SESLHD GUIDELINE COVER SHEET

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KEY TERMS	Hydroxychloroquine, chloroquine, Plaquenil®, visual field, macula, optic nerve
SUMMARY	This guideline describes the staff responsibilities and assessment required when monitoring patients for ocular toxicity when undergoing hydroxychloroquine (Plaquenil®) treatment.

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Assessment of Hydroxychloroquine Retinopathy

Section 1 - Background

Hydroxychloroquine is prescribed for treatment of rheumatoid arthritis, mild systemic and discoid lupus erythematosus; and suppression and treatment of malaria[1].

Hydroxychloroquine ocular toxicity includes keratopathy, ciliary body involvement, lens opacities, and retinopathy. Hydroxychloroquine retinopathy is the major concern as it may be irreversible, and structural and functional deficits can occur even following cessation of therapy. Discontinuing the drug in the early stages can prevent permanent damage therefore monitoring patients for early detection of asymptomatic retinal structural changes is important[1].

Hydroxychloroquine is known to cause retinal toxicity of the para-foveal region affecting the photoreceptors initially and then causes disruption to the RPE. Fundus examination in early and moderate toxicity are generally unremarkable, but may show subtle areas of foveal depigmentation, which can be confirmed by correlation with auto fluorescence imaging. However, a significant amount of damage from toxicity can be present without any visible RPE (retinal pigment epithelium) damage seen on OCT or Bull's-eye maculopathy[2].

Most patients who develop hydroxychloroquine toxicity have no visual symptoms, but few may develop paracentral scotomas more noticeable when reading. Further exposure of hydroxychloroquine can lead to maculopathy encroaching the fovea that can affect visual acuity. Cystoid macular oedema may sometimes develop and then lead to RPE disruptions and retinal atrophy that affect peripheral and night vision[2].

Visual Acuity is rarely affected unless severe retinal toxicity is present due to RPE involvement. Paracentral scotomas may be reported by some patients. Cystoid macula oedema may develop. Signs of advanced hydroxychloroquine toxicity include widespread RPE and retinal atrophy (Bulls eye maculopathy), which results in loss of vision, peripheral vision and night vision[2]. In patients of Asian ethnicity, an extra macular pattern of damage can often be seen that can lead to peri-central visual field changes along the arcades.

Risk factors for developing hydroxychloroquine retinal toxicity are high doses (e.g., > 5 mg/kg actual body weight per day) and cumulative dose ≥ 1000 g. The maximum recommended daily dose is 5 mg/kg (actual weight). In most patients dosing at 400 mg hydroxychloroquine will result in 1000 g cumulative dose at 7 years[3]. Patients treated on higher doses are recommended to have baseline screening followed by annual screening from treatment initiation[3]. Patients with renal and liver disease and concomitant tamoxifen use are also recommended to have a baseline assessment followed by annual screening[3].

At recommended doses, the risk of toxicity is <1% up to 5 years, and up to 10 years is < 2% but rises to almost 20% after 20 years of using hydroxychloroquine[2]. If there are no signs of toxicity after 20 years, there is a 4% chance of developing toxicity the following year[2].

Section 2 - Definitions

Term	Definition
Orthoptist	Orthoptists are allied health professionals who specialise in the study of ocular motility and visual development. Their primary role is to investigate and diagnose visual system dysfunctions involving vision, eye movement, eye alignment and binocularity in children and adults. Orthoptics focuses on the non-surgical treatment of amblyopia and strabismus. They specialise in visual function assessment and neuromuscular anomalies.
Fundus Autofluorescence (FAF)	A type of retinal imaging that provides diagnostic information about the metabolism of the photoreceptors and retinal pigment epithelium (RPE). Images show distribution of the fluorescent pigment, lipofuscin in the RPE. Hyopfluorescence may be due to reduced RPE lipofuscin from RPE loss or atrophy. Hyperfluorescence may be due to excessive RPE lipofuscin accumulation from inability of the RPE to process lipofuscin or high turnover of photoreceptor outer segments.
Humphrey Visual field test (HVF)	A non-invasive test for assessing a patients' peripheral vision using automated quantitative threshold testing.
Hydroxychloroquine and chloroquine	Antimalarial drugs used in treatment of inflammatory conditions like rheumatoid arthritis; mild systemic and discoid lupus erythematosus and suppression and treatment of malaria.
Hydroxychloroquine ocular toxicity	Hydroxychloroquine can cause ocular toxicity including keratopathy, ciliary body involvement, lens opacities, and retinopathy affecting the retinal pigment epithelium. Risk factors are high doses and cumulative dose ≥ 1000 g.
mfERG	Multifocal electroretinogram enables rapid assessment of retinal function from many areas simultaneously using a contrast reverse stimulus. It is useful in discriminating between optic nerve and retinal disease including early hydroxychloroquine toxicity.
Photoreceptors	Retinal cells responsible for visual function. Cone photoreceptors are responsible for detection of colour and fine detail while rod photoreceptors are responsible for detection of light movement in dim environments.
Retinal Pigment Epithelium (RPE)	The RPE is responsible for the absorption of light and nutrients. RPE closely interacts with the photoreceptions in the maintenance of the visual function. Failure of RPE functions can result in loss of visual function.

