# Retina Trials: Design, Analysis, and Challenges

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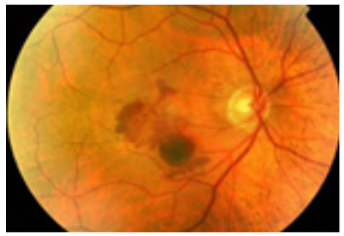
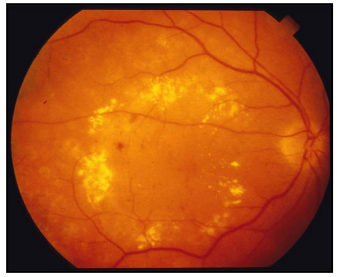
# Common Retina Indications

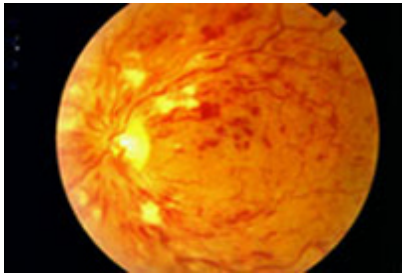
- AMD – Age related macular degeneration
  - Leading cause of visual impairment among the elderly (>50 years)

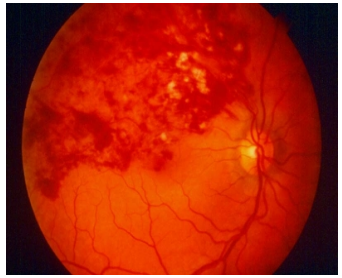


- DME – Diabetic macular edema
  - swelling of the retina due to leaking of fluid from blood vessels within the macula
  - can develop at any stage of the underlying disease

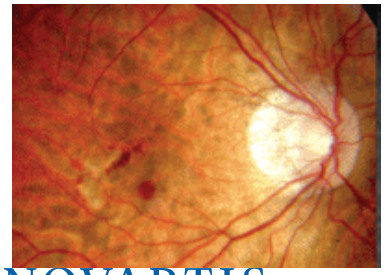


- RVO – Retinal vein occlusion
  - Two types, typically due to macular edema
  - CRVO- Central RVO
  - BRVO – Branch RVO
  - BRVO is more common than CRVO





- PM – Pathologic myopia secondary to Choroidal neovascularization(CNV)
  - High myopia associated with the stretching and elongation of the eye resulting in the degeneration of the RPE and Bruchs membrane leading to the growth of CNV under and into the retina



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# Common Retina Indications

- ROP – Retinopathy of prematurity
  - Infants born prematurely with retinopathy of prematurity
- Extended indications
  - VEGF driven CNV other than AMD or PM
  - VEGF driven ME other than DME or RVO
- Other indications being considered
  - ...

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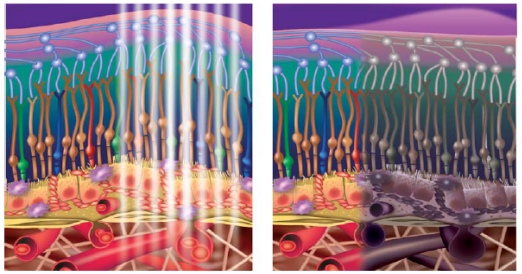
# Treatment Options

## Thermal Laser Photocoagulation:

- Destroys abnormal blood vessels and surrounding tissue therefore only suitable for lesions away from the macula (juxta or extra foveal). 50% of lesions return closer to the macula
- Often lower vision following treatment than prior but less subsequent sight loss
- Rarely used

