EDNA: Early Detection of Neovascular Age-related macular degeneration (AMD)

HEALTH ECONOMICS ANALYSIS PLAN (HEAP)

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1. BACKGROUND

Neovascular age-related macular degeneration (nAMD) causes severe visual loss and is the most common cause of blindness in persons > 50 years of age in the western world (Royal College of Ophthalmologists, 2013). In recent years, there have been major advances in the clinical management of patients with nAMD, notably the introduction of biological therapies targeting vascular endothelial growth factor (VEGF), a protein implicated in the pathogenesis of this disease. Anti VEGF treatments have improved visual outcomes compared with laser therapies which were the mainstay in past decades (Rosenfeld 2006, Brown 2006). With anti VEGF treatments, although visual improvement occurs in some one-third and a further 40% of those treated will maintain visual acuity at their immediate pre-treatment level, there is a considerable residual burden of visual morbidity. This residual burden of visual disability is evident in the outcomes reported in the pivotal clinical trials as well as in subsequent trials and post licensing studies (Martin 2012). For example, 40% of patients will have acuities of 20/50 or worse after two years of intensive treatment and the proportion of those with 20/20 or better acuity (normal vision) is small (less than 5%) (Martin 2012). The reality is that normal vision is still a long way from being achieved. There are a multitude of reasons why the present treatments do not restore normal macular function. These include (a) the presence of a neovascular network with a large component of mature vessels which do not regress or permanently close with anti VEGF treatment (b) glial and fibrous tissue that distort the delicate cellular architecture of the retina, (c) neural and retinal pigment epithelium (RPE) cell loss. Thus, permanent morphological damage of the macular tissues at the time of presentation and a degree of irreversible visual loss remain important barriers to visual recovery. Therefore, there is a strong rationale to detect the onset of nAMD at a stage when the cellular constituents of the retina have the potential to recover, prior to the onset of fibrosis and when the neovascular complexes have not matured to the point where they are less likely to regress.

There is a body of evidence in the literature to indicate that when nAMD occurs in the first eye, it often remains undetected for long periods and patients are unaware of a visual deficit because the fellow eye usually has good function and masks the deficit (Royal College of Ophthalmologists, 2013). Patients are often more alert to alterations in visual function in the second eye. However, evidence indicates the second eye too has suffered considerable losses of acuity by the time the patient has sought help. In one study which followed up patients

enrolled in a laser prevention trial the average acuity at presentation when nAMD was detected in the better seeing eye was 20/100 which represents more than a quadrupling of the visual angle (Maguire 2008). Reasons for the delay in presentation included: (a) development of the lesion at an extrafoveal location with no early impact on acuity; (b) a sudden onset of a bleed or an acute increase in exudation with involvement of the fovea by these manifestations; and (c) adjustment to minor changes in visual function. Approximately 8-10% of patients with nAMD in one eye will develop the same condition in the fellow eye per year. Detection of nAMD at a stage when damage to the retina is not permanent with prompt initiation of treatment could result in better preservation of sight. Therefore, there is a clear need for an easily and rapidly performed cost-effective monitoring test that will detect the onset of nAMD with high diagnostic accuracy.

2. EDNA STUDY AIM AND OBJECTIVES

Aim: To identify the optimum non-invasive test strategy that will robustly detect nAMD in fellow eyes during follow-up in secondary care of persons with nAMD in the first affected eye.

Objectives:

Primary objective: determine the diagnostic monitoring performance of the interventions (ETDRS visual acuity, fundus evaluation of signs of nAMD, the Amsler test, clinical assessment of images captured by OCT, and patient's subjective assessment of vision, against the reference standard of fundus fluorescein angiography).

Secondary objectives:

1. **develop an economic model to identify an optimal monitoring regime (in terms of cost-effectiveness).**
2. develop a risk prediction model using baseline characteristics to predict the development of nAMD in the study eye.
3. create a cohort (including a Biobank) which can be used for future prognostic and diagnostic studies.

3. OVERVIEW OF THE PLANNED ECONOMIC ANALYSIS

The following sections of this document provide details on the methods and analysis plans required to meet secondary objective 1 above. It should be read in conjunction with the EDNA study protocol (EDNA Protocol, V4 11_05_18) and statistical analysis plan.

