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RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) - A Prospective Population-based Cohort Study

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Abstract:

Purpose: Hydroxychloroquine (HCQ) is an important medication for patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other rheumatic diseases. Although it is well-tolerated and cost-effective, the risk of HCQ retinal toxicity is of increasing concern. The aim of this study is to re-examine the HCQ retinal toxicity incidence rate, risk factors and clinical course after discontinuation.

Methods: We designed a prospective population-based cohort study in adult patients with SLE or RA, currently receiving HCQ for five or more years, who are residents of British Columbia (BC), Canada. Based on administrative data, we identified 5,508 eligible participants (1,346 SLE and 4,162 RA). They will participate in annual or bi-annual retinal screening over five years in alignment with the recently revised American Academy of Ophthalmology (AAO) guidelines. To standardize procedures for retinal screening, imaging, diagnostic criteria, severity staging and data transfer, a consensus meeting was convened in December 2019 with participation of BC retinal specialists and the research team. Agreement was attained on: use of Spectral Domain-Optical Coherence Tomography as the primary objective screening modality; classification of images into categories of normal, equivocal or abnormal; and transferring the equivocal and abnormal images plus corresponding subjective test results via cloud-based server from each clinic to a reading center. Confirmation of HCQ retinal toxicity diagnoses and severity staging

will be performed by three independent and masked reviewers. The incidence of HCQ retinal toxicity will be calculated, accounting for the competing risk of death. Hazard ratios for each risk factor will be calculated for the risk of HCQ retinopathy, after adjusting for confounders. We will also estimate the risk of HCQ retinal toxicity progression over five years.

Ethics and dissemination: This study has received approval from the University of British Columbia Clinical Research Ethics Board [H20-00736] and the Vancouver Coastal Health Research Institute.

Strengths and limitations:

- ✓ To the best of our knowledge, this is the first prospective, population-based cohort study designed to address the incidence rate, risk factors for and clinical course of hydroxychloroquine (HCQ)-induced retinal toxicity and progression.
- ✓ Access to British Columbia's (BC) administrative health data from the single-payer health care system allowed us to establish a large population-based cohort of all individuals with systemic lupus erythematosus or rheumatoid arthritis, exposed to HCQ for at least five years in BC.
- ✓ Linking participant self-report demographic and medical history, retinal imaging, and administrative health data will allow for calculation of an accurate risk of HCQ-induced retinal toxicity, which will provide vital safety information for patients, physicians, and policy makers.

- ✓ A structured consensus meeting led to the development of a novel and pragmatic standard operational protocol for the screening and follow up of patients on long-term HCQ medication for retinal toxicity.
- ✓ Five years of follow up may be inadequate to capture long-term results for the cases with five to ten years of HCQ medication.
- ✓ It is possible that nonadherence to the dosage of prescribed HCQ treatment may occur before or during study. This issue can only be addressed through evaluation of serum levels of HCQ, which should be considered in future studies.

Key words: Hydroxychloroquine (HCQ); Retinal toxicity; Prospective population-based cohort study; Consensus; Macular SD-OCT; Reading center.

Introduction:

The antimalarial medication hydroxychloroquine (HCQ) has been the cornerstone in the treatment of severe rheumatic conditions for decades, most commonly systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), both of which cause marked disability and premature death.(1-5) HCQ is inexpensive and has been shown to be highly effective in controlling SLE and RA disease activity, reducing joint and organ damage and long-term disabilities. HCQ is also considered to be one of the very well-tolerated medications for rheumatic diseases [*i.e.*, better than nonsteroidal anti-inflammatory drugs, like ibuprofen or naproxen], (6, 7) and is considered sufficiently safe to be recommended for pregnant patients with SLE.(8, 9)

A landmark trial led by Esdaile et al., showed that HCQ discontinuation after achieving disease control, led to a 2.5 times higher risk of SLE flare up and 6.1 times higher risk of severe flare up in vital organs (e.g., kidney involvement, vasculitis) within 6 months of HCQ withdrawal.(3) Moreover, a long-term study by the same group, on the effect of HCQ withdrawal in SLE, using an intent-to-treat analysis, showed a potential protective effect against a major flare for those randomized to continue HCQ (OR=0.43 [95% CI: 0.17, 1.12]).(10) These findings had a significant impact on clinical practice, making HCQ a universal therapy in SLE regardless of disease activity and severity. Since then, many studies have confirmed wide-ranging benefits of HCQ, including improved survival, reduced disease activity, and lower risks of nephritis, pregnancy complications, venous thromboembolism, dyslipidemia, and insulin resistance in patients with SLE.(11-13) Recently, a retrospective population-based study by our group using the

administrative health data of the residents of British Columbia (BC), Canada, with incident SLE and incident HCQ use between 1997 and 2015, showed a 71% and 83% lower risk of death among SLE patients who adhered to HCQ in comparison to SLE patients who were non-adherent or discontinued the medication, respectively. (14, 15)

Despite being considered relatively safe, it has been reported that with long-term use, HCQ can accumulate in the retinal pigment epithelial cells and may cause progressive outer retinal toxicity, retinal pigment epithelial and photoreceptor cell death and secondary vision loss. Based on the accumulating evidence of HCQ retinal toxicity, the American Academy of Ophthalmology (AAO) recommends annual screening for patients receiving HCQ for five years or more.(16) Retinal toxicity had a previously estimated occurrence of 0.5-2% in long-term users.(16) However, a 2014 retrospective study using the US Kaiser Permanente Northern California (KPNC) database demonstrated that among users of HCQ with use ≤5 mg/kg of their real body weight, the risk was <2% for five to ten years of therapy, but almost 20% after 20 years of use. Conversely, patients with a mean daily use >5 mg/kg had approximately a 10% risk of retinal toxicity for five to ten years of HCQ use and almost a 40% risk after 20 years. (17) This is at least 10 times higher than previously published rates and caused alarm to patients and physicians.(18-20) Retinal toxicity secondary to HCQ is a major concern expressed by patients and clinicians. It is one of the main reasons for non-adherence to HCQ.(21-25) However, this study reported 32% missing data and did not adjust for the competing risk of death, thus results might have been susceptible to selection bias and overestimation of the true risk. (17, 26)

A systematic review on the risk of HCQ retinopathy and its risk factors in patients with rheumatic diseases found that most previous studies have been case series or retrospective

cohorts. (27) This included a few prospective studies, all of which were limited in size (58 to 225 patients) and duration of follow-up (1 to 3 years). (19, 26, 27) Recently a joint statement has been published by the American College of Rheumatology, the AAO, the American Academy of Dermatology and Rheumatologic Dermatology Society, on HCQ ocular safety. They indicated that there is a critical lack of data from a population-based prospective study on HCQ retinal toxicity. (28) A prospective study to better estimate the risk, risk factors and clinical course of HCQ retinal toxicity is therefore needed.

To address this, we established a prospective population-based cohort study to follow patients with RA and SLE with a minimum of five years of HCQ use, for potential retinal toxicity. To enable development of a standard operating protocol (SOP) for this study, a consensus meeting was convened among board certified practicing rheumatologists and retinal specialists from BC, including specialists from both urban and rural areas. The objective of the meeting was to identify and agree upon a SOP for screening and follow up for the retinal exams and assessments. The SOP was to align with the most up to date principles of evidence-based screening protocols for HCQ retinal toxicity, feasible in a routine practice of retinal ophthalmologists so as to maximize patient and practitioner participation.

Cohort Description/Methods:

Design:

A prospective population-based cohort study among patients diagnosed with RA or SLE, with five or more years HCQ use, between January 1990 and December 2020, in BC and who were alive. The patients will be followed for at least five years, from July 2021 to Dec 2026.

Goals:

The main aims of our prospective and population-based study are to: 1) determine the incidence rate of retinopathy in HCQ users of ≥ 5 years duration of treatment, 2) determine the risk factors for HCQ retinopathy and 3) describe the clinical course of retinopathy following HCQ discontinuation, based on retinal examination, multimodal retinal imaging, visual fields and patient reported outcomes from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). (29)

Data source:

We will use administrative data extracted from Population Data BC (PopData) which is an extensive data resource for applied health services and population health research used by our group and others. (30-36) PopData covers the entire population of BC from 1990 onwards (5.1 million in 2021). Individuals can be traced over time and ultimately as the data expands longitudinally, over their lifespan. The main linkable databases include the following files: Medical Services Plan (physician visits and procedures data)(37), Hospital Separation (discharge summaries including up to 25 diagnostic codes)(38), PharmaNet (all medications dispensed for all BC residents)(39), Vital Statistics (date and cause of death)(40) and the BC Cancer registry(41). We have previously developed a unique Laboratory Services link that provides laboratory results linked to the administrative data as well as survey data collected from consenting individuals.

Patient and Public Involvement:

No patient was involved in the development of the research question and outcome measures, study design and conduct of study.

