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

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3 1 **RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) - A Prospective**
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6 2 **Population-based Cohort Study**
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10
11 25 **Abstract:**
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15 26 **Purpose:** Hydroxychloroquine (HCQ) is an important medication for patients with systemic
16
17 27 lupus erythematosus (SLE), rheumatoid arthritis (RA) and other rheumatic diseases. Although it
18
19 28 is well-tolerated and cost-effective, the risk of HCQ retinal toxicity is of increasing concern. The
20
21 29 aim of this study is to re-examine the HCQ retinal toxicity incidence rate, risk factors and clinical
22
23 30 course after discontinuation.
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28 31 **Methods:** We designed a prospective population-based cohort study in adult patients with
29
30 32 SLE or RA, currently receiving HCQ for five or more years, who are residents of British Columbia
31
32 33 (BC), Canada. Based on administrative data, we identified 5,508 eligible participants (1,346 SLE
33
34 34 and 4,162 RA). They will participate in annual or bi-annual retinal screening over five years in
35
36 35 alignment with the recently revised American Academy of Ophthalmology (AAO) guidelines. To
37
38 36 standardize procedures for retinal screening, imaging, diagnostic criteria, severity staging and
39
40 37 data transfer, a consensus meeting was convened in December 2019 with participation of BC
41
42 38 retinal specialists and the research team. Agreement was attained on: use of Spectral Domain-
43
44 39 Optical Coherence Tomography as the primary objective screening modality; classification of
45
46 40 images into categories of normal, equivocal or abnormal; and transferring the equivocal and
47
48 41 abnormal images plus corresponding subjective test results via cloud-based server from each
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50 42 clinic to a reading center. Confirmation of HCQ retinal toxicity diagnoses and severity staging
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3 43 will be performed by three independent and masked reviewers. The incidence of HCQ retinal
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5 44 toxicity will be calculated, accounting for the competing risk of death. Hazard ratios for each
6
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8 45 risk factor will be calculated for the risk of HCQ retinopathy, after adjusting for confounders.
9
10 46 We will also estimate the risk of HCQ retinal toxicity progression over five years.

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13 47 **Ethics and dissemination:** This study has received approval from the University of British
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15
16 48 Columbia Clinical Research Ethics Board [H20-00736] and the Vancouver Coastal Health
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19 49 Research Institute.

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22 50 **Strengths and limitations:**

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25 51 ✓ To the best of our knowledge, this is the first prospective, population-based cohort
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28 52 study designed to address the incidence rate, risk factors for and clinical course of
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31 53 hydroxychloroquine (HCQ)-induced retinal toxicity and progression.
- 32
33 54 ✓ Access to British Columbia's (BC) administrative health data from the single-payer health
34
35
36 55 care system allowed us to establish a large population-based cohort of all individuals
37
38
39 56 with systemic lupus erythematosus or rheumatoid arthritis, exposed to HCQ for at least
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41
42 57 five years in BC.
- 43
44 58 ✓ Linking participant self-report demographic and medical history, retinal imaging, and
45
46
47 59 administrative health data will allow for calculation of an accurate risk of HCQ-induced
48
49
50 60 retinal toxicity, which will provide vital safety information for patients, physicians, and
51
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53 61 policy makers.

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3 62 ✓ A structured consensus meeting led to the development of a novel and pragmatic
4
5
6 63 standard operational protocol for the screening and follow up of patients on long-term
7
8 64 HCQ medication for retinal toxicity.
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11 65 ✓ Five years of follow up may be inadequate to capture long-term results for the cases
12
13
14 66 with five to ten years of HCQ medication.
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16
17 67 ✓ It is possible that nonadherence to the dosage of prescribed HCQ treatment may occur
18
19 68 before or during study. This issue can only be addressed through evaluation of serum
20
21 69 levels of HCQ, which should be considered in future studies.
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28 71 Key words: Hydroxychloroquine (HCQ); Retinal toxicity; Prospective population-based cohort
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30 72 study; Consensus; Macular SD-OCT; Reading center.
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73 Introduction:

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

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

1
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3 94 administrative health data of the residents of British Columbia (BC), Canada, with incident SLE
4
5 95 and incident HCQ use between 1997 and 2015, showed a 71% and 83% lower risk of death
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8 96 among SLE patients who adhered to HCQ in comparison to SLE patients who were non-
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11 97 adherent or discontinued the medication, respectively. (14, 15)
12

13
14 98 Despite being considered relatively safe, it has been reported that with long-term use, HCQ can
15
16 99 accumulate in the retinal pigment epithelial cells and may cause progressive outer retinal
17
18 100 toxicity, retinal pigment epithelial and photoreceptor cell death and secondary vision loss.
19
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21 101 Based on the accumulating evidence of HCQ retinal toxicity, the American Academy of
22
23 102 Ophthalmology (AAO) recommends annual screening for patients receiving HCQ for five years
24
25
26 103 or more.(16) Retinal toxicity had a previously estimated occurrence of 0.5-2% in long-term
27
28 104 users.(16) However, a 2014 retrospective study using the US Kaiser Permanente Northern
29
30
31 105 California (KPNC) database demonstrated that among users of HCQ with use ≤ 5 mg/kg of their
32
33 106 real body weight, the risk was $<2\%$ for five to ten years of therapy, but almost 20% after 20
34
35 107 years of use. Conversely, patients with a mean daily use >5 mg/kg had approximately a 10%
36
37
38 108 risk of retinal toxicity for five to ten years of HCQ use and almost a 40% risk after 20 years. (17)
39
40
41 109 This is at least 10 times higher than previously published rates and caused alarm to patients and
42
43 110 physicians.(18-20) Retinal toxicity secondary to HCQ is a major concern expressed by patients
44
45 111 and clinicians. It is one of the main reasons for non-adherence to HCQ.(21-25) However, this
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48 112 study reported 32% missing data and did not adjust for the competing risk of death, thus results
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51 113 might have been susceptible to selection bias and overestimation of the true risk. (17, 26)
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54 114 A systematic review on the risk of HCQ retinopathy and its risk factors in patients with
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56 115 rheumatic diseases found that most previous studies have been case series or retrospective
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3 116 cohorts. (27) This included a few prospective studies, all of which were limited in size (58 to 225
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6 117 patients) and duration of follow-up (1 to 3 years). (19, 26, 27) Recently a joint statement has
7
8 118 been published by the American College of Rheumatology, the AAO, the American Academy of
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11 119 Dermatology and Rheumatologic Dermatology Society, on HCQ ocular safety. They indicated
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13 120 that there is a critical lack of data from a population-based prospective study on HCQ retinal
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15 121 toxicity. (28) A prospective study to better estimate the risk, risk factors and clinical course of
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18 122 HCQ retinal toxicity is therefore needed.

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21 123 To address this, we established a prospective population-based cohort study to follow patients
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23 124 with RA and SLE with a minimum of five years of HCQ use, for potential retinal toxicity. To
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26 125 enable development of a standard operating protocol (SOP) for this study, a consensus meeting
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28 126 was convened among board certified practicing rheumatologists and retinal specialists from BC,
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31 127 including specialists from both urban and rural areas. The objective of the meeting was to
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33 128 identify and agree upon a SOP for screening and follow up for the retinal exams and
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35
36 129 assessments. The SOP was to align with the most up to date principles of evidence-based
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38 130 screening protocols for HCQ retinal toxicity, feasible in a routine practice of retinal
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41 131 ophthalmologists so as to maximize patient and practitioner participation.

132 **Cohort Description/Methods:**

133 **Design:**

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

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3 137 **Goals:**
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6 138 The main aims of our prospective and population-based study are to: 1) determine the
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9 139 incidence rate of retinopathy in HCQ users of ≥ 5 years duration of treatment, 2) determine the
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11 140 risk factors for HCQ retinopathy and 3) describe the clinical course of retinopathy following
12
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14 141 HCQ discontinuation, based on retinal examination, multimodal retinal imaging, visual fields
15
16 142 and patient reported outcomes from the 25-item National Eye Institute Visual Function
17
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19 143 Questionnaire (NEI VFQ-25). (29)
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22 144 **Data source:**
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25 145 We will use administrative data extracted from Population Data BC (PopData) which is an
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28 146 extensive data resource for applied health services and population health research used by our
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30 147 group and others. (30-36) PopData covers the entire population of BC from 1990 onwards (5.1
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33 148 million in 2021). Individuals can be traced over time and ultimately as the data expands
34
35 149 longitudinally, over their lifespan. The main linkable databases include the following files:
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37
38 150 Medical Services Plan (physician visits and procedures data)(37), Hospital Separation (discharge
39
40 151 summaries including up to 25 diagnostic codes)(38), PharmaNet (all medications dispensed for
41
42
43 152 all BC residents)(39), Vital Statistics (date and cause of death)(40) and the BC Cancer
44
45 153 registry(41). We have previously developed a unique Laboratory Services link that provides
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48 154 laboratory results linked to the administrative data as well as survey data collected from
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50 155 consenting individuals.
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53 156 **Patient and Public Involvement:**
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3 157 No patient was involved in the development of the research question and outcome measures,
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6 158 study design and conduct of study.
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9 159 Study population (SLE and RA cohorts):
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12 160 Adults (aged ≥ 18 years) with RA or SLE were identified from outpatient physician billing files or
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14 161 from the hospital discharge database using International Classification of Diseases ninth (ICD-9)
15
16 162 and tenth (ICD-10) revision diagnostic codes. SLE and RA cases are defined using at least two
17
18 163 ICD codes for SLE and RA, at least 2 months apart within a 2-year window period from 1990-
19
20 164 2020. The validity of this algorithm to identify RA patients has been evaluated to have a positive
21
22 165 predictive value (PPV) of 82%. (42) Similarly, for identifying SLE patients, the validity of this
23
24 166 algorithm when one ICD code is from hospitalization and the other by a rheumatologist, has
25
26 167 been evaluated to have a PPV of 97% in Swedish registry data. (43) In our previous studies,
27
28 168 > 80% of SLE cases had at least one code from hospitalization or from a rheumatologist. (35, 44,
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30 169 45)
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37 170 Using these algorithms, we identified 4,104 SLE patients and 21,265 RA patients who had
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39 171 started HCQ since January 1, 1997 in BC. Of those, 1,346 SLE and 4,162 RA patients (total N =
40
41 172 5,508) had taken HCQ for at least five years by December 2020. Only rare cases who had used
42
43 173 chloroquine before commencing HCQ for SLE or RA will be excluded from this study. There will
44
45 174 be no exclusion criteria for patients with any underlying systemic disease, ocular disease and/or
46
47 175 ocular surgeries with macular involvement. These may include diabetic macular edema, cystoid
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49 176 macular edema, retinal vascular occlusive disease, age-related macular degeneration, inherited
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51 177 retinal dystrophy, and uveitis. However, patients with advanced macular anatomical alterations
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178 due to comorbidities, which could interfere with an HCQ retinal toxicity diagnosis, may be
179 excluded in data analysis (with provided explanation).