Fig 1. Thermal laser photocoagulation

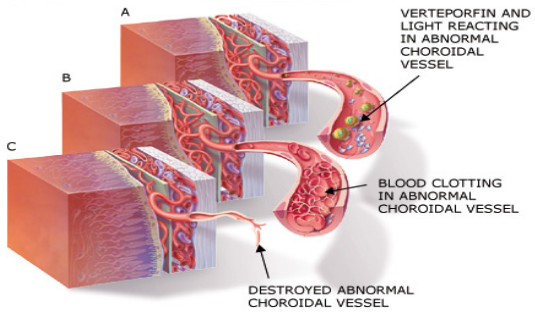


Laser beam aimed at CNV

Immediate damage to RPE overlying CNV

## Photodynamic Therapy(PDT):

- Cool laser in conjunction with intravenous Visudyne (verteporfin)
- Cauterises abnormal blood vessels whilst sparing healthy tissue
- Slows rate of vision loss. Patients do not on average gain vision

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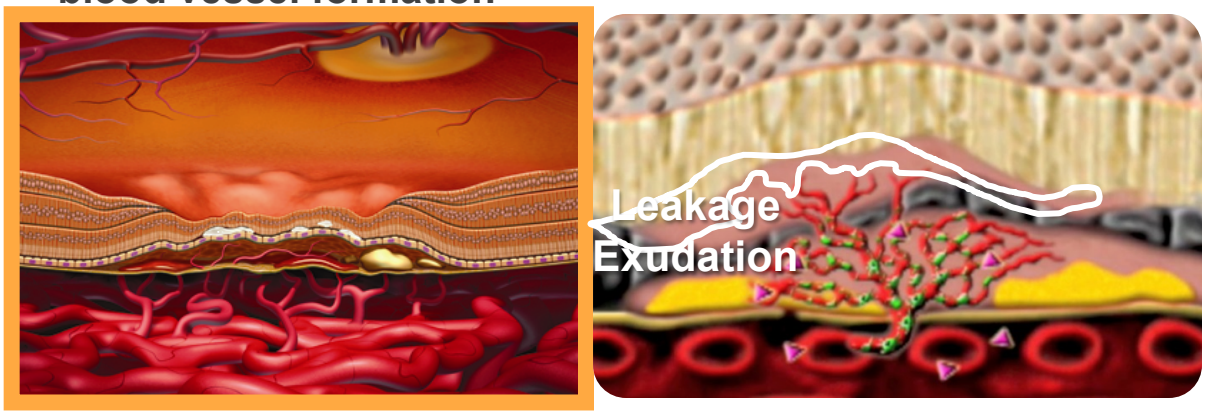
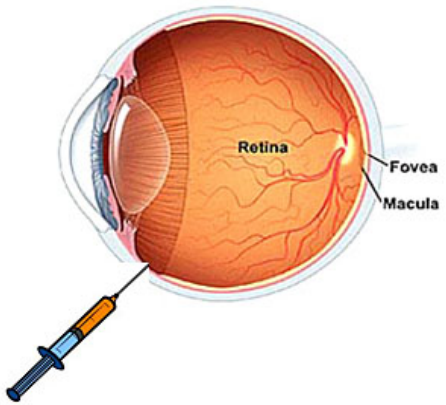
# Treatment Options

- **VEGF has been shown to cause neovascularization and leakage.**
- **Anti-VEGF can reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation**




## Anti VEGF Therapy:

- **Macugen** (pegaptanib). Selective $VEGFA_{165}$ inhibitor. Pre-filled syringe; No mean gain in vision.
- **Lucentis** (ranibizumab). Blocks all known VEGFA isoforms. Patients on average gain vision. First approved 2006.
- **Eylea** (aflibercept). Blocks VEGFA , PlGF and VEGFB. Patients on average gain vision. First approved 2011.

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# Trial Design

- The study design evolved due to new drug discovered and Change of Heathy Authority requirement.
- Comparator selection
  - Laser,  PDT
  - Lucentis (First approved 2006), Eylea (First approved 2011)
- Dose regimen
  - Regular dose (Monthly, Bi-monthly...)
  - PRN(Pro Re Nata = as needed)

  Heathy authority request to reduce the public burden.