Study population (SLE and RA cohorts):

Adults (aged ≥ 18 years) with RA or SLE were identified from outpatient physician billing files or from the hospital discharge database using International Classification of Diseases ninth (ICD-9) and tenth (ICD-10) revision diagnostic codes. SLE and RA cases are defined using at least two ICD codes for SLE and RA, at least 2 months apart within a 2-year window period from 1990-2020. The validity of this algorithm to identify RA patients has been evaluated to have a positive predictive value (PPV) of 82%. (42) Similarly, for identifying SLE patients, the validity of this algorithm when one ICD code is from hospitalization and the other by a rheumatologist, has been evaluated to have a PPV of 97% in Swedish registry data. (43) In our previous studies, > 80% of SLE cases had at least one code from hospitalization or from a rheumatologist. (35, 44, 45)

Using these algorithms, we identified 4,104 SLE patients and 21,265 RA patients who had started HCQ since January 1, 1997 in BC. Of those, 1,346 SLE and 4,162 RA patients (total N = 5,508) had taken HCQ for at least five years by December 2020. Only rare cases who had used chloroquine before commencing HCQ for SLE or RA will be excluded from this study. There will be no exclusion criteria for patients with any underlying systemic disease, ocular disease and/or ocular surgeries with macular involvement. These may include diabetic macular edema, cystoid macular edema, retinal vascular occlusive disease, age-related macular degeneration, inherited retinal dystrophy, and uveitis. However, patients with advanced macular anatomical alterations

due to comorbidities, which could interfere with an HCQ retinal toxicity diagnosis, may be excluded in data analysis (with provided explanation).

Recruitment:

Eligible participants identified from our population-based RA and SLE database who fulfill the inclusion criteria will receive an invitation letter containing the study information as well as a consent form. After obtaining informed consent from patients, we will contact the rheumatologists or primary care physicians to inform them of their patient's participation in the study and send reminders for baseline screening and annual referrals, as per 2016 AAO guidelines and current standard of care, to the participating retina specialists' clinics who we will call the "retina specialist network of the INTACT study". Rheumatologists and primary care physicians throughout BC may also refer eligible patients based on the inclusion criteria to the retina specialist network of the INTACT study, after obtaining informed consent.

Self-report questionnaire:

Participants will fill out a self-report questionnaire (See Supplementary File 1 – Patient self-report questionnaire) to collect information on risk factors, confounders, and patient reported outcomes, at the time of their first retina exam as part of this study. This data will be updated at each annual visit. The survey questionnaire will collect information on potential risk factors such as chronic kidney disease, diabetes, hypertension, liver disease, retinal or macular disease as well as comorbidities, race, current HCQ dose, weight, height, and disease duration.(16) Data on medications with a known risk of retinopathy (e.g. tamoxifen, anastrozole) will be collected in the self-report questionnaire as well as obtained from PharmaNet.(46)

Patients with the confirmed diagnosis of HCQ-induced retinopathy will be asked to fill out the NEI VFQ-25, to provide a better understanding of the impact of this side effect on their daily lives. (29)

Consensus description/Methods:

On December 14, 2019, a consensus meeting was convened in Richmond, BC. Participants in the consensus meeting were project team members, including, three board-certified academic retinal specialists (D.M., K.P.V., S.L.), five board-certified academic rheumatologists (D.E., G.M., J.E., J.A.A.Z., K.S.), one pharmaco-epidemiologist (M.E.), and one knowledge broker (A.H.). All practicing retinal specialists in BC were invited (n= 33), of which 24 attended the consensus meeting and agreed to participate in the study (the 'retina specialist network of the INTACT study'). In addition, research coordinators from ophthalmology clinics, research staff from Arthritis Research Canada and a guest speaker (Ronald B. Melles, M.D.) attended the meeting.

The consensus meeting commenced with a presentation by the guest speaker who highlighted and discussed key findings from the KPNC study. Two academic retinal specialists (K.P.V., S.L.) then gave presentations, highlighting key points from the AAO 2016 revised recommendations on HCQ retinal toxicity screening exams by SD-OCT imaging and automated visual field (VF) test.

After the presentations, two consensus sessions, led by the knowledge broker, were held to identify and address the main challenges that were highlighted in the presentations and were pertinent to developing the SOP:

1) To develop the process for annual HCQ retinal toxicity screening and follow up exams by the retina specialist network of the INTACT study for patients with an HCQ retinal

toxicity diagnosis. These were to be based on the latest AAO 2016 revised recommendations (16) using at least one objective test of 3 potential options: SD-OCT, Fundus Auto-fluorescence (FAF) or Multifocal Electroretinography (mfERG) confirming the subjective standard automated VF assessment.

2) To define the standardized criteria for detecting normal versus abnormal SD-OCT imaging, define equivocal cases versus definite cases, and determine appropriate follow up procedures for patients in each group.

3) To determine standardized severity stages of retinal toxicity in cases with abnormal diagnoses.

The consensus session began with individual reflection. Participants were asked to independently identify and record on post-it notes, potential concerns regarding the implementation of the standardized screening and operational protocols relevant to their routine office practice and the potential challenges with eye examination protocols, SD-OCT imaging and automated VF assessment. The knowledge broker then collected and categorized the responses. The categories were shared with participants who then voted to identify the following five main challenges:

I. Standardization of SD-OCT image acquisition and automated VF assessment.

II. Criteria for diagnosis of HCQ retinal toxicity.

III. Classification of HCQ retinopathy into different severity stages of disease.

IV. Data collection training of medical office assistants (MOA) and research staff at the clinics.

V. Data storage and transfer to the Eye Care Centre at Vancouver General Hospital (VGH) and Arthritis Research Canada.

The second phase of the process was achieved through small group discussions of five participants. Each group was assigned one of the five main challenges and asked to brainstorm logical and feasible solutions for the challenge which could be included in the SOP.

Following the small group discussions, a representative from each group presented a summary of their discussion to the large group. This permitted further discussion to elucidate key points that had been most salient or missing from the small group discussions. The knowledge broker then summarized the options for each of the main challenges and all participants voted. If 100% agreement on the solution(s) for each of the challenges was not initially achieved, another cycle of discussion was undertaken enabling consensus to be reached on the solutions for all challenges.

Consensus results/proposed solutions:

The group made the following consensus statements for the five categories mentioned above (Figure 1- HCQ retinal toxicity screening protocol flowchart for INTACT study: The consensus results).

I. Standardization of SD-OCT image acquisition and automated VF exam assessment:

- ✓ Only three types of SD-OCT machines are acceptable for this study: Spectralis OCT (Heidelberg Engineering), Cirrhus HD-OCT (Carl Zeiss Meditec), and Topcon

3D-OCT 2000 (Topcon Corporation). At least one of these three machines is available in every retinal clinic participating in this study. Additionally, the same machine(s) must be used for a patient at all of their visits.

✓ To completely demonstrate pathologies of the macular area including, foveal, para-foveal and peri-foveal zones, macular SD-OCT scan should cover a minimum of 20 degrees x 20 degrees for non-Asian patients and 30 degrees x 30 degrees for Asian patients. Block size and raster technique will be machine-specific. For Heidelberg SD-OCT machines, a 12 mm x 9 mm cube scan was recommended.

✓ Each scan must be able to clearly delineate both inner and outer retinal bands. Specifically, the outer retinal bands at the para-foveal and peri-foveal zones should be in focus and clearly visible. The presence of vessel shadowing will ensure a high-quality scan.

✓ SD-OCT imaging must be done for all patients as the main screening exam.

✓ If a patient's SD-OCT scan is normal, that patient will be scheduled for their next appointment in a year. However, if the scan is considered equivocal or abnormal, the patient must be evaluated with standard automated 10-2 VF (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) assessment. If the

10-2 scan is also considered equivocal or abnormal, then a standard automated 24-2 or 30-2 VF assessment must be done. For Asian participants, both the standard automated 10-2 and 24-2 or 30-2 VF must be performed in all cases with equivocal or abnormal SD-OCT scans.

✓ FAF imaging was defined as complementary (to the SD-OCT and automated VF) objective screening exam. Its performance will be left to the discretion of the retina specialist network of the INTACT study, based on their clinical judgement (not mandatory).

II. Criteria for diagnosis of HCQ retinal toxicity:

✓ All patients on HCQ must be examined according to the standard of care and current guidelines regardless of any comorbidities. However, diagnosis of HCQ retinopathy will be determined by the clinician's (retina specialist network of INTACT study) interpretation of results based on standard images that will be sent to them as guidance packages which are in accordance with the peer reviewed publications, of macular SD-OCT and standard automated VF findings in HCQ retinal toxicity (16, 47). The standard images will be prepared by the INTACT study team's experienced academic retinal specialists (D.M., K.P.V. and S.L.).

✓ All scans must only be classified as no signs of HCQ retinal toxicity (normal), suspicious signs of HCQ retinal toxicity (equivocal) or typical signs of HCQ retinal

toxicity (abnormal) by the retinal specialist and recorded by checking the box that applies in a reporting form that will be sent to researchers at the VGH Eye Care Centre (see Supplementary File 2- Retina Specialist Reporting Form).