180 Recruitment:

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

190 Self-report questionnaire:

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

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3 199 Patients with the confirmed diagnosis of HCQ-induced retinopathy will be asked to fill out the
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5 200 NEI VFQ-25, to provide a better understanding of the impact of this side effect on their daily
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8 201 lives. (29)
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11 202 Consensus description/Methods:

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15 203 On December 14, 2019, a consensus meeting was convened in Richmond, BC. Participants in
16
17 204 the consensus meeting were project team members, including, three board-certified academic
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19 205 retinal specialists (D.M., K.P.V., S.L.), five board-certified academic rheumatologists (D.E., G.M.,
20
21 206 J.E., J.A.A.Z., K.S.), one pharmaco-epidemiologist (M.E.), and one knowledge broker (A.H.). All
22
23
24 207 practicing retinal specialists in BC were invited (n= 33), of which 24 attended the consensus
25
26
27 208 meeting and agreed to participate in the study (the 'retina specialist network of the INTACT
28
29 209 study'). In addition, research coordinators from ophthalmology clinics, research staff from
30
31
32 210 Arthritis Research Canada and a guest speaker (Ronald B. Melles, M.D.) attended the meeting.
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34
35 211 The consensus meeting commenced with a presentation by the guest speaker who highlighted
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37 212 and discussed key findings from the KPNC study. Two academic retinal specialists (K.P.V., S.L.)
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39 213 then gave presentations, highlighting key points from the AAO 2016 revised recommendations
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41 214 on HCQ retinal toxicity screening exams by SD-OCT imaging and automated visual field (VF) test.
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45 215 After the presentations, two consensus sessions, led by the knowledge broker, were held to
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47 216 identify and address the main challenges that were highlighted in the presentations and were
48
49
50 217 pertinent to developing the SOP:

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53 218 1) To develop the process for annual HCQ retinal toxicity screening and follow up exams by
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56 219 the retina specialist network of the INTACT study for patients with an HCQ retinal
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3 220 toxicity diagnosis. These were to be based on the latest AAO 2016 revised
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6 221 recommendations (16) using at least one objective test of 3 potential options: SD-OCT,
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8 222 Fundus Auto-fluorescence (FAF) or Multifocal Electroretinography (mfERG) confirming
9
10 223 the subjective standard automated VF assessment.

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13 224 2) To define the standardized criteria for detecting normal versus abnormal SD-OCT
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15 225 imaging, define equivocal cases versus definite cases, and determine appropriate follow
16
17 226 up procedures for patients in each group.

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20 227 3) To determine standardized severity stages of retinal toxicity in cases with abnormal
21
22 228 diagnoses.

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26 229 The consensus session began with individual reflection. Participants were asked to
27
28 230 independently identify and record on post-it notes, potential concerns regarding the
29
30 231 implementation of the standardized screening and operational protocols relevant to their
31
32 232 routine office practice and the potential challenges with eye examination protocols, SD-OCT
33
34 233 imaging and automated VF assessment. The knowledge broker then collected and categorized
35
36 234 the responses. The categories were shared with participants who then voted to identify the
37
38 235 following five main challenges:

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43 236 I. Standardization of SD-OCT image acquisition and automated VF assessment.
44
45 237 II. Criteria for diagnosis of HCQ retinal toxicity.
46
47 238 III. Classification of HCQ retinopathy into different severity stages of disease.
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49 239 IV. Data collection training of medical office assistants (MOA) and research staff at the
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51 240 clinics.
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3 241 V. Data storage and transfer to the Eye Care Centre at Vancouver General Hospital (VGH)
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5
6 242 and Arthritis Research Canada.
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11 244 The second phase of the process was achieved through small group discussions of five
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13 245 participants. Each group was assigned one of the five main challenges and asked to brainstorm
14
15 246 logical and feasible solutions for the challenge which could be included in the SOP.
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19 247 Following the small group discussions, a representative from each group presented a summary
20
21 248 of their discussion to the large group. This permitted further discussion to elucidate key points
22
23 249 that had been most salient or missing from the small group discussions. The knowledge broker
24
25 250 then summarized the options for each of the main challenges and all participants voted. If 100%
26
27 251 agreement on the solution(s) for each of the challenges was not initially achieved, another cycle
28
29 252 of discussion was undertaken enabling consensus to be reached on the solutions for all
30
31 253 challenges.
32
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34 254 Consensus results/proposed solutions:

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37 255 The group made the following consensus statements for the five categories mentioned above
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39 256 (Figure 1- HCQ retinal toxicity screening protocol flowchart for INTACT study: The consensus
40
41 257 results).
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47 258 I. Standardization of SD-OCT image acquisition and automated VF exam assessment:
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51 259
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53 260 ✓ Only three types of SD-OCT machines are acceptable for this study: Spectralis
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55 261 OCT (Heidelberg Engineering), Cirrus HD-OCT (Carl Zeiss Meditec), and Topcon
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3 262 3D-OCT 2000 (Topcon Corporation). At least one of these three machines is
4
5
6 263 available in every retinal clinic participating in this study. Additionally, the same
7
8 264 machine(s) must be used for a patient at all of their visits.
9

10 265
11
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13 266 ✓ To completely demonstrate pathologies of the macular area including, foveal,
14
15 267 para-foveal and peri-foveal zones, macular SD-OCT scan should cover a
16
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18 268 minimum of 20 degrees x 20 degrees for non-Asian patients and 30 degrees x 30
19
20 269 degrees for Asian patients. Block size and raster technique will be machine-
21
22
23 270 specific. For Heidelberg SD-OCT machines, a 12 mm x 9 mm cube scan was
24
25 271 recommended.
26

27 272
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30 273 ✓ Each scan must be able to clearly delineate both inner and outer retinal bands.
31
32 274 Specifically, the outer retinal bands at the para-foveal and peri-foveal zones
33
34
35 275 should be in focus and clearly visible. The presence of vessel shadowing will
36
37 276 ensure a high-quality scan.
38

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41
42 278 ✓ SD-OCT imaging must be done for all patients as the main screening exam.
43
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45 279
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47 280 ✓ If a patient's SD-OCT scan is normal, that patient will be scheduled for their next
48
49 281 appointment in a year. However, if the scan is considered equivocal or
50
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52 282 abnormal, the patient must be evaluated with standard automated 10-2 VF
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54 283 (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) assessment. If the
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3 284 10-2 scan is also considered equivocal or abnormal, then a standard automated
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5 285 24-2 or 30-2 VF assessment must be done. For Asian participants, both the
6
7
8 286 standard automated 10-2 and 24-2 or 30-2 VF must be performed in all cases
9
10 287 with equivocal or abnormal SD-OCT scans.

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15 289 ✓ FAF imaging was defined as complementary (to the SD-OCT and automated VF)
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17
18 290 objective screening exam. Its performance will be left to the discretion of the
19
20 291 retina specialist network of the INTACT study, based on their clinical judgement
21
22 292 (not mandatory).

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29 294 II. Criteria for diagnosis of HCQ retinal toxicity:

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31 295 ✓ All patients on HCQ must be examined according to the standard of care and
32
33
34 296 current guidelines regardless of any comorbidities. However, diagnosis of HCQ
35
36 297 retinopathy will be determined by the clinician's (retina specialist network of
37
38 298 INTACT study) interpretation of results based on standard images that will be
39
40 299 sent to them as guidance packages which are in accordance with the peer
41
42
43 300 reviewed publications, of macular SD-OCT and standard automated VF findings
44
45 301 in HCQ retinal toxicity (16, 47). The standard images will be prepared by the
46
47
48 302 INTACT study team's experienced academic retinal specialists (D.M., K.P.V. and
49
50 303 S.L.).

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53 304 ✓ All scans must only be classified as no signs of HCQ retinal toxicity (normal),
54
55
56 305 suspicious signs of HCQ retinal toxicity (equivocal) or typical signs of HCQ retinal

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3 306 toxicity (abnormal) by the retinal specialist and recorded by checking the box
4
5
6 307 that applies in a reporting form that will be sent to researchers at the VGH Eye
7
8 308 Care Centre (see Supplementary File 2- Retina Specialist Reporting Form).
9
10
11 309 ✓ Abnormal, equivocal, and a random sample of normal scans (thirty in Year 1 and
12
13 310 Year 2) must be sent to the VGH Eye Care Centre for secondary review and
14
15 311 validation.
16
17
18 312 ✓ The three study team retinal specialists (D.M., K.P.V., and S.L.) will be
19
20 313 considered as the gold standard. Two of them (K.P.V. and S.L.) will review the
21
22 314 images of all patients reported as equivocal or abnormal by the “retina specialist
23
24 315 network of the INTACT study” in addition to the random sample of normal scans
25
26 316 (thirty in Year 1 and Year 2) from them. Confirmation of diagnosis is based on
27
28 317 the agreement between two reviewers at the VGH Eye Care Centre.
29
30
31
32 318 ✓ The third retina specialist (D.M.) will only review images with any discrepancy in
33
34 319 the diagnosis. Eventually the final decision will be achieved by the third masked
35
36 320 reviewer (agreement between D.M. and one of the first two reviewers).
37
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44
45 323 III. Severity stages of disease (i.e., classification of HCQ retinopathy into mild, moderate
46
47 324 and severe).
48
49 325 ✓ Retina specialists at their clinics will not need to classify the severity staging.
50
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3 326 ✓ The two study team retina specialists (K.P.V., and S.L.) will classify HCQ
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5
6 327 retinopathy as mild, moderate, or severe HCQ retinal toxicity after confirmation
7
8 328 of diagnosis.

9
10 329 ✓ Again, with any discrepancy in the severity staging by the first two reviewers,
11
12
13 330 the third masked reviewer (D.M.) will assess and make the final decision, which
14
15 331 is based on agreement of his and one of the two other reviewers' assessment.
16
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19
20 333 IV. Data collection training of medical office assistants (MOA) and research staff at the
21
22
23 334 clinics.

24
25 335 ✓ There will be a main research lead (N.D.) for all clinics and one research lead
26
27
28 336 assigned at each clinic (e.g., nurse, research coordinator, research assistant).
29
30 337 The main research lead will be responsible for training of the other centre leads
31
32 338 and the coordination of the overall flow at each centre.
33
34

35 339
36
37 340 V. Data storage and transfer to the VGH Eye Care Centre and Arthritis Research Canada:
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39
40 341 ✓ There are two types of data to be stored and transferred to Arthritis Research
41
42 342 Canada and the VGH Eye Care Centre, specifically the patient self-report and
43
44
45 343 retina specialist report questionnaires and the ocular imaging (i.e., SD-OCT and
46
47 344 automated VF assessment or FAF).

48
49 345 ✓ Questionnaires, including both patient self-report and retina specialist reports
50
51
52 346 will be stored in individual patient files in a locked filing cabinet at Arthritis
53
54 347 Research Canada. This data will be linked to provincial administrative health data
55
56

1
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3 348 by PopData upon completion of the study. The research team will be unable to
4
5
6 349 identify individuals after linkage.
7
8 350 ✓ A cloud server will be used to store the data including the SD-OCT digital images
9
10 351 as well as automated VF assessments, from the retina clinics, which will be
11
12 352 accessible to the three readers at the VGH Eye Care Centre. Briefly, there will be
13
14 353 a separate folder allocated for each retina clinic, wherein each clinic will only be
15
16 354 able to access and upload the images and data of their own patients. The three
17
18 355 readers at the VGH Eye Care Centre will be able to access all folders through a
19
20 356 secure website.
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26 357 Data analysis plan

