

**The MATE study: a 24 month, multicentre, pilot,
randomised controlled trial comparing standard care with
individualised treat and extend regimen for treatment of
neovascular age-related macular degeneration with
aflibercept**

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Abstract:

Purpose: Various treatment regimens have been described for anti-vascular endothelial growth factors (VEGF) in neovascular age-related macular degeneration (nvAMD). Recently, these include treating nvAMD with aflibercept using a 'Treat & Extend' (T&E) regimen. However, important questions regarding efficacy and treatment burden remain unanswered. The MATE study was a 24-month, prospective, multicentre, pilot, randomised controlled trial (RCT) comparing standard care with T&E in treating patients with aflibercept, in order to inform a future large-scale RCT.

Methods: The study adopted a mixed methodology, with the primary outcome to assess feasibility by recruitment rates and in-depth interviews of trial staff at the end of recruitment and year one. All interviews were transcribed and analysed using thematic analysis. Forty patients were randomised to receive aflibercept for nvAMD as per either standard care or a T&E regimen across the UK in six NHS Ophthalmology units. Baseline demographics, mean change in visual acuity and central retinal thickness from baseline to 12 and 24 months, and number of treatments and visits over 24 months were collected as secondary outcomes.

Results: The recruitment rate was 3.07 participant/month. Key themes in recruitment phase interviews were human factors, protocol-related issues, recruitment processes and challenges; key themes in year one interviews were variation in practice and challenges. Both arms showed a trend towards gain in visual acuity in the first year which was not maintained in the standard care arm at the end of 24 months. These were achieved with one less treatment in the T&E arm.

Conclusion: Minimising set up delays, optimising recruitment strategy, accounting for variation in practice at sites are key factors in the recruitment and running of a multicentre, randomised controlled trial in this context.

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Archana Airody

Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously presented for an award at this or any other University. All sources are acknowledged as references.

I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.

I have been involved in this project from conception of the idea, obtaining regulatory approval (IRAS application), study design and have written the study protocol under the guidance of Professor R Gale. I have provided clinical care for all the patients at my site for the full study duration. I have worked closely with the trial manager and Chief Investigator to ensure the study is delivered as per protocol at the other sites.

All the data collection, conducting of qualitative interviews, transcribing the interviews, analysis of both qualitative and quantitative components has been done by me under the guidance of my supervisors (Professor R Gale and Dr Heidi Baseler). In addition, I have written the qualitative data chapters under the supervision of one of my Thesis Advisory Panel member, Dr Julie Seymour.

Data from this project has been presented by me at both regional and international conferences. Details of which are given below:

Data from Chapter 6 were presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting, Hawaii, USA (April 2018) and published in abstract form:

- Airody A, Dorey T, Mankowska A, Balaskas K, Mukherjee R, Empeslidis T et al. The Mate study: treating neovascular age-related macular degeneration with aflibercept: a pilot, 24 month randomised controlled trial comparing standard care with treat and extend regimen (12-month results). *Investigative Ophthalmology and Visual Science*. 2018; 59: 798.

Data from Chapter 4 were presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting, Vancouver, Canada (April 2019) and published in abstract form:

- Airody A, Seymour J, Dorey T, Szczerbicki T, Mankowska A, Balaskas K et al. How to set up a successful multicentre randomised controlled trial in the field of neovascular age – related macular degeneration treatment? Lessons from the MATE pilot study. *Investigative Ophthalmology and Visual Science*. 2019; 60: 1168.

Data from Chapter 6 were presented as a free paper at the European Society of Retina Specialists annual congress, Paris, France (September 2019).

- Airody A, Szczerbicki T, Allgar V, Downey L, Baseler H, Morland A et al. The MATE study: a 24-month, pilot, randomised controlled trial comparing standard care with individualised treat and extend regimen with intravitreal aflibercept for neovascular age – related macular degeneration. (24 months results)

I have also presented the lessons learnt from the recruitment phase of this study (from chapter 4) at the Retinal Ophthalmologists Sharing Expertise Across Services (ROSES) meeting 2018 held at Bury, UK. Good practice learnt from the recruitment phase of this study was shared with other research active centres taking part in neovascular age related macular degeneration treatments research.

Archana Airody

Chapter 1 : Introduction and objectives the MATE study: a 24 month, multicentre, pilot, randomised controlled trial comparing standard care with individualised treat and extend regimen for treatment of neovascular age-related macular degeneration with aflibercept

1.1. Introduction

Age related macular degeneration (AMD) is a leading cause of sight loss in the developed world¹. By the year 2020, 196 million people have been projected to be suffering from AMD with a projected increase to 288 million by the year 2040². The prevalence of late forms of AMD (i.e. geographic atrophy and neovascular AMD) increases with age with an estimated prevalence of 263,000 cases of neovascular AMD (nvAMD) in the UK alone³. NvAMD accounts for the majority of cases with severe visual loss due to AMD⁴.

The pathogenesis of neovascular AMD is multifactorial involving interplay of oxidative damage and accumulation of lipofuscin in the Retinal Pigment Epithelial (RPE) cells. This in turn leads to chronic inflammation, complement activation and accumulation of extracellular waste, cell debris, eventually leading to growth of new blood vessels i.e. choroidal neovascular membrane. This final process is Vascular Endothelial Growth Factor (VEGF) driven and results in exudation, pigment epithelial detachments, haemorrhage and cell death⁵.

Treatments for neovascular age related macular degeneration have evolved significantly over the last decade. Previous treatments, mainly consisting of laser photocoagulation and photodynamic therapy, aimed to cauterise and occlude the neovascular complex, and at best prevented moderate to severe visual loss^{6,7}.

Anti-Vascular Endothelial Growth Factors agents are directed against VEGF and are administered intravitreally. These include ranibizumab, bevacizumab and aflibercept, and are currently the mainstay of treatment for neovascular age related macular degeneration. Ranibizumab is a recombinant monoclonal Ab fragment which blocks all active isoforms of VEGF. Bevacizumab is a full length humanised monoclonal Ab

that targets all isoforms of VEGF. Aflibercept is a human recombinant fusion protein made up of immunoglobulin binding domain of VEGF receptors 1 and 2 and Fc fragment of human Ig G1⁸.

Landmark clinical trials such as ANCHOR and MARINA have proven that intravitreal ranibizumab stabilises vision in a majority of patients, and in fact a third of patients show a 15 letter gain in visual acuity^{9, 10}. However, treatments were required on a monthly basis with a significant cost and burden to the patient. The SEVEN UP study, which is a cross-sectional analysis of a cohort from the ANCHOR and MARINA trials, shows that the initial gain in visual acuity is maintained only if treatments were repeated on a monthly basis¹¹. Infrequent or quarterly treatment (EXCITE and PIER) resulted in the loss of vision gain during early treatment^{12,13}. An ‘as required’ individualized regimen in the PRONTO study demonstrated similar efficacy outcomes but still required monthly visits for monitoring of neovascular activity¹⁴. This was reproduced in the CATT and IVAN studies^{15,16} which compared ‘pro re nata’ i.e ‘prn’ with monthly treatment regimens for both ranibizumab and bevacizumab. In patients in whom disease activity is well controlled (i.e. absence of activity) by anti-VEGF agents, there is always the risk of reactivation of disease¹⁷. The SEVEN UP study and other real-world data reveal that these medications are needed on a long term basis at regular, frequent intervals to maintain initial visual gains^{11, 18}.

This emphasises the fact that not only do these eyes need regular treatment, but they also need regular monitoring of disease activity. This places a high demand on services and is currently a key concern of medical retina services across the country and the world. A recent publication reported that the lack of capacity in NHS eye clinics resulted in delay in follow-ups and sight loss, especially in patients with chronic diseases such as age-related macular degeneration¹⁹

The VIEW studies demonstrated that in the first year of treatment, after a loading phase, aflibercept treatment gave patients the opportunity to attend only every 8 weeks with similar efficacy outcomes. In the second year, treatment intervals may be

extended²⁰. This has been received as a significant step forward in reducing the burden of treatment and this posology has become standard of care (SC).

Below is a brief description of anti-VEGF dosing in neovascular AMD with main focus on available literature related to Treat and Extend regimen.

Anti-VEGF agent dosing can be divided into two phases – an induction phase comprising of monthly injections for first 3 months, followed by a maintenance phase. The treatment regimen used in the maintenance phase in the long term is mainly affected by efficacy, safety and treatment burden. Treatment regimens have evolved over time to find the optimal treatment interval with maximal visual gain and minimal treatment burden^{21, 8}.

Treatment regimens for anti-VEGF agents can be classified as either *reactive* or *proactive*.

In *reactive* regimens, treatment is administered when there is evidence of disease activity, i.e. presence of intra- or sub-retinal fluid, and drop in visual acuity explained by neovascular activity. These regimes can be tolerant or intolerant of disease activity. Examples include the CATT style regimen, which is intolerant of any disease activity, and the SAILOR type regimen, which is tolerant of some fluid^{21,22}. However, regimes tolerant of disease activity and less frequent treatment tend to have less visual gain or are unable to maintain initial VA gains in the long run. Moreover, with each episode of disease reactivation there is a risk of irreversible sight loss. Reactivation of neovascular disease has been found to be preceded by reduced intraocular VEGF suppression²³. To minimise this risk, treatment regimens using a *proactive* approach aim to treat patients ideally before reactivation to keep the neovascular activity suppressed. They may be fixed monthly, bimonthly or quarterly regimens or individualised ‘treat and extend’ regimens.

1.1.1 Treat and Extend regimes

The main factors determining the use of anti-VEGF agents in the long term are efficacy, safety and treatment burden. In order to decrease the chances of reactivation of disease activity and to individualise the treatment regime, there is a trend towards proactive therapy, i.e. treat and extend regimes. Furthermore, clinicians are more likely to use individualised treatment regimens compared to the fixed regimens used in the original phase III trials²⁴. A ‘treat and extend’ (T & E) individualised treatment regime uses the initial phases of a regimen to find a dosing frequency suitable for an individual in the longer term. These individualised regimens are tailored according to the patient’s response to treatment and aim to reduce the frequency of patient visits and injections while aiming to minimise loss in vision. While inter-individual treatment intervals vary, intra-individual treatment intervals are stable²⁵. The aim is to continually suppress VEGF activity, find the optimal treatment interval for an individual patient whilst minimising the treatment burden.

A summary of literature around using Treat and Extend regimes in neovascular AMD mainly with Ranibizumab followed by Bevacizumab and aflibercept is presented in the tables below. Various studies (as shown in Tables 1.1 and 1.2), including both real world and clinical trial data, have shown similar outcomes with fewer patient visits with a T & E regimen compared to monthly or *prn* treatment regimens.

Current evidence with Treat and Extend (T&E) regime for neovascular age related macular degeneration (nvAMD):

Table 1.1 shows a summary of currently available clinical trials/cohort studies data on Treat and Extend regimens:

Name of study/author	Type of study	Drug used	T & E regimen	Results
ALTAIR study²⁶	Randomised controlled trial comparing two	Aflibercept	Treat and Extend	2 weekly arm: VA gain of

	<p>‘treat and extend’ regimes</p> <p>Japanese population</p> <p>52 weeks duration</p> <p>255 patients – 124 in the 2 weekly adjustment arm and 123 in the 4 weekly adjustment arm</p>		<p>Maximum extension up to 16 weeks</p> <p>Initial 3 monthly intravitreal aflibercept and then extended either 2 weeks or 4 weekly depending on the arm</p> <p>Extended if no fluid; maintained at their interval if residual but decreased fluid</p> <p>Shortened interval if persistent or new fluid</p>	<p>9 ETDRS letters at 52 weeks</p> <p>With a mean of 7.2 injections</p> <p>42.30% were extended beyond 12 weeks</p> <p>4 weekly arm:</p> <p>VA gain of 8.4 ETDRS letters at 52 weeks</p> <p>With a mean of 6.9 injections</p> <p>49.40% of patients were extended beyond 12 weeks</p>
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ATLAS study²⁷	<p>Prospective, multicentre, open label study</p> <p>40 eyes of 40 patients</p> <p>2 years follow up</p>	Aflibercept	Treat and Extend	<p>Mean gain from baseline (58.9 letters) of 7.2 letters at year 1 and 2.4 letters at year 2.</p> <p>Mean number of injections were 8 and 6.5 during first and second year respectively.</p> <p>12 week or longer treatment intervals in 35% and 38% of patients in year 1 and 2 respectively.</p>

<p>TREX – AMD^{28,29}</p>	<p>Randomised controlled trial comparing monthly Vs T and E regime (1:2 randomisation)</p> <p>60 patients in total</p>	<p>Ranibizumab (RBZ)</p>	<p>Monthly versus Treat and Extend (TREX)</p>	<p>Year 1: Mean VA gain of 9.2 and 10.5 letters from baseline in the monthly and TREX arm respectively</p> <p>Mean number of injections through 12 months: 13 in monthly arm and 10.1 in TREX arm</p> <p>Year 2: Mean VA gain of 10.5 and 8.7 letters from baseline in the monthly and TREX arm</p>

				<p>respectively</p> <p>Mean number of injections through 24 months: 25.5 in monthly arm and 18.6 in TREX arm</p>
TREND study ³⁰	<p>Randomised controlled trial</p> <p>12 months, non-inferiority trial, with a 5 letter non-inferiority margin,</p>	Ranibizumab (RBZ)	<p>Treat and Extend</p> <p><i>Treat and Extend regime:</i></p> <p>First 2 injections were monthly (baseline</p>	<p>T and E arm: Mean (Least squares) gain of 6.2 letters at year 1 with a mean of 8.7 treatments</p>

	<p>Phase 3b, multicentre</p> <p>650 patients in total</p> <p>1:1 randomisation monthly (n=327): Treat and Extend (n=323)</p>		<p>and month 1) and then depending on disease activity on OCT extended by 2 weeks to a maximum of 12 weeks.</p>	<p>Monthly arm:</p> <p>Mean (Least squares) gain of 8.1 letters at year 1 with a mean of 11.1 treatments</p>
<p>LUCAS study³¹</p>	<p>Multicentre, randomised, non-inferiority trial with a 5 letter non-inferiority margin</p> <p>1year duration</p> <p>447 patients in total with a 1:1 randomisation to</p>	<p>Ranibizumab (RBZ) and Bevacizumab (BCZ)</p>	<p>Treat and Extend</p>	<p>At year one, mean gain in VA was 7.9 letters in BCZ group and 8.2 in RBZ group.</p> <p>This was achieved with a mean of 8.9 treatments in BCZ group and 8 in the RBZ</p>

	RBZ or BCZ arm			group.
Toalster et al³²	Prospective, multicentre, non-randomised trial 45 patients from 5 sites	Ranibizumab	Treat and Extend Initial monthly injections as part of induction phase for first 3 months, then 2 weekly extension based on level of disease activity on OCT and 1-line or more loss of VA with fluid on OCT with a maximum extension of up to 12	Mean baseline VA of 0.46 LogMAR improved to a mean of 0.36 at 12 months. This was achieved with a mean of 8 injections

			weeks	
Abedi et al³³	Prospective cohort study 2 years duration 120 patients	Ranibizumab or Bevacizumab	Treat and Extend Monthly treatment till no activity from CNVM, then 2 weekly extension till a maximum of 12 weeks. On reactivation, intervals were shortened by 2 weeks from previous disease activity free interval	Mean gain in VA of +9.1 ETDRS letters from baseline at 12 months and +8 at 24 months Mean of 8.6 injections in the first year and 5.6 injections in the second year
Canadian Treat and Extend	Randomised controlled trial,	Ranibizumab	Treat and Extend Versus	Non – inferiority was met

<p>Analysis trial³⁴</p>	<p>Non-inferiority design with 5 letter margin</p> <p>1: 1 randomisation of monthly Versus Treat and Extend</p> <p>12 months duration</p> <p>Total of 526 patients with T&E arm n=268</p> <p>Monthly arm n=258</p>		<p>monthly</p> <p>T&E regimen – treat monthly until stability and then extend treatment intervals by 2 weeks. If signs of reactivation - reduce intervals by 2 weeks if on a 6-8 weekly follow up or reduce intervals by 4 weeks if on 10 – 12 weeks follow up.</p> <p>Resume extending treatment intervals by 2 weeks</p>	<p>with mean gain in VA of 8.4 letters in the T&E arm compared to 6 letters in monthly treatment arm</p> <p>At 12 months, T&E arm needed mean of 9.4 injections and monthly arm, a mean of 11.6 injections</p>
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			once stability is achieved	
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Table 1.2 shows a summary of currently available real-world data on Treat and Extend regimens:

Name of study/author	Type of study	Drug used	T and E regime	Results
Arnold et al 2015³⁵	Observational Outcomes from Fight Retinal Blindness (FRB) registry 1198 eyes from 1011 patients 24 months duration	Combination of Ranibizumab (RBZ), Bevacizumab (BCZ), Aflibercept (AFL)	Treat and Extend Details of regime not specified Retreatment intervals varied mainly from 4 to 12weeks Few patients were treated at 16 weeks	+5.3 ETDRS letters gain at 24 months Mean of 13 injections over 24 months
Barthelmes et al 2016³⁶	Observational Outcomes	<i>Aflibercept</i> (AFL) monotherapy	Treat and Extend	+ 6 ETDRS letters gain at 24 months Mean of 7.8

	<p>from Fight Retinal Blindness (FRB) registry</p> <p>136 eyes of 123 patients</p> <p>24 months duration</p>		<p>Details of regimen not specified</p>	<p>and 5.7 injections in first and second year respectively</p>
<p>Essex et al 2016³⁷</p>	<p>Observational</p> <p>Outcomes from ‘maintenance phase’ of T and E regimen from FRB registry</p> <p>Comparison between short (< or = 3 injections) and longer induction phase (> 3</p>	<p>Combination of RBZ, BCZ and AFL</p>	<p>Treat and Extend</p> <p>Details of regimen not specified</p>	<p>Mean change in VA during maintenance phase +1.0 at 12 months, -0.6 at 24 months and -1.5 ETDRS letters at 36 months</p> <p>Most common interval of first reactivation is 8 weeks</p>

	injections) 36 months duration (< 12 months follow up excluded)			Longer induction group had worse VA outcome and earlier disease reactivation.
Mrejen et al 2015³⁸	Observational study Retrospective real-world data 210 eyes of 183 patients	All 3 (RBZ, BCZ, AFL) agents used, mainly RBZ monotherapy, followed by combination of RBZ and AFL. AFL monotherapy in 2 out of 210 eyes only	Treat and Extend regimen	One-line (ETDRS) improvement with a peak at 18 months; maintained over 6 years Mean of 8.3 anti-VEGF injections/year

<p>Rayess et al 2015³⁹</p>	<p>Retrospective, interventional, consecutive case series</p> <p>3-year treatment outcomes</p> <p>212 eyes from 196 patients</p>	<p>1 to 3 years of treatment with RBZ or BCZ</p>	<p>Treat and Extend regimen</p>	<p>34.4% eyes had gained > or equal to 3 lines of visual acuity</p> <p>20/139 – mean baseline VA improved to 20/79 at 1yr, 20/69 and 20/64 at years 2 and 3 respectively.</p>
<p>Mekjaic et al 2018⁴⁰</p>	<p>Retrospective, observational study from Slovenia</p> <p>115 eyes of 105 patients</p>	<p>2 years of treatment with <i>Aflibercept</i></p>	<p>Treat and Extend</p>	<p>+6.5 ETDRS letters gain at 12 months which is maintained at +7.0 letters at 24 months</p> <p>Mean number of injections 8.4 in first year and 6.1 in second year</p>

<p>Gupta et al 2010⁴¹</p>	<p>Retrospective, interventional, consecutive case series</p> <p>92 eyes of 92 patients</p> <p>Mean follow up of 1.52 years</p>	<p>Treatment with RBZ</p> <p>First study to evaluate cost implications of a T&E regime</p>	<p>Treat and Extend</p> <p>Monthly treatments till exudation free macula and then extended by 2 weeks up to 12 weeks.</p> <p>Intervals were reduced by 2 weeks from previous interval if signs of neovascular activity on OCT or macular haemorrhage.</p> <p>After 12 weeks, patients had option of either</p>	<p>Mean Snellen VA improved from 20/135 at baseline to 20/77 at 1 year and 20/83 at 2 years</p> <p>32% gained > or = 3 lines and 96% lost < 3 lines of VA.</p>
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			treatment and return in 12 weeks or no treatment and return at 8 weeks	
Calvo et al⁴²	Analytical, retrospective observational study 3 years duration comparison T and E with Treat and Observe (resembles PRN) 30 eyes in each group	Ranibizumab	Treat and Extend regimen Versus Treat and Observe – monthly treatments till inactive and then monthly assessment. On reactivation, same cycle repeats	Both arms showed improvement in VA TAE: 0.73 to 0.46 LogMAR TAO: 0.85 to 0.58 LogMAR No difference between two arms No difference in number of treatments in both arms Mean of 20.3 (TAE) and

				18.41 TAO
Chen YN et al 2016⁴³	Retrospective case note review 79 eyes with 9 months or more follow up during 'extension phase' of T&E regimen	Ranibizumab	Treat and Extend	Mean gain of 8.4 ETDRS letters at the end of induction phase. Mean change of -0.5 letters during the extension phase of T&E Average of 8.6 injections per year
Oubraham et al 2011⁴⁴	Retrospective case note review 38 patients with Inject and Extend regime 52 patients with ' <i>prn</i> ' or <i>as needed</i> regime	Ranibizumab	Inject and Extend versus ' <i>prn</i> or <i>as needed</i> regime'	Inject and Extend: Mean gain in VA +10.8 at 1 year Mean number of treatments 7.8 in 1 year '<i>prn</i>' or <i>as needed</i>: Mean gain in VA +2.3 at 1

	52 (+ or – 4 weeks) follow up			year Mean number of treatments 5.2 in 1 year
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Berg et al showed that ranibizumab and bevacizumab were comparable in maintaining visual gains using a treat and extend regimen³¹. The TREX-AMD trial comparing monthly treatment with treat and extend using ranibizumab showed similar functional and anatomical outcomes with significantly fewer treatments in the treat and extend cohort^{28,29}. Benefits of Treat and Extend regimens using ranibizumab have been established both in real world and clinical trials⁴⁵.

VEGF suppression time in the aqueous humour is twice as longer for aflibercept I comparison to ranibizumab suggesting that aflibercept suppresses VEGF longer than ranibizumab⁴⁶.

VIEW trial showed that 8 weekly treatment with aflibercept is non inferior to monthly ranibizumab treatment. Fauser et al showed that intraocular VEGF suppression following administration of aflibercept for neovascular AMD lasted up to 10 weeks thus making a case for longer intervals between treatments with aflibercept in neovascular AMD⁴⁷. Increasing number of clinicians are moving towards a proactive treat and extend strategy in an attempt to continually suppress VEGF activity to prevent recurrences and reduce the need for number of assessment visits and treatment. This will help in reducing the treatment burden both for patients and health care professionals across the globe⁴⁸.

Despite increasing popularity and preference for treat and extend regimens⁴⁸ and a move towards using longer lasting medication like aflibercept, there are no head-to-

head trials to comparing Treat and Extend (T and E) with Standard Care (per label of aflibercept), especially with aflibercept. In Treat and Extend regimens using aflibercept, both 2 weekly and 4 weekly extensions have shown visual gains in observational studies and clinical trial settings^{25,26,37,40}. However, unlike ranibizumab and bevacizumab, there is a paucity of robust evidence comparing the treatment regimens with regards to aflibercept^{49,50}.

For such a comparison to be made a properly designed, large scale randomised controlled trial comparing a T and E regimen with Standard of Care (SC) is required. This would require significant patient numbers and resources. Hence, the MATE study was designed as a pilot randomised controlled trial to compare standard care (per label of aflibercept) with a treat and extend regimen of aflibercept for neovascular age related macular degeneration to help inform a future large-scale RCT.

1.2 Aims and objectives:

The primary outcome of this study was to evaluate the feasibility and acceptability of this study and whether processes (for example, recruitment, and randomisation, treatment and follow-up assessments),resources (deals with assessing time and resources problems that could occur in the main study), management (deals with potential human and data management issues) and scientific (deals with potential safety issues and inform sample size calculation for main study if needed) can run smoothly, are adequate and inform a large scale randomised controlled trial.

The secondary outcome, which would be the main purpose of future randomised controlled trials, was to compare the two treatment regimens with regards to functional and anatomical outcomes and the treatment burden.

Chapter 2 ‘Methodology of the MATE study’ describes the rationale for the mixed methodology used to assess primary and secondary outcomes of the MATE study, incorporating both qualitative and quantitative measures.

Chapter 3 ‘Quantitative analysis of recruitment phase of the MATE study’ addresses the primary outcome (feasibility for running a large-scale randomised controlled trial) by evaluating the success of recruitment to the study using quantitative measures.

Chapter 4 ‘Qualitative analysis of recruitment phase of the MATE study addresses the primary outcome by evaluating the recruitment phase of the study using qualitative methods

Chapter 5 ‘Lessons learnt from the MATE study addresses the primary outcome by evaluating the set up and running of the MATE study mainly addressing the resources and management component of the primary outcome using qualitative methods

Chapter 6 ‘the MATE study: 24 – month efficacy outcomes of a pilot randomised controlled trial comparing standard care with individualised treat and extend regimen with intravitreal aflibercept for neovascular age-related macular degeneration, address the secondary outcome of this study using quantitative methods.

Chapter 7 ‘Discussion and conclusion’ summarises the lessons learnt from this study, their generalisability and sets goals for future work

Chapter 2: Methodology of the MATE study

The MATE study is a multicentre, pilot, randomised controlled trial comparing two treatment regimens (standard care versus individualised treat and extend regimen) of intravitreal aflibercept for neovascular age related macular degeneration. Lessons learnt from this pilot trial will inform a large scale RCT which will be powered to find the difference between the two treatment regimens. A mixed methodology approach using a combination of qualitative and quantitative research has been used to understand the processes involved in this complex intervention.

This chapter describes pilot and feasibility studies, the mixed methods approach and how the different components of the thesis come together to meet the study objectives.

2.1 Pilot and feasibility studies

The Medical Research Council (MRC) guidance encourages researchers to pilot interventions as part of processes evaluation of complex interventions⁵¹. A pilot or a feasibility study refers to a study conducted in preparation of major study⁵². Various definitions of pilot or feasibility studies exist in literature. There is an overlap in definitions of pilot and feasibility studies and clear distinctions are hard to make. The NETSCC defines pilot studies as miniature versions of the main study which evaluate if all components of the trial work well together. They resemble the main study, including assessment of the primary outcome^{53,54}. The term ‘pilot trial’ is best reserved only for a miniature trial which mimics the final trial and is designed to see if all components work optimally⁵⁵. Feasibility studies are performed before a main trial and collect information needed in study design, such as time needed to recruit or collect data, and participant acceptability of randomisation, amongst others. In contrast to pilot studies, feasibility studies do not evaluate the primary outcome and need not be a randomised trial⁵³.

Types of pilot studies are defined below:

- 1) Internal pilot: An 'internal pilot' is one where the data collected during the pilot phase is used in the main study.
- 2) External pilot: An 'external pilot' is one where data collected during the pilot phase informs the main study but is not used in the main study.

The decision of whether a study will be an internal or external pilot should be made at the beginning of the pilot study. Moving forward from the pilot phase, if there are significant changes to the eligibility criteria or study protocol then it is recommended the study be an external pilot as it is representative of a different study population⁵⁴.

The main focus of a pilot study is usually feasibility, with plans to analyse the feasibility data with pre-set criteria for success of the pilot. The decision to proceed to a larger trial is based on these success criteria.

The reasons for conducting a pilot study may be grouped under four broad headings – process, resources, management and scientific.

Process: looks at the feasibility of processes that are important for the success of the main study like recruitment rates, adherent to protocol, adequacy of eligibility criteria and withdrawal rates amongst others.

Resources: look at whether the available resources are sufficient for the study. for example – time, clinical and non – clinical resources.

Management: mainly data management and human factors including challenges faced by the study teams.

Scientific: includes assessment of treatment safety, calculation of sample size of the main study if needed, estimation of treatment effect⁵².

All or some of the above aspects may be studied in a pilot study and would depend on the individual study and the reason it is being conducted. The main reasons for the MATE study and how each of them is met is described in section 2.1.3.

Based on the pre-defined criteria, researchers may decide to go ahead with a larger study as it is, i.e. no change to the protocol or with minor modifications, or stop or go ahead with major amendments^{52,54}. This pilot study will be deemed a success if the following pre – specified criteria are met:

1. Recruitment of 80% of patients within the recruitment window
2. 20 % or less withdrawal rate from the study at 2 years

The data derived from both the primary and the secondary outcomes will be used to decide if this protocol and trial processes work well for the future main study. The decision would be one of the following based on the data available at the end of study:

- Stop - main study not feasible
- Go ahead with modifications
- Go ahead without modifications but with close monitoring
- Go ahead without modifications

Whilst recruitment rates, retention rates, estimate of treatment effect and its variance are calculated by quantitative methods, acceptability of randomisation, willingness to participate and overall acceptability and challenges of the intervention are best evaluated using qualitative methods⁵⁶.

Hence, this study used a combination of quantitative methods (in the form of recruitment rates, analysis of screening logs and secondary outcome analysis) and qualitative interviews of trial staff at the end of recruitment phase and at the end of year one to understand the processes, acceptability and feasibility of the current model. Specific details are described in section 2.1.3 later in this chapter.