Retinopathy	Is caused by various disorders that causes damage to retina of the eye resulting in loss of vision and in some severe cases blindness.
Spectral Domain Optical Coherence Topography (SD-OCT)	Is a non-invasive high resolution imaging test used to take cross section images of the retina

Section 3 - Responsibilities

Orthoptists are responsible for:

- Ensuring the visual assessments for patients on hydroxychloroquine (Plaquenil®) align with this guideline and when visual assessments are modified or not consistent with this guideline, to ensure documentation in the healthcare record reflects this.
- Triaging referrals for patients on hydroxychloroquine requiring investigation for ocular hydroxychloroquine toxicity (SSEH only).
- Performing orthoptic assessments that meet the Orthoptic Competency Standards[5]
- Orthoptists are to perform patient identification in accordance to protocol outlined in the NSW Health Policy Directive PD2017_032 - Clinical Procedure Safety, and document that this has occurred in the patient's healthcare record/eMR.
- Documentation of clinical assessments in patients' healthcare record complies with NSW Health Policy Directive PD2012_069 – Health Care Records- Documentation and Management and SESLHDPDR/336 – Documentation in the Health Care Record.
- Clinical handover to appropriate ophthalmologist team for any incidental findings on assessment.

Nurses are responsible for:

- Triaging referrals for any patients on hydroxychloroquine (Plaquenil®) or chloroquine requiring investigation for ocular toxicity.
- Performing patient identification in accordance to protocol outlined in the NSW Health Policy Directive PD2017_032 - Clinical Procedure Safety, and document that this has occurred in the patient's healthcare record/eMR.
- Performing visual acuity testing and colour vision as required (NB: colour vision testing is performed by nurses at POWH).
- Documentation of clinical assessments in patients' healthcare record complies with the NSW Health Policy Directive PD2012_069 - Health Care Records - Documentation and Management
- Clinical handover to ophthalmology team and orthoptists when required.

Medical staff are responsible for:

- Performing patient identification in accordance to protocol outlined in the NSW Health Policy Directive PD2017_032 - Clinical Procedure Safety, and document that this has occurred in the patient's healthcare record/eMR
- Documentation of clinical assessments in the patients' healthcare record complies with the NSW Health Policy Directive PD2012_069 - Health Care Records - Documentation and Management
- Clinical handover when required.
- Medical staff to document recommended review or follow up plan, including relevant referrals for further investigation.

Section 4 – Training Requirements

Orthoptists must have completed competency assessments for the following:

- Optical Coherence Tomography (OCT)
- Humphrey Visual Field (HVF)
- Fundus Autofluorescence (FAF)

Section 5 – Clinical Assessment Guidelines

Baseline assessment

It is recommended that a baseline assessment be performed prior to commencing hydroxychloroquine (Plaquenil®), or, within first year of use[5], however some patients may not be referred within this time.
All patients beginning long-term hydroxychloroquine or chloroquine therapy should have a baseline ophthalmologic examination within the first year of starting the drug to document any complicating ocular conditions and to establish a record of the fundus appearance and functional status[4].

Minimum requirements of clinical assessment at baseline and follow up include[3, 6, 7, 8] (see Appendix 2):

- History – including medication dose, duration of use
- Best corrected visual acuity
  - If BCVA is less than 6/6, VA should be then tested using a pinhole. If there is an improvement of VA of 2 lines or more with pinhole, a subjective refraction should be performed to determine potential BCVA
- Humphrey Visual Field (HVF) 10-2 threshold testing
- Additional wider field testing HVF 24-2 OR 30-2 in Asian patients (particularly East Asian background)[6]
- Spectral Domain (SD) - OCT imaging of macula - (wide field line or volume scans of at least 9mm)[7, 8]
- FAF – widefield or montage (including macula and just beyond vascular arcades)
- Pupil assessment (prior to dilation)

Following the above assessment, whilst not sufficient for screening (low screening), dilated fundus examination is important for detection of associated/other retinal and macular disorders.

