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| Classification: Official |
| Publication approval reference: PAR1183 |

Hydroxychloroquine and chloroquine retinopathy monitoring

Regional Medicines Optimisation Committee (RMOC) advice

July 2022, Version 1.0

1. Purpose

This document addresses how to keep patients safe from the risk of irreversible retinopathy and loss of vision, during long term hydroxychloroquine therapy. Current specialised retinal imaging techniques allow early detection of pre-symptomatic retinopathy. Advice has been requested from the Regional Medicines Optimisation Committee regarding the most appropriate and practical approach for the ophthalmology monitoring of patients who are receiving long term hydroxychloroquine therapy.

1. RCOphth clinical guidelines
   * + 1. The Royal College of Ophthalmologists (RCOphth) published updated clinical guidelines in December 2020: ‘Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring’ available at: <https://www.rcophth.ac.uk/standards-publications-research/clinical-guidelines/>
       2. The updated RCOphth December 2020 guideline addresses the potential implementation challenges of the previous RCOphth January 2020 guideline. A key change is the removal of formal ophthalmologist monitoring at baseline, with monitoring only starting after five years of therapy (unless additional risk factors are present or prescribed chloroquine). This should decrease the upfront resource cost of commissioning a hydroxychloroquine monitoring service without compromising safety. The RCOphth update is welcome due to the challenges raised as well as the additional COVID-19 pressures on the service.
       3. The key issues are summarised in the executive summary of the above document:[[1]](#endnote-1)

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| Recent data have highlighted that hydroxychloroquine retinopathy is more common than previously reported. The prevalence following long- term use appears to be around 7.5% and depending on dose and duration of therapy can increase to 20-50% after 20 years of therapy. Risk increases for patients taking more than 5mg/kg/day. The retinopathy is manifest as damage to the photoreceptors and subsequent degeneration of the retinal pigment epithelium (RPE). This may produce a ‘Bull’s eye maculopathy’ and central visual loss. This is important as the only intervention to prevent further damage is stopping the drug.  The risk is increased for patients taking more than 5mg/kg/day, those also taking tamoxifen, and those with renal impairment. While most affected patients demonstrate parafoveal toxicity (2-6 degrees from the fovea), some patients may exhibit pericentral toxicity (greater than 7 degrees from the fovea) which necessitates monitoring outside the macula. Chloroquine retinopathy appears to follow a similar, but more rapid, course when compared to hydroxychloroquine retinopathy.  Following the publication of the RCOphth recommendations for monitoring in hydroxychloroquine and chloroquine users in 2018,[[2]](#endnote-2) additional high-quality published evidence has prompted a review of the guideline. A systematic review of the literature was undertaken to identify studies of high-quality relating specifically to the timing of monitoring and the tests that should be performed. The selected studies included two recent large, high-quality audits of U.K. hydroxychloroquine monitoring services which were undertaken in accordance with the 2018 recommendations.[[3]](#endnote-3), [[4]](#endnote-4) |

* + - 1. The first consideration is therefore to increase awareness of the risks through signposting the College’s guidelines and also highlighting situations in which risk is increased.
      2. Attention should be drawn to the current RCOphth guidelines in the following section:

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| After careful review of the existing peer reviewed literature, we recommend that all patients be referred for annual monitoring after five years of therapy and be reviewed annually thereafter whilst on therapy. At each monitoring visit, patients should undergo imaging with both spectral-domain optical coherence tomography (SD-OCT) and widefield fundus autofluorescence imaging (FAF). If widefield FAF is not available, FAF can be acquired in several photographic fields to encompass the macula and extra-macular areas.  Patients with abnormalities on either SD-OCT or widefield FAF should undergo central, static, automated visual field testing appropriate to the location of the abnormality seen on SD-OCT or FAF; patients with paracentral defects may benefit from 10-2 visual field testing, and those with paracentral disease may benefit from 30-2 visual field testing. Patients with structural abnormalities consistent with hydroxychloroquine retinopathy, but with no abnormality identified on repeated visual field testing should undergo multifocal electroretinography.  Monitoring may be started one year after therapy is initiated if additional risk factors exist e.g. very high dose of drug therapy (greater than 5mg/kg/day hydroxychloroquine), concomitant tamoxifen therapy or renal insufficiency (eGFR less than 60ml/min/1.73m2).  Chloroquine appears to be more retinotoxic than hydroxychloroquine and so we recommend that monitoring begins after one year of therapy for all patients on chloroquine, using the same tests.  Baseline testing for new initiators of hydroxychloroquine or chloroquine is no longer recommended. This amendment is supported by recent evidence of a low rate of drug discontinuation as a result of baseline testing (less than 4%). Furthermore, it is recognised that a significant proportion of patients discontinue hydroxychloroquine in the first five years of therapy, either due to adverse effects or insufficient clinical response. Adequate monitoring may not be possible with retinal co-pathology. This may be identified at the first monitoring episode and a discussion with the patient and prescribing physician about the suitability of continued hydroxychloroquine therapy may be arranged. There is no specific recommendation for patients to arrange annual community optometry assessments, or any specific form of self-assessment, before monitoring commences.  Monitoring may be best incorporated into the hospital eye service via virtual clinics. Alternatively, they may be commissioned in the community similar to a diabetic retinopathy service. The results of monitoring should be communicated back to the prescribing doctor, patient and GP as normal, possible or definite hydroxychloroquine retinopathy. It is the prescribing doctor’s responsibility to ensure their patients are adequately monitored and to act on the results of monitoring. A useful aide memoir for these guidelines for hydroxychloroquine is the 5 x 5 rule (ideally keep dosage < 5mg/kg/day and screen after five years of drug use). |

It should be noted that the RCOphth recommendation to keep dosage < 5mg/kg/day is based on actual body weight. This differs from the manufacturer’s and British National Formulary recommended maximum dose of 6.5mg/kg/day, which is based on ideal body weight.

