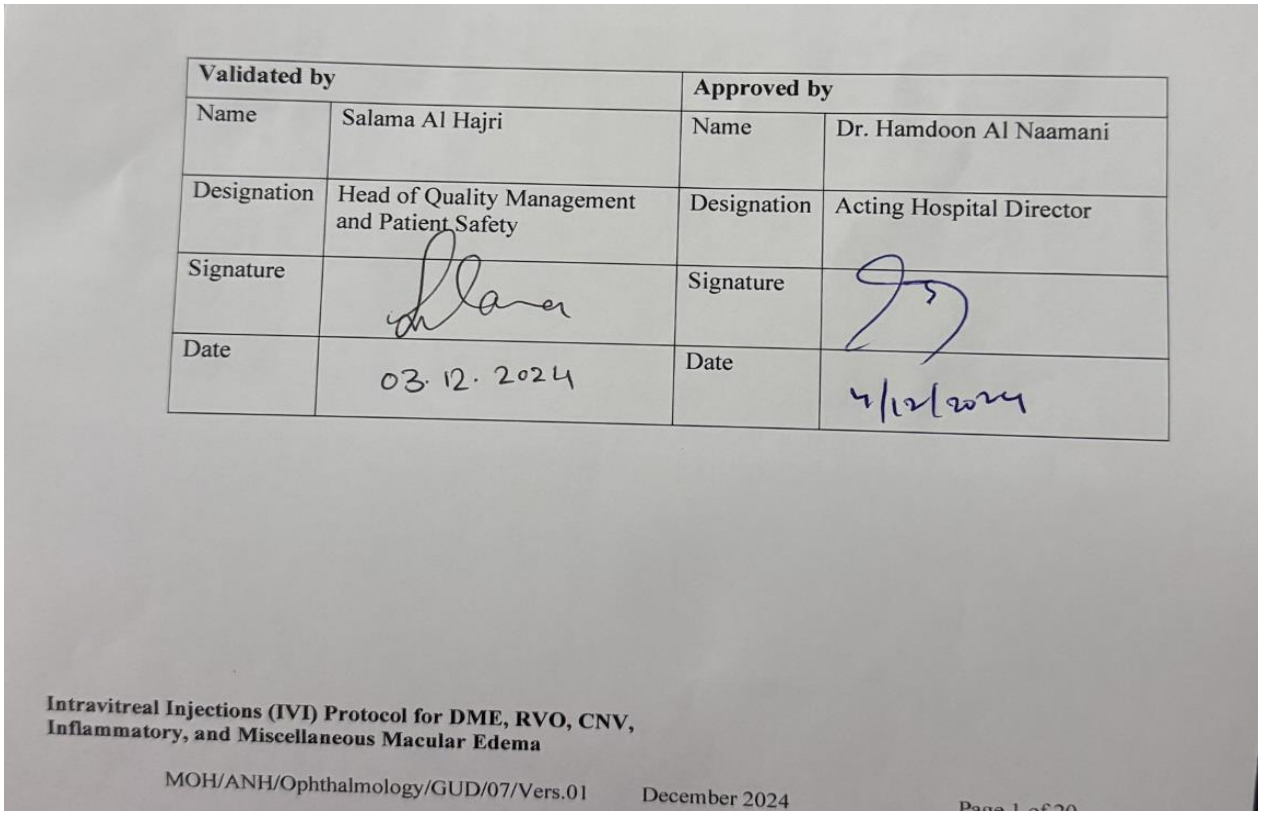
وزارة الصحة
Ministry of Health
المديرية العامة لمستشفى خولة
Directorate General of Khoula Hospital

Document Title	**Intravitreal Injections (IVI) Protocol for DME, RVO, CNV, Inflammatory, and Miscellaneous Macular Edema**	
Document Type	**Protocol**	
Directorate/Institution	**Al- Nahdha Hospital**	
Document Author	**Dr. Majid Al- Shaibi**	
Designation	**Ophthalmologists**	
Document Reviewer	**Dr. Nasra Al- Habsi**	**Aisha Al Rawahi**
Designation	**Head of Ophthalmology Department**	**Quality Management and Patient Safety**
Release Date	**December 2024**	
Review Frequency	**3 years**	



Validated by		Approved by	
Name	Salama Al Hajri	Name	Dr. Hamdoon Al Naamani
Designation	Head of Quality Management and Patient Safety	Designation	Acting Hospital Director
Signature		Signature	
Date	03. 12. 2024	Date	4/12/2024

Intravitreal Injections (IVI) Protocol for DME, RVO, CNV, Inflammatory, and Miscellaneous Macular Edema