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28
29 358 1) Determine the incidence rate of retinopathy in HCQ users with ≥ 5 years duration of
30
31 359 treatment: We will calculate the overall incidence and dose-specific risk (i.e., cumulative
32
33 360 incidence) of HCQ retinal toxicity. Each eligible and consenting individual will be
34
35 361 followed from the study baseline until the end of the 5-year study period, disenrollment
36
37 362 or death, whichever occurs first. These person-time data with events will then be used
38
39 363 to calculate the cumulative incidence, employing established methods for left truncated
40
41 364 data and the competing risk of death.
42
43
44
45 365 2) Determine the risk factors for HCQ retinopathy: We will examine the relationship of
46
47 366 purported risk factors for HCQ retinopathy among participants, including relevant
48
49 367 measures of HCQ exposure (daily dose, daily dose in mg/kg for actual body weight
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51 368 (ABW), daily dose in mg/kg for ideal body weight (IBW), total cumulative lifetime dose,
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3 369 and duration of exposure), other putative predictors (i.e., older age, female sex, chronic
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6 370 kidney disease, other concomitant drug use with potential retinal toxicity [i.e.,
7
8 371 tamoxifen, anastrozole] or underlying retinal disease), and any other factors that
9
10 372 emerge during the study period. First, we will compare the age-standardized incidence
11
12 373 rates of HCQ retinopathy according to the risk factor categories. Then, we will obtain
13
14 374 the point and interval estimates of the hazard ratio (HR) of each candidate risk factor for
15
16 375 the risk of incident HCQ retinopathy, mutually adjusting for potential risk factors. Also,
17
18 376 we will use Cox proportional hazard regression models, accounting for the competing
19
20 377 risk of death and left truncation of event time. (48-52)
21
22
23 378 3) Describe the clinical course of retinopathy following HCQ discontinuation: We will follow
24
25 379 all newly identified HCQ retinal toxicity cases on an annual basis during the study period
26
27 380 (5 years) and assess the rate of pathological progression of retinopathy, defined as any
28
29 381 worsening of both SD-OCT imaging and VF assessment. We will estimate the risk of
30
31 382 progression according to initial retinopathy stage (mild, moderate, and severe)
32
33 383 accounting for the competing risk of death. (53, 54)
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41 384 Strengths and limitations

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44 385 To the best of our knowledge, this is the first prospective, population-based cohort study
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46 386 designed to examine the incidence rate, risk factors and clinical course progression (after
47
48 387 discontinuation) of HCQ-induced retinal toxicity in Canada. Our access to province-wide
49
50 388 administrative health data for the total five million residents of BC is a significant strength.
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53 389 The estimated sample size is 5,508 patients including 1,346 SLE and 4,162 RA patients who
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3 390 have been on HCQ treatment for five years or more. In this prospective study, we will have
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6 391 person-time data with events and risk factors including but not limited to HCQ dose for
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8 392 ABW versus IBW, chronic renal failure, comorbidities and others, with annual updates of
9
10 393 data for five consecutive years. We will be able to calculate the cumulative incidence of
11
12 394 HCQ-induced retinopathy considering the competing risk of death as well as HRs for each
13
14 395 risk factor. These results will provide vital information for patients, physicians, and policy
15
16 396 makers.
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20

21 397 Our study benefits from the collaboration of retinal specialists from urban and rural parts of
22
23 398 BC. Our province-wide retinal specialist network developed a novel SOP during a consensus
24
25 399 meeting for screening and follow up of the patients based on the most recent AAO
26
27 400 guidelines. Our study is not without potential limitations. First, there may be participant
28
29 401 loss, due to declining to participate, emigration, and study drop-out. Another limitation of
30
31 402 our study is possible nonadherence to the amount of prescribed HCQ treatment.
32
33 403 PharmaNet data will capture medication dispensed, however participants taking less than
34
35 404 the prescribed dose, will not be captured. This issue can only be mitigated through
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37 405 evaluation of the serum level of HCQ, which should be taken into account in future studies.
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44 406 Privacy and confidentiality

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47 407 We have implemented measures to keep all personal information of patients secure, including
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49 408 names, contact information, Personal Health Numbers, self-report questionnaires, and medical
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51 409 reports. These will be kept in secure locations accessible only to a restricted number of study
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53 410 personnel at Arthritis Research Canada and retinal clinics. Patients' names will be replaced by a
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3 411 unique ID code upon patient's informed consent and enrollment in the study that will be
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6 412 consistent on every study document and imaging, throughout the study. The digital information
7
8 413 including the imaging will be housed on a secure cloud server with the most up-to-date security
9
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11 414 protections.

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17 416 Contributors: Conception and design of the study: J.A.A.Z., D.M. and J.M.E.

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20 417 Consensus meeting chair persons/moderators: A.H., D.E., D.M., G.M., J.E., J.A.A.Z., K.S., K.P.V.
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22 418 and R.B.M.

23
24
25 419 Drafting of the standard operating protocols and the manuscript: A.L., D.O., N.D. and S.M.

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28 420 Critical revision of the manuscript for important intellectual content: A.H., D.M., J.A.A.Z., J.E.,
29
30 421 M.D. and S.L.

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34 422 All authors gave final approval of the submitted manuscript.

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38
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47
48 427 the authors, and do not reflect the opinions or policies of the Data Steward(s).

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429 **References:**

- 430 1. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR
431 recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the
432 EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Annals Rheum Dis.*
433 2008 Feb;67(2):195-205.
- 434 2. Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. *Lupus.*
435 2008 Apr;17(4):271-3.
- 436 3. Canadian Hydroxychloroquine Study Group. A Randomized study of the effect of withdrawing
437 hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med.* 1991;324:150-4.
- 438 4. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic
439 lupus erythematosus. *Arthritis Rheum.* 2006 Aug;54(8):2550-7.
- 440 5. Yurkovich M, Vostretsova K, Chen W, Avina-Zubieta JA. Overall and cause-specific mortality in
441 patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res*
442 (Hoboken). 2014 Apr;66(4):608-16.
- 443 6. Dos Reis Neto ET, Kakehasi AM, de Medeiros Pinheiro M, Ferreira GA, Marques CDL, da Mota
444 LMH, et al. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated
445 inflammatory rheumatic diseases. *Adv Rheumatol.* 2020 Jun 9;60(1):32.
- 446 7. Worth C, Yusuf IH, Turner B, Gourier H, Brooks EE, Mort DO, et al. An audit of the use of
447 hydroxychloroquine in rheumatology clinics. *Rheumatol Adv Prac.* 2018;2(1):rky013.
- 448 8. Abarientos C, Sperber K, Shapiro DL, Aronow WS, Chao CP, Ash JY. Hydroxychloroquine in
449 systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. *Expert Opin Drug*
450 *saf.* 2011 Sep;10(5):705-14.
- 451 9. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, et al.
452 Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-
453 associated cardiac manifestations of neonatal lupus. *Circulation.* 2012 Jul 3;126(1):76-82.
- 454 10. Tsakonas E, Joseph L, Esdaile JM, Choquette D, Senécal JL, Cividino A, et al. A long-term study of
455 hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian
456 Hydroxychloroquine Study Group. *Lupus.* 1998;7(2):80-5.
- 457 11. Alarcon GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alen J, Bastian HM, et al. Effect of
458 hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA,
459 a multiethnic US cohort (LUMINA L). *Ann Rheum Dis.* 2007 Sep;66(9):1168-72.
- 460 12. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and
461 in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep.* 2011 Feb;13(1):77-80.
- 462 13. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis and*
463 *rheumatism.* 2006 Nov;54(11):3640-7.
- 464 14. Jorge A, McCormick N, Lu N, Zheng Y, Esdaile JM, De Vera M, et al. Hydroxychloroquine and
465 Mortality Among Patients with Systemic Lupus Erythematosus in the General Population. *Arthritis Care*
466 *Res (Hoboken).* 2020 May 14;10.
- 467 15. Hoque MR, Avina-Zubieta JA, De Vera MA, Qian Y, Esdaile JM, Xie H. Impact of Antimalarial
468 Adherence on Mortality among Patients with Newly Diagnosed Systemic Lupus Erythematosus: A
469 Population-based Cohort Study. *Arthritis Care Res (Hoboken).* 2021 Jan 7.
- 470 16. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, American Academy of Ophthalmology.
471 Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision).
472 *Ophthalmology.* 2016 Jun;123(6):1386-94.
- 473 17. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term
474 hydroxychloroquine therapy. *JAMA Ophthalmol.* 2014 Dec;132(12):1453-60.

- 1
2
3 475 18. Avina-Zubieta JA, Galindo-Rodriguez G, Newman S, Suarez-Almazor ME, Russell AS. Long-term
4 476 effectiveness of antimalarial drugs in rheumatic diseases. *Ann Rheum Dis*. 1998 Oct;57(10):582-7.
5 477 19. Mavrikakis I, Sfrikakis PP, Mavrikakis E, Rougas K, Nikolaou A, Kostopoulos C, et al. The incidence
6 478 of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal.
7 479 *Ophthalmology*. 2003 Jul;110(7):1321-6.
8 480 20. Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ, Peterson T. Incidence of hydroxychloroquine
9 481 retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum*. 1997
10 482 Aug;40(8):1482-6.
11 483 21. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Aymard G, Leroux G, Marra D, et al. Very low
12 484 blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of
13 485 systemic lupus erythematosus. *Ann Rheum Dis*. 2007 Jun;66(6):821-4.
14 486 22. Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, Le Guern V, Leroux G, Marra D, et al.
15 487 Adherence to treatment in systemic lupus erythematosus patients. *Best Prac Res Clin Rheumatol*. 2013
16 488 Jun;27(3):329-40.
17 489 23. Iudici M, Pantano I, Fasano S, Pierro L, Charlier B, Pigeon M, et al. Health status and
18 490 concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-
19 491 adherence in systemic lupus patients with prolonged inactive disease. *Lupus*. 2018 Feb;27(2):265-72.
20 492 24. Liu LH, Fevrier HB, Goldfien R, Hemmerling A, Herrinton LJ. Understanding Nonadherence with
21 493 Hydroxychloroquine Therapy in Systemic Lupus Erythematosus. *Rheumatol*. 2019 Oct;46(10):1309-15.
22 494 25. Costedoat-Chalumeau N, Houssiau F, Izmirly P, Le Guern V, Navarra S, Jolly M, et al. A
23 495 Prospective International Study on Adherence to Treatment in 305 Patients With Flaring SLE:
24 496 Assessment by Drug Levels and Self-Administered Questionnaires. *Clin Pharmacol Ther*. 2018
25 497 Jun;103(6):1074-82.
26 498 26. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy - implications of
27 499 research advances for rheumatology care. *Nat Rev Rheumatol*. 2018 Dec;14(12):693-703.
30 500 27. Jorge A, Rai SK, Choi HK. The Risk of Hydroxychloroquine Toxic Retinopathy and Its Risk Factors
31 501 in the Treatment of Rheumatic Diseases: A Systematic Review [abstract]. *Arthritis Rheumatol* . 2017;69
32 502 (suppl 10).
33 503 28. Rosenbaum JT, Costenbader KH, Desmarais J, Ginzler EM, Fett N, Goodman SM, et al. ACR, AAD,
34 504 RDS, and AAO 2020 Joint Statement on Hydroxychloroquine Use with Respect to Retinal Toxicity.
35 505 *Arthritis Rheumatol*. 2021 Feb 9.
36 506 29. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, et al. Development of the 25-
37 507 item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001 Jul;119(7):1050-8.
38 508 30. Aviña-Zubieta JA, Abrahamowicz M, Choi HK, Rahman MM, Sylvestre MP, Esdaile JM, et al. Risk
39 509 of cerebrovascular disease associated with the use of glucocorticoids in patients with incident
40 510 rheumatoid arthritis. *Ann Rheum Dis*. 2011;70:990-5.
41 511 31. Avina-Zubieta JA, McCormick N, Sayre, E.C. , Sadatsafavi M, Esdaile JM, Marra C. Longitudinal
42 512 Analysis of Direct Medical Costs for Systemic Lupus Erythematosus in British Columbia, Canada: a
43 513 Population-Based Study. *Ann Rheum Dis*. 2013;71:458.
44 514 32. Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with
45 515 rheumatoid arthritis, psoriatic arthritis and psoriasis. *Ann Rheum Dis*. 2010;69:2114-7.
46 516 33. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between
47 517 disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and
48 518 psoriasis. *JAMA*. 2011;305:2525-31.
49 519 34. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of
50 520 retinal detachment. *JAMA*. 2012 Apr 4;307(13):1414-9.
51 521 35. McCormick N, Reimer K, Famouri A, Marra CA, Avina-Zubieta JA. Filling the gaps in SARDs
52 522 research: collection and linkage of administrative health data and self-reported survey data for a general