- ✓ Abnormal, equivocal, and a random sample of normal scans (thirty in Year 1 and Year 2) must be sent to the VGH Eye Care Centre for secondary review and validation.
- ✓ The three study team retinal specialists (D.M., K.P.V., and S.L.) will be considered as the gold standard. Two of them (K.P.V. and S.L.) will review the images of all patients reported as equivocal or abnormal by the "retina specialist network of the INTACT study" in addition to the random sample of normal scans (thirty in Year 1 and Year 2) from them. Confirmation of diagnosis is based on the agreement between two reviewers at the VGH Eye Care Centre.
- ✓ The third retina specialist (D.M.) will only review images with any discrepancy in the diagnosis. Eventually the final decision will be achieved by the third masked reviewer (agreement between D.M. and one of the first two reviewers).

III. Severity stages of disease (i.e., classification of HCQ retinopathy into mild, moderate and severe).

- ✓ Retina specialists at their clinics will not need to classify the severity staging.

- ✓ The two study team retina specialists (K.P.V., and S.L.) will classify HCQ retinopathy as mild, moderate, or severe HCQ retinal toxicity after confirmation of diagnosis.
- ✓ Again, with any discrepancy in the severity staging by the first two reviewers, the third masked reviewer (D.M.) will assess and make the final decision, which is based on agreement of his and one of the two other reviewers' assessment.

IV. Data collection training of medical office assistants (MOA) and research staff at the clinics.

- ✓ There will be a main research lead (N.D.) for all clinics and one research lead assigned at each clinic (e.g., nurse, research coordinator, research assistant). The main research lead will be responsible for training of the other centre leads and the coordination of the overall flow at each centre.

V. Data storage and transfer to the VGH Eye Care Centre and Arthritis Research Canada:

- ✓ There are two types of data to be stored and transferred to Arthritis Research Canada and the VGH Eye Care Centre, specifically the patient self-report and retina specialist report questionnaires and the ocular imaging (i.e., SD-OCT and automated VF assessment or FAF).
- ✓ Questionnaires, including both patient self-report and retina specialist reports will be stored in individual patient files in a locked filing cabinet at Arthritis Research Canada. This data will be linked to provincial administrative health data

by PopData upon completion of the study. The research team will be unable to identify individuals after linkage.

✓ A cloud server will be used to store the data including the SD-OCT digital images as well as automated VF assessments, from the retina clinics, which will be accessible to the three readers at the VGH Eye Care Centre. Briefly, there will be a separate folder allocated for each retina clinic, wherein each clinic will only be able to access and upload the images and data of their own patients. The three readers at the VGH Eye Care Centre will be able to access all folders through a secure website.

Data analysis plan

1) Determine the incidence rate of retinopathy in HCQ users with ≥ 5 years duration of treatment: We will calculate the overall incidence and dose-specific risk (i.e., cumulative incidence) of HCQ retinal toxicity. Each eligible and consenting individual will be followed from the study baseline until the end of the 5-year study period, disenrollment or death, whichever occurs first. These person-time data with events will then be used to calculate the cumulative incidence, employing established methods for left truncated data and the competing risk of death.
2) Determine the risk factors for HCQ retinopathy: We will examine the relationship of purported risk factors for HCQ retinopathy among participants, including relevant measures of HCQ exposure (daily dose, daily dose in mg/kg for actual body weight (ABW), daily dose in mg/kg for ideal body weight (IBW), total cumulative lifetime dose,

and duration of exposure), other putative predictors (i.e., older age, female sex, chronic kidney disease, other concomitant drug use with potential retinal toxicity [i.e., tamoxifen, anastrozole] or underlying retinal disease), and any other factors that emerge during the study period. First, we will compare the age-standardized incidence rates of HCQ retinopathy according to the risk factor categories. Then, we will obtain the point and interval estimates of the hazard ratio (HR) of each candidate risk factor for the risk of incident HCQ retinopathy, mutually adjusting for potential risk factors. Also, we will use Cox proportional hazard regression models, accounting for the competing risk of death and left truncation of event time. (48-52)

3) Describe the clinical course of retinopathy following HCQ discontinuation: We will follow all newly identified HCQ retinal toxicity cases on an annual basis during the study period (5 years) and assess the rate of pathological progression of retinopathy, defined as any worsening of both SD-OCT imaging and VF assessment. We will estimate the risk of progression according to initial retinopathy stage (mild, moderate, and severe) accounting for the competing risk of death. (53, 54)

Strengths and limitations

To the best of our knowledge, this is the first prospective, population-based cohort study designed to examine the incidence rate, risk factors and clinical course progression (after discontinuation) of HCQ-induced retinal toxicity in Canada. Our access to province-wide administrative health data for the total five million residents of BC is a significant strength. The estimated sample size is 5,508 patients including 1,346 SLE and 4,162 RA patients who

have been on HCQ treatment for five years or more. In this prospective study, we will have person-time data with events and risk factors including but not limited to HCQ dose for ABW versus IBW, chronic renal failure, comorbidities and others, with annual updates of data for five consecutive years. We will be able to calculate the cumulative incidence of HCQ-induced retinopathy considering the competing risk of death as well as HRs for each risk factor. These results will provide vital information for patients, physicians, and policy makers.

Our study benefits from the collaboration of retinal specialists from urban and rural parts of BC. Our province-wide retinal specialist network developed a novel SOP during a consensus meeting for screening and follow up of the patients based on the most recent AAO guidelines. Our study is not without potential limitations. First, there may be participant loss, due to declining to participate, emigration, and study drop-out. Another limitation of our study is possible nonadherence to the amount of prescribed HCQ treatment. PharmaNet data will capture medication dispensed, however participants taking less than the prescribed dose, will not be captured. This issue can only be mitigated through evaluation of the serum level of HCQ, which should be taken into account in future studies.

Privacy and confidentiality

We have implemented measures to keep all personal information of patients secure, including names, contact information, Personal Health Numbers, self-report questionnaires, and medical reports. These will be kept in secure locations accessible only to a restricted number of study personnel at Arthritis Research Canada and retinal clinics. Patients' names will be replaced by a

unique ID code upon patient's informed consent and enrollment in the study that will be consistent on every study document and imaging, throughout the study. The digital information including the imaging will be housed on a secure cloud server with the most up-to-date security protections.

Contributors: Conception and design of the study: J.A.A.Z., D.M. and J.M.E.

Consensus meeting chair persons/moderators: A.H., D.E., D.M., G.M., J.E., J.A.A.Z., K.S., K.P.V. and R.B.M.

Drafting of the standard operating protocols and the manuscript: A.L., D.O., N.D. and S.M.

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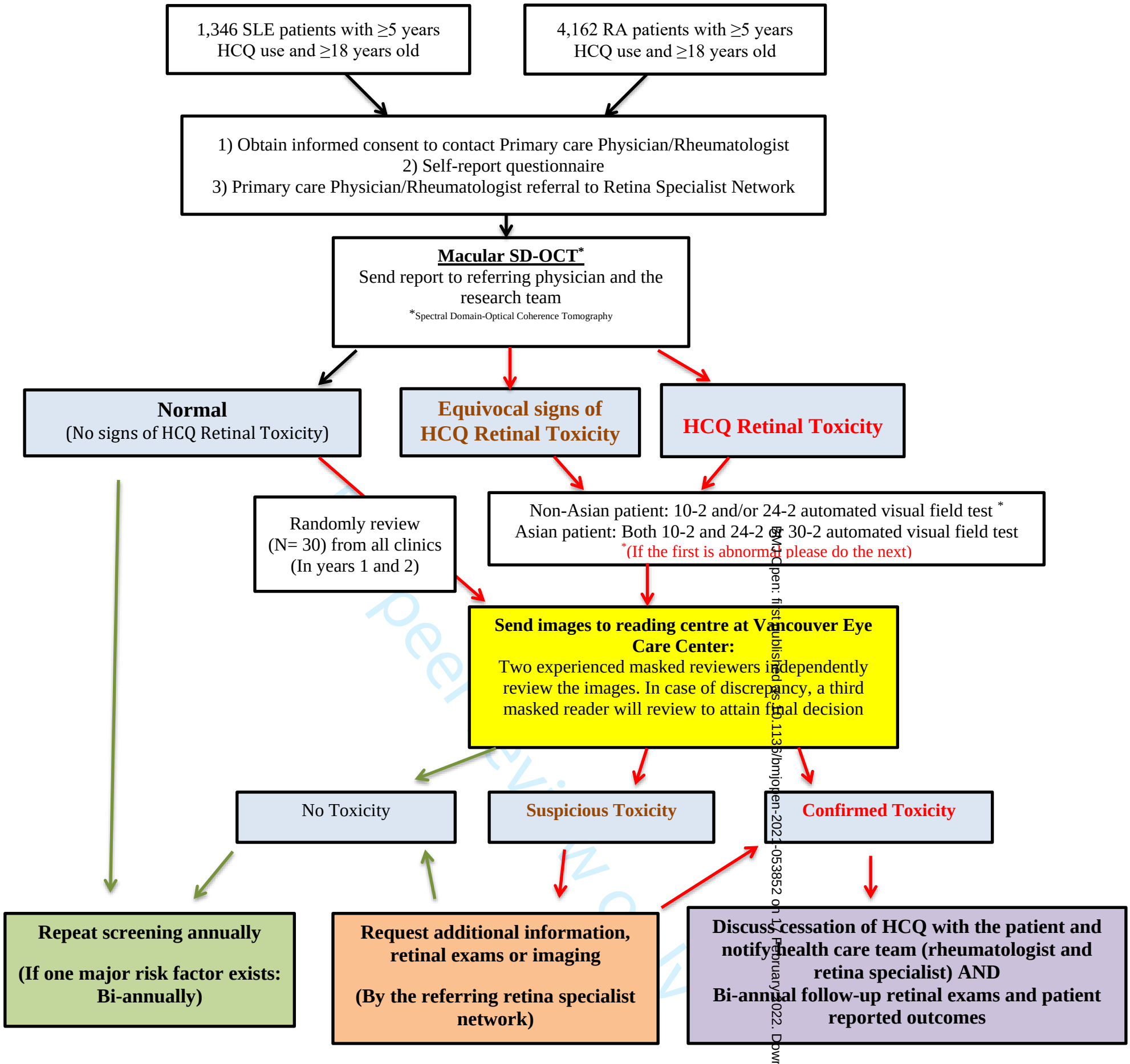
Figure 1- HCQ Retinal Toxicity Screening Protocol Flowchart for INTACT Study: The Consensus Results