MOH/ANH/Ophthalmology/GUD/07/Vers.01 December 2024 Page 1 of 20

Table of Contents

Acronyms

Anti- VEGF	Anti-vascular Endothelial Growth Factor
IVI	Intravitreal Injection
DME	Diabetic Macular Edem
RVO	Retinal Vascular Occlusion
AMD	Age-related Macular Degeneration
ROP	Retinopathy Of Prematurity
CNV	Choroidal Neovascularization
PCV	Polypoidal choroidal vasculopathy

Definitions

- Poor response in DME/RVO is defined as <20% reduction from the baseline in the central retinal thickness (CRT) and visual acuity (VA).
- Poor response in wAMD is defined as <25% reduction from the baseline in CRT, with persistent or new intraretinal fluid (IRF), subretinal fluid (SRF), or minimal change in VA (i.e., change in VA of 0+4 letters).
- Non-response in wAMD is defined as an increase in fluid (IRF, SRF, and CRT), or increasing hemorrhage compared to the baseline, and/or loss of >5 letters compared to the baseline or best-corrected vision subsequently.
- The choice of approved anti-VEGF agent is to be determined by the treating ophthalmologist.

✓ FDA-approved anti-VEGF agents in DME: Vabysmo, Beovu, Eylea, and Lucentis.
✓ FDA-approved anti-VEGF agents in RVO: Vabysmo Eylea and Lucentis.
✓ FDA-approved anti-VEGF agents in wAMD: Vabysmo, Beovu, Eylea, and Lucentis.
✓ FDA-approved anti-VEGF agents in mCNV: Lucentis.
✓ FDA-approved agents in inflammatory macular edema: Ozurdex.
✓ Eylea has been found to work well in patients with Coats disease, RAM, retinal hemangioma hence we advocate for its use when required

- Our recommendation is to keep longer-acting anti-VEGF agents (like Vabysmo, Eylea) as first-line agents in the appropriate setting.

Intravitreal Injections (IVI) Protocol for DME, RVO, CNV, Inflammatory, and Miscellaneous Macular Edema

1. Introduction

1.1 Background Information

Macular edema is a prevalent complication seen in various ocular conditions, including diabetic retinopathy (DME), retinal vein occlusion (RVO), choroidal neovascularization (CNV), and others. Understanding each type of macular edema is important for tailored treatment approaches.

1.2 Scientific Rationale

Macular edema significantly impacts vision and quality of life, making its management a critical aspect of ophthalmologic care. Advances in treatment modalities, including anti-VEGF therapy, corticosteroids, and laser photocoagulation, provide opportunities for improved patient outcomes. However, clear and consistent guidelines are essential to ensure optimal use of these therapies.

2. Aim(s) and Objectives

The purpose of this guideline is to provide clear treatment algorithms and recommendations for the treatment of DME, RVO, CNV, inflammatory, and miscellaneous macular edema.

This guideline aims to enhance patient outcomes by ensuring that therapeutic decisions are grounded in evidence-based practices and personalized to each patient's unique clinical status and specific needs. By adhering to these principles, healthcare providers can deliver more effective and appropriate care, ultimately improving the overall quality of treatment and patient satisfaction.

3. Scope

This guideline is intended to serve as a comprehensive framework for healthcare providers managing macular edema across various etiologies, including diabetic macular edema (DME), retinal vein occlusion (RVO), choroidal neovascularization (CNV), inflammatory macular edema, and other miscellaneous causes**.**

4. Methods and procedures see appendix 1:

4.1 Treatment of Diabetic macular edema (DME) see appendix 2:

4.1.1 anagement Approach for DME **see appendix 1 & 2:**

4.1.1.1 Non-Center-Involved DME with VA 6/7.5 or better

- Close monitoring is advised to detect potential progression to center-involved DME.
- Consider **focal laser therapy** targeting microaneurysms located **1000–1500 microns from the fovea**.