- 1
2
3 523 population-based cohort of individuals with and without diagnoses of systemic autoimmune rheumatic
4 524 disease (SARDs) from British Columbia, Canada. *BMJ open*. 2017 Jun 21;7(6):e013977.
- 5 525 36. Bernatsky S, Lix L, O'Donnell S, Lacaille D, Network C. Consensus statements for the use of
6 526 administrative health data in rheumatic disease research and surveillance. *The Journal of rheumatology*.
7 527 2013 Jan;40(1):66-73.
- 8 528 37. British Columbia Ministry of Health [creator] (2017): Medical Services Plan (MSP) Payment
9 529 Information File. Population Data BC [publisher]. Data Extract. MOH (2017).
10 530 <https://www.popdata.bc.ca/data/health/msp>
- 11 531 38. Canadian Institute for Health Information [creator] (2017): Discharge Abstract Database
12 532 (Hospital Separations). Population Data BC [publisher]. Data Extract. MOH (2017).
13 533 <http://www.popdata.bc.ca/data/health/dad>
- 14 534 39. BC Ministry of Health [creator] (2018): PharmaNet. BC Ministry of Health [publisher]. Data
15 535 Extract. Data Stewardship Committee (2018). <http://www.popdata.bc.ca/data/health/PharmaNet>
- 16 536 40. BC Vital Statistics Agency [creator] (2017): Vital Statistics Deaths. Population Data BC [publisher].
17 537 Data Extract. BC Vital Statistics Agency (2017). <http://www.popdata.bc.ca/data/population/vsdeaths>
- 18 538 41. BC Cancer Registry Data (2017).. Population Data BC [publisher]. Data Extract. BC Cancer (2017).
19 539 <http://www.popdata.bc.ca/data/health/bccancer>.
- 20 540 42. Chang J, Rogers P, Lacaille D. Can American College of Rheumatology criteria for rheumatoid
21 541 arthritis be assessed using self-report data? – Comparison of self-reported data with chart review.
22 542 *Arthritis Rheum* 2011;63(Suppl):S49.
- 23 543 43. Arkema EV, Jonsen A, Ronnblom L, Svenungsson E, Sjowall C, Simard JF. Case definitions in
24 544 Swedish register data to identify systemic lupus erythematosus. *BMJ Open*. 2016 Jan 4;6(1):e007769.
- 25 545 44. Avina-Zubieta JA, Vostretsova K, De Vera MA, Sayre EC, Choi HK. The risk of pulmonary
26 546 embolism and deep venous thrombosis in systemic lupus erythematosus: A general population-based
27 547 study. *Semin Arthritis Rheum*. 2015 Oct;45(2):195-201.
- 28 548 45. McCormick N, Marra CA, Sadatsafavi M, Kopec JA, Aviña-Zubieta JA. Excess Productivity Costs of
29 549 Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjogren's Syndrome: A General Population-Based
30 550 Study. *Arthritis Care Res*. 2019 Jan.;71(1):142-54.
- 31 551 46. Eisner A, Luoh SW. Breast cancer medications and vision: effects of treatments for early-stage
32 552 disease. *Current Eye Research*. 2011 Oct;36(10):867-85.
- 33 553 47. Lally DR, Heier JS, Baumal C, Witkin AJ, Maler S, Shah CP, et al. Expanded spectral domain-OCT
34 554 findings in the early detection of hydroxychloroquine retinopathy and changes following drug cessation.
35 555 *Int Retina Vitreous*. 2016;2:18.
- 36 556 48. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of
37 557 Competing Risks. *Circulation*. 2016 Feb 9;133(6):601-9.
- 38 558 49. Geskus RB. Cause-Specific Cumulative Incidence Estimation and the Fine and Gray Model Under
39 559 Both Left Truncation and Right Censoring. *Biometrics*. 2011;67:39-49.
- 40 560 50. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model
41 561 specific population value and confidence interval estimation. *Stat Med*. 2004;23:2109-23.
- 42 562 51. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort
43 563 data: a simulation study. . *Stat Med*. 2004;23:3803-20.
- 44 564 52. Beyersmann J, Schumacher M. Time-dependent covariates in the proportional subdistribution
45 565 hazards model for competing risks. *Biostatistics* 2008;9:765-76.
- 46 566 53. Gaynor JJ, Feuer EJ, Tan CC, Wu DH, Little CR, Straus DJ, et al. On the use of cause-specific failure
47 567 and conditional failure probabilities: examples from clinical oncology data. *J Am Stats Assoc*
48 568 1993;88:400-9.

1
2
3 569 54. Beiser A, D'Agostino R, Seshadri SR, Sullivan LM, P.A. W. Computing estimates of incidence,
4 570 including lifetime risk: Alzheimer's disease in the Framingham Study. The Practical Incidence Estimators
5 571 (PIE) macro. Stat Med. 2000;19:1495-522.

6
7 572

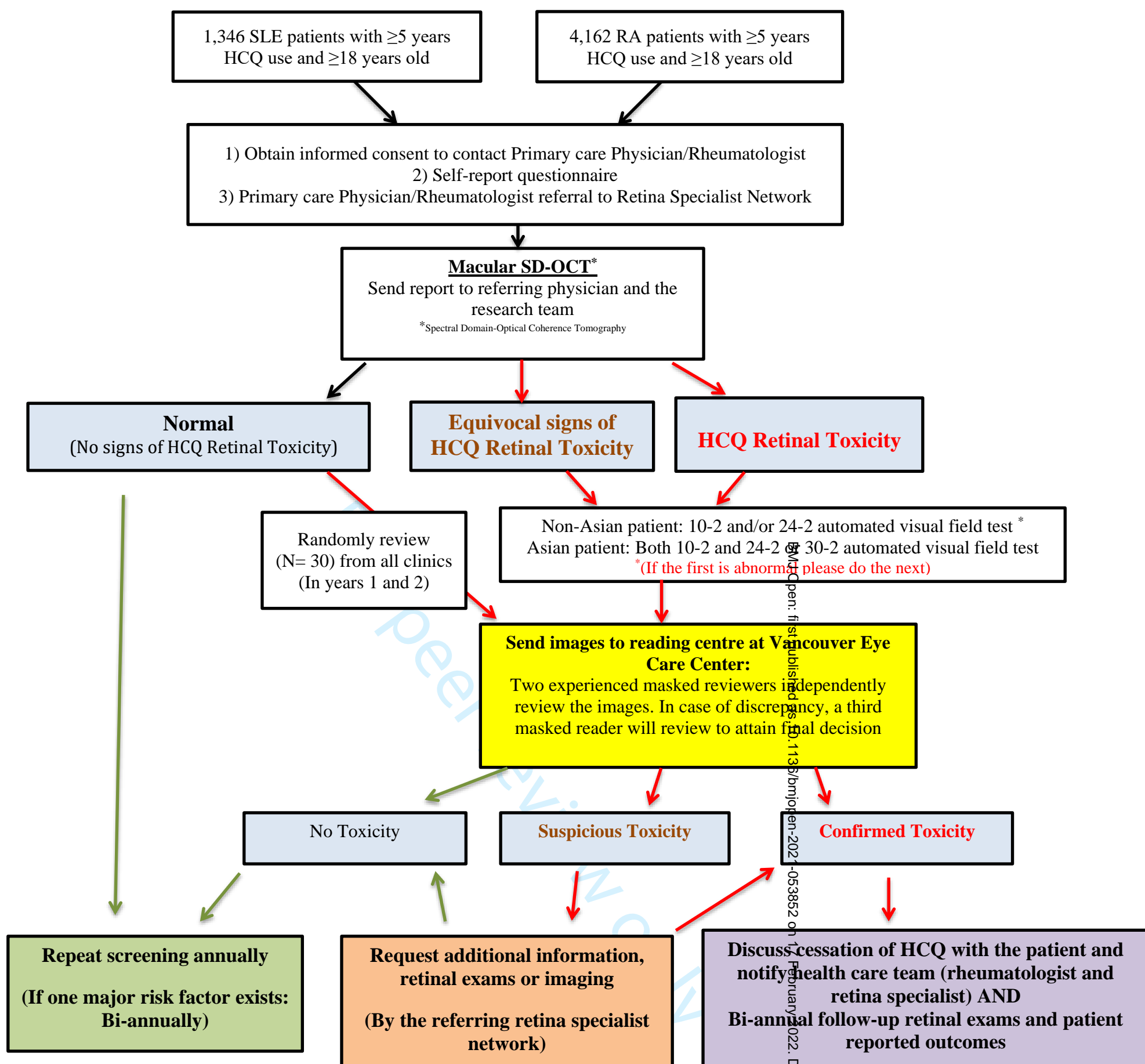
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16 575 Figure 1- HCQ Retinal Toxicity Screening Protocol Flowchart for INTACT Study: The Consensus

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18 576 Results

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



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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 anastrozole? 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

For peer review only

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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 Cirrus 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:



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:

For peer review only

Please turn to the next page

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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 20-6 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:

For peer review only

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	

1	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	
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	
14	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	
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	
20				
21	Other information			
22	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
23				
24				

*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, Vitreoretinal < OPHTHALMOLOGY, RHEUMATOLOGY, Medical retina < OPHTHALMOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

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3 1 **RetINal Toxicity And HydroxyChloroquine Therapy (INTACT) – Protocol for a**
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6 2 **prospective population-based cohort study**
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27 **Abstract:**

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

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

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3 43 abnormal images plus corresponding subjective test results via cloud-based server from each
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5
6 44 clinic to a reading center. Confirmation of HCQ retinal toxicity diagnoses and severity staging
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8 45 will be performed by three independent and masked reviewers. The incidence of HCQ retinal
9
10 46 toxicity will be calculated, accounting for the competing risk of death. Hazard ratios for each
11
12
13 47 risk factor will be calculated for the risk of HCQ retinopathy, after adjusting for confounders.
14
15
16 48 We will also estimate the risk of HCQ retinal toxicity progression over five years.

17
18
19 49 **Ethics and dissemination:** This study has received approval from the University of British
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21 50 Columbia Clinical Research Ethics Board [H20-00736] and the Vancouver Coastal Health
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23
24 51 Research Institute.