2.2 Qualitative approach

Qualitative research involves the use of methods to understand the ‘how, why and what’ aspects of particular research questions. The methods used to explore these issues may include observation, interviews and discussions, thus including an active involvement of the researcher with the participants in arriving at conclusions about

the problems at hand⁵⁷. Unlike quantitative research, qualitative research does not involve numbers, use statistics or test hypotheses to arrive at results. Instead, the data collected are descriptive in nature; views of the participants are collected, or the environment is observed, and interpretations are made based on these data^{57,58}.

Philosophies of research:

The various *philosophies or paradigms* of research govern the research methods used and how data is further handled or 'the reality' constructed.

- Positivist approach: Quantitative methods use this approach, in that all forms of subjectivity are eliminated and the data or the results are not influenced by the person collecting or analysing the data. Here, numerical data are analysed using statistical tests and conclusions are made based on the results. Modern science views the world this way, with the belief that there is one reality and it does not change irrespective of the person investigating it^{58, 59}.
- Interpretivist approach: Here, the belief is that there is more than one reality and it varies depending on the time, person evaluating it and the circumstances of evaluation. Each person says his or her version of the reality and all of this is partial. The results are interpreted based on what people say about their life experiences^{58, 59}.
- Critical theory: Here, the belief is that reality is influenced by the researcher and that he/she brings a certain amount of bias to the research, which should be accounted for⁶⁰. The research question guides the study design, but the ontological and epistemological perspectives of the researcher determine what is considered as knowledge and the sources of this knowledge.

These in turn influence the data collection methods chosen for a study.

Qualitative data collection methods:

Interviews:

Interviews are traditionally face-to-face meetings, but with the advent of newer forms of communication these may not necessarily be so. They may be structured, semi-structured, in-depth, focus groups or group discussions. Structured interviews are

considered a quantitative method as the responses of the participant are fixed and do not depend on the person administering the interview. There is also limited opportunity for exploring these in detail. Semi-structured in-depth interviews, though performed with a small number of participants, give an opportunity to know and understand the views and beliefs of the participants. They enable the researcher to further probe the topic of interest in greater detail by following probes and questioning their beliefs and practices further^{58, 61}. Depending on the mode of contact, interviews may be face-to-face, telephonic, or internet based. They may also be formal or casual, informal talks (for example as part of an ethnographic exercise). Focus groups are useful when collective responses from different people are needed. These groups may be specifically convened for the purpose of the study or the researcher may decide to join a pre-existing group and evaluate the topic of interest.

Observation:

The ideal form of qualitative research would be to observe people in their natural settings and learn about their practices and way of life. Ethnography uses both observational methods and interviews.

The role of the researcher may vary during the study; Gold describes the role of researcher in an observational study as follows:

- The complete participant: This is the ideal scenario. Here, the researcher is an insider and is a part in the community being studied.
- Participant as observer: The researcher is part of the study setting for a reason which is not their research, but this also gives them an opportunity to perform their research there.
- Observer as participant: Here, the researcher would not normally be a part of the community or setting and their presence is based on their research.
- Complete observer: Here, the researcher is not physically present in the scenario but has an opportunity to observe this community. For example, a surgeon views the video recordings of surgeries performed by juniors and colleagues⁶².

Document or artefact analysis:

Here, documents (public or not), videos or audio recordings are described and analysed, and interpretations are made in context to their time, relevance and purpose of publication⁶¹.

Researcher as tool in data collection:

Various authors explore this concept of researcher as a tool of data collection in qualitative research. The critical theory believes that the researcher brings bias into a study. This can be negated or accounted for to some extent by acknowledging this bias and finding ways to minimise it either prior to or during the study.

Interview methods:

Various *characteristics of the researcher* can influence data collection. They are summarised by Miyazaki and Taylor⁶³ below:

- Physical: These are characteristics of the researcher that are obvious to the participant and include age, race, gender and ethnicity. Differences in the gender between researcher and participant have resulted in conflicting evidence in the literature, with no particular trend favouring same-sex pairing or otherwise. However, females were more likely to have a better response rates to interviews using telephonic interviews or with non-verbal cues.

Race and ethnicity were found to be important in research, particularly in racial related topics. Participants usually wanted to avoid offending or hurting the feelings of the interviewer if they were of a different racial background.

Older age produced a better response to interviews; however, there is limited evidence regarding how people of different age groups behaved with researchers from a different age group. This form of bias is of particular relevance whilst interviewing children and the elderly.

- Psychological: These characteristics are not obvious to the participants at the first instance; instead, they become evident during the course of the interview. For

example, different interviewers have different styles of interviewing, which may range from being friendly or neutral to being terse and to the point. It has been found that researchers with a friendly and warm nature were more likely to gather data better.

- **Background:** These characteristics are more concealed than the physical characteristics of the interviewer. They are not obvious, but may become evident by body language, non-verbal cues, mannerisms or a researcher's standpoint on the particular topic being studied ⁶³.

The relationship between the interviewer and interviewee is unique and is influenced by factors mentioned above. In addition, the data quality is influenced by whether one interviews a known or unknown person. For example, data quality can be influenced by the familiarity of the language used between them, or if the interview is conducted in the natural setting of the participant or an alien or new place, which might place the researcher in a position of power. Sometimes, the participant may perceive that the researcher is more knowledgeable than the participant, and this power dynamic will affect the data collected^{63,64}.

In responsive interviewing, there is a more friendly approach and the bond created extends beyond the period of research. This allows for rich and detailed information to be collected; however, ethical issues about data disclosure used in the study may arise. The reactions of the interviewer may also be influenced by the responses given by the interviewee, and there is a constant process of thinking and following up leads ⁶³.

How do we decrease the researcher bias? There are several ways to address researcher bias.

- First, one can take account of researcher characteristics by describing researcher characteristics. Reflection and understanding the interview style of each person also helps to account for this bias to some extent.
- Secondly, one can identify one's strengths and weaknesses prior to the study. One can use practice interviews, or make interviewing a team effort, as

various members of the team bring different expertise. All these help in decreasing the researcher bias.

- Thirdly, one can decrease the level of interaction between the researcher and participant. For example, this could be done through telephonic interviews or mailing questionnaires. Research has shown that telephonic interviews may decrease the influence a researcher has on the participant, though not necessarily⁶³.

2.3 Mixed methodology approach

A mixed methods approach is being increasingly used in healthcare research. This approach has high validity as it allows combining numerical with narrative data in the analysis. Gaps in understanding of processes in complex interventions can be filled by using qualitative methods alongside a quantitative approach⁶⁴. Qualitative research has been conducted in conjunction with randomized controlled trials. It may be performed before, during or after a clinical trial to explore the components of a trial or in preparation of a clinical trial as in a feasibility study. This enables researchers to explore the experiences of the trial participants, trial processes or even nonparticipation in a trial further⁶⁶.

Qualitative studies have been useful to answer questions pertaining to acceptability, practicality and implementation of a study⁵². The various components of a clinical trial can be 'tested' by conducting the trial in miniature as a pilot randomized controlled trial. However, the resources, management, processes and participant acceptability of the intervention are best evaluated by a qualitative study⁵⁶.

In-depth interviews of the trialists give an opportunity to explore the trial processes to understand the set up and running of a clinical trial.

In a mixed methods approach, data is collected, analysed and inferences made using both qualitative and quantitative methods. The need to use both methods and how they relate to each other should be specified. Triangulation of data from both approaches facilitates the integration of findings and helps find answers to the research questions⁶⁷.

- Parallel data analysis: here data collection and analysis of both data sets is performed separately, and findings are brought together at the interpretation stage.
- Sequential data analysis: here data from one method are analysed in a particular sequence with a purpose of informing rather than integrating with the other method
- Concurrent data analysis: here data from one method is integrated with the other set by either ‘quantising or qualitisng’ the data and inferences made.

Mixed methodology approach used in the MATE study:

In the MATE study, the qualitative methods have been used parallel with quantitative methods to answer the research question. The details of how qualitative and quantitative methods have been used in parallel to meet the objectives of the study are described below:

Primary outcome:

Process - processes evaluation was done in two stages. Firstly, analysis of the recruitment phase and secondly, the set up and running of this study.

The analysis of screening logs gives the screen failure rate (quantitative data) and reasons for non – participation. Recruitment rates were derived from the screening logs maintained at each site (quantitative data). These quantitative measures were used in parallel with data derived from qualitative face to face interviews of trial staff conducted at the end of recruitment.

Study set up and study procedures like randomisation, adequacy of eligibility criteria, data collection forms and challenges in running of the study were studied using qualitative face to face interviews of trial staff (mainly principal investigators and study sponsor) conducted at the end of recruitment and end of year one. These were used in parallel with plotting the participant flow using a CONSORT style diagram to give the number of participants who discontinued the study i.e. withdrawal rate (quantitative data).

Resources – adequacy of resources such as time, capacity, finances, equipment or staffing constraints were addressed using qualitative methods in the form of face to face interviews of key trial staff at the end of recruitment and end of year one.

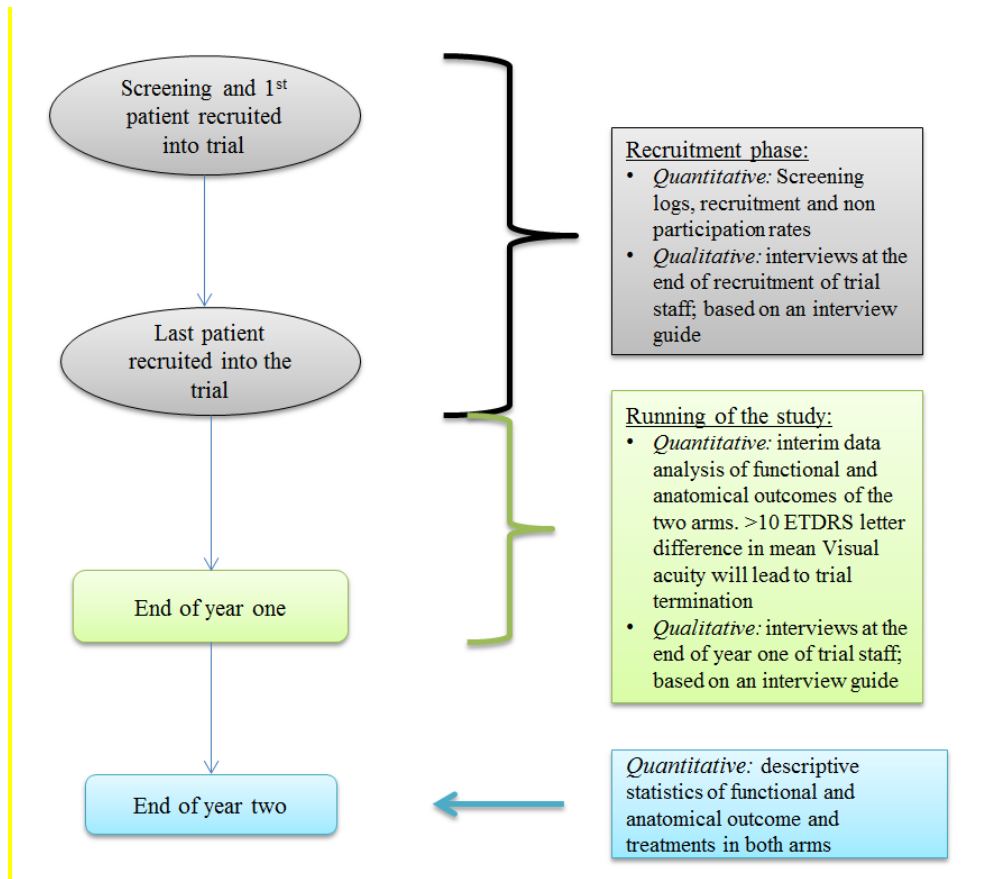
Management - data management issues and the challenges faced at each site were studied using qualitative methods in the form of face to face interviews of key trial staff at the end of recruitment and year one.

Scientific - assessment of safety between the treatment regimens was assessed using quantitative methods in the form of an interim data analysis at the end of year one. At which point if there was a difference in visual acuity of more than 10 ETDRS letters between the two arms the trial would be terminated.

Secondary outcome:

The secondary outcome of this study is to compare efficacy outcomes between the two arms without significance testing. This is done using quantitative methods using descriptive statistics of visual acuity, central retinal thickness and number of treatments and visits to assess treatment burden. A brief overview of the trial design is given below with a flow chart depicting how the qualitative and quantitative components of the study fit to answer the research question.

Figure 2.1: shows the interplay of the qualitative and quantitative components in the MATE study



Furthermore, specific methodological details that go beyond what has already been described here are described within each individual chapter in this thesis.

Chapter 3: Quantitative analysis of recruitment phase of the MATE study

This chapter is presents the quantitative analysis of recruitment phase of the MATE study. Part One presents analysis of screening logs and part two presents analysis of recruitment rates.

3.1 Part one – Analysis of screening logs

3.1.1 Introduction

The Clinical Data Interchange Standards Consortium (CDISC) defines screening as a process of active consideration of subjects for enrolment into a trial⁶⁸. CONSORT guidance recommends collecting information about the screening phase of a clinical trial, though no clear guidance is available about the exact information to be collected. This is intended to help in evaluating selection bias during recruitment⁶⁹. The Screened, Eligible, Approached and Randomised (SEAR) framework has been recently recommended to supplement CONSORT guidance and suggests that details about participants should be collected as part of a screening log for a study, including ones approached and eventually not found to be eligible. The screening and recruitment phase of any trial is labour intensive and can have multiple challenges inherent to the trial design, staff (e.g. training) or the patient population being approached⁷⁰.

Screening logs provide valuable information about recruitment hurdles in real time and can identify potential site specific and trial specific problems which can be addressed to facilitate recruitment^{70,71}.

Prolonged recruitment and high screen failure rates add to expenses, prolong study timelines and result in a suboptimal use of resources. These all add to research ‘waste’ and use up valuable and limited resources which could be used elsewhere⁷².

Much of the literature about screening logs and screen failures come from oncology and neurosurgery trials. Varied meanings have been used in these studies for ‘screen failures’. Strictly speaking they should include participants who are consented and undergo screening procedures. But sometimes in large scale trials this ‘screen failure’ term is used to define all those who have been considered for participation but do not meet eligibility criteria ⁷³⁻⁷⁵.

There is no standardised definition of screen failure and guidance on data that needs to be collected. The National Institute of Health (NIH) defines screening logs as a ‘document that provides information on all individuals that were evaluated for participation in a research study’⁷⁶. Change in regulations can also affect data collected as part of screening⁷⁷ thus affecting the quality of screening logs. For example, 23% of screening logs in the POINT trial did not have any data⁷⁸. Only 36% of the sites had ‘usable’ screening logs in the RESTART trial⁷⁸. With this amount of variability, Elm and colleagues argue whether it is worthwhile to collect screening information⁷⁸. This poor-quality data does not add value and has limited generalizability; but does take up valuable time and resources of an already overstretched research team.

Maintaining a screening log early in the study along with reasons for non-participation and screen failure can provide insight to the recruitment processes and modification needed to facilitate recruitment. Quality of screening logs maintained by a site has also been found to be an early indicator of overall site performance in a trial⁸⁰.

There is lack of published literature about screening logs, screen failure and screening processes in general in ophthalmology. We evaluate screening logs as part of processes evaluation of the MATE pilot study.

3.1.2 Aims

To evaluate the screening logs as part of processes evaluation in the MATE study.

3.1.3 Methods

The MATE study was conducted in six NHS medical retina units across the United Kingdom from December 2015 to January 2019. Part of the primary outcome was to study the processes involved in recruitment in this study. All six sites were requested to maintain a log of the participants approached and the outcome. If participation was declined, where possible the reasons were noted. Number of participants approached, number screened, and number of screen failures including the reason for these outcomes were recorded where possible. Screen failure rate and non-participation rate were calculated. Reasons for non-participation and screen failure were analysed.

3.1.4 Results

A total of 93 participants were given the Patient Information Sheet (PIS) across all the sites and approached to take part in this study between December 2015 and January 2017.

Thirty-eight declined participation and 54 were screened. Of these, 44 were recruited into the study and 10 failed screening procedures. One participant was given the PIS but not screened for the study as they were recruited into a competing study (competing for the same patient population) with a closer deadline for end of recruitment. Four participants were withdrawn by the study sponsor as non-refracted visual acuity had been used for screening and hence eligibility could not be confirmed. These results are summarised in the diagram below (Figure 3.1.1).

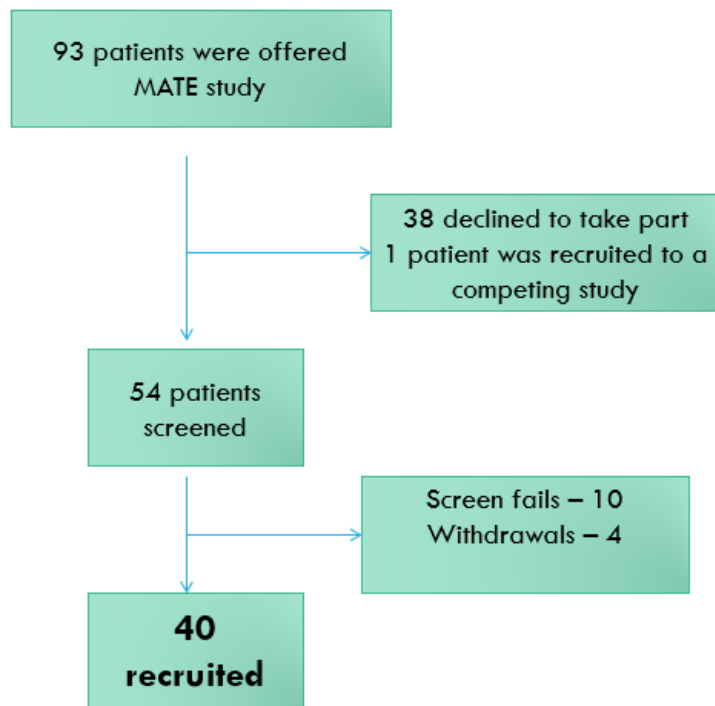


Figure 3.1.1: Diagram summarising screening phase of MATE study

Further details regarding screening, broken down by site, are presented in Table 3.1.1.

Table 3.1.1: Overall summary of screening log.

Site	Offered PIS	Number Declined	Number Screened	Screen fails	Number recruited	Withdrawals	Other
001	26	13	12	1	11	0	1*
002	11	3	8	0	8	0	
003	14	5	9	1	8	0	
004	10	2	8	3	5	0	
005	10	4	6	1	3	2^	
006	22	11	11	4	5*	3 ^s	
Tota	93	38	54	10	40	4	1

1							
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*offered PIS but recruited to competing study

^ By sponsor as non-refracted VA used at screening visit

§one patient after 1st visit; two patients by sponsor as non - refracted VA used at screening visit

Screen failure:

The overall screen failure rate in the MATE study across all sites was 18.51%.

Table 3.1.2 summarises the reasons for individual screen fails, broken down by site. Reasons for screen fails are summarised across sites are displayed in Figure 3.1.2.

Table 31.2: Number of screen failures per site with reasons.

Site	Number of screen fails	Reason for screen fail (with numbers)
001	1	High blood pressure (1)
002	0	
003	1	VA too good to qualify (1)
004	3	Patient refused screening procedures (FFA) post consent (1) VA too good to qualify (2)
005	1	On long term oral steroids (1)
006	4	Transfer to another hospital (1) Blepharitis (1) VA too good to qualify (1) Could not have screening procedures - FFA due to fear (1)

REASONS FOR SCREEN FAIL

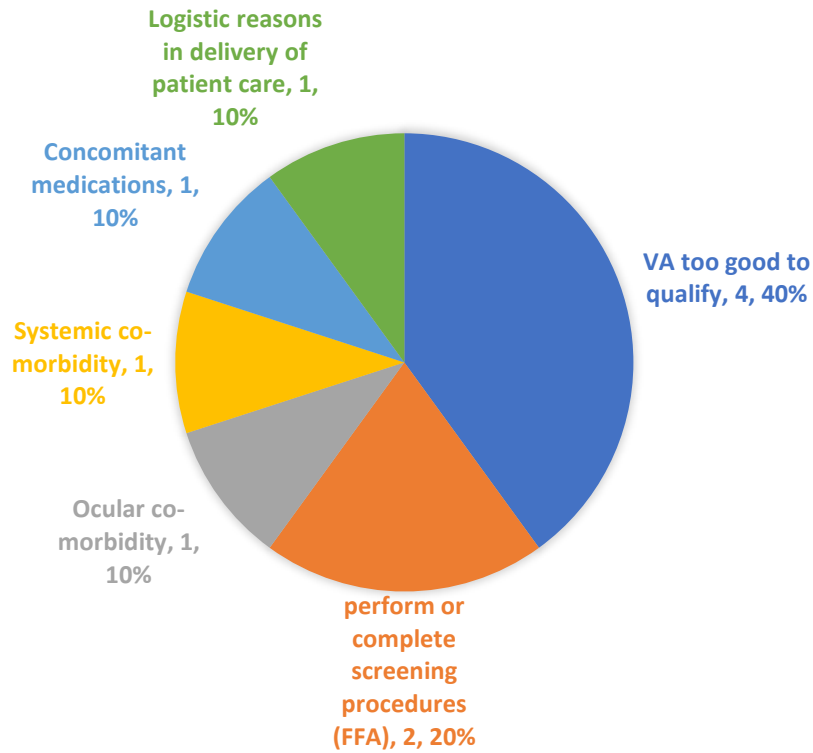


Figure 3.1.2: Summary of reasons for screen failure

Visual acuity rated too good to qualify for the study at the screening visit was the most common reason for screen failure (40%) followed by inability to perform screening procedures (20%). High blood pressure was the reason for screen failure in one patient.

Non-participation

The non-participation rate in the MATE study was 40.8%. The reasons for non-participation, broken down by site, are listed in Table 3.1.3. An overall summary of reasons is presented in Figure 3.1.3.

Table 3.1.3: Number of patients declined per site with reasons for non – participation in the trial

<u>Site</u>	<u>Number declined</u>	<u>Reasons for non-participation (with numbers)</u>
001	14	<p>Not eligible (but not screened) (1)</p> <p>Declined -no reason given; incl. one recorded as patient decision (7)</p> <p>Declined – long wait for IMP (1)</p> <p>Declined – does not want to travel (1)</p> <p>Self- discharge (1)</p> <p>Discharged from clinic (1)</p> <p>Being treated in another hospital (1)</p> <p>*OTHER – PIS given but recruited to competing study with a closer deadline (1)</p>
002	3	Not interested (3)
003	5	<p>Not interested in taking part (2)</p> <p>Has Alzheimer’s disease (1)</p> <p>Patient declined – no reason given (1)</p> <p>Patient would prefer treatment locally (1)</p>
004	2	<p>Declined trial participation due to transport issues (1)</p> <p>Declined – no reason given (1)</p>
005	4	Not had enough time to read PIS and wants treatment in another hospital (1)

		<p>Not eligible (but not screened) (1)</p> <p>Screening appointment date not convenient (1)</p> <p>Failed to attend screening appointment (1)</p>
006	11	<p>Declined trial participation – no reason given (2)</p> <p>Declined after reading PIS; concerned about risks (1)</p> <p>Patient has Alzheimer’s; partner thinks it is too much for them (1)</p> <p>Kidney disease; could not have FFA (1)</p> <p>Mobility issues, makes frequent attendance difficult (1)</p> <p>Keen to take part after discussion but read PIS – did not want treatment (1)</p> <p>Keen following discussion but declined after reading PIS; due to length of study (1)</p> <p>Declined as wanted treatment at another hospital (1)</p> <p>Moved/transferred care to another hospital (1)</p> <p>Patient cancelled all further appointments for a few months – reason not known (1)</p>

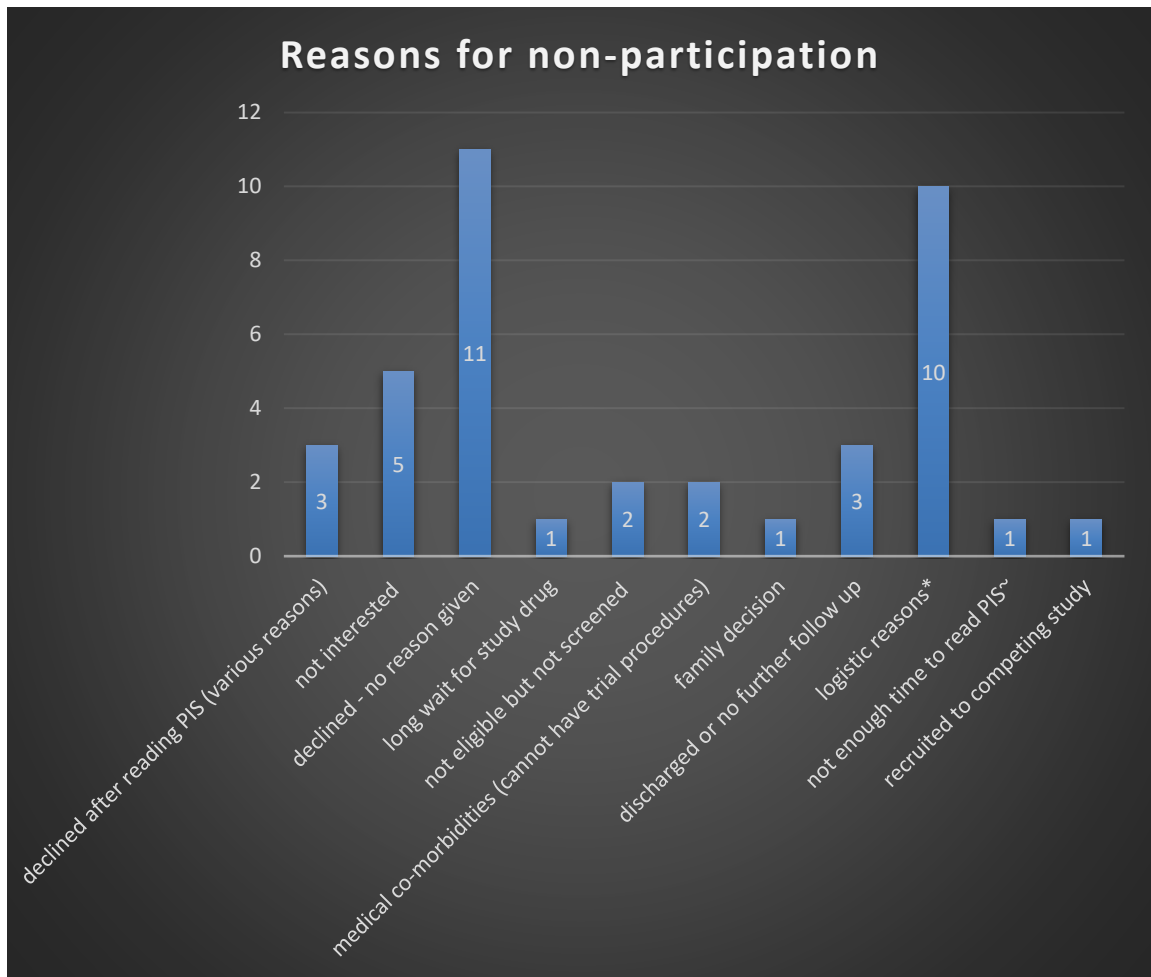


Figure 3.1.3: Summary of reasons for non- participation

(* includes – travel related reasons, screening appointment date not convenient and patient preference for treatment in another hospital; ~ more than one reason given by patient for declining trial participation)

In 28.9% of the cases, no reason was given for not wanting to take part in the trial, followed by logistic reasons (includes travel related concerns, screening appointment not at a convenient time and treatment preference in another hospital) in 26.3%, and a further 10% were not interested in the research. Three patients declined to take part after reading the PIS; reasons included concerns about risks, the length of the study and not wanting treatment.

3.1.5 Discussion

Maintaining screening logs has been recommended as good practice^{69,70}. In this study, all patients who were consented underwent screening procedures and those found not to be eligible for the study were classified as ‘screen failures’.

Table 3.1.4 showing a comparison of screen failure rates with other studies in literature. * reported as screen failure rates

Name of the study	Type of study with speciality	Screen failure rate	Screen failure + Non participation rate
MATE study	Multicentre, pilot RCT - Ophthalmology	18.51%	48.75%
Wong SE et al⁷³	Phase II/III therapeutic trials in Genitourinary malignancies	25 % (21-29%) Mean (range)	
Wang D et al⁷⁴	Oncology clinical trials (all except phase I)		75.8%*
Wang D et al⁷⁴	Oncology phase I clinical trials		78.2%*
POINT study⁷⁸	Multicentre RCT of patients with transient ischemic attacks		95%*
RESTART study⁷⁹	Multicentre RCT on use of anti-platelets after intracerebral		92%*

	haemorrhage		
Mckane et al⁸²	Phase 1 clinical trials for solid tumours	24.6%	
Duchesne et al⁸¹	RCT comparing treatments in prostate cancer	42.7%	75.7%*
Slieker et al⁸⁰	2 Multicentre RCTs on neuroprotection in severe traumatic brain injury (TBI)	80% and 90%	

Table 3.1.4 shows the variation in the definition of screen failure rates used in the literature. While some studies include only those that consented and underwent screening procedures, others use the term ‘screen failure rate’ to include both screen fails and non-participation.

The screen failure and non-participation rate varies with the complexity, setting (acute or not), and the phase of the trials. Not meeting the trial eligibility criteria is the most common cause for screen failure in our study. This is in keeping with other studies in literature^{71,80,81}.