An economic decision analytic model will be developed to assess the cost-effectiveness of the different test monitoring strategies for patients with nAMD in one eye. Single test strategies will be compared against each other in a primary analysis. However, the cost-effectiveness of certain test combinations may also be explored. It is anticipated that the modelling will follow an individual simulation approach, whereby individual patients (with characteristics matching those of patients in the prospective EDNA cohort) will be simulated to pass through the model one at a time. Patients will be individually sampled and defined by a limited set of baseline characteristics that may influence progression to nAMD (e.g. gender, age, type of nAMD in the first eye) based on the statistical analysis. Based on the follow-up data of the EDNA cohort, time to event analysis will be used to derive monthly probabilities of conversion of the second eye to active nAMD. This survival analysis will inform estimates of the rate of conversion to nAMD for simulated individuals in the economic model. Conversion rates may be derived by nAMD subtype in the first eye (RAP, CNV), if this is found to be significantly predictive of progression in the second eye.

Following conversion to nAMD, study eyes will be modelled to lose vision at rates observed for untreated eyes in existing published literature, until they are appropriately identified by a monitoring strategy and treatment is initiated. Untreated post-conversion rates of visual loss will be primarily informed by a review of existing trials where nAMD interventions are compared against placebo (Wong et al. 2006; Rosenfield et al. 2006). In addition, visual acuity data are being collected on EDNA participants after development of nAMD as part of the FASBAT study (FASBAT study protocol V7) and case note extraction on EDNA participants who convert during study follow-up but who are not treated immediately. This data will provide an additional source to help validate the modelled projections. Once identified as converted, patients may either be monitored until their vision drops below a given VA treatment threshold or treated immediately with anti-VEGF therapy. Alternative scenarios will explore the impact of the two approaches. Once treatment is initiated in the second eye, patients will be modelled to gain, maintain and lose vision in line with treated cohorts (e.g. Rosenfield et al. 2006; IVAN Study Investigators. 2012; Chakravarthy et al. 2013; Chakravarthy et al, 2015). Again, post treatment visual acuity data being collected as

part of the FASBAT study (FASBAT Study Protocol, Version 7) and case note extraction will be used to help validate modelled projections.

Based on their modelled nAMD status and visual acuity in the second eye, patients will be assigned to one of several discrete visual acuity health states and assigned a quality of life weight and costs applicable to that state. The time spent by individuals in different model states will be multiplied by the appropriate utility weights to generate quality adjusted life years (QALYs).

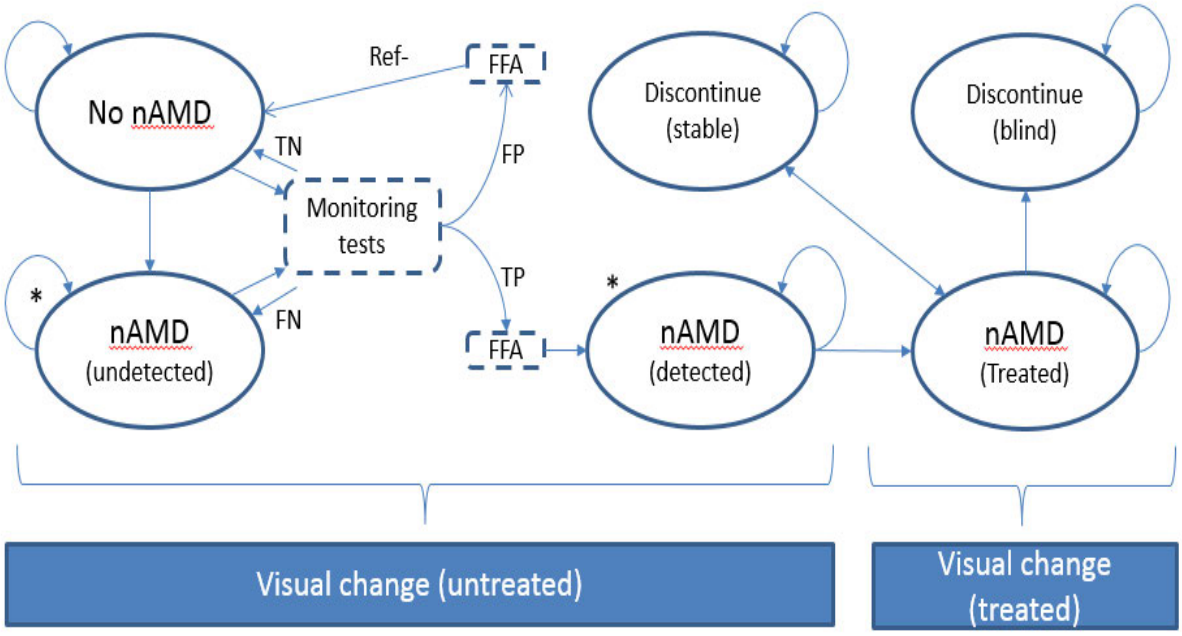
The estimated accuracy of alternative diagnostic tests, derived from the statistical analysis, will be embedded in the natural history model to assess the clinical and cost-effectiveness of adopting alternative monitoring strategies (based on the five diagnostic tests being evaluated in EDNA) for the early detection of nAMD in the second eye (i.e. the EDNA study eye). Frequency of monitoring will be determined by the observed frequency of testing in the EDNA cohort over the follow-up period. Sensitivity and specificity for each test will be derived using Analysis A3 for estimating person level diagnostic accuracy as described in statistical analysis plan (see EDNA Statistical Analysis Plan). This approach, which uses the index test results at the last study visit only, provides the best estimate of diagnostic performance at a single point in time, which is necessary for modelling expected differences in the time from conversion to diagnosis when using the different tests.