4.1.1.2 Center-Involved DME with VA 6/7.5 or better

- **Observation**: Monitor closely if asymptomatic or minimally symptomatic.
- If **symptomatic**, initiate treatment with an **FDA-approved anti-VEGF agent**

4.1.1.3 Center-Involved DME with VA 6/9 or worse

- **Young phakic patients (without recent stroke)**:
  - Start treatment with **FDA-approved anti-VEGF agents**.
- **Recent stroke (within 3 months)**:
  - If pseudophakic and no contraindications to steroids:
    - Consider a **Dexamethasone implant** (Ozurdex).
      - If contraindicated due to:
        - **Steroid response** or **uncontrolled glaucoma**:
          - Observe for 3 months or opt for **focal laser therapy** if microaneurysms are suitable for laser.
          - Proceed with an **FDA-approved anti-VEGF agent after 3 months.**

4.1.2 Monitoring and Adjusting Treatment

4.1.2.1 Positive Response (e.g., ≥20% reduction in CMT or VA improvement):

- Continue treatment with the same anti-VEGF agent until the retina is dry.
- Transition to a **treat-and-extend protocol**:
  - Gradually increase intervals between injections while maintaining retinal dryness.
  - Discontinue treatment after **>1 year of sustained retinal dryness**.

4.1.2.2 Challenges in Maintaining Dry Retina:

- Consider transitioning to **longer-acting anti-VEGF agents** for sustained effect.

4.1.3 Special Considerations

4.1.3.1 Pseudophakic patients or those planning cataract surgery:

- Evaluate history of **uncontrolled glaucoma** and **steroid response**:
  - If absent, consider **Dexamethasone implant** (Ozurdex).
  - If present, anti-VEGF agents may be safer compared to corticosteroids.

4.1.3.2 Vitrectomized eyes (non-silicone oil-filled):

- Tailor therapy based on individual patient response and clinical judgment.

4.2 Treatment of Central Retinal Vein Occlusion (RVO) **see appendix 3:**

Management Approach of Retinal Vein Occlusion (RVO) with Macular Edema

4.2.1.1 Phakic Patients (Young, No Recent Stroke)

- **Initiate Treatment**:
  - Start with an **FDA-approved anti-VEGF agent**
- **Monitor Response**:
  - Perform **OCT imaging** after loading doses to evaluate treatment effectiveness.

A. Fully Responsive Patients:

- **Criteria**: No fluid detected on OCT.
- **Management**:
  - Gradually extend follow-up intervals using a **treat-and-extend protocol**.
  - Consider **discharging** if the retina remains dry after one year of extended intervals.
  - For **recurrences of cystoid macular edema (CMO)** during extensions:
    - Switch to a **longer-acting FDA-approved anti-VEGF agent** or a **dexamethasone implant** (if no contraindications).

B. Poor or No Response:

- **Criteria**: Less than a 20% reduction in central macular thickness (CMT) with fluid present on OCT.
- **Management**:
  - Switch to another **FDA-approved anti-VEGF agent**.
  - If no contraindications, consider a **dexamethasone implant**.

C. Partial Response:

- **Criteria**: At least a 20% reduction in CMT but persistent CMO.
- **Management**:

- Reload with anti-VEGF injections every three months.
- If persistent CMO, switch to another **FDA-approved anti-VEGF agent** or consider a **dexamethasone implant**.

4.2.1.2 Pseudophakic Patients or Those Scheduled for Cataract Surgery

- **Considerations**:
  - For patients with a history of **glaucoma or steroid response:**
    - Consider **dexamethasone implant** if there are no contraindications to steroids.
  - Monitor intraocular pressure (IOP) closely in such cases.

4.2.1 General Notes

4.2.2.1 Longer-Acting Options:

- For recurrent cases or challenges maintaining a dry retina, switch to **longer-acting anti-VEGF agents** or **dexamethasone implants**.

4.2.2.2 Steroid Contraindications:

- Avoid steroids in patients with a history of **uncontrolled glaucoma** or a **significant steroid response**.

4.2.2.3 Customization:

- Tailor treatment strategies based on **response to initial therapy**, **systemic conditions**, and **ocular history**.

4.3 Treatment of wAMD, PCV and mCNV **see appendix 4:**

4.3.1 Wet AMD and Polypoidal Choroidal Vasculopathy Management Approach

4.3.1.1 Initial Treatment

- **Loading Dose**:
  - Administer a **loading dose** of an **FDA-approved anti-VEGF agent**
  - **Monitor Response**:
    - Assess for **response** via OCT and visual acuity (VA):
      - Evaluate **intraretinal fluid (IRF)**, **subretinal fluid (SRF)**, central retinal thickness (CRT), and hemorrhage compared to baseline.
        - **Non-Response**:
          - Indicators include:
            - Increased fluid (IRF, SRF, CRT).
            - Worsened hemorrhage compared to baseline.
            - Loss of >5 letters from baseline or best-corrected vision (BCVA).
        - **Action**: Switch to another **FDA-approved anti-VEGF agent**.