Figure 1- HCQ Retinal Toxicity Screening Protocol Flowchart for INTACT Study: The Consensus Results



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Site-Study Patient ID: _____

INTACT Study – Patient self-report questionnaire

Please take a few minutes to fill out this form.
Your answers will be kept confidential.

Thank you for your participation.

Place Sticker Here:

Date of care provision: _____/_____/_____
(mm/dd/yyyy)

Full name of provider: _____

General Patient Information (Please fill in your information below and check (✓) any boxes that apply to you): *(To be filled out by the patient)*

Mobile Phone Number: ( )

Landline Phone Number: ( )

Address:

City: Province: Postal Code:

Email Address: @

Secondary Email Address: @

Gender:

☐ Male ☐ Female ☐ Trans male ☐ Trans female

☐ Other, please specify:

☐ I prefer not to answer this question

Ethnicity:

☐ White
☐ East Asian
☐ South Asian
☐ South-East Asian
☐ Black
☐ Hispanic or Latino
☐ Indigenous/Aboriginal
☐ Pacific Islander
☐ Other, please specify:
☐ I prefer not to answer

INTACT Study: Patient Questionnaire **Site-Study Patient ID:**

Weight: kg OR lbs

Height: ft in OR cm

Medical History (Please check (✓) any boxes below that apply to you): *(To be filled out by the patient)*

- Which one of the following is your current diagnosis?

☐ Systemic Lupus Erythematosus ☐ Rheumatoid Arthritis

- Have you been diagnosed by a medical doctor with any of the following conditions?

☐ Diabetes ☐ High Blood Pressure ☐ Chronic Kidney Disease ☐ Breast Cancer

☐ Inherited Retinal Dystrophy ☐ Glaucoma ☐ Age Related Macular Degeneration

- Are you currently using tamoxifen? ☐ Yes | ☐ No
- Are you currently using anastrazole? ☐ Yes | ☐ No
- Have you ever had eye surgery? ☐ Yes | ☐ No

If yes, please specify what type of eye surgery:

- Have you ever had an eye injection (intravitreal injection)? ☐ Yes | ☐ No

If yes, please specify the reason:

INTACT Study: Patient Questionnaire **Site-Study Patient ID:**

Hydroxychloroquine/Plaquenil (the same drug) Information (Please check (✓) any boxes below that apply to you): *(To be filled out by the patient)*

- Are you currently taking hydroxychloroquine (HCQ)/plaquenil? ☐ Yes | ☐ No
- How long in total have you been taking HCQ/plaquenil?

☐ 5-10 years ☐ 10-15 years ☐ 15-20 years ☐>20 years

- Current daily dose of HCQ/plaquenil: mg
- Total number of HCQ/plaquenil pills per week: of ☐ 200 mg OR ☐ 400 mg
- Do you take a different HCQ/plaquenil dose on one or more specific days of the week?
- ☐ Yes | ☐ No
- If yes, please specify which day(s) of week: of ☐ 200 mg OR ☐ 400 mg

- Have you ever stopped taking HCQ/plaquenil for more than 3 months?

☐ Yes | ☐ No

- If yes, please specify the date you stopped taking HCQ/plaquenil (MM/YYYY):

_____/_____

- Did you start taking HCQ again? ☐ Yes | ☐ No

If yes, please specify the date you started taking HCQ/plaquenil again

(MM/YYYY): _____/_____

INTACT Study: Patient Questionnaire **Site-Study Patient ID:**

- Please specify the reason why you stopped taking HCQ/plaquenil?

Side effects:

- ☐ Rash
- ☐ Eye Toxicity
- ☐ Abdominal/Stomach Upset
- ☐ Lack of medication effectiveness
- ☐ Fear of side effects
- ☐ Cost of medication
- ☐ Tired of taking pills
- ☐ No Reason
- ☐ Other, please specify:

- Who recommended the discontinuation of HCQ?

- ☐ Rheumatologist
- ☐ Family doctor
- ☐ Ophthalmologist (eye physician)
- ☐ Optometrist
- ☐ Nurse
- ☐ A friend
- ☐ Myself
- ☐ Other, please specify:

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Thank you for taking your time to fill out the form

Site-Study Participant ID:

INTACT Study – Retina Specialist Reporting Form

Place Sticker Here:

Date of care provision: _____/_____/_____ (mm/dd/yyyy)

Full name of provider: _____

SD-OCT Results

- Please specify SD-OCT you used:

☐ Spectralis HRA-OCT ☐ Cirrhus HD-OCT ☐ Topcon 3D-OCT

- Morphological appearance of SD-OCT scans:

☐ Disruption of the interdigitation zone (IZ) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Decreased reflectivity of the ellipsoid zone (EZ) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Disruption of the EZ **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Disruption of the retinal pigment epithelium (RPE) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Disruption of the external limiting membrane (ELM) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Thinning of the outer nuclear layer (ONL) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Flying saucer sign

☐ Other please specify:

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Site-Study Participant ID:

Your evaluation regarding HCQ related findings in macular SD-OCT, please check (✓) the box below as it may apply:

☐ **Abnormal (typical signs of HCQ related retinal toxicity)**

☐ **Equivocal (suspicious signs of HCQ related retinal toxicity)**

☐ **Normal (no signs of HCQ related retinal toxicity)**

Comments:

Please turn to the next page

INTACT Study: Retina specialist Reporting Form **Site-Study Participant ID: _____**

Supplemental Testing (if abnormal or equivocal OCT results)

- Visual Acuity Results: OD: OS:
- **Please specify automated visual field machine used:**

☐ Humphrey ☐ Occulus Centerfield

- Perimetry test performed: ☐ 10-2 ☐ 24-2 ☐ 30-2
- **10-2** automated perimetry:

☐ A defect within 2 6 degrees from fixation on gray scale, sparing the central 2 degrees

☐ Scattered patches of relative scotoma

☐ Paracentral scotoma

☐ Partial ring defect sparing the central 2 degrees

☐ A complete ring defect sparing the central 2 degrees

☐ Other; please specify:

- **24-2 or 30-2** automated perimetry:

☐ A defect within 10 20 degrees from fixation on gray scale, sparing the central 2 degrees

☐ Scattered patches of relative scotoma

☐ Pericentral scotoma

☐ Partial ring defect sparing the central 2 degrees

☐ A complete ring defect sparing the central 2 degrees

☐ Other; please specify:

INTACT Study: Retina specialist Reporting Form **Site-Study Participant ID: _____**

Supplemental Testing (if applicable)

➢ Fundus auto-fluorescence findings (FAF):

☐ Hyper-autofluorescence **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Hypo-autofluorescence **at** ☐ fovea , ☐ parafovea , ☐ perifovea

➢ Macular appearance:

☐ Macular granularity

☐ Loss of foveal reflex

☐ Broadening of foveal reflex

☐ Retinal pigment epithelium irregularities

☐ ❓❓❓❓❓

☐ Other, please specify:

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-17
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	18
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	18
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	18
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) – Protocol for a prospective population-based cohort study

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Secondary Subject Heading:	Rheumatology, Epidemiology
Keywords:	Toxicity < THERAPEUTICS, Vetreoretinal < OPHTHALMOLOGY, RHEUMATOLOGY, Medical retina < OPHTHALMOLOGY, EPIDEMIOLOGY

RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) – Protocol for a prospective population-based cohort study

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Abstract:

Purpose: Hydroxychloroquine (HCQ) is an important medication for patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other rheumatic diseases. Although it is well-tolerated and cost-effective, the risk of HCQ retinal toxicity is of increasing concern. The aim of this study is to re-examine the HCQ retinal toxicity incidence rate, risk factors and clinical course after discontinuation.