3.1. Model structure

The finer details of the model structure will be subject to change as the analyses progresses. However, the model will be structured around disease status (no nAMD, nAMD), diagnosis status (undetected, detected) and treatment status (untreated / treated). Change in visual acuity is modelled at the level of the individual within each of the model states and there is a simplifying assumption that patients maintain their baseline VA in the study eye (second eye) until it progresses to nAMD. The VA categorisation is currently based on the approach used in a recent health technology assessment of OCT for the diagnosis and guiding of treatment in nAMD (Mowatt et al., 2014), and classifies patients into one of five states based on ETDRS letters in the best seeing eye: ≥70; 55-69; 35-54; 20-34; and <20 ETDRS letter score. This may be further refined in the final model depending on availability of suitable health state utility data. A planned simplifying assumption is to assume that VA in the

second eye is broadly representative of VA in the Best Seeing Eye throughout the modelled time horizon. A simplified schematic of the structure is provided in Figure 1 below.

Figure 1: Simplified schematic of the model structure



Notes: VA (visual acuity); TN (true negative); FN (false negative); TP (true positive); FFA (fluorescein angiography). Whether or not FFA would be triggered by all positive test results in standard practice is questionable and alternative assumptions will be explored. *Scope also exists to specify conversion risks and test sensitivity/specificity by nAMD subtype (as determined by the first eye).

3.2. Data collection and analysis for populating the economic model

3.2.1 Time to conversion and onward progression

It is anticipated that progression to active nAMD in the model will be informed by parametric survival analysis of the time to conversion data collected in EDNA. Alternative parametric distributions will be explored, and the model with the best fit to the observed data will be selected based on statistical measures of goodness of fit, such as the Bayesian information criterion, and the plausibility of future projections. The benefit of using parametric survival analysis is that it will enable projection of the rate of conversion beyond study follow up (i.e. 36 months). This may be important for estimating the cost-effectiveness of alternative monitoring strategies over the longer term. The survival model may incorporate key baseline patient level covariates found to influence the rate of progression to nAMD, creating potential

for the model to assess the cost-effectiveness of risk stratified approaches to monitoring. Mortality will be modelled using age/sex specific UK life tables, with any necessary adjustment required to reflect any changes in mortality associated with modelled disease status (e.g. blindness).

It is anticipated that some patients who convert to nAMD will be identified early by sensitive monitoring tests prior to noticeable vision loss occurring. Based on variation in treatment protocols and guidance across participating sites, it is not expected that all these individuals will receive immediate treatment, and some will continue to be monitored for progression and visual loss. Data available at EDNA exit and from follow-up in the FASBAT study or case note extraction, will provide some more information on the rate of VA loss in those who do not receive treatment until their vision has dropped below a certain threshold; e.g. VA < 6/12 in England (https://www.nice.org.uk/guidance/ta155/chapter/1-Guidance). The model base case will assume treatment initiation upon conversion and scenario analysis will explore the impact of treatment initiation based on current guidance. Visual change in the model for untreated and treated nAMD are currently based on monthly probabilities of gaining 15 letters or more, losing between 15 and 30 letters, and losing > 30 letters, derived from the placebo and treatment arm if MARINA trial, respectively (Rosenfeld et al, 2006; Mowatt et al., 2014). However, the approach and data source may be refined in the final model to allow for more granular changes.

