding sample stability and test reproducibility, hsCRP will be used for the calculation of the ACR/EULAR criteria and disease activity measures; ESR will not be used.

6.2.2 Joint Assessment, Definitions of Inflammatory Arthritis, and Joint Tenderness

IA: IA is defined as the presence of a swollen joint(s) that is (are) consistent with RA-like synovitis, in the determination of the examiner, and graded as present (1) or absent (0). At each study visit, the examiner will perform a joint count to identify RA-like synovitis (excluding the hip which cannot be evaluated for swelling on physical examination), and record these findings. A single examiner across visits for a given subject is highly encouraged, though not required.

Tenderness: Tenderness is defined as subject-reported sensation of pain with examination (examiner direct joint pressure sufficient to blanch the nail bed of the examiner), or with passive range-of-motion of the joint by the examiner. At each post-screening study visit, the examiner will perform a joint count to identify joint tenderness, and record these findings.

6.2.3 Determination of disease activity

6.2.3.1 Disease Activity Score (DAS)

The DAS is a validated instrument widely used to assess RA disease activity in research and clinical practice [24, 171]. In particular, the versions of the DAS that are commonly used in outcomes assessment in RA includes either a 28 or 44 joint count, and measurement of CRP – with this being entitled the DAS28 (or 44) CRP. The DAS28-CRP will be the primary measure for evaluating disease activity. Results are calculated using an established formula and yield continuous variables (See Appendix 15.3, *Formulas*). The items for the DAS scores will be using

the modified MDHAQ for Subject Global Health (see below), joint examination form for tender and swollen joints, and the hsCRP from laboratory testing.

6.2.3.2 **Modified Multi-Dimensional Health Assessment Questionnaire (MDHAQ)**

The modified MDHAQ is a validated instrument to assess RA activity in research and clinical practice [24, 172]. It contains questions for the self-assessment of current function (e.g. were you able to get in/out of bed), as well as scales (0 to 10) for pain, global health, and fatigue. In addition, when combined with physician joint counts (tender and swollen) and CRP testing, information from the modified MDHAQ can be used to calculate a variety of measures in RA including the DAS28-CRP (see above), the CDAI, and the RAPID-3. This questionnaire will be completed at each post-Screening study visit.

6.2.3.3 **Patient Reported Outcomes Measurement Information System**

Patient-reported outcome measures (PROs) use subject responses to questions to produce numeric values representing patients' state of well-being or suffering as well as ability or lack of ability to function. The NIH funded leading investigators to develop a "psychometrically validated, dynamic system to measure PROs efficiently in study participants with a wide range of chronic diseases and demographic characteristics." The PROMIS initiative is part of the NIH goal to develop systems to support NIH-funded research supported by all of its institutes and centers. PROMIS measures cover physical, mental, and social health and can be used across chronic conditions. More information is available at: www.nihpromis.org. For this trial, the NIH PROMIS measure Profile (29 v2.0) will be used, and will be scored to yield continuous variables.

For this trial, the NIH PROMIS measure Profile (29 v2.0) will be completed at Baseline, then annually and at the time of diagnosis.

6.2.3.4 **Questionnaire Assessment of Self-Reported Symptoms**

Self-reported joint symptoms such as pain, stiffness, and swelling may be important measures in predicting future onset of IA [173], as well as in determining response to therapy. However, existing measures of disease activity do not assess joint symptoms in specific areas in adequate detail. As such, a novel questionnaire has been developed that can assess patient-reported joint symptoms of pain, stiffness and swelling in specific joint regions (e.g. metacarpophalangeal joints (MCPs)). These questionnaires will be completed at each post-Screening study visit, and can be scored to yield continuous variables, or can be scored to yield joint symptoms by regions.

6.2.3.5 **X-ray Imaging**

The presence of erosions serves to distinguish RA from other forms of IA (e.g. RA from SLE); in addition, the presence of erosions is an indicator of disease severity [174, 175]. Therefore, at the time of initial identification of a swollen joint(s) that is (are) consistent with RA-like synovitis in the clinical trial, subjects will undergo x-ray imaging of bilateral hands, wrists and feet within 14 days, if possible. Subjects may undergo study-related x-ray imaging a maximum of 4 times throughout study participation. Of note, even if RA-like synovitis is identified outside of these joints areas, these are the only joints that will be evaluated given that they are most commonly

evaluated with x-rays in RA and in other joints findings of erosions may be less clear. The feet will receive two views (anterior-posterior and lateral oblique) and the hands/wrists will receive two views (posterior-anterior and ball catcher).

All females who have the ability to become pregnant will complete a pregnancy test prior to receiving x-rays. A negative result on the pregnancy test must be confirmed prior to the female subject undergoing x-ray procedures. If the pregnancy test yields a positive result, see protocol section 6.5.11, *Special Considerations for Pregnant Subjects*, for additional details.

These x-rays will be read and scored by a central reader who is blinded to the status of the subject to determine the presence/absence and location of any erosions, and this result will be reported to the study site to determine if a subject has met the study's primary endpoint, see protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint,*, for additional details. In addition, the x-rays will be scored using the modified Sharp's score by a central reader. The presence/absence of erosions as well as the Sharp's score can be analyzed in aggregate at the study's completion.

6.3 Environmental and other factors

Multiple environmental and other factors have been associated with increased risk for developing RA (reviewed in [65]). For example, factors associated with increased risk for RA including smoking, parity, recent pregnancy, and periodontal inflammation. Factors associated with decreased risk for RA including oral contraceptive use, high fish intake, and moderate alcohol intake. As such, certain factors may play a role in the prediction of development of RA in CCP positive individuals, or in response to therapy. These factors will be assessed by means of an epidemiologic questionnaire (assessed at Baseline, then annually, and at the time of diagnosis, if applicable) and a dietary questionnaire (administered at Baseline, the End of Study/Month 36 visit, and at the time of diagnosis visit, as applicable).

6.4 Mechanistic Specimens and Studies

6.4.1 Genetic risk factors

Specific gene sequences within the MHC that are, in aggregate, termed the shared epitope (SE) are strongly associated with development of RA [63]. DNA extracted from peripheral blood will be analyzed to determine the presence of this risk factor for each study subject who consents to the optional DNA specimen collection.

6.4.2 HCQ Levels

HCQ levels will be used as a covariant for analyses [176]. A single specimen will be collected from all subjects during the treatment phase of the study. At the completion of the study, after subject treatment assignments are unblinded, HCQ level specimens from subjects randomized to the HCQ treatment arm will be analyzed. Specimens from subjects randomized to the placebo treatment arm will be stored for future studies to broaden our understanding of issues related to the pathogenesis, prediction, and prevention of classifiable RA.

6.4.3 Mechanistic studies

Mechanistic studies will be performed to evaluate the relationship between treatment with HCQ and alterations in biomarkers suggesting improved autoimmunity and/or reduced inflammation, as well as mechanisms of progression to RA. Specifically, we will explore the following scientific hypotheses and concepts:

Impact of HCQ use on biomarkers

- Decreasing levels of the autoantibodies RF and anti-CCP in the HCQ arm compared to the placebo arm would indicate an abrogation of autoimmunity.
- Contraction of the breadth and evolution of specific ACPA reactivities in the HCQ arm compared to the placebo arm would indicate improved autoimmunity.
- Lower levels or contraction of the number of inflammatory markers, including hsCRP, cytokines, and chemokines, in the HCQ arm compared to the placebo arm represent reduced inflammation.

Progression to RA

- Elevation of certain ACPAs sequences early in the trial period among those who develop RA may suggest key antigenic targets in the earliest phases of loss of tolerance in RA.
- Elevations of specific cytokines and chemokines levels among those who develop RA will be evaluated to determine when in the time course of development certain processes are most important, and which processes may be most important in the transition from autoimmunity in absence of clinically-apparent RA to clinically-apparent RA.
- Profiles of autoantibodies and inflammatory markers present at baseline (or developing during the study) that correlate well with (i) the likelihood of IA, (ii) the timing of development of IA, or (iii) the response to HCQ may suggest important pathways in the development of IA and/or identify potential predictors of impending RA or response to HCQ.

To evaluate these key hypotheses and concepts, serum for analyses of Core Outcomes (anti-CCP, IgM RF, and hsCRP) will be collected at Baseline and approximately every 6 months throughout the entirety of the study. Core Outcomes will also be collected at any visit where the joint exam is consistent with RA-like inflammatory arthritis. In addition, serum for the autoantibodies and plasma for circulating cytokines/chemokines will be collected at specific time points outlined in the Schedule of Events (Tables 6.1 and 6.2).

6.4.4 Specimen Storage for Future Use and Genetic Research

As noted above, serum and plasma are required for the key mechanistic studies. Residual serum and plasma from these planned studies as well as additional serum, plasma, peripheral blood mononuclear cells (PBMCs), RNA, and urine will also be collected and stored for future studies designed to explore the mechanisms underlying the response to HCQ, as well as to broaden our understanding of issues related to the pathogenesis, prediction and prevention of classifiable RA. These specimens will be collected at specific time points outlined in the Schedule of Events

(Tables 6.1 and 6.2) and at any visit where the joint exam is consistent with RA-like inflammatory arthritis.

DNA for identification of the SE risk factor will be optional for all subjects. Residual DNA from this analysis will be stored until the end of study and used to confirm results. In addition, if subjects also consent to future genetic research, then residual DNA may be stored for future use. Serum, plasma, PBMCs, RNA, and urine will be stored for all subjects for future research as noted above.

6.5 Evaluations by Study Visit

6.5.1 Pre-Screening

This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study Pre-Screening procedures. As noted in Section 4.3, *Strategies for Recruitment and Retention,* study personnel may use 3 different approaches for identifying and recruiting potential subjects. Pre-Screening procedures at the study site will vary by method of recruitment as outlined below:

FDRs of probands with RA:
Study site personnel will do the following:

a. Explain the study to each proband (i.e. RA patient) and providing them with study-approved materials to share with their FDR(s). In addition, study site personnel are responsible for distributing letters to probands informing them about the trial, and distributing other promotional materials such as hard-copy flyers or e-mails that could be used to identify FDRs.
b. When the site is contacted by the FDR, consent the FDR for an ARA08 Pre-Screening Evaluation.
c. Ask the FDR to complete a Pre-Screening Questionnaire (see Appendix 15.5.1, *Pre-Screening Questionnaire)*
d. Draw an anti-CCP specimen for evaluation at local laboratory.
    - *Note: If clinic data collected within the last 12 months indicate that the anti-CCP assay -specific positivity criterion is met, do not draw this specimen at the Pre-Screening visit; clinic data may be used.*
e. Invite the FDR to an ARA08 Screening Visit if the anti-CCP assay-specific positivity criterion is met, and there is no evidence of RA or IA based on the Questionnaire.
    - *Anti-CCP assay-specific positivity criterion:*
        - *Anti-CCP3/Anti-CCP3.1 assay result ≥ 40, or*
        - *Anti-CCP2 or any other ACPA assay yielding a positive result per assay normal ranges*

Population Screening:

1. Participants recruited at events or facilities serving a more general population (e.g. health fair or clinic) are consented and screened in multiple steps. Study site personnel will do the following:
    a. Consent the subject for the ARA08 Pre-Screening Evaluation (which includes taking a brief questionnaire and a blood draw).
    b. Ask the subject to complete a Pre-Screening Questionnaire (see Appendix 15.5.1, *Pre-Screening Questionnaire*)
    c. Draw an anti-CCP specimen for evaluation at the local laboratory.
    d. Review results of the anti-CCP test and the Pre-Screening Questionnaire.
    e. Invite the participant to an ARA08 Screening Visit if the anti-CCP assay-specific positivity criterion is met, and there is no evidence of RA based on the questionnaire.
        - *Anti-CCP assay-specific positivity criterion:*
            - *Anti-CCP3/Anti-CCP3.1 assay result ≥ 40, or*
            - *Anti-CCP2 or any other ACPA assay yielding a positive result per assay normal ranges*

2. Other recruitment strategies may include CCP testing of samples from blood banks and biorepositories, providing appropriate consent has been obtained.
    a. Subjects with Anti-CCP levels meeting the anti-CCP assay-specific positivity criterion will be contacted per site institutional guidelines.

Rheumatology patients who are anti-CCP positive and without IA:
Study site personnel are responsible for the following:

a. Identify potential subjects using clinic registries and medical records, and make local practitioners aware of this clinical trial.
b. Contact individuals who are potential subjects.
c. If clinic data collected within the last 12 months, indicate that the anti-CCP assay-specific positivity criterion is met, and there is no evidence of RA, then invite the patient to an ARA08 Screening Visit.
d. If additional information is needed, then:
    i. Consent the patient for an ARA08 Pre-Screening Evaluation.
    ii. Ask the patient to complete a Pre-Screening Questionnaire (if needed) (see Appendix 15.5.1, *Pre-Screening Questionnaire*)
    iii. Draw an anti-CCP specimen for evaluation at the local laboratory (if needed).
    iv. Invite the subject to an ARA08 Screening Visit if the anti-CCP assay-specific positivity criterion is met, and there is no evidence of RA based on the questionnaire.
        - *Anti-CCP assay-specific positivity criterion:*
            - *Anti-CCP3/Anti-CCP3.1 assay result ≥ 40, or*
            - *Anti-CCP2 or any other ACPA assay yielding a positive result per assay normal ranges*

If the anti-CCP result does not meet the assay-specific positivity criterion, the potential subject may be Pre-Screened again 6 months after their initial Pre-Screening anti-CCP test.

6.5.2 Screening Visit

Unless otherwise specified, the screening evaluations must be performed within 30 days prior to the Baseline/Randomization Visit.

The following labs, procedures, and assessments will determine subject eligibility:

1. Main study informed consent form
2. Demographics
3. Medical History
4. Prior and Concomitant Medications
5. Physical examination (full)
6. Vital Signs including heart rate, sitting systolic and diastolic blood pressure, height, weight, and waist circumference
7. NYHA classification assessment for heart disease
8. Joint Examination – Physician's Assessment that includes a swollen joint count to identify RA-like synovitis

   Note: Midfoot and hip joints are not evaluated for swelling.

   IMPORTANT: Subjects with swollen joints that are consistent with RA-like synovitis should NOT be randomized or treated.
9. Anti-CCP3 analyzed at the University of Colorado

   Note: anti-CCP3 results from the central lab that are assessed within 6 weeks of the screening visit are valid for evaluation of eligibility and do not need to be redrawn.
10. Screening Chemistries/ Hematologies: Serum creatinine, ALT, AST; WBC, platelets, ANC, hemoglobin
11. Infectious disease testing that includes: HIV-1/HIV-2 Antigen/Antibody, Hepatitis B Surface Antigen, Hepatitis C Antibody. In addition, if Hepatitis C antibody is positive, then viral load should also be tested unless there is documentation of prior Hepatitis C treatment and a report confirming an undetectable viral load ≥12 weeks after the completion of Hepatitis C therapy.

    Note: If any of the infectious disease tests yield a positive result, the site will report these results to the subject and perform other follow-up per institutional guidelines.
12. A retinal exam by an ophthalmologist or optometrist that includes a dilated funduscopic exam, visual field (10-2) and Optical Coherence Tomography (OCT) to be conducted prior to the Baseline visit (after all other screening eligibility criteria have been confirmed). *Note: Results from the initial screening visit retinal examination may be used to assess eligibility for up to 6 months.*

6.5.3 Baseline/Randomization Visit

The baseline evaluations must be performed within 30 days of the Screening visit.

1. Medical History
2. Prior/Concomitant Medications
3. Physical Exam (symptom-driven)
4. Vital Signs including heart rate and sitting systolic/diastolic blood pressure
5. STAT Urine pregnancy test (for women of child-bearing potential)
6. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
    - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
    - *The midfoot joints will not be evaluated for either tenderness or swelling.*
    - *The hip joints will not be evaluated for swelling.*
7. Randomization

    IMPORTANT: Subjects with tender joints and/or swollen joints that are consistent with RA-like synovitis at the time of the Baseline/Randomization Visit should NOT be randomized or treated.

    Note: Sites utilizing a central pharmacy may randomize subjects prior to the Baseline visit after initial eligibility at Screening has been confirmed, but if tender joints and/or swollen joints that are consistent with RA-like synovitis are noted at baseline, do NOT dispense the study medication to the subject.
8. Subject Questionnaires
    - Profile 29 v2.0
    - Epidemiologic Questionnaire
    - Dietary Assessment Questionnaire
    - Self-reported Joint Symptoms, including modified MDHAQ
    - Evaluate family member participation
9. Specimen collection for **real-time** core outcome testing (hsCRP, IgM-RF, Anti-CCP3) and serum for mechanistic studies.
10. Specimen collection for mechanistic studies: PBMC/plasma, RNA, and urine. *Note: DNA will be collected from subjects who consent to the optional specimen for shared epitope analysis.*
11. Dispense study therapy

    Notes:

- ***Female subjects cannot receive study therapy until eligibility can be confirmed via STAT urine pregnancy test.***
- ***The first dose of study therapy will be given in clinic. The subject will be observed per institutional standards.***

6.5.4 Treatment Period

6.5.4.1 Treatment Clinic Visits: Week 6, Week 12, & Week 36 (Visit Windows: +/- 7 days)

1. AE Assessment
2. Concomitant Medications
3. Physical Exam (symptom-driven)
4. Vital Signs including heart rate and sitting systolic/diastolic blood pressure
5. Self-reported Joint Symptoms, including modified MDHAQ
6. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
   - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
   - *The midfoot joints will not be evaluated for either tenderness or swelling.*
   - *The hip joints will not be evaluated for swelling.*
7. Evaluate family member participation

Items 8-11 are only applicable to subjects who have not been diagnosed with clinically-apparent RA at a prior visit.

8. Procedures conditional on results of the Joint Examination
   - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.
   - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis, no additional assessments are needed, proceed as noted below.
9. Subject self-reported pregnancy status
10. Dispense study therapy

    Note: If study therapy is discontinued at this visit, the HCQ level specimen will be collected, provided it has not been previously collected.
11. Pill Counts (at each clinic visit)

6.5.4.2 **Mid-Treatment Clinic Visit: Week 24 (Visit Windows: +/- 7 days)**

1. AE Assessment
2. Concomitant Medications
3. Physical Exam (symptom-driven)
4. Vital Signs including heart rate and sitting systolic/diastolic blood pressure
5. Hematology: Hemoglobin, hematocrit, WBC (with differential), and platelet count
6. Chemistry: Serum creatinine, ALT, and AST

   Note: Abnormal lab values meeting the criteria noted in Section 5.8.1, *Study Treatment Discontinuation,* should be confirmed within 4 weeks, prior to discontinuation.
7. Self-reported Joint Symptoms, including modified MDHAQ
8. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
   - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
   - *The midfoot joints will not be evaluated for either tenderness or swelling.*
   - *The hip joints will not be evaluated for swelling.*
9. Evaluate family member participation

Items 10-14 are only applicable to subjects who have not been diagnosed with clinically-apparent RA at a prior visit.

10. Procedures conditional on results of the Joint Examination
    - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.
    - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis;
      - Specimen collection for **future** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies
11. Specimen collection for HCQ Level analysis
      - *Note: This specimen will be collected at the Week 24 visit, provided the specimen was not collected previously.*
12. Subject self-reported pregnancy status
13. Dispense study therapy

14. Pill Counts (at each clinic visit)

6.5.4.3 End of Treatment: Week 52 (Visit Window: +/- 14 days)

1. AE Assessment
2. Concomitant Medications
3. Physical Exam (full)
4. Vital Signs including heart rate and sitting systolic/diastolic blood pressure
5. Subject Questionnaires
   - Profile 29 v2.0
   - Self-reported Joint Symptoms, including modified MDHAQ
   - Evaluate family member participation
6. Hematology: Hemoglobin, hematocrit, WBC (with differential), and platelet count
7. Chemistry: Serum creatinine, ALT, and AST
8. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
   - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
   - *The midfoot joints will not be evaluated for either tenderness or swelling.*
   - *The hip joints will not be evaluated for swelling.*

Item 9 is only applicable to subjects with a previous diagnosis of clinically-apparent RA:

9. Specimen collection for real-time core outcome testing: hsCRP only

Items 10 - 14 are only applicable to subjects who have not been diagnosed with clinically-apparent RA.