Half-way through the recruitment period (August, 2016) a change in eligibility criteria regarding blood pressure requirements was made to facilitate recruitment. Changes in eligibility criteria and study population account for 16% of all protocol amendments⁸³.

In our study, four participants were withdrawn by the study sponsor following consenting and undergoing screening procedures. This was because non-refracted visual acuity was used during screening, and hence eligibility could not be confirmed. This issue was resolved by further training of trial staff (optometrists and investigators) about trial related procedures.

Screen failures can have financial implications both for the sponsor and the site⁸⁴. While usually there is a financial incentive to the site for every participant recruited,

there may not always be a payment for patients screened for a study, which means that the site is not being paid for this additional work. This is something to be considered at a trial planning stage both from a recruitment point of view and if there is a possibility of high screen failure rate for a study, the sites might want to have an agreement in place for this additional workload.

In our study the non-participation rate was 40.8%, which is much lower than other studies shown in Table 3.1.4. Of these, 92% were due to patients declining to take in the study, except for three participants (7.8%) who were discharged from clinical care. In contrast to other studies in literature, there were no instances of investigators declining to recruit ^{75,81}.

Based on qualitative analysis of interviews following the recruitment phase of the MATE study (presented in chapter 4 in this thesis), we found that this was likely due to the study being an open trial, offering medication currently used as first line therapy on the NHS and majority of trial procedures being in line with routine clinical care.

We find that recording the reasons for non-participation also gives useful insight to trial participation. Although a reason for non-participation was not recorded in the majority of cases, and approximately 10% of patients were simply not interested in taking part in research, the remaining reasons were informative. The next most common group of reasons for non-participation in this study included logistic reasons related to travel or that the screening appointments were not convenient for participants. Therefore, early in the study (January 2016), protocol amendments were made to facilitate screening by performing screening and baseline visits on the same day. This was to minimise burden both on patients and trial staff.

In this study, some patients found the patient information sheet (PIS) to be too long or complex. These issues can be resolved by producing a shorter version or a summary PIS. Inviting patients to discuss the trial procedures and the nature of their commitment to the trials by dedicated research team members may help resolve some of the issues raised here.

3.1.6 Conclusion

Screening logs including reasons for non-participation provide useful information about recruitment processes. Data from this study is helpful in designing and planning other large scale randomised controlled trials involving treatments for age related macular degeneration and other medical retina conditions like diabetic macular oedema and macular oedema secondary to retinal vein occlusion requiring anti – VEGF treatments.

3.2 Quantitative analysis of the recruitment phase in the MATE study - Part two: Recruitment rates

3.2.1 Introduction

Randomised controlled trials are considered the best form of evidence⁸⁵. A great deal of effort and resources go into the planning and delivery of multicentred randomised clinical trials. One of the main challenges for research teams across the globe is to recruit to time and target⁸⁶. Poor recruitment is the most common cause for randomised controlled trials to be discontinued. This raises important ethical considerations of exposing patients to interventions without proven benefit and waste of valuable resources as these studies which fail to meet their end points are less likely to get published⁸⁷. Lack of resources, strong preferences to a particular form of treatment and decreased patient pool are few factors noted to impede recruitment⁸⁷. There are very few studies looking at interventions to facilitate or improve patient participation in clinical trials⁸⁵. Several studies in oncology, mental health and family practice use a combination of qualitative and quantitative approaches to explore the barriers and facilitators of recruitment^{89,90,91}. Qualitative approaches help understand the ‘why’ aspect of recruitment trends in a study.

However, it may not always be possible to extrapolate the recruitment trends and results from other subspecialties to ophthalmology. In contrast to some other subspecialties, for example, the majority of eye conditions are not life threatening, and the interventions may not be as complex or require significant changes in the participant’s lifestyle. These factors could influence recruitment rates, either

negatively or positively. There is a lack of literature around recruitment in ophthalmology clinical trials and macular degeneration.

Between 1997 and 2001, the Submacular Surgery Trials Research Group enrolled over 300 patients into three randomised controlled trials evaluating the role of surgical removal of subfoveal choroidal neovascular lesions secondary to age related macular degeneration and other conditions⁹². One of the aspects of the study was to compare patient accrual between community- and university-based centres. Although the overall trial performance was to a high standard in both the groups, the community centres tended to perform to a lower level. Regular feedback about performance and monitoring ensured good performance from the research teams⁹³.

More recently, inspired by the slow recruitment in the SCORE – CRVO trial (Standard Care versus Corticosteroid for Retinal Vein Occlusion – Central Retinal Vein Occlusion), the SCORE 2 (Study of Comparative Treatments for Retinal Vein Occlusion 2) team implemented a few techniques to enhance recruitment and evaluated their usefulness with the help of a questionnaire. Study design features such as the supply of the study drug by sponsor, the ability to screen and randomise on the same day, imposing less restrictive eligibility criteria and not including a sham arm were found to facilitate recruitment. Motivational emails from the trial physician leadership and the monthly e-newsletter SCORECARD from the sponsor were perceived by the research teams to be useful in staying focussed on recruitment⁹⁴.

Trial drift is a known phenomenon in clinical trials. As the recruitment period increases there is a general lack of interest and reduced knowledge base among the trial personnel in turn leading to slower recruitment. This is commonly due to staff turnover resulting in less trained staff, competing studies and a limited patient pool. This can be addressed by proper planning, communication and re-training of the research teams⁹⁵.

The MATE study uses a mixed-methods approach to explore areas around recruitment into multicentred randomised controlled trials in neovascular age-related macular degeneration. To the best of our knowledge this is the first study of its kind and lessons learnt from this trial will help plan large-scale RCTs of macular degeneration

and other conditions in ophthalmology. The current chapter focuses on the quantitative data acquired around recruitment to the study.

3.2.2 Methods

The MATE study was a pilot, 24 month, multicentred, randomised controlled trial comparing standard care with individualised treat and extend regimen for aflibercept in neovascular age-related macular degeneration. 40 patients were recruited in six NHS medical retina units across the United Kingdom from December 2015 to January 2019.

As part of the processes evaluation around the recruitment phase of the study recruitment timelines, total recruitment period, mean recruitment duration with median and range, recruitment rates (per site, per month) and enrolment risk time were calculated for the whole trial and the individual participating sites.

3.2.3 Results

Screening log results are presented in the previous section (part A) of this chapter.

Table 3.2.1 lists the key dates during the recruitment phase.

<i>Recruitment Time point</i>	<i>Date</i>
Date of study activation (Green light)	30 th December 2015
First participant recruited	27 January 2016
Last Participant recruited	25 January 2017
Total recruitment period (days)	393 days (approximately 13 months)

Recruitment period:

Total recruitment period for the study was 393 days (approximately 13 months) extending from 30th December 2015 to 25th January 2017.

The mean recruitment duration of the study was 194 days (SD 100.75); with a median of 223.5 days and range of 129 -393 days. The individual site level details are given in Table 3.2.2 below.

Table 3.2.2: shows individual site recruitment details

Site	Site target	Site initiation date (green light)	First patient screened date	First participant consented date	Last participant recruited date	Site recruitment window (days)
001	8	30-Dec-15	20-Jan-16	27-Jan-16	25-Jan-16	393
002	8	06-May-16	08-Jun-16	08-Jun-16	21-Sep-16	139
003	8	19-Apr-16	26-Apr-16	26-Apr-16	08/11/2016	203
004	5	06-May-16	24-May-16	02-Aug-16	28-Sep-16	146
005	10	31-May-16	27-Jul-16	17-Jul-16	06-Oct-16	129
006	4	31-May-16	05-Jul-16	05-Jul-16	01-Nov-16	155

The original recruitment window was 6 months. This was extended to 13 months to meet the recruitment target, with last 4 months being competitive recruitment where the sites competed with each other to fill up the last few spaces available in the study.

Recruitment rates in the study are as follows:

The overall recruitment rate in the study was 3.07 participants per month. During the study, sites recruited at a rate of 6.67 participants per site. Recruitment rate per site per month was 0.51 participant/per month/ per site.

Enrolment risk time was defined as the time from site activation to overall trial level enrolment cessation for each site. This was divided by the number of participants enrolled to calculate the enrolled risk per month. The enrolled risk time varied from 4.63 to 13 months with a mean of 6.45 months. The enrolled risk per month varied between sites from 0.56 to 1.25 as shown in Table 3.2.3.

Table 3.2.3: Enrolled risk time and enrolled risk per month

Site	Enrolled risk time (in months)	Enrolled risk per month
001	13	1.18
002	4.63	0.56
003	6.76	0.87
004	4.86	1.25
005	4.30	0.70
006	5.16	1.00

Recruitment timeline

Figure 3.2.1 below demonstrates recruitment activity across all sites by month. The highest recruitment of 7 participants each was in the months of June and September 2016. The lowest recruitment was in December 2015 and March 2016.

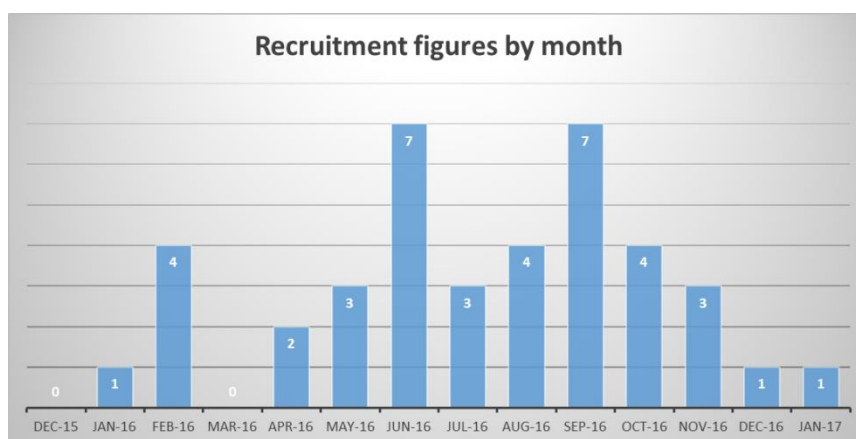


Figure 3.2.1: Recruitment pattern across all sites per month.

Recruitment activity was on an increasing trend from April 2016, when more sites joined the study. Recruitment tailed off towards the last three months during the recruitment extension phase.

Individual site recruitment patterns are shown in Figure 3.2.2. Note that site 003 had spurts of recruitment activity in the months of May and October 2016, the reasons of which are described in the qualitative data analysis in Chapter 4.

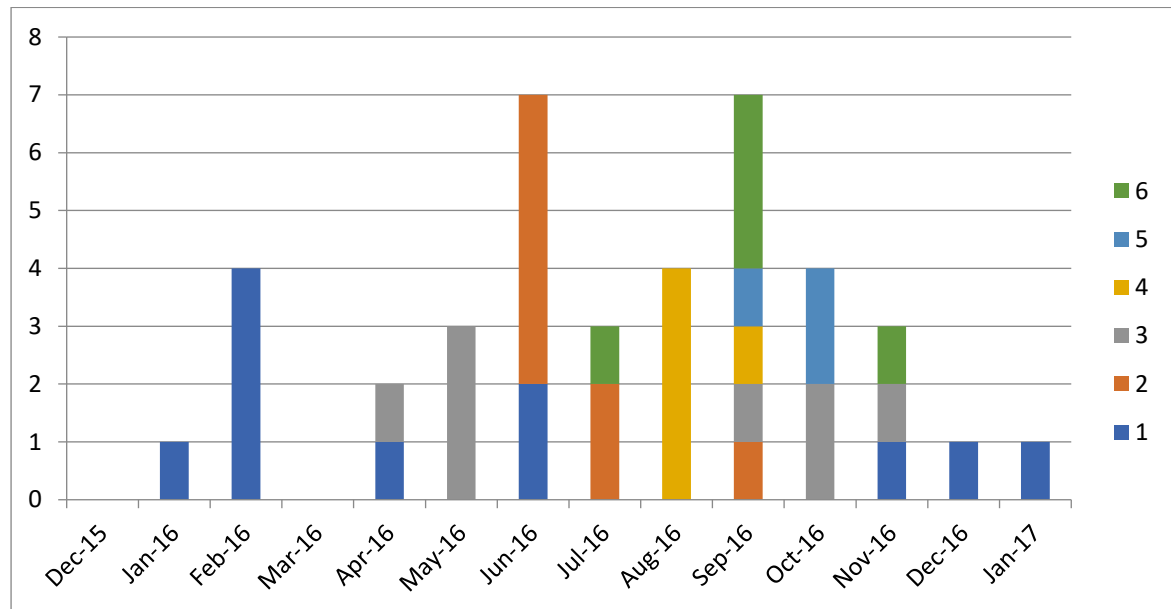


Figure 3.2.2: shows recruitment figures per site. Here Y- axis represents the number of participants recruited and X – axis denotes time. Colours in the legend denote the six study sites

3.2.4 Discussion

There is limited literature regarding recruitment level data in neovascular AMD treatment trials. The only other comparable ophthalmology trials particularly relevant to neovascular AMD treatment are the Submacular Surgery Trials^{92,93}. These trials were complex, surgical trials for choroidal neovascular membrane secondary to mainly neovascular AMD. They differ in eligibility criteria and trial procedures although they involve the same patient population.

The other group of studies with published recruitment literature in ophthalmology are the retinal vein occlusion (RVO) treatment trials⁹⁴. They involve a different disease pathology and slightly younger age group but are similar in treatments involved. i.e. intravitreal injection treatments, making them good for comparison with our study.

Recruitment rates

Recruitment rate overall per month was lower in the MATE study compared to other studies (as shown in Table 3.2.4 below) but recruitment rate per month per site was better than in the rest of the studies. This may be explained by the fact that all the other studies were multinational trials with large numbers of sites, and hence recruited more patients overall per month, whilst individual sites recruited fewer patients per month. The SCORE – 2 study reported better recruitment rates in comparison to other retinal vein occlusion studies. This was attributed to trial design features that included no control arm, allowing patients with prior anti-VEGF treatment to take part in the study, same day screening and randomisation, study sponsor providing the drug and good communication of trial leadership with the sites⁹⁴.

Table 3.2.4: Comparison of recruitment rates across similar ophthalmology treatment studies^{92, 96-98}.

Study <small>(duration of recruitment)</small>	No. of sites	Recruitment period <small>(months)</small>	No. of participants	Recruitment rate (RR) <small>(participants/month)</small>	RR (participants /month /site)
SCORE <small>IVTA for MO in CRVO (Nov 2004 – Feb 2018)</small>	66	40	271	6.7	0.1
CRUISE Ranibizumab <small>for MO in CRVO (July 2007 – Dec 2008)</small>	95	18	392	21.7	0.23
SCORE – 2 <small>Bevacizumab Vs Aflibercept for MO in CRVO Non inferiority (Sept 2014 – Nov 2015)</small>	66	14	362	25.7	0.39
SSG Trials <small>CNV 2^o to nvAMD & other causes 3 RCTs (April 1997 – Sept 2001)</small>	27 <small>(6 closed before year one)</small>	54	336	6.22	0.23
MATE <small>Pilot RCT, aflibercept in nvAMD T & E Vs SC (Dec 2015 – Jan 2017)</small>	6	13	40	3.07	0.51

Enrolled risk time

Enrolled risk time is an indicator of individual site level recruitment activity and captures the duration each site was active and recruiting to the study. Table 3.2.5 compares the enrolled risk times for the MATE study and a comparable study, the SCORE study. Enrolled risk time for MATE study sites ranged from 4.3 to 13 months and was comparable to the SCORE trial⁹⁴. However, the individual site level recruitment activity was greater in the MATE study than in the SCORE study sites.

The SCORE study sites found that private practices fared better than academic institutes. In our study all the sites were similar and NHS ophthalmology units. It has been shown that as the time a site is active for recruitment increases, the level of engagement and involvement by recruiting staff decreases. This may be due to staff turnover, competing studies leading to a decrease in knowledge base and change in priorities⁹⁵. An example for this in our study is site number three, where there was a gap of four months in recruitment during the recruitment window due to other studies competing for the Principal Investigator’s time. These are described in detail in the next chapter in the qualitative report on recruitment phase of this study. Hence, once a site is active for recruitment, the aim should be to meet the site recruitment targets as promptly as possible. This minimises expenditure and the need to open more sites at a later date to enrol the required number of patients.

Table 3.2.5: Comparison of enrolled risk time⁹⁴

	MATE	SCORE
Enrolled risk time (months)	4.3 to 13	4.92 to 14.09
Enrolled risk per month	0.57 to 1.43	Academics sites 0.24 Private practices 0.45

3.2.5 Conclusion

Recruitment rates are useful in future trial planning to know the number and time required for similar neovascular AMD treatment trials. Once a site is active for recruitment, the priority should be to recruit the desired number of participants within the minimum possible time period.

Chapter 4: Qualitative analysis of recruitment phase of the MATE study

4.1 Introduction

In the chapter, results from the qualitative analysis of the recruitment phase of MATE study are presented.

Recruitment difficulties in randomised controlled trials (RCT) across specialities are a well-known fact. A review of trials funded by two UK funding agencies showed that only 38% of trials recruited to target⁹⁹. Inability to recruit to time and target can lead to premature termination of the trial, unable to power studies to give meaningful results, waste of scarce resources and delay in availability of useful treatments to the general population. Researchers are encouraged to share knowledge regarding recruitment rate and difficulties as this would help in future RCT planning¹⁰⁰.

Recruitment pathways can differ from trial to trial and across specialities¹⁰¹. Recruitment and conduct of RCTs involve a complex interplay of social, cultural, behavioural and economic factors involving both the patients and clinicians. These are best explored using qualitative methods⁸⁵. Quantitative techniques establish the how many and when questions, but qualitative techniques allow the how and why questions to be answered by enabling the meanings and experiences of the event to be explored with participants⁵⁷.

Qualitative methods may be used alongside clinical trials or in the pilot or feasibility stage prior to the main study to explore any difficulties that may arise later in the main trial⁵⁵. However, the QuinteT group of researchers recommend integrating qualitative methods with quantitative methods and triangulation of evidence to understand recruitment processes and barriers early on in a study and implement solutions during the conduct of these trials^{102,103}.

Lack of eligible patients and patient refusal to participate in clinical trials have been noted to be reasons for recruitment difficulties in glaucoma drug trials. Researchers

have been advised to be cautious in estimating the number of participants in these studies^{104,105}.

Recently, slow recruitment into the SCORE – CRVO (Standard Care versus Corticosteroid for Retinal Vein Occlusion – Central Retinal Vein Occlusion) trial prompted the investigators to look at their recruitment rates and techniques to improve recruitment. They found favourable study design features, monthly newsletters to sites from the sponsor and good communication between trial leadership to the study sites to facilitate recruitment⁹⁴.

Much of the published literature is from recruitment experiences in complex randomised controlled trials outside of Ophthalmology^{89,106,107,108}. Ophthalmology clinical trials are unique in that the patients may not be having life threatening conditions needing complex surgical and medical treatments or hospital admissions. However, eye diseases can cause significant anxiety amongst patients about their visual prognosis. Neovascular age-related macular degeneration (AMD) in particular if not treated promptly can lead to irreversible loss of vision. Here, we use qualitative methods to explore the set up and recruitment processes in a multicentre, pilot, randomised controlled trial in the field of neovascular AMD treatments.

4.2 Aims

To evaluate the feasibility of set up and recruitment of the study.

4.3 Methods

The MATE study is a mixed methodology study; this section is the qualitative component of recruitment phase.

Qualitative, semi structured interviews were conducted of key trial staff alongside quantitative methods to evaluate processes around recruitment (results from quantitative methods have been presented in chapter three). This study was conducted in accordance to the ethical principles stated in the Declaration of Helsinki. Prior regulatory and ethical approval was obtained.

Settings and participants:

The trial participating centres were selected based on site selection criteria described below:

Site inclusion criteria:

The participating centres should have:

- 1) Clinical experience with treating neovascular age related macular degeneration
- 2) Good Clinical Practice training
- 3) Preferably experience with conducting clinical trials

Site exclusion criteria:

The participating centres should not have:

- 1) Inadequate resources to run the trial

The study was conducted in six NHS Ophthalmology medical retina units across the United Kingdom between December 2015 and January 2019. The study sites were a mix of university hospitals and NHS foundation trusts (/district hospitals). Some were established research centres while others were relatively small research units with support provided by generic (non-ophthalmic) research nurse and administrative staff. In some sites there were dedicated research clinics with dedicated research sessions, in others research culture was such that research activity was embedded into clinical work. The sites differed in the way they delivered their AMD treatment services and in where research activity was embedded in within NHS service delivery or when research was carried out by co-investigators from the wider team, this affected delivery of the study.

Table 4.1 summarises characteristics of each of the MATE study sites.

Site	Investigator experience	NHS - AMD service set up	Treatment regimen used for nvAMD	Type of injectors in AMD clinics	Dedicated Ophthalmic research team (nurse and administration)	Type of research clinics
A	Experienced PI with a vast	One stop	Treat and Extend	At the start of study –	Yes	Dedicated research

	experience in leading and designing macular degeneration randomised clinical trials.	service	(T&E)	doctors 2 nd half of study – combination of doctor, nurse and other Allied Health Professionals (AHP)		sessions run by investigators from research team
B	First randomised controlled trial	One stop service	Standard care	Nurse /AHP	Yes	Dedicated research sessions run by investigators from research team
C	Senior researcher - lead on many medical retina treatment trials	Two stop service with a virtual clinic component	Treat and extend	Nurses/AHP	Yes	Dedicated research sessions run by investigators part of the wider medical retina team on a rota
D	Senior researcher - lead on many medical retina treatment trials	One stop service	Treat and Extend	Nurses/AHP	Yes	Research activity embedded in NHS AMD

						service sessions
E	Had lead one nvAMD treatment trial and many observational studies	Two stop service	Standard Care	Doctors	Yes	Dedicated research sessions run by the Principal Investigator
F	Previously lead on one nvAMD treatment trial	One stop service	Standard Care	Nurses/AHP	No (generic research team)	Research activity embedded in NHS AMD service sessions

The trial manager, chief investigator and principal investigators at all the sites were interviewed at the end of recruitment phase of the study. In addition, the lead pharmacy representative was also interviewed but this interview has been grouped together with the end of year one interviews, alongside other members of the sponsor team.

Data collection:

The trial manager, chief investigator and principal investigators at all the sites were approached by one of the researchers (AA) for the interviews. Prior written, informed consent to participate and for the interviews to be audio recorded was obtained before data collection.

Face to face audio recorded, in depth, semi – structured interviews of key trial personnel (trial manager, chief investigator (who is also the principal investigator at one of the sites and principal investigators of all the remaining five sites) were

conducted by one of the investigators (AA) at the end of recruitment period. The interviews lasted between 5 to 22 minutes and were conducted in English. The interview guide developed following literature review and review by a qualitative researcher (one of my Thesis advisory panel members) explored the following topics - study set up, recruitment, randomisation, resources, administrative support, problems and challenges, adherence to protocol, masking , format and structure of the CRFs (source data) and time and budgetary constraints (detailed interview guide is in appendix 5). These topics explored the set up and recruitment of the study. Interviews were audio recorded and transcribed verbatim by AA. Field notes were taken immediately after the interviews. The interview guide was modified after the first couple of interviews to include additional topics around treatment regimens at the individual sites, type of the macular degeneration service, recruitment strategy and site-specific problems (details are in appendix 6)

In order to maintain anonymity of the participants, interviews were labelled in the order of conducting the interviews i.e. S1 is subject 1, S2 is subject 2, S3 is subject 3, S4 is subject 4, S5 is subject 5, S6 is subject 6 and S7 is subject 7.

Analytical approach:

Thematic analysis approach was used as described below.

Following Braun and Clarke¹⁰⁹, the steps of thematic analysis include:

1. Familiarisation with data, systematic generation of initial codes and collation of data relevant to each code (AA).
2. Searching of themes (direct and implicit content) and gathering relevant data (AA).
3. Reviewing themes (AA, HB and RPG): Joffe¹¹⁰ suggests 10-20% of interview material should be double coded to provide, transparency, reliability and concordance. The importance of a theme is not necessarily dependent on quantifiable measures, but rather in whether it captures something important in relation to the overall research question.

4. Defining and naming themes (AA): Ensuring clarity between themes and choice of vivid and compelling generative quotes (quotes from the data exemplifying the direct or implicit discussion of the theme) rather than illustrative quotes chosen by researcher to illustrate previously expected categories⁵⁷.

The above steps were applied to all the interviews. All interviews were coded by two researchers (AA and HB). Specialist software was not used. Initial codes and preliminary codebooks of emerging themes were iteratively refined after two coders reached agreement. These preliminary codebooks were applied to subsequent interviews. Regular meetings between the researchers (AA, HB and RPG) were held where codebooks were reviewed and refined. All themes and codebooks were reviewed and contrasted a final codebook was developed, expanding and merging codes as relevant to capture data relevant to the overall research questions. Disagreement in codes and themes were resolved by discussion amongst investigators (AA, HB and RPG) to ensure concordance. This final codebook was used to recode all transcripts. The coded quotes were organised by themes and sub themes. Data collection and analysis is iterative where findings from interviews conducted early on were used to improve the trial and modify interview guide.

4.4 Results

Seven participants were approached and all of them agreed to participate. A total of seven interviews were conducted. These are – one interview of the trial manager, one interview of the chief investigator who is also the principal investigator at one of the sites and five interviews – one each of the principal investigators at the remaining five sites.

The results from these seven interviews for recruitment and set up phase are below with quotations from the interviews presented in boxes. A thematic map of the key themes is presented below in Figure 4.1.

THEMATIC MAP – RECRUITMENT AND SET UP



Figure 4.1: Thematic map of interviews for recruitment and set up phase.

4.4.1 Recruitment processes

Recruitment target

Meeting the recruitment target was important for both investigators and study sponsors. Competitive recruitment during the last few months of the recruitment period was a cause of worry for one of the investigators as they were worried about meeting their recruitment target. Sites which met their target were appreciated.

S3: So, the first 8 patients we had, we recruited all 8 of that and we recruited, consecutively 8 patients. The first 8 that came, all of them were recruited

S1: Site (name of the site) are particularly good, they have got their 8 patients.

S4: So, we did set a fairly conservative recruitment target of 5-6, which we did achieve.

S5: The fact that it was competitive recruitment, made me anxious as a Principal

Investigator. Because I am quite worried about not recruiting to target for any studies.

Recruitment strategy

Recruitment strategy varied from Principal investigator being the sole recruiter to experienced members of the research team intercepting patients when they first present to clinic with suspected neovascular age related macular degeneration (AMD). Leaflets in clinics to remind staff about studies open to recruitment, individualised approach based on type of study, dedicated clinics to streamline all new referrals for possible neovascular AMD, thorough discussion and encouragement to take part in a trial on voluntary basis and offering all potentially eligible patients the opportunity to take part in the study were other strategies adopted by our research teams.

S2: So, our philosophy is that if a clinical trial is available to a patient then it should be offered in parallel to the regional clinical care.

S2: Now, not all patients are suitable. So, we worked around it by having strategies for capturing every patient that came through to the new AMD or the new macula clinic. So, having an experienced member of the research team intercepting those patients at their first appearance and priming them that this was available. So, they had an opportunity to think about it. If we didn't do that, the patients could be missed and then it would be too late.

S3: We have dedicated fast track clinics for patients with supposed macular degeneration. Yes, that is where we pick our patients from and that is where we picked our patients from! And we had leaflets everywhere in clinic, to help identify which studies you need, it was very easy to identify patients. Because, I do fast track clinics myself, all patients went through me.

S4: So, obviously there is no, one model fits all in terms of recruitment. So, it is tailored to each individual project. I personally oversee two such sessions a week, so all patients were approached in the macula treatment clinic. There was a

thorough discussion of the possibility to be involved on a voluntary basis in this research project.

S5: only that I as Principal Investigator (PI), tend to do a lot of the screening and eligibility. You probably need to have a deeper level of understanding about the study to actually counsel somebody at baseline and recruit them. So, I just took the responsibility myself to bring everybody in. there is nothing quite like being the PI and having to you know, having the responsibility. So, that's the strategy.

S7: We used to, when we had the (name of another trial) running, any treatment naïve patient would be offered standard or trial drug.

Ease of recruitment

The research teams found this an easy study to recruit to. This was due to the study using an established drug in a prevalent condition, with both study arms receiving the treatment and not much was different from clinical practice. Investigators felt comfortable approaching patients to take part in this study as one investigator describes 'the patients did not feel they were taking a big leap of faith.' There were mixed opinions about available patient pool. Some centres having relatively low number of new patients and others felt there were adequate number of patients to be approached to take part in the study. The site which commented on having limited patient pool (S2) were surprisingly the highest recruiters to the study.

S2: So, I have been pleased with that. And actually, the feedback, I have had from other sites, it has been relatively easy to recruit compared to other studies.

S2: And with a relatively low number of new patients coming per month, round about 9-10. It's only left a small pool of patients available to be offered the study. And that contributes to the delays..

S3: And this study, at least I personally found very easy to recruit. Because we are not changing much. They were not receiving anything which is drastically different. They did not feel, or patients did not feel that they are not; they were

taking a big leap of faith. So that was, so that was easy, we did not find that particularly problematic

S4: in terms of MATE, cause it pertains to a patient population that is quite prevalent. In (name of the site), it is quite common and broadly nationally as well. There were no great difficulties anticipated in terms of identifying the patients for recruitment.