4.3.1.2 Maintenance Therapy

- **Positive Response**:
  - If the retina becomes dry, maintain **monthly intravitreal injections** until stability is achieved.
  - Transition to a **Treat-and-Extend (TnE) regimen**:
    - Gradually extend treatment intervals by 2 weeks while maintaining dryness.
  - **Successful TnE Approach**:
    - Continue extending intervals by 2 weeks as tolerated.
    - **Discontinuation**:
      - Consider stopping treatment if the retina remains dry for **more than 1 year**.
- **Disease Reactivation**:
  - If reactivation occurs:
    - Revert to the **previously effective interval**.
    - If extensions remain challenging, switch to a **longer-acting anti-VEGF agent**.

4.3.1.3 Managing Treatment Burden

- If the treatment burden remains high despite anti-VEGF therapy:
  - **Photodynamic Therapy (PDT)**:
    - Use for **classic or predominantly classic and PCV lesions**.
  - **Focal Laser Therapy**:
    - Can be considered sometimes in **extrafoveal lesions** in PCV.

4.4 Treatment of Miscellaneous Macular edema **see appendix 5:**

4.2.3 Patients diagnosed with non-inflammatory macular edema, which cannot be effectively treated with laser therapy, should undergo treatment with anti-VEGF injections.

4.2.4 For patients with inflammation unresponsive to topical treatment, intravitreal dexamethasone should be administered. If steroids are contraindicated, anti-VEGF injections should be used instead.

5. Measurement of Effect

To evaluate effectiveness, specific metrics will be monitored and analyzed, including:

5.1 Clinical Outcomes:

Improvement in visual acuity, reduction in central macular thickness as measured by optical coherence tomography (OCT), and resolution of edema over defined follow-up periods.

5.2 Healthcare Impact:

Reduction in referral rates to tertiary care centers, improved resource utilization, and streamlined workflows within MOH outpatient eye clinics.

5.3 Cost-Effectiveness:

Analysis of the economic impact of adopting the guideline, including cost savings from optimized resource use and reduced complications requiring advanced interventions.

Document History and Version Control

Version	Description	Review Date
1	Initial Release	December 2027

Reference

1. International Council of Ophthalmology. (2017). **ICO Guidelines for Diabetic Eye Care. ** [Online] Available at: [http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf] (http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf) [Accessed 26 October 2020].

2. Early Treatment Diabetic Retinopathy Study Research Group. (1987). **Treatment Techniques and Clinical Guidelines for Photocoagulation of Diabetic Macular Edema, Early Treatment Diabetic Retinopathy Study Report Number 2. ** *Ophthalmology, 94*(7), pp.761-774.

