Treatment of severe **D**iabetic macular oedema with **A**nti-vascular endothelial growth factor (anti-VEGF) monotherapy versus treatment with Anti-VEGF followed by subthreshold **M**icropulse las**E**r when the thickness of the central retina goes below 400 microns: a pragmatic randomised equivalence trial (**DAME**).

Protocol Number	24014NL-UC
Protocol Version	V2.0 Final
Protocol Date	09/09/2024
Protocol Amendment Number	1
Ethics Reference Number	<Ethics reference number>
ISRCTN	<ISRCTN number>
SWAT ISRCTN	<ISRCTN number>
Sources of Monetary or Material Support	
Funder	National Institute of Health and Care Research (NIHR) Health Technology Assessment Programme (HTA); NIHR157427 https://fundingawards.nihr.ac.uk/award/NIHR157427
Sponsor Details	
Sponsor	Belfast Health and Social Care Trust (BHSCT) Non Clinical Support Building Royal Victoria Hospital 274 Grosvenor Road Belfast, BT12 6BA Northern Ireland
Chief Investigator	Professor Noemi Lois Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland

NIHR Funder Statement

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Project Reference NIHR 157427). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

PROTOCOL AUTHORISATION

Protocol Title	Treatment of severe **D**iabetic macular oedema with **A**nti-vascular endothelial growth factor (anti-VEGF) monotherapy versus treatment with Anti-VEGF followed by subthreshold **M**icropulse las**E**r when the thickness of the central retina goes below 400 microns: a pragmatic randomised equivalence trial (DAME)
Protocol Acronym	DAME
Protocol Number	24014NL-UC
Protocol Version Number/Date	V2.0 Final_09/09/2024
Protocol Amendments	v1.0 to v2.0 Change made to the indemnity (section 17.6) to include conduct of the focus groups

A review of the protocol has been completed and is understood and approved by the following:

Noemi Lois		_____ / _____ / _____
Chief Investigator Name	Signature	Date
Christina Campbell		_____ / _____ / _____
Statistician	Signature	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 6

1. STUDY SUMMARY 8

2. STUDY TEAM 10

3. ROLES AND RESPONSIBILITIES 11

3.1. FUNDER 11
3.2. CONTRIBUTORSHIP 11
3.3. SPONSOR 11
3.4. TRIAL OVERSIGHT COMMITTEES 11
3.4.1. Trial Management Group (TMG) 11
3.4.2. Trial Steering Committee (TSC) 11
3.4.3. Data Monitoring and Ethics Committee (DMEC) 12
3.4.4. User Involvement or Any Other Relevant Committees 12

4. BACKGROUND AND RATIONALE 13

4.1. BACKGROUND INFORMATION 13
4.2. RATIONALE FOR THE STUDY 13
4.3. RATIONALE FOR THE INTERVENTION 14
4.4. RATIONALE FOR COMPARATOR 15

5. STUDY AIM AND OBJECTIVES 15

5.1. RESEARCH HYPOTHESIS 15
5.2. STUDY AIM 15
5.3. STUDY OBJECTIVES 15

6. STUDY DESIGN 15

6.1. STUDY DESIGN 15
6.2. INTERNAL PILOT 15
6.3. STUDY SCHEMATIC DIAGRAM 16
6.4. END OF STUDY 17

7. TRIAL SETTING AND PARTICIPANT ELIGIBILITY CRITERIA 17

7.1. STUDY SETTING 17
7.2. ELIGIBILITY CRITERIA 17
7.2.1. Inclusion Criteria 17
7.2.2. Exclusion Criteria 17
7.3. CO-ENROLMENT GUIDELINES 17

8. TRIAL TREATMENT 17

8.1. TRIAL INTERVENTION AND COMPARATOR 17
8.1.1. Comparator Arm: Anti-VEGF Monotherapy (standard care) 18
8.1.2. Intervention Arm: Subthreshold Micropulse Laser (SML) 18
8.2. RESCUE TREATMENT 18
8.2.1. Rescue Treatment Comparator Arm: Anti-VEGF Monotherapy (standard care) 18
8.2.2. Rescue Treatment Intervention Arm: Subthreshold Micropulse Laser (SML) 18
8.2.3. Rescue Treatment Comparator and Intervention Arms 18
8.3. TREATMENT ADHERENCE 21
8.4. TREATMENT DISCONTINUATION 21
8.5. POST-TRIAL CARE 21