S4: the identification was done in the macula treatment centre, which is a dedicated service for treating patients with wet AMD and other macular pathologies with intravitreal treatments. Commonly, 2-3 wet AMD patients attend the macula treatment centre on a daily basis. The clinics run every day. I personally oversee two such sessions a week.

S5: I think we came on board slightly later than other sites, but given how common the pathology is, I felt that it was possible to deliver it and indeed it was.

S5: very easy because we get around 25 new patients a month with wet AMD and start injections. So, there were plenty of people to approach.

S5: yes, it was easy (refers to recruitment). Generally, patients coming in with wet AMD are very anxious about their disease; they were keen to get treatment. They very much approved of the fact that MATE was using an established drug, which has already proven to work.

S7: we were informing them (in a previous study) that this drug is not licensed but we are trying to evaluate it. Whereas we don't have the same problem with (name of MATE study drug)

S7: people who wanted to get in, they got in. Especially, when you explain them it is the standard NHS treatment

S8: we never experienced problems in recruitment of patients with AMD, So, I don't, I don't find it difficult at all.

Recruitment period

Individual sites found the recruitment duration to be adequate. Last few months of recruitment period was competitive, which though did not cause any difficulty, was a cause for concern.

S4: we came on board slightly later than other sites, but given how common the pathology is, I felt that it was possible to deliver and indeed it was.

S5: well more than adequate for us (refers to recruitment period), because as I say we didn't have any problems. The fact that it was competitive recruitment made me anxious as a PI.

S8: it was all adequate (refers to recruitment period)

4.4.2 Protocol related factors

Eligibility criteria

Eligibility criteria in this study were found to be generous and like other neovascular AMD trials. Visual acuity entry criteria better than NICE guidance was found to be beneficial and stricter blood pressure requirements for entry into the study was thought to impede recruitment. This was then amended during the latter half of the recruitment period to facilitate recruitment.

S2: I think the inclusion/exclusion criteria are relatively generous in which, by that I mean they are quite true to real life study design

S3: So, we did not have any problems with inclusion/exclusion criteria. The only thing that we were slightly nervous about was the blood pressure, which was updated, which was a bit stricter to start with.

The rest of the inclusion/exclusion is fairly standard for most of the AMD studies.

S5: From memory I don't think we had any problems with that at all. In fact, the

inclusion criteria being better than NICE guidance was very positive. Because I think, I can't remember how many of our 8 patients, there were certainly patients who would not have been eligible under NICE guidance. And their vision going downhill rapidly, and they were quite keen to. So that was very attractive and useful.

S8: They (refers to eligibility criteria) were absolutely fine. There wasn't anything unreasonable. And it wasn't anything that it will make the recruitment of subjects difficult.

Standard NHS treatment and licensed treatment

The study drug being currently available on the NHS and licensed for the treatment of neovascular AMD. This was a positive factor for recruitment as patients were more willing to sign up.

S3: and this study, at least I personally found very easy to recruit. Because we are not changing much, they were not receiving anything which is drastically different. They did not feel, or the patients did not feel that they were taking a big leap of faith.

S4: This is a project that does not involve any additional risk or harm or other inconveniences on top what is expected from routine clinical care. And so, that also to some extent facilitates the process of identifying and recruiting patients for this work.

S5: So, yes it was very easy. I mean I think, you know. Generally, patients coming in with wet AMD are very anxious about their disease; they are very keen to get treatment. They are you know, very much approved of the fact that MATE was using an established drug, which had already been proven to work. And it was really more of treatment protocols that we are testing. So, it was not a difficult thing to try and persuade people to be involved at all.

S7: people who wanted to get in, got in. Especially when you explain them it is the standard NHS treatment

S7: We tell them it is the standard treatment, only thing is your data will be collected and then utilised for research purpose and then of course you are not identified, and your GP will be aware of it, that's all.

S7: and it is not that we are using that is not licensed.

Protocol breach

Not following the recommended screening procedures as per protocol resulted in inability to confirm patients' eligibility for trial participation. This led to withdrawal of four patients (from two different sites) from the study by the study sponsor. The main reason for this was trial staff not being familiar with screening procedures. Lack of Principal Investigator (PI) oversight and absence of usual investigating team including optometrists contributed to this protocol breach. Presented below are excerpts from the trial manager and the PIs interviews, there is a disparity in how this issue is perceived by the two parties. While both the PIs consider this to be a minor issue, for the trial manager it is a 'big issue'. Withdrawal of these patients resulted in delay in recruitment prolonging the overall study recruitment period.

S1 Their (refers to the site) biggest issue that I have faced with them was they had a different optometrist and different PI, co-investigator sorry on the same day. And the procedure that we ask them to follow for refraction was not followed. They did 'pin-hole', which probably not too ... (not clear). But either way couldn't therefore then verify their eligibility. They have then been treated with their injection and we couldn't confirm that they actually sat between the 78 – 24 ETDRS letters. So, we had to withdraw 2 patients there. They were both on the same day, same optometrist and same co-investigator. Not overseen by the PI. He sort of delegated; as you do, you know.

S1: and then finally (name of the site). So, again unfortunately, we had two patients; they were all about the same time that has to be withdrawn from (name of site). Again, it was an optometry issue. This time no optom was available. And they

decided that it would be okay to use a previous vision, previously documented vision. Didn't document it on the CRF but obviously it wasn't performed to our protocol. So again we couldn't confirm eligibility.

S4 Err, I have, we had a minor issue for two of the patients we recruited to begin with, which who then had to be withdrawn from the study. well, the issue was that, the only, because of the majority of the procedures related to this study were recommended to be carried out as per routine care, including imaging fluorescein, assessments etc. Other than the involvement of the optometrist which needed to be on one hand masked and on the other hand following specific protocol for taking vision and so, on for two of the patients that were consented on one day, when I was not in clinic and unfortunately so it just happened that the optometrist involved was not fully aware of the requirements to, of the protocol and so the visual acuity did not follow the specific refraction protocol specified by the study. And so, we had to withdraw these patients, yes.

S7 we didn't have any challenges or difficulties, but it started in (month) last year, where unfortunately is was away a lot. And some of the patients who got recruited they didn't have the proper let us say initiation and we had to drop them off. We actually recruited 5 or 6 patients. There was some problem with the optom not being there and although I did pick this out but somehow, they entered into the trial and we had to drop them, so we were left with three. But after that we had a smooth..

Randomisation

Randomisation is explored from two aspects: one, the process involved in randomising a participant in the study. Two, patients' perspectives on being randomised to standard care or treat and extend arms.

Processes around randomisation

Electronic randomisation service as used in this study which was easy to set up and user friendly.

S1: So, we opted for (name of the company) as the service, randomisation for us. We went through due diligence and, it is an electronic randomisation service. They are certain, we, they ask us to outline what we want to be documented to ensure accurate randomisation (describes process of setting up the service in detail). We sent this to the company, and they have been great.

S2: From the staff point of view, it has been a relatively straightforward process because the randomisation process was set up through an external company or external website. So, the processes were well tried and actually to my knowledge it hasn't failed, it hasn't.

Patient perspective on randomisation

Investigators' perceptions of patient acceptability to randomisation are presented here. These were varied and ranged from no concerns with patient acceptability, preference to treat and extend arm, patients being treatment naïve and hence receptive to being counselled to either arm; and investigator assumption that patients comprising of an elderly population, would not be interested in details of treatment regimes. Equipoise and uncertainty in outcomes between the two arms were not always communicated to the patients.

S2: Well, generally the patients haven't minded (referring to randomisation). Whether they fall into one arm or into the other. I haven't heard any concerns from patients with regards to that.

S4: I in a couple of cases the patient would have preferred to be randomised in the treat and extend arm. Because of the possibility as explained that if they are responding very well to the treatment, they would need to come less frequently and have treatment at extended intervals.

AA: and they (patients) were okay with which ever arm they were getting randomised?

S5: they (patients) were, I think partly because they didn't come with a fixed idea of what they were, you know they came on the day as a new patient and were very open to being

counselled about licensed regimen but then also about the fact that percentage of patients would have 7 or 8 injections in the first year. Whereas potentially they might not have needed that many. And then equally you know there were some patients who perhaps will not be doing well on the fixed regimen and would have preferred to have had more frequent injection dosing. So that sort of concept that although aflibercept regimen is almost like one size fits all. For the average patient it works very well. But there is not individuality. So, I think that was and then obviously the concern that you are going of label, which is why it is research. So, I think that was an easy concept to (AA – to tell people)

S5: yeah, yes it was fine.

S7: (nods head in disagreement). To tell you the truth, I don't think most patients figure out what randomisation is. I think most of these patients, who have these treatments, they are quite elderly. If they are having the treatment, they are having the treatment, that's it. They are not bothered about which arm and what arm and how? The only thing they are bothered about it is if their vision doesn't improve, or their vision falls down. Then they will come to the doctor, why is my vision not better?

S8: (referring to randomisation) they (patients) didn't have any issues, they understood that they would either go on the standard NHS regime or they will go on the treat and extend. And we did explain how the two weeks increase, the gaps between treatments, when they don't have active disease, when don't have the certain sub retinal fluid, intra retinal fluid and other criteria. And then if that appears again, then the gaps have to be shortened. So that's been explained and it have been taken nicely by patients.

4.4.3 Human factors

Investigator bias

Unbeknownst to them, our investigators introduced bias into the recruitment process. Their perceptions of patient benefit from trial participation, focussing on benefits of treat and extend regime, seeing the same team and being examined by a consultant each time were highlighted as advantages of trial participation.

S4: So, it clearly explained treat and extend approach to treatment makes good sense and is well received by patients. Rather that was my experience.

S4: I don't think we had anyone that actually refused to take part. Because the case for taking part is a fairly strong one, there is a possibility of either receiving standard of care or a permissive approach to treatment, tailored to each individual patient. In the best-case scenario, result in ensuring that there is no over treatment. In that the treatment intervals are individualised to fit the needs of this particular patients. So, there is a quite strong rationale and potential benefit for patients to take part.

S8: (referring to randomisation) they (patients) didn't have any issues, they understood that they would either go on the standard NHS regime or they will go on the treat and extend. And we did explain how the two weeks increase, the gaps between treatments, when they don't have active disease, when don't have the certain sub retinal fluid, intra retinal fluid and other criteria. And then if that appears again, then the gaps have to be shortened. So that's been explained, and it have been taken nicely by patients.

S8: and also, we highlighted the fact that, the benefits of being on the trial. That they will be actually be monitored more closely and more. You know they will be seeing consultant most of the time, so we highlighting the benefits. The benefits that one can have by enrolling in a trial.

Communication between sites and sponsor

Communication between sites and sponsor was in the form of emails, telephone calls, site visits and teleconferences between chief investigator and the principal investigators. This was useful to trouble shoot, send recruitment updates, pointers and provide useful tips for recruitment. Sites were appreciative of the support and prompt responses received from the sponsor during recruitment. Relationships built by the trial manager with the sites has had a positive impact in setting up and running the study and recruitment in particular. Relationship built by the chief investigator with the site clinician had a positive impact in acquiring new sites and encouraging recruitment.

S7: I think the communication is quite good. (Referring to sponsor).

S4: So, I think we were initially approved through the clinical research network; enquire about interest in getting involved with the MATE study. We liaised with the Chief Investigator to gain some more information. I expressed interest to take that on board as Principal Investigator for (name of site).

S8: Everything is functioning well. We have also found the communication between us as a centre and the chief investigator also the team, the sponsors of the trial is very good.

S3: We had (name of site research co-ordinator) helping in research co-ordination type problems, sort of issues and (name of MATE clinical trial manager) was a great help. (Name of MATE clinical trial manager) is always on the other side of emails, so is very helpful.

S1: I would like to think I have a good relationship with all the teams I work with across all the sites. They are all very communicative via email, telephone you know, I am very keen to when, I go for the Site Initiation Visit to point out that you know I am just at the end of the telephone and of they have any queries to ring.

S1: So, I do get on particularly well, I would like to think with most of them to the

point that actually (name of MATE study site) recommended me to, we were approached not long ago by another site. (name of MATE study site) had recommended us as a study to another site and they were interested in participating. So that I think, that's positive.

S1: updates, you know, updates on recruitment any kind of general, frequently asked questions or pointers that we need to put out we do. We have also just done a round of telephone conferenced with (name of chief investigator) and PIs.

S1: I am in constant communication with them (name of site). They send their very data regularly.

Dedicated members of research teams recruiting patients

Sites found that dedicated members of research teams with an understanding of the trial, recruiting patients helped with recruitment. Intercepting patients early in their clinical care pathway and introducing the trial was a useful method.

S5: I think whilst my colleagues are very good at doing the assessments and get involved in the trial when it is running, you probably need to have a deeper level of understanding about the study to actually counsel somebody at baseline and recruit them. So, I just took the responsibility myself to bring everybody in.

S4: I personally oversee two such sessions a week. So, the patients were approached.

S2: So, our philosophy is that if a clinical trial is available to a patient then it should be offered in parallel to the regional clinical care. Having an experienced number of the research team intercepting those patients at their first appearance and priming them that this was available.

S2: having experienced nursing staff, fellow staff and clinical trial assistant, staff working collaboratively has helped as well.

4.4.4 Challenges

Delays

Delays were in the form of both delays in study set up and site set up. Obtaining regulatory approvals like from MHRA, ethical approval and from the study sponsor led to delay in study set up. Halfway through the recruitment period of the MATE study it was clear that more sites needed coming on board to meet the recruitment target. This coincided with change in regulatory approval system to HRA system across the country leading to delays in site set up. Once approvals were obtained setting up of sites needs planning to fit around staff availability and time of the year. This extended the recruitment window beyond the initial planned 6 months.

S1: also, the 3 new sites that we selected. So, we, recruitment was slow, so we actually ended up with six sites as opposed to five.

S1: so, they couldn't be approached initially because they didn't have HRA approval. So, half way through MATE we changed approval system nationwide. So, we had to draw up a whole new document set to be delivered to them and because it was a new process the HRA took a little while. So, we didn't get HRA approval until the end of April. And obviously every time you add a new site or change your PI, you have to because this is CTIMP, you have to put in a substantial amendment that takes 35 days. So, everything do you know took longer. Actually, the last site initiation, so we did the first site initiation in (name of the site) early December, the last one was at (name of the site), which was the 4th of July. So, it took a, because of all the processes and everything that has to be done, it took that long to bring the last site on board with all the changes.

S2: setting up of sites seemed a very straightforward thing but it has to be delivered in an appropriate way and timed to fit with the time of the year and fit with staff availability

S2: the anticipated set up to occur within few months but it got delayed a few months beyond that, about a year or so. So many of the delays came through the local, came from the sponsor, to ensure they were happy with the study, the study design. And then finding the appropriate time for ethical approval.

S2: The study set up took longer than anticipated. There were a number of hurdles once the grant was approved to be able to set the study up. The first major hurdle was gaining ethical approval and approval from the regulatory authorities. Through the inherent delays of those we found the timelines were set back.

S7: we didn't have any challenges or difficulties but it (referring to the study) started in august last year, where unfortunately I was away a lot.

Limited resources

MATE is a portfolio study meaning it could access nursing and administrative support from the local CLRN network. Each patient recruited into the study brought an additional financial payment and study drug was provided free of cost by the sponsor to the sites. Lack of optometry slots was a limiting factor to recruit additional patients. After initially agreeing to participate in the study, one of the sites withdrew due to in availability of optometrists at their site. Limited finances or budgetary constraints in the study meant that sites further away from the lead site could not be recruited into participate in the study. Individual sites felt they had the resources to participate in this study but overall limited resources both staff and finances contributed to recruitment delays.

S1: also, in my first week, both (name of the site) and one of the other sites (name of the site) pulled out. And their reasons for not participating were staffing, staffing issues. (Name of the site) had optometry issues and (name of the site) had, I think it was referral actually. They had a diminished pool of patients that they could approach.

S1: At which point it was decided that we would, it was already on portfolio, but that we would open it up to sites to approach us. We had quite a lot of interest particularly from (name of a region). But because of budget and constraints, time constraints things like that, we decided against going so far afield.

S1: We also contacted each network lead for those closest to us to ask them to offer our study out, rather than waiting for sites to come to us. So again, we had a couple, who

were interested but then, we unable to participate, again staffing issues was the main reason, mostly optometrists.

S2: The resources are scarce within the NHS setting and this study effectively has to compete with other studies for those scarce resources. So, we have to make a, we have to prioritise which resources are important to this study and to other studies. So, that is both staff and nursing staff, medical staff and optometry staff. For example, there is only a certain amount of optometry slots available we can access. So, that has limited to a certain extent our ability to recruit

Site withdrawals

Two sites who had expressed interested to take part in the study and who were found to be eligible as per the site feasibility questionnaire had to withdraw after initial confirmation of participation. One site with drew due to lack of optometry support and the other had a change in their macular degeneration service provision and stopped getting new referrals for neovascular age related macular degeneration. Once initial feasibility assessment was complete, getting a site to commit to take part in the study was a challenge.

S2: We set ourselves an ambitious target of recruiting all our patients within 6 months. But it became clear, because there was a staggered set up of all the sites. And indeed, some sites pulling out, not wanting to take part in the study, that wasn't going to be met. So, recruitment took nearly twice that length at 12 months instead of 6 months. So, the main barriers I found was actually once sites had initially committed verbally, getting a written commitment and getting feasibility obtained in detail from each of the sites. It took a lot of time.

S2: So, the main reason the sites didn't want to take part was not because of the quality of the study but their capability to deliver the study. Often because of competing studies or the conventional care is delivered within the setting. So, two sites didn't want to take part, we then had to find additional sites who could take on the study.

S2: The principal things, I would do is, I would get a firmer commitment from potential sites, maybe do a more robust feasibility to be absolutely sure that they are committed to the study. I would want to ensure that the timelines for set up are closer, shorter.

S1: also, in my first week, both (name of the site) and one of the other sites (name of the site) pulled out. And their reasons for not participating were staffing, staffing issues. (Name of the site) had optometry issues and (name of the site) had, I think it was referral actually. They had a diminished pool of patients that they could approach.

Patient withdrawal

One patient withdrew following the baseline visit as they found the study procedures onerous. 4 other patients had to be withdrawn from the study after the baseline visit as their eligibility could not be confirmed. Details of this has been covered under 'protocol breach' section.

S1: (name of the site), they got their 5 patients, one withdrew just after screening. They screened and entered and had their baseline but withdrew. But then they decided that, the patient went home and decided actually it felt onerous. They decided to withdraw you know absolutely their right to do.

Competing for Principal Investigator (PI)'s time

Though there were no competing neovascular AMD (nvAMD) trials running in the sites during MATE recruitment, other studies not related to nvAMD competed for the recruiting investigators time. This was seen at a site where Principal Investigator was the sole recruiter to the study.

S5: the slight difficulty was just the fact that we haven't got a huge number of people in the research team. So, around the time we were also recruiting to two other studies actively. So, our recruitment for MATE was very much in 'fits and starts'. I think we got the first two or three patients within a week or so. And then

there was a big gap and then we got the last five all bunched together because we were concentrating on recruiting to another study where the deadline was closer than the MATE deadline. So, actually it was just that we were prioritising another study in the middle of that recruitment period. When you have expressed an interest in these, you don't quite know how it is all going to fall in terms of, I mean the other study had nothing to do with wet AMD, so they weren't competing for patients.

Building teams

The need to have a research team with other consultant colleagues or fellows interested in research who could recruit into studies was found to be important as a sustainable, long term plan to recruitment. Majority of our sites do not mention other colleagues (doctors) being involved in recruitment as the PI is sole recruiter into the study. One site had PI and another doctor as part of the research team who could recruit to the trial and they were the site with highest recruitment figures.

S2: Having an experienced member of the research team intercepting those patients at their first appearance and priming them that this (referring to trial) was available. So they had an opportunity to think about.

S2: having experienced nursing staff, fellow staff and clinical trial assistant, staff working collaboratively has helped as well.

S5: based on previous studies that has worked quite well (refers to being sole recruiter). I think most people if they are doing normal NHS jobs they tend to forget about research. There is nothing quite like being the PI and having to you know having the responsibility. So that's the strategy (refers to being sole recruiter). I think as the years go on and we do more research. I think it could possibly get harder to do that. But you know ideally to have say fellows or colleagues who are very, you know my colleagues are very interested in research, but they don't want to be PIs themselves. They just want to be co-investigators. So, I would like to think that in the future I will get a consultant colleague, who wants

to be PI for a study and won't just be me doing all the counselling and screening.

4.5 Summary and Discussion

The MATE study was initially set out to recruit 40 patients from 5 NHS ophthalmology units across the United Kingdom within a 6-month recruitment window. The reality being this target was achieved in 13 months across 6 sites. Despite the extension to the original recruitment window, this would place MATE amongst successfully recruiting studies. Recruitment success or successful recruitment has been varyingly defined in literature^{111,112}.

Analysis of these interviews help us understand the recruitment journey of this trial, especially factors directly or indirectly affecting recruitment.

Individual investigators in this study found this an easy study to recruit to and met their site recruitment targets. Meeting 'targets' was important to both sponsors and sites and competitive recruitment generated some level of anxiety amongst investigators. They adopted various strategies for recruitment like offering the study to all potential participants, having leaflets in clinics about studies open to recruitment, Principal Investigators taking responsibility for recruitment and recruiting all patients themselves and having dedicated members of research team intercept patients early on in their clinical journey and having a conversation about participating in clinical trials. Team approach and a sense of ownership of a trial by the teams helps not only in recruitment but also in the smooth running of a trial¹¹³.

However, the study itself faced hurdles and challenges throughout the recruitment journey in the form of delays in set up of new sites, sites previously committed to the study withdrawing their participation, changes in regulations and participant withdrawal due to lack of confirmation of eligibility.

The factors affecting MATE recruitment can be grouped as below:

- 1) Factors facilitating recruitment i.e. have a positive impact on recruitment:

- Investigators bias
- Easy study to recruit to
- Dedicated members of research teams recruiting patients
- Good communication and support from sponsor
- Eligibility criteria better than NICE guidance for treatment of neovascular AMD
- Both arms of the study receiving trial drug, which is the current treatment available on NHS for neovascular AMD.

Investigators in this study were favourable towards treat and extend regimen. They highlighted the ability to extend treatment intervals and possibility less treatments in the long run. Being seen by the same team at each visit was also highlighted as a favourable feature to take part in the study. Equipoise, differences between treatment arms and no evidence in literature to support this belief about Treat and Extend regimen being better than standard care was not presented to patients. Investigators relied on their clinical experience and judgement here.

It was also felt that this being an elderly population, they may not be interested in the finer details of the trial as long as they were on the current treatment available on the NHS. The fact that these patients were treatment naïve made them easier to be counselled to accept either treatment arm.

Though this helped in presenting the trial in good light to potential participants, unbeknownst to them the recruiters introduced bias and highlighted the benefits of trial participation. Investigators perception of potential benefit to patients has had a positive effect on recruitment to this study.

Strong personal views or preferences to either of the study arms by recruiters is a known phenomenon and can sometimes deter recruitment into a clinical trial^{114,115}.

Our investigators though affected by their personal views and experience as clinicians, this has in fact been beneficial to the trial.

Recruiters into a study are not always comfortable in communicating equipoise, uncertainty to patients. While some may not be comfortable approaching all eligible

patients, others may be biased about treatment options due to their clinical experience and beliefs. Patients' beliefs, concerns may not always be explored during informed consent process either due to lack of training to the recruiters in this process or their prior prejudices and belief about the trial treatment arms¹¹⁶. Training programs to train recruiters such that they are comfortable in approaching all eligible patients for a study, present uncertainty and equipoise with influencing patient opinions one way or other have been recommended as an intervention to improve recruitment in complex clinical trials^{90,117}.

With MATE being an open trial and both arms offered the same medication available on NHS for patients with neovascular AMD, recruitment has been relatively easy, and recruiters also felt comfortable to approach potential participants. Eligibility criteria with visual acuity entry criteria better than NICE guidance in UK was an added incentive for patients to participate in this study and access treatment early on in their disease journey.

Patient preferences to either treatment arms have known to be a deterrent to trial participation¹¹⁸. This has not been a problem in our study as both arms get the current recommended medication. This is also the reason why investigators are comfortable approaching patients for trial participation as one investigator describes 'this not being a leap of faith' (S3, principal investigator)

Open trials, favourable study design features with incentives for patients are known to facilitate recruitment^{94,119}. Increasing awareness of health problems, involving lay members of public, use of electronic databases to identify potential patients, financial incentives and telephone reminders have all been found to be effective recruitment strategies^{119,120,119}. There is no one method fits all and recruitment strategies and facilitators vary from trial to trial depending on the disease pathology and trial design. It is advised to study these factors early on in the form of a feasibility study, keep a close watch on recruitment patterns of individual sites, give early feedback to sites to ensure prompt and smooth recruitment¹²². Despite recruitment troubles in majority of randomised controlled trials there is a lack of research into studies comparing recruitment techniques and strategies^{121,123}.

2) Factors deterring recruitment i.e. have a negative impact or slow down recruitment:

- Set up delays
- Site withdrawal
- Patient withdrawal
- Limited resources (both staff and finances)
- Changes in the regulatory approval scenario across the country
- Competition for Principal Investigator's time.

The MATE study faced delays in meeting its recruitment target. The original recruitment window of 6 months had to be extended to 13 months for the study to reach its target. The study experienced delays in three levels:

- 1) first level – from awarding of the grant in early 2015 to the initiation of the study there was a delay of approximately 12 months, this was the time needed for approval of study design by the sponsor and obtaining regulatory approvals in the form of ethics committee and Medicine and Healthcare products Regulatory Agency (MHRA) approvals.
- 2) second level – once the study had started and two of the pre-identified sites had withdrawn, there was a delay in bringing new sites on board. This was due to a change in the approvals system across the country to Health Research Authority (HRA). The HRA system was designed to streamline and smoothen research application process in England¹²⁴.
- 3) Third level – site level gaps or delays in recruitment due to holiday season and other studies competing for Principal Investigators (PI) time. These issues were mainly seen in sites where PIs were the sole recruiters for the study. Sites initiated ('green light' issued just before PI was going to be away on annual leave. And in a site where PI was the sole recruiter there was a gap of 3 months where no patients were recruited as they focussed on another trial with a closer deadline for recruitment. Building teams and involving more clinicians in research has been a priority of Royal College of Ophthalmologists. While a site may be research active, involvement of clinicians may be limited by their workload in busy ophthalmology departments^{125,126}.

Mixed methodology summary of recruitment phase of the MATE study:

A combination of quantitative and qualitative methods helps understand the recruitment journey of the MATE study.

The overall screen failure rate in the MATE study across all sites was 18.51%. Most common reason for screen failure was failure to meet the eligibility criteria. The total non-participation rate was 40.8%. No reason was stated in about one fourths of the patients approached and logistic reasons for not taking part formed the next most common group for not taking part in the study.

The overall recruitment rate in the study was 3.07 participants per month. During the study, sites recruited at a rate of 6.67 participants per site. Recruitment rate per site per month was 0.51 participant/per month/ per site.

Though the overall recruitment rate was less than other studies in literature but the individual sites recruited better on a monthly basis ^{73,74,75,77,78}.

If we look at the MATE recruitment timeline, the original planned recruitment period had to be extended to 13 months. There reasons for this delay and the interplay of various factors become obvious from the results of the qualitative interviews.

MATE recruitment timeline:

MATE opened its first site for recruitment in December 2015 and did not get its first patient until January 2016. Similarly, investigator leave (in august, school holidays) contributed to delays in recruitment. The recruitment timeline graph (figure 4.2) below shows the role of these factors contributing to delays in recruitment. Competitive recruitment (amongst study sites) in the last few months of recruitment helped to renew interest in the study and the drive to meet targets.

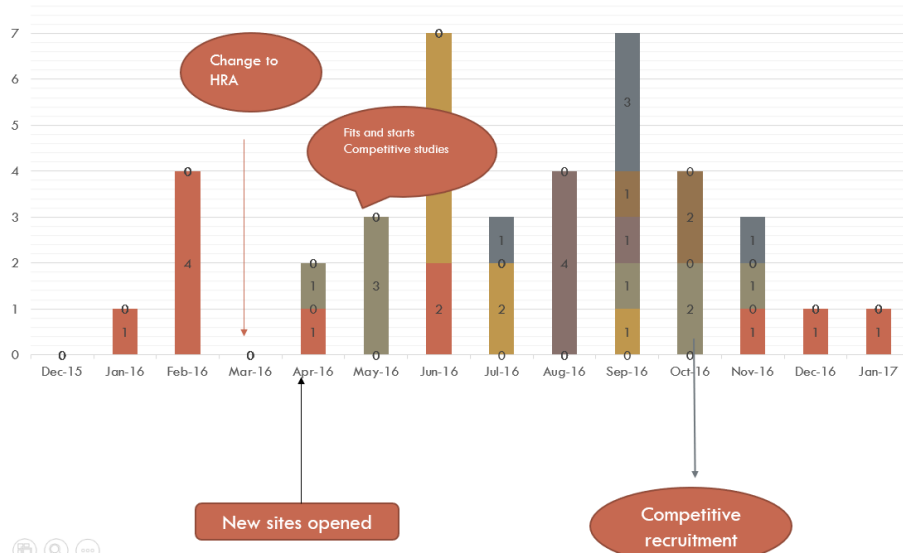


Figure 4.2: showing recruitment timeline of the MATE study

Site and patient withdrawal from the study affected recruitment adversely. Pre-identified sites had to withdraw due to lack of resources mainly optometry services and change in service provision leading to reduced new referrals. Limited optometry services at some sites lead to capacity constraints limiting the number of patients recruited per site and the days on which research clinics could be run, hence eligible patients opting out of the trial. Financial constraints placed a geographical restriction on new sites that could be taken on board.