3. International Diabetes Federation. (2019). **Diabetic Macular Edema. ** pp.1-25.

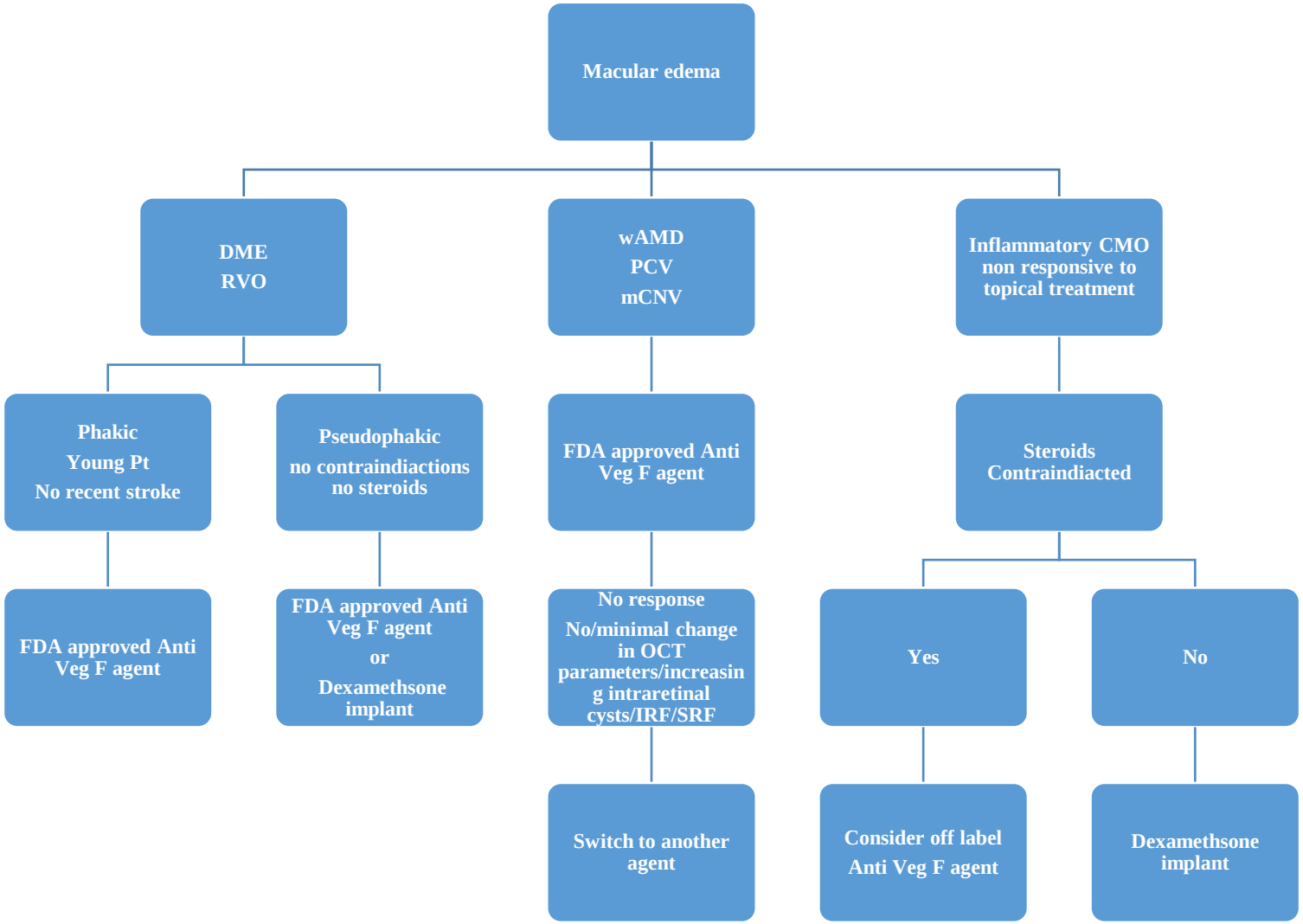
4. Cornel, S., Adriana, I., Mihaela, T., Speranta, S., Algerino, D., Mehdi, B., & Jalaladin, H. (2015). **Anti-vascular endothelial growth factor indications in ocular disease. ** *Romanian Journal of Ophthalmology, 59*(4), pp.235-242.

5. Elman, M., Aiello, L., Beck, R., Bressler, N., Bressler, S., Edwards, A., Ferris, F., Friedman, S., Glassman, A., Miller, K., Scott, I., Stockdale, C., & Sun, J. (2010). **Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema. ** *Ophthalmology, 117*(6), pp.1064-1077.e35.