3.2.2 Diagnostic accuracy

Alternative monitoring/diagnostic strategies for the second eye will be embedded in the natural history model, applying the sensitivity/specificity estimates obtained for the alternative tests. Since the cost-effectiveness modelling is based on expected changes in VA following conversion to nAMD, and VA loss ≥ 10 ETDRS letters is one of the index tests, this creates a challenge with respect to embedding test sensitivity in the economic model; i.e. the VA test cannot be positive in true cases where no visual loss has yet occurred, and by definition must be positive in true cases where visual loss ≥ 10 ETDRS letters has occurred. In addition, it is likely that the sensitivity of the subjective visual change test is highly correlated with actual visual change, and the same may also be true, to a lesser extent, for other index tests. It will therefore be desirable to assess test sensitivity for nAMD with and without visual loss (≥ 10 ETDRS letters) at the time of detection. By doing this for the alternative diagnostic strategies and embedding the correlated sensitivities in the natural

history model of visual change, we will be better able to estimate the expected time gain from conversion to detection associated with more sensitive tests which can detect disease prior to vision loss occurring. Sensitivity and specificity for each diagnostic test will be estimated based on the test result from the last monitoring visit in EDNA. As indicated above, this relates to approach 3 for person level diagnostic accuracy as described in the statistical analysis plan (see SAP).

3.2.3 Downstream treatment pathways

Patients who develop nAMD in their second eye will be modelled to receive treatment upon detection, and their vision will be modelled to improve / deteriorate at the rates observed for treated eyes. However, scenario analysis will explore the impact of initiating treatment only if visual acuity drops below 6/12 as per NICE treatment guidelines. The proportion of patients following different treatment protocols (fixed dosing; treat and extend; pro-re nata) for the second eye will be obtained from the FASBAT dataset. The expected costs of these treatment strategies will be informed by estimates of mean numbers of injections and monitoring visits by year of treatment observed in available clinical trials (e.g. IVAN Study Investigators., 2012; Chakravarthy et al., 2013). Those modelled to remain unidentified by any specific strategy (post conversion) will continue to progress at rates observed for untreated eyes. Therefore, the model will capture visual acuity and associated health related quality of life benefits of early detection and treatment post conversion. Following treatment over several years, it is possible that patients discontinue treatment as their disease stabilises or their vision drops consistently below a lower VA threshold. This lower threshold for futility of treatment is currently set to <18 ETDRS letters but this may be revised in the final analysis depending on clinical opinion. Discontinuation for other reasons will be determined if possible, from rates reported in the long-term follow-up of available RCTs.

3.2.4 Health state utilities

Available health state utility data for quality adjusting survival time by visual acuity status in nAMD has been identified from searches of the published literature. Searches have identified several potential sources (e.g. Tosh et al., 2012; Espallargues et al., 2005; Butt et al., 2013; Butt el al., 2015; Butt et al., 2017; Dixon et al., 2015; Hodgoson et al., 2017; Brown et al., 2000; Czoski-Murray et al., 2009). An emphasis will be on identifying values based on the reported health status of UK patients with nAMD but scored using a UK population tariff. Since there is suggestion that the EQ-5D may lack sensitivity to changes in VA, directly

elicited values for specific visual acuity states will be considered where these have been elicited from a UK general population sample using an appropriate valuation technique. Current values applied in the model are based on Brown et al., 2000, as per the model developed for the recent HTA report on OCT for the diagnosis of nAMD (Mowett et al., 2014). The precise VA categorisation and utility values applied may change in the final model.

Table 1: Current health state utility inputs applied by VA categories in the model

VA ETDRS letters	Utility weight
≥70	0.89
55-69	0.81
35-54	0.57
20-34	0.52
<20	0.40

3.2.5 Costs

Health service costs will be obtained where possible from standard UK sources (BNF; Department of Health, 2018; PSSRU, 2019). Costs of health and social care associated with adverse visual acuity outcomes will be identified from a review of existing cost of illness studies applicable to the UK (e.g. Meads and Hyde, 2003). In order to obtain more accurate marginal costs of performing the different types of monitoring tests on the second eye at clinic visits, it is likely that a micro costing approach will be required. This will require inputs on resource uilisation, which will be based on clinical opinion across participating sites. This will focus on the staff time and grades, and equipment required to undertake the different procedures. Values applied in the model are currently adapted from existing literature and are subject to change in the final model (Table 2).

There is an assumption in the model that prior to conversion of the second eye, it is the treatment and monitoring of the first eye that drives the frequency of outpatient visits. Thus, estimated marginal costs of testing the second eye at these monitoring/treatment visits are to be applied. From the point of conversion of the second eye, it is assumed that treatment and monitoring of the second eye drives the visit frequency. So, from this point onwards, full treatment and monitoring costs are applied. To inform these post-conversion treatment and

monitoring costs for the second eye, we will utilise mean numbers of treatments and monitoring visits by year from treatment initiation, tailored to the different types of treatment protocol being followed where possible (Table 3). These estimates of resource use will be derived from the data reported in available clinical trials (e.g. Martin et al., 2012; Rosenfeld et al. 2006; IVAN Study Investigators., 2012; Chakravarthy et al. 2013; Chakravarthy et al. 2015).