Lack of training on trial procedures to optometrists and sub-investigators in the study lead to withdrawal of patients from the study. This was picked up early on and retraining of involved staff with support from sponsor helped resolve this issue.

Our study shows the complex interplay between changing research environment, availability of resources, knowledge base including team composing of the research teams and human factors involved in recruitment processes. With each factor having a knock-on effect on another and adding to delays in recruitment.

Delays in recruiting new staff, lack of clinician time, low budget, dropping of pre-identified sites, delay in regulatory processes have all been documented as having a negative impact on recruitment⁹¹.

Recruiting more sites, training staff in screening procedures and consent¹⁰⁶, providing incentives to clinicians¹²⁷, taking the process of consent away from doctors to nurses¹¹² have all helped with reducing the recruitment period.

Lessons from this study will help in designing a future RCT, mainly by budgeting the future study better, planning the recruitment phase to try and recruit participants in minimal possible time period. Training of investigators to communicate equipoise to the participants, regular monitoring, training and support of the research teams to ensure not only are they confident in screening and recruitment processes but they also deliver the trial to protocol.

4.5.1 Reflective piece by the interviewer (AA)

I interviewed all the site Principal investigators and the trial managers as per the MATE study protocol and predesigned interview guide at the end of study recruitment.

I have a significant involvement in running this trial, right from initially being involved in writing the protocol, application for regulatory approval (IRAS application), design and sending out site feasibility questionnaires till the appointment of a clinical trial manager. Once a trial manager was appointed, we would regularly be in contact in the form of email, telephone communication and bimonthly meetings to discuss the running of the trial. I am also one of the co-investigators at the lead site (same as the Chief Investigator's site) and regularly see the MATE patients in the research clinic. Hence, in my interviews I am an insider at two levels¹²⁸.

One, I am aware of the day to day events happening in running of this study both at my site and the challenges or difficulties seen at other sites. I have a close working relationship with the Chief Investigator and the Trial Manager. In both these interviews there have been instances where familiarity of events has made us not explain processes or events in detail, which is a common problem¹²⁸. I have made a conscious effort to revisit and explore these events in detail by further questioning in the same interview. Equally, familiarity with clinical terminology and running clinical trials had helped in teasing out the finer aspects and challenges in running the study,

Second, I know some of the investigators at other sites as colleagues from the same sub-speciality. Mutual respect, having a working relationship outside of this study has made the interviews a positive experience¹²⁸.

Planning the sequence of interviews was important; I interviewed the trial manager first. This helped me know challenges, working patterns, events specific to each site and explore them in detail at individual interviews. For example, there was an incident with pharmacy at one of the sites which did not come up during the PI interviews and I had to ask a leading a question to explore this aspect.

In spite of all this preparation and being an insider there were few aspects in recruitment and running this trial at the other sites which were new and unexpected. The interview guide was modified to explore these new findings (modified interview guide presented later in appendix 6).

After the first couple of interviews it was clear, each site has a different recruitment strategy which needed exploring. And hence, I would specifically ask for it (from S4 onwards).

My initial assumptions were – all sites would know treat and extend, have dedicated research teams (as opposed to generic ones) with research sessions, did not think Principal Investigator could be the only recruiting doctor at a site and one stop AMD treatment service with doctor injectors as the norm. The reality was an exact opposite to this. These show my limited experience and biased view of running clinical trials based on my experience of running an AMD treatment service and research clinic at my site. I spent time and designed questions to explore the research team and AMD service set up in the second set of interviews to bring out the variability, which would be an expected thing in any multicentre clinical trial in real life.

And last but not the least, conducting qualitative interviews has been a learning experience and a new skill for me and a new experience for the staff I have interviewed. My confidence in conducting interviews improved after the first couple of interviews and feedback from our qualitative researcher in our team. The fact that the first two interviews was with people I was familiar with (trial manager and chief

investigator), and their feedback helped me modify my interview technique for the future interviews. Overall, being an insider has helped acquire better quality data.

There were mixed responses from the sites regarding interviews, some were forthcoming while in a few (usually PIs who were new to me) there was some scepticism regarding the purpose of these interviews. They viewed me to be someone whose was checking upon them and their running of the trial. However, once the purpose of the interviews and my role in conducting the interviews was clarified these sites were forthcoming and engaging in the interviews.

4.5 Conclusion

Optimising delays, training trial personnel about study procedures, good communication between sponsor and teams and favourable study design features facilitate recruitment. This study highlights the need to have an individualised recruitment strategy tailored to site and study. Recruitment process is a complex interplay of human factors, regulatory factors and study design.

Chapter 5: Lessons from running the MATE pilot trial: a qualitative report

5.1 Introduction

This chapter presents the experience of running the MATE study both from a sponsor and investigators' perspective. A protocol amendment allowed the sponsor representative and study monitor to be interviewed. The sponsor team is represented by sponsor representative, lead pharmacy, clinical trials manager and the monitor. Investigators include both the chief investigator and individual site principal investigators. Some aspects of set up of this study including lead pharmacy perspective are explored in this chapter with main focus on running this study.

5.2 Aims

To evaluate the feasibility of set up and running this study as part of the primary outcome.

5.3 Methods

The MATE study is a mixed methodology study; this section is the qualitative component to study the feasibility of running this study.

Qualitative, semi structured interviews were conducted of key trial staff to understand processes around running of this study. This study was conducted in accordance to the ethical principles stated in the Declaration of Helsinki. Prior regulatory and ethical approval was obtained.

Settings and participants:

The study was conducted in six NHS Ophthalmology medical retina units across the United Kingdom between December 2015 and January 2019. The nature of individual sites has been described in chapter 4, section 4.3.

The study sponsor team comprising of trial manager, study monitor and sponsor representative were interviewed. The chief investigator (who is the principal investigator at one of the sites) and principal investigators of all the other sites were interviewed at the end of year one of this study

Data collection:

The study sponsor team comprising of trial manager, study monitor, lead pharmacy (from end of recruitment) and sponsor representative were interviewed. along with chief investigator and principal investigators at all the sites were approached by one of the researchers (AA) for the interviews. Prior written, informed consent to participate and for the interviews to be audio recorded was obtained before data collection.

Face to face audio recorded, in depth, semi – structured interviews of key trial personnel (sponsor representative, monitor, trial manager, chief investigator (who is also the principal investigator at one of the sites and principal investigators of all the remaining five sites) were conducted by one of the investigators (AA) at the end of year one. The interviews lasted between 4 to 21 minutes and were conducted in English.

The interview guide for the sponsor representative explored the following topics – challenges in setting up and running a clinical trial, administration, finances, site selection processes and protocol adherence.

The interview guide for the study monitor explored the following topics – data collection methods and quality of data collected, challenges in monitoring, communication and case report forms (CRFs).

The interview guide for lead pharmacy explored challenges, day to day running of the trial from a pharmacy point of view including drug storage and transfer.

The interview guide for chief investigator and principal investigators at each site developed following literature review and review by a qualitative researcher (one of my Thesis advisory panel members) explored the following topics - resources, administrative support, problems and challenges, adherence to protocol, communication, masking , format and structure of the CRFs (source data) and time and budgetary constraints, treatment regime at each site, type of macular degeneration treatment service and type of research teams. A detailed interview guide for all groups is in appendix 5.

In order to maintain anonymity of the participants, interviews were labelled in continuity with the recruitment set of interviews. If any participant had been interviewed in the recruitment phase and were interviewed again, then they would retain their original number and additional interview number was added to it to indicate that this was their second interview. For example, the interview in this round of subject 1 would be labelled as S1, I2. S1 is subject 1 from the previous set of interviews and I2 would indicate this is their second interview in this study.

If any participant was interviewed for the first time in this round, then they got numbers in continuation with the recruitment phase interviews. For example, there were eight interviews in the recruitment phase, so new trial personnel interviews would be subject 9 – S9, subject 10 – S10 and so on.

Analytical approach:

Thematic analysis approach was used as described below.

Following Braun and Clarke¹⁰⁹, the steps of thematic analysis include:

1. Familiarisation with data, systematic generation of initial codes and collation of data relevant to each code (AA).
2. Searching of themes (direct and implicit content) and gathering relevant data (AA).

3. Reviewing themes (AA, HB and RPG): Joffe¹¹⁰ suggests 10-20% of interview material should be double coded to provide, transparency, reliability and concordance. The importance of a theme is not necessarily dependent on quantifiable measures, but rather in whether it captures something important in relation to the overall research question.
4. Defining and naming themes (AA): Ensuring clarity between themes and choice of vivid and compelling generative quotes (quotes from the data exemplifying the direct or implicit discussion of the theme) rather than illustrative quotes chosen by researcher to illustrate previously expected categories⁵⁷.

The above steps were applied to all the interviews. All interviews were coded by two researchers (AA and HB). Specialist software was not used. Initial codes and preliminary codebooks of emerging themes were iteratively refined after two coders reached agreement. These preliminary codebooks were applied to subsequent interviews. Regular meetings between the researchers (AA, HB and RPG) were held where codebooks were reviewed and refined. All themes and codebooks were reviewed and contrasted a final codebook was developed, expanding and merging codes as relevant to capture data relevant to the overall research questions. Disagreement in codes and themes were resolved by discussion amongst investigators (AA, HB and RPG) to ensure concordance. This final codebook was used to recode all transcripts. The coded quotes were organised by themes and sub themes. Data collection and analysis is iterative where findings from interviews conducted early on were used to improve the trial and modify interview guide.

5.4 Results

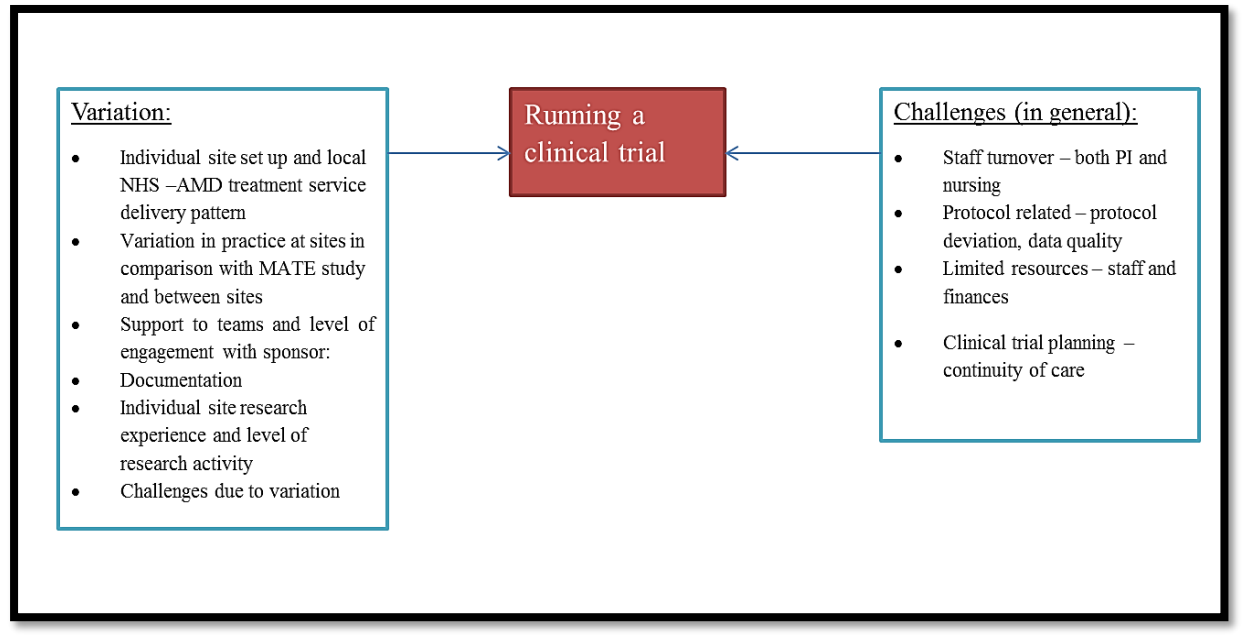
Nine participants were approached and all of them agreed to participate. A total of nine interviews were conducted.

In addition, interviews of lead pharmacy representative, trial manager and chief investigator conducted at the end of recruitment were included for analysis alongside

other nine interviews conducted at the end of year one. A total of twelve interviews were analysed to understand the set up and running of the MATE study.

The results are as below with thematic map of key themes presented in figure 5.1.

Figure 5.1 showing thematic map of key themes



5.4.1 Variation

Individual site set up and local National Health Service (NHS) service delivery pattern for the intravitreal anti-VEGF service for neovascular AMD

The local National Health Service – AMD treatment service set up varied at each site. Some sites used Treat and Extend regimen routinely while others were not familiar with Standard Care (fixed treatment) regimen. Services were either one-stop or a two-stop service where consultation and treatment were performed on the same day or not respectively. Research activity in some centres was embedded into NHS clinical sessions due to limited availability of staff.

S4, I2: Pg1, lines 32 -35: the treat and extend approach is very common. This is the prevalent approach for treating patients with wet AMD. And so, it was such in line with usual practice and usual way in approaching these patients and so we did not find any particular difficulties in that...

S5, I2, pg 2, lines 35 to 41 and 51-52: So, the unusual thing with MATE for us was Standard Care in year 1. So actually, it is the arm where they are treat and extend from day one, which fits better with what we do in the NHS. So, I think It's no problem at all, we are very used to that, and we are very used to going up and down by 2 weeks. And it seems to be the way that the world is evolving generally with treat and extend, so it is not a such an unusual thing to do really. It's fine.

S7, I2: I do one diabetic clinic, one vein occlusion clinic a week – on a (day of the week) morning, where the MATE trial patients come. Because on the (day of the week), we have the Optometrist available who needs to do their refraction and BCVA.

S7, I2: I wouldn't say it (referring to treat and extend) it is routine at the moment but we are trying to move towards it.

S8, I2: pg 2, lines 5-11: No, we don't do routinely treat and extend in site E. Primarily because we cannot have one stop service. We are two stop service- AMD service. And the reason we still two stop AMD service is we have only one clean room.

Variation in practice at sites in comparison with MATE study and between sites

Individual practices of treating neovascular AMD and running research clinics differed at each site. While the basics are the same, there were differences in what was considered 'standard care' at each site. For examples, Fundus Fluorescein Angiography was not routinely performed at one of the sites for the diagnosis of neovascular AMD and they had to make additional arrangements for this to be done to confirm eligibility in the MATE study.

While ‘treat and extend’ regimen with assessments and treatment on the same day (one –stop service) was considered standard at one site, other sites had fixed treatment regimen similar to the ‘standard care’ arm of MATE study or ‘*pro re nata*’ (*prn*) as their local site standard practice in their NHS clinics. There was a mix and match of treatment regimens with one stop/two stop services and whether there were dedicated research sessions where only research patients were seen or research activity was embedded into NHS clinics with wider members of the team involved in research and not just the core research team.

While investigators felt comfortable in adapting their practices to requirements in the MATE study, the sponsor team found this affected the sites ability to adhere to protocol at times. These differences in finer details of anti – VEGF treatment and running trials were not anticipated by the sponsor team and they felt experienced research teams with experienced PIs and research nurses dealt with this better.

Differences in local practices were noted in pharmacy too, usually in the way site documentation was maintained, safety systems and back up. Monitoring and visiting each site in person to explore their practices early on in the study helps to trouble shoot and plan for these differences. Pharmacy manual written for this study describes pharmacy processes based on the experience at sponsor site and in hindsight liaising with site pharmacies about their practices either during site selection or site initiation meeting would help in taking into account the variation in pharmacy practice. This would improve generalisability of pharmacy manual at the sites.

S1, I2: There is a lot of variation in practice, so whilst kind of the basics are there that everybody does, there are definitely differences.

S1, I2: one site they took the description of standard care to mean, their standard care. So this was site F, so they didn’t treat because that’s what they would normally do when they are in clinic. So, they took standard care to mean that.

S9: it’s mainly also because the, although large part of the clinic, clinics and visits for MATE were as per standard care. What we discovered it’s called a ‘standard of care’, it’s not necessarily the same standard of care in every hospital. So, I

think this just show the discrepancies between different sites. Then, it's may be not necessarily something that we thought of in advance. and it only came to, our attention when we did a couple of visits. When we saw, 'there is a little bit of a problem here, little bit of a problem there'. And that caused issues with adherence to the protocol. Erm, and again I think, it depends how sites are, how experienced they are in running studies, PIs and research nurses.

S8,I2: So, it is very different to our clinical practice (referring to treat and extend and one stop clinic) . However, because obviously, we have some reasonable kind of experience in, I personally treat you know AMD for 12 years at a very senior level. So, have reasonable experience with the disease and treatment regimes. So it wasn't a problem for us to utilise treat and extend.

S3: Nothing different (referring to local site practice). Mainly because we have our own research sessions, we do not do research patients in between other patients. We had plenty of time to each patient.

S1, I2: site E, they were slightly different, so they do not operate treat and extend. So, it took them a little bit of time to feel comfortable with it. They have slight differences again in practices. So, they don't do Fundus Fluorescein Angiography (FFA) and we had to ask them to do so for screening. So, they put that in place. So, they assess post IMP injections, they do not assess using blood pressure and tonometry. So, that has been a little bit kind of backwards and forwards figuring out with them how we were going to work that, but in the end after speaking to (name of CI), we have just documented that we are allowing them to follow their normal practice.

S6: the pharmacy manual is written very much in the way of how we would do something here. But it have been quite useful to may be, go, may be have site selection visits and site initiation visits. Where you go to the sites and just look at how they do things and ask and then that would have sort of may be incorporate some of their, some of what they say and what they do.

S9: I think in terms of multi-site studies err, it's not only how the team works but it is also the support departments. With this one it is a Investigational Medicinal

Product (IMP) study, therefore pharmacy is involved. And again what we found out, every single site worked in a very different way. So, you can see how they are organised in certain pharmacies also, they are very experienced in running Clinical Trial of Investigational Medicinal Product (CTIMP) studies, they are all well organised. They have got good systems in place, including like electronic temperature monitoring for fridges, for storage areas. Whereas other sites not as much. Erm, we found out that, there was a site where for example their fridges were not connected to a backup generator in case of a power cut and somehow, they were not aware of it, till it happened. (smiles) So its yeah, and I think it's just yeah, again when setting up a study, it is to remember not to work on assumption that every site will be set up in that way.

Support to teams and level of engagement with sponsor

The level of support needed for each site differed with the team composition and set up. It was easier to communicate with sites with dedicated ophthalmology research staff mainly nurses and support staff than generic research teams which are shared across specialities. Having knowledge of terminology used in ophthalmology made communication and clarification of queries easy.

Some sites are generally more communicative than others. Varying the level of support based on the need and ability of sites is key. Assuming minimal knowledge and educating sites is better than trying to solve problems at a later date. Level of engagement with sites by the sponsor depends on the type of research team set up and the problems encountered during the trial. Some sites are comfortable interpreting the protocol and following it accordingly and others need guidance in day to day running of trials.

There was no correlation with the experience of the Principal Investigator (PI) and the amount of support needed, as the 'self-contained' site in this study had a 'first time' PI but it was a site with a dedicated ophthalmology research team experienced in

running clinical trials. (characteristics of MATE study sites are described later in this chapter).

S1, I2: differences in how the teams are set up and that impacts quite a lot on the level of support that each team requires.

S1, I2: it's a Clinical Trial of Investigational Medicinal Product (CTIMP) and I completely appreciate all those things, I think being pragmatic and err, varying the type of support on what I do with everybody very much depends on who I am working with.

S1, I2: all the sites are pretty communicative. I think, site B is quite self-contained, I hear from them the least. Erm, and they follow the protocol, so they send their data every three months. Whereas the other sites send them quite regularly. And again, it just depends; it is back to this variation. So, site F we had a few teething problems with. They send me their data and they ask me to check their appointments. I kind of have that level of involvement with them. Whereas site B for example just manage things. They are quite self-contained.

S1, I2: there are sites that have specific research nurses or research teams that are dedicated to ophthalmology. So obviously know the language that surrounds it. Know the patient pathway, things like that. So often when you liaise directly with them, they are err, quite knowledgeable. So, it is quite easy to resolve any issues. For some sites, it is the generic team. So, they are absolutely you know pulled from pillar to post. Might be working in you know, different err topic areas. So it's whilst the fundamentals of research are absolutely there you know we have a mix up with language where you might you know, one site has said 'Oh the OCT was not done' and then in the next breath they have said the 'the Ophthalmoscopy was not done'. And actually, you know trying to unpick all of that and figure out what was it that they actually meant, to resolve queries can sometimes be quite time consuming. Some sites don't have dedicated staff for research. It is just part of a clinician's role. So, one of our sites has a nurse who is the clinical nurse specialist who manages so many studies, not just MATE. And, I think that is something that we need to be mindful of, whilst it my most of the time my every day, for the

research teams it is just one of their many studies that they deal with.

S2: And it became clear in the amount of support each of those sites and their institutions needed. Everything from the Principal investigator through to the pharmacy, through on to the shop floor, nursing staff as well. I think our lesson is it best to assume a small amount of knowledge and to educate everybody from that assumption rather than assuming that everybody has a high level of functioning, that way hopefully catch the possible education that needs to be done or needs to be shared.

Documentation

GCP validity:

Local site level guidance on validity of documents like Good Clinical Practice (GCP) certificates differed and sponsor in this instance was flexible with accepting local arrangements at sites.

S1, I2: Making sure Curriculum Vitae (CV)s and Good Clinical Practice (GCP) certificates are erm, in date, appropriate, that kind of thing there is variation. Some sites go do annual; some do three yearly. You know, you have to kind of be flexible with those types of things.

Recording of adverse events (AEs):

Adverse event reporting differed considerably between sites. This issue was raised at the trial management group and on further investigation no concerns in maintaining records were found. This would depend on how well the patients were at each site and extent of detail in adverse events questioning from patients at each site.

S1, I2: So, we have a really big difference in the number of AEs recorded for each site. So, we have three sites – A, B and C, they have by far and large, particularly site C. Actually, more so than site A, loads of AEs, absolutely loads and loads. Erm, sites D, E and F have fewer; in fact, I don't think site E have any. Erm, so

whilst Serious Adverse Events (SAE)s are coming in, and I have had SAEs from nearly all the sites.

S1, I2: But we had already discussed this at the trial management group. I went to monitor to go through the notes and there was nothing in the notes that suggested anything had been missed, it's you know, we ask them to ask these questions at every visit. So again, I suppose it depends on how well the patients are and how the questions are asked.

Individual site research experience and level of research activity

MATE study sites were a mix, with some sites being more research active than others. They differed in the site of NHS trusts and experience in conducting randomised controlled trials, some more experienced than others. This mirrors 'real life' clinical trial scenario with a mix of sites having an established reputation for conducting and delivering clinical trials and others who are early on in their research journey.

S1, I2: so, some again are just more experienced. Some do lots and lots of studies, it depends on the site. Obviously, we have got quite a variation in the size of the trust we use and the level of research activity that goes on in each place you know. Site B and site C are really big hospitals. Site D and site E's pretty big and site F is probably our smallest one; you know they do not do quite as much research.

S2: so, we have a range of experience from different sites. So, some sites are very experienced in delivering randomised controlled trials and other are not.

Challenges due to variation

Protocol related including deviation:

Differences in research clinic and general AMD service delivery set up causes unique challenges at sites. Where research activity was embedded with NHS clinics, not

highlighting clearly led to a patient being treated <28 days (the minimum gap between two treatment should be 28 days) and with non - trial stock. This led to a protocol breach and change in practice at that site of having separate injection lists for NHS and trial patients and highlighting trial patients on these lists.

Another site which had their clinic trial pharmacy in a different building would dispense the drug prior to clinic visit for the drug to be stored onsite. This was to minimise delays on the day of clinic visit, led to patient being treated with non- trial stock medication. Though patient received aflibercept (from NHS stock), details of temperature monitoring were lost.

Sponsor found that though sites claimed to have participated in CTIMPs before, it was better to perform checks and go through finer details of trial delivery at the beginning of trial and iron out differences in practice than try to solve problems at a later date.

S1: It not only coincide with them injecting at 22 days but on that particular day they also used non trial stock. The ophthalmologist injecting it wasn't clear on their list (NHS list) that this was a trial patient. They just picked aflibercept and treated as they would. So, then they have made changes such as, they have now separate trial lists, they have their pharmacy check the dates of prescription.

S6: yes, I think at one site, I can't remember which site it was. Erm, yeah I kind of think, they sort of dispense it prior to clinic visit. They pre dispense medication. It goes into a fridge and then at clinic visit they are injected with it. But I think sometimes, the patient was just injected with normal stock, which obviously they are getting the same drug, but you don't have the data on how they are stored.

S9: I think it's just yeah, again when setting up a study, it is to remember not to work on assumption that every site will be set up in that way. Even though they say, 'Oh, we have done CTIMP before', but going there and doing these due diligence checks before you go. Because, it is much easier to sort of identify them at the very beginning and try to rectify before actually the study starts, because it is much more difficult to do it later.

Burden to sites – capacity issues

Sites experience capacity issues in their clinics due to this study not allowing nurse injectors to perform study treatments. Another reason causing capacity constraints and adding to delay in clinic was not being able to use drug from the stock available in NHS clinics and replacing it at a later date. Not using nurse injectors resulted in increasing demands on ‘doctor time’ in a clinic, thus limiting the number of patients seen in a clinic. This also resulted in delays in clinic and interrupted the patient flow.

While sponsors were aware of these capacity constraints and aware of additional needs this study placed on an already stretched service, they were unable to accommodate these needs especially allowing allied health professionals performing study treatments. The reasons being stricter regulatory requirements in drug studies like the MATE study and not factoring these differences at sites at an earlier stage in protocol design. They felt that if this study was to be done again, identifying study sites and liaising with them during study design phase of the trial would enable them to factor in the differences in practices at sites to make the study user friendly and fair to the sites.

Multicentre studies in general were labour intensive for the sponsor. They were challenging in terms of monitoring, communication and accommodating trial protocol to fit needs at the various sites.

S4: I guess ideally, if with hindsight you know if you were designing the protocol again; it could have seem possible to depending on negotiations with sponsor to allow for non- medical practitioners to do injections. That is a quite a minimal disruption. Because we don't hold separate clinical trial clinics. So, we embed the activity within the usual macula clinics.

S5: the main problem, I think, I have raised with (Name of CI), which is that we really could have done with nurse injectors. It is really difficult. Because we have a doctor in the eye clinic who is seeing patients from sometimes 3 or 4 different trials and obviously MATE patients are mixed into that. And then they (referring to doctor) have to leave the clinics, go, get changed, come down and do the injection. I think this has caused more delays to patients as well. It really limits how many

research patients we can book on a research clinic.

S5, I2: I think it's just that we do all the research work on a Tuesday afternoon, because that is generally the day where there is most meetings and people are doing audit and research generally. I think we can't fit it all to a Tuesday afternoon, it spills into other times during the week and then you feel obliged to see the research patients as an extra because you want to affect NHS numbers

S5: I mean generally it has not been a difficult study to run at all. Few of the time constraints are few things like nurse injecting and having to go and get the drug (research clinic is in a separate building to clinical trial pharmacy). Compared to NHS clinics where we have just got fridges full of drugs. So, I mean, I think in other studies that we have done, where it is the normal drug, that you are using, you know it comes in the same box for the research study as it is in the NHS clinics. We have been able to use NHS supply and then replace it at a later date.

S5, I2: The challenge all the way along with MATE has been not being able to use nurse injectors. So, we have one doctor on a Tuesday afternoon who does the research clinic. And in an ideal world they do all the assessments and they assess the eye for co-morbidities, and they overview adverse events and all of that. And then ideally, we like to pass them on to the nurse to do the injection. It's just restricted our research capacity slightly.

S10: drug studies as well have significantly more requirements in terms of regulatory requirements. Erm, and we have to as sponsor ensure that each of the sites is err, adhering to those requirements. And that means monitoring those sites, which we do take a responsibility for. Communicating regularly with those sites, getting updates from those sites, data, querying those sites. So, err and how responsive the site is and how erm, how much we have to amend or flex the protocol to accommodate processes at those sites, always means it is a much more

labour - intensive process to have additional sites on board. And the more sites you have, the more work it is and erm, and some sites are more problematic than others for whatever reason.

S10: and some are much more straight forward. I think we would learn from this, that would do a lot more due diligence at sites, before hand for all multi-centred studies to make sure that we can accommodate and they can to be fair to the sites too, that they can accommodate the study without it being a burden to them or their processes or the way they would normally do things.

S10: The challenges have all be in relation to having additional sites. And additional sites that do things potentially quite differently to each other in really busy clinics. You know Ophthalmology clinics are notoriously busy and some of the sites are very poorly staffed in terms of research staff in those clinics. Erm, running on a real skeletal sort of service and PIs are expected to do, more than probably they would need to do normally with those patients which I think is a burden for them. Obviously, with more funding we could resource those sites better.

S10: I think identifying sites much earlier on, looking at their clinics and the way they work, would help us to finalise the study design and protocol, so actually you could potentially fit in their clinics a little bit easier.

5.4.2 Challenges (in general)

Staff turnover – both PI and nursing

Staff turnover at sites presented challenges at sites. It affected the level of handover, training and knowledge about the study. Sponsor had to ensure that new staff were aware of the trial procedures and needs.