10. Procedures conditional on results of the Joint Examination
    - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.
    - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis;
      - Specimen collection for **real-time** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies

- Specimen collection for mechanistic studies: PBMC, plasma, RNA, and urine. *Note: DNA will be collected from subjects who consent to future genetic testing.*

11. Specimen collection for HCQ Level analysis
    - *Note: This specimen will be collected at the Week 52 visit, in the event the specimen collection was missed at Week 24 and has not been previously collected.*
12. Subject self-reported pregnancy status
13. Epidemiologic Questionnaire
14. Pill Counts

6.5.4.4 Treatment Telephone Assessments (Weeks 18, 30, & 42, Visit Window: +/- 7 days)

After the Baseline visit, subjects will be contacted by study personnel (via a telephone call) at Week 18, 30, and 42. The following information will be obtained during the telephone assessments:

1. Assessment of toxicities and adverse reactions
2. Review of study drug dosing, administration and storage
3. Assessment of joint symptoms
4. Assessment of pregnancy status (if applicable)
5. Invitation for questions
6. Update of contact information

If joint symptoms suggest evidence of new IA defined as new or worsening joint pain, stiffness or swelling since the last study visit or symptoms suggestive of an AE, then the subject will be instructed to return to the clinic for an unscheduled visit as soon as possible (see Section 6.5.8, *Unscheduled Visits*).

Telephone assessments will not occur after a subject is diagnosed with definite RA, IA with erosion(s), or is found to be taking a prohibited medication for the treatment of IA/RA (see Section 5.6, *Prohibited Medications)*.

6.5.5 Follow-up Visits

6.5.5.1 Follow-up Telephone Assessments (Months 15, 21, 27, & 33, Visit Window: +/- 14 days)

After the Week 52 visit, subjects will be contacted by study personnel (via a telephone call) at Months 15, 21, 27, and 33. The following information will be obtained during the telephone assessments:

1. AE Collection (*Month 15 only*)
2. Assessment of joint symptoms

3. Invitation for questions
4. Update of contact information

If there is evidence of new IA defined as new or worsening joint pain, stiffness or swelling since the last study visit or symptoms suggestive of an AE, the subject will be instructed to return to the clinic for an unscheduled visit as soon as possible (see Section 6.5.8, *Unscheduled Visits*).

Telephone assessments will not occur after a subject is diagnosed with definite RA, IA with erosion(s), or is found to be taking a prohibited medication for the treatment of IA/RA (see Section 5.6, *Prohibited Medications)*.

6.5.5.2 Follow-up Clinic Visit: Month 18 (Visit Windows: +/- 14 days)

1. AE Assessment (see Section 7.3.2*, Collection Period*)
2. Concomitant Medications
3. Physical Exam (symptom-driven)
4. Self-reported Joint Symptoms, including modified MDHAQ
5. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
    - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
    - *The midfoot joints will not be evaluated for either tenderness or swelling.*
    - *The hip joints will not be evaluated for swelling.*
6. Evaluate family member participation

Items 7 & 8 are only applicable to subjects who have not been diagnosed with clinically-apparent RA.

7. Procedures conditional on results of the Joint Examination:
    - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.
    - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis;
        - Specimen collection for the **future** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies
8. Subject self-reported pregnancy status

6.5.5.3 **Follow-up Clinic Visit: Month 24 (Visit Windows: +/- 14 days)**

1. SAE Assessment (see Section 7.3.2*, Collection Period*)
2. Concomitant Medications
3. Physical Exam (symptom-driven)
4. Vital Signs including heart rate and sitting systolic/diastolic blood pressure
5. Subject Questionnaires
   - Profile 29 v2.0
   - Self-reported Joint Symptoms, including modified MDHAQ
   - Evaluate family member participation
6. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
   - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
   - *The midfoot joints will not be evaluated for either tenderness or swelling.*
   - *The hip joints will not be evaluated for swelling.*

   Items 7 - 9 are only applicable to subjects who have not been diagnosed with clinically-apparent RA.
7. Procedures conditional on results of the Joint Examination
   - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.
   - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis;
     - Specimen collection for **future** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies
8. Epidemiologic Questionnaire
9. Subject self-reported pregnancy status

6.5.5.4 **Follow-up Clinic Visit: Month 30 (Visit Windows: +/- 14 days)**

1. SAE Assessment (see Section 7.3.2*, Collection Period*)
2. Concomitant Medications
3. Physical Exam (symptom-driven)
4. Self-reported Joint Symptoms, including modified MDHAQ

5. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
    - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
    - *The midfoot joints will not be evaluated for either tenderness or swelling.*
    - *The hip joints will not be evaluated for swelling.*
6. Evaluate family member participation

    Items 7 & 8 are only applicable to subjects who have not been diagnosed with clinically-apparent RA.
7. Procedures conditional on results of the Joint Examination
    - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.
    - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis;
        - Specimen collection for **future** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies
8. Subject self-reported pregnancy status

6.5.5.5 End of Study Clinic Visit: Month 36/Early Termination (Visit Windows: +/- 14 days)

1. Demographics
2. SAE Assessment (see Section 7.3.2*, Collection Period)*
3. Concomitant Medications
4. Physical Exam (full)
5. Vital Signs including heart rate and sitting systolic/diastolic blood pressure and weight and waist circumference
6. Subject Questionnaires
    - Profile 29 v2.0
    - Self-reported Joint Symptoms, including modified MDHAQ
    - Evaluate family member participation
7. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*

- *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
- *The midfoot joints will not be evaluated for either tenderness or swelling.*
- *The hip joints will not be evaluated for swelling.*

Item 8 is only applicable to subjects with a previous diagnosis of clinically-apparent RA.

8. Specimen collection for **real-time** core outcome testing: hsCRP only

Items 9 - 11 are only applicable to subjects who have not been diagnosed with clinically-apparent RA.

9. Procedures conditional on results of the Joint Examination:
   - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit. *Note: After the results of these evaluations are received and the 2010 ACR/EULAR score has been calculated, the site will call the subjects to inform them of their results and the subjects will be referred to clinical care. Subjects **will not** return to the clinical site after the Month 36 visit for additional diagnosis follow-up.*
   - If the subject **does not have** a swollen joint that is consistent with RA-like synovitis;
     - Specimen collection for **real-time** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies
     - Specimen collection for mechanistic studies: PBMC, plasma, RNA, and urine. *Note: DNA will be collected from subjects who consent to future genetic testing.*
10. Subject Questionnaires:
    - Epidemiologic Questionnaire
    - Dietary Assessment Questionnaire
11. Subject self-reported pregnancy status
12. Specimen collection for HCQ Level analysis
    - *Note: This specimen will be collected at the Early Termination visit if the specimen was not collected previously and the visit occurs during the treatment period.*

6.5.5.6 **Time of Diagnosis Clinic Visit**

If a subject is diagnosed with clinically-apparent RA (as defined in protocol section 2.1, *Primary Objective)* prior to the Month 36 visit, the subject will return for a Time of Diagnosis visit, which will supersede any regularly scheduled visit with which it overlaps. During the Time of Diagnosis visit the following evaluations will occur:

1. Demographics
2. Concomitant Medications
3. AE Assessment (see Section 7.3.2*, Collection Period*)
4. Physical Exam (full)
5. Vital Signs including heart rate and sitting systolic/diastolic blood pressure and weight and waist circumference
6. Subject Questionnaires
   - Profile 29 v2.0
   - Epidemiologic Questionnaire
   - Dietary Assessment Questionnaire
   - Self-reported Joint Symptoms, including modified MDHAQ
   - Evaluate family member participation
7. Joint Examination – Physician's Assessment (including a swollen/tender joint count). *Note: The count will include 66 tender/64 swollen joints.*
   - *The ankle joint(s) on each limb will be counted as a single joint that includes the talo-tibial joint (also called the talo-crural joint), subtalar joint (also called talo-calcaneal joint), and inferior tibio-fibular joint).*
   - *The midfoot joints will not be evaluated for either tenderness or swelling.*
   - *The hip joints will not be evaluated for swelling.*
8. Specimen collection for **future** core outcome testing (hsCRP, IgM-RF, and anti-CCP3) and serum for mechanistic studies will be completed.
9. Specimen collection for mechanistic studies: PBMC, plasma, RNA, and urine. *Note: DNA will be collected from subjects who consent to future genetic testing.*
10. Specimen collection for HCQ Level analysis
    - *Note: This specimen will be collected at the Time of Diagnosis visit if the specimen was not collected previously and the visit occurs during the treatment period.*
11. Discontinue study therapy
12. Pill Counts (if subject is diagnosed during the treatment period)
13. Refer subject to clinical care

14. Encourage subject to return for all remaining planned study visits. See Section 6.5.9, *Evaluations Triggered by a Swollen Joint,* for testing that will no longer be completed at post-diagnosis visits.

6.5.6 Early Withdrawal Visit

Subjects who withdraw early from the study will be asked to complete an Early Withdrawal Visit (aka End of Study Clinic Visit/Month 36). All scheduled exams, procedures, and laboratory tests scheduled for the Month 36 visit will be performed at this visit. Data from subjects who do not complete all study visits will still be included in the Intent-to-Treat (ITT) and safety analyses.

Subjects who withdraw from the study regardless of the reason and have not been diagnosed with clinically-apparent RA will be asked to consent to annual phone calls (Weeks 52, Month 24, Month 36) to answer inquiries about the development of RA and related information.

Note: Premature discontinuation of study drug is not a reason for early withdrawal from the study. Subjects who discontinue study drug early should be encouraged to continue in the study. (See Section 5.8.1, *Study Treatment Discontinuation*.)

6.5.7 Visit Windows

All study procedures should be performed within the designated visit window (i.e., ± n days) for each scheduled visit (see Tables 6.1 and 6.2, *Schedule of Events*). Whenever possible, a rescheduled visit should remain within the designated visit window. The coordinating center should be notified if the study procedures for any scheduled visit cannot be performed within the designated window.

6.5.8 Unscheduled Visits

Unscheduled visits may occur if a subject has developed adverse effects or joint symptoms that need to be evaluated by study personnel. Subjects will be instructed to contact study personnel if these symptoms/AEs develop, and the subject will be seen for a study visit, as soon as possible.

At these unscheduled visits, the same procedures will be performed as are done at the other interval study visits. Additionally, other safety assessments (e.g. physical examination, laboratory assessments) may be performed at the discretion of the investigator.

The following evaluations will be performed at each unscheduled visit:

1. AE Assessment *(If visit occurs prior to Month 18)*
2. Concomitant Medications
3. Physical Exam (symptom-driven, including joint exam)
    - If the subject **has 1 or more** swollen joints that are consistent with RA-like synovitis and the subject has not been previously diagnosed with clinically-apparent RA, refer to protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for a list of additional assessments that are required to be completed at this visit.

- If the subject **does not have** a swollen joint that is consistent with RA-like synovitis, the subject will continue with the visit as noted below. Specimens for core outcome testing and mechanistic studies will not be collected at this visit.

4. Vital Signs including heart rate, sitting systolic/diastolic blood pressure
5. Self-reported Joint Symptoms, including modified MDHAQ
6. Subject self-reported pregnancy status
7. If study therapy is discontinued at this visit, the HCQ level specimen will be collected, provided it has not been previously collected.
8. If needed for evaluation of safety related to drug toxicity during the treatment period, the following assessments will be performed:
   - Hematology: hemoglobin, hematocrit, WBC (with differential) , and platelet count
   - Chemistry: serum creatinine, ALT, and AST

   Note: Abnormal lab values meeting the criteria noted in Section 5.8.1, *Study Treatment Discontinuation,* should be confirmed within 4 weeks, prior to discontinuation.
9. Evaluate family member participation

Additional evaluations may be performed according to investigator discretion.

6.5.9 Evaluations Triggered by a Swollen Joint

At any study visit, either regularly scheduled or unscheduled, if a swollen joint(s) that is consistent with RA-like synovitis is identified during the joint examination, the following items will be completed **during the study visit:**

- Specimen collection for **real-time** core outcome testing: hsCRP, IgM-RF, and anti-CCP3 and serum for mechanistic studies
- Specimen collection for mechanistic studies (at the initial occurrence of RA-like synovitis only): PBMC/plasma RNA, and urine. *Note: DNA will be collected from subjects who consent to future genetic testing.*
- X-rays will be performed (at the first occurrence and every 6 months thereafter, if applicable). See protocol section 6.2.3.5, *X-ray Imaging*, **prior** to conducting x-rays on female subjects (who have the ability to become pregnant).
- A follow-up visit will be scheduled within the next 3 to 6 weeks. This visit may coincide with a regularly scheduled visit or may be conducted as an unscheduled visit.
- *Note: Subjects will continue to take study medication until the diagnosis of clinically-apparent RA has been confirmed and the subject returns to the site for a Time of Diagnosis Visit (see Section 6.5.5.6, Time of Diagnosis Clinic Visit).*

After the study visit, once the results from the core outcome tests and x-ray are available, the score for the 2010 ACR/EULAR Classification Criteria will be calculated, and at the 3-6 week follow-up visit, the following may occur:

1) If the subject has definite RA per the 2010 ACR/EULAR Classification Criteria (i.e. score ≥ 6), the follow-up visit will become a Time of Diagnosis visit (refer to Section 6.5.5.6, *Time of Diagnosis Clinic Visit)*.
2) If a swollen joint consistent with RA-like synovitis is identified by joint examination, the ACR/EULAR score is <6, and x-rays identify the presence of at least 1 erosion the follow-up visit will become a Time of Diagnosis visit (refer to Section 6.5.5.6, *Time of Diagnosis Clinic Visit)*.

Note: After the Time of Diagnosis visit, the subject will resume routine study clinic visits in order to follow the natural history of RA; with the following exceptions:

- Scheduled telephone assessments at Weeks 18, 30, and 42, and Months 15, 21, 27, and 33 will not occur.
- After the Time of Diagnosis visit, biologic samples (blood, urine) for mechanistic specimens and core outcome specimens (anti-CCP3, IgM-RF, and hs-CRP) will not be collected and the dietary and epidemiologic questionnaires will not be completed.
- Routine safety labs samples will be collected at Week 24 and Week 52 regardless of subject diagnosis and prohibited medications.
- HsCRP will be collected at Week 52 and Month 36.

Note: See Appendix 15.2.1*, Evaluations Triggered by a Swollen Joint Flow Chart,* for a figure containing the information noted above.

3) If a swollen joint consistent with RA-like synovitis is identified by joint examination, but the ACR/EULAR score is <6, and no erosions are observed on the x-ray, the subject will be informed of this at the 3-6 week follow-up visit, and the following will occur:
    - The subject will be instructed to continue taking the study therapy.
    - The subject will be instructed to return to the clinic every 6 weeks (for either an unscheduled visit or a regularly scheduled visit that falls within the next 6 weeks) until:
        - The synovitis resolves and is not present at two consecutive visits (unscheduled or planned) 6 weeks apart, then the subject will resume routine interval study visit follow-up with routine core outcome testing and mechanistic specimen draws.
        - The subject develops definite RA by 2010 ACR/EULAR Classification Criteria or erosions on follow-up x-rays then the follow-up visit will become a Time of Diagnosis visit as outlined above (refer to Section 6.5.5.6, *Time of Diagnosis Clinic Visit).*

- *Note:* If synovitis persists but does not meet 2010 ACR/EULAR Classification Criteria for RA, x-rays may be repeated at 6-month intervals to assess for development of erosions provided the subject is not pregnant. If a swollen joint(s) that is consistent with RA-like synovitis is identified during the joint examination during the 3-6 week follow-up visit, follow blood draws according to Appendix 15.2.1, *Evaluations Triggered by a Swollen Joint Flow Chart*.

6.5.10 Procedures for Subjects Diagnosed with Inflammatory or Rheumatoid Arthritis by an Outside Physician

If a subject is diagnosed with IA or RA outside of the ARA08 study, the subject will return to the study site as soon as possible (this may be accomplished through a planned routine study visit or an unscheduled visit). During the visit, the site personnel will obtain additional information regarding the diagnosis including **any medications the subject is taking in response to the diagnosis. Study drug should be discontinued at the time the study team becomes aware that the subject has started prohibited medications.**

Procedures for this visit are dependent upon medications taken in response to the diagnosis of IA/RA and are outlined below. A graphic representation of this decision process can be found in Appendix 15.2.2, *Flow Diagram: Procedures for Subjects Diagnosed with IA/RA by an Outside Physician*.

1) If the subject **is taking** a medication for IA/RA (see Section 5.6, *Prohibited Medications):*
    a. The study medication will be permanently discontinued, if this visit occurs during the treatment period.
    b. Assessments for an Time of Diagnosis Clinic Visit will be conducted (see Section 6.5.5.6*, Time of Diagnosis Clinic Visit*)
    c. The subject will undergo x-ray imaging provided an x-ray has not been conducted in the past 6 months and the subject is not pregnant. See protocol section 6.5.11, *Special Considerations for Pregnant Subjects*, **prior** to conducting x-rays on female subjects (who have the ability to become pregnant).
    d. The subject will be referred to clinical care, and will be encouraged to return for all remaining planned study visits.

    After this visit, the subject returns for routine follow-up visits according to the planned study visit schedule outlined in Sections 6.5.4, *Treatment Period*, and 6.5.5, *Follow-up Visits*. However, several assessments will not be conducted at subsequent visits, as outlined below:

    - Scheduled telephone assessments at Weeks 18, 30, and 42, and Months 15, 21, 27, and 33 will not occur.
    - Biologic samples (blood, urine) for mechanistic specimens and core outcome specimens (anti-CCP3, IgM-RF, and hs-CRP) will not be collected.

- The dietary and epidemiologic questionnaires will not be completed at visits occurring after this visit.
- Routine safety labs samples will be collected at Week 24 and Week 52 regardless of subject diagnosis and prohibited medications.
- HsCRP will be collected at Week 52 and Month 36 for the evaluation of the DAS28 – CRP secondary efficacy endpoint.

2) If the subject **is not taking** a medication for the IA/RA diagnosis, the site investigator will conduct a joint examination.
    a. If the site investigator **identifies** a swollen joint during the joint examination, he/she will follow the steps outlined in Section 6.5.9 *Evaluations Triggered by a Swollen Joint.*
    b. If the joint examination **does not** identify any swollen joints, the subject will continue with routine study visits as planned. No specimens will be collected at this visit.

Note: See Appendix 15.2.2*, Procedures for Subjects Diagnosed with IA/RA by an Outside Physician Joint Flow Chart,* for a figure containing the information noted above.

6.5.11 Special Considerations for Pregnant Subjects

A subject who becomes pregnant during her participation in the study:

- Will discontinue study therapy per protocol section 5.8.1, *Study Treatment Discontinuation,* if the pregnancy occurs during the treatment period.
- Cannot receive x-rays during the pregnancy
- Will otherwise be followed as all other subjects participating in the study.