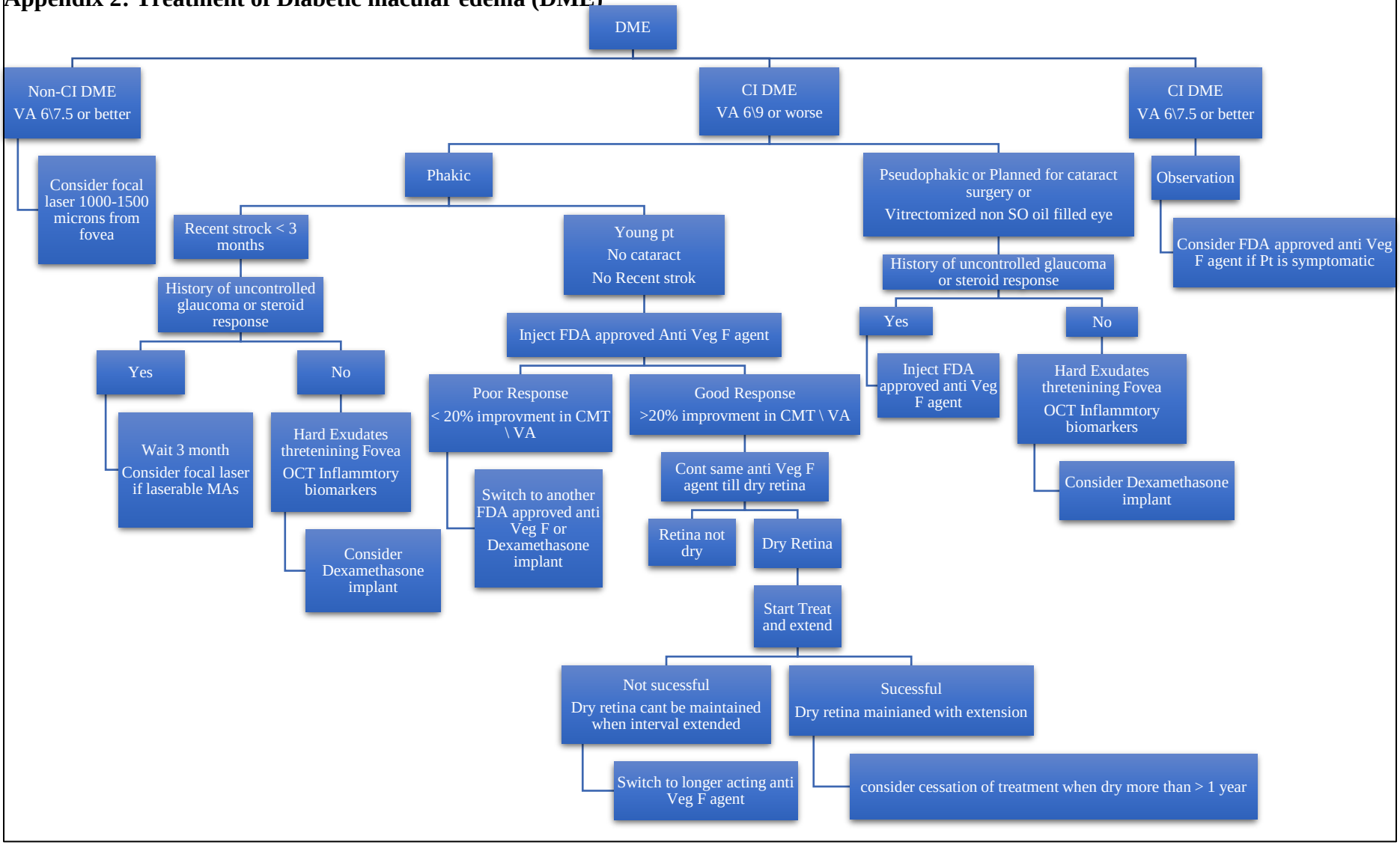
6. Wong, T., Sun, J., Kawasaki, R., Ruamviboonsuk, P., Gupta, N., Lansingh, V., Maia, M., Mathenge, W., Moreker, S., Muqit, M., Resnikoff, S., Verdaguer, J., Zhao, P., Ferris, F., Aiello, L., & Taylor, H. (2018). **Guidelines on Diabetic Eye Care. ** *Ophthalmology, 125*(10), pp.1608-1622.
7. Schmidt-Erfurth, U., Garcia-Arumi, J., Bandello, F., Berg, K., Chakravarthy, U., Gerendas, B., Jonas, J., Larsen, M., Tadayoni, R., & Loewenstein, A. (2017). **Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). ** *Ophthalmologica, 237*(4), pp.185-222.
8. Herbaut, A., Fajnkuchen, F., Qu-Knafo, L., Nghiem-Buffet, S., Bodaghi, B., & Giocanti-Auregan, A. (2017). **Switching to Aflibercept in Diabetic Macular Edema Not Responding to Ranibizumab and/or Intravitreal Dexamethasone Implant. ** *Journal of Ophthalmology, 2017*, pp.1-8.
9. Gonzalez, V., Campbell, J., Holekamp, N., Kiss, S., Loewenstein, A., Augustin, A., Ma, J., Ho, A., Patel, V., Whitcup, S., & Dugel, P. (2016). **Early and Long-Term Responses to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data. ** *American Journal of Ophthalmology, 172*, pp.72-79.
10. Al-khersan, H., Hariprasad, S., & Salehi-Had, H. (2019). **Dexamethasone and Anti-VEGF Combination Therapy for the Treatment of Diabetic Macular Edema. ** *Ophthalmic Surgery, Lasers and Imaging Retina, 50*(1), pp.4-7.
11. La Mantia, A., Hawrami, A., Laviers, H., Patra, S., & Zambarakji, H. (2018). **Treatment of refractory diabetic macular edema with a fluocinolone acetonide implant in vitrectomized and non-vitrectomized eyes. ** *International Journal of Ophthalmology, 11*(12), pp.1951-1956.
12. Parodi, M., & Bandello, F. (2017). **Is Laser Still Important in Diabetic Macular Edema as Primary or Deferral Therapy? ** *Dev Ophthalmol, 60*, pp.125-130.
13. Nicolo, M., Musetti, D., Marenco, M., Cotti, L., Bonetto, M., Giacomini, M., & Traverso, C. (2020). **Real-Life Management of Diabetic Macular Edema with Dexamethasone Intravitreal Implant: A Retrospective Analysis of Long-Term Clinical Outcomes. ** *Journal of Ophthalmology, 2020*, pp.1.