Methods: We designed a prospective population-based cohort study in adult patients with SLE or RA, currently receiving HCQ for five or more years, who are residents of British Columbia (BC), Canada. Based on administrative data, we identified 5,508 eligible participants (1,346 SLE and 4,162 RA). They will participate in annual or bi-annual retinal screening over five years in alignment with the recently revised American Academy of Ophthalmology (AAO) guidelines. To standardize procedures for retinal screening, imaging, diagnostic criteria, severity staging and data transfer, a consensus meeting was convened in December 2019 with participation of BC retinal specialists and the research team. Agreement was attained on: use of Spectral Domain-Optical Coherence Tomography as the primary objective screening modality; classification of images into categories of normal, equivocal or abnormal; and transferring the equivocal and

abnormal images plus corresponding subjective test results via cloud-based server from each clinic to a reading center. Confirmation of HCQ retinal toxicity diagnoses and severity staging will be performed by three independent and masked reviewers. The incidence of HCQ retinal toxicity will be calculated, accounting for the competing risk of death. Hazard ratios for each risk factor will be calculated for the risk of HCQ retinopathy, after adjusting for confounders. We will also estimate the risk of HCQ retinal toxicity progression over five years.

Ethics and dissemination: This study has received approval from the University of British Columbia Clinical Research Ethics Board [H20-00736] and the Vancouver Coastal Health Research Institute.

Strengths and limitations:

- ✓ To the best of our knowledge, this is the first prospective, population-based cohort study designed to address the incidence rate, risk factors for and clinical course of hydroxychloroquine (HCQ)-induced retinal toxicity and progression.
- ✓ Access to British Columbia's (BC) administrative health data from the single-payer health care system allowed us to establish a large population-based cohort of all individuals with systemic lupus erythematosus or rheumatoid arthritis, exposed to HCQ for at least five years in BC.
- ✓ Linking participant self-report demographic and medical history, retinal imaging, and administrative health data will allow for calculation of an accurate risk of HCQ-induced

retinal toxicity, which will provide vital safety information for patients, physicians, and policy makers.

- ✓ A structured consensus meeting led to the development of a novel and pragmatic standard operational protocol for the screening and follow up of patients on long-term HCQ medication for retinal toxicity.
- ✓ Five years of follow up may be inadequate to capture long-term results for the cases with five to ten years of HCQ medication.
- ✓ It is possible that nonadherence to the dosage of prescribed HCQ treatment may occur before or during study. This issue can only be addressed through evaluation of serum levels of HCQ, which should be considered in future studies.

Key words: Hydroxychloroquine (HCQ); Retinal toxicity; Prospective population-based cohort study; Consensus; Macular SD-OCT; Reading center.

Introduction:

The antimalarial medication hydroxychloroquine (HCQ) has been the cornerstone medication in the treatment of systemic lupus erythematosus (SLE), and often in mild to moderate rheumatoid arthritis (RA), alone or in combination; both diseases are chronic with marked disability and premature death. (1-5) HCQ is inexpensive and has been shown to improve survival in SLE patients and to reduce synovitis and physical disabilities in RA patients. (6-10) HCQ is also considered to be one of the very well tolerated medications for rheumatic diseases [*i.e.*, better than nonsteroidal anti-inflammatory drugs, like ibuprofen or naproxen], (11, 12) and is considered sufficiently safe to be recommended for pregnant patients with SLE. (13, 14)

A landmark trial led by Esdaile et al., showed that HCQ discontinuation after achieving disease control, led to a 2.5 times higher risk of SLE flare up and 6.1 times higher risk of severe flare up in vital organs (e.g., kidney involvement, vasculitis) within 6 months of HCQ withdrawal. (3) Moreover, a long-term study by the same group, on the effect of HCQ withdrawal in SLE, using an intent-to-treat analysis, showed a potential protective effect against a major flare for those randomized to continue HCQ (OR=0.43 [95% CI: 0.17, 1.12]). (15) These findings had a significant impact on clinical practice, making HCQ a universal therapy in SLE regardless of disease activity and severity. Since then, many studies have confirmed wide-ranging benefits of HCQ, including improved survival, reduced disease activity; and lower risks of nephritis, pregnancy complications, venous thromboembolism, dyslipidemia, and insulin resistance in patients with SLE. (16-18) Recently, a retrospective population-based study by our group using the administrative health data of the residents of British Columbia (BC), Canada with incident

SLE and incident HCQ use between 1997 and 2015 showed a 71% and 83% lower risk of death among SLE patients, who adhered to HCQ in comparison to SLE patients, who were non-adherent or discontinued the medication, respectively. (6, 7)

Despite being considered relatively safe, it has been reported that with long-term use, HCQ can accumulate in the retinal pigment epithelial cells and may cause progressive outer retinal toxicity with retinal pigment epithelial and photoreceptor cell death and secondary vision loss. Based on the accumulating evidence of HCQ retinal toxicity, the American Academy of Ophthalmology (AAO) recommends annual screening for patients receiving HCQ for five years or more. (19) Retinal toxicity had a previously estimated occurrence of 0.5-2% in long-term users. (19) However, a 2014 retrospective study using the US Kaiser Permanente Northern California (KPNC) database demonstrated that among users of HCQ with use ≤5 mg/kg of their real body weight, the risk was <2% for five to ten years of therapy, but almost 20% after 20 years of use. Conversely, patients with a mean daily use >5 mg/kg had approximately a 10% risk of retinal toxicity for five to ten years of HCQ use and almost a 40% risk after 20 years. (20) This is at least 10 times higher than previously published rates and caused alarm to patients and physicians. (21-23) Retinal toxicity secondary to HCQ is a major concern expressed by patients and clinicians. It is one of the main reasons for non-adherence to HCQ. (24-28) However, this study reported 32% missing data and did not adjust for the competing risk of death, thus results might have been susceptible to selection bias and overestimation of the true risk. (20, 29)

A systematic review on the risk of HCQ retinopathy and its risk factors in patients with rheumatic diseases found that most previous studies have been case series or retrospective cohorts. (30) This included a few prospective studies, all of which were limited in size (58 to 225

patients) and duration of follow-up (1 to 3 years). (22, 29, 30) Recently a joint statement has been published by the American College of Rheumatology, the AAO, the American Academy of Dermatology and Rheumatologic Dermatology Society, on HCQ ocular safety. They indicated that there is a critical lack of data from a population-based prospective study on HCQ retinal toxicity. (31) A prospective study to better estimate the risk, risk factors and clinical course of HCQ retinal toxicity is therefore needed.

To address this, we established a prospective population-based cohort study to follow patients with RA and SLE with a minimum of five years of HCQ use, for potential retinal toxicity. To enable development of a standard operating protocol (SOP) for this study, a consensus meeting was convened among board certified practicing rheumatologists and retinal specialists from BC, including specialists from both urban and rural areas. The objective of the meeting was to identify and agree upon a SOP for screening and follow up for the retinal exams and assessments. The SOP was to align with the most up to date principles of evidence-based screening protocols for HCQ retinal toxicity, feasible in a routine practice of retinal ophthalmologists to maximize patient and practitioner participation.

Cohort Description/Methods:

Design:

A prospective population-based cohort study among patients diagnosed with RA or SLE, with five or more years HCQ use, between January 1990 and December 2020, in BC and who were alive. The patients will be followed for at least five years, from July 2021 to Dec 2026.

Goals:

The main aims of our prospective and population-based study are to: 1) determine the incidence rate of retinopathy in HCQ users of ≥ 5 years duration of treatment, 2) determine the risk factors for HCQ retinopathy and 3) describe the clinical course of retinopathy following HCQ discontinuation, based on retinal examination, multimodal retinal imaging, visual fields and patient reported outcomes from the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). (32)

Data source:

We will use administrative data extracted from Population Data BC (PopData) which is an extensive data resource for applied health services and population health research used by our group and others. (33-39) PopData covers the entire population of BC from 1990 onwards (5.1 million in 2021). Individuals can be traced over time and ultimately as the data expands longitudinally, over their lifespan. The main linkable databases include the following files: Medical Services Plan (physician visits and procedures data) (40), Hospital Separation (discharge summaries including up to 25 diagnostic codes) (41), PharmaNet (all medications dispensed for all BC residents) (42), Vital Statistics (date and cause of death) (43) and the BC Cancer registry (44). We have previously developed a unique Laboratory Services link that provides laboratory results linked to the administrative data as well as survey data collected from consenting individuals.

Patient and Public Involvement:

No patient was involved in the development of the research question and outcome measures, study design and conduct of study.