Table 6.1: Schedule of Events (Pre-Treatment through End of Treatment)

	Pre-Treatment	Eligibility		Subject Call (Week)	Evaluations Triggered by Swollen Joint	Treatment (Week)				End of Treatment (Week)	Time of Diagnosis Clinic Visit	Unscheduled Visit
Time Point	Pre-screening	Screening	Baseline	18, 30 & 42	Any post-Baseline visit	6	12	24	36	52		
Visit Windows (Days)		-30 days	NA	±7 days		±7 days				±14 days		
Clinical Blood Draw (mL)	NA	22	NA	NA	NA	NA	NA	9	NA	9	NA	9
Research Blood Draw (mL)	5	5	66	NA	66	NA	NA	10	NA	66	66	NA
Visit Draw Total (mL)	5	27	66	NA	66	NA	NA	19	NA	75	66	9
General Assessments												
Pre-Screening ICF	X[1]											
Pre-Screening Questionnaire	X											
Main Study ICF		X										
Demographics		X									X	
Medical History		X	X									
Prior/Concomitant Medications		X	X			X	X	X	X	X	X	X
Physical Exam[2]		X	X			X	X	X	X	X	X	X
Vital Signs including heart rate, sitting systolic/diastolic blood pressure, * include height (Screening only), weight, & waist circumference		X*	X			X	X	X	X	X	X*	X
NHYA Classification[3]		X										
Retinal Exam[4]		X[5]										
Randomization			X[6]									
AE/SAE Assessment						X	X	X	X	X	X	X
Profile 29 v2.0			X							X	X	
Epidemiologic Questionnaire			X							X[8]	X	
Dietary Assessment Questionnaire			X								X	
Self-Reported Joint Symptoms, including modified MDHAQ			X			X	X	X	X	X	X	X
Evaluate family member participation[7]			X			X	X	X	X	X	X	X
Pregnancy Status Check				X[8]		X[8]	X[8]	X[8]	X[8]	X[8]		X[8]
Treatment Telephone Assessments[9]				X[8]								
Annual Phone Call for Withdrawn Subjects										X[10]		
Disease Status												
Joint Examination – Physician's Assessment : 64 swollen joint count		X[11]										
Joint Examination – Physician's Assessment : 64 /66 tender/ swollen joint count[12]			X[11]			X 13	X[13]	X[13]	X[13]	X[13]	X	X[13]
Anti-CCP3	X[14]	X										
Real Time Core Outcome Testing (hsCRP, IgM-RF, Anti-CCP3) & serum[15]			X		X[16]					X[17]		
Future Core Outcome Testing (hsCRP, IgM-RF, Anti-CCP3) & serum								X[8]			X	
2010 ACR/EULAR Criteria					X							
X-ray as needed[18]					X[18]							
Clinical Laboratory Assessments												
Screening Chemistries/Hematologies: Serum creatinine, ALT, AST, WBC, Platelets, ANC, Hemoglobin		X										
Infectious Disease Screen: HIV-1/HIV-2 Antigen/Antibody, Hep B Surface Antigen, Hep C Antibody		X[19]										
STAT Urine Pregnancy Test			X[20]		X[18]							
Chemistries: Serum creatinine, ALT, & AST								X[21]		X		X[21, 22]
Hematologies: Hemoglobin, Hematocrit, WBC (with differential), & Platelet count								X[21]		X		X[21, 22]
Required Mechanistic Specimens[16]												
PBMC/Plasma/DNA, RNA, Urine[23]			X		X[24]					X[8]	X	
HCQ Level[25] *(1 time draw during treatment period)*						X[26]	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]
Study Product												
Dispense Study Product[27]			X[6]			X[8]	X[8]	X[8]	X[8]			

Pill Count						X[8]	X[8]	X[8]	X[8]	X[8]	X	

[1] Subjects identified through the first degree relative or general population recruitment strategies **will** be given, and subjects identified through a review of clinic records **may** be given, a Pre-Screening consent form to indicate their consent to undergo Pre-Screening procedures as described in Section 6.5.1, *Pre-Screening*.

[2] Physical Exam: Full PE at Screen, Week 52, Time of Diagnosis and Month 36/Early Termination. Symptom-driven PE at all other clinic visits.

[3] NHYA Classification: See Section 15.4, *NYHA Classification*.

[4] If a subject develops ocular symptoms, the subject will be referred to clinical care (see section 5.8.1, *Study Treatment Discontinuation).*

[5] A retinal exam by an ophthalmologist or optometrist that includes a dilated funduscopic exam, visual field (10-2) and OCT should be conducted prior to the Baseline visit (after all other screening eligibility criteria have been confirmed). *Note: Results from the initial screening visit retinal examination may be used to assess eligibility for up to 6 months.*

[6] **Subjects with swollen joints that are consistent with RA-like synovitis at the time of the Baseline/Randomization Visit should NOT be randomized or treated. Sites utilizing a central pharmacy may randomize subjects prior to the Baseline visit after initial eligibility at Screening has been confirmed, but if swollen joints that are consistent with RA-like synovitis are noted at baseline, do NOT dispense study therapy to the subject**. *Note: The first dose of study therapy will be given in clinic. The subject will be observed per institutional standards.*

[7] All participants should complete the "Participation of First Degree Relatives" questionnaire. If the subject consents to linking his/her information with a participating family members, please follow the Process for Linking First Degree Relatives in the Manual of Operations.

[8] These procedures will be conducted if the subject **has not** been previously diagnosed with clinically-apparent RA.

[9] Telephone Assessment: Coordinators will call subjects at Week 18, 30, and 42 to assess toxicities to HCQ, AEs, a review of study drug dosing and storage, joint symptoms, pregnancy status, answer subject questions, and confirm contact information.

[10] Subjects who have withdrawn from the study and consent to annual phone calls will be asked about development of RA and related information.

[11] **If a subject has a swollen joint consistent with RA-like synovitis, do not randomize or dispense study drug to the subject.**

[12] Note: The count will include 66 tender/64 swollen joints. The midfoot joints will not be evaluated for either tenderness or swelling. The hip joints will not be evaluated for swelling.

[13] If the subject has 1 or more swollen joints that are consistent with RA-like synovitis, then complete additional assessments as outlined in section 6.5.9, *Evaluations Triggered by a Swollen Joint*.

[14] If a subject found through the rheumatology clinic has already had Anti-CCP levels assessed in the previous 12 months, historical results may be used to assess eligibility at Pre-Screening. Pre-Screening specimens will be analyzed at the site local laboratory.

[15] Results from real time core outcome testing specimens will be reported back to the sites for review of the 2010 ACR/EULAR criteria.

[16] Collection of core outcome test and mechanistic studies specimens will be discontinued after a subject has been diagnosed with clinically-apparent RA and the Time of Diagnosis visit has been completed. Subjects who have swollen joints consistent with RA-like synovitis with no erosions will follow the normal schedule for core outcome testing collection.

[17] Subjects who have been previously diagnosed with clinically-apparent RA will have hsCRP (only) assessed at Week 52.

[18] X-rays may be conducted every 6 months if needed. All subjects with swollen joints consistent with RA-like synovitis will have at least 1 x-ray but follow-up x-rays are not needed if clinically-apparent RA is diagnosed (see Section 3.1, *Description of Study Design*). At most, a subject may undergo study-related x-ray imaging 4 times throughout his/her participation in the study. Female subjects who have child bearing potential cannot undergo x-ray imaging unless a STAT urine pregnancy test is negative.

[19] If any of the infectious disease tests yield a positive result, consult exclusion criteria in Section 4.2, *Exclusion Criteria*, for subject eligibility. The site will report these results to the subject and perform other follow-up per institutional guidelines.

[20] Female subjects cannot receive the initial dose of study product until eligibility can be confirmed via a STAT urine pregnancy test.

[21] Note: Abnormal lab values meeting the criteria noted in Section 5.8.1, *Study Treatment Discontinuation*, should be re-tested within 4 weeks, prior to discontinuation.

[22] If needed for evaluation of safety related to drug toxicity during the treatment period, the chemistry and hematology draws will be collected.

[23] DNA collection is optional. This specimen will be collected at the Baseline visit for subjects who consent to the collection for analysis of the shared epitope. DNA will be collected at subsequent visits for subjects who consent to future genetic testing.

[24] Specimens for mechanistic studies will be collected at the **initial** finding of RA-like synovitis.

[25] It is strongly recommended that the HCQ level specimen be drawn 4 or more hours after the last HCQ dose.

[26] The HCQ level specimen will be collected at one time point for each subject. The specimen collection may occur at the Week 24, Week 52, or at any visit where study therapy is discontinued (including Time of Diagnosis and Early Termination visits) provided the specimen was not collected previously.

[27] Please refer to protocol section 5.3.2, *Administration*, for the study therapy distribution schedule.

Table 6.2: Schedule of Events (Follow-Up)

	Subject Call (Months)	Evaluations Triggered by a Swollen Joint[28]	Follow-Up (Months)			End of Study (Month)	Time of Diagnosis Clinic Visit	Unscheduled Visit
Time Point	**15, 21, 27, & 33**	**At any visit**	**18**	**24**	**30**	**36/ Early Termination**		
Visit Windows (Days)	**±14 days**		**±14 days**					
Clinical Blood Draw (mL)	NA	NA	NA	NA	NA	NA	NA	NA
Research Blood Draw (mL)	NA	66	10	10	10	66	66	NA
Visit Draw Total (mL)	NA	66	10	10	10	66	66	NA
General Assessments								
Demographics						X	X	
Concomitant Medications			X	X	X	X	X	X
Physical Exam[29]			X	X	X	X	X	X
Vital Signs including heart rate & sitting systolic/diastolic blood pressure				X				X
Vital Signs including heart rate, sitting systolic/diastolic blood pressure, weight, & waist circumference						X	X	
AE/SAE Assessment			X[30]	X[30]	X[30]	X[30]		X[30]
Profile 29 v2.0				X		X	X	
Epidemiologic Questionnaire				X[31]		X[31]	X	
Dietary Assessment Questionnaire						X[31]	X	
Self-Reported Joint Symptoms, including modified MDHAQ			X	X	X	X	X	X
Evaluate family member participation[32]			X	X	X	X	X	X
Pregnancy Status Check			X[31]	X[31]	X[31]	X[31]		X[31]
Follow-up Telephone Assessments[33]	X[31]							
Annual Phone Call for Withdrawn Subjects				X[34]		X[34]		
Disease Status								
Joint Examination – Physician's Assessment: 64 /66 tender/swollen joint count[35]			X[36]	X[36]	X[36]	X[36]	X	X[36]
Real Time Core Outcome Testing (hsCRP, IgM-RF, Anti-CCP3) & serum[37]		X[38]				X[39]		
Future Core Outcome Testing (hsCRP, IgM-RF, Anti-CCP3) & serum			X[31]	X[31]	X[31]		X	
2010 ACR/EULAR Criteria[40]		X						
X-ray as needed[41]		X[41]						
Clinical Laboratory Assessments								
Hematologies: Hemoglobin, Hematocrit, WBC (with differential), & Platelet count								X[42]
Chemistries: Serum creatinine, ALT, & AST								X[42]
STAT Urine Pregnancy Test		X[41]						
Required Mechanistic Specimens[31]								
PBMC/Plasma/DNA, RNA, Urine[43]		X[44]				X[31]	X	
HCQ Level[45]						X[46]	X[46]	

[28] See protocol section 6.5.9, *Evaluations Triggered by a Swollen Joint*, for additional details.

[29] Physical Exam: Full PE at Screen, Week 52, Time of Diagnosis and Month 36/Early Termination. Symptom-driven PE at all other clinic visits.

[30] Non-serious adverse events will not be collected after Month 18. SAEs will be collected for the duration of the study.

[31] These procedures will be conducted if the subject **has not** been previously diagnosed with clinically-apparent RA.

[32] All participants should complete the "Participation of First Degree Relatives" questionnaire. If the subject consents to linking his/her information with a participating family members, please follow the Process for Linking First Degree Relatives in the Manual of Operations.

[33] Follow-up Telephone Assessments: Coordinators will call subjects at Months 15, 21, 27, and 33 to assess AEs (until Month 15); joint symptoms, answer subject questions, and confirm contact information.

[34] Subjects who have withdrawn from the study and consent to annual phone calls will be asked about development of RA and related information.

[35] Note: The count will include 66 tender/64 swollen joints. The midfoot joints will not be evaluated for either tenderness or swelling. The hip joints will not be evaluated for swelling.

[36] If the subject has 1 or more swollen joints that are consistent with RA-like synovitis, then complete additional assessments as outlined in section 6.5.9, *Evaluations Triggered by a Swollen Joint*.

[37] Results from real time core outcome testing specimens will be reported back to the sites for review of the 2010 ACR/EULAR criteria.

[38] Collection of core outcome tests and mechanistic studies specimens will be discontinued after a subject has been diagnosed with clinically-apparent RA and the Time of Diagnosis visit has been completed. Subjects who have swollen joints consistent with RA-like synovitis with no erosions will follow the normal schedule for core outcome testing collection.

[39] Subjects who have been previously diagnosed with clinically-apparent RA will only have hsCRP assessed at this time point.

[40] Review the 2010 ACR/EULAR Criteria results if subject has 1 or more swollen joints that are consistent with RA-like synovitis.

[41] X-rays may be conducted every 6 months if needed. All subjects with swollen joints consistent with RA-like synovitis will have at least 1 x-ray but follow-up x-rays are not needed if clinically-apparent RA is diagnosed (see Section 3.1, *Description of Study Design*). At most, a subject may undergo study-related x-ray imaging 4 times throughout his/her participation in the study. Female subjects who have child bearing potential cannot undergo x-ray imaging unless a STAT urine pregnancy test is negative.

[42] Chemistry and hematology assessments may be performed, if needed.

[43] DNA will be collected for subjects who consent to future genetic testing.

[44] Specimens for mechanistic studies will be collected at the **initial** finding of RA-like synovitis.

[45] It is strongly recommended that the HCQ level specimen be drawn 4 or more hours after the last HCQ dose.

[46] The HCQ level specimen will be collected at one time point for each subject. The specimen collection may occur at the Week 24, Week 52, or at any visit where study therapy is discontinued (including Time of Diagnosis and Early Termination visits) provided the specimen was not collected previously.

7 SAFETY MONITORING AND REPORTING

7.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting that data. AEs that are classified as serious must be reported promptly (per Section 7.5, *Reporting of Adverse Events*) and appropriately to the sponsor (DAIT/NIAID), principal investigators in the trial, and IRBs. Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, and applies the standards set forth in the NCI-CTCAE), Version 4.0*: http://ctep.cancer.gov/reporting/ctc.html.

7.2 Definitions

7.2.1 Adverse Event (or Adverse Experience)

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of AEs in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice)." [From OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and AEs (1/15/07)" http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm.]

7.2.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug (21 CFR 312.32(a)).

7.2.3 Unexpected Adverse Reaction

A SAR is considered "unexpected" if it is not listed in the hydroxychloroquine package insert or is not listed at the specificity or severity that has been observed.

7.2.4 Serious Adverse Event

An AE or SAR is considered "serious" if, in the view of either the investigator or DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death

2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization (The event is considered an AE if the subject enters the emergency room of a hospital but is not admitted, but is considered a SAE if the subject is admitted into the hospital for at least 24 hours.)
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.3 Collection and Recording of Adverse Events

7.3.1 Investigational Product

The investigational product in this protocol is hydroxychloroquine.

7.3.2 Collection Period

AEs of NCI-CTCAE Grade 2 and above will be collected from the time the subject signs the main clinical trial informed consent until he/she initiates study intervention or until he/she is determined to be ineligible to receive study intervention, if the investigator determines that the AE is related to a study-mandated procedure, treatment, or change in treatment.

Regardless of whether the above is applicable, for all participants, AEs of NCI-CTCAE Grade 2 and above will be collected from the time of initiation of study intervention (i.e., the administration of the first dose of study drug (HCQ/placebo), as defined in Section 6.5.3, *Baseline/Randomization Visit),* until Month 18 or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

Serious adverse events will be collected throughout the duration of the subject's participation in the study.

7.3.3 Collecting Adverse Events

AEs (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Questioning the subject in an objective manner.
- Receiving an unsolicited complaint from the subject.
- An abnormal value or result from a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, or an electrocardiogram) can also

indicate an AE, as defined in Section 7.4, *Grading and Attribution of Adverse Events*.

7.3.4 Recording Adverse Events

AEs of NCI-CTCAE Grade 2 and above will be recorded from the time the subject signs the main clinical trial informed consent until he/she initiates study intervention or until he/she is determined to be ineligible to receive study intervention, if the investigator determines that the AE is related to a study-mandated procedure, treatment, or change in treatment.

From the initiation of study therapy through Month 18 or until 30 days after the subject prematurely withdraws or is withdrawn from the study, the investigator will record and grade AEs of NCI-CTCAE Grade 2 and above on the appropriate AE electronic case report form (AE eCRF) regardless of their severity or relation to study medication or study procedure.

Once recorded, an AE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

7.3.5 Recording Serious Adverse Events

Serious AEs will be recorded on the appropriate AE eCRF and on the SAE eCRF throughout the subject's participation in the study. All requested information on the AE eCRF and SAE eCRF should be provided, if available, for submission to the Statistical and Clinical Coordinating Center (SACCC) and DAIT/NIAID.

If a site investigator discovers a new SAE within 30 days after the end of study participation, the SAE will be reported.

Once recorded, an SAE will be followed until it resolves with or without sequelae.

7.4 Grading and Attribution of Adverse Events

7.4.1 Grading Criteria

The study site will grade the severity of AEs experienced by the study subjects according to the criteria set forth in the NCI-CTCAE v4.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs. The NCI- CTCAE has been reviewed by the Protocol Chair(s) and has been deemed appropriate for the subject population to be studied in this protocol.

AEs will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event, not recorded.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

If NCI-CTCAE criteria are defined for grading an abnormal value or result from a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, or an electrocardiogram), then a treatment-emergent AE is defined as an increase in grade from Baseline (Day 0) or from the last post-Baseline value that doesn't meet grading criteria. Changes in grade from screening to Baseline (Day 0) will also be recorded as outlined in Section 7.3.2, *Collection Period*. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an AE if changes in therapy or monitoring are implemented.

AEs that are related to disease activity will be graded according to the plan outlined above. However, an increase in disease activity leading to an AE should also be reflected in standard measures of disease activity measured at study visits.

7.4.2 Attribution Definitions

The relation, or attribution, of an AE to an investigational product will initially be determined by the site investigator. The site investigator will also record the initial determination of attribution on the appropriate AE eCRF. The relation of an AE to the study intervention will be determined using the descriptors and definitions provided in Table 7.4.1, NCI-CTCAE attribution of AEs. Final determination of attribution for safety reporting will be decided by DAIT/NIAID.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Table 7.4.1. NCI-CTCAE attribution of adverse events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy)
Unrelated Categories		
1	Unrelated	The adverse event is clearly not related.
2	Unlikely	The adverse event is unlikely related.
Related Categories		
3	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probable	The adverse event is likely related.
5	Definite	The adverse event is clearly related.

7.5 Reporting of Adverse Events

7.5.1 Reporting of Adverse Events to DAIT/NIAID

This section describes the responsibilities of the site investigator to report AEs to the SACCC. Timely reporting of AEs is required by 21 CFR and ICH E6 guidelines. For this study, AEs of NCI-CTCAE Grade 2 and higher will be reported.

Unless otherwise noted below in Section 7.5.1.1, *Procedure for Adverse Events Requiring 24 Hour Reporting,* as requiring 24 hour reporting, AEs must be recorded on the appropriate AE eCRF within five (5) business days of the site learning of the event(s).

7.5.1.1 Procedure for Adverse Events Requiring 24 Hour Reporting

The AEs that are bulleted below must be reported by site investigators to the SACCC regardless of relationship or expectedness to study intervention within a 24 hour period of discovering the AE:

- All SAEs per 21 CFR 312.32 definitions (see Section 7.2.4, *Serious Adverse Event*).
- All NCI-CTCAE Grade 3 or greater events possibly, probably, or definitely related to HCQ;
- Any event that the site considers serious but is not easily categorized.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol-mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

The following process for reporting of the AEs bulleted above ensures compliance with the ICH guidelines and the FDR CFR regulations. When an investigator identifies such an AE, he or she must notify the SACCC within 1 business day of discovering the AE, and complete and submit the AE/SAE eCRF within one business day following initial notification. The SACCC is responsible for notifying DAIT/NIAID upon receipt of the site's notification of the AE and sending a SAE report form to DAIT/NIAID within two business days after receipt of the AE/SAE eCRF from the site.

7.5.1.2 Procedure for Standard Adverse Event Reporting

All other AEs (Section 7.3.3, *Collecting Adverse Events*) must be recorded by the site on the appropriate AE eCRF within 5 business days of the site learning of the AE(s).

7.5.2 DAIT/NIAID Reporting to the Health Authority

This clinical study has been granted exemption from investigational new drug application (IND) regulations by the FDA in accordance with 21 CFR 312.2(b) of the regulations, therefore, AEs will not be reported to the FDA by the study sponsor (NIAID).

7.5.3 Reporting of Adverse Events to IRBs

All investigators must report AEs and SAEs in a timely fashion to their respective IRBs in accordance with applicable regulations and local reporting guidelines.

7.6 Pregnancy Reporting

This study includes pregnancy information as safety data. Although pregnancy is not an SAE, information about any pregnancy should be reported promptly to the SACCC on the same timeline as an SAE for tracking purposes (Section 7.5.1.1, *Procedure for Adverse Events Requiring 24 Hour Reporting*).

All pregnancies identified during the study must be followed to conclusion and the outcome of each must be reported. The investigator should be informed immediately of any pregnancy in a study subject. A pregnant subject should be instructed to stop taking study medication. The investigator should report to the SACCC all pregnancies within one business day (as described in Section 7.5.1.1, *Procedure for Adverse Events Requiring 24 Hour Reporting*) using the Pregnancy eCRF. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject should continue until the conclusion of the pregnancy, and a follow-up Pregnancy eCRF detailing the outcome of the pregnancy should be submitted to the SACCC.

Information requested about the delivery will include:

- Subject's enrollment ID
- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at one minute, five minutes, and 24 hours after birth, if available
- Any abnormalities.

Should the pregnancy result in a congenital abnormality or birth defect, an SAE must be submitted to the SACCC using the SAE reporting procedures described above.