1. Responsibilities

The [Clinical Council for Eye Health Commissioning (CCEHC) statement](https://www.college-optometrists.org/news/2020/march/ccehc-statement-on-responsibilities-for-a-hydroxyc) (February 2020) clarified the responsibilities for the commissioning and delivery of hydroxychloroquine monitoring and included the following points:

Responsibility for commissioning services for monitoring HCQ retinopathy rests with those who commission the services that require the prescription of HCQ and the primary prescribers of HCQ, with advice from ophthalmologists for developing referral and monitoring pathways.

Responsibility for arranging monitoring assessment for HCQ retinopathy lies with the primary prescriber. This includes identification of the eligible patient population and arranging for monitoring.

Responsibility for providing the monitoring assessment lies with the provider of the monitoring service and ophthalmologist/lead service clinician.

Where a shared care protocol is in place this must specify where responsibilities lie.

1. RMOC advice

It is recognised that a number of healthcare systems are facing challenges in implementing the RCOphth guidance so are considering whether a less stringent standard can be adopted to enable early detection of hydroxychloroquine retinopathy. This question has been considered by the South RMOC, although as noted above the guidance has now changed with the removal of the need for baseline monitoring.

### The conclusions reached by the South RMOC are as follows:

* + - 1. There is an increase in the incidence of avoidable patient harm from sight loss due to the increased number of patients taking hydroxychloroquine for longer periods of time, and the occurrence of retinopathy is more prevalent than previously thought as a result of improvements in imaging technology.
      2. As hydroxychloroquine toxicity is dose and duration dependent, more should be done to manage risks. Hydroxychloroquine dosing is weight based, and until recently only 200mg strength tablets were available making it more challenging to accurately tailor doses for individual patients. For example, patients with a body weight between 40 and 80kg receiving 400mg daily would be receiving a high dose (>5mg/kg). A 300mg formulation is now licensed in the UK so this may prove to be appropriate for some patients.
      3. Patients at greater risk, such as those with significant renal impairment or taking concomitant tamoxifen, should be reviewed to confirm that hydroxychloroquine is the most appropriate therapy. Tamoxifen is a retinal toxin by itself and has an adverse synergism with hydroxychloroquine.
      4. Many ophthalmology services are over stretched so risks to vision from all causes needs to be considered in prioritising resource. When considered against screening programmes, however, it should be noted that other diseases may be developing naturally, whereas doctors prescribing hydroxychloroquine are introducing a therapeutic intervention that has the potential to cause harm; this may be considered to result in a greater responsibility to monitor the patient.
      5. Healthcare systems should develop an action plan to meet the RCOphth guidance and consider process developments implemented in localities that have successfully met the recommendations. This may be through a commissioned pathway for monitoring hydroxychloroquine retinopathy.
      6. Clinicians responsible for prescribing hydroxychloroquine should ensure the retinopathy monitoring is as specified in the RCOphth guidance with formal ophthalmologist monitoring. Standard community optometrist review does not meet the RCOphth recommendations and risks false reassurance.
      7. In healthcare systems choosing to monitor patients at a level less than that proposed by the RCOphth, the rationale and agreement should be clearly documented, including the measures being taken to ensure patient safety, and consideration made as to increasing the level of monitoring over time. If the service is unable to implement the RCOphth guidance, inclusion in the commissioner and provider risk registers should be considered.

1. Conclusion

The risk of retinopathy for patients undergoing long term hydroxychloroquine therapy can be markedly reduced through implementation of the RCOphth guidance and the advice summarised in this document.

# References

1. The Royal College of Ophthalmologists. [Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring](https://www.rcophth.ac.uk/wp-content/uploads/2020/12/Hydroxychloroquine-and-Chloroquine-Retinopathy-Monitoring-Executive-Summary.pdf) Executive Summary. December 2020. [↑](#endnote-ref-1)
2. The Royal College of Ophthalmologists recommendations on screening for hydroxychloroquine and chloroquine users in the United Kingdom: executive summary. Eye (London, England). 2018;32(7):1168-73. [↑](#endnote-ref-2)
3. Marshall E, Robertson M, Kam S, Penwarden A, Riga P, Davies N. Prevalence of hydroxychloroquine retinopathy using 2018 Royal College of Ophthalmologists diagnostic criteria. Eye (London, England). 2020:1-6. [↑](#endnote-ref-3)
4. Gobbett A, Kotagiri A, Bracewell C, Smith J. Two years’ experience of screening for hydroxychloroquine retinopathy. Eye (London, England). 2020. [↑](#endnote-ref-4)