Where possible, it is recommended that an mfERG should be performed (or the patient referred for an mfERG) when abnormal changes are detected on SD-OCT.

Follow up assessment

If no signs of retinal toxicity are reported by the ophthalmology team on initial ‘baseline’ screening, and patient does not exhibit major risk factors, annual screening should commence after 5 years (see Appendix 1)

Major risk factors that warrant annual screening following baseline assessment include [3, 7, 8]:

- Daily dose hydroxychloroquine > 5 mg/kg (actual body weight)
- Use of chloroquine (any dose)
- eGFR <50

- Duration of use > 5 years, assuming no other risk factors
- Renal impairment
- Concomitant tamoxifen
- Concomitant retinal/macular disease

If results are questionable, screening should be repeated within 1 month to determine repeatability of results.

Other factors to be considered in determining appropriate review period include:

- Treatment dose
- Dose-response relationship – amount and duration of treatment
- Pre-existing visual or ocular conditions

Section 6 - Documentation

All documentation must comply with the NSW Health Policy Directive PD2012_069 - Health Care Records – Documentation and Management and SESLHDPR/336 – Documentation in the Health Care Record.

Prior to commencing a patient assessment the clinician is required to perform patient identification in accordance to protocol outlined in the NSW Health Policy Directive PD2017_032 - Clinical Procedure Safety, and document that this has occurred in the patient's healthcare record/eMR.

In the event there is deviation from the recommendations in this guideline, it is expected that the clinician clearly documents the reason for this.

Section 7 – References

1. Uslu H, Gurler B, Yildirim A, et al. Effect of Hydroxychloroquine on the Retinal Layers: A Quantitative Evaluation with Spectral-Domain Optical Coherence Tomography. J Ophthalmol. 2016

2. Marmor, MF, Kellner, U, Lai, TYY et al. (2016) Recommendation on Screening for Chloroquine and Hydroxychloroquine Retinopathy. Ophthalmology, Vol.123, pp.1386-1394

3. Guidelines for Screening for Hydroxychloroquine Retinopathy; RANZCO 15th April 2021

4. Orthoptic Scope of Practice; Orthoptics Australia

5. Australian Orthoptic board Competency Standards for Orthoptists (20th July 2015)

6. American Academy of Ophthalmology Recommendations for Screening for Chloroquine and Hydroxychloroquine Retinopathy 2016 – (Accessed 20th August 2021)

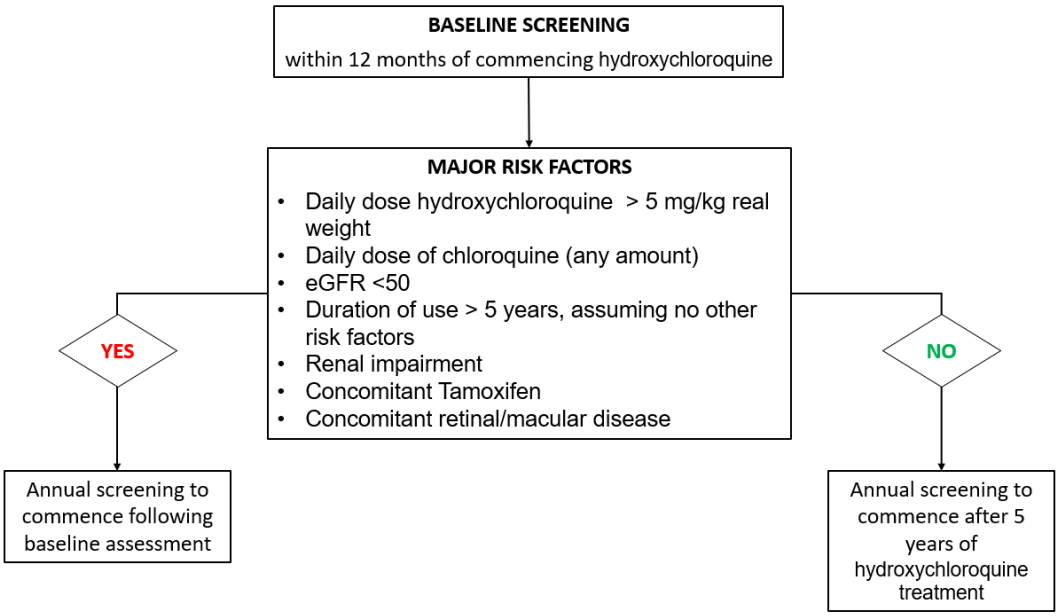
7. Anh SJ, Joung J, Lim HW, Lee BR. (2017) Optical Coherence Tomography Protocols for Screening of Hydroxychloroquine Retinopathy in Asian Patients. American Journal of Ophthalmology, Vol. 184, pp 11-18. https://doi.org/10.1016/j.ajo.2017.09.025

8. Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring; The Royal College of Ophthalmologists; December 2020

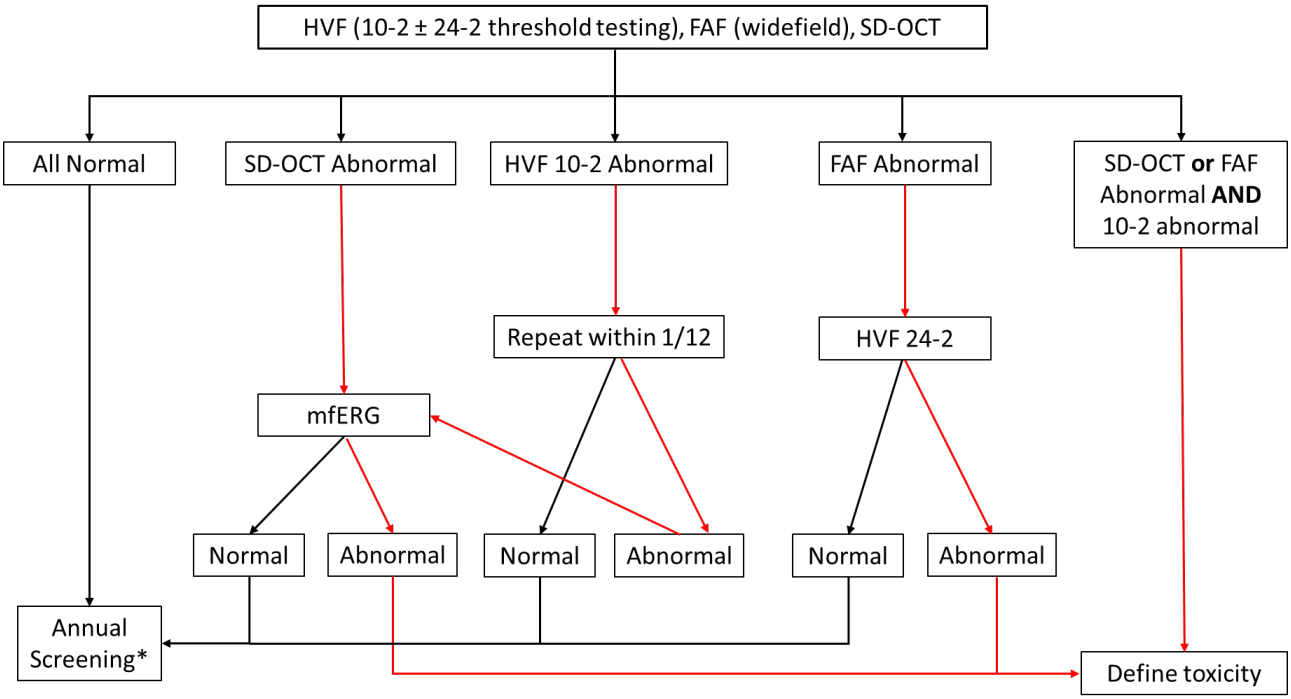
Version and Approval History

Date	Version	Version and approval notes
July 2023	1	New document. Endorsed at SSEH Medication Safety Committee, District Drug and Therapeutic Committee and District Clinical and Quality Council.

Appendix 1: Baseline Assessment and Risk Factors flowchart



Appendix 2: Baseline and follow up screening assessment



* Dependent on presence of major risk factors

Abnormal OCT = focal interruption of outer segment lines or macular volume loss

Abnormal FAF = HyperAF, can preceed SD-OCT changes