7.7 Reporting of Other Safety Information

An investigator should promptly notify the SACCC when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an AE.

7.8 Review of Safety Information

7.8.1 Medical Monitor Review

The study management team will receive monthly reports from the SACCC compiling new and accumulating safety information on, including but not limited, to AEs, SAEs, and pregnancies recorded by the sites on appropriate eCRFs.

In addition, the Medical Monitor will receive SAE and pregnancy reports for review and triage after the SACCC is made aware of these events (See Sections 7.5.1, *Reporting of Adverse Events to DAIT/NIAID*, and 7.6, *Pregnancy Reporting*).

7.8.2 DSMB Review

The Data and Safety Monitoring Board (DSMB) will review accumulating safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews or emergency meetings (see Section 5.8.3, *Safety Stopping Guidance*). The DSMB will have the discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity.

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Sample Size and Power

For the primary analysis, we are interested in demonstrating a long-term impact (3 year) of a 1-year course of HCQ treatment on preventing the development of clinically-apparent RA (defined in Section 2.1, *Primary Objective*) in high-risk subjects. As such, rather than comparing full survival curves between treatment arms, the sample size for this study was selected to achieve sufficient power to compare survival curves at a fixed point 3 years after initiating treatment with HCQ. Survival for this study is defined as absence of clinically-apparent RA. Estimated risks will be derived from a Kaplan-Meier curve using censored time-to-event data to account for attrition under the assumption of non-informative censoring.

For the assumptions used in these calculations, we relied on the published data summarized in Section 1.1.3, *Classification of RA* [85, 86, 90, 173]. Since this study will be enrolling subjects with ≥2 times the ULN for anti-CCP3 (i.e. ≥40 units) and following them for 3 years, we assume that the untreated subjects in the ARA08 study should have at least a 50% risk of developing clinically-apparent RA by 3 years. In the HCQ arm, we hope to achieve a 50% reduction in risk, to ~25% developing clinically-apparent RA (or 75% survival), over the 3 year time frame.

For the primary analysis, the test statistic will be computed using a method described by Klein (2007) [177]. Klein et al compared performance of several Wald-type chi-square statistics derived by dividing the difference of transformed Kaplan-Meier (KM) survival estimates for each arm by the associated variance derived using the delta-method. For this study, we compared the performance of the log(-log) and logit transformations (referred to as X^2_3 and X^2_5, respectively, in Klein (2007)). The logit transformation was selected for this study, because it had slightly higher power in simulation studies. To estimate power, the test statistic was computed for 1000 simulated trials, and power was estimated as the percentage of simulated trials where the test was rejected at α=0.05. We assumed time to failure follows an exponential distribution. As such, a 50% risk (or 50% survival) at 3 years implies the hazard per year (λ) equals 0.231 for the control arm. If the risk falls to 25% (or 75% survival) at 3 years for the treatment arm, then λ = 0.096, and the hazard ratio equals 2.4 for untreated compared to treated subjects. In a retrospective

cohort study of subjects with palindromic rheumatism, the hazard ratio (HR) for development of RA based on 3 1/3 years of follow-up was ~3 for untreated subjects compared to subjects treated with anti-malarials [112]. As such, attaining a hazard ratio of 2.4 for this study is a reasonable goal.

For example, with 80 subjects per arm, the study has 90% power to detect a reduction in risk from 50% to 25% at 3 years. Under the null case (hazard ratio=1), the test was rejected 4.6% of the time. If the risk for controls is 50%, but the HR drops to 2.1, then power is 81%. If the risk for controls is 35% and the HR remains at 2.4, then power is 77%. Given the long duration of follow-up, the sample size will be increased to 100 subjects per arm to allow for attrition of up to 20% (equally distributed across groups).

8.2 Analysis Populations

8.2.1 Safety Population

The safety population (SP), which will be used for all safety analysis, will include all subjects for whom study treatment is initiated.

8.2.2 Intent-to-Treat Population

The Intent-to-Treat population will include all randomized subjects.

8.2.3 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will include all randomized subjects who receive at least one dose of study drug and meet entry criteria. The primary efficacy analyses will be based on the mITT population. Subjects who, for whatever reason, do not complete their assigned therapy will be included in the mITT population in the groups to which they were randomized.

8.2.4 Per Protocol Population

The Per Protocol (PP) population will be defined as those subjects in the mITT population who receive at least 80% of the assigned treatment protocol with no substantive deviations from protocol procedures that would impact evaluation of efficacy. A masked data review panel will evaluate deviations from the protocol including, for example, violations of entry criteria, departures from assigned treatment regimen, use of prohibited therapy or HCQ prescribed outside of the study, failure to complete study visits, or to complete visits within the specified visit windows. The panel may exclude subjects from the PP population if protocol deviations would be expected to impact the primary efficacy endpoint. Primary and secondary efficacy analyses may be replicated on the PP population.

8.3 Statistical Methods

In presenting data from this trial, continuous data will be summarized in tables listing the mean, standard deviation or standard error, median, and number of subjects in a group. Categorical data

will be summarized in tables listing the frequency and the percentage of subjects in a group. These summaries will be presented separately for subjects on the two treatment arms.

8.3.1 Efficacy Analysis

8.3.1.1 Primary Efficacy Analysis

The primary efficacy analysis is designed to test the hypothesis that HCQ will slow or prevent the onset of clinically-apparent RA in high-risk subjects. The analysis will be based on the KM estimated risk of clinically-apparent RA at 36 months. The KM curves will be plotted along with 95% confidence intervals. The null hypothesis, "H0: survival at 3 years is equal across arms", will be tested against the two-sided alternative with α=0.05. The test statistic will be a Wald-type chi-square statistic derived by dividing the difference of the logit-transformed KM survival estimates for each arm by the associated variance derived using the delta-method. The logit-transformed Wald-type chi-squared statistic has better test performance than the untransformed version in that the nominal Type I error is better retained. Subjects who choose to take off-study HCQ on a continuous basis will be censored at the time this therapy begins. This analysis will ignore stratification by site and method of recruitment, because the unstratified test statistic has been shown to have better test performance [177].

The primary analysis ignores the possible impact of within-family correlation. The propensity to progress to RA could be more similar within families than between families or across individuals in the population, in which case observations in this study would not be independent. Due to operational difficulties in linking family members, we expect to have incomplete information on familial clustering, so we will not be able to account for this potential correlation in the primary analysis. Because families tend to be small and not all family members will be eligible or willing to participate, we anticipate the impact of clustering to be small. We will, however, perform sensitivity analyses to assess the potential impact of clustering. We are asking participants if they have FDRs who are participating. If the proportion who answer affirmative is small, the impact of clustering is likely to be minimal. In addition, participants have the option of linking their study records with those of their relatives. If family clusters are identified through this process, we can estimate the treatment effect from a marginal Cox model for clustered data using the method of Lee, Wei, and Amato [178] and compare these to estimates derived from the usual Cox model assuming independent observations. We could also compare estimates for the risk of developing RA derived from logistic regression models fit using generalized estimating equations under difference assumptions about the within-family correlation structure; independent versus exchangeable [179].

8.3.1.2 Secondary Efficacy Analyses

All secondary analyses will be conducted in an exploratory fashion with p-values and confidence intervals presented as descriptive statistics with no adjustments for multiple comparisons. Tests will be two-sided and interval estimates will be generated at the 95% confidence level. All efficacy analyses will be repeated using the PP population.

The KM estimates for the two arms will be compared using the log-rank test, and survival at 12 months will be compared using methods analogous to those described for the primary efficacy analysis. The two arms will also be compared after control of appropriate covariates using a Cox proportional hazards model. The modeling will also evaluate the relationship between time to onset of clinically-apparent RA (or IA) and covariates such as site, method of recruitment, age, sex, race, baseline characteristics, genetic and environmental factors, and biomarkers.

Treatment group comparisons of longitudinal changes in secondary efficacy endpoints, including disease activity scales, subject self-evaluation scores, and patient reported outcome scores (See Section 3.3.1, *Secondary Efficacy Endpoints*) will be evaluated using repeated measures random regression models. Models will be fit to allow piece-wise fixed-effect for time during the 12-month treatment period and during the subsequent follow-up period through 36 months. A random slope and intercept will be fit for each subject assuming an unstructured covariance matrix. Additional models may be developed to evaluate the relationship of endpoints with appropriate covariates.

8.3.2 Safety Analysis

All safety analyses will be performed using the Safety Population.

The frequency of AEs will be summarized by system organ class, preferred term, severity (grade), and relationship to study treatment. Relationship to study treatment will be categorized as either treatment related (possibly, probably, or definitely related to study medication) or unrelated (unlikely related or unrelated). Similar analyses will be performed for SAEs. To account for differential duration of study participation among subjects, the summaries will also include the event rate (i.e. number of events per person-time) in addition to the number and percent of events and subjects experiencing events.

For each key safety endpoint defined in Section 3.3.2, *Secondary Safety Endpoints* the proportion of subjects experiencing at least one event in each treatment group will be reported and the treatment groups compared based on Fisher's Exact Test.

Laboratory parameters will be summarized both overall and by treatment group using appropriate descriptive statistics. For each lab parameter, the number and percent of subjects that have an increase, decrease, or no change from Baseline to Week 52, Month 24, and 36 will be displayed for each treatment group and pooled across treatment arms. For parameters with an explicit NCI-CTCAE grading criterion, change from baseline will be indicated by a change in grade. For parameters that do not have an explicit NCI-CTCAE grading criterion, observed values will be categorized as 'high' (defined as >ULN), 'normal' (defined as ≥ lower limit of normal (LLN) and ≤ ULN), or 'low' (defined as <LLN). Then, a change from baseline will be indicated as a change in category.

Laboratory data will also be plotted to show patterns over time. Summary statistics including 25th percentile, median, and 75th percentile will be plotted for each visit by treatment group. Lines connecting individual subject results from subjects with Grade 2 or higher values will be overlaid on each figure. For lab results that are not gradable, results from subjects with values outside of 2 *ULN or 0.5*LLN will be overlaid.

All safety comparisons and associated p-values are considered exploratory, not as formal tests of hypothesis. As such, no adjustments will be made for multiple comparisons and all p-values must be interpreted cautiously.

8.3.3 Mechanism/Immunological Analysis

Descriptive statistics and plots (including, but not limited to, those described subsequently) will be used to gain an understanding of the data prior to developing any statistical models. Means, medians, standard deviations, minimums, and maximums will be computed for each continuous biomarker at each time point for treatment groups and separately for subjects who do/do not experience clinically significant disease reactivation. For dichotomous biomarkers (i.e. + or -), frequencies and percents will be computed at each time point for treatment groups and separately for subjects who do/do not experience clinically-apparent RA. In addition, the biomarkers can be treated as 'counts' – for example, the number of autoantibodies positive in the ACPA array, and then analyzed as continuous variables to test a hypothesis that HCQ treatment results in decreased number of ACPAs. To gain a better understanding of trends over time, summary statistics (e.g., means, medians, or percents) will be plotted versus time at the relevant time points. Plots for individual subjects may also be useful.

Multivariate model may be considered to evaluate the relationships between treatment group and alterations of biomarkers that may suggest improved underlying autoimmunity and/or inflammation.

8.4 Interim Analysis

Results of interim analyses will be reported to the DSMB for planned Data Review Meetings. Reports prepared for these meetings will focus on study conduct and subject safety and may include information on enrollment, randomization, site activation status and site performance, subject status (including premature discontinuations from study treatment and early withdrawals from the study), demographics, baseline characteristics, and safety analyses.

If subject accrual is slower than expected or the rate of conversion to clinically-apparent RA is lower than anticipated, a non-binding futility analysis will evaluate the prospects for study success under these conditions. Because of this study's potential for providing insight on the progression of RA in this high-risk population, "study success" for ARA08 is broadly defined. If the primary analysis fails to demonstrate a treatment group difference at Month 36, the study would still be considered successful if the secondary analysis demonstrated a significant difference in survival curves over the course of the study. Furthermore, even in the absence of significant treatment effects for primary or secondary analyses, the mechanistic studies to evaluate changes associated with the onset of RA may still be worthwhile.

Final interim analysis plans for efficacy and futility will be finalized upon completion of enrollment. A single nonbinding futility analysis will be performed at a time point when at least 50% of expected information is available. If this analysis indicates that there is little chance of detecting a significant difference between the arms, the study may be stopped for futility. To evaluate futility, we will compute a Z-score test statistic based on the difference of logit transformed survival estimates (HCQ-placebo). A Z-score <0.3 would suggest the futility. For example, a simulation study assuming a study of 140 subjects showed that if the risk of RA is the

same for both groups (i.e. 50% for both arms), then chance of triggering the futility criterion is 62%. On the other hand, if the design assumptions are correct (50% risk for placebo, 25% for HCQ), then the chance of triggering the futility criterion is 2%, and power is 82%.
In addition, up to 3 interim analyses may be conducted to stop the study early for overwhelming evidence of efficacy provided the overall power for the primary endpoint analysis is maintained at greater than 80%. For example, under the design assumptions in Section 8.1, *Sample Size and Power,* and assuming enrollment is stopped at 4.5 years with 140 independent subjects (i.e. no other family members participating), and 20% loss over 3 years of follow-up (i.e. exponential loss), a simulation study using an O'Brien-Fleming alpha-spending rule showed that power would be 82% with 2 interim analyses at 4.75 and 5.75 years compared to 83% power with no interim analyses.

8.5 Other Statistical Considerations

8.5.1 Subgroups

Exploratory analyses of the primary and secondary objectives may be conducted for the following subgroups defined by age, sex, race, baseline characteristics, genetic and environmental factors, and biomarkers. Additionally, exploratory analyses of responder subgroups and/or subgroups defined through the mechanistic and immunological studies may be conducted.

Subgroups that are differentially distributed between treatment groups and may be considered as potential covariates for adjustment in the Cox proportional hazard and longitudinal models noted above.

8.5.2 Multi-center Studies

As noted above, analyses of survival estimates at fixed points in time will not be stratified. Site and method of recruitment will be included as fixed covariates in models for secondary efficacy analyses. All safety analyses will be based on pooled data with no adjustment or stratification.

8.5.3 Multiple Comparisons and Multiplicity

This study has a single primary analysis to be tested at α=0.05. Consequently, no adjustments for multiplicity are needed for Type I error protection.

The secondary efficacy analyses are considered to be supportive with p-values and confidence intervals presented as descriptive measures of strength of evidence rather than formal statistical inference. Therefore, no multiplicity adjustments are needed for this study.

8.5.4 Missing Data

Standard procedures will be used to ensure that data are as complete and accurate as possible. A full accounting will be made for all missing endpoint data.

For the primary efficacy analysis, we assume non-informative censoring for subjects who leave the study prior to Month 36 with no evidence of clinically-apparent RA. For withdrawn or lost

subjects who consented to yearly phone calls, data collected on RA diagnoses and HCQ use will be used to inform sensitivity analyses on the KM curves. Additional sensitivity analyses may be performed by estimating KM curves under different assumptions about the disease status of subjects lost prior to Month 36. Attrition and compliance rates will be compared between arms.

For the random regression models, all available data for subjects will be included and contribute to the analysis without imputation. If diagnostics suggest that the models are inadequate, sensitivity analyses (e.g. analysis of covariance (ANCOVA)) may be considered.

8.5.5 Changes to the Statistical Analysis Plan (SAP)

A detailed description of the planned analyses will be provided in a SAP to be completed and signed off prior to the completion of the trial. Major changes from this protocol will be noted in the SAP. If there is sufficient reason to do so, revised plans may be issued during the course of the study. Changes to the SAP that are made subsequent to database lock will be documented in the clinical study report.

9 ACCESS TO SOURCE DATA AND DOCUMENTS

Each participating site will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. After study completion, the data may be placed in a DAIT- approved central storage location. However, as a part of the quality assurance and legal responsibilities of an investigation, each site must permit authorized representatives of the sponsor(s) and the SACCC to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other subject data may be copied (obscuring any personally identifying information). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. Participating sites will normally be notified in advance of auditing visits.

All subject records and study documentation will be kept for at least 2 years after the protocol is completed. This will include all documentation of AEs, records of study drug receipt and distribution, and all IRB correspondence.

10 DATA COLLECTION, QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies. However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by the National Institutes of Health.

The investigator will report all major protocol deviations to DAIT and the SACCC per the instructions in the Autoimmunity Centers of Excellence (ACE) Manual of Procedures. The

SACCC will forward reports of protocol deviations to the responsible DAIT/NIAID medical officer for review as specified in the Manual of Procedures.

The SACCC is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical subject charts. Data from these source materials will be transmitted to the SACCC via one of two mechanisms. Data collected electronically at central laboratories will be transferred electronically directly from the laboratory to the SACCC using standard secure data transfer procedures. Data collected at the clinical sites will be transmitted to the SACCC using an internet-based remote data entry system. Clinical site personnel use an internet browser to key data into eCRFs; each CRF page is submitted to the clinical database electronically as the page is completed. Univariate data validation tests are performed as the data are keyed. The clinical database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time, authorized site personnel may log in to the remote data entry system, review and correct previously entered data, or key additional data. The data will be further validated per the study data validation plan via a series of computerized and manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

The SACCC will periodically visit the participating clinical sites and audit the source documents in order to validate the data in the SACCC central database. Data will be provided using the subject's screening or enrollment number, the SACCC will not collect personally identifying information such as the subject's name or social security number. Subjects will provide demographic information such as race, ethnicity, and birth date.

Data collected by the SACCC will be held in the strictest confidence, and are protected from access that could reveal personally identifying information about any subject in the trial.

11 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

The study will be conducted according to GCP guidelines, U.S. 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards.

11.1 Compliance with Good Clinical Practices

This trial will be conducted in compliance with the protocol, current GCPs recommended by the ICH and the applicable regulatory requirements for participating institutions. These include the tenets of the Declaration of Helsinki and review and approval by the appropriate ethics review committee or IRBs of participating organizations. The SACCC will assure compliance through a program of quality assurance audits performed both at participating sites and within the SACCC

for data quality and adherence to protocol requirements. The SACCC is operated by Rho Federal Systems Division, Inc. (RhoFED), Durham, North Carolina under a cooperative agreement with NIAID.

11.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and associated informed consent documents by an appropriate ethics review committee or IRB. Any amendments to the protocol or consent materials must be approved by the IRB before they are placed into use. In both the United States and in other countries, only institutions holding a current Federal Wide Assurance issued by the Office of Human Research Protection (OHRP) at the Department of Health and Human Services (DHHS) may participate.

The investigator will inform the IRB of serious or unexpected AEs that might occur during the study and are likely to affect the safety of the subjects, or the conduct of the study. The investigators will comply fully with all IRB requirements for both the reporting of AEs, protocol or consent form changes, as well as any new information pertaining to the use of the study medication that might affect the conduct of the study.

11.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki, as well as compliance with all IRB requirements, will be implemented in the study, before any protocol-specified procedures are carried out. A standard consent form for subject participation will be provided with the protocol to each institution. Any modifications to the standard information in the template will require review and approval by DAIT/NIAID. Informed consent will be obtained in accordance with 21 CFR 50.52. Information may be given to subjects in oral, written, or video form by the investigator. All prospective subjects will be given ample time to read the consent form, and ask questions, before signing.

If subjects are to be enrolled who do not speak and read English, the consent materials must be translated into the language appropriate for the enrolling subject. Translated documents must be certified to contain the complete descriptions provided in the English version of the document. If an interpreter is used to provide or assist in describing the consent materials to an enrolling subject, the interpreter must also sign the consent materials certifying their involvement with the consent process.

After completion, a copy of the signed consent form will be given to the subject. The original signed consent form will be kept on file in the subject's study chart, available for inspection by regulatory authorities, both federal and institutional.

11.4 Data and Safety Monitoring Board

The responsibility for reviewing the ethical conduct of the study and for monitoring reports of evidence of adverse or beneficial effect is assigned to the DAIT Autoimmunity DSMB. The DSMB is an independent group composed of biomedical ethic experts, physicians, and other scientists who are responsible for continuing review of study information. The DSMB makes

recommendations to DAIT/NIAID on issues affecting the course and conduct of this clinical study.

11.5 Study Termination

In the event that the study is discontinued, sites will immediately notify subjects to terminate study agent and return for a close-out visit to the site within 30 days.

12 FINANCING AND INSURANCE

Participating institutions must comply with their institution's policies on compensation, insurance, and indemnity. Institutions must have adequate liability insurance coverage to satisfy their local and national requirements for study participation.