At one site, finding a replacement PI was a challenge. Sites and regulatory authorities have strict eligibility criteria for drug trials. This limits the number of investigators

who can take on this role. Lack of eligible and interested investigators may result in withdrawal of that study site. While both sites and sponsor endeavour to find replacement staff, sometimes it may well be beyond their ability to find a replacement and this is one of the frustrations of multisite studies.

S10: if I recall correctly, one of the PIs is leaving or has left?! I believe we are struggling to identify an investigator to take over at this site. So, erm, and really this is one of the frustrations of multi-site studies. If they are unable to find a replacement investigator, then we will not be able to continue at that site. Erm, and it is entirely out of our hand. We have to accept the fact that they are well they may be interested but they may not have the staff, who want to step up to be a PI or, they just decided that at this point that is something they no longer interested in being involved in. I think it is primarily the fact that they can't find an investigator who wants to take on the PI role for this study. Err, or who is, because it is drug trial, I suspect that limits the number of investigators who would be erm, willing or able to step up to be PI. It might, sites may have different requirements about staff that can be PIs on drug trials and whether it is a somebody who has been a PI on a drug trial before.

S1, I2: Site E for example, they had a lot of staff turnover this year. So we had, err, this is the fourth nurse that I worked with at site E. So, level of handover, level of training, things like that erm, impact on it.

Protocol related – protocol deviations, data quality

Emphasising to sites the importance of adhering to protocol and retaining study participants, especially in CTIMP studies is key to good data quality. Clinical judgement of the investigators in treating nvAMD sometimes interfered with treatment decisions leading to protocol breaches. This did not lead to patient safety issues but was closely monitored from an early stage in the study to maintain data quality. Close monitoring early on in the study is necessary to confirm eligibility of trial participants. Managing missing data, data cleansing and quality assurance is better and user friendly with electronic CRFs than paper CRFs.

Educating patients and investigators about importance of adhering to protocol to ensure data is of the quality it is meant to be. Having a data management plan early on in the study, planning first monitoring visit during the initial recruitment period i.e. when the first 2 or 3 patients are in the study at each site. Sponsor and Chief Investigator worked synergistically by reviewing treatment decisions and shared knowledge amongst sites especially in treatment decisions and common pitfalls. Engaging with sites and reminding them of trial milestones is needed for complete data capture.

Strict regulations by regulatory authorities (like Medicines and Healthcare products Regulatory Agency) in conduct of drug trials mean stringent monitoring, raising queries with sites and liaising with them. At one site, when source data could not be confirmed and lack of engagement from the site in this matter lead to a suspected serious breach. However, this then opened up channels of communication and better engagement from the site to resolve the issue. This highlights the need for high level of monitoring needed in drug trial to ensure patient safety and high data standards.

S9: Especially, CTIMP studies. And just making it very clear that they have to adhere to the protocol, because, we, well their adherence to the protocol depends whether we are gonna get quality data at the end of the study. Erm, whereas I think, sometimes the clinical judgement sort of slightly interfere with the protocol.

Because, obviously clinicians will use their own judgment as they are, as they do in normal clinics. However, for a CTIMP study they have to follow the protocol. So, I think it's just making that very, very clear at the beginning. I think some of this lead to breaches of protocol, Even though patient safety was not compromised in any way, it was just to make sure that you have got a quality data.

S9: So, I think again when we started at the very beginning, we have realised that there might be some parts of the Case Report Forms (CRF) weren't very user friendly. So, we had loads at the initial visit we had loads, quite a large number of missing data. Just the boxes were left blank. And because the CRF is the source data for this study, it is really important.

ya, because then you can't retrieve them, most of them you could not really retrieve them from anywhere. Other than someone's memory, which is not really the

source. (smiles)

Erm, so yes, went through the visits, the trial manager, she has done couple of amendments to the CRFs. Just to make it a bit more user friendly and highlight certain points. The key sort of data that we need, need to have there. So, anything that is missing, as a monitor I can't, I can't judge, I can't say 'oh, this is not a very important piece of data, I can just ignore it', I have to query every single piece of data that is missing, so we use data clarification forms. I think more and more clear now that actually electronic CRFs would be much better going forward. With paper ones it is a bit tricky, because you can miss the box, you can still move on to the next one whereas your electronic system would stop you.

S9: it is more sort of looking at the data management at the very beginning of the study and making a plan how you are gonna deal with this.

S9: initially obviously we had quite a few (refers to protocol breach) and I think that's why monitoring is really important, at the beginning of the study. And it is always very crucial to go and check the first let us say 2 or 3 patients, depending on the study. I think that's what we decide for MATE was between two to five patients to go and check.

S2, I2: sponsor has a internal investment in this trial as much as I do to ensure that is of absolute highest quality. So, we work together synergistically to ensure that we are producing the trial of quality and high standard.

S2, I2: main challenges are retaining the patients within. So, ensuring that patients understand the importance of maintaining treatment. Ensuring that the patients are continued to be treated with adherence to the protocol. So that the data is of the quality it should be. We ensure adherence to the protocol by data monitoring and in particular looking at some treatment decisions. So, I have had a look at some of the individual treatment decisions along with trial manager to ensure that there was adherence to extension or stability.

S10: for this study obviously, we have had issues at one site where we have had to do a serious breach, a potential serious breach notification to the MHRA. So, we were, we on the request really of the trial manager and the fact that we weren't

getting adequate responses to queries that were being raised with that site. We had to do a suspected breach notification to the MHRA, worked really closely with the PI there, the team and their R and D department tried to resolve some of the issues in the light of that and I think it happened actually that they worked really closely with us and together we have managed to address all those issues and seem to be much more straight forward going forwards so.

S10: well there were certain issues with pharmacy at this site and then err there were issues in terms of CRF. Basically, it was down to CRF completion and in consistencies in the way CRF was being completed at site. Erm, leading to some things in appearing that they have been done and yet there was no sort of source evidence that they had been done. It was just a real lack of clarification as to where that data was coming from on the CRF and it was really important for us as a, with a drug study in particular that we are clear, where the data is, for that bit of CRF. And erm, we had several conversations, trying to resolve where data had come from and various different erm, different views from the nurse and the PI as to where some of that data had come from and how the confusion arisen. Erm, and so in the light of that we had to put through a suspected serious breach and we have managed to resolve all the issues. All those issues have been resolved through communication with the team – with the nurse, their PI and their Research and Development team got really heavily involved in those communications. And also, I think it opened a channel of communication, which means the site seems to be much more engaged now in terms of asking advice in advance if they are unclear about something

S1, I2: Monitoring you often pick up things but they are by and large the same things that you pick up. It's more just about trying to keep MATE on everybody's radar. Obviously, now we are now, you know 2 years in. So, trying to keep it on everybody's radar, keep it high priority. As I said because the appointments don't fall neatly at 12 and 24 months and they are our milestones trying to remind people and keep them engaged with when those appointments are coming up is quite important so we don't lose any data.

Limited resources

Limited resources both finances and staffing affected the running of the trial as a whole and at each site. From an overall study point of view, the general lack of resources in NHS, particularly research resources affected the way sponsor funded each site for trial procedures. It was felt that commercially funded studies had funds to support site better by paying for additional trial procedures not performed as part of routine care or to employ staff to run the trials. Both NHS trusts and investigators have to choose research studies to fit in to available resources and they may not always be able to participate in studies of their interest.

In this study, limited budget had to be stretched between employing new staff to support the trial manager, monitoring visits to sites and organising teleconferences and investigators meetings to maintain communication with sites. Sponsor found managing multicentre drug trials be a burden in comparison to single centre studies. They had less control and limited resources and budget made this tricky. In future, they would be hesitant to sponsor multicentre trials with limited budget. Going forwards adequate funding of multisite studies is needed to be able to deliver these studies

At a site level, limited staff and availability of physical space to run clinics meant having to schedule research clinics at certain times of the week and has also affect the capacity of research clinics. Research units are having to turn down studies due to lack of capacity as these patients would not be seen on time. This problem is not study specific and is common across research units.

In a site with dedicated research sessions found that due to capacity issues in research clinics they had to book these patients in NHS clinics for the principal investigator to see as an 'additional patient' on their NHS clinic list without affecting 'numbers' on these lists, which could lead to knock on capacity issues. The PI willingly made these arrangements to avoid protocol deviations in the study but found it uncomfortable to switch their mindset to 'research mode' in the middle of busy NHS clinics affecting the quality of initial data capture. Which meant going through the data again to ensure correct documentation leading to additional work at an already over stretched site.

A problem relevant to ophthalmic studies involving imaging is storage of images and the expenses these would incur if performed in a large scale. These expenses need to be factored in future planning of clinical trials.

S2, I2: I was a little naïve about the total budget that was required for erm, activities such as teleconferences to communicate to PIs, to have investigators meetings etc. And for the amount of monitoring that was required and visiting sites. So, that has put a little bit of pressure on the budget.

S2, I2: The next, for a personal challenge is, in ensuring communication with the trial manager. She has been very busy in cleansing err data, that's taking up a lot of time. So, we have looked at bringing more staff to help her do that.

S10: Most NHS trusts like ourselves are having to pick and choose the studies that we get involved in. Err, because we just don't have the resource to spread across and to, to resource each study that comes to us.

S10: Commercial studies there is much more flexibility there (refers to finances). They are much better funded, there is often much more flexibility for us to go back and say well we can't do this, we would have to do this specially. Or we would have to run this blood test or we would have to outsource it. And they will offer us more funds to be able to cover that additional costs for us. Or indeed staffing funds and all sorts. For MATE, erm it is not brilliantly funded in terms of covering, certainly the first part in terms on covering actually what was involved at the sites.

S10: Sponsoring a multi-centre study is much more of a burden than a single centre study. We have much less control as a sponsor, erm and we spread our resources obviously even thinner.

S5, I2: I think we are very restricted with our research resources and we are working in a clinic that is already short of space and short of staff and short of rooms. So we have had a bit of a crisis in the last 12 months, in that we used to have I think 4 imaging technicians who were GCP trained and were trained in the imaging protocols. And for a period recently we had gone down to one. That's been

very stressful and very hard work for that one individual.

S5, I2: the only thing that worries me resource wise, I think isn't generally covered and again not specific to MATE, but erm we are now spending a lot of money on server storage for images. So, a lot of the research studies involve more stringent imaging than we would do in the NHS clinic. And I think if we ever were to be a very large research unit, we would have to look at that from an Information and Technology (IT) perspective

S5, I2: I think you know, probably in common with lot of units there are research studies being turned because we have not got enough resources. The things we would like to do but we can't do because we know that we don't have enough capacity to see all those patients on time. So, I think nothing to do with MATE specifically really, it's just that normally things are very. I think it's just that we do all the research work on a Tuesday afternoon, because that is generally the day where there is most meetings and people are doing audit and research generally. I think we can't fit it all to a Tuesday afternoon, it spills into other times during the week and then you feel obliged to see the research patients as an extra because you want to affect NHS numbers. And then I feel like it is a little bit. Well it is difficult in the middle of a busy clinic to switch into research mode. And to be sure you have , you know quite often I have passed the paper notes off to Clinical trials administrator and then find that I there is something I have missed off because you know it is not quite as thorough as doing it in on a Tuesday afternoon. It is better than them breaching protocol, but it is still not comfortable really.

S10: the funding is, in hindsight it is a great thing. The funding for phase one is really insufficient. We would be reluctant to embark on another drug trial, multicentre drug trial with such limited funding. It is real challenge to keep an eye on that budget. And there is no flex in there really at all.

Clinical trial planning – continuity of care

Continuity of care for patients in NHS clinics following clinical trial participation and passing on information about treatment received during the trial is an important but less thought of area in clinical trial planning. This is more of a problem in recent years with the use of Electronic medical records to record clinic visit details in NHS clinics. It is relevant to patients participating in trials on anti-VEGF treatments which are available on the NHS than on other treatments or other areas of medicine where trial treatment may not be available on NHS. Meaning the patients go on a different treatment or no treatment and details of trial treatment has no impact on future care.

S5, I2: the final thing is making the transition back into NHS care, at the end from research.

you need, have to be sure that whilst we are doing everything the source documentation, most of our care occurs on Electronic patient records system. So, once when somebody say would leave the end of MATE and come into an NHS clinic. We have to be sure that the NHS staff know what's gone before in the research study. I don't think we have been very good with that in the past, though it would be on Electronic patient records system, 'patient enrolled into MATE study' but there might not be a detailed story as to.. which is then you know going forward you need to make decisions in the NHS clinic as to. So, that is a bit of a missed element of planning clinical trials really. I suppose for other areas of medicine, you might be in a clinical trial, having a treatment and then the trial ends and then the treatment stops and you go to a completely different type of care. Whereas a lot of the anti-VEGF patients are coming off the end of a trial and going into NHS clinics

5.5 Discussion

This chapter highlights the conduct of trial following the recruitment phase. The main challenges noted are as below:

1. Variation in set up of NHS AMD treatment services and research delivery
2. Monitoring and ensuring data quality

3. Adherence to protocol
4. Staff turnover affecting overall trial conduct and, in some instances, finding replacement PI
5. Capacity and burden of this study on pre-existing AMD treatment services and research clinics
6. Interplay of NHS AMD treatment clinics and research delivery at sites affecting trial delivery
7. Continuity of care for patients following participation in research
8. Limited resources both staff and finances – additional trial procedures placed burden on already stretched services placed burden on sites. Sponsors though keen to provide help in the form of additional funding or staff were unable to due to limited funds.

5.5.1 Variation

Variation in set up and delivery of AMD treatment services across UK have been previously reported. Just over half the centres in this report offered a ‘one – stop’ AMD treatment service and FFA (Fundus Flourescein Angiography) was not used routinely for diagnosis of neovascular AMD. Though doctors performed majority of injection treatments there was an increasing reliance on nurse practitioners to perform these injection treatments to meet capacity demands¹²⁹.

Macula treatment services are high volume clinics which are constantly evolving to meet increased demand. Allied health professionals like specialist optometrists, nurse practitioners and orthoptists are involved in various components of the care pathway. They may be involved from initial triage of patients to administration of treatments^{130,131}. When research activity is embedded in routine clinics, it would help if studies can adapt to fit into these pathways. In addition to having a logistic advantage, it helps in generalisability of results from these trials.

In this study, sponsors were aware of the additional needs placed on the sites by MATE study like performing FFA at baseline and not allowing nurse practitioners to perform study treatments. Identifying and involving sites early on in the study design

would have helped resolve some of the issues. However, they are limited by stricter regulations in drug trials and limited funding in this study.

Variation in trial delivery and interleaving of research activity with NHS clinics created capacity issues at sites and sometimes led to protocol breaches (as described in results). Adherence to trial protocol is important, particularly in CTIMPS mainly for patient safety and validity of results. Investigators were affected by their clinical judgement in treatment decisions. Close monitoring of treatment decisions by the Chief Investigator, educating the sites about potential pit falls and treatment regimen, having a data management plan early on in the study ensured quality assurance of the data.

Unwarranted variation in delivery of healthcare is a recognised challenge in NHS, this leads to inefficient use of resources. Right care is working closely with GPs, commissioners and Royal College of Ophthalmologists to design best value care pathway in the different sub specialities of ophthalmology like glaucoma, age related macular degeneration and cataract¹³².

Variation in clinical trial delivery and its interplay with NHS service delivery has not been studied before in the field of neovascular AMD treatment trials. Variation in conduct of trial procedures has been reported previously in breast cancer studies. This is less likely to affect the results in randomised trials but may affect initial trial procedures¹³³. Collaborative research networks in neonatology have addressed the influence of centre-variation on patient population, study design and conduct of studies. Having research active centres across a wide geographic area, standardisation of procedures, maintaining a database which helps in study design and provides insight of the participating centres neonatology practices have helped in standardising outcomes and generalisability of trial results¹³⁴.

5.5.2 Staff turnover

Staff turnover is one of the known causes for trial drift. Staff turnover can occur both at site and sponsor level. It has impact on overall knowledge a team has about the study and has knock on effect on study results. Educating sites about trial procedures,

changes in protocol and documenting this training is important in maintaining interest and knowledge level during a study⁹⁵.

One of the MATE sites needed replacing the Principal Investigator (PI) halfway through the trials. Drug trials have strict eligibility requirements specified by regulatory bodies on who can be a PI, these have been outlined in the methodology chapter. This is mainly for patient safety and ensuring proper conduct of a trial¹³⁵.

Sponsors have to be aware of the possibility of the sites withdrawal if PI cannot be replaced by a suitable candidate.

5.5.3 Site selection and data management

Selecting appropriate sites is key to delivery of any study. Sites with poor patient recruitment may not justify the costs in maintaining them; furthermore, they may also adversely affect study outcomes. Site selection strategies like maintaining pre-trial registries, identifying local regional leader, developing individual site performance metrics, site selection surveys, visits, interviews, patient population served by a site have been described in literature^{136,137}. Hurtado – Chong et al describe a standardised, multistep approach to site selection which involves site selection questionnaires, objective site selection criteria and responses from telephone interviews¹³⁸.

In the MATE study, sites were chosen based on responses from a site selection questionnaire (appendix 7) and pre-specified criteria (described in chapter four). The sponsor team felt that site selection visits would be a better method in selecting sites as this gives an understanding of working of a site. Identifying and involving sites at an early stages helps in designing the protocol to suit the individual site needs. Sponsors are keen to liaise sites to help the study ‘fit in’ existing care pathways.

A study sponsor has overall responsibility of conducting a study. They work in close liaison with the chief and principal investigators at each site to deliver trials to a high clinical and ethical standard¹³⁸. Working closely with sites to ensure participant eligibility, protocol adherence, data capture at milestones and quality assurance of data are part of data management responsibilities of a sponsor¹³⁸. Having a data management plan early on the study helps in this regard. An Independent Data

Management committee was formed to advise the sponsor and ensure patient safety. An interim analysis of efficacy outcomes was performed, with a criterion to stop the study should the difference in visual acuity outcomes between each arm be > 10 ETDRS letters.

5.5.4 Continuity of care following participation in research

Some of the MATE study sites use Electronic Patient Records in their NHS clinics. One of our investigators raised a valid concern about passing on information about treatments received during the trial on to the NHS team to ensure smooth transition of care. This would be a valid scenario both with studies having paper based CRFs and electronic CRFs. More and more NHS trusts are opting to go ‘paperless’ and have electronic databases maintain records in routine clinical practice¹⁴¹. This is a unique problem to neovascular AMD treatment studies and in the United Kingdom, as these anti – VEGF treatments are available on NHS and studies have demonstrated the need for long term treatment with anti- VEGF agents to maintain vision in this condition¹¹. Though our study does not explore solutions for this problem, incorporating this in future trials planning is useful. (This aspect will be explored in the end of study interviews, which are not part of this thesis).

5.5 Conclusion

Variation in research delivery, site set up, research team composition can affect delivery of a clinical trial. Liaising with study teams early in the clinical trial journey to understand their research team and resources and modify study protocol where possible to fit in their needs is helpful. With busy departments like Ophthalmology, resources are stretched and factoring in the variation in practice at the different sites is useful to ensure smooth delivery of a clinical trial and support the teams better. Staff turnover at sites is a challenge in the trials running for longer duration. Continuity of care after participation in clinical trials is a missed element in clinical trial planning.

Chapter 6: The *MATE study*: a 24-month efficacy outcomes of a pilot, randomized controlled trial comparing standard care with individualized treat and extend regimen with intravitreal aflibercept for neovascular age-related macular degeneration

6.1 Introduction

This chapter presents the secondary outcomes from the MATE pilot study. Comparison of between the two arms in the form of significance testing has not been done; this is in keeping with good practice in pilot studies.

6.2 Methods

Trial design:

This was a multi-centre two-armed, pilot randomised controlled trial with patients randomised to an allocation ratio of 1:1 to receive aflibercept 2mg intravitreal injection for neovascular age related macular degeneration following one of the treatment regimens described below.

Arm A: Standard Care (S of C) – In this group, the follow up intervals were arranged as per the Summary of Product Characteristics (SmPC) of aflibercept.

Arm B: Individualised Treat and Extend (T&E) – Here, the follow up intervals were individualised based on the response to treatment and level of activity of the choroidal neovascular membrane.

*June 2018 onwards Summary of Product Characteristics (SmPC) of aflibercept changed to treat and extend regimen after the initial three doses of monthly intravitreal aflibercept.

Participants:

This study was conducted in accordance to the ethical principles stated in the Declaration of Helsinki. Prior regulatory and ethical approval was obtained. Treatment naïve neovascular AMD patients were recruited into the study from the six Ophthalmology medical retina departments of the participating NHS hospitals across the United Kingdom.

The key inclusion and exclusion criteria for participant eligibility were as follows:

Patient inclusion criteria:

- Visual impairment predominantly due to neovascular age related macular degeneration (nvAMD)
- Active, treatment naïve, angiographically active choroidal neovascular membrane in the study eye secondary to nvAMD with any part of the lesion or its sequelae (e.g. sub retinal fluid, haemorrhage, pigment epithelial detachment, sub retinal pigment epithelium (RPE) fluid) in a sub foveal location.
- Visual acuity of 78-24 ETDRS letters at screening and baseline in the study eye
- Age \geq 50 years
- Able to provide written, informed consent to the study
- Able and willing to attend for hospital visits at the frequency required
- If both eyes are eligible at baseline, the eye with worse visual acuity will be the study eye, although the final decision will rest with the investigator. Any deviation from entering the eye with worse visual acuity at baseline into the study worst seeing eye will be explained and documented in the patient notes and the case report forms (source data). The choice of eye selected for inclusion into the study will be determined and documented before the patient is randomised. A patient who has both eyes that may be eligible may therefore undergo a different treatment regimen in each eye; however, they will be treated with aflibercept in

both eyes. Hospital visits will be co-ordinated to minimise the number of attendances required and therefore the inconvenience for the patient.

Patient exclusion criteria:

- Inability to comply with the study or follow up procedures
- Pregnant or lactating women
- Women of childbearing potential, unless they are using effective methods of contraception during treatment and for 90 days after their last injection. (Effective methods include male sterilization, female sterilization, intrauterine device, oral, injectable or implantable hormonal methods of contraception where inhibition of ovulation is the primary mode of action), total abstinence (only if it is the patient's preferred and usual lifestyle, i.e. not a declaration of abstinence for the duration of the trial, periodic abstinence or withdrawal)
- Males with female partners of childbearing potential who do not agree to an effective form of contraception during treatment and for 90 days after their last injection
- Previous treatment for choroidal neovascularisation in the study eye.
- Fibrosis consisting of more than 50% of the lesion or involving the centre of the fovea.
- Co-existing pathology within 0.5disc diameters of the fovea that could prevent an improvement in visual acuity in the opinion of the investigator (e.g. macular hole, dense epi - retinal membrane)
- Cataract (causing significant visual impairment), aphakia, vitreous haemorrhage, retinal detachment, proliferative retinopathy or CNV due to any cause other than AMD at screening and baseline.
- Known allergy to aflibercept or fluorescein.
- History of cerebrovascular accident, transient ischaemic attack or myocardial infarction within 3 months of the screening visit.
- Any type of systemic disease or treatment that may affect or expect to affect the clinical status of the patient to a significant degree.
- Blood pressure of >170mmHg systolic or >110mmHg diastolic at screening or baseline.

- Any active periocular infection or inflammation at screening or baseline.
- Uncontrolled glaucoma (30mmHg) at screening or baseline.
- Neovascularisation of the iris at screening or baseline
- Treatment with any anti-angiogenic drugs to either eye within 3 months of baseline.
- Nd-YAG laser capsulotomy within the last 2 months or expected within 6 months of baseline in the affected eye.
- Use of other investigational drugs within 30 days.
- Use of systemic anti-vascular endothelial growth factor agents within 3 months prior to baseline.
- Use of systemic corticosteroids for at least 30 consecutive days within the 3 months prior to baseline
- Current or planned medications known to be toxic to the lens, retina or optic nerve e.g. hydroxychloroquine, desferoxamine, tamoxifen or ethambutol

Participant identification and informed consent

The doctor identified potentially eligible patients at their normal ophthalmology appointment. Patients were given a Patient Information Sheet (PIS) (appendix 1 and 2) at this instance. Adequate time was given to consider trial participation; however, patients could consent to take part in the study within 24 hours of being approached if they wished to.

Written informed consent was obtained by all patients before performing any trial related procedures. No trial related procedures were performed before obtaining informed consent; however, fundus fluorescein angiography performed up to 14 days prior to screening was allowed to be used in the trial.

Forty patients were recruited into the study. Each participant has been involved in the trial for 24 months. At each visit (except the screening visit), participants underwent measurement of vital signs, clinical examination, refraction to Best Corrected Visual Acuity (BCVA), and Optical Coherence Tomography (OCT) of the macula. Participants in both arms of the study were treated with Aflibercept 2 mg in 0.05ml. This was administered by intravitreal injection by a standard procedure using

appropriate aseptic precautions by a qualified ophthalmologist trained in administering intravitreal injections as described in the SmPC of aflibercept.

A summary of visit schedule and treatment regimen is presented below and outlined in a diagram:

Visit 1: Screening visit – This comprised of informed consent, confirmation of eligibility, ocular and medical history, clinical examination, refracted BCVA and Ocular Coherence Tomography of the macula.

Visit 2: Baseline visit and randomisation to:

Treatment arm A (Standard Care, S of C):

Phase 1: Monthly treatments for 3 consecutive months.

Phase 2: 8 weekly treatment until the end of year one.

Phase 3: Treatment intervals extended at the discretion of the treating physician.

Treatment arm B (Treat and Extend, T and E):

Phase 1: Monthly treatment for 3 consecutive months.

Phase 2: The treatment interval progressively extended by two weeks allowing a treatment interval to be found to maintain stability. The treatment interval was capped at 12 weeks.

Phase 3: If there was relapse in activity or reactivation within the 12-week capped regimen, the treatment interval was reduced by 2 weeks until stability was once again reached.

Phase 4: Further extension of the interval.

Final safety visit (common to both arms): 24 months after randomisation

For all the visits after the baseline visit there was a visit window of +/- 7 days from the actual scheduled visit date, with treatment no more frequently than 28 days.

Re-treatment criteria:

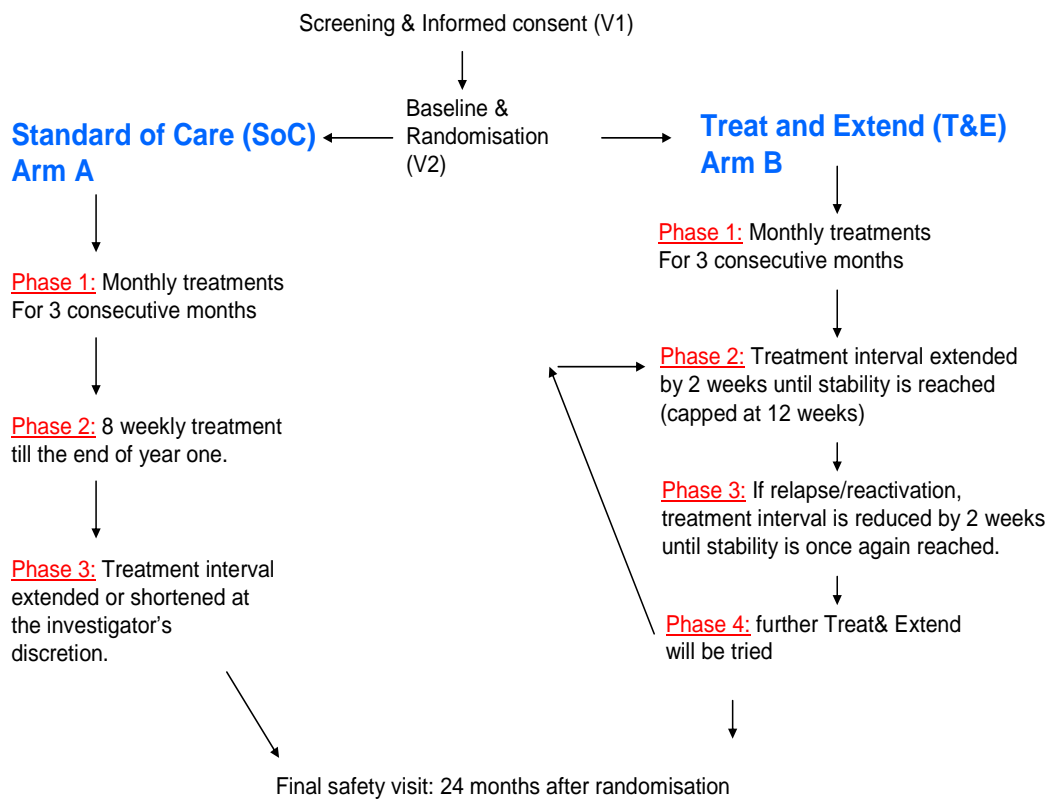
A treatment (intravitreal aflibercept) was administered if there were any signs and symptoms related to the activity of the choroidal neovascular membrane, such as loss of visual acuity, new onset of or increasing visual distortion, intra-retinal fluid (IRF), sub-retinal fluid (SRF), pigment epithelial detachment (PED) or new onset haemorrhage, at the discretion of the investigator.

Guidance for extending intervals:

- Where the examination revealed no signs of exudative disease the period until the next visit was extended by 2 weeks longer than the period since the patient's last visit. For example, if it was 4 weeks since the last treatment, the interval would be extended to 6 weeks.
- If there were signs of exudative disease, the interval to the next visit would be shortened by 2 weeks. For example, if the last treatment was 8 weeks ago, the next visit would be scheduled for 6 weeks.
- A minimum shortest duration between dose scheduling visits was 4 weeks and the 'extending' of intervals was capped at 12 weeks.