Study population (SLE and RA cohorts):

Adults (aged ≥ 18 years) with RA or SLE were identified from outpatient physician billing files or from the hospital discharge database using International Classification of Diseases ninth (ICD-9) and tenth (ICD-10) revision diagnostic codes. SLE and RA cases are defined using at least two ICD codes for SLE and RA, at least 2 months apart within a 2-year window period from 1990-2020. The validity of this algorithm to identify RA patients has been evaluated to have a positive predictive value (PPV) of 82%. (45) Similarly, for identifying SLE patients, the validity of this algorithm when one ICD code is from hospitalization and the other by a rheumatologist, has been evaluated to have a PPV of 97% in Swedish registry data. (46) In our previous studies, > 80% of SLE cases had at least one code from hospitalization or from a rheumatologist. (38, 47, 48)

Using these algorithms, we identified 4,104 SLE patients and 21,265 RA patients who had started HCQ since January 1, 1997 in BC. Of those, 1,346 SLE and 4,162 RA patients (total N = 5,508) had taken HCQ for at least five years by December 2020. Only rare cases who had used chloroquine before commencing HCQ for SLE or RA will be excluded from this study. There will be no exclusion criteria for patients with any underlying systemic disease, ocular disease and/or ocular surgeries with macular involvement. These may include diabetic macular edema, cystoid macular edema, retinal vascular occlusive disease, age-related macular degeneration, inherited retinal dystrophy, and uveitis. However, patients with advanced macular anatomical alterations

due to comorbidities, which could interfere with an HCQ retinal toxicity diagnosis, may be excluded in data analysis (with provided explanation).

Recruitment:

Eligible participants identified from our population-based RA and SLE database who fulfill the inclusion criteria will receive an invitation letter containing the study information as well as a consent form. After obtaining informed consent from patients, we will contact the rheumatologists or primary care physicians to inform them of their patient's participation in the study and send reminders for baseline screening and annual referrals, as per 2016 AAO guidelines and current standard of care, to the participating retina specialists' clinics who we will call the "retina specialist network of the INTACT study". Rheumatologists and primary care physicians throughout BC may also refer eligible patients based on the inclusion criteria to the retina specialist network of the INTACT study, after obtaining informed consent.

Self-report questionnaire:

Participants will fill out a self-report questionnaire (See Supplementary File 1 – Patient self-report questionnaire) to collect information on risk factors, confounders, and patient reported outcomes, at the time of their first retina exam as part of this study. This data will be updated at each annual visit. The survey questionnaire will collect information on potential risk factors such as chronic kidney disease, diabetes, hypertension, liver disease, retinal or macular disease as well as comorbidities, race, current HCQ dose, weight, height, and disease duration. (19) Data on medications with a known risk of retinopathy (e.g. tamoxifen, anastrozole) will be collected in the self-report questionnaire as well as obtained from PharmaNet. (49)

Patients with the confirmed diagnosis of HCQ-induced retinopathy will be asked to fill out the NEI VFQ-25, to provide a better understanding of the impact of this side effect on their daily lives. (32)

Consensus description/Methods:

On December 14, 2019, a consensus meeting was convened in Richmond, BC. Participants in the consensus meeting were project team members, including, three board-certified academic retinal specialists (D.A.L.M., K.P.V., S.D.L.), three board-certified academic rheumatologists (J.A.A.Z. J.M.E., K.S.), one pharmaco-epidemiologist (M.E.), and one knowledge broker (A.H.). All practicing retinal specialists in BC were invited (n= 27), of which 18 attended the consensus meeting and agreed to participate in the study (the retina specialist network of the INTACT study). In addition, research coordinators from ophthalmology clinics, research staff from Arthritis Research Canada and a guest speaker (Ronald B. Melles, M.D.) attended the meeting.

The consensus meeting commenced with a presentation by the guest speaker who highlighted and discussed key findings from the KPNC study. Two academic retinal specialists (K.P.V., S.D.L.) then gave presentations, highlighting key points from the AAO 2016 revised recommendations on HCQ retinal toxicity screening exams by SD-OCT imaging and automated visual field (VF) test.

After the presentations, two consensus sessions, led by the knowledge broker, were held to identify and address the main challenges that were highlighted in the presentations and were pertinent to developing the SOP:

1) To develop the process for annual HCQ retinal toxicity screening and follow up exams by the retina specialist network of the INTACT study for patients with an HCQ retinal toxicity diagnosis. These were to be based on the latest AAO 2016 revised recommendations (16) using at least one objective test of three potential options: SD-OCT, Fundus Auto-fluorescence (FAF) or Multifocal Electroretinography (mfERG) confirming the subjective standard automated VF assessment.
2) To define the standardized criteria for detecting normal versus abnormal SD-OCT imaging, define equivocal cases versus definite cases, and determine appropriate follow up procedures for patients in each group.
3) To determine standardized severity stages of retinal toxicity in cases with abnormal diagnoses.

The consensus session began with individual reflection. Participants were asked to independently identify and record on post-it notes, potential concerns regarding the implementation of the standardized screening and operational protocols relevant to their routine office practice and the potential challenges with eye examination protocols, SD-OCT imaging and automated VF assessment. The knowledge broker then collected and categorized the responses. The categories were shared with participants who then voted to identify the following five main challenges:

I. Standardization of SD-OCT image acquisition and automated VF assessment.
II. Criteria for diagnosis of HCQ retinal toxicity.
III. Classification of HCQ retinopathy into different severity stages of disease.

IV. Data collection training of medical office assistants (MOA) and research staff at the clinics.

V. Data storage and transfer to the Eye Care Centre at Vancouver General Hospital (VGH) and Arthritis Research Canada.

The second phase of the process was achieved through small group discussions of five participants. Each group was assigned one of the five main challenges and asked to brainstorm logical and feasible solutions for the challenge which could be included in the SOP.

Following the small group discussions, a representative from each group presented a summary of their discussion to the large group. This permitted further discussion to elucidate key points that had been most salient or missing from the small group discussions. The knowledge broker then summarized the options for each of the main challenges and all participants voted. If 100% agreement on the solution(s) for each of the challenges was not initially achieved, another cycle of discussion was undertaken enabling consensus to be reached on the solutions for all challenges.

Consensus results/proposed solutions:

The group made the following consensus statements for the five categories mentioned above (Figure 1- HCQ retinal toxicity screening protocol flowchart for INTACT study: The consensus results).

I. Standardization of SD-OCT image acquisition and automated VF exam assessment:

- ✓ Only three types of SD-OCT machines are acceptable for this study: Spectralis OCT (Heidelberg Engineering), Cirrhus HD-OCT (Carl Zeiss Meditec), and Topcon 3D-OCT 2000 (Topcon Corporation). At least one of these three machines is available in every retinal clinic participating in this study. Additionally, the same machine(s) must be used for a patient at all of their visits.

- ✓ To completely demonstrate pathologies of the macular area including, foveal, para-foveal and peri-foveal zones, macular SD-OCT scan should cover a minimum of 20 degrees x 20 degrees for non-Asian patients and 30 degrees x 30 degrees for Asian patients. This difference in macular SD-OCT scanning is based on the AAO guidelines for HCQ retinopathy screening recommendations, according to the findings on racial differences for HCQ retinopathy involvement of macula. (19, 50) Block size and raster technique will be machine-specific. For Heidelberg SD-OCT machines, a 12 mm x 9 mm cube scan was recommended.

- ✓ Each scan must be able to clearly delineate both inner and outer retinal bands. Specifically, the outer retinal bands at the para-foveal and peri-foveal zones should be in focus and clearly visible. The presence of vessel shadowing will ensure a high-quality scan.

- ✓ SD-OCT imaging must be done for all patients as the main screening exam.

- ✓ If a patient's SD-OCT scan is normal, that patient will be scheduled for their next appointment in a year. However, if the scan is considered equivocal or abnormal, the patient must be evaluated with standard automated 10-2 VF (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) assessment. If the 10-2 scan is also considered equivocal or abnormal, then a standard automated 24-2 or 30-2 VF assessment must be done. For Asian participants, both the standard automated 10-2 and 24-2 or 30-2 VF must be performed in all cases with equivocal or abnormal SD-OCT scans.

- ✓ FAF imaging was defined as complementary (to the SD-OCT and automated VF) objective screening exam. Its performance will be left to the discretion of the retina specialist network of the INTACT study, based on their clinical judgement (not mandatory).

II. Criteria for diagnosis of HCQ retinal toxicity:

- ✓ All patients on HCQ must be examined according to the standard of care and current guidelines regardless of any comorbidities. However, diagnosis of HCQ retinopathy will be determined by the clinician's (retina specialist network of INTACT study) interpretation of results based on standard images that will be sent to them as guidance packages which are in accordance with the peer reviewed publications, of macular SD-OCT and standard automated VF findings in HCQ retinal toxicity (19, 51). The standard images will be prepared by the

INTACT study team's experienced academic retinal specialists (D.A.L.M., K.P.V. and S.D.L.).

- ✓ All scans must only be classified as no signs of HCQ retinal toxicity (normal), suspicious signs of HCQ retinal toxicity (equivocal) or typical signs of HCQ retinal toxicity (abnormal) by the retinal specialist and recorded by checking the box that applies in a reporting form that will be sent to researchers at the VGH Eye Care Centre (see Supplementary File 2- Retina Specialist Reporting Form).
- ✓ Abnormal, equivocal, and a random sample of normal scans (thirty in Year 1 and Year 2) must be sent to the VGH Eye Care Centre for secondary review and validation.
- ✓ The three study team retinal specialists (D.A.L.M., K.P.V., and S.D.L.) will be considered as the gold standard. Two of them (K.P.V. and S.D.L.) will review the images of all patients reported as equivocal or abnormal by the "retina specialist network of the INTACT study" in addition to the random sample of normal scans (thirty in Year 1 and Year 2) from them. Confirmation of diagnosis is based on the agreement between two reviewers at the VGH Eye Care Centre.
- ✓ The third retina specialist (D.A.L.M.) will only review images with any discrepancy in the diagnosis. Eventually the final decision will be achieved by the third masked reviewer (agreement between D.A.L.M. and one of the first two reviewers).