13 PUBLICATION POLICY

The ACE Publication Policy will apply to publication of study results. Authorized participants may find details regarding the policy statement on the ACE internet website. Site investigators are encouraged to communicate and publish study results with prior notification of and review by DAIT, NIAID.

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15 APPENDICES

Appendices may include:

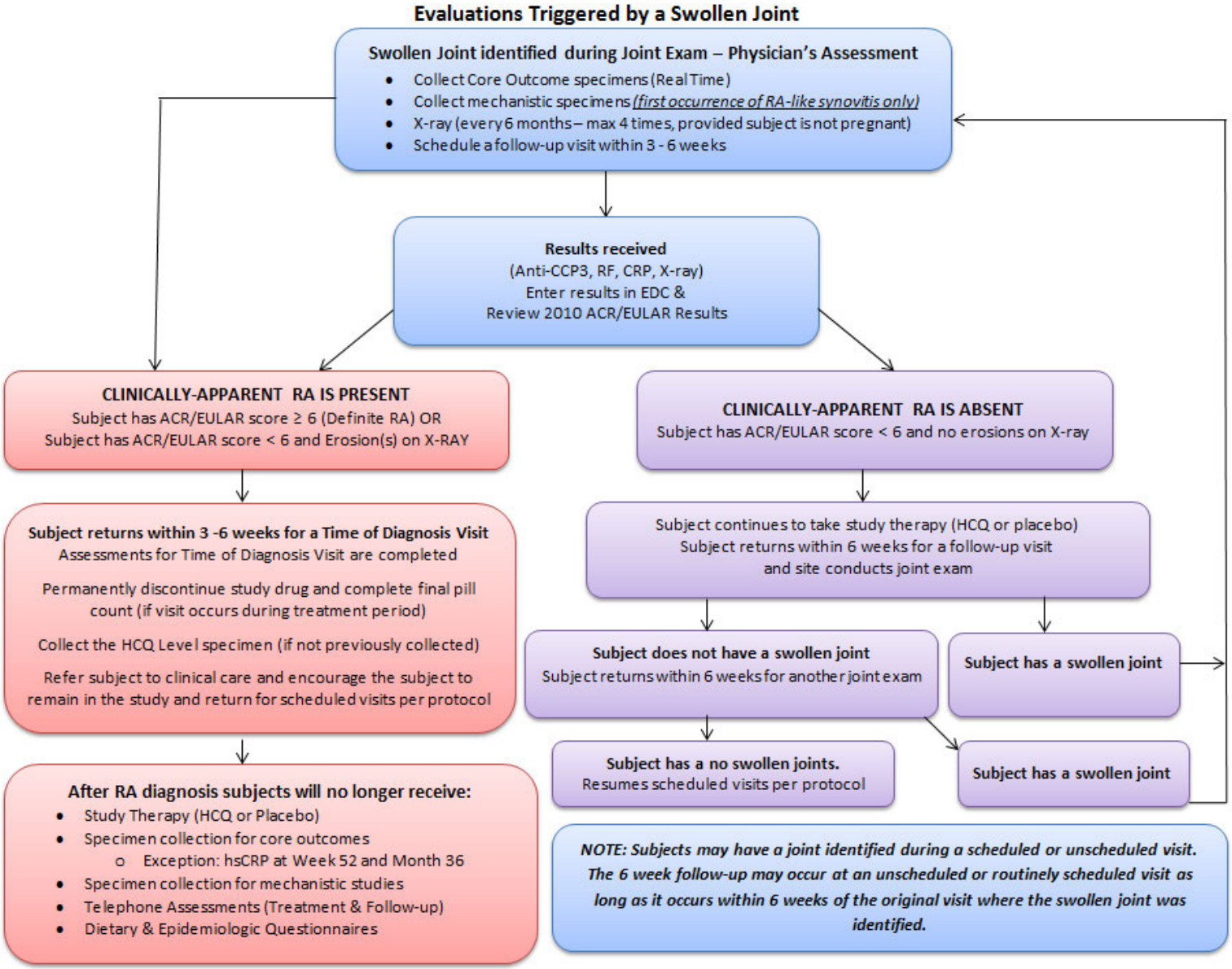
- 2010 ACR/EULAR RA Classification Criteria
- Flow Diagrams:
  - Evaluations Triggered by a Swollen Joint
  - Procedures for Subjects Diagnosed with IA/RA by an Outside Physician
- Formulas (IBW, Cockcroft-Gault, DAS28-CRP)
- NHYA Classification
- Subject Questionnaires

15.1 2010 ACR/EULAR RA Classification Criteria

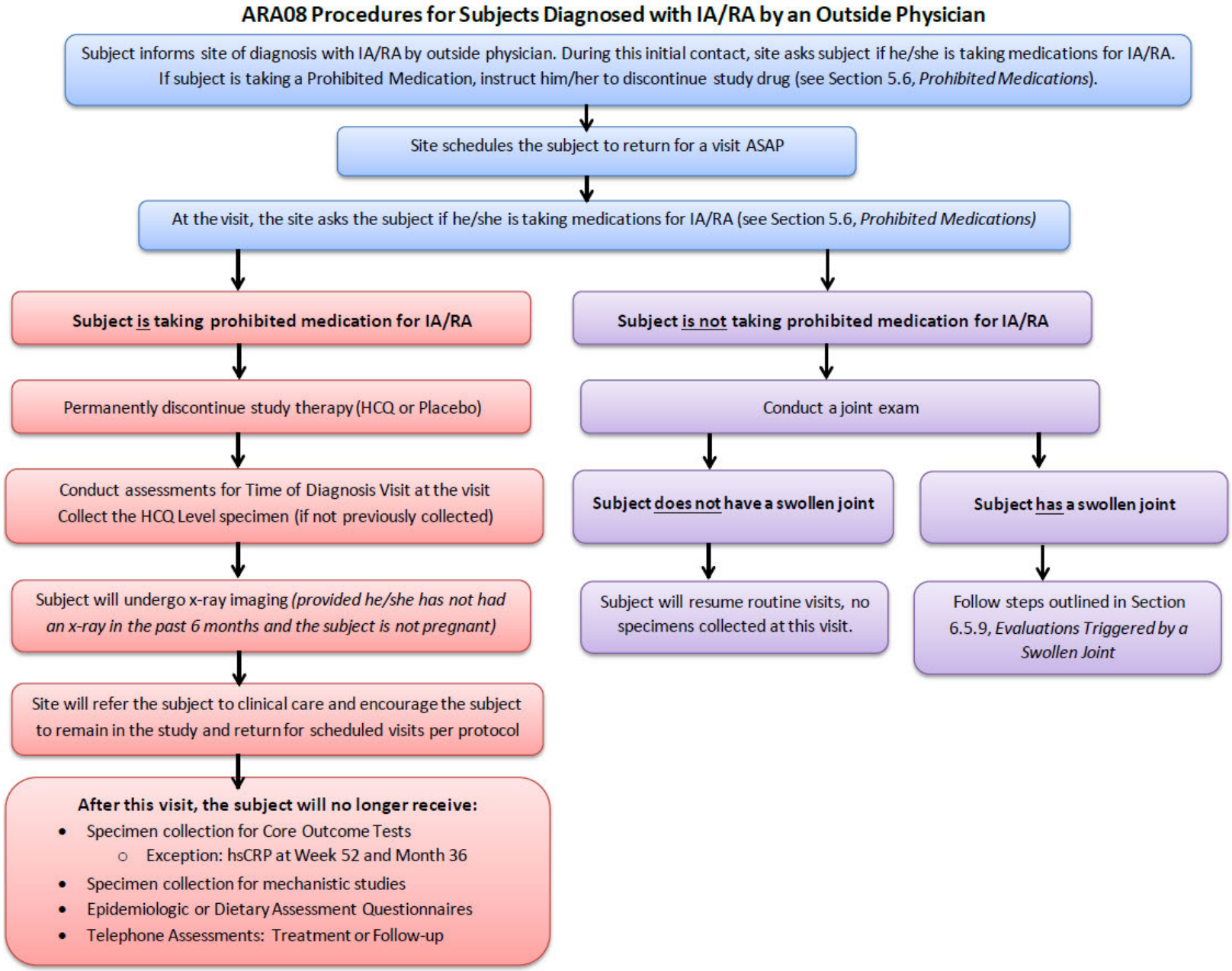
2010 ACR/EULAR RA Classification Criteria[62]	
Who should be tested? Patients with ≥1 swollen joint consistent with synovitis not better explained by another disease. If the patient meets these initial criteria with a score of ≥6/10 they can be classified as having 'definite RA':	
A. Joint involvement*	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least 1 small)	5
B. Serology (at least 1 test needed)	
Negative RF and ACPA	0
Low positive RF or ACPA	2
High positive RF or ACPA**	3
C. Acute-phase reactants	
Normal CRP	0
Abnormal CRP	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1
* Joint involvement refers to any swollen or tender joint on examination. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. "Large joints" refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. *Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement. **High positive is equivalent to >3 times the upper limit of normal based on the reference range of the laboratory that assesses the biomarker.	

15.2 Flow Diagrams

15.2.1 Evaluations Triggered by a Swollen Joint Flow Chart



15.2.2 Procedures for Subjects Diagnosed with IA/RA by an Outside Physician Flow Chart



15.3 Formulas

- Ideal Body Weight (Kg)
  - Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet, or subtract 1kg for every inch under 5 feet.
  - Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet, or subtract 1kg for every inch under 5 feet.
- Cockcroft-Gault Formula: CrCl = (140-age [in years]) * (Wt [in kg]) * (0.85 if female) / (72 * Cr [in mg/dl])
- DAS28-CRP Formula: DAS28-4(crp) = 0.56*SQRT(TJC28) + 0.28SQRT(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96
  - TJC28 = # tender joints of 28 counted
  - SJC28=#swollen joints of 28 counted
  - GH = Patient Global Assessment on a 21 point scale
  - CRP = C-reactive protein (mg/L)

15.4 NYHA Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

15.5 Subject Questionnaires

15.5.1 Pre-Screening Questionnaire

ARA08: StopRA Optional Source Document Manual of Procedures

ARA08 PRE-SCREENING QUESTIONNAIRE
OPTIONAL SOURCE DOCUMENT

Assessment Date (DD/MON/YYYY): _____

Please answer the following questions.

QUESTION	ANSWER
1) Please write your full name to the right.	_____
2) Have you been diagnosed by a health care provider with rheumatoid arthritis?	☐ NO ☐ YES

_____ _____

Signature of Subject **Date** *(DD/MON/YYYY)*

FOR COORDINATOR USE:
Please use this space to note any additional information needed to schedule the Screening visit (contact information, alternate phone numbers, general availability, etc.) If the subject meets the Anti-CCP assay-specific positivity criterion (Anti-CCP3/Anti-CCP3.1 assay result ≥ 40, or Anti-CCP2 or any other assay yielding a positive result per assay normal ranges) and has not been previously diagnosed with rheumatoid arthritis, contact the subject to schedule a screening visit, and create a subject ID in the ARA08 RAVE EDC system, see the Manual of Procedures for instructions.

ARA08: Pre-Screening Questionnaire Page 1 of 1 18 JAN 2018

15.5.2 Self-Reported Demographics

15.5.2.1 Self-Reported Demographics: Screening

ARA08 SUBJECT SELF-REPORTED DEMOGRAPHICS- SCREENING REQUIRED SOURCE DOCUMENT

Rave EDC Folder: Screening

Subject ID: _____ **Assessment Date (DD/MON/YYYY):** _____

Instructions
Please complete the survey by checking the box or boxes that most closely identify your race, ethnicity, employment status, education, and income. Check multiple boxes if necessary. Initial and date this form as indicated and return it to your ARA08 site coordinator.

Section 1: Date of Birth & Gender
(EDC Page: Demographics)

1) Please note your date of birth.	_____ DD/MON/YYYY
2) Please note your gender.	☐ Female ☐ Male ☐ Decline to Answer

Section 2: Ethnicity
(EDC Page: Demographics)

Please note your ethnicity:		
Hispanic or Latino (A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino".)		
☐ Hispanic or Latino	☐ Not Hispanic or Latino	☐ Unknown
Jewish		
☐ Jewish	☐ Not Jewish	☐ Unknown
If Jewish, please specify		
☐ Ashkenazi	☐ Sephardic	☐ Unknown

Section 3: Race

(EDC Page: Demographics)

Please note your race:			
American Indian or Alaska Native (A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.)	☐ Yes ☐ No	**Asian** (A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.)	☐ Yes ☐ No
Black or African American (A person having origins in any of the black racial groups of Africa.)	☐ Yes ☐ No	**Native Hawaiian or Other Pacific Islander** (A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.)	☐ Yes ☐ No
White (A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.)	☐ Yes ☐ No	**Unknown**	☐ Yes ☐ No

Please note your predominant race (Check one):		
☐ White	☐ Black or African American	☐ Asian
☐ American Indian or Alaska Native	☐ Native Hawaiian or Other Pacific Islander	☐ Unknown

To the best of your knowledge, your 4 Grandparents or their ancestors came from:	
Maternal Grandmother	_____
Maternal Grandfather	_____
Paternal Grandmother	_____
Paternal Grandfather	_____

ARA08: StopRA REQUIRED Source Document Manual of Procedures

Section 4: Current Employment
(EDC Page: Socioeconomic Status & Education)

1) What is your current employment?

- ☐ Retired
- ☐ Homemaker
- ☐ Student
- ☐ Disabled
- ☐ On Sick Leave
- ☐ On Maternity Leave
- ☐ Unemployed
- ☐ Employed (Complete questions 2 &3)

2) If you are employed, what is your current occupation?

_____

3) What is your employment status?

- ☐ Full Time
- ☐ Part Time
- ☐ Modified/Seasonal

Section 5: Education & Income
(EDC Page: Socioeconomic Status & Education)

1) What is the highest level of education you have completed? *(Please check the highest level of schooling completed).*

- ☐ Grade school
- ☐ High School
- ☐ GED
- ☐ College
- ☐ Graduate school

2) What was your household income, before taxes, for the past year?

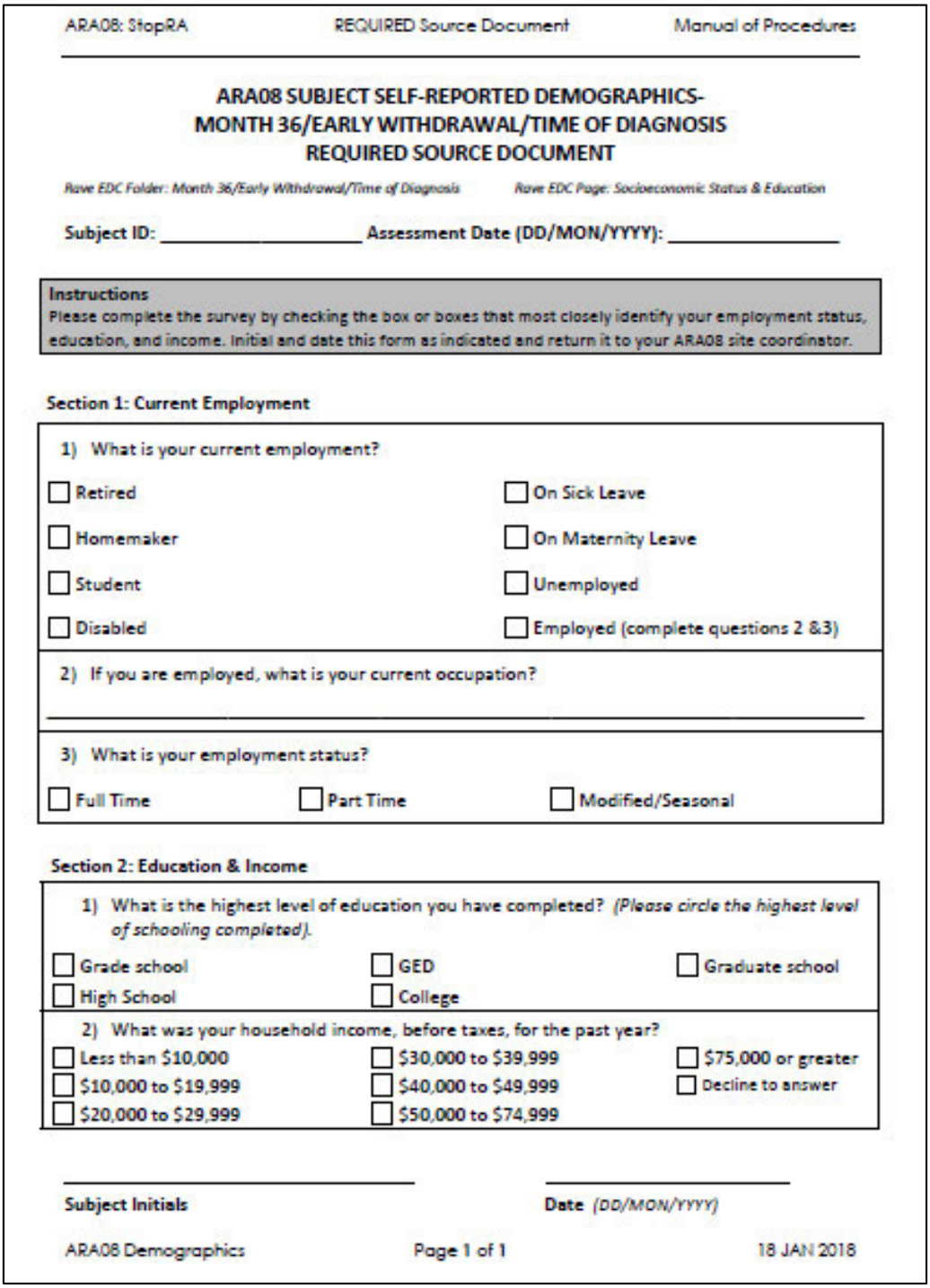
- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $74,999
- ☐ $75,000 or greater
- ☐ Decline to answer

_____ _____

Subject Initials **Date** *(DD/MON/YYYY)*

ARA08 Demographics Page 3 of 3 18 JAN 2018

15.5.2.2 Self-Reported Demographics: End of Study



ARA08: StopRA REQUIRED Source Document Manual of Procedures

ARA08 SUBJECT SELF-REPORTED DEMOGRAPHICS-
MONTH 36/EARLY WITHDRAWAL/TIME OF DIAGNOSIS
REQUIRED SOURCE DOCUMENT

Rave EDC Folder: Month 36/Early Withdrawal/Time of Diagnosis *Rave EDC Page: Socioeconomic Status & Education*

Subject ID: _____ **Assessment Date (DD/MON/YYYY):** _____

Instructions
Please complete the survey by checking the box or boxes that most closely identify your employment status, education, and income. Initial and date this form as indicated and return it to your ARA08 site coordinator.

Section 1: Current Employment

1) What is your current employment?

- ☐ Retired
- ☐ Homemaker
- ☐ Student
- ☐ Disabled
- ☐ On Sick Leave
- ☐ On Maternity Leave
- ☐ Unemployed
- ☐ Employed (complete questions 2 &3)

2) If you are employed, what is your current occupation?

_____

3) What is your employment status?

- ☐ Full Time
- ☐ Part Time
- ☐ Modified/Seasonal

Section 2: Education & Income

1) What is the highest level of education you have completed? *(Please circle the highest level of schooling completed).*

- ☐ Grade school
- ☐ High School
- ☐ GED
- ☐ College
- ☐ Graduate school

2) What was your household income, before taxes, for the past year?