Unscheduled visits for safety reasons were allowed at the discretion of the Principal Investigator or the delegated investigator; however, the minimum time interval between two aflibercept treatments was 28 days.

Figure 6.1 summarising the visit schedule and treatment regimen.



Outcome measure:

The secondary outcome was to evaluate the efficacy outcomes of the two arms and treatment burden. (This would be the primary outcome of the future phase three randomised controlled trial which this study will inform). Visual acuity data and central retinal thickness on Optical Coherence Tomography (OCT) were collected to evaluate efficacy. Treatment burden was evaluated by the number of visits and treatments in each arm.

Sample size:

Sample size was comprised of 40 patients of whom 20 each were randomised to arm A (SC) and arm B (Individualised T& E). As this was a pilot study, no sample size calculation was made. This study will help inform sample size calculations for a future phase 3 clinical trial, which will study the outcomes described in the secondary outcomes of the present study.

Secondary outcome analysis:

Data collection:

Baseline demographics, visual acuity in ETDRS letters and central retinal thickness in microns were collected as part of efficacy outcomes. Number of treatments and visits were collected to evaluate treatment burden.

Data Analysis :

All the patients who had data post baseline were analysed. The flow of participants through this study was reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Number of participants discontinuing the study was used to calculate the withdrawal rate.

In line with recommendations about good practice in the analysis of feasibility and pilot studies, no comparisons of the outcomes between the two arms of the trial were conducted. Descriptive statistics were calculated for recruitment rates and for baseline characteristics. These are presented as means and standard deviations (SD). Descriptive statistics in the form of means with standard deviation were calculated for the efficacy outcomes and treatment burden measures.

1. Mean change in ETDRS visual acuity at 12 and 24 months between the two arms
2. Percentage of patients gaining and losing more than or equal to 15 ETDRS letters at 12 and 24 months
3. Mean change in central retinal thickness compared with baseline at 12 months and 24 months between the two arms
4. Mean number of treatments in the study eye at 12 and 24 months
5. Mean number of visits for the study eye at 12 and 24 months

6.3 Results

Participant flow through the trial is summarized in the figure 6.2 below:

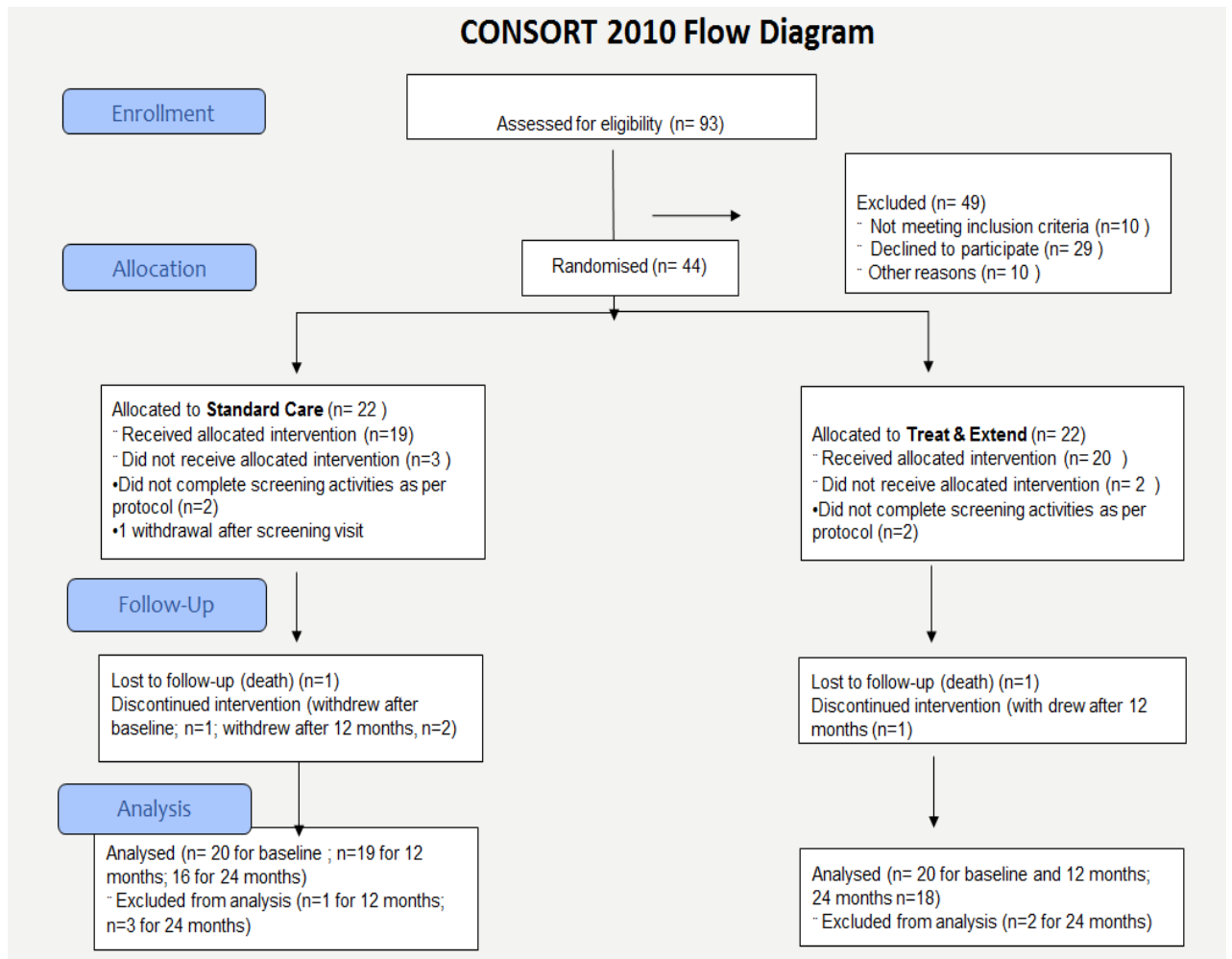


Figure 6.2: CONSORT style diagram⁶⁸ showing participant flow through the MATE trial

Figure 6.2 shows the participant flow throughout the MATE trial, 34 out of the 40 patients complete the trial at 24 months. The withdrawal or non-completion rate is 15%.

6.3.1 Baseline demographics

Table 6.1 shows baseline demographics for both arms of the study. Both groups were comparable with respect to age and gender. Mean age at baseline was 80 (SD 6.9) years in the T & E arm and 81 (SD 7.2) years in the SC arm. There was a female preponderance in both groups. The most common type of choroidal neovascular

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membrane (CNVM) in the T&E arm was ‘predominantly classic’, while in the SC arm ‘occult’ was the most common variety.

Table 6.1: Baseline demographics, including angiographic type of CNVM

	Treat and Extend (T&E)	Standard Care (SC)
Mean age at baseline (SD) in years	80 (SD 6.9)	81 (SD 7.2)
Number of females	11	11
Number of males	9	9
Angiographic type of CNVM		
Predominantly classic	8	4
Minimally classic	5	4
Occult	5	12
Retinal Angiomatous proliferation (RAP)	1	0
Polypoidal Choroidal Vasculopathy (PCV)	1	0

6.3.2 Treat and Extend (T&E) arm

Visual Acuity (VA):

In the T&E arm, the mean visual acuity (VA) increased initially from a baseline value of 63.7 (SD 10.0) ETDRS letters to 69.3 (SD 15.8) letters at 12 months and then reduced slightly to 65.8 (SD 18.3) letters at 24 months (Figure 6.3). This resulted in a mean change in VA from baseline of + 5.7 (SD 15.6) ETDRS letters at 12 months and +2.9 (SD 19.2) letters at 24 months.

Central Retinal Thickness (CRT):

In the T&E arm, the mean CRT decreased from a baseline value of 406.6 (SD 114.6) microns to 258.8 (SD 52.5) microns at 12 months and 247.6 (SD 56.7) microns at 24 months (Figure 6.4). The mean change in CRT from baseline was -147.8 (SD 104) microns at 12 months and -164.8 (SD 117.8) microns at 24 months.

Number of treatments and visits:

In the T&E arm, the mean number of treatments and visits was 9.5 (SD 1.8) at 12 months and 16.4 (SD 3.8) at 24 months (Figure 6.4).

Percentage gaining or losing > or = 15 ETDRS letters vision:

In the T&E arm, five out of 18 eyes (28%) achieved a VA gain of 15 ETDRS letters or more from baseline; three out of 18 eyes (17%) lost 15 letters or more compared to baseline. In eyes losing 15 letters or more, the reasons were fibrosis and macular haemorrhage (in two patients).

6.3.3. Standard Care (SC) arm

Visual Acuity (VA):

In the SC arm, the mean visual acuity (VA) was maintained from a baseline value of 60.8 (SD 12.5) ETDRS letters to 60.8 (SD 21.3) letters at 12 months, and then declined to 58.0 (SD 25.4) letters at 24 months (Figure 6.3). The SC arm showed a mean change in VA from baseline of + 0.7 (SD 18.6) ETDRS letters at 12 months, declining to -2.4 (SD 23.6) letters at 24 months.

Central Retinal Thickness (CRT):

In the SC arm, the mean CRT decreased from a baseline value of 414.3 (SD 144.5) microns to 308.9 (SD 83.5) microns at 12 months and 277.6 (SD 78.4) microns at 24 months (Figure 6.4). The mean change in CRT from baseline was -116.5 (SD 111.2) microns at 12 months and -148.8 (SD 122.5) microns at 24 months.

Number of treatments and visits:

In the SC arm, the mean number of treatments and visits was 8.3 (SD 0.7) at 12 months and 17.3 (SD 2) at 24 months (Figure 6.4).

Percentage gaining or losing > or = 15 ETDRS letters vision:

In the SC arm, three out of 17 eyes (18 %) achieved a VA gain of 15 ETDRS letters or more from baseline; five out of 17 eyes (29 %) lost 15 letters or more compared to baseline. In eyes losing 15 letters or more, the reasons were neovascular reactivation (in two patients) and one each had fibrosis, atrophy and Retinal Pigment Epithelium (RPE) rip.

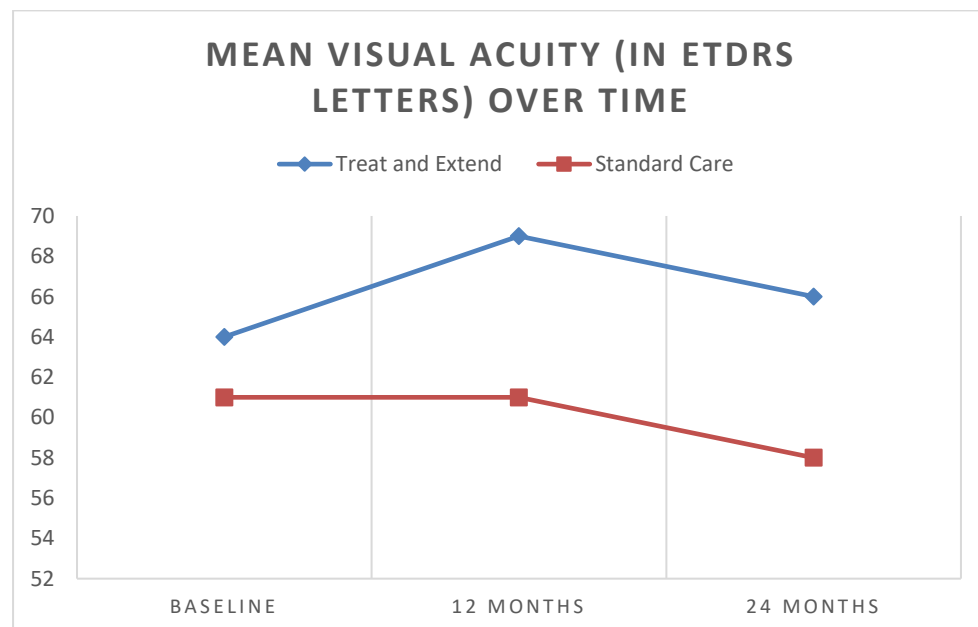


Figure 6.3: Mean visual acuity (in ETDRS letters) over time (in T&E arm, n=20 at baseline and 12 months, n=18 at 24 months; in SC arm n= 20 at baseline, n = 19 at 12 months and n=17 at 24 months)

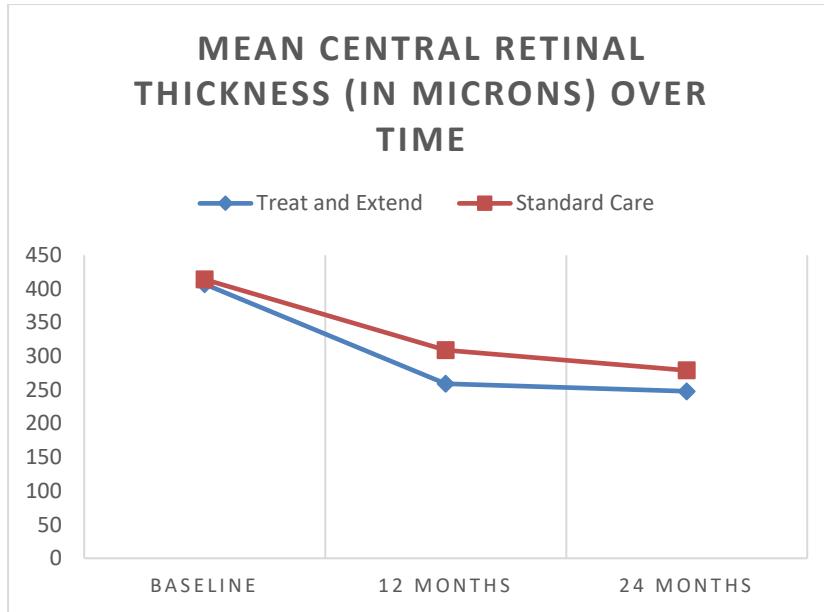


Figure 6.4: Mean central retinal thickness (CRT) in microns over time (in T&E arm, n=20 at baseline and 12 months, n=18 at 24 months; in SC arm n= 20 at baseline, n=19 at 12 months and n=17 at 24 months)

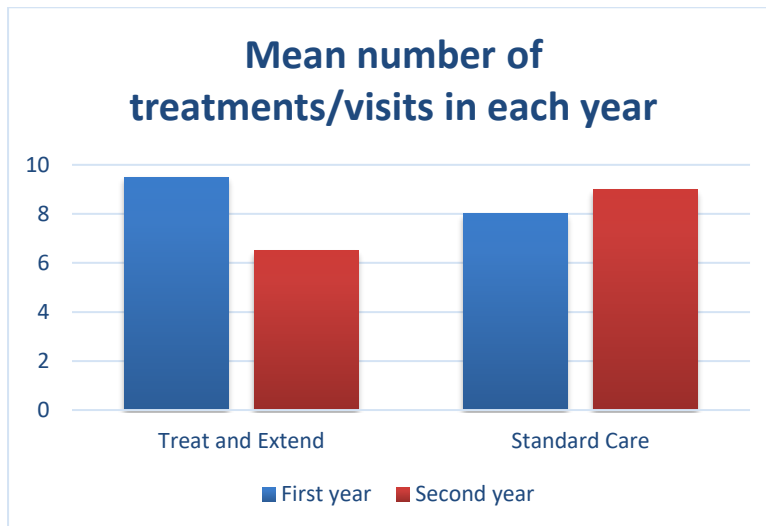


Figure 6.5: Comparison of mean number of treatments and visits in each year in both groups

6.3.4 Treatment intervals at 24 months

Whole cohort:

The mean treatment interval at 24 months for the whole cohort was 8.46 (SD 2.98) weeks.

60% had an interval of 8 weeks or more and 30% were treated at a 12-weekly interval.

Figure 6.6 below shows the distribution of treatment intervals at 24 months for the whole cohort.

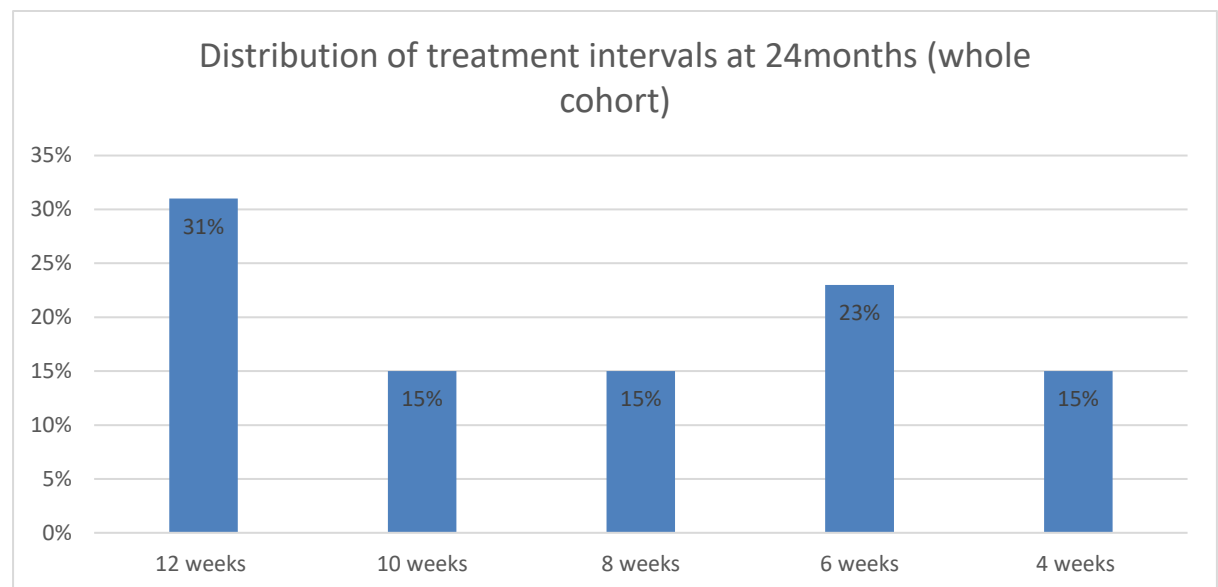


Figure 6.6: Distribution (in percentage) of treatment intervals (in weeks) at 24 months for the whole cohort (n=39)

Treat and Extend arm

The mean treatment interval at 24 months for the T&E arm was 9.6 (SD 2.64) weeks.

85% had an interval of 8 weeks or more and 40% were treated at a 12-weekly interval.

Standard Care (SC) arm:

The mean treatment interval at 24 months for the SC arm was 7.26 (SD 2.9) weeks.

34% had an interval of 8 weeks or more and 21% were treated at a 12-weekly interval.

Figure 6.7 shows a comparison of treatment intervals at 24 months between the two arms.

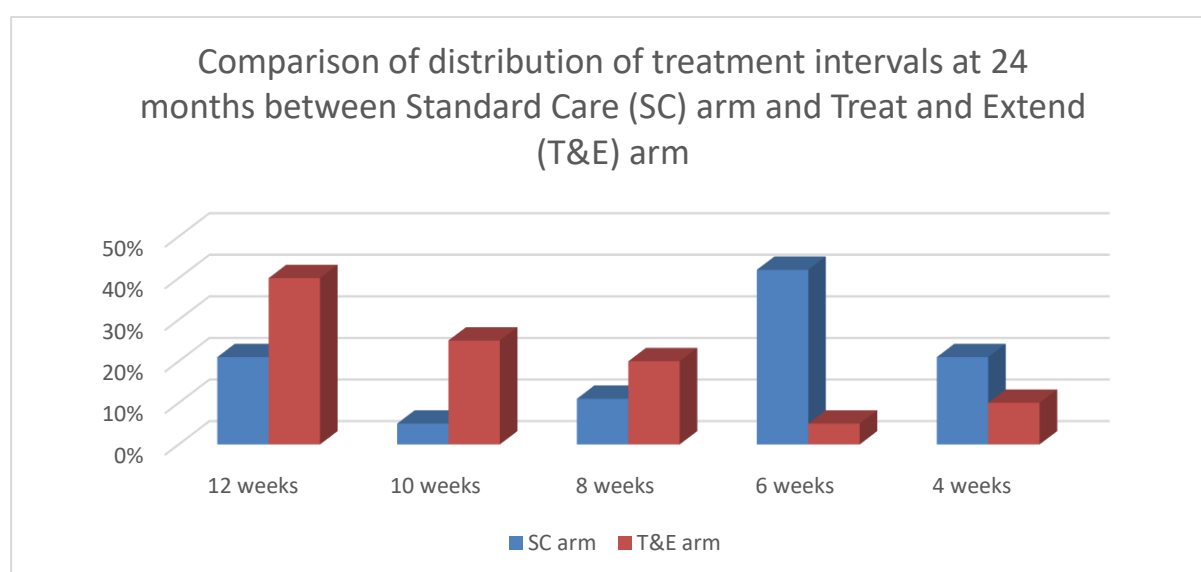


Figure 6.7: Comparison of distribution (in percentage) of treatment intervals (in weeks) at 24 months between Standard Care (n=19) and Treat and Extend (n=20)

6.4 Discussion

6.4.1 Treat and Extend arm

The T&E arm shows a mean visual gain of +5.7 letters at 12 months, which is +3 letters at 24 months; this is achieved with a mean of 9.5 treatments in the first year. This visual gain is in keeping with other studies evaluating a T&E regimen, such as the ALTAIR study²⁶. However, the two-weekly extension arm showed a gain of 9 ETDRS letters at 52 weeks with a mean of 7.2 treatments. The ATLAS²⁷ study is a

prospective, multicentre, open labelled study evaluating a treat and extend regimen aflibercept, showed similar visual gains at year 2. The ability to extend treatment intervals to 12 weeks is similar to other prospective studies with a similar regimen^{26,27}. Barthemes et al. and Mekjaic et al. also demonstrate a mean visual gain with aflibercept using T&E regimen with 13.6 and 14.5 treatments in 2 years^{36,40}. Barthelmes et al. were able to extend approximately one-fourth of the cohort to a treatment of 12 weeks or more³⁶.

Table 6.2 below compares the T&E arm of our study with other studies using a similar treat and extend strategy for aflibercept in neovascular AMD.

Table 6.2: Comparison of T&E arm with other studies using a similar regimen both in clinical trial and real-world settings

Outcomes at 2 years	MATE study T&E arm	ALTAIR Study (2 weekly extension arm; 52 week follow up) ²⁶	ATLAS study (DeCroos et al. 2017) ²⁷	Barthelmes ³⁶ et al. 2016	Mekjaic ⁴⁰ et al. 2018
Mean change in VA	+2.9	+9	+2.4	+6	+7
Mean change in CRT	-164.8	-	-139	-	-
Number of treatments	16.4	7.2	14.5	13.6	14.5

Eyes gaining 15 letters or more (%)	28%	32.5%	22.5%	-	-
Eye losing 15 letters or more (%)	17%	-	22.5%	-	-
Percentage with 12 weeks or more treatment intervals	40%	42.30% at 1 year	38%	24%	-

6.4.2. Standard care arm

The SC arm showed a mean visual gain of +0.7 letters at 12 months, thereafter, showing a decline of -2.4 letters at 24 months. This is not in keeping with other studies evaluating a similar regimen, such as the 2q8 arm of the VIEW study and real-world data, which reported a mean gain in visual acuity^{142,143}. This can be explained by outliers in the SC arm of the MATE study: five patients lost more than 30 ETDRS letters vision from baseline, due to two patients having a reactivation of the neovascular activity in the second year and one patient each having fibrosis, atrophy and a RPE rip.

Fewer treatments in real world studies may reflect the variability between clinicians and centres in implementing a treat and extend regimen in the second year^{142,143}. Almuhtaseb et al. found that aggressive treatment in the second year maintains the visual acuity gains achieved in the first year¹⁴³.

Table 6.3 below compares the SC arm of this study with other studies using a similar treatment strategy for aflibercept in neovascular AMD.

Table 6.3: Comparison of the SC arm with other studies using a similar regimen both in clinical trials and in a real-world scenario.

Outcomes at 2 years	MATE study SC arm	VIEW study 2q8 arm (96 week follow up) ²⁰	Eleftheriadou et ¹⁴² al.2018	Almuhtaseb ¹⁴³ et al. 2017
Mean change in VA	-2.4	+7.6	+6.4	+2.8
Mean change in CRT	-148.8	-133	-74.7	-
Mean number of treatments	17.3	11.2	12	Mean of 7-8 treatments in 1st year and then mean of 3.7 treatments in 2 nd year
Eyes gaining 15 letters or more (%)	18%	33.4%	28.2%	21%
Eye losing 15 letters or more (%)	29%	-	9.2%	12%

In both the arms, the central retinal thickness shows an expected declining trend which is maintained through the second year. This is in keeping with other studies reported in literature as shown in Tables 6.2 and 6.3.

6.5. Conclusion

Both arms show a trend towards gain in visual acuity in the first year which is not maintained in the standard care arm at the end of 24 months. This is explained by outliers with a greater than or equal to 15 letter loss in visual acuity in the standard care arm. These outcomes are achieved with one less treatment in the treat and extend arm. Approximately one third of patients can be extended to 12 weekly treatment intervals and about two thirds need treatments at intervals of 8 weeks or above.

Chapter 7 - Discussion and conclusion:

Age-related macular degeneration (AMD) is a leading cause of sight loss in the developed world. Neovascular AMD accounts for the majority of cases with severe visual loss due to AMD. Anti-Vascular Endothelial Growth Factor agents (VEGF) such as ranibizumab, bevacizumab and aflibercept are the mainstay of treatment for neovascular AMD, and not only do they stabilise vision in most patients, but about one third of them show a 15-letter visual gain. However, these treatments are required on a monthly or bi-monthly basis with regular monitoring of disease activity in between. This comes with a significant cost and burden to the patient and care providers. The SEVEN UP study, which is a cross-sectional analysis of a cohort from the ANCHOR and MARINA trial, shows that the initial gain in visual acuity is maintained only if treatments were repeated monthly¹¹.

Anti-VEGF treatment regimens have evolved over time and there is a trend towards individualised treat and extend regimens, which aim to find the optimal treatment interval for an individual with minimal number of treatments and maximal visual gain. The general trend to move towards longer lasting medications like aflibercept is to reduce treatment burden on patients, clinicians and the NHS. An individualised treat and extend regimen using longer lasting aflibercept would reduce this burden and expense even further. Currently, there is a gap in the literature, especially for aflibercept, in comparing treat and extend regimens with standard care for aflibercept, and if this is deliverable in the National Health Service (NHS). It would require a large scale randomised controlled trial (RCT) to answer this question. Hence, before embarking on a major trial we undertook the MATE study, which is a pilot randomised controlled trial designed to compare standard care (per label of aflibercept) with a treat and extend regimen of aflibercept for neovascular age related macular. Data from this study will be invaluable in designing and planning other large scale randomised controlled trials involving treatments for age related macular degeneration and medical retina treatment trials in general.

The MATE study adopted a mixed methodology approach, in which qualitative, in-depth interviews of key trial staff were conducted at end of recruitment and end of year one to inform feasibility and conduct of the study. Recruitment rates, nonparticipation rates and reasons for non-participation derived from analysis of screening logs complement the information from the qualitative interviews and help understand the recruitment processes involved in this study.

Overall recruitment rate per month 3.07 participants per month in the MATE study. This was lower compared to other studies but recruitment rate per month per site was better than in the rest of the studies^{92,93,94}. This may be explained by the fact that all the other studies were multinational trials with large numbers of sites, and hence recruited more patients overall per month, whilst individual sites recruited fewer patients per month. Recruitment rates are useful in future trial planning to know the number and time required for similar neovascular AMD treatment trials. The original recruitment duration in this study was planned to be 6 months, but it was extended to 13 months to meet the target of 40 participants. It was found that, once a site is active for recruitment, the priority should be to recruit the desired number of participants within the minimum possible time.

Recruitment process is a complex interplay of human factors, regulatory factors and study design. Optimising delays, training trial personnel about study procedures, good communication between sponsor and teams and favourable study design features facilitate recruitment. This study highlights the need to have an individualised recruitment strategy tailored to site and study. Investigator bias and inability to convey equipoise between the two arms to trial participants by the recruitment team were other findings of this study which had a positive impact on study recruitment. This is similar to experiences of research of other specialities as reported by the QuinteT team of investigators, however on their studies investigator bias and inability to convey equipoise had a negative impact on study recruitment^{101,102,103}. These factors can be mitigated by providing study specific training in informed consent to the trial staff involved in recruitment processes.

Variation in research delivery, site set up, research team composition can affect delivery of a clinical trial. Liaising with study teams early on in the clinical trial

journey i.e. in protocol development stage to understand their research team and resources and modify study protocol where possible to fit in their needs is helpful. With busy departments like Ophthalmology, resources are stretched and factoring in the variation in practice at the different sites is useful to ensure smooth delivery of a clinical trial and support the teams better. Staff turnover at sites is a challenge in the trials running for longer duration. For example, in our study we faced a high research nurse turnover at one of our sites. This particular site changed their research nurse four times in the duration of one year. Our clinical trial manager supported this team in the form of regular training of new members of staff about the trial specific procedures and with regular phone calls and reminder emails of study milestones. Having a data management plan early on in the study and the flexibility to monitor any sites more often if there were issues with data quality also helps in protocol adherence and supporting the teams.