III. Severity stages of disease (i.e., classification of HCQ retinopathy into mild, moderate and severe).

- ✓ Retina specialists at their clinics will not need to classify the severity staging.
- ✓ The two study team retina specialists (K.P.V. and S.D.L.) will classify HCQ retinopathy as mild, moderate, or severe HCQ retinal toxicity after confirmation of diagnosis.
- ✓ Again, with any discrepancy in the severity staging by the first two reviewers, the third masked reviewer (D.A.L.M.) will assess and make the final decision, which is based on agreement of his and one of the two other reviewers' assessment.

IV. Data collection training of medical office assistants (MOA) and research staff at the clinics.

- ✓ There will be a main research lead (N.D.) for all clinics and one research lead assigned at each clinic (e.g., nurse, research coordinator, research assistant). The main research lead will be responsible for training of the other centre leads and the coordination of the overall flow at each centre.

V. Data storage and transfer to the VGH Eye Care Centre and Arthritis Research Canada:

- ✓ There are two types of data to be stored and transferred to Arthritis Research Canada and the VGH Eye Care Centre, specifically the patient self-report and

retina specialist report questionnaires and the ocular imaging (i.e., SD-OCT and automated VF assessment or FAF).

- ✓ Questionnaires, including both patient self-report and retina specialist reports will be stored in individual patient files in a locked filing cabinet at Arthritis Research Canada. This data will be linked to provincial administrative health data by PopData upon completion of the study. The research team will be unable to identify individuals after linkage.
- ✓ A cloud server will be used to store the data including the SD-OCT digital images as well as automated VF assessments, from the retina clinics, which will be accessible to the three readers at the VGH Eye Care Centre. Briefly, there will be a separate folder allocated for each retina clinic, wherein each clinic will only be able to access and upload the images and data of their own patients. The three readers at the VGH Eye Care Centre will be able to access all folders through a secure website.

Data analysis plan

1) Determine the incidence rate of retinopathy in HCQ users with ≥ 5 years duration of treatment: We will calculate the overall incidence and dose-specific risk (i.e., cumulative incidence) of HCQ retinal toxicity. Each eligible and consenting individual will be followed from the study baseline until the end of the 5-year study period, disenrollment or death, whichever occurs first. These person-time data with events will then be used

to calculate the cumulative incidence, employing established methods for left truncated data and the competing risk of death.

2) Determine the risk factors for HCQ retinopathy: We will examine the relationship of purported risk factors for HCQ retinopathy among participants, including relevant measures of HCQ exposure (daily dose, daily dose in mg/kg for actual body weight (ABW), daily dose in mg/kg for ideal body weight (IBW), total cumulative lifetime dose, and duration of exposure), other putative predictors (i.e., older age, female sex, chronic kidney disease, other concomitant drug use with potential retinal toxicity [i.e., tamoxifen, anastrozole] or underlying retinal disease), and any other factors that emerge during the study period. First, we will compare the age-standardized incidence rates of HCQ retinopathy according to the risk factor categories. Then, we will obtain the point and interval estimates of the hazard ratio (HR) of each candidate risk factor for the risk of incident HCQ retinopathy, mutually adjusting for potential risk factors. Also, we will use Cox proportional hazard regression models, accounting for the competing risk of death and left truncation of event time. (52-56)

3) Describe the clinical course of retinopathy following HCQ discontinuation: We will follow all newly identified HCQ retinal toxicity cases on an annual basis during the study period (5 years) and assess the rate of pathological progression of retinopathy, defined as any worsening of both SD-OCT imaging and VF assessment. We will estimate the risk of progression according to initial retinopathy stage (mild, moderate, and severe) accounting for the competing risk of death. (57, 58)

4) Determine the level of agreement between the reviewers at the reading center (gold standard) and the network of retina specialists: We will use Cohen's kappa statistic to measure agreement on the HCQ retinopathy diagnosis (normal versus equivocal versus abnormal) between the reviewer's at the reading center and the network of retina specialists (interrater). We will also measure the level of agreement both on the HCQ retinopathy diagnosis and on the HCQ retinopathy staging, between the reviewers at the reading center (intrarater).

Strengths and limitations

To the best of our knowledge, this is the first prospective, population-based cohort study designed to examine the incidence rate, risk factors and clinical course progression (after discontinuation) of HCQ-induced retinal toxicity in Canada. Our access to province-wide administrative health data for the total five million residents of BC is a significant strength. Our estimated sample size is 5,508 patients (including 1,346 SLE and 4,162 RA patients) of those who have been on HCQ treatment for five years or more. In this prospective study, we will have person-time data with events and risk factors including but not limited to HCQ dose for ABW versus IBW, chronic renal failure, comorbidities and others, with annual updates of data for five consecutive years. We will be able to calculate the cumulative incidence of HCQ-induced retinopathy considering the competing risk of death as well as HRs for each risk factor. These results will provide vital information for patients, physicians, and policy makers.

Our study benefits from the collaboration of retinal specialists from urban and rural parts of BC. Our province-wide retinal specialist network developed a novel SOP during a consensus meeting for screening and follow up of the patients based on the most recent AAO guidelines. Our study is not without potential limitations. First, there may be participant loss, due to declining to participate, emigration, and study drop-out. We include patients with five years or more of HCQ use in both SLE and RA cohorts, but there is a potential limitation for 18% of patients in the RA cohort to have a false positive diagnosis of RA due to the 82% PPV by the algorithm we are using to identify RA patients. Another limitation of our study is possible non-adherence to the amount of prescribed HCQ treatment. PharmaNet data will capture medication dispensed, however participants taking less than the prescribed dose, will not be captured. This issue can only be mitigated through evaluation of the serum level of HCQ, which should be taken into account in future studies. Another potential limitation of our study is that we may not be able to collect adequate information to evaluate HCQ retinopathy in patients with concurrent retinal disease because they may have already avoided starting HCQ medication.

Privacy and confidentiality

We have implemented measures to keep all personal information of patients secure, including names, contact information, Personal Health Numbers, self-report questionnaires, and medical reports. These will be kept in secure locations accessible only to a restricted number of study personnel at Arthritis Research Canada and retinal clinics. Patients' names will be replaced by a unique ID code upon patient's informed consent and enrollment in the study that will be

consistent on every study document and imaging, throughout the study. The digital information including the imaging will be housed on a secure cloud server with the most up-to-date security protections.

Ethics and dissemination:

The INTACT study was approved by the University of British Columbia's Clinical Research Ethics Board (H20-00736) and the Vancouver Coastal Health Research Institute (V20-00736). All participants will provide informed consent before inclusion in this study. Study results will be disseminated via peer-reviewed scientific journals and will be presented to academics and researchers at scientific conferences. A plain language summary of study results will be disseminated among participants following study completion.

Contributors:

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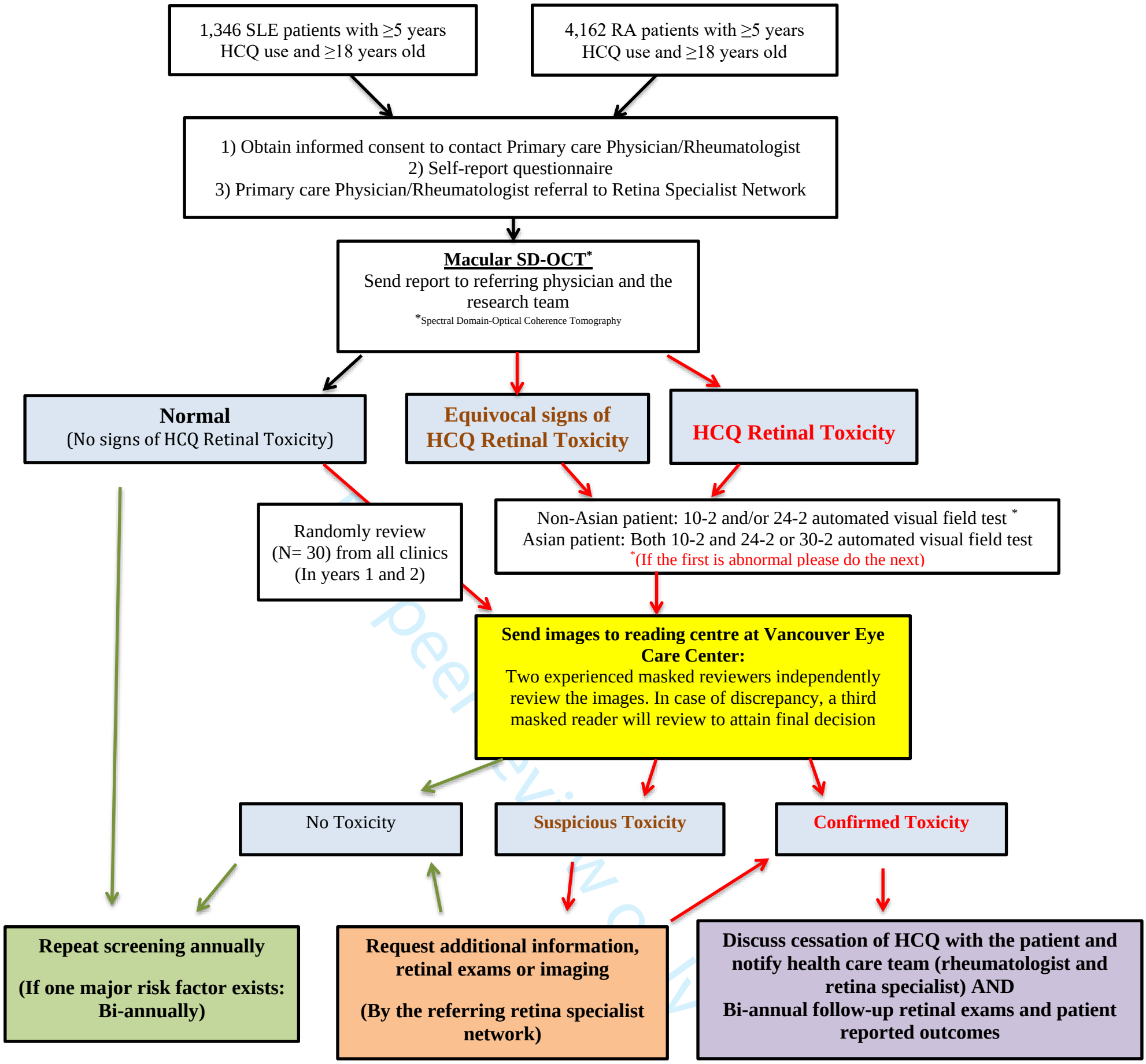
Figure 1- HCQ Retinal Toxicity Screening Protocol Flowchart for INTACT Study: The Consensus