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $74,999
- ☐ $75,000 or greater
- ☐ Decline to answer

_____ _____

Subject Initials **Date** *(DD/MON/YYYY)*

ARA08 Demographics Page 1 of 1 18 JAN 2018

15.5.3 Self-Reported Joint Symptoms including modified MDHAQ

ARA08: StopRA REQUIRED Source Document Manual of Procedures

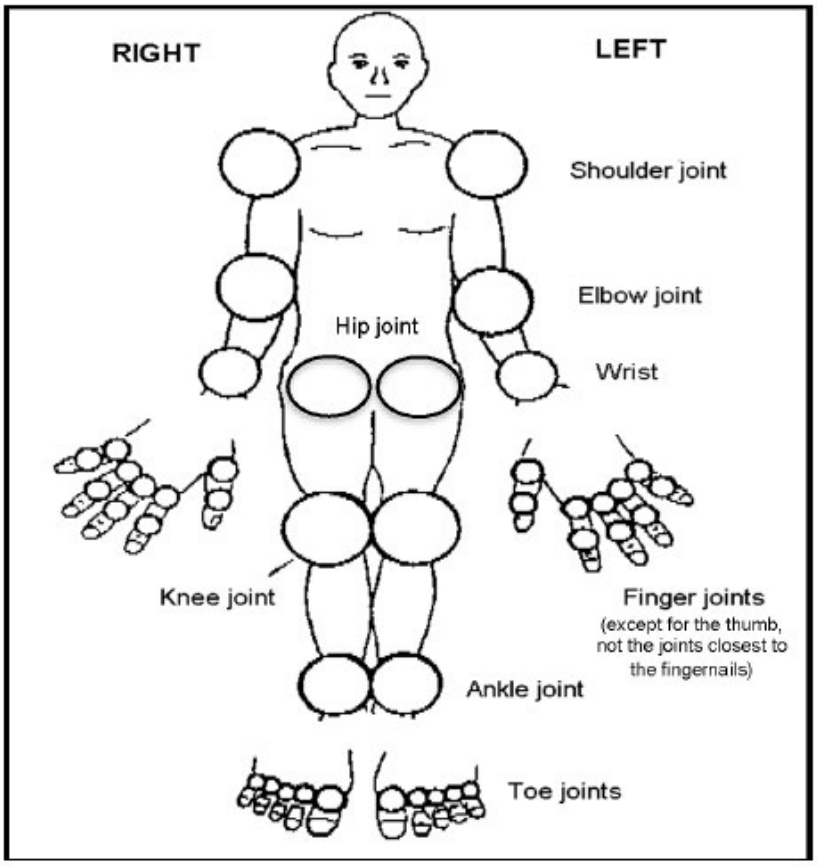
ARA08 SUBJECT SELF-REPORTED JOINT SYMPTOMS
REQUIRED SOURCE DOCUMENT

Rave EDC Page: Subject Self-Reported Joint Symptoms

Subject ID: _____ **Assessment Date (DD/MON/YYYY):** _____

Section 1: Painful Joints

QUESTION	ANSWER
Have you had any joints that are PAINFUL today or over the last week?	☐ YES (Please mark on the figure with an X all of your joints that are PAINFUL today or during the past week.) ☐ NO (Jump to Section 2 on the next page)



Circle the number that best describes the pain in or around your joints that you felt today or over the past week: *(Note to coordinator: EDC Page: MDHAQ)*

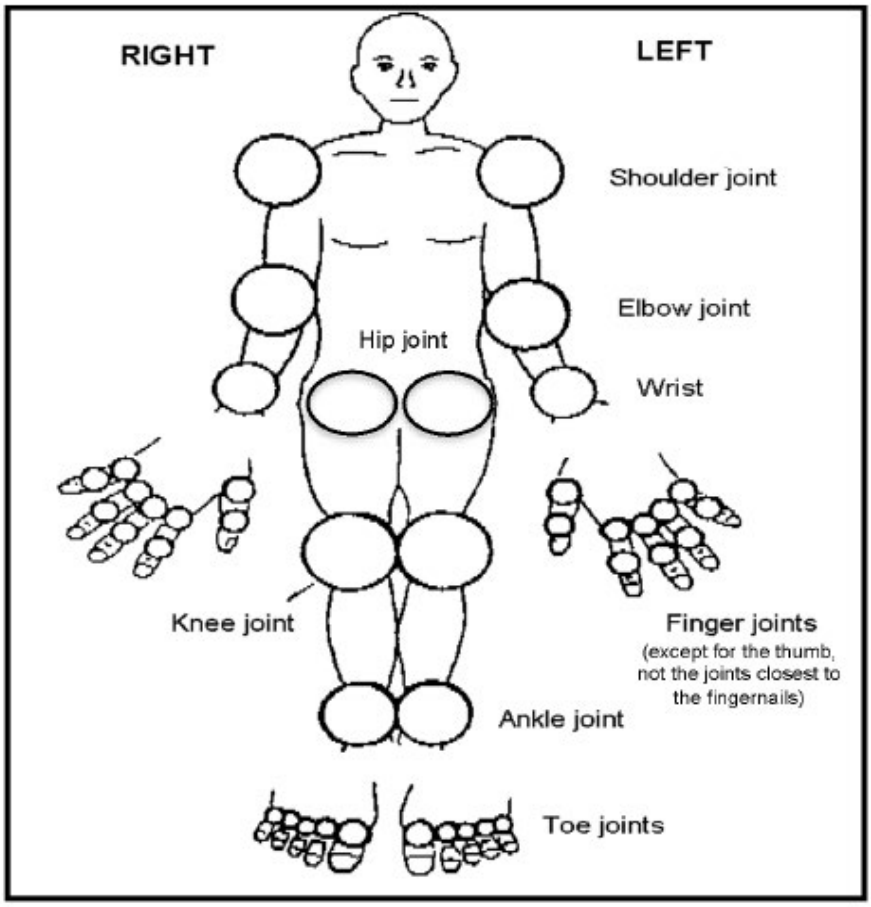
No Pain ○ Extreme Pain
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

ARA08: Subject Self-Reported Joint Symptoms Page 1 of 4 17 APR 2018

ARA08: StopRA REQUIRED Source Document Manual of Procedures

Section 2: Swollen Joints

QUESTION	ANSWER
Have you had any joints that are SWOLLEN today or over the past week?	☐ YES (Please mark on the figure with an X all of your joints that have SWELLING today or during the past week.) ☐ NO (Jump to Section 3 on the next page)

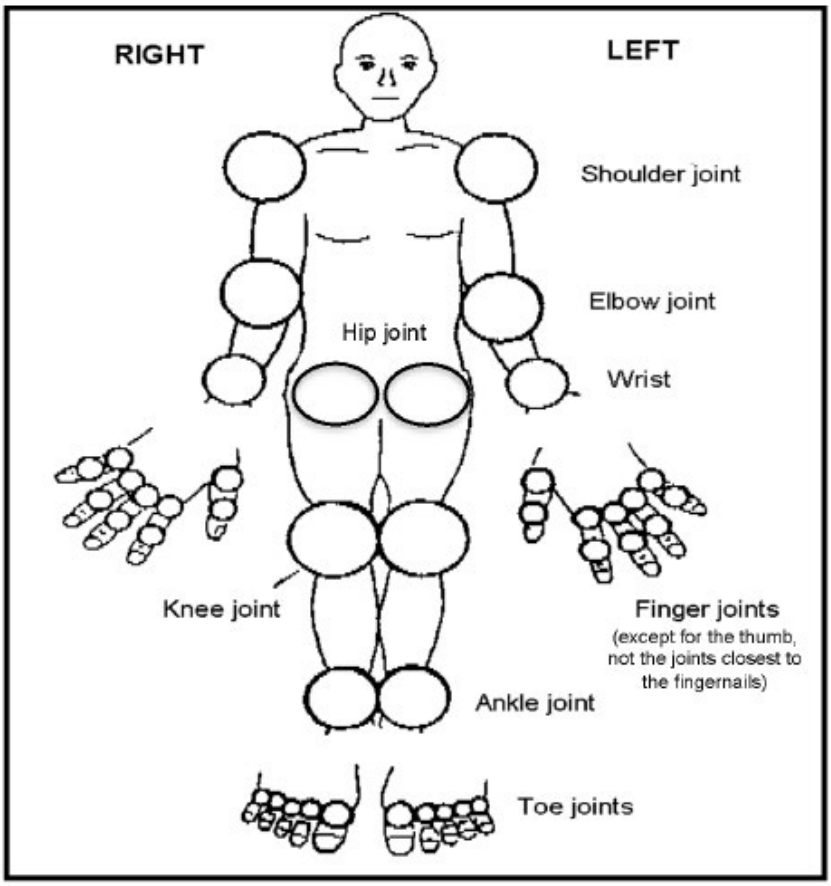


ARA08: Subject Self-Reported Joint Symptoms Page 2 of 4 17 APR 2018

ARA08: StopRA REQUIRED Source Document Manual of Procedures

Section 3: Stiff Joints

QUESTION	ANSWER
Have you had any joints that are STIFF today or over the past week?	☐ YES (Please mark on the figure with an X all of your joints that have STIFFNESS today or during the past week.) ☐ NO (Jump to Section 4 on the next page)



If you have stiffness, circle the number that best describes the stiffness (all over or in your joints) you felt today or over the past week : *(Note to coordinator: EDC Page: MDHAQ)*

No Stiffness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	Extreme Stiffness
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10	

When you awaken in the morning OVER THE PAST WEEK, how long does your joint stiffness last? _____ minutes

ARA08: Subject Self-Reported Joint Symptoms Page 3 of 4 17 APR 2018

Section 4: FATIGUE

How much of a problem has UNUSUAL fatigue or tiredness been for you TODAY OR OVER THE PAST WEEK? *(Note to coordinator: EDC Page: MDHAQ)*

Fatigue is no problem	○ 0	○ 0.5	○ 1.0	○ 1.5	○ 2.0	○ 2.5	○ 3.0	○ 3.5	○ 4.0	○ 4.5	○ 5.0	○ 5.5	○ 6.0	○ 6.5	○ 7.0	○ 7.5	○ 8.0	○ 8.5	○ 9.0	○ 9.5	○ 10	Fatigue is a major problem

Section 5: OVERALL HEALTH & ABILITY

Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing TODAY OR OVER THE PAST WEEK: *(Note to coordinator: EDC Page: MDHAQ)*

Very Well	○ 0	○ 0.5	○ 1.0	○ 1.5	○ 2.0	○ 2.5	○ 3.0	○ 3.5	○ 4.0	○ 4.5	○ 5.0	○ 5.5	○ 6.0	○ 6.5	○ 7.0	○ 7.5	○ 8.0	○ 8.5	○ 9.0	○ 9.5	○ 10	Very Poorly

Please place an "X" next to the best answer for your abilities TODAY OR OVER THE PAST WEEK: *(Note to coordinator: EDC Page: MDHAQ)*

OVER THE LAST WEEK, were you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
a. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
b. Get in and out of bed?	0	1	2	3
c. Lift a full cup or glass to your mouth?	0	1	2	3
d. Walk outdoors on flat ground?	0	1	2	3
e. Wash and dry your entire body?	0	1	2	3
f. Bend down to pick up clothing from the floor?	0	1	2	3
g. Turn regular faucets on and off?	0	1	2	3
h. Get in and out of a car, bus, train, or airplane?	0	1	2	3
i. Walk two miles or three kilometers, if you wish?	0	1	2	3
j. Participate in recreational activities and sports as you would like, if you wish?	0	1	2	3

Signature of Subject **Date** *(DD/MON/YYYY)*

15.5.4 Subject Epidemiologic Questionnaire: Baseline & Follow-up

15.5.4.1 Subject Epidemiologic Questionnaire: Baseline

ARA08: StopRA REQUIRED Source Document Manual of Procedures

ARA08 SUBJECT EPIDEMIOLOGIC QUESTIONNAIRE- BASELINE
REQUIRED SOURCE DOCUMENT

Rave EDC Folder: Baseline

Subject ID: _____ **Assessment Date (DD/MON/YYYY):** _____

Instructions
This questionnaire will evaluate your medical history and environmental exposures.

Please answer the questions below.

Section 1: FAMILY HISTORY OF RHEUMATOID ARTHRITIS
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Does anyone in your family have rheumatoid arthritis?	☐ Yes (Continue) ☐ No (Skip to Section 2) ☐ Unknown(Skip to Section 2)
2) Which family member(s) has been diagnosed with rheumatoid arthritis?	☐ Parent (Mother or Father) ☐ Sibling (Full Brother/Sister) ☐ Child (Biologic Child) ☐ Other (Specify: _____) ☐ Other (Specify: _____) ☐ Other (Specify: _____) ☐ Other (Specify: _____)

Section 2: ORAL HEALTH
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Have you ever been told by a dentist or dental hygienist that you have gingivitis, gum or periodontal disease?	☐ Yes ☐ No ☐ Don't Know
2) Have you ever been told by a dentist or dental hygienist that you have deep gingival pockets?	☐ Yes ☐ No ☐ Don't Know

Section 3: SMOKING HISTORY
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Have you smoked more than 100 cigarettes in your lifetime?	☐ Yes (Continue) ☐ No (Skip to Section 4)
2) Do you currently smoke cigarettes?	☐ Yes (Continue) ☐ No (Skip to Question 5)

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Current Smokers	
3) On average, how many cigarettes per day do you currently smoke?	_____ cigarettes/day
4) On average, how many years have you smoked at this level?	_____ years (Skip to Section 4)
Past Smokers	
5) When did you permanently stop smoking?	_____ (month/year)
6) On average, how many cigarettes did you smoke per day when you were smoking?	_____ cigarettes/day
7) How many years in total did you smoke at that level?	_____ years

Section 4: TOBACCO USE

(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Have ever used any other form of tobacco (besides cigarettes)?	☐ Yes (Continue) ☐ No (Skip to Section 5)
Cigars	
2) Do you smoke cigars?	☐ Yes (Continue) ☐ No (Skip to Pipes)
3) On average, how many cigars do you smoke per day?	_____ cigars/day
4) How many years have you used cigars?	_____ years
Pipes	
5) Do you smoke a pipe?	☐ Yes (Continue) ☐ No (Please skip to Chew/Snuff)
6) On average, how many bowls do you smoke per day?	_____ bowls/day
7) How many years have you used pipes?	_____ years
Chew/Snuff	
8) Do you use chew/snuff?	☐ Yes (Continue) ☐ No (Skip to Electronic cigarettes)
9) How many wads of chew/snuff do you use per day?	_____ wads/day
10) How many years (in total) have you used chew/snuff?	_____ years

Electronic Cigarettes (e-cigarettes or 'vaping')	
11) Do you use electronic cigarettes?	☐ Yes (Continue) ☐ No (Skip to Section 5)
12) If yes, how often are you using electronic cigarettes?	☐ One day a week or less ☐ 2 to 4 days a week ☐ 5 or more days a week (Continue)
13) How many years (in total) have you used e-cigarettes?	_____ years

Section 5: EXPOSURE TO TOBACCO SMOKE
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Did your parents smoke while you were living with them?	☐ No ☐ Mother Only ☐ Father Only ☐ Both Mother & Father
2) As an adult, how many years have you lived with someone who smoked regularly?	☐ None or less than 1 year ☐ 1-4 years ☐ 5-9 years ☐ 10–19 years ☐ 20–29 years ☐ 30-39 years ☐ 40 or more years
3) Are you currently exposed to cigarette smoke from other people at home?	☐ No ☐ Occasionally ☐ Regularly
4) Are you currently exposed to cigarette smoke from other people at work?	☐ No ☐ Occasionally ☐ Regularly

THE REMAINING SECTIONS (SECTIONS 6 & 7) ARE TO BE FILLED OUT BY FEMALE PARTICIPANTS ONLY.

Hormones affect the way your body works, and may affect how individuals develop rheumatoid arthritis. Levels of hormones are affected by various events in your life, such as pregnancy, breastfeeding and menstruation. The purpose of the following questions is to get a broad view of your hormone history.

IF YOU ARE A MALE PARTICIPANT, PLEASE SIGN AND DATE BELOW.

_____ _____

Signature of Subject **Date** *(DD/MON/YYYY)*

ARA08: StopRA REQUIRED Source Document Manual of Procedures

Section 6: MENSTRUAL HISTORY
(EDC Page: Menstrual History)

QUESTION	ANSWER
1) At what age did you start menstruating?	_____(years)
2) Do you currently have "regular" menstrual cycles? *(For most women, periods come every 20-40 days. This can be on or off birth control.)*	☐ Yes (Skip to Question 4) ☐ No (Continue) ☐ Unsure (Skip to Question 4)
3) If No, *(you currently do not have regular menstrual cycles)*, what is the main reason for this?	☐ I have started going through menopause ☐ I already went through menopause ☐ I am taking birth control that affects my periods ☐ I stopped taking birth control pills and my period hasn't come back ☐ I am taking another medication that stops or affects how often I have my period ☐ I have an IUD ☐ I had a hysterectomy ☐ I am currently pregnant or breastfeeding ☐ Other reason not listed above
4) Have you gone through menopause or do you think you are currently going through menopause? *(Symptoms can include hot flashes, irregular menstrual cycles or periods, and mood swings.)*	☐ Yes (Continue) ☐ No (Skip to Question 7) ☐ Unsure (Skip to Question 7)
5) If Yes, at what age did the symptoms of menopause start?	_____(years)
6) Was it a natural menopause that was not caused by medical treatment?	☐ Yes ☐ No ☐ Don't Know
7) Have you permanently stopped menstruating? *(This means you have not had a period for at least 12 months.)*	☐ Yes (Continue) ☐ No (Skip to Question 9) ☐ Don't Know (Skip to Question 9)
8) If Yes, at what age did you permanent stop menstruating?	_____(years)
9) Have you had a hysterectomy *(uterus or womb removed)*?	☐ Yes (Continue) ☐ No (Skip to Question 12) ☐ Unsure (Skip to Question 12)
10) If Yes, at what age did you have a hysterectomy?	_____(years)
11) What type of hysterectomy did you have? *(A partial hysterectomy removes the uterus but leaves the cervix. A complete hysterectomy removes the entire uterus and cervix.)*	☐ Partial ☐ Complete ☐ Don't Know

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12) Have you had one or both of your ovaries removed?	☐ Yes (Continue) ☐ No (Skip to Section 7) ☐ Don't Know (Skip to Section 7)
13) If Yes, how many of your ovaries have been removed?	☐ One ☐ Two ☐ Don't Know
14) At what age(s) were your ovaries removed?	_____(age)

Section 7: PREGNANCY HISTORY

(EDC Page: Pregnancy History)

QUESTION	ANSWER
1) Have you ever been pregnant?	☐ Yes ☐ No (Sign at bottom of page) ☐ Prefer not to answer (Sign at bottom of page)

If Yes, complete the following table.

For each pregnancy that you may have had, please describe the details of each pregnancy in the table below. This includes miscarriages, abortions, tubal or ectopic pregnancies, stillbirths, and live births

Pregnancy	How many weeks did the pregnancy last?	Did this pregnancy result in a live birth?	Birth Month and year	What type of delivery?	Did you breastfeed this child?	How many months did you breastfeed this child?
	40 weeks is considered full term	*If Yes, continue to right. If No, add the next pregnancy until all pregnancies are listed.*			*If yes, continue to the right. If no, go to the next pregnancy*	
1.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
2.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
3.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
4.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
5.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
6.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	

_____ _____

Signature of Subject **Date** *(DD/MON/YYYY)*

15.5.4.2 Subject Epidemiologic Questionnaire: Follow-up

ARA08: StopRA REQUIRED Source Document Manual of Procedures

ARA08 SUBJECT EPIDEMIOLOGIC QUESTIONNAIRE – FOLLOW-UP
REQUIRED SOURCE DOCUMENT

Rave EDC Folder: Week 52/Month 24/Month 36/Early Withdrawal/Time of Diagnosis

Subject ID: _____

Assessment Date (DD/MON/YYYY): _____

Instructions
This questionnaire will evaluate your medical history and environmental exposures since you last completed these forms on / /
DD MON YYYY

Please answer the questions below.