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26
27 52 **Strengths and limitations:**

- 28
29
30 53 ✓ To the best of our knowledge, this is the first prospective, population-based cohort
31
32 54 study designed to address the incidence rate, risk factors for and clinical course of
33
34 55 hydroxychloroquine (HCQ)-induced retinal toxicity and progression.
- 35
36
37
38 56 ✓ Access to British Columbia's (BC) administrative health data from the single-payer health
39
40 57 care system allowed us to establish a large population-based cohort of all individuals
41
42 58 with systemic lupus erythematosus or rheumatoid arthritis, exposed to HCQ for at least
43
44 59 five years in BC.
- 45
46
47
48 50 ✓ Linking participant self-report demographic and medical history, retinal imaging, and
49
50 61 administrative health data will allow for calculation of an accurate risk of HCQ-induced
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3 62 retinal toxicity, which will provide vital safety information for patients, physicians, and
4
5
6 63 policy makers.
7

8
9 64 ✓ A structured consensus meeting led to the development of a novel and pragmatic
10
11 65 standard operational protocol for the screening and follow up of patients on long-term
12
13 66 HCQ medication for retinal toxicity.
14
15

16
17 67 ✓ Five years of follow up may be inadequate to capture long-term results for the cases
18
19 68 with five to ten years of HCQ medication.
20
21

22 69 ✓ It is possible that nonadherence to the dosage of prescribed HCQ treatment may occur
23
24 70 before or during study. This issue can only be addressed through evaluation of serum
25
26
27 71 levels of HCQ, which should be considered in future studies.
28
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32
33 73 Key words: Hydroxychloroquine (HCQ); Retinal toxicity; Prospective population-based cohort
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36 74 study; Consensus; Macular SD-OCT; Reading center.
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75 **Introduction:**

76 The antimalarial medication hydroxychloroquine (HCQ) has been the cornerstone medication in
77 the treatment of systemic lupus erythematosus (SLE), and often in mild to moderate
78 rheumatoid arthritis (RA), alone or in combination; both diseases are chronic with marked
79 disability and premature death. (1-5) HCQ is inexpensive and has been shown to improve
80 survival in SLE patients and to reduce synovitis and physical disabilities in RA patients. (6-10)
81 HCQ is also considered to be one of the very well tolerated medications for rheumatic diseases
82 [*i.e.*, better than nonsteroidal anti-inflammatory drugs, like ibuprofen or naproxen], (11, 12)
83 and is considered sufficiently safe to be recommended for pregnant patients with SLE. (13, 14)
84 A landmark trial led by Esdaile et al., showed that HCQ discontinuation after achieving disease
85 control, led to a 2.5 times higher risk of SLE flare up and 6.1 times higher risk of severe flare up
86 in vital organs (e.g., kidney involvement, vasculitis) within 6 months of HCQ withdrawal. (3)
87 Moreover, a long-term study by the same group, on the effect of HCQ withdrawal in SLE, using
88 an intent-to-treat analysis, showed a potential protective effect against a major flare for those
89 randomized to continue HCQ (OR=0.43 [95% CI: 0.17, 1.12]). (15) These findings had a
90 significant impact on clinical practice, making HCQ a universal therapy in SLE regardless of
91 disease activity and severity. Since then, many studies have confirmed wide-ranging benefits of
92 HCQ, including improved survival, reduced disease activity; and lower risks of nephritis,
93 pregnancy complications, venous thromboembolism, dyslipidemia, and insulin resistance in
94 patients with SLE. (16-18) Recently, a retrospective population-based study by our group using
95 the administrative health data of the residents of British Columbia (BC), Canada with incident

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3 96 SLE and incident HCQ use between 1997 and 2015 showed a 71% and 83% lower risk of death
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6 97 among SLE patients, who adhered to HCQ in comparison to SLE patients, who were non-
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8 98 adherent or discontinued the medication, respectively. (6, 7)
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10
11 99 Despite being considered relatively safe, it has been reported that with long-term use, HCQ can
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14 100 accumulate in the retinal pigment epithelial cells and may cause progressive outer retinal
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16 101 toxicity with retinal pigment epithelial and photoreceptor cell death and secondary vision loss.
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18 102 Based on the accumulating evidence of HCQ retinal toxicity, the American Academy of
19
20
21 103 Ophthalmology (AAO) recommends annual screening for patients receiving HCQ for five years
22
23 104 or more. (19) Retinal toxicity had a previously estimated occurrence of 0.5-2% in long-term
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25
26 105 users. (19) However, a 2014 retrospective study using the US Kaiser Permanente Northern
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28 106 California (KPNC) database demonstrated that among users of HCQ with use ≤ 5 mg/kg of their
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31 107 real body weight, the risk was $< 2\%$ for five to ten years of therapy, but almost 20% after 20
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33 108 years of use. Conversely, patients with a mean daily use > 5 mg/kg had approximately a 10%
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36 109 risk of retinal toxicity for five to ten years of HCQ use and almost a 40% risk after 20 years. (20)
37
38 110 This is at least 10 times higher than previously published rates and caused alarm to patients and
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41 111 physicians. (21-23) Retinal toxicity secondary to HCQ is a major concern expressed by patients
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43 112 and clinicians. It is one of the main reasons for non-adherence to HCQ. (24-28) However, this
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46 113 study reported 32% missing data and did not adjust for the competing risk of death, thus results
47
48 114 might have been susceptible to selection bias and overestimation of the true risk. (20, 29)
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51 115 A systematic review on the risk of HCQ retinopathy and its risk factors in patients with
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54 116 rheumatic diseases found that most previous studies have been case series or retrospective
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56 117 cohorts. (30) This included a few prospective studies, all of which were limited in size (58 to 225
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3 118 patients) and duration of follow-up (1 to 3 years). (22, 29, 30) Recently a joint statement has
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6 119 been published by the American College of Rheumatology, the AAO, the American Academy of
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8 120 Dermatology and Rheumatologic Dermatology Society, on HCQ ocular safety. They indicated
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11 121 that there is a critical lack of data from a population-based prospective study on HCQ retinal
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13 122 toxicity. (31) A prospective study to better estimate the risk, risk factors and clinical course of
14
15 123 HCQ retinal toxicity is therefore needed.

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18 124 To address this, we established a prospective population-based cohort study to follow patients
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20
21 125 with RA and SLE with a minimum of five years of HCQ use, for potential retinal toxicity. To
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23 126 enable development of a standard operating protocol (SOP) for this study, a consensus meeting
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25
26 127 was convened among board certified practicing rheumatologists and retinal specialists from BC,
27
28 128 including specialists from both urban and rural areas. The objective of the meeting was to
29
30
31 129 identify and agree upon a SOP for screening and follow up for the retinal exams and
32
33 130 assessments. The SOP was to align with the most up to date principles of evidence-based
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35
36 131 screening protocols for HCQ retinal toxicity, feasible in a routine practice of retinal
37
38 132 ophthalmologists to maximize patient and practitioner participation.

39 40 41 133 **Cohort Description/Methods:**

42 43 44 45 134 **Design:**

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48 135 A prospective population-based cohort study among patients diagnosed with RA or SLE, with
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51 136 five or more years HCQ use, between January 1990 and December 2020, in BC and who were
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53 137 alive. The patients will be followed for at least five years, from July 2021 to Dec 2026.

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3 138 **Goals:**
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7 139 The main aims of our prospective and population-based study are to: 1) determine the
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9 140 incidence rate of retinopathy in HCQ users of ≥ 5 years duration of treatment, 2) determine the
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11 141 risk factors for HCQ retinopathy and 3) describe the clinical course of retinopathy following
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14 142 HCQ discontinuation, based on retinal examination, multimodal retinal imaging, visual fields
15
16 143 and patient reported outcomes from the 25-item National Eye Institute Visual Function
17
18
19 144 Questionnaire (NEI VFQ-25). (32)
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22 145 **Data source:**
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24

25 146 We will use administrative data extracted from Population Data BC (PopData) which is an
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27
28 147 extensive data resource for applied health services and population health research used by our
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30 148 group and others. (33-39) PopData covers the entire population of BC from 1990 onwards (5.1
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33 149 million in 2021). Individuals can be traced over time and ultimately as the data expands
34
35 150 longitudinally, over their lifespan. The main linkable databases include the following files:
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37
38 151 Medical Services Plan (physician visits and procedures data) (40), Hospital Separation (discharge
39
40 152 summaries including up to 25 diagnostic codes) (41), PharmaNet (all medications dispensed for
41
42
43 153 all BC residents) (42), Vital Statistics (date and cause of death) (43) and the BC Cancer registry
44
45 154 (44). We have previously developed a unique Laboratory Services link that provides laboratory
46
47
48 155 results linked to the administrative data as well as survey data collected from consenting
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50 156 individuals.
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53 157 **Patient and Public Involvement:**
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3 158 No patient was involved in the development of the research question and outcome measures,
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6 159 study design and conduct of study.
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9 160 Study population (SLE and RA cohorts):
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11
12 161 Adults (aged ≥ 18 years) with RA or SLE were identified from outpatient physician billing files or
13
14 162 from the hospital discharge database using International Classification of Diseases ninth (ICD-9)
15
16 163 and tenth (ICD-10) revision diagnostic codes. SLE and RA cases are defined using at least two
17
18 164 ICD codes for SLE and RA, at least 2 months apart within a 2-year window period from 1990-
19
20 165 2020. The validity of this algorithm to identify RA patients has been evaluated to have a positive
21
22 166 predictive value (PPV) of 82%. (45) Similarly, for identifying SLE patients, the validity of this
23
24 167 algorithm when one ICD code is from hospitalization and the other by a rheumatologist, has
25
26 168 been evaluated to have a PPV of 97% in Swedish registry data. (46) In our previous studies,
27
28 169 > 80% of SLE cases had at least one code from hospitalization or from a rheumatologist. (38, 47,
29
30 170 48)
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37 171 Using these algorithms, we identified 4,104 SLE patients and 21,265 RA patients who had
38
39 172 started HCQ since January 1, 1997 in BC. Of those, 1,346 SLE and 4,162 RA patients (total N =
40
41 173 5,508) had taken HCQ for at least five years by December 2020. Only rare cases who had used
42
43 174 chloroquine before commencing HCQ for SLE or RA will be excluded from this study. There will
44
45 175 be no exclusion criteria for patients with any underlying systemic disease, ocular disease and/or
46
47 176 ocular surgeries with macular involvement. These may include diabetic macular edema, cystoid
48
49 177 macular edema, retinal vascular occlusive disease, age-related macular degeneration, inherited
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51 178 retinal dystrophy, and uveitis. However, patients with advanced macular anatomical alterations
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3 179 due to comorbidities, which could interfere with an HCQ retinal toxicity diagnosis, may be
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5
6 180 excluded in data analysis (with provided explanation).
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8

9 181 **Recruitment:**

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11
12 182 Eligible participants identified from our population-based RA and SLE database who fulfill the
13
14
15 183 inclusion criteria will receive an invitation letter containing the study information as well as a
16
17 184 consent form. After obtaining informed consent from patients, we will contact the
18
19
20 185 rheumatologists or primary care physicians to inform them of their patient's participation in the
21
22 186 study and send reminders for baseline screening and annual referrals, as per 2016 AAO
23
24 187 guidelines and current standard of care, to the participating retina specialists' clinics who we
25
26
27 188 will call the "retina specialist network of the INTACT study". Rheumatologists and primary care
28
29
30 189 physicians throughout BC may also refer eligible patients based on the inclusion criteria to the
31
32 190 retina specialist network of the INTACT study, after obtaining informed consent.
33
34

35 191 **Self-report questionnaire:**

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37
38 192 Participants will fill out a self-report questionnaire (See Supplementary File 1 – Patient self-
39
40
41 193 report questionnaire) to collect information on risk factors, confounders, and patient reported
42
43 194 outcomes, at the time of their first retina exam as part of this study. This data will be updated
44
45
46 195 at each annual visit. The survey questionnaire will collect information on potential risk factors
47
48 196 such as chronic kidney disease, diabetes, hypertension, liver disease, retinal or macular disease
49
50
51 197 as well as comorbidities, race, current HCQ dose, weight, height, and disease duration. (19)
52
53 198 Data on medications with a known risk of retinopathy (e.g. tamoxifen, anastrozole) will be
54
55
56 199 collected in the self-report questionnaire as well as obtained from PharmaNet. (49)
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3 200 Patients with the confirmed diagnosis of HCQ-induced retinopathy will be asked to fill out the
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5
6 201 NEI VFQ-25, to provide a better understanding of the impact of this side effect on their daily
7
8 202 lives. (32)
9