As this is a pilot trial, significance testing for comparison between the two arms was not performed. However, both arms show a trend towards gain in visual acuity in the first year which is only maintained in the Treat and Extend arm, but not maintained in the standard care arm at the end of 24 months. This may be explained by outliers with $> \text{ or } = 15$ letter loss in visual acuity in the standard care arm. These outcomes are achieved with one less treatment in the treat and extend arm. Approximately, one third of patients can be extended to 12 weekly treatment intervals and about two thirds need treatments at interval 8 weeks or above. This trend is similar to findings from other clinical trial and real world data using a treat and extend strategy with anti-VEGF medications^{26, 27, 36, 40}. This provides preliminary evidence to justify testing a treat and extend regimen for aflibercept in a large scale randomised controlled trial.

This leads us onto the next question of whether this pilot study is a success or not.

Success of the pilot study and recommendations for good practice in planning future trials:

This pilot study is a success as it meets both its success criteria. With a withdrawal rate of 15% and meeting its recruitment target of 40 participants albeit with a longer recruitment window, this study is a success.

However, modifications are needed in both the recruitment and running of the study to ensure a tighter recruitment window and smoothen the running of a future planned large-scale study.

The recommendations based on lessons from this study are as below:

During the study set up stage, careful site selection with planned site selection visits help in choosing the right teams and getting a firmer commitment from sites.

Involving all stakeholders at an early stage, where possible, from a protocol development stage is useful in considering variations in local care delivery. Planning regulatory approvals and opening new sites to maintain a tighter and shorter recruitment window. For example, timing the opening of a site to fit with investigator annual leave or competing studies at a site.

At the recruitment stage, good support from sponsor team, favourable trial eligibility criteria (for example, visual acuity entry criteria better than NICE guidance in this study), early monitoring systems in place have a positive impact on recruitment.

Another strategy to boost recruitment found to be useful in our study was opening up the study for competitive recruitment as sites are keen on meeting their individual recruitment target.

Sharing of good practice between sites in the form of newsletters, reminders for milestone visits, training and re-training of research teams to be up to date with trial specific procedures are helpful in smooth delivery of a study. Adapting the amount and nature of sponsor support to the individual site needs is recommended during the study.

Impact of the study and future research:

The MATE study has been a learning journey for me, and others involved. The results of this research have already had an impact in three main areas.

Firstly, on a personal level I have learnt many new skills during the course of this study and progressed as a researcher. Learning to use qualitative research has been a highlight. My job as Clinical Research Fellow in Ophthalmology has placed me in a

good position to apply the lessons from this study to my day to day research practice. Going forwards, my approach to recruitment to any new study is focussed and planned. Once a study is open to recruitment, together with my team I plan the resources, best ways to approach a patient for the study and to try and achieve the recruitment target on time. Time management, liaising early on with study sponsors for finding solutions to problems both during the recruitment and running of any study are few changes I have made in my practice. I am in a good position to share this information and train other members of my team and beyond to follow these practices too. An example of this is when I presented the results of the recruitment phase from this study at a regional meeting of medical retina specialists (see author's declaration for details).

Secondly, the MATE study sites differed in their clinical practices and research experience. Guided by the results of interim analysis at year one of the MATE study and their increasing confidence and comfort at using Treat and Extend (T&E) regime, one of the MATE study sites changed their practice in NHS macular degeneration treatment clinics to T&E regimen (information via personal communication by the Principal Investigator). A treat and extend strategy using aflibercept for neovascular AMD in the NHS has been recommended to reduce treatment burden and optimise visual outcomes¹⁴⁴. Results from our study though preliminary provide encouraging basis for this practice, and justification to explore this in a large scale randomised controlled study.

Thirdly, the sponsor of this study has used their experience from the MATE study in the design of a multicentre oncology trial (information from personal communication by email and interviews at the end of year one). The main lessons they have incorporated to change their strategy are – involving all the stake holders including the study sites at the protocol development stage to design a site-specific modification of the trial pathway to fit into their local cancer care pathway. This ensured firmer commitment towards the study from the site. In addition to questionnaires, site selection visits have been incorporated into site selection process. There is focus on training staff on trial specific procedures both before and during the study.

Dissemination of results:

In addition to presenting results from this study in regional and international meetings to disseminate the results of this study (outlined in author's declaration), there is a publication plan in place to publish the results in peer reviewed journals. A paper following the CONSORT pilot study guidelines and another paper summarising the set-up and recruitment – including lessons from quantitative and qualitative components of the MATE study are being written up by me.

Future work:

Future work for me and my team would involve submitting a grant application for a RCT comparing aflibercept with newer treatments for neovascular AMD and use of qualitative research methods in gaining patient's perspective about participation in medical retina treatment trials.

To conclude, the MATE study meets its success criteria and provides preliminary data for the future planned RCT. The current model is deliverable with some changes as outlined above in the recruitment and running of the future planned study. This research made impact in the form of changing treatment practices in medical retina fraternity and also providing data for teams who have already adopted treat and extend regimens using aflibercept. Lessons learnt from the recruitment and conduct of this study are being applied in other setting up studies in other specialities like oncology.

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Appendices

Appendix 1 – Patient Information Sheet – MATE study

MATE study

An invitation

You are being invited to take part in a research study with a medicine Aflibercept (Eylea) for treating neovascular or wet age related macular degeneration. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team members will go through the information sheet and the consent form with you and answer any questions you have.

Please take some time to read it carefully and discuss it with your family, friends and GP if you wish, before making up your mind.

Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear.

About the study:

The purpose of this pilot study is to assess the feasibility of conducting a large study to compare two different treatment regimens for Aflibercept (Eylea), a treatment for the people suffering from poor vision due to neovascular or wet age related macular degeneration. The aim is to achieve and maintain a best benefit of your visual function and avoid unnecessary injections at the same time. A pilot study is a small scale study often done to test the plan and method of a research study.

The study will last for approximately 24 months, during this time you will be asked to come to the clinic for up to 26 visits. The duration of the visits varies and will depend on the procedures required by the study protocol. During the study you will receive monthly Aflibercept injections for the first 3 months, and then as often as your study doctor thinks you need it for the following 21 months.

The success of this study will depend on us being able to recruit 80% of participants on time and with 80% or more participants completing the study successfully.

It is planned that 40 patients will participate in this study at about 5 sites in the United Kingdom. Parts of this study may be used for educational purposes but this will not affect the running of the study.

This study is being organised by the <name of sponsor>

PART 1

What is the purpose of the study?

If your eye doctor diagnoses you with wet age related macular degeneration, the standard recommended treatment for this condition is an injection into the eye. The name of the injection is an anti – Vascular Endothelial Growth Factor (VEGF) medicines like Eylea (Aflibercept). Your eye doctor will go through the risks and benefits of this treatment with you.

The Standard treatment regimen with Eylea comprises of initial 3 doses of monthly injections into the eye followed by an injection every 8 weeks in the first year.

This study compares Standard treatment with a treatment regimen individualised to you depending on the level of disease activity in your eye. One of the main aspects this study looks at is whether such a study can be delivered safely and effectively in NHS settings.

Why have I been invited?

Your doctor has diagnosed you with visual impairment due to Neovascular Age Related Macular Degeneration (AMD) or wet AMD and you may be suitable to take part in this study.

Do I have to take part?

No, it is up to you to decide whether or not you take part.

If you do decide to take part, you will be asked to sign the consent form. You will be given a copy of the information sheet and signed consent form to keep.

You will be free to leave the study at any time, with or without giving a reason and this will not affect your future treatment and care.

What will happen to me if I take part?

You will visit the clinic more often

You will be asked to visit the hospital eye clinic up to 26 times during the 24 month study period. Some visits will be in the morning, some in the afternoon.

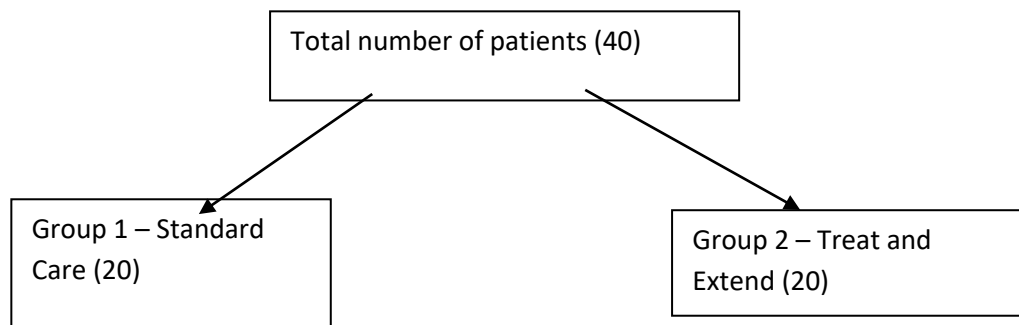
You will be given medication

You will receive monthly injections of 2mg Aflibercept for the first three months and then further injections for the next 21 months. Overall you could receive up to 24 injections of 2mg Aflibercept into the eye.

Two treatment regimens are being tested in this study:

Group 1: After the initial 3 injections, you will receive further treatment with Aflibercept and the treatment interval will be decided by your doctor.

Group 2: After the initial 3 injections, you will receive further treatment with Aflibercept every 8 weeks up to 1 year and then the treatment interval will be decided by your doctor.



The treatment group you will be given is selected at random. You have an equal chance of receiving either of the two treatments.

You may be prescribed antimicrobial (anti septic) drops to administer into your eye for 3 days after the study drug treatment.

You will have some special tests done.

You will have some special tests to examine your eyes and to assess your eyesight. You will also be asked to complete questionnaires at some visits about how you are feeling and your vision.

You will have some health checks.

You will have your blood pressure and pulse rate measured at most visits. At the first visit your height and weight will be measured.

Expenses and payments:

There are no expenses or payments available with this study

What other treatments are there for wet AMD?

Please discuss other available treatments for wet AMD with the study doctor, who will explain to you the advantages and disadvantages of these treatments.

What are the possible benefits of taking part?

We hope that the treatment regimen given to you in this study will help your wet AMD but this cannot be guaranteed. The information we get from this study may help us develop new treatment regimens for wet AMD. This may benefit you and other patients in the future.

The knowledge gained from the previously completed clinical research studies in wet AMD have shown that Aflibercept may improve your vision, stabilise your vision or slow the progression of vision loss.

Who cannot take part in this study?

Pregnant or breast-feeding women cannot take part.

As with any drug, we do not know whether Aflibercept can harm an unborn or breast-fed baby. Therefore pregnant or breast-feeding women cannot take part in this study.

If there is a possibility that you might become pregnant, your urine sample will be tested for pregnancy at the start of the study. The study doctor will discuss suitable contraceptive (birth control) methods with you.

If you have private medical or life insurance:

Please check with your insurer that it is acceptable under the terms of your policy for you to take part in this research.

If any other health problem shows up:

It is possible that the health checks carried out before and during the study could show up a problem that you didn't know about. If this happens, you will be referred for suitable treatment and you may be told that you are not suitable to take part in this study. Your GP will also be informed.

Other therapies and medicines:

Please tell your study doctor about all medicines you are using or intend to use during the study – some of these may mean that you cannot take part in the study. Even those you buy without a prescription. Some medicines are not allowed during the study, your study doctor will tell you about these.

What are the side effects and risks of taking part?

Risks of Eylea treatment:

Like all medicines, Aflibercept (Eylea) can cause side effects, although not everybody gets them. Please do not be alarmed by the list of possible side effects. You may not experience any of them but you need to be aware of them.

Most common adverse reactions (> or = 1%) in wet AMD studies

- Bloodshot eyes (bleeding of the conjunctiva)
- Eye pain
- Cataract (clouding of the lens)
- Detachment of the jelly inside the eye from the light sensitive layer at the back of the eye (vitreous detachment)
- Appearance of small particles or spots in the field of vision (floaters)
- Increased eye pressure
- Increased blood flow in the white part of the eye (conjunctival hyperaemia)
- Stripping of the corneal surface (corneal abrasion)
- Foreign body sensation in the eye
- Dry eye
- Itching of the eye
- Increased watering of the eye
- Blurred vision
- Inflammation inside the eye
- Swelling of the eyelids (fluid build up in the eyelid)
- Swelling of the cornea (fluid build up in the cornea)
- Retinal pigment epithelial tear
- Detachment of the retinal pigment epithelium
- Injection site haemorrhage

Less common adverse reactions (< or =) 1% in wet AMD studies

- Hypersensitivity reactions
- Retinal detachment (detachment of the light sensitive layer of the eye)
- Retinal tear
- Endophthalmitis (infection of the inner eye)

Other possible risks and discomforts

Heart attacks and strokes have been linked with substances that block VEGF (Vascular Endothelial Growth Factor) production like Aflibercept (Eylea), when the substance was not only present in the eye, but was taken up into the blood stream and therefore reached other parts of the body. There is, therefore, a theoretical risk of stroke as a result of injection of Aflibercept (Eylea) into the eye.

If you have experienced a stroke or transient ischemic attack (mini stroke) in the past, the risk may be higher. You should discuss with your study doctor if this affects you and whether any special care is recommended for your condition. If you experience symptoms of stroke during the study, such as weakness or paralysis of the limbs or face, difficulty in speaking or understanding, please seek medical attention as immediate medical care may be needed.

Possible discomfort with other tests during the study (not different from clinical care):

Eye examinations include eye drops to measure the pressure of the eyes and for dilating the pupils so the study doctor can view the inside of the eye. Rarely, people are allergic or sensitive to these drops.

Fluorescein angiography is used routinely in the diagnosis of eye diseases and involves taking pictures of your eyes. Your eyes will be dilated with eye drops which will cause your vision to be temporarily blurred for a few hours. You will receive an injection in your arm of a dye which may cause minor discomfort. The most common side effects of these procedures included nausea and vomiting; however, occasionally allergic reactions (rarely including serious allergic reactions) and fainting may occur. The dye may stain your skin and urine; this will last approximately 1 day. On rare occasions, hypotension (low blood pressure), cardiac arrest and even death may occur. In rare instances where a nurse, doctor or a laboratory technician sustains an exposure to your blood, tissue or body fluids by needle sticks, cut or splash to damaged skin, it may be necessary to test your blood, tissue or body fluid sample for certain viral infections including Hepatitis B and C and HIV on the sample already available or you may have to give a new blood sample if we do not have your blood samples already.

What if new information becomes available during the study?

Sometimes, during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study.

If you decide to stop taking part in the study, your doctor will advise on the most suitable treatment for you. If you decide to continue in the study, you will be asked to sign a new Consent form.

Also, on receiving new information, your study doctor might consider it best to take you out of the study. He/she will explain the reasons and arrange for your care to continue.

You may be taken out of study if:

1. Staying in the study would be harmful
2. You need treatment not allowed in the study
3. You do not follow study procedures as directed by the study doctors.
4. You become pregnant.
5. The study is stopped.

Any new information about the study medicine will be given to you so that you may decide to continue or leave the study.

If you decide to leave the study you should tell the study doctor or the study staff. They will make sure that proper procedures are followed and a final clinical assessment visit is made for your safety.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What happens at the end of the study?

About six months after the study ends, your study doctor will know the results of the study and have more information regarding the safety of Aflibercept. You will be given a copy of the results once they are publicly available, if you want a copy.

Any report that is published about the study will not identify you or any other patient taking part.

Aflibercept was licensed by the regulatory authorities for use in patients with the visual impairment due to neovascular age related macular degeneration in 2013, and the National Institute for Health and Clinical Excellence (NICE) have recommended that this treatment can be funded by the National Health Service (NHS).

You will be prescribed a suitable treatment

Once the study has ended your further treatment will be arranged by your treating doctor and continued as per the current NHS guidance at that time.

What information about me will be collected?

The information (data) collected in the study will include:

- Personal data – information that could be used to identify you, such as your initials and date of birth.
- Sensitive personal data- information about your health and medical history
- To protect your right to privacy, there are Data Protection Laws in European Union Member states. These laws control:
 1. How personal and sensitive personal data (including your biological samples) is collected.
 2. How can it be used?
 3. Where it can be passed on to?

When you give this information to someone (known as the data controller) they must comply with the Data Protection Laws and only use the data in ways for which you have given permission. The data controller for the study is <name of sponsor>

What will the information be used for?

The information collected in this study will be used to find out how safe and effective the medication is for treating the condition being studied. It may also be used when asking regulatory authorities for approval to market the medication. The data will be retained for at least 15 years. If and when it is disposed of, this will be done securely.

The results of the study may be used in presentations or published in scientific reports. Any presentation or published report about the study will not name or otherwise identify you.

In future, <name of sponsor> may wish to use information from the study for future research into the causes and treatment of the condition being studied.

What is already known about the drug being tested?

Aflibercept is currently licensed in the United Kingdom, United States, Australia and Europe for the treatment of patients with wet AMD. Aflibercept has been used in 2042 patients till date in various studies. Studies have shown that Aflibercept is safe, well tolerated and effective in treating wet AMD.

More details of the study

If you agree to join this study, you will receive treatment with Aflibercept 2mg as follows:

Aflibercept: you will receive three injections of 2mg Aflibercept into your eye on Days 1, 30 and 60. During the following months, your study doctor will decide how frequently you need to visit. In total, during the study you may receive up to 24 monthly Aflibercept injections in the study eye. Only one eye will be chosen as the 'study eye' and will be selected by the study doctor based on the severity of your

vision in each of your eyes. If necessary your other eye can be treated in the way your doctor feels appropriate, but will not be included in this study.

The treatment takes around 10 minutes and you will lie in a reclining chair or on a bed. Prior to each treatment, anaesthetic drops will be placed in your eye which will be cleaned with an antiseptic. A small device (speculum or eyelid clamp) will keep your eyelids open. The conjunctiva over the white part of your eye will be numbed (anesthetised) with eye drops.

The study medication will then be injected into the white part of your eye (into the 'vitreous jelly') this is not painful although you might feel slight pressure.

After each injection, the study doctor will check your vision as well as the eye pressure of the study eye.

You may be instructed to self administer antiseptic eye drops to your study eye 4 times daily at home for 3 days after each injection.

What happens at the study visits?

At some visits the study doctor will check your blood pressure and pulse to make sure the treatment isn't causing any problems.

Always feel free to ask the doctor or nurse any questions you may have about the medication, the procedures or the study in general.

Sometimes it may be necessary to repeat a test if the original test could not be assessed or if the study doctor or nurse will let you know if a test needs to be repeated and why.

Special procedures

You may have some special tests to examine your eyes and to test how well you can see. It is likely that you will have some eye drops before these tests. At every visit your visual acuity (sharpness of central vision) will be tested by looking at eye test charts to assess how well you can see letters. You will also have an examination of your retina and a measure of how much swelling there is in both eyes. You will have an optical coherence tomography (OCT) test which involves light being shone into your eyes to check the thickness of your retina.

The following eye test will happen at some visits:

- A test to determine your eye pressure (intraocular pressure).
- A photographic examination of the inside of your eye and a fluorescein angiogram, in which dye is injected into your arm and special pictures are taken of your eye.
- A photograph of the inner lining of the eye known as 'fundus photography'.

The study visit schedule at a glance

Screening Visit: (Visit Number 0)

Lasts for about 2-4 hours*

Comprehensive eye examination will be performed and your eligibility to take part in the study will be assessed.

Baseline visit: (Visit number 1)

Lasts for about 2-4 hours*

If found eligible, you will be randomised to one of the study groups and you will receive your first study treatment.

Treatment visits: (Visits 2 up to 24)

Lasts for about 2-4 hours*

You will get the study treatment as per the study protocol.

End of study visit (Visit Number 26, month 24)

Lasts for 2 to 4 hours*

* The times shown here are estimates; they will be different at different hospitals. The appointments may be in the morning or in the evening.

If you are unable to keep an appointment, please contact the hospital as soon as possible to make alternative arrangements.

A comprehensive eye examination along with OCT will be performed at all study visits.

Where can I get more information?

If you have more questions about this study, you can contact the study doctor whose name and number are at the end of this information sheet.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

What will happen if I don't want to carry on with the study?

Your decision to take part in this study is voluntary. This means that you are free to decide to join the study or not join this study. You are also free to leave the study at any time and without any reason.

All data up until the date of your withdrawal will be used. You retain the right to decide whether data from any post- withdrawal assessments can be used. If you withdraw from the study, researchers, authorized persons from <name of sponsor> will still require access to your medical notes to verify the data collected up to the date of your withdrawal.

Further care of your eye condition will continue unhindered in NHS hospital eye clinics.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the research team who will do their best to answer your questions <insert research team's contact details>. If you remain unhappy and wish to complain formally, you can do so via PALS. Details can be obtained from Patient advice and Liaison Service < insert PALS contact number>.

NHS Based research

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for compensation from York Teaching Hospitals NHS Trust. If compensation is not granted you will be free to take legal action, when according to legal principles, legal costs may need to be paid by yourself. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?

Your data will be collected

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the <name of sponsor> organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Your medical records will be checked

To make sure the information collected in the study is accurate, it will be need to be checked by researchers and authorised persons working on behalf of York Teaching

Hospitals NHS Foundation Trust and for government health departments. You are asked to give permission for these authorised people to see your medical records. They will keep the information confidential and your rights to privacy will be protected.

We may need to trace you in the future

Some studies are followed up over a number of years. If the organisers were to lose contact with you in future, they might need to trace you through information held by the NHS and the General Register Office.

Involvement of your general practitioner (GP)

This study involves medicinal products. We will ask your consent to notify your GP of your participation in the study so as to ensure your GP can continue to offer best informed care to you.

What will happen to the results of the research study?

We intend to publish the results of this trial in the medical literature/journals.

We will let you know in writing, the conclusions of the study, once all the results have been analysed and published.

Who is organising and funding the research?

This research trial is being organised by <insert name of sponsor> and funded by <insert name of funder>. It will be run by the medical staff in the hospital outpatient clinics of the participating sites.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the North Yorkshire Research Ethics Committee.

Further information and contact details

You have been given this copy of the patient information sheet and a copy of your consent form.

Any queries please use contact details overleaf:

<insert contact details of site>

Appendix 2 - MATE study - Patient information sheet - Pregnancy related information:

(To be given to patient where relevant only)

If you are a woman who could become pregnant:

You should not plan to become pregnant during the study; as we don't yet know whether the study medicine is safe for an unborn baby.

If necessary, you should use two reliable, medically approved methods of contraception (such as the Pill, an IUD, and condoms). The study doctor will discuss this with you. If you cannot use contraception for any reason, the doctor will advise you not to have sex during this time.

A urine pregnancy test will be performed to confirm you are not pregnant. This test will be repeated at the end of the study if the doctor deems it necessary.

If you think you may have become pregnant during this study, you must tell the doctor immediately.

If you do become pregnant during the course of the study, we would ask you to tell your study doctor immediately so we can help decide appropriate action. You will be taken out of the study if you become pregnant. We would discuss referral for specialist counselling on the possible risks to your unborn baby and arrangements will be offered to monitor the health of both yourself and your unborn baby.

If you are a man whose partner could become pregnant:

You and your partner should use two reliable, medically approved methods of contraception (such as the Pill, an IUD, condoms) during the study and for up to 30 days afterwards. The study doctor will discuss this with you. If you or your partner cannot use contraception for any reason, the doctor will advise you not to have sex during this time.

If you think your partner may have become pregnant during the study, tell the doctor immediately.

If your partner has become pregnant they will be given an information sheet and asked to sign a consent form requesting them to provide information on their pregnancy and its outcome to <insert name of the site>. This information would be collected by the study doctor and /or the research team and arrangements will be offered to monitor the health of your partner and your unborn baby.

Appendix 3 – Consent form – MATE study

Patient Identification Number for this trial:

CONSENT FORM

MATE STUDY:

Name of Researcher: _____

Please

Initial:

1. I confirm that I have read and understand the information sheet dated _____ (version __.__)) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from York Teaching Hospital NHS Foundation Trust and from authorised regulatory authorities. I give permission for these individuals to have access to my records.

4. I agree to my GP being informed of my participation in the study.

5. I agree to take part in the above study.

Name of Patient:

Signature: _____

Date: _____

Name of Person taking consent: (if different from researcher)

Signature: _____

Date: _____

Appendix 4 –Participant information sheet and consent for interviews – MATE study

Staff Interviews: Participant Information & Consent

Information about the interviews:

Dear colleague,

As you are aware MATE study is a pilot study and involves the understanding of the set up and running of a clinical trial as the primary outcome. This is best studied using qualitative methods such as unstructured interviews as this would give a voice to those involved in the day to day running of the trial.

One of the researchers (Dr Archana Airody) will perform face to face interviews with the relevant staff (as outlined in the appendix 7 of the MATE protocol) at the end of recruitment, end of year one and at the end of study, to study the various aspects of set up and running of the trial. Interviews are expected to last approximately 20 minutes and will be audio recorded with your permission. Participation in the interviews is voluntary; however your participation is key to the success of this aspect of the study and would be very much appreciated. All data collected will be anonymised (both for individuals and sites).

Many thanks

MATE investigators team

Consent:

I agree to take part in the feasibility aspect of the MATE study and consent to the interviews.

I understand that my participation is voluntary.

I agree to audio recording of the interview.

I understand that data collected will be anonymised and analysed by the MATE investigator team and the sponsors of the study, York teaching hospital NHS foundation Trust. Data will be stored by the sponsors as per the Data Management Plan of the MATE study.

Signature of the participant	Name of the participant	Date
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Signature of the interviewer	Name of Interviewer	Date
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Appendix 5 - interview guide

End of recruitment:

Trial personnel interviewed:

- Clinical Trials Manager,
- Principal Investigator of individual sites (including chief investigator)
- Pharmacy representative

Topics explored:

- Study set up – challenges, strengths and weaknesses with examples/scenarios

- Recruitment – reasons for refusal to take part in the study, eligibility criteria, recruitment period
- Randomisation – how easy, how difficult, patient perspectives on randomisation
- Resources – clinical and non-clinical
- Administrative support
- Problems/challenges in practice to MATE
- Adherence to protocol
- Masking
- Formats and structure of the CRFs – adequate?
- Time and budgetary constraints
- Pharmacy: challenges, day to day running of pharmacy, drug transfer and storage, pharmacy manual.

End of year one:

Trial personnel interviewed:

- Clinical Trials Manager,
- Principal Investigator of individual sites (including chief investigator:
- Sponsor representative
- Study monitor

Topics explored:

- Resources – clinical and non-clinical
- Administrative support
- Problems/challenges in practice to MATE
- Adherence to protocol
- communication
- Masking
- Formats and structure of the CRFs – adequate?
- Time and budgetary constraints
- Treatment regime at their site
- Type of AMD service – one stop/ two stop

- Research teams – ophthalmology Vs generic
- Recruitment strategy if any
- Site specific problems (interviewer aware of them from prior interviews)

Monitor:

- Do participating centres understand the questions and other data collection methods? Do they respond with missing or unsuitable data?
- Data collection and quality assurance of data
- Communication with sites
- Case report forms (CRF) - adequacy
- Challenges in monitoring and set up.

Sponsor representative:

- Challenges in setting up an running of clinical trial
- Administration and finances
- Site selection process and challenges
- Protocol adherence

Appendix 6 - additional questions to the interview guide (modified)

- Treatment regime at their site
- Type of AMD service – one stop/ two stop
- Research teams – ophthalmology Vs generic
- Recruitment strategy if any
- Site specific problems (interviewer aware of them from prior interviews)

Appendix 7 – Site Information form

Name of Principal Investigator (PI)?

Site Name and Address:

Telephone number:	Fax number:
E-mail:	
What is the best way to contact you? <input type="checkbox"/> Phone <input type="checkbox"/> Fax <input type="checkbox"/> Email <input type="checkbox"/> Other, please specify:	
What is the out of hours emergency contact number for your research team?	

Name of main contact for study set up?	
Telephone number:	Fax number:
E-mail:	
What is the best way to contact you? <input type="checkbox"/> Phone <input type="checkbox"/> Fax <input type="checkbox"/> Email <input type="checkbox"/> Other, please specify:	

Name(s) of Research and Development Facilitator who will deal with local approval?	
Telephone number:	Fax number:
E-mail:	
What is the best way to contact you? <input type="checkbox"/> Phone <input type="checkbox"/> Fax <input type="checkbox"/> Email <input type="checkbox"/> Other, please specify:	

Do you have the equipment and trained staff to perform the study assessments like slit lamp, tonometer?
Do you have a SD-OCT machine? Please could you indicate the machine type (with model and version) you will be using :
Do you have the equipment for Fundus photography and Fluorescein angiography? Please could you indicate the machine type with the model you will be using: Are you able to send images on a flash drive?
Do you have a certified visual acuity alley / ETDRS chart? When and by whom

was this certified?

Do you have certified optometrists to perform a refraction and visual acuity at each visit?

Name the main contact for pharmacy:

Telephone number:

Fax number:

E-mail:

What is the best way to contact you : Telephone/ E-mail

Please can you confirm that pharmacy have been contacted about this study and are happy to store the study drug (Aflibercept) vials in the fridge and have room and temperature monitoring to do this?

Do you have the resources (sufficient staff with sufficient time) to support the study?

Please give details:

Role	Name	Telephone No. and Email
Co - Investigators		
Research Nurses		
Study Co-ordinator		
Trials Pharmacist		
Optometrist		
Imaging technician/Photographer		

How many new neovascular age related macular degeneration patients do you see per month?

Do you think you will be able to recruit 9 participants over the 6 month recruitment period?

Yes/No

If 'No' how many participants do you think you will be able to recruit over the 6 month recruitment period?

What would be your main concerns with this study?

Many thanks for completing this form.

Please return by e mail your completed form to Archana Airody <insert contact details>