Section 1: FAMILY HISTORY OF RHEUMATOID ARTHRITIS
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Since the last time you completed this questionnaire for this study, has anyone in your family been diagnosed with rheumatoid arthritis?	☐ Yes (Continue below) ☐ No (Skip to Section 2) ☐ Unknown (Skip to Section 2)
2) Which family member was diagnosed with rheumatoid arthritis?	☐ Parent (Mother or Father) ☐ Sibling (Full Brother/Sister) ☐ Child (Biologic Child) ☐ Other (Specify: _____) ☐ Other (Specify: _____) ☐ Other (Specify: _____) ☐ Other (Specify: _____)

Section 2: ORAL HEALTH
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Since the last time you completed this questionnaire for this study, have you been told by a dentist or dental hygienist that you have gingivitis, gum or periodontal disease?	☐ Yes ☐ No ☐ Don't Know
2) Since the last time you completed this questionnaire for this study, have you ever been told by a dentist or dental hygienist that you have deep gingival pockets?	☐ Yes ☐ No ☐ Don't Know

ARA08: Epidemiologic Questionnaire Page 1 of 5 18 JAN 2018

ARA08: StopRA REQUIRED Source Document Manual of Procedures

Section 3: SMOKING HISTORY

(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Since the last time you completed this questionnaire for this study, did you ever smoke cigarettes or use another form of tobacco?	☐ Yes (Continue) ☐ No (Skip to Section 4)
2) Do you currently smoke cigarettes or use any other form of tobacco?	☐ Yes (Skip to Question 4) ☐ No (Continue to Question 3)
3) If you do not currently smoke cigarettes or use any other form of tobacco, when did you quit?	_____ month/year (Skip to Section 4)
Cigarettes	
4) Do you smoke cigarettes?	☐ Yes (Continue) ☐ No (Skip to Cigars)
5) On average, how many cigarettes per day do you currently smoke?	_____ cigarettes/day (Continue)
Cigars	
6) Do you smoke cigars?	☐ Yes (Continue) ☐ No (Skip to next Pipes)
7) On average, how many cigars do you smoke per day?	_____ cigars/day
Pipes	
8) Do you smoke a pipe?	☐ Yes (Continue) ☐ No (Skip to next Chew/Snuff)
9) On average, how many bowls do you smoke per day?	_____bowls/day
Chew/Snuff	
10) Do you use chew/snuff?	☐ Yes (Continue) ☐ No (Skip to Electronic Cigarettes)
11) How many wads of chew/snuff do you use per day?	_____ wads/day
Electronic Cigarettes (e-cigarettes or 'vaping')	
12) Do you use electronic cigarettes?	☐ Yes (Continue) ☐ No (Skip to Section 4)
13) If yes, how often are you using electronic cigarettes?	☐ One day a week or less ☐ 2 to 4 days a week ☐ 5 or more days a week (Continue)

ARA08: Epidemiologic Questionnaire Page 2 of 5 18 JAN 2018

ARA08: StopRA REQUIRED Source Document Manual of Procedures

Section 4: EXPOSURE TO TOBACCO SMOKE
(EDC Page: Epidemiologic Questionnaire)

QUESTION	ANSWER
1) Are you currently exposed to cigarette smoke from other people at home?	☐ No ☐ Occasionally ☐ Regularly
2) Are you currently exposed to cigarette smoke from other people at work?	☐ No ☐ Occasionally ☐ Regularly

THE REMAINING SECTIONS (SECTIONS 5 & 6) ARE TO BE FILLED OUT BY FEMALE PARTICIPANTS ONLY.

Hormones affect the way your body works, and may affect how individuals develop rheumatoid arthritis. Levels of hormones are affected by various events in your life, such as pregnancy, breastfeeding and menstruation. The purpose of the following questions is to get a broad view of your hormone history.

IF YOU ARE A MALE PARTICIPANT, PLEASE SIGN AND DATE BELOW.

_____ _____

Signature of Subject **Date** *(DD/MON/YYYY)*

Section 5: MENSTRUAL HISTORY
(EDC Page: Menstrual History)

QUESTION	ANSWER
1) Do you currently have "regular" menstrual cycles? *(For most women, periods come every 20-40 days. This can be on or off birth control.)*	☐ Yes (Skip to Question 3) ☐ No (Continue) ☐ Unsure (Skip to Question 3)
2) If No, *(you currently do not have regular menstrual cycles)*, what is the main reason for this?	☐ I have started going through menopause ☐ I already went through menopause ☐ I am taking birth control that affects my periods ☐ I stopped taking birth control pills and my period hasn't come back ☐ I am taking another medication that stops or affects how often I have my period ☐ I have an IUD ☐ I had a hysterectomy ☐ I am currently pregnant or breastfeeding ☐ Other reason not listed above

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3) Since the last time you completed this questionnaire for this study, have you gone through menopause or do you think you are currently going through menopause? *(Symptoms can include hot flashes, irregular menstrual cycles or periods, and mood swings.)*	☐ Yes (Continue) ☐ No (Skip to Question 6) ☐ Unsure (Skip to Question 6)
4) If Yes, at what age did the symptoms of menopause start?	_____(years)
5) Was it a natural menopause that was not caused by medical treatment?	☐ Yes ☐ No ☐ Don't Know
6) Since the last time you completed this questionnaire for this study, have you permanently stopped menstruating? *(This means you have not had a period for at least 12 months.)*	☐ Yes (Continue) ☐ No (Skip to Question 8) ☐ Don't Know (Skip to Question 8)
7) If Yes, at what age did you permanent stop menstruating?	_____(years)
8) Since the last time you completed this questionnaire for this study, have you had a hysterectomy *(uterus or womb removed)*?	☐ Yes (Continue) ☐ No (Skip to Question 11) ☐ Unsure (Skip to Question 11)
9) If Yes, at what age did you have a hysterectomy?	_____(years)
10) What type of hysterectomy did you have? *(A partial hysterectomy removes the uterus but leaves the cervix. A complete hysterectomy removes the entire uterus and cervix.)*	☐ Partial ☐ Complete ☐ Don't Know
11) Since the last time you completed this questionnaire for this study, have you had one or both of your ovaries removed?	☐ Yes (Continue) ☐ No (Skip to Section 6) ☐ Don't Know (Skip to Section 6)
12) If Yes, how many of your ovaries have been removed?	☐ One ☐ Two ☐ Don't Know
13) At what age(s) were your ovaries removed?	_____(years)

Section 6: PREGNANCY HISTORY

Note: Questions 1-3 are not recorded in RAVE EDC.

QUESTION	ANSWER
1) Since the last time you completed this questionnaire for this study, did you become pregnant?	☐ Yes (Continue) ☐ No ☐ Prefer not to answer
2) Are you currently pregnant?	☐ Yes (Continue to Question 3) ☐ No (Please complete the following table if applicable) ☐ Prefer not to answer
3) If you are currently pregnant, how many weeks along are you?	_____ weeks

ARA08: StopRA REQUIRED Source Document Manual of Procedures

For each pregnancy that you may have had since the last time you completed these questions for this study, please describe the details of each pregnancy in the table below. This includes miscarriages, abortions, tubal or ectopic pregnancies, stillbirths, and live births.

(EDC Page: Pregnancy History)

Pregnancy	How many weeks did the pregnancy last?	Did this pregnancy result in a live birth?	Birth Month and year	What type of delivery?	Did you breastfeed this child?	How many months did you breastfeed this child?
	40 weeks is considered full term	*If Yes, continue to right. If No, add the next pregnancy until all pregnancies are listed.*			*If yes, continue to the right. If no, go to the next pregnancy*	
1.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
2.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
3.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	
4.		☐ Yes ☐ No		☐ C-section ☐ Vaginal	☐ Yes ☐ No	

Signature of Subject **Date** *(DD/MON/YYYY)*

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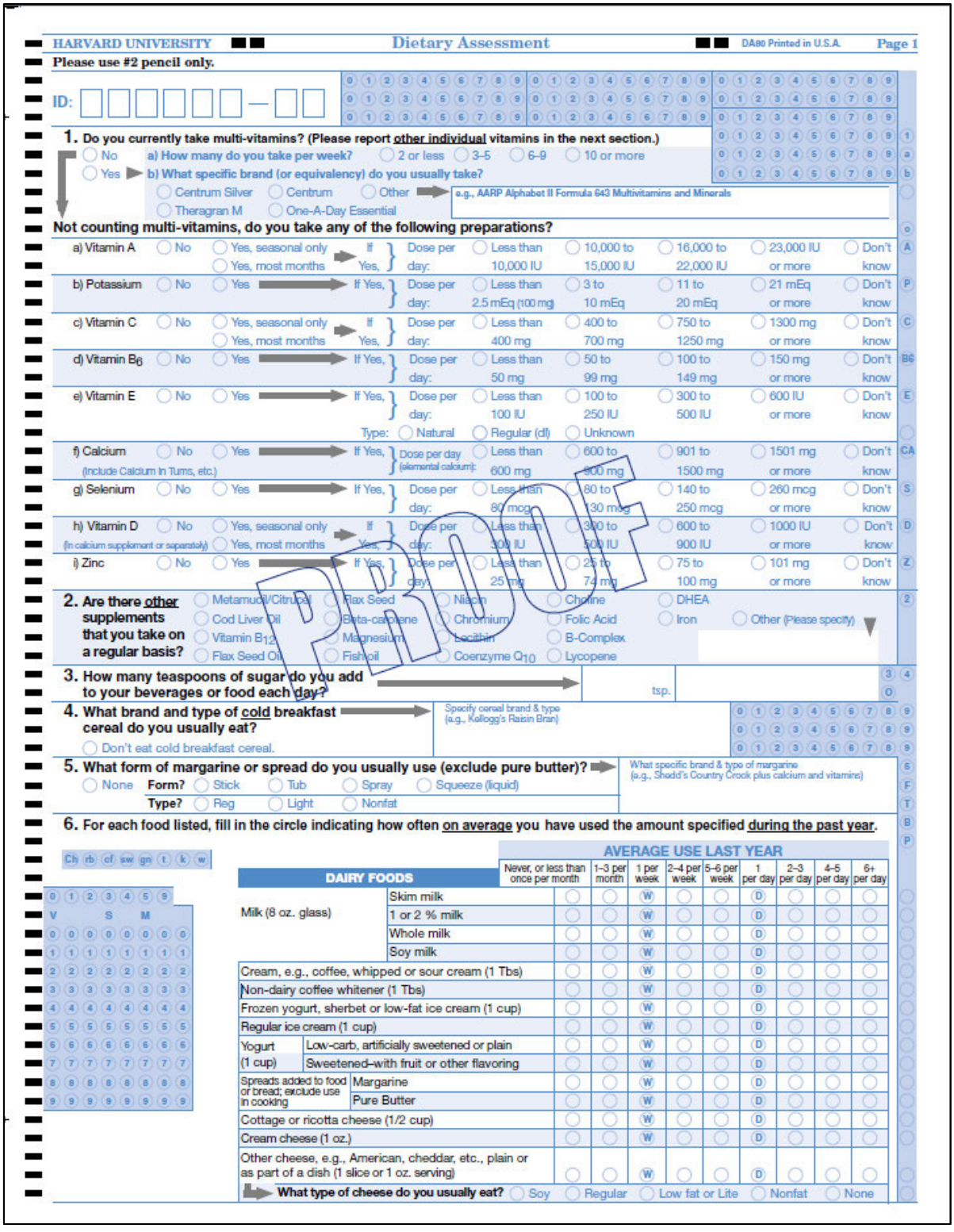
15.5.5 Dietary Assessment Questionnaire



HARVARD UNIVERSITY

Dietary Assessment

DA80 Printed in U.S.A.

Page 1

Please use #2 pencil only.

ID:

1. Do you currently take multi-vitamins? (Please report other individual vitamins in the next section.)
   - No
   - Yes
     - a) How many do you take per week? 2 or less 3–5 6–9 10 or more
     - b) What specific brand (or equivalency) do you usually take? Centrum Silver Centrum Other (e.g., AARP Alphabet II Formula 643 Multivitamins and Minerals) Theragran M One-A-Day Essential

Not counting multi-vitamins, do you take any of the following preparations?

a) Vitamin A	No	Yes, seasonal only / Yes, most months	If Yes, Dose per day:	Less than 10,000 IU	10,000 to 15,000 IU	16,000 to 22,000 IU	23,000 IU or more	Don't know
b) Potassium	No	Yes	If Yes, Dose per day:	Less than 2.5 mEq (100 mg)	3 to 10 mEq	11 to 20 mEq	21 mEq or more	Don't know
c) Vitamin C	No	Yes, seasonal only / Yes, most months	If Yes, Dose per day:	Less than 400 mg	400 to 700 mg	750 to 1250 mg	1300 mg or more	Don't know
d) Vitamin B_6	No	Yes	If Yes, Dose per day:	Less than 50 mg	50 to 99 mg	100 to 149 mg	150 mg or more	Don't know
e) Vitamin E	No	Yes	If Yes, Dose per day:	Less than 100 IU	100 to 250 IU	300 to 500 IU	600 IU or more	Don't know
			Type:	Natural	Regular (dl)	Unknown		
f) Calcium (Include Calcium in Tums, etc.)	No	Yes	If Yes, Dose per day (elemental calcium):	Less than 600 mg	600 to 900 mg	901 to 1500 mg	1501 mg or more	Don't know
g) Selenium	No	Yes	If Yes, Dose per day:	Less than 80 mcg	80 to 130 mcg	140 to 250 mcg	260 mcg or more	Don't know
h) Vitamin D (in calcium supplement or separately)	No	Yes, seasonal only / Yes, most months	If Yes, Dose per day:	Less than 300 IU	300 to 500 IU	600 to 900 IU	1000 IU or more	Don't know
i) Zinc	No	Yes	If Yes, Dose per day:	Less than 25 mg	25 to 74 mg	75 to 100 mg	101 mg or more	Don't know

2. Are there other supplements that you take on a regular basis?
   Metamucil/Citrucel · Flax Seed · Niacin · Choline · DHEA · Cod Liver Oil · Beta-carotene · Chromium · Folic Acid · Iron · Other (Please specify) · Vitamin B_{12} · Magnesium · Lecithin · B-Complex · Flax Seed Oil · Fish oil · Coenzyme Q_{10} · Lycopene

3. How many teaspoons of sugar do you add to your beverages or food each day? ____ tsp.

4. What brand and type of cold breakfast cereal do you usually eat? (Specify cereal brand & type (e.g., Kellogg's Raisin Bran))
   - Don't eat cold breakfast cereal.

5. What form of margarine or spread do you usually use (exclude pure butter)? (What specific brand & type of margarine (e.g., Shedd's Country Crock plus calcium and vitamins))
   - None
   - Form? Stick Tub Spray Squeeze (liquid)
   - Type? Reg Light Nonfat

6. For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.

DAIRY FOODS		AVERAGE USE LAST YEAR: Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Milk (8 oz. glass)	Skim milk	○	○	W	○	○	D	○	○	○
	1 or 2 % milk	○	○	W	○	○	D	○	○	○
	Whole milk	○	○	W	○	○	D	○	○	○
	Soy milk	○	○	W	○	○	D	○	○	○
Cream, e.g., coffee, whipped or sour cream (1 Tbs)		○	○	W	○	○	D	○	○	○
Non-dairy coffee whitener (1 Tbs)		○	○	W	○	○	D	○	○	○
Frozen yogurt, sherbet or low-fat ice cream (1 cup)		○	○	W	○	○	D	○	○	○
Regular ice cream (1 cup)		○	○	W	○	○	D	○	○	○
Yogurt (1 cup)	Low-carb, artificially sweetened or plain	○	○	W	○	○	D	○	○	○
	Sweetened–with fruit or other flavoring	○	○	W	○	○	D	○	○	○
Spreads added to food or bread; exclude use in cooking	Margarine	○	○	W	○	○	D	○	○	○
	Pure Butter	○	○	W	○	○	D	○	○	○
Cottage or ricotta cheese (1/2 cup)		○	○	W	○	○	D	○	○	○
Cream cheese (1 oz.)		○	○	W	○	○	D	○	○	○
Other cheese, e.g., American, cheddar, etc., plain or as part of a dish (1 slice or 1 oz. serving)		○	○	W	○	○	D	○	○	○

What type of cheese do you usually eat? Soy Regular Low fat or Lite Nonfat None

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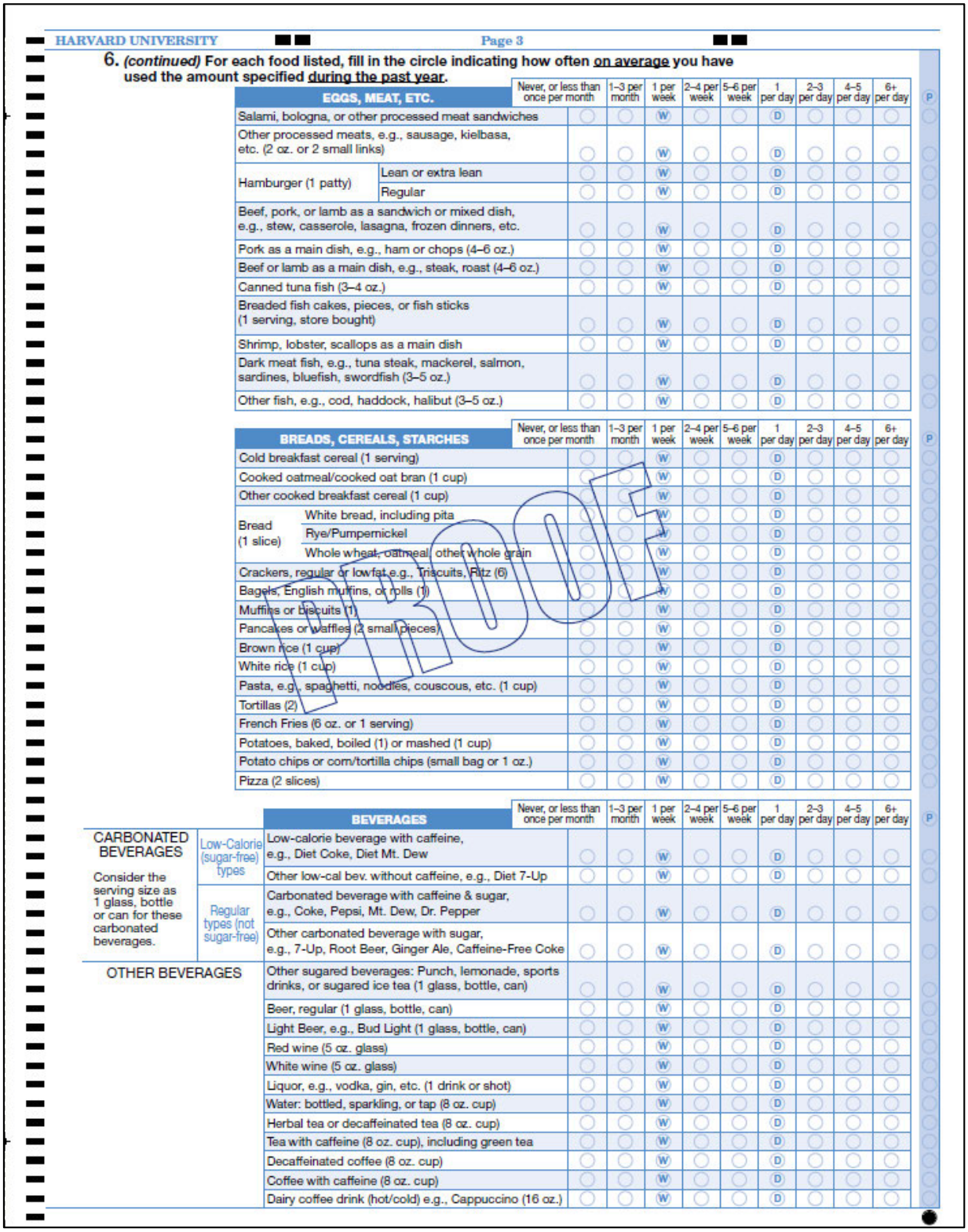
6. ***(continued)*** **For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.**

Please try to average your seasonal use of foods over the entire year. For example, if a food such as cantaloupe is eaten 4 times a week during the approximate 3 months that it is in season, then the average use would be once per week.