14. Kulikov, A., Sosnovskii, S., Berezin, R., Maltsev, D., Oskanov, D., & Gribanov, N. (2017). **Vitreoretinal interface abnormalities in diabetic macular edema and effectiveness of anti-VEGF therapy: an optical coherence tomography study. ** *Clinical Ophthalmology, 11*, pp.1995-2002.
15. Schmidt-Erfurth, U., Garcia-Arumi, J., Gerendas, B. S., Midena, E., Sivaprasad, S., Tadayoni, R., Wolf, S., Loewenstein, A., & European Society of Retina Specialists (EURETINA). (2019). **Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA). ** *Ophthalmologica, 242*, pp.187-204. https://doi.org/10.1159/000502041.
16. The Royal College of Ophthalmologists. (2022). **Retinal Vein Occlusion (RVO) Clinical Guidelines.

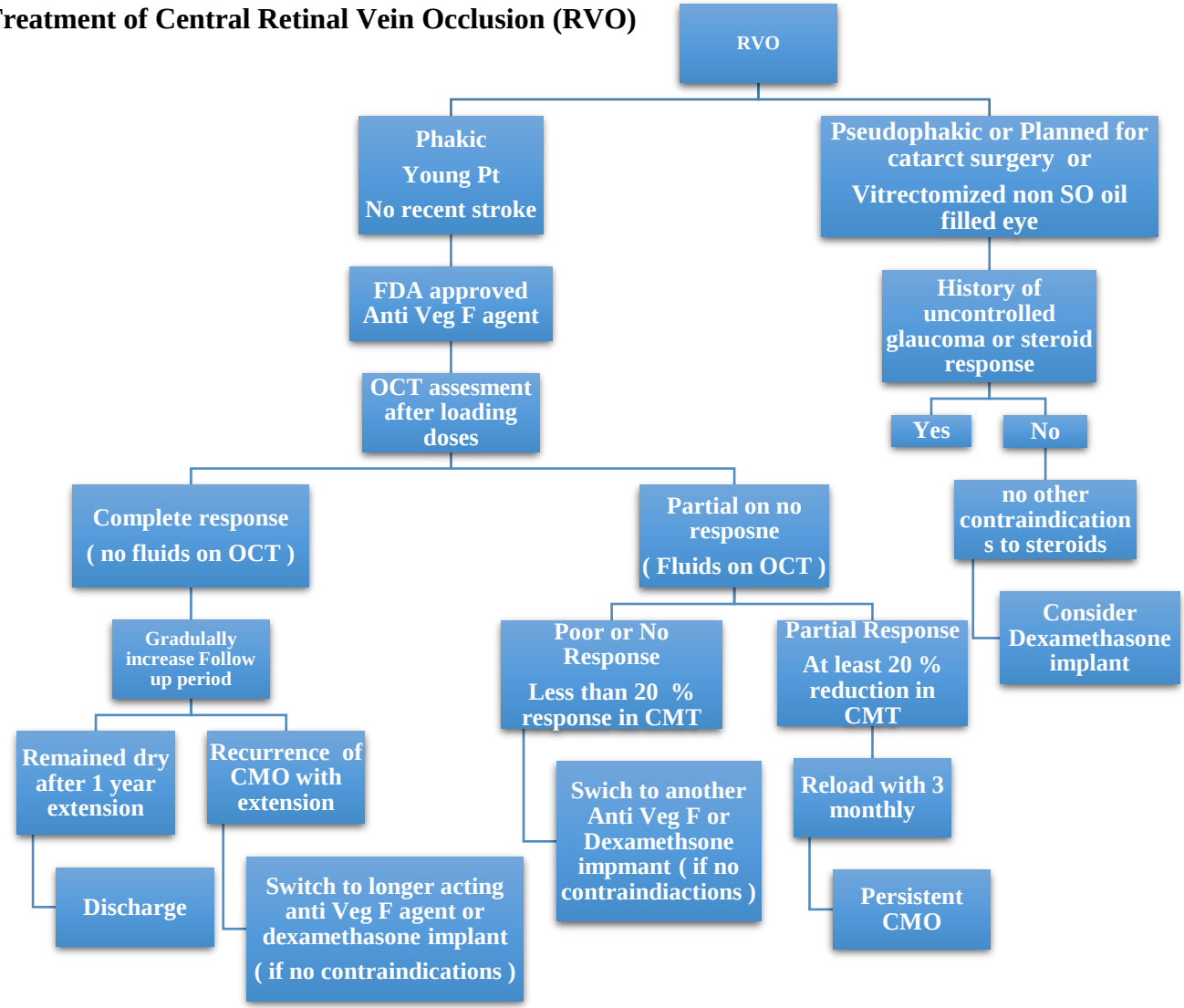
Appendix 1: Management Approach for DME



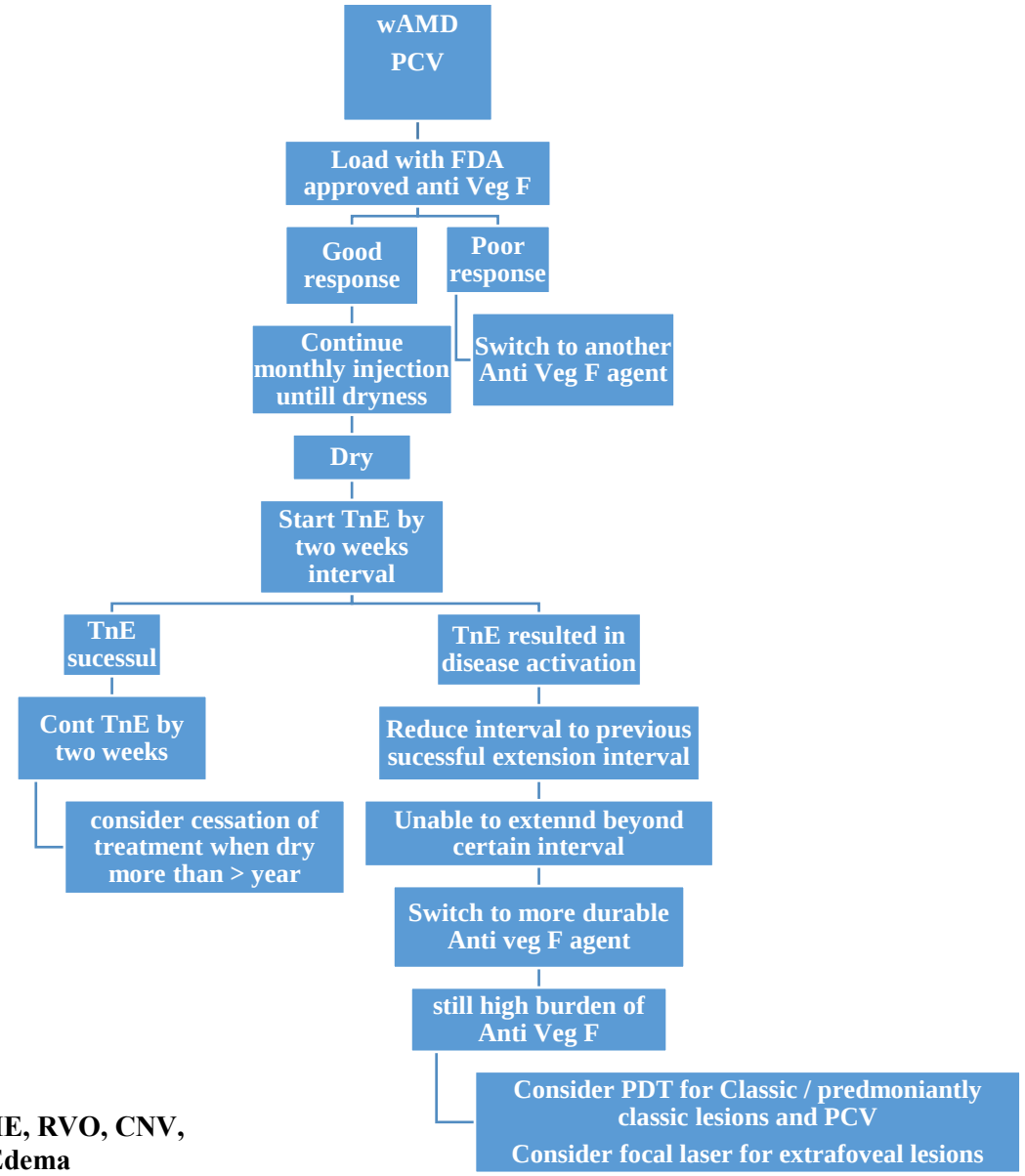
Appendix 2: Treatment of Diabetic macular edema (DME)



Appendix 3: **Treatment of Central Retinal Vein Occlusion (RVO)**



Appendix 4: **Treatment of wAMD, PCV and mCNV**



Appendix 5: **Treatment of Miscellaneous Macular edema**