Results

Figure 1- HCQ Retinal Toxicity Screening Protocol Flowchart for INTACT Study: The Consensus Results



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Site-Study Patient ID: _____

INTACT Study – Patient self-report questionnaire

Please take a few minutes to fill out this form.
Your answers will be kept confidential.

Thank you for your participation.

Place Sticker Here:

Date of care provision: _____/_____/_____
(mm/dd/yyyy)

Full name of provider: _____

General Patient Information (Please fill in your information below and check (✓) any boxes that apply to you): *(To be filled out by the patient)*

Mobile Phone Number: ( )

Landline Phone Number: ( )

Address:

City: Province: Postal Code:

Email Address: @

Secondary Email Address: @

Gender:

☐ Male ☐ Female ☐ Trans male ☐ Trans female

☐ Other, please specify:

☐ I prefer not to answer this question

Ethnicity:

☐ White
☐ East Asian
☐ South Asian
☐ South-East Asian
☐ Black
☐ Hispanic or Latino
☐ Indigenous/Aboriginal
☐ Pacific Islander
☐ Other, please specify:
☐ I prefer not to answer

INTACT Study: Patient Questionnaire **Site-Study Patient ID:**

Weight: kg OR lbs

Height: ft in OR cm

Medical History (Please check (✓) any boxes below that apply to you): *(To be filled out by the patient)*

- Which one of the following is your current diagnosis?

☐ Systemic Lupus Erythematosus ☐ Rheumatoid Arthritis

- Have you been diagnosed by a medical doctor with any of the following conditions?

☐ Diabetes ☐ High Blood Pressure ☐ Chronic Kidney Disease ☐ Breast Cancer

☐ Inherited Retinal Dystrophy ☐ Glaucoma ☐ Age Related Macular Degeneration

- Are you currently using tamoxifen? ☐ Yes | ☐ No
- Are you currently using anastrazole? ☐ Yes | ☐ No
- Have you ever had eye surgery? ☐ Yes | ☐ No

If yes, please specify what type of eye surgery:

- Have you ever had an eye injection (intravitreal injection)? ☐ Yes | ☐ No

If yes, please specify the reason:

INTACT Study: Patient Questionnaire **Site-Study Patient ID:**

Hydroxychloroquine/Plaquenil (the same drug) Information (Please check (✓) any boxes below that apply to you): *(To be filled out by the patient)*

- Are you currently taking hydroxychloroquine (HCQ)/plaquenil? ☐ Yes | ☐ No
- How long in total have you been taking HCQ/plaquenil?

☐ 5-10 years ☐ 10-15 years ☐ 15-20 years ☐>20 years

- Current daily dose of HCQ/plaquenil: mg
- Total number of HCQ/plaquenil pills per week: of ☐ 200 mg OR ☐ 400 mg
- Do you take a different HCQ/plaquenil dose on one or more specific days of the week?
- ☐ Yes | ☐ No
- If yes, please specify which day(s) of week: of ☐ 200 mg OR ☐ 400 mg

- Have you ever stopped taking HCQ/plaquenil for more than 3 months?

☐ Yes | ☐ No

- If yes, please specify the date you stopped taking HCQ/plaquenil (MM/YYYY):

_____/_____

- Did you start taking HCQ again? ☐ Yes | ☐ No

If yes, please specify the date you started taking HCQ/plaquenil again

(MM/YYYY): _____/_____

INTACT Study: Patient Questionnaire **Site-Study Patient ID:**

➢ Please specify the reason why you stopped taking HCQ/plaquenil?

Side effects:

- ☐ Rash
- ☐ Eye Toxicity
- ☐ Abdominal/Stomach Upset
- ☐ Lack of medication effectiveness
- ☐ Fear of side effects
- ☐ Cost of medication
- ☐ Tired of taking pills
- ☐ No Reason
- ☐ Other, please specify:

➢ Who recommended the discontinuation of HCQ?

- ☐ Rheumatologist
- ☐ Family doctor
- ☐ Ophthalmologist (eye physician)
- ☐ Optometrist
- ☐ Nurse
- ☐ A friend
- ☐ Myself
- ☐ Other, please specify:

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Thank you for taking your time to fill out the form

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Site-Study Participant ID:

INTACT Study – Retina Specialist Reporting Form

Place Sticker Here:

Date of care provision: _____/_____/_____ (mm/dd/yyyy)

Full name of provider: _____

SD-OCT Results

- Please specify SD-OCT you used:

☐ Spectralis HRA-OCT ☐ Cirrhus HD-OCT ☐ Topcon 3D-OCT

- Morphological appearance of SD-OCT scans:

☐ Disruption of the interdigitation zone (IZ) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Decreased reflectivity of the ellipsoid zone (EZ) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Disruption of the EZ **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Disruption of the retinal pigment epithelium (RPE) **at** ☐ fovea , ☐ parafovea ,

☐ perifovea

☐ Disruption of the external limiting membrane (ELM) **at** ☐ fovea , ☐ parafovea ,

☐ perifovea

☐ Thinning of the outer nuclear layer (ONL) **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Flying saucer sign

☐ Other please specify:

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Site-Study Participant ID:

Your evaluation regarding HCQ related findings in macular SD-OCT, please check (✓) the box below as it may apply:

☐ **Abnormal (typical signs of HCQ related retinal toxicity)**

☐ **Equivocal (suspicious signs of HCQ related retinal toxicity)**

☐ **Normal (no signs of HCQ related retinal toxicity)**

Comments:

Please turn to the next page

INTACT Study: Retina specialist Reporting Form **Site-Study Participant ID: _____**

Supplemental Testing (if abnormal or equivocal OCT results)

- Visual Acuity Results: OD: OS:
- **Please specify automated visual field machine used:**

☐ Humphrey ☐ Occulus Centerfield

- Perimetry test performed: ☐ 10-2 ☐ 24-2 ☐ 30-2
- **10-2** automated perimetry:

☐ A defect within 2–6 degrees from fixation on gray scale, sparing the central 2 degrees

☐ Scattered patches of relative scotoma

☐ Paracentral scotoma

☐ Partial ring defect sparing the central 2 degrees

☐ A complete ring defect sparing the central 2 degrees

☐ Other; please specify:

- **24-2 or 30-2** automated perimetry:

☐ A defect within 10–20 degrees from fixation on gray scale, sparing the central 2 degrees

☐ Scattered patches of relative scotoma

☐ Pericentral scotoma

☐ Partial ring defect sparing the central 2 degrees

☐ A complete ring defect sparing the central 2 degrees

☐ Other; please specify:

INTACT Study: Retina specialist Reporting Form **Site-Study Participant ID: _____**

Supplemental Testing (if applicable)

➢ Fundus auto-fluorescence findings (FAF):

☐ Hyper-autofluorescence **at** ☐ fovea , ☐ parafovea , ☐ perifovea

☐ Hypo-autofluorescence **at** ☐ fovea , ☐ parafovea , ☐ perifovea

➢ Macular appearance:

☐ Macular granularity

☐ Loss of foveal reflex

☐ Broadening of foveal reflex

☐ Retinal pigment epithelium irregularities

☐ Bull's eye maculopathy

☐ Other, please specify:

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-17
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	18
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	18
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	18
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.