FRUITS	Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Raisins (1 oz. or small pack) or grapes (1/2 cup)	○	○	W	○	○	D	○	○	○
Prunes or dried plums (6 prunes or 1/4 cup)	○	○	W	○	○	D	○	○	○
Prune juice (small glass)	○	○	W	○	○	D	○	○	○
Bananas (1)	○	○	W	○	○	D	○	○	○
Cantaloupe (1/4 melon)	○	○	W	○	○	D	○	○	○
Avocado (1/2 fruit or 1/2 cup)	○	○	W	○	○	D	○	○	○
Fresh apples or pears (1)	○	○	W	○	○	D	○	○	○
Apple juice or cider (small glass)	○	○	W	○	○	D	○	○	○
Oranges (1)	○	○	W	○	○	D	○	○	○
Orange juice (small glass) — Calcium fortified	○	○	W	○	○	D	○	○	○
Orange juice (small glass) — Regular (not calcium fortified)	○	○	W	○	○	D	○	○	○
Grapefruit (1/2) or grapefruit juice (small glass)	○	○	W	○	○	D	○	○	○
Other fruit juices (small glass)	○	○	W	○	○	D	○	○	○
Strawberries, fresh, frozen or canned (1/2 cup)	○	○	W	○	○	D	○	○	○
Blueberries, fresh, frozen or canned (1/2 cup)	○	○	W	○	○	D	○	○	○
Peaches or plums (1 fresh or 1/2 cup canned)	○	○	W	○	○	D	○	○	○
Apricots (1 fresh, 1/2 cup canned or 5 dried)	○	○	W	○	○	D	○	○	○

VEGETABLES	Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Tomatoes (2 slices)	○	○	W	○	○	D	○	○	○
Tomato or V-8 juice (small glass)	○	○	W	○	○	D	○	○	○
Tomato sauce (1/2 cup) e.g., spaghetti sauce	○	○	W	○	○	D	○	○	○
Salsa, picante or taco sauce (1/4 cup)	○	○	W	○	○	D	○	○	○
String beans (1/2 cup)	○	○	W	○	○	D	○	○	○
Beans or lentils, baked, dried or soup (1/2 cup)	○	○	W	○	○	D	○	○	○
Tofu, soy burger, soybeans, miso or other soy protein	○	○	W	○	○	D	○	○	○
Peas or lima beans (1/2 cup fresh, frozen, canned)	○	○	W	○	○	D	○	○	○
Broccoli (1/2 cup)	○	○	W	○	○	D	○	○	○
Cauliflower (1/2 cup)	○	○	W	○	○	D	○	○	○
Cabbage or coleslaw (1/2 cup)	○	○	W	○	○	D	○	○	○
Brussels sprouts (1/2 cup)	○	○	W	○	○	D	○	○	○
Carrots, raw (1/2 carrot or 2–4 sticks)	○	○	W	○	○	D	○	○	○
Carrots, cooked (1/2 cup) or carrot juice (2–3 oz.)	○	○	W	○	○	D	○	○	○
Corn (1 ear or 1/2 cup frozen or canned)	○	○	W	○	○	D	○	○	○
Mixed or stir-fry vegetables (1/2 cup), veg. soup (1 cup)	○	○	W	○	○	D	○	○	○
Yams or sweet potatoes (1/2 cup)	○	○	W	○	○	D	○	○	○
Dark orange (winter) squash (1/2 cup)	○	○	W	○	○	D	○	○	○
Eggplant, zucchini or other summer squash (1/2 cup)	○	○	W	○	○	D	○	○	○
Kale, mustard greens or chard (1/2 cup)	○	○	W	○	○	D	○	○	○
Spinach, cooked (1/2 cup)	○	○	W	○	○	D	○	○	○
Spinach, raw as in salad (1 cup)	○	○	W	○	○	D	○	○	○
Iceberg or head lettuce (1 serving)	○	○	W	○	○	D	○	○	○
Romaine or leaf lettuce (1 serving)	○	○	W	○	○	D	○	○	○
Celery (2–3 sticks)	○	○	W	○	○	D	○	○	○
Peppers: green, yellow or red (3 slices)	○	○	W	○	○	D	○	○	○
Onions as a garnish or in salad (1 slice)	○	○	W	○	○	D	○	○	○
Onions as a cooked vegetable, rings or soup (1/2 cup)	○	○	W	○	○	D	○	○	○

EGGS, MEAT, ETC.	Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Eggs (1) — Omega-3 fortified including yolk	○	○	W	○	○	D	○	○	○
Eggs (1) — Regular eggs including yolk	○	○	W	○	○	D	○	○	○
Beef or pork hot dogs (1)	○	○	W	○	○	D	○	○	○
Chicken or turkey hot dogs or sausage (1)	○	○	W	○	○	D	○	○	○
Chicken/turkey sandwich or frozen dinner	○	○	W	○	○	D	○	○	○
Other chicken or turkey, with skin (3 oz.)	○	○	W	○	○	D	○	○	○
Other chicken or turkey, without skin (3 oz.)- including ground	○	○	W	○	○	D	○	○	○
Bacon (2 slices)	○	○	W	○	○	D	○	○	○



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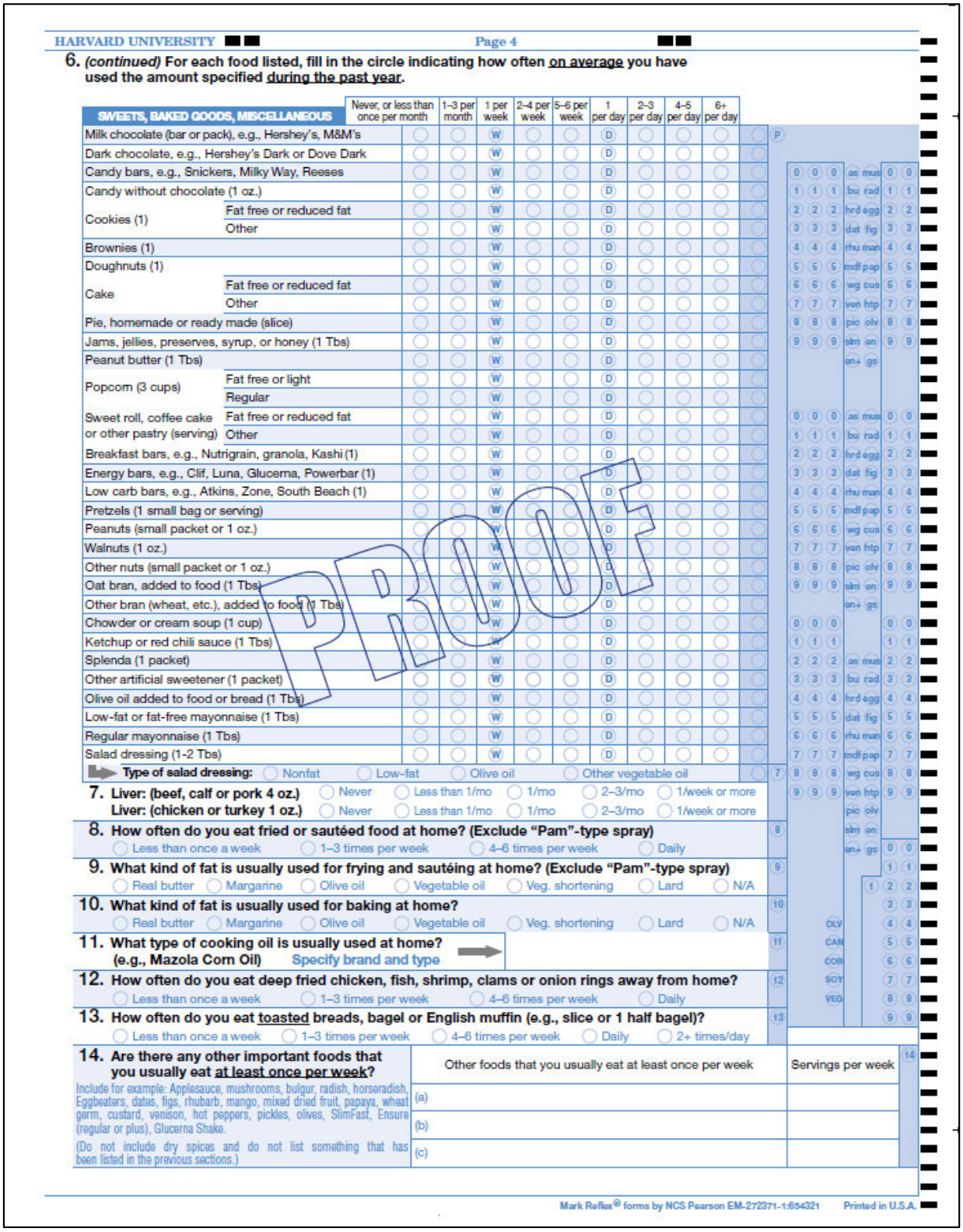
6. *(continued)* **For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.**

EGGS, MEAT, ETC.		Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Salami, bologna, or other processed meat sandwiches		○	○	W	○	○	D	○	○	○
Other processed meats, e.g., sausage, kielbasa, etc. (2 oz. or 2 small links)		○	○	W	○	○	D	○	○	○
Hamburger (1 patty)	Lean or extra lean	○	○	W	○	○	D	○	○	○
	Regular	○	○	W	○	○	D	○	○	○
Beef, pork, or lamb as a sandwich or mixed dish, e.g., stew, casserole, lasagna, frozen dinners, etc.		○	○	W	○	○	D	○	○	○
Pork as a main dish, e.g., ham or chops (4–6 oz.)		○	○	W	○	○	D	○	○	○
Beef or lamb as a main dish, e.g., steak, roast (4–6 oz.)		○	○	W	○	○	D	○	○	○
Canned tuna fish (3–4 oz.)		○	○	W	○	○	D	○	○	○
Breaded fish cakes, pieces, or fish sticks (1 serving, store bought)		○	○	W	○	○	D	○	○	○
Shrimp, lobster, scallops as a main dish		○	○	W	○	○	D	○	○	○
Dark meat fish, e.g., tuna steak, mackerel, salmon, sardines, bluefish, swordfish (3–5 oz.)		○	○	W	○	○	D	○	○	○
Other fish, e.g., cod, haddock, halibut (3–5 oz.)		○	○	W	○	○	D	○	○	○

BREADS, CEREALS, STARCHES		Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Cold breakfast cereal (1 serving)		○	○	W	○	○	D	○	○	○
Cooked oatmeal/cooked oat bran (1 cup)		○	○	W	○	○	D	○	○	○
Other cooked breakfast cereal (1 cup)		○	○	W	○	○	D	○	○	○
Bread (1 slice)	White bread, including pita	○	○	W	○	○	D	○	○	○
	Rye/Pumpernickel	○	○	W	○	○	D	○	○	○
	Whole wheat, oatmeal, other whole grain	○	○	W	○	○	D	○	○	○
Crackers, regular or lowfat e.g., Triscuits, Ritz (6)		○	○	W	○	○	D	○	○	○
Bagels, English muffins, or rolls (1)		○	○	W	○	○	D	○	○	○
Muffins or biscuits (1)		○	○	W	○	○	D	○	○	○
Pancakes or waffles (2 small pieces)		○	○	W	○	○	D	○	○	○
Brown rice (1 cup)		○	○	W	○	○	D	○	○	○
White rice (1 cup)		○	○	W	○	○	D	○	○	○
Pasta, e.g., spaghetti, noodles, couscous, etc. (1 cup)		○	○	W	○	○	D	○	○	○
Tortillas (2)		○	○	W	○	○	D	○	○	○
French Fries (6 oz. or 1 serving)		○	○	W	○	○	D	○	○	○
Potatoes, baked, boiled (1) or mashed (1 cup)		○	○	W	○	○	D	○	○	○
Potato chips or corn/tortilla chips (small bag or 1 oz.)		○	○	W	○	○	D	○	○	○
Pizza (2 slices)		○	○	W	○	○	D	○	○	○

BEVERAGES		Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
CARBONATED BEVERAGES Consider the serving size as 1 glass, bottle or can for these carbonated beverages.	Low-Calorie (sugar-free) types	Low-calorie beverage with caffeine, e.g., Diet Coke, Diet Mt. Dew	○	○	W	○	○	D	○	○	○
		Other low-cal bev. without caffeine, e.g., Diet 7-Up	○	○	W	○	○	D	○	○	○
	Regular types (not sugar-free)	Carbonated beverage with caffeine & sugar, e.g., Coke, Pepsi, Mt. Dew, Dr. Pepper	○	○	W	○	○	D	○	○	○
		Other carbonated beverage with sugar, e.g., 7-Up, Root Beer, Ginger Ale, Caffeine-Free Coke	○	○	W	○	○	D	○	○	○
OTHER BEVERAGES		Other sugared beverages: Punch, lemonade, sports drinks, or sugared ice tea (1 glass, bottle, can)	○	○	W	○	○	D	○	○	○
		Beer, regular (1 glass, bottle, can)	○	○	W	○	○	D	○	○	○
		Light Beer, e.g., Bud Light (1 glass, bottle, can)	○	○	W	○	○	D	○	○	○
		Red wine (5 oz. glass)	○	○	W	○	○	D	○	○	○
		White wine (5 oz. glass)	○	○	W	○	○	D	○	○	○
		Liquor, e.g., vodka, gin, etc. (1 drink or shot)	○	○	W	○	○	D	○	○	○
		Water: bottled, sparkling, or tap (8 oz. cup)	○	○	W	○	○	D	○	○	○
		Herbal tea or decaffeinated tea (8 oz. cup)	○	○	W	○	○	D	○	○	○
		Tea with caffeine (8 oz. cup), including green tea	○	○	W	○	○	D	○	○	○
		Decaffeinated coffee (8 oz. cup)	○	○	W	○	○	D	○	○	○
		Coffee with caffeine (8 oz. cup)	○	○	W	○	○	D	○	○	○
		Dairy coffee drink (hot/cold) e.g., Cappuccino (16 oz.)	○	○	W	○	○	D	○	○	○



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6. ***(continued)*** **For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.**

SWEETS, BAKED GOODS, MISCELLANEOUS	Never, or less than once per month	1–3 per month	1 per week	2–4 per week	5–6 per week	1 per day	2–3 per day	4–5 per day	6+ per day
Milk chocolate (bar or pack), e.g., Hershey's, M&M's	○	○	W	○	○	D	○	○	○
Dark chocolate, e.g., Hershey's Dark or Dove Dark	○	○	W	○	○	D	○	○	○
Candy bars, e.g., Snickers, Milky Way, Reeses	○	○	W	○	○	D	○	○	○
Candy without chocolate (1 oz.)	○	○	W	○	○	D	○	○	○
Cookies (1) — Fat free or reduced fat	○	○	W	○	○	D	○	○	○
Cookies (1) — Other	○	○	W	○	○	D	○	○	○
Brownies (1)	○	○	W	○	○	D	○	○	○
Doughnuts (1)	○	○	W	○	○	D	○	○	○
Cake — Fat free or reduced fat	○	○	W	○	○	D	○	○	○
Cake — Other	○	○	W	○	○	D	○	○	○
Pie, homemade or ready made (slice)	○	○	W	○	○	D	○	○	○
Jams, jellies, preserves, syrup, or honey (1 Tbs)	○	○	W	○	○	D	○	○	○
Peanut butter (1 Tbs)	○	○	W	○	○	D	○	○	○
Popcorn (3 cups) — Fat free or light	○	○	W	○	○	D	○	○	○
Popcorn (3 cups) — Regular	○	○	W	○	○	D	○	○	○
Sweet roll, coffee cake or other pastry (serving) — Fat free or reduced fat	○	○	W	○	○	D	○	○	○
Sweet roll, coffee cake or other pastry (serving) — Other	○	○	W	○	○	D	○	○	○
Breakfast bars, e.g., Nutrigrain, granola, Kashi (1)	○	○	W	○	○	D	○	○	○
Energy bars, e.g., Clif, Luna, Glucerna, Powerbar (1)	○	○	W	○	○	D	○	○	○
Low carb bars, e.g., Atkins, Zone, South Beach (1)	○	○	W	○	○	D	○	○	○
Pretzels (1 small bag or serving)	○	○	W	○	○	D	○	○	○
Peanuts (small packet or 1 oz.)	○	○	W	○	○	D	○	○	○
Walnuts (1 oz.)	○	○	W	○	○	D	○	○	○
Other nuts (small packet or 1 oz.)	○	○	W	○	○	D	○	○	○
Oat bran, added to food (1 Tbs)	○	○	W	○	○	D	○	○	○
Other bran (wheat, etc.), added to food (1 Tbs)	○	○	W	○	○	D	○	○	○
Chowder or cream soup (1 cup)	○	○	W	○	○	D	○	○	○
Ketchup or red chili sauce (1 Tbs)	○	○	W	○	○	D	○	○	○
Splenda (1 packet)	○	○	W	○	○	D	○	○	○
Other artificial sweetener (1 packet)	○	○	W	○	○	D	○	○	○
Olive oil added to food or bread (1 Tbs)	○	○	W	○	○	D	○	○	○
Low-fat or fat-free mayonnaise (1 Tbs)	○	○	W	○	○	D	○	○	○
Regular mayonnaise (1 Tbs)	○	○	W	○	○	D	○	○	○
Salad dressing (1-2 Tbs)	○	○	W	○	○	D	○	○	○

Type of salad dressing: ○ Nonfat ○ Low-fat ○ Olive oil ○ Other vegetable oil

7. Liver: (beef, calf or pork 4 oz.) ○ Never ○ Less than 1/mo ○ 1/mo ○ 2–3/mo ○ 1/week or more
Liver: (chicken or turkey 1 oz.) ○ Never ○ Less than 1/mo ○ 1/mo ○ 2–3/mo ○ 1/week or more

8. How often do you eat fried or sautéed food at home? (Exclude "Pam"-type spray)
○ Less than once a week ○ 1–3 times per week ○ 4–6 times per week ○ Daily

9. What kind of fat is usually used for frying and sautéing at home? (Exclude "Pam"-type spray)
○ Real butter ○ Margarine ○ Olive oil ○ Vegetable oil ○ Veg. shortening ○ Lard ○ N/A

10. What kind of fat is usually used for baking at home?
○ Real butter ○ Margarine ○ Olive oil ○ Vegetable oil ○ Veg. shortening ○ Lard ○ N/A

11. What type of cooking oil is usually used at home? (e.g., Mazola Corn Oil) Specify brand and type

12. How often do you eat deep fried chicken, fish, shrimp, clams or onion rings away from home?
○ Less than once a week ○ 1–3 times per week ○ 4–6 times per week ○ Daily

13. How often do you eat toasted breads, bagel or English muffin (e.g., slice or 1 half bagel)?
○ Less than once a week ○ 1–3 times per week ○ 4–6 times per week ○ Daily ○ 2+ times/day

14. Are there any other important foods that you usually eat at least once per week?
Include for example: Applesauce, mushrooms, bulgur, radish, horseradish, Eggbeaters, dates, figs, rhubarb, mango, mixed dried fruit, papaya, wheat germ, custard, venison, hot peppers, pickles, olives, SlimFast, Ensure (regular or plus), Glucerna Shake.
(Do not include dry spices and do not list something that has been listed in the previous sections.)

Other foods that you usually eat at least once per week	Servings per week
(a)	
(b)	
(c)	

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15.5.6 Profile 29 (v2.0)

ARA08: StopRA REQUIRED Source Document Manual of Procedures

ARA08 PROMIS-29
REQUIRED SOURCE DOCUMENT
Rave EDC Page: PROMIS-29

Subject ID: _____ **Assessment Date** (DD/MON/YYYY):_____

	Physical Function	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1	Are you able to do chores such as vacuuming or yard work?	❑	❑	❑	❑	❑
2	Are you able to go up and down stairs at a normal pace?	❑	❑	❑	❑	❑
3	Are you able to go for a walk of at least 15 minutes?	❑	❑	❑	❑	❑
4	Are you able to run errands and shop?	❑	❑	❑	❑	❑
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
5	I felt fearful…	❑	❑	❑	❑	❑
6	I found it hard to focus on anything other than my anxiety…	❑	❑	❑	❑	❑
7	My worries overwhelmed me…	❑	❑	❑	❑	❑
8	I felt uneasy…	❑	❑	❑	❑	❑
	Depression **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
9	I felt worthless…	❑	❑	❑	❑	❑
10	I felt helpless…	❑	❑	❑	❑	❑
11	I felt depressed…	❑	❑	❑	❑	❑
12	I felt hopeless…	❑	❑	❑	❑	❑
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
13	I feel fatigued…	❑	❑	❑	❑	❑
14	I have trouble starting things because I am tired…	❑	❑	❑	❑	❑

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	Fatigue In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
15	How run-down did you feel on average?	❑	❑	❑	❑	❑
16	How fatigued were you on average?	❑	❑	❑	❑	❑
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
17	My sleep quality was…	❑	❑	❑	❑	❑
	Sleep Disturbance **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
18	My sleep was refreshing…	❑	❑	❑	❑	❑
19	I had a problem with my sleep…	❑	❑	❑	❑	❑
20	I had difficulty falling asleep…	❑	❑	❑	❑	❑
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
21	I have trouble doing all of my regular leisure activities with others…	❑	❑	❑	❑	❑
22	I have trouble doing all of the family activities that I want to do…	❑	❑	❑	❑	❑
23	I have trouble doing all of my usual work (include work at home)…	❑	❑	❑	❑	❑
24	I have trouble doing all of the activities with friends that I want to do…	❑	❑	❑	❑	❑
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
25	How much did pain interfere with your day to day activities?	❑	❑	❑	❑	❑
26	How much did pain interfere with work around the home?	❑	❑	❑	❑	❑
27	How much did pain interfere with your ability to participate in social activities?	❑	❑	❑	❑	❑
28	How much did pain interfere with your household chores?	❑	❑	❑	❑	❑

	Pain Intensity **In the past 7 days…**											
29	How would you rate your pain on average?	❑ 0 No pain	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10 Worst imaginable pain

Subject Initials: _____ **Date survey completed:** _____
(DD/MON/YYYY)