10 11 203 Consensus description/Methods: 12

13
14 204 On December 14, 2019, a consensus meeting was convened in Richmond, BC. Participants in
15
16
17 205 the consensus meeting were project team members, including, three board-certified academic
18
19
20 206 retinal specialists (D.A.L.M., K.P.V., S.D.L.), three board-certified academic rheumatologists
21
22 207 (J.A.A.Z. J.M.E., K.S.), one pharmaco-epidemiologist (M.E.), and one knowledge broker (A.H.). All
23
24
25 208 practicing retinal specialists in BC were invited (n= 27), of which 18 attended the consensus
26
27 209 meeting and agreed to participate in the study (the retina specialist network of the INTACT
28
29
30 210 study). In addition, research coordinators from ophthalmology clinics, research staff from
31
32 211 Arthritis Research Canada and a guest speaker (Ronald B. Melles, M.D.) attended the meeting.
33
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35 212 The consensus meeting commenced with a presentation by the guest speaker who highlighted
36
37
38 213 and discussed key findings from the KPNC study. Two academic retinal specialists (K.P.V.,
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40 214 S.D.L.) then gave presentations, highlighting key points from the AAO 2016 revised
41
42
43 215 recommendations on HCQ retinal toxicity screening exams by SD-OCT imaging and automated
44
45 216 visual field (VF) test.
46
47
48 217 After the presentations, two consensus sessions, led by the knowledge broker, were held to
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51 218 identify and address the main challenges that were highlighted in the presentations and were
52
53 219 pertinent to developing the SOP:
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3 220 1) To develop the process for annual HCQ retinal toxicity screening and follow up exams by
4
5
6 221 the retina specialist network of the INTACT study for patients with an HCQ retinal
7
8 222 toxicity diagnosis. These were to be based on the latest AAO 2016 revised
9
10 223 recommendations (16) using at least one objective test of three potential options: SD-
11
12 224 OCT, Fundus Auto-fluorescence (FAF) or Multifocal Electroretinography (mfERG)
13
14 225 confirming the subjective standard automated VF assessment.
15
16
17 226 2) To define the standardized criteria for detecting normal versus abnormal SD-OCT
18
19 227 imaging, define equivocal cases versus definite cases, and determine appropriate follow
20
21 228 up procedures for patients in each group.
22
23
24 229 3) To determine standardized severity stages of retinal toxicity in cases with abnormal
25
26 230 diagnoses.
27
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30

31 231 The consensus session began with individual reflection. Participants were asked to
32
33 232 independently identify and record on post-it notes, potential concerns regarding the
34
35 233 implementation of the standardized screening and operational protocols relevant to their
36
37 234 routine office practice and the potential challenges with eye examination protocols, SD-OCT
38
39 235 imaging and automated VF assessment. The knowledge broker then collected and categorized
40
41 236 the responses. The categories were shared with participants who then voted to identify the
42
43 237 following five main challenges:
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47

- 48 238 I. Standardization of SD-OCT image acquisition and automated VF assessment.
49
50
51 239 II. Criteria for diagnosis of HCQ retinal toxicity.
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53 240 III. Classification of HCQ retinopathy into different severity stages of disease.
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3 241 IV. Data collection training of medical office assistants (MOA) and research staff at the
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6 242 clinics.

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8 243 V. Data storage and transfer to the Eye Care Centre at Vancouver General Hospital (VGH)
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10 244 and Arthritis Research Canada.

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15
16 246 The second phase of the process was achieved through small group discussions of five
17
18 247 participants. Each group was assigned one of the five main challenges and asked to brainstorm
19
20
21 248 logical and feasible solutions for the challenge which could be included in the SOP.

22
23
24 249 Following the small group discussions, a representative from each group presented a summary
25
26 250 of their discussion to the large group. This permitted further discussion to elucidate key points
27
28
29 251 that had been most salient or missing from the small group discussions. The knowledge broker
30
31 252 then summarized the options for each of the main challenges and all participants voted. If 100%
32
33 253 agreement on the solution(s) for each of the challenges was not initially achieved, another cycle
34
35
36 254 of discussion was undertaken enabling consensus to be reached on the solutions for all
37
38
39 255 challenges.

40
41
42 256 Consensus results/proposed solutions:

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44
45 257 The group made the following consensus statements for the five categories mentioned above
46
47
48 258 (Figure 1- HCQ retinal toxicity screening protocol flowchart for INTACT study: The consensus
49
50 259 results).

51
52
53 260 I. Standardization of SD-OCT image acquisition and automated VF exam assessment:

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3 262 ✓ Only three types of SD-OCT machines are acceptable for this study: Spectralis
4
5
6 263 OCT (Heidelberg Engineering), Cirrus HD-OCT (Carl Zeiss Meditec), and Topcon
7
8 264 3D-OCT 2000 (Topcon Corporation). At least one of these three machines is
9
10
11 265 available in every retinal clinic participating in this study. Additionally, the same
12
13 266 machine(s) must be used for a patient at all of their visits.

14
15 267
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17
18 268 ✓ To completely demonstrate pathologies of the macular area including, foveal,
19
20 269 para-foveal and peri-foveal zones, macular SD-OCT scan should cover a
21
22
23 270 minimum of 20 degrees x 20 degrees for non-Asian patients and 30 degrees x 30
24
25 271 degrees for Asian patients. This difference in macular SD-OCT scanning is based
26
27
28 272 on the AAO guidelines for HCQ retinopathy screening recommendations,
29
30 273 according to the findings on racial differences for HCQ retinopathy involvement
31
32 274 of macula. (19, 50) Block size and raster technique will be machine-specific. For
33
34
35 275 Heidelberg SD-OCT machines, a 12 mm x 9 mm cube scan was recommended.

36
37 276
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39
40 277 ✓ Each scan must be able to clearly delineate both inner and outer retinal bands.
41
42 278 Specifically, the outer retinal bands at the para-foveal and peri-foveal zones
43
44
45 279 should be in focus and clearly visible. The presence of vessel shadowing will
46
47 280 ensure a high-quality scan.

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49 281
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52 282 ✓ SD-OCT imaging must be done for all patients as the main screening exam.
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3 284 ✓ If a patient's SD-OCT scan is normal, that patient will be scheduled for their next
4
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6 285 appointment in a year. However, if the scan is considered equivocal or
7
8 286 abnormal, the patient must be evaluated with standard automated 10-2 VF
9
10
11 287 (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) assessment. If the
12
13 288 10-2 scan is also considered equivocal or abnormal, then a standard automated
14
15 289 24-2 or 30-2 VF assessment must be done. For Asian participants, both the
16
17
18 290 standard automated 10-2 and 24-2 or 30-2 VF must be performed in all cases
19
20 291 with equivocal or abnormal SD-OCT scans.
21
22

23 292
24
25 293 ✓ FAF imaging was defined as complementary (to the SD-OCT and automated VF)
26
27
28 294 objective screening exam. Its performance will be left to the discretion of the
29
30 295 retina specialist network of the INTACT study, based on their clinical judgement
31
32 296 (not mandatory).
33
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37
38 298 II. Criteria for diagnosis of HCQ retinal toxicity:
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40
41 299 ✓ All patients on HCQ must be examined according to the standard of care and
42
43
44 300 current guidelines regardless of any comorbidities. However, diagnosis of HCQ
45
46 301 retinopathy will be determined by the clinician's (retina specialist network of
47
48 302 INTACT study) interpretation of results based on standard images that will be
49
50
51 303 sent to them as guidance packages which are in accordance with the peer
52
53 304 reviewed publications, of macular SD-OCT and standard automated VF findings
54
55
56 305 in HCQ retinal toxicity (19, 51). The standard images will be prepared by the
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3 306 INTACT study team's experienced academic retinal specialists (D.A.L.M., K.P.V.
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5
6 307 and S.D.L.).
7
8 308 ✓ All scans must only be classified as no signs of HCQ retinal toxicity (normal),
9
10 309 suspicious signs of HCQ retinal toxicity (equivocal) or typical signs of HCQ retinal
11
12 310 toxicity (abnormal) by the retinal specialist and recorded by checking the box
13
14 311 that applies in a reporting form that will be sent to researchers at the VGH Eye
15
16 312 Care Centre (see Supplementary File 2- Retina Specialist Reporting Form).
17
18 313 ✓ Abnormal, equivocal, and a random sample of normal scans (thirty in Year 1 and
19
20 314 Year 2) must be sent to the VGH Eye Care Centre for secondary review and
21
22 315 validation.
23
24 316 ✓ The three study team retinal specialists (D.A.L.M., K.P.V., and S.D.L.) will be
25
26 317 considered as the gold standard. Two of them (K.P.V. and S.D.L.) will review the
27
28 318 images of all patients reported as equivocal or abnormal by the "retina specialist
29
30 319 network of the INTACT study" in addition to the random sample of normal scans
31
32 320 (thirty in Year 1 and Year 2) from them. Confirmation of diagnosis is based on
33
34 321 the agreement between two reviewers at the VGH Eye Care Centre.
35
36 322 ✓ The third retina specialist (D.A.L.M.) will only review images with any
37
38 323 discrepancy in the diagnosis. Eventually the final decision will be achieved by the
39
40 324 third masked reviewer (agreement between D.A.L.M. and one of the first two
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42 325 reviewers).
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3 328 III. Severity stages of disease (i.e., classification of HCQ retinopathy into mild, moderate
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5
6 329 and severe).
- 7
8 330 ✓ Retina specialists at their clinics will not need to classify the severity staging.
9
10 331 ✓ The two study team retina specialists (K.P.V. and S.D.L.) will classify HCQ
11
12 332 retinopathy as mild, moderate, or severe HCQ retinal toxicity after confirmation
13
14 333 of diagnosis.
15
16 334 ✓ Again, with any discrepancy in the severity staging by the first two reviewers,
17
18 335 the third masked reviewer (D.A.L.M.) will assess and make the final decision,
19
20 336 which is based on agreement of his and one of the two other reviewers'
21
22 337 assessment.
23
24
25
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27 338
- 28
29 339 IV. Data collection training of medical office assistants (MOA) and research staff at the
30
31 340 clinics.
32
33
34 341 ✓ There will be a main research lead (N.D.) for all clinics and one research lead
35
36 342 assigned at each clinic (e.g., nurse, research coordinator, research assistant).
37
38 343 The main research lead will be responsible for training of the other centre leads
39
40 344 and the coordination of the overall flow at each centre.
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- 45
46 346 V. Data storage and transfer to the VGH Eye Care Centre and Arthritis Research Canada:
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48 347 ✓ There are two types of data to be stored and transferred to Arthritis Research
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50 348 Canada and the VGH Eye Care Centre, specifically the patient self-report and
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3 349 retina specialist report questionnaires and the ocular imaging (i.e., SD-OCT and
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6 350 automated VF assessment or FAF).

7
8 351 ✓ Questionnaires, including both patient self-report and retina specialist reports
9
10 352 will be stored in individual patient files in a locked filing cabinet at Arthritis
11
12
13 353 Research Canada. This data will be linked to provincial administrative health data
14
15 354 by PopData upon completion of the study. The research team will be unable to
16
17
18 355 identify individuals after linkage.

19
20 356 ✓ A cloud server will be used to store the data including the SD-OCT digital images
21
22 357 as well as automated VF assessments, from the retina clinics, which will be
23
24
25 358 accessible to the three readers at the VGH Eye Care Centre. Briefly, there will be
26
27
28 359 a separate folder allocated for each retina clinic, wherein each clinic will only be
29
30 360 able to access and upload the images and data of their own patients. The three
31
32 361 readers at the VGH Eye Care Centre will be able to access all folders through a
33
34
35 362 secure website.

363 Data analysis plan

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

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2
3 369 to calculate the cumulative incidence, employing established methods for left truncated
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6 370 data and the competing risk of death.