9. ASSIGNMENT OF TREATMENT 21

9.1. SEQUENCE GENERATION 21
9.2. ALLOCATION CONCEALMENT MECHANISM 21
9.3. ALLOCATION IMPLEMENTATION 21
9.4. MASKING 21

10. OUTCOME MEASURES 22
10.1. PRIMARY OUTCOME MEASURE 22
10.2. SECONDARY OUTCOME MEASURES 22
10.3. SAFETY OUTCOMES 22
10.4. DEFINITION OF STUDY EYE 23
11. SCREENING, CONSENT AND RECRUITMENT 23
11.1. RECRUITMENT STRATEGY 23
11.2. SCREENING PROCEDURE 23
11.3. INFORMED CONSENT PROCEDURE 23
11.4. WITHDRAWAL OF CONSENT 24
12. SCHEDULE OF ASSESSMENTS 25
12.1. PARTICIPANT SCHEDULE 25
12.2. DEMOGRAPHICS 26
12.3. PREVIOUS MEDICAL AND OPHTHALMIC HISTORY 26
12.4. HBA1C 26
12.5. CLINICAL OUTCOMES 26
12.5.1. Best-Corrected Visual Acuity (BCVA) 26
12.5.2. Central Retinal Thickness (CRT) 27
12.5.3. Trial Treatment 27
12.5.4. Safety Outcomes and Adverse Events 27
12.6. STUDY INSTRUMENTS FOR PARTICIPANT FOLLOW UP 27
12.6.1. EuroQol-5 Dimension-5 Level (EQ-5D-5L) 27
12.6.2. National Eye Institute Visual Function Questionnaire (NEI VFQ-25) 28
12.6.3. Health Service Use Questionnaire 28
12.6.4. Patient Cost Questionnaire 28
12.6.5. Participant Treatment Experience Visual Analogue Score (VAS) 28
12.6.6. The Theoretical Framework of Acceptability (TFA) Questionnaire 28
12.6.7. Participant Focus Groups 29
12.6.8. Participant Follow Up and Retention 29
13. DATA COLLECTION AND MANAGEMENT 29
13.1. DATA COLLECTION 29
13.2. DATA QUALITY 29
13.3. DATA MANAGEMENT 30
14. STATISTICAL CONSIDERATIONS 30
14.1. SAMPLE SIZE 30
14.2. DATA ANALYSIS 30
14.2.1. Statistical Methods 30
14.2.2. Missing Data 31
14.2.3. Analysis of Quality of Life Data 31
14.2.4. Health Economics Evaluation 31
14.2.5. Participant Experience and Acceptability 32
14.2.6. Nested Process Evaluation to Assess Implementation and Scalability Aspects Post-Trial 32
14.2.7. Study Within A Trial (SWAT) 33
15. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 33
15.1. DEFINITIONS OF ADVERSE EVENTS 33
15.2. ADVERSE EVENT RECORDING AND REPORTING 33
15.3. ASSESSMENT OF CAUSALITY 34
15.4. ASSESSMENT OF SEVERITY 35
15.5. ASSESSMENT OF SERIOUSNESS 35
15.6. ASSESSMENT OF EXPECTEDNESS 35
15.7. SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) 35
15.8. RECORDING AND REPORTING OF URGENT SAFETY MEASURES 36
16. DATA MONITORING 36

16.1. DATA ACCESS 36
16.1. MONITORING ARRANGEMENTS 36
17. REGULATIONS, ETHICS AND GOVERNANCE 36
17.1. REGULATORY AND ETHICAL APPROVALS 36
17.2. PROTOCOL AMENDMENTS 36
17.3. GOOD CLINICAL PRACTICE 37
17.4. PROTOCOL COMPLIANCE 37
17.5. PARTICIPANT CONFIDENTIALITY 37
17.6. INDEMNITY 37
17.7. RECORD RETENTION 37
17.8. COMPETING INTERESTS 37
18. DISSEMINATION/PUBLICATIONS 38
18.1. PUBLICATION POLICY 38
18.2. AUTHORSHIP POLICY 38
18.3. DATA SHARING STATEMENT 38
19. REFERENCES 38

LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
AR	Adverse Reaction
BCVA	Best-Corrected Visual Acuity
BHSCT	Belfast Health and Social Care Trust
CARF	Central Angiographic Resource Facility
CI	Chief Investigator
CI	Confidence Interval
CI-DMO	Centre-Involving Diabetic Macular Oedema
CFIR	Consolidated Framework for Implementation Research
CONSORT	Consolidated Standards of Reporting Trials
CONSERVE	CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances
CRF	Case Report Form
CRT	Central Retinal Subfield Thickness
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DAME	Diabetic Macular Oedema with Anti-VEGF monotherapy versus treatment with Anti-VEGF followed by subthreshold Micropulse Laser
DOB	Date of Birth
DIAMONDS	Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser trial
DMEC	Data Monitoring and Ethics Committee
DMO	Diabetic Macular Oedema
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data capture
ERIC	Expert Recommendations for Implementing Change
ETDRS	Early Treatment Diabetic Retinopathy Study
EQ-5D-5L	EuroQol Five Dimension Five Level
GCP	Good Clinical Practice
GLM	General Linear Models
GP	General Practitioner
HEAP	Health Economic Analyses Plan
HTA	Health Technology Assessment
HES	Hospital Eye Services
HRA	Health Research Authority
ICH	International Conference of Harmonisation
ICF	Informed Consent Form
ISF	Investigator Site File
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat
MHRA	Medicine and Healthcare Products Regulatory Agency
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health and Care Research
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy
PSS	Personal Social Services
PI	Principal Investigator
PIP	Pillar Integration Process

PLWD	People Living With Diabetes
PPI	Participant and Public Involvement
PRP	Panretinal Photocoagulation
QALY	Quality Adjusted Life Years
QoL	Quality of Life
QUB	Queen's University Belfast
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPE	Retinal Pigment Epithelium
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SD-OCT	Spectral Domain- Optical Coherence Tomography
SDV	Source Data Verification
SML	Subthreshold Micropulse Laser
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SWAR	Study Within A Review
SWAT	Study Within A Trial
TFA	Theoretical Framework of Acceptability
TIA	Transient ischaemic attack
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VAS	Visual Analogue Score
VFQ-UI	Visual Function Questionnaire Utility Index

1. STUDY SUMMARY

Scientific title	Treatment of severe Diabetic macular oedema with Anti-vascular endothelial growth factor (anti-VEGF) monotherapy versus treatment with Anti-VEGF followed by subthreshold Micropulse lasEr when the thickness of the central retina goes below 400 microns: a pragmatic randomised equivalence trial.
Public title	Treatment of severe Diabetic macular oedema with Anti-vascular endothelial growth factor (anti-VEGF) monotherapy versus treatment with Anti-VEGF followed by subthreshold Micropulse lasEr when the thickness of the central retina goes below 400 microns: a pragmatic randomised equivalence trial.
Health condition(s) or problem(s) studied	Severe diabetic macular oedema (DMO).
Study Design	Pragmatic, allocation-concealed, single-masked (outcome assessors), multicentre, randomised (1:1), equivalence trial.
Study Aim and Objectives	**Aim** To conduct a pragmatic randomised equivalence trial to assess clinical- and cost-effectiveness, safety, participant experience and acceptability of Subthreshold Micropulse Laser (SML) applied after the Central Retinal Subfield Thickness (CRT) is <400µm following initial anti-VEGF injections, compared to continued anti-VEGF monotherapy, in people who originally presented with severe DMO (CRT ≥400µm). DAME incudes a nested process evaluation to assess post-trial implementation and scalability. **Objective** To determine if, in people presenting with severe DMO (CRT ≥400µm) who are initially treated with anti-VEGFs, treatment with SML after their CRT has decreased to <400µm is equivalent (equivalence margin +/- 5 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) to continuing anti-VEGF monotherapy for preserving/improving best-corrected