Table 2: Table of unit costs (NHS perspective)

Resource	Unit costs	Source	Notes
Ophthalmology outpatient visit	£95	NHS Reference costs 17/18	Code 130 Outpatient consultant led appointment in ophthalmology
OCT (equipment, testing and interpretation)	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
OCT (second eye)	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
Fundus slit-lamp examination (equipment and staff time)	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
Fundus examination (second eye)	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
Visual Acuity test	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
Amsler test	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
Patient's subjective assessment of vision	To be finalised	EDNA centre costing survey	Bottom-up calculations based on staff time, equipment and consumables
Fluorescein angiography (FFA)	£121	HRG 2017-18	BZ86B Outpatient intermediate vitreous retinal procedures
Ranibizumab (Lucentis) injection	£551	BNF, 2019	1.65mg/0.165ml solution for injection pre-filled syringes

			(Novartis Pharmaceuticals UK Ltd)
Aflibercept (Eylea injection)	£816	BNF, 2019	2mg/50microlitres solution for injection vials (Bayer Plc)
Bevacizumab (Avastin injection)	TBC based on prices paid	EDNS centres	1.25 mg per injection
Cost of blindness (Health service perspective)	£517 per month in year 1 £498 per month from year 2 onwards	Mowatt, 2013	Cost per month

Notes; details of test costs to be finalised

Table 3 Resource use (second eye)

Resource	Measure	Source	Notes
Average frequency of diagnostic/ monitoring visits	Tests per year	EDNA data	To be informed by numbers of test visits prior to conversion
Average number of post-diagnosis monitoring visits in Year 1		Published trials (TBC)	
Average number of post-diagnosis monitoring visits in Year 2		Published trials (TBC)	
Average number of injections in Year 1		Published trials (TBC)	
Average number of injections in Year 2		Published trials (TBC)	

Notes; frequencies to be confirmed from available literature

4.0 Model based analysis

The analysis will capture cumulative health and social care costs from the perspective of the NHS and QALYs accruing to patients under alternative monitoring strategies over a lifetime horizon. Future costs and QALYs will be discounted a rate of 3.5% per annum, in line with NICE guidelines (http://www.nice.org.uk/aboutnice/howwework/devnicetech/guidetothemethodsoftechnologyappraisal.jsp).

Incremental cost-effectiveness ratios will be estimated by comparing each strategy to the next less costly strategy (excluding those strategies that are more costly and less effective than an alternative option). Table 4 provides a dummy table for presenting the numerical output from the model. The net monetary benefit (NMB) approach will be used to help interpret the cost-effectiveness findings. The NMB approach transforms the cost-effectiveness ratio for each strategy into a linear combination of the two components, using a ceiling willingness to pay threshold (Rc) per unit of effect:

[NMB = (Effects*Rc)-Costs]

By calculating the NMB for each strategy, using a range of plausible values for Rc, the strategy with the greatest net monetary benefit can be identified by at each value of Rc.

Probabilistic sensitivity analysis will be conducted to characterise the joint uncertainty in the modelled outputs (cost and QALYs) arising from the combined uncertainty surrounding all input parameters. An appropriate probability distribution will be assigned to each input parameter and Monte Carlo simulation will be used to analyse the model a large number of times, with a value for each parameter drawn at random from its assigned probability distribution for each model run. The output from this probabilistic analysis will be presented as cost-effectiveness acceptability curves (CEACs) and acceptability frontiers (CEAFs) (Briggs et al., 2006). CEACs present the probability of alternative strategies generating the greatest net monetary benefit for different ceiling ratios (Rc) of willingness to pay per QALY gained, while acceptability frontiers present the probability of the strategy with the highest expected net monetary benefit (at different values of Rc) being cost-effective. Further deterministic sensitivity analyses will be undertaken to assess the impact on findings of uncertainty surrounding key model input parameters and structural assumptions.

Table 4: **Dummy cost-effectiveness results table**

Monitoring strategy	Mean costs (£)	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	NMB at Rc = £20,000 per QALY (£)
1.	C1	-	Q1			
2	C2	C2-C1	Q2	Q2-Q1	C2-C1/ Q2-Q1	
3	C3	C3-C2	Q3	Q3-Q2	C3-C2/ Q3-Q2	
n	Cn	C_n-C_{n-1}	Q4	Q_n-Q_{n-1}	(C_n-C_{n-1})/ (Q_n-Q_{n-1})	

*ICER Incremental cost-effectiveness ratio

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