7
8 371 2) Determine the risk factors for HCQ retinopathy: We will examine the relationship of
9
10 372 purported risk factors for HCQ retinopathy among participants, including relevant
11
12 373 measures of HCQ exposure (daily dose, daily dose in mg/kg for actual body weight
13
14 374 (ABW), daily dose in mg/kg for ideal body weight (IBW), total cumulative lifetime dose,
15
16 375 and duration of exposure), other putative predictors (i.e., older age, female sex, chronic
17
18 376 kidney disease, other concomitant drug use with potential retinal toxicity [i.e.,
19
20 377 tamoxifen, anastrozole] or underlying retinal disease), and any other factors that
21
22 378 emerge during the study period. First, we will compare the age-standardized incidence
23
24 379 rates of HCQ retinopathy according to the risk factor categories. Then, we will obtain
25
26 380 the point and interval estimates of the hazard ratio (HR) of each candidate risk factor for
27
28 381 the risk of incident HCQ retinopathy, mutually adjusting for potential risk factors. Also,
29
30 382 we will use Cox proportional hazard regression models, accounting for the competing
31
32 383 risk of death and left truncation of event time. (52-56)

33
34
35 384 3) Describe the clinical course of retinopathy following HCQ discontinuation: We will follow
36
37 385 all newly identified HCQ retinal toxicity cases on an annual basis during the study period
38
39 386 (5 years) and assess the rate of pathological progression of retinopathy, defined as any
40
41 387 worsening of both SD-OCT imaging and VF assessment. We will estimate the risk of
42
43 388 progression according to initial retinopathy stage (mild, moderate, and severe)
44
45 389 accounting for the competing risk of death. (57, 58)
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3 390 4) Determine the level of agreement between the reviewers at the reading center (gold
4
5
6 391 standard) and the network of retina specialists: We will use Cohen's kappa statistic to
7
8 392 measure agreement on the HCQ retinopathy diagnosis (normal versus equivocal versus
9
10 393 abnormal) between the reviewer's at the reading center and the network of retina
11
12
13 394 specialists (interrater). We will also measure the level of agreement both on the HCQ
14
15 395 retinopathy diagnosis and on the HCQ retinopathy staging, between the reviewers at
16
17
18 396 the reading center (intrarater).

21 397 Strengths and limitations

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23
24 398 To the best of our knowledge, this is the first prospective, population-based cohort study
25
26
27 399 designed to examine the incidence rate, risk factors and clinical course progression (after
28
29 400 discontinuation) of HCQ-induced retinal toxicity in Canada. Our access to province-wide
30
31
32 401 administrative health data for the total five million residents of BC is a significant strength.
33
34 402 Our estimated sample size is 5,508 patients (including 1,346 SLE and 4,162 RA patients) of
35
36
37 403 those who have been on HCQ treatment for five years or more. In this prospective study,
38
39 404 we will have person-time data with events and risk factors including but not limited to HCQ
40
41
42 405 dose for ABW versus IBW, chronic renal failure, comorbidities and others, with annual
43
44 406 updates of data for five consecutive years. We will be able to calculate the cumulative
45
46
47 407 incidence of HCQ-induced retinopathy considering the competing risk of death as well as
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49 408 HRs for each risk factor. These results will provide vital information for patients, physicians,
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51 409 and policy makers.
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3 410 Our study benefits from the collaboration of retinal specialists from urban and rural parts of
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5
6 411 BC. Our province-wide retinal specialist network developed a novel SOP during a consensus
7
8 412 meeting for screening and follow up of the patients based on the most recent AAO
9
10 413 guidelines. Our study is not without potential limitations. First, there may be participant
11
12
13 414 loss, due to declining to participate, emigration, and study drop-out. We include patients
14
15 415 with five years or more of HCQ use in both SLE and RA cohorts, but there is a potential
16
17
18 416 limitation for 18% of patients in the RA cohort to have a false positive diagnosis of RA due to
19
20 417 the 82% PPV by the algorithm we are using to identify RA patients. Another limitation of our
21
22
23 418 study is possible non-adherence to the amount of prescribed HCQ treatment. PharmaNet
24
25 419 data will capture medication dispensed, however participants taking less than the
26
27
28 420 prescribed dose, will not be captured. This issue can only be mitigated through evaluation
29
30 421 of the serum level of HCQ, which should be taken into account in future studies. Another
31
32
33 422 potential limitation of our study is that we may not be able to collect adequate information
34
35 423 to evaluate HCQ retinopathy in patients with concurrent retinal disease because they may
36
37
38 424 have already avoided starting HCQ medication.

40 425 Privacy and confidentiality

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44 426 We have implemented measures to keep all personal information of patients secure, including
45
46 427 names, contact information, Personal Health Numbers, self-report questionnaires, and medical
47
48
49 428 reports. These will be kept in secure locations accessible only to a restricted number of study
50
51 429 personnel at Arthritis Research Canada and retinal clinics. Patients' names will be replaced by a
52
53
54 430 unique ID code upon patient's informed consent and enrollment in the study that will be

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2
3 431 consistent on every study document and imaging, throughout the study. The digital information
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5
6 432 including the imaging will be housed on a secure cloud server with the most up-to-date security
7
8 433 protections.

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11 434 **Ethics and dissemination:**

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14
15 435 The INTACT study was approved by the University of British Columbia's Clinical Research Ethics
16
17 436 Board (H20-00736) and the Vancouver Coastal Health Research Institute (V20-00736). All
18
19 437 participants will provide informed consent before inclusion in this study. Study results will be
20
21
22 438 disseminated via peer-reviewed scientific journals and will be presented to academics and
23
24 439 researchers at scientific conferences. A plain language summary of study results will be
25
26
27 440 disseminated among participants following study completion.

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29
30 441 **Contributors:**

31
32
33 442 Substantial contributions to the conception or design of the work: J.A.A.Z, J.M.E., S.D.L,
34
35 443 D.A.L.M.

36
37
38
39 444 Substantial contributions to the planning and implementation of the work: B.A., R.D.B., S.B.B.,
40
41 445 M.B., L.C., M.D., M.E., M.E., D.G., E.H., H.H., M.H., A.J., A.L., Z.M., E.N., K.P.V., S.S., K.S.

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43
44 446 Consensus meeting chair persons/moderators: J.A.A.Z., A.H., D.A.L.M., J.M.E., K.P.V., K.S.

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47 447 Drafting of the work: N.D., A.L., S.M., D.O.

48
49
50 448 Revising the work critically for important intellectual content: J.A.A.Z., N.D., M.D., J.M.E., A.H,
51
52 449 S.D.L., D.A.L.M.

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4
5

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11
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13

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17 455 the authors, and do not reflect the opinions or policies of the Data Steward(s).
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457 **References:**

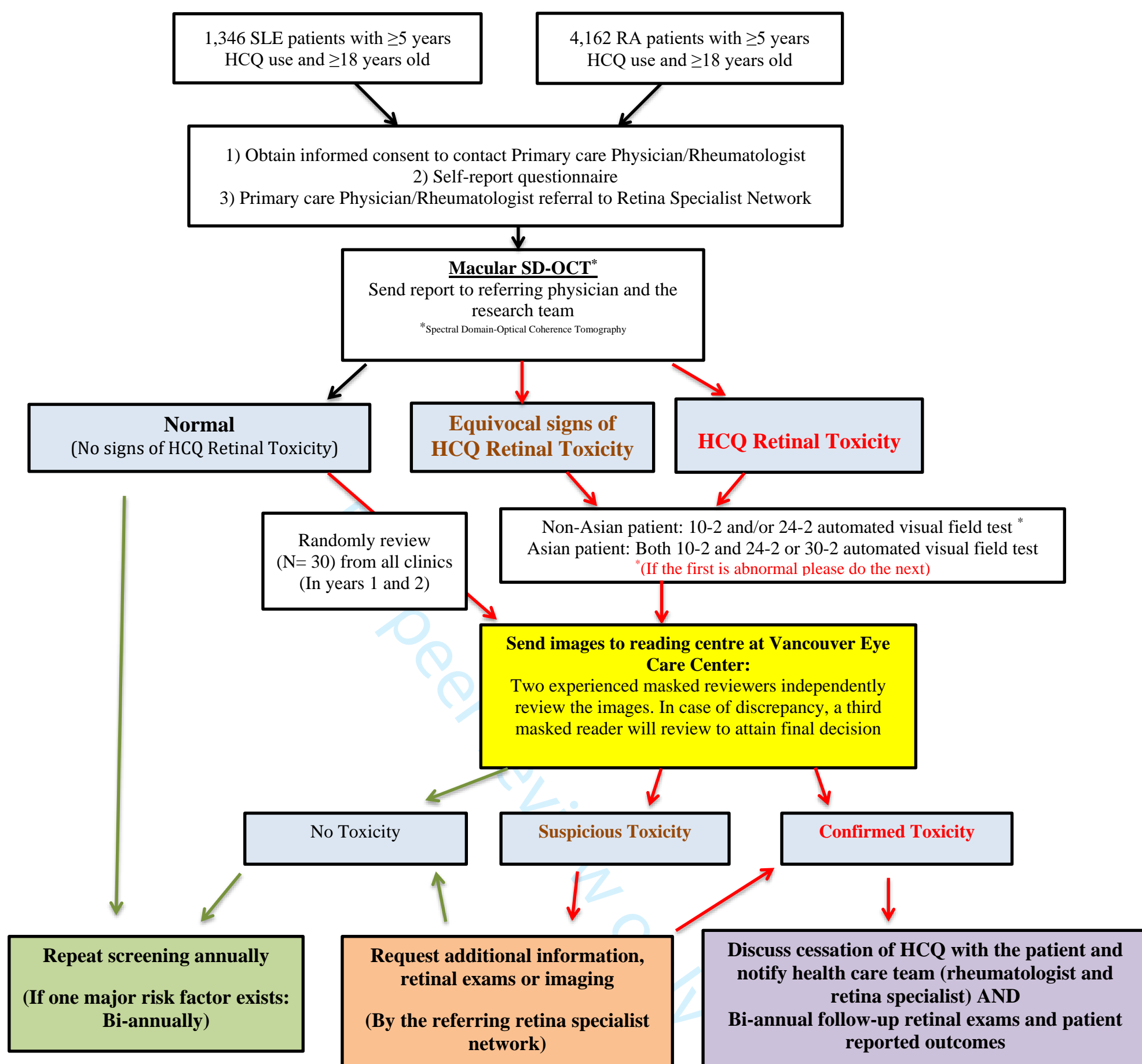
- 458 1. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR
459 recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the
460 EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Annals of the*
461 *rheumatic diseases*. 2008;67(2):195-205.
- 462 2. Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. *Lupus*.
463 2008;17(4):271-3.
- 464 3. Canadian, Hydroxychloroquine, Study, Group. A randomized study of the effect of withdrawing
465 hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med*. 1991;324(3):150-4.
- 466 4. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic
467 lupus erythematosus. *Arthritis and rheumatism*. 2006;54(8):2550-7.
- 468 5. Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in
469 patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis care &*
470 *research*. 2014;66(4):608-16.
- 471 6. Jorge A, McCormick N, Lu N, Zheng Y, Esdaile J, De Vera M, et al. Hydroxychloroquine and
472 Mortality Among Patients With Systemic Lupus Erythematosus in the General Population. *Arthritis care*
473 *& research*. 2021;73(8):1219-23.
- 474 7. Hoque MR, Aviña-Zubieta JA, De Vera MA, Qian Y, Esdaile JM, Xie H. Impact of Antimalarial
475 Adherence on Mortality among Patients with Newly Diagnosed Systemic Lupus Erythematosus: A
476 Population-based Cohort Study. *Arthritis care & research*. 2021. (Online ahead of print)
- 477 8. Feldman CH, Yazdany J, Guan H, Solomon DH, Costenbader KH. Medication Nonadherence Is
478 Associated With Increased Subsequent Acute Care Utilization Among Medicaid Beneficiaries With
479 Systemic Lupus Erythematosus. *Arthritis care & research*. 2015;67(12):1712-21.
- 480 9. Adams EM, Yocum DE, Bell CL. Hydroxychloroquine in the treatment of rheumatoid arthritis. *The*
481 *American journal of medicine*. 1983;75(2):321-6.
- 482 10. The HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis:
483 the HERA Study. *The American journal of medicine*. 1995;98(2):156-68.
- 484 11. dos Reis Neto ET, Kakehasi AM, de Medeiros Pinheiro M, Ferreira GA, Marques CDL, da Mota
485 LMH, et al. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated
486 inflammatory rheumatic diseases. *Advances in Rheumatology*. 2020;60(1):32.
- 487 12. Worth C, Yusuf IH, Turner B, Gourier H, Brooks EE, Mort DO, et al. An audit of the use of
488 hydroxychloroquine in rheumatology clinics. *Rheumatology advances in practice*. 2018;2(1):rky013.
- 489 13. Abarientos C, Sperber K, Shapiro DL, Aronow WS, Chao CP, Ash JY. Hydroxychloroquine in
490 systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. *Expert opinion on*
491 *drug safety*. 2011;10(5):705-14.
- 492 14. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, et al.
493 Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-
494 associated cardiac manifestations of neonatal lupus. *Circulation*. 2012;126(1):76-82.
- 495 15. Tsakonas E, Joseph L, Esdaile JM, Choquette D, Sénécal JL, Cividino A, et al. A long-term study of
496 hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. *The Canadian*
497 *Hydroxychloroquine Study Group. Lupus*. 1998;7(2):80-5.
- 498 16. Alarcón GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alén J, Bastian HM, et al. Effect of
499 hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA,
500 a multiethnic US cohort (LUMINA L). *Annals of the rheumatic diseases*. 2007;66(9):1168-72.
- 501 17. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and
502 in antiphospholipid antibody-positive patients. *Current rheumatology reports*. 2011;13(1):77-80.