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# Trial Design

- Treatment masking
  - No “blinding” in ophthalmology trial, we call it “masking”.
  - Complicate masking requirement that need more training for site personnel
    - VA assessor
    - Evaluating investigator
    - Treating investigator

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# Trial Analysis

*Primary variables*

- Best-corrected visual acuity (BCVA): Score calculated based on the number of letters read and the algorithm according to the ETDRS worksheet, usually range from 0 to 100.


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# Trial Analysis

*Primary variables*

- Image data
  - OCT(optical coherence tomography),
  - FA(Fluorescein Angiography)
  - CF(Color Fundus)
- Ophthalmic examination
  - Intraocular pressure

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# Trial Endpoints

*Primary & secondary endpoints*

- Primary endpoint
  - Change from baseline BCVA to the average level of BCVA over all monthly assessments from Month 1 to Month x.

$$\text{Average } \Delta \text{ BCVA} = \frac{\Delta \text{ BCVAM1} + \Delta \text{ BCVAM2} + \ldots \Delta \text{ BCVAMx}}{x}$$

- Secondary endpoints
  - Change in BCVA from baseline to Month x / by visit
  - OCT parameter analysis
  - FA/CF parameter analysis
  - ...

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# Trial Endpoints

*Primary endpoint variable imputation*

- Primary endpoint variable missing data imputation rule
  - ➢LOCF (last observation carried forward)
  - ➢MV-LOCF (Mean-value last observation carried forward)

LOCF and MV-LOCF are older method. And both are still used when specified in protocol as the primary analysis due to some special reasons, e.g. protocol developed few year ago, extension study to keep consistent with core study.

  - ➢MI (Multiple imputation), recommended now

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# More on Retina Trial Specifics

*Eye*

- Usually choose one eye as study eye
- Information of both eye is collected, trial analysis focus on study eye
- Since both are related, some efficacy analysis need to be performed on both study and non-study eyes.
- Adverse event be analyzed by ocular and non-ocular.

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# More on Retina Trial Specifics

*Reading center (RC) data*

- RC is responsible on assessment of disease images
  - There are large amount images such as OCT, FA and CF.
- Reliable reading center is critical on data quality
  - Check RC technical ability and quality of following procedure.

    For example, a RC did not follow the stamping guidance. This incidence caused re-reading of all images and led to submission delay for 6 months.
  - Check RC to ensure it can provide all needed parameters.
  - Check RC standard to ensure it is consistent with protocol definition.
- Interact with RC during trial
  - Check real data whether RC follows standard at early stage to avoid re-reading images
  - Request regular data transfer to track progress.

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# Conducting Trail in China

*Challenges*

- Health Authority
  - Guidance changing time to time
  - Not enough staff to review submission package
- Site
  - China has lot of sites and specific disease populations, however ones that qualify for retina clinical trail are not many or qualify but not available due to various reasons.
  - Enrollment competition,  some sites have multiple trials ongoing at the same time.

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# Conducting Trail in China

*Challenges*

- Reading center
  - Not enough qualify RC to choose from
  - Not enough expertise on retina disease knowledge
- Source data
  - Lot of  data issues due to inexperienced site and/or RC,
    - Which increased workload of the Clinical, CRA, DM, Stat and programmer.
  - Some cases caused trial team extra time on discussion and implement new rule.
    - Not follow protocol
    - Take concomitant medication
    - Take traditional Chinese medicine
    - Fewer AEs than global trials

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# Tips for Trial Programmer

- To ensure trial reporting more smoothly with high quality, trial programmer could consider:
  - Good understanding of study design and SAP, in order to create clear and accurate derived dataset specifications.
  - Plan ahead with detail timeline (Analysis data and output of each milestone e.g. dry-run, DBL).
  - Check source data issue at early stage.
  - Work closely with core members early to get  agreement on outputs.
  - Regular meeting with core function(DM/Bios) to get the lastest status or communicate the key issue.

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# Any question?

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# Thank You

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