- 1
2
3 503 18. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis and*
4 504 *rheumatism*. 2006;54(11):3640-7.
- 5 505 19. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for
6 506 Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 2016;123(6):1386-
7 507 94.
- 8 508 20. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term
9 509 hydroxychloroquine therapy. *JAMA ophthalmology*. 2014;132(12):1453-60.
- 10 510 21. Aviña-Zubieta JA, Galindo-Rodriguez G, Newman S, Suarez-Almazor ME, Russell AS. Long-term
11 511 effectiveness of antimalarial drugs in rheumatic diseases. *Annals of the rheumatic diseases*.
12 512 1998;57(10):582-7.
- 13 513 22. Mavrikakis I, Sfrikakis PP, Mavrikakis E, Rougas K, Nikolaou A, Kostopoulos C, et al. The incidence
14 514 of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal.
15 515 *Ophthalmology*. 2003;110(7):1321-6.
- 16 516 23. Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ, Peterson T. Incidence of hydroxychloroquine
17 517 retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis and rheumatism*.
18 518 1997;40(8):1482-6.
- 19 519 24. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Aymard G, Leroux G, Marra D, et al. Very low
20 520 blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of
21 521 systemic lupus erythematosus. *Annals of the rheumatic diseases*. 2007;66(6):821-4.
- 22 522 25. Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, Le Guern V, Leroux G, Marra D, et al.
23 523 Adherence to treatment in systemic lupus erythematosus patients. *Best practice & research Clinical*
24 524 *rheumatology*. 2013;27(3):329-40.
- 25 525 26. Iudici M, Pantano I, Fasano S, Pierro L, Charlier B, Pingeon M, et al. Health status and
26 526 concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-
27 527 adherence in systemic lupus patients with prolonged inactive disease. *Lupus*. 2018;27(2):265-72.
- 28 528 27. Liu LH, Fevrier HB, Goldfien R, Hemmerling A, Herrinton LJ. Understanding Nonadherence with
29 529 Hydroxychloroquine Therapy in Systemic Lupus Erythematosus. *The Journal of rheumatology*.
30 530 2019;46(10):1309-15.
- 31 531 28. Costedoat-Chalumeau N, Houssiau F, Izmirly P, Le Guern V, Navarra S, Jolly M, et al. A
32 532 Prospective International Study on Adherence to Treatment in 305 Patients With Flaring SLE:
33 533 Assessment by Drug Levels and Self-Administered Questionnaires. *Clinical pharmacology and*
34 534 *therapeutics*. 2018;103(6):1074-82.
- 35 535 29. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy - implications of
36 536 research advances for rheumatology care. *Nature reviews Rheumatology*. 2018;14(12):693-703.
- 37 537 30. Jorge A, Rai SK, Choi HK. The Risk of Hydroxychloroquine Toxic Retinopathy and Its Risk Factors
38 538 in the Treatment of Rheumatic Diseases: A Systematic Review [abstract]. *Arthritis Rheumatol* 2017;69
39 539 (suppl 10).
- 40 540 31. Rosenbaum JT, Costenbader KH, Desmarais J, Ginzler EM, Fett N, Goodman SM, et al. American
41 541 College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and
42 542 American Academy of Ophthalmology 2020 Joint Statement on Hydroxychloroquine Use With Respect
43 543 to Retinal Toxicity. *Arthritis & rheumatology (Hoboken, NJ)*. 2021;73(6):908-11.
- 44 544 32. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item
45 545 National Eye Institute Visual Function Questionnaire. *Archives of ophthalmology (Chicago, Ill : 1960)*.
46 546 2001;119(7):1050-8.
- 47 547 33. Aviña-Zubieta JA, Abrahamowicz M, Choi HK, Rahman MM, Sylvestre MP, Esdaile JM, et al. Risk
48 548 of cerebrovascular disease associated with the use of glucocorticoids in patients with incident
49 549 rheumatoid arthritis: a population-based study. *Annals of the rheumatic diseases*. 2011;70(6):990-5.

- 1
2
3 550 34. Avina-Zubieta JA, McCormick N, Sayre EC, Sadatsafavi M, Esdaile JM, Marra C. Longitudinal
4 551 Analysis of Direct Medical Costs for Systemic Lupus Erythematosus in British Columbia, Canada: a
5 552 Population-Based Study. *Ann Rheum Dis*. 2013;71:458.
6 553 35. Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with
7 554 rheumatoid arthritis, psoriatic arthritis and psoriasis. *Annals of the rheumatic diseases*.
8 555 2010;69(12):2114-7.
9 556 36. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between
10 557 disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and
11 558 psoriasis. *Jama*. 2011;305(24):2525-31.
12 559 37. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of
13 560 retinal detachment. *Jama*. 2012;307(13):1414-9.
14 561 38. McCormick N, Reimer K, Famouri A, Marra C, Avina-Zubieta A. Filling the gaps in SARDs research:
15 562 Collection and linkage of administrative health data and self-reported survey data for a general
16 563 population-based cohort of individuals with and without diagnoses of systemic autoimmune rheumatic
17 564 disease (SARDs) from British Columbia, Canada. *BMJ Open*. 2017;7:e013977.
18 565 39. Bernatsky S, Lix L, O'Donnell S, Lacaille D. Consensus statements for the use of administrative
19 566 health data in rheumatic disease research and surveillance. *The Journal of rheumatology*. 2013;40(1):66-
20 567 73.
21 568 40. British Columbia Ministry of Health [creator] (2017): Medical Services Plan (MSP) Payment
22 569 Information File. [Internet]. Population data BC. 2020. Available from:
23 570 <https://www.popdata.bc.ca/data/health/msp>
24 571 41. Canadian Institute for Health Information [creator] (2017): Discharge Abstract Database
25 572 (Hospital Separations) [Internet]. Population Data BC 2020. Available from:
26 573 <http://www.popdata.bc.ca/data/health/dad>.
27 574 42. BC Ministry of Health [creator] (2018): PharmaNet. [Internet]. BC Ministry of Health 2020.
28 575 Available from: <http://www.popdata.bc.ca/data/health/PharmaNet>
29 576 43. BC Vital Statistics Agency [creator] (2017): Vital Statistics Deaths [Internet]. Population Data BC
30 577 2020. Available from: <http://www.popdata.bc.ca/data/population/vsdeaths>.
31 578 44. BC Cancer Registry Data (2017) [Internet]. Population Data BC 2020. Available from:
32 579 <http://www.popdata.bc.ca/data/health/bccancer>.
33 580 45. Chang J, Rogers P, Lacaille D. Can American College of Rheumatology Criteria for Rheumatoid
34 581 Arthritis Be Assessed Using Self-Report Data?-Comparison of Self-Reported Data with Chart Review 2011.
35 582 S49-S p.
36 583 46. Arkema EV, Jönsen A, Rönnblom L, Svenungsson E, Sjöwall C, Simard JF. Case definitions in
37 584 Swedish register data to identify systemic lupus erythematosus. *BMJ Open*. 2016;6(1):e007769.
38 585 47. Aviña-Zubieta JA, Vostretsova K, De Vera MA, Sayre EC, Choi HK. The risk of pulmonary
39 586 embolism and deep venous thrombosis in systemic lupus erythematosus: A general population-based
40 587 study. *Seminars in arthritis and rheumatism*. 2015;45(2):195-201.
41 588 48. McCormick N, Marra CA, Sadatsafavi M, Kopec JA, Aviña-Zubieta JA. Excess Productivity Costs of
42 589 Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjögren's Syndrome: A General Population-Based
43 590 Study. *Arthritis care & research*. 2019;71(1):142-54.
44 591 49. Eisner A, Luoh S-W. Breast Cancer Medications and Vision: Effects of Treatments for Early-stage
45 592 Disease. *Current eye research*. 2011;36:867-85.
46 593 50. Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine
47 594 toxicity. *Ophthalmology*. 2015;122(1):110-6.
48 595 51. Lally DR, Heier JS, Baumal C, Witkin AJ, Maler S, Shah CP, et al. Expanded spectral domain-OCT
49 596 findings in the early detection of hydroxychloroquine retinopathy and changes following drug cessation.
50 597 *International journal of retina and vitreous*. 2016;2:18.

- 1
2
3 598 52. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of
4 599 Competing Risks. *Circulation*. 2016;133(6):601-9.
5 600 53. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under
6 601 both left truncation and right censoring. *Biometrics*. 2011;67(1):39-49.
7 602 54. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model
8 603 specific population value and confidence interval estimation. *Statistics in medicine*. 2004;23 13:2109-23.
9 604 55. Thiébaud AC, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort
10 605 data: a simulation study. *Stat Med*. 2004;23(24):3803-20.
11 606 56. Beyersmann J, Schumacher M. Time-dependent covariates in the proportional subdistribution
12 607 hazards model for competing risks. *Biostatistics (Oxford, England)*. 2008;9(4):765-76.
13 608 57. Gaynor JJ, Feuer EJ, Tan CC, Wu DH, Little CR, Straus DJ, et al. On the Use of Cause-Specific
14 609 Failure and Conditional Failure Probabilities: Examples from Clinical Oncology Data. *Journal of the*
15 610 *American Statistical Association*. 1993;88(422):400-9.
16 611 58. Beiser A, D'Agostino RB, Sr., Seshadri S, Sullivan LM, Wolf PA. Computing estimates of incidence,
17 612 including lifetime risk: Alzheimer's disease in the Framingham Study. *The Practical Incidence Estimators*
18 613 *(PIE) macro*. *Stat Med*. 2000;19(11-12):1495-522.

21
22 614 **Figure 1- HCQ Retinal Toxicity Screening Protocol Flowchart for INTACT Study: The Consensus**
23
24 615 **Results**

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

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 anastrozole? 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:

Thank you for taking your time to fill out the form

For peer review only

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 Cirrus 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:



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:

For peer review only

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	

1	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	
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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6	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	
13	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	
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	
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17	Other information			
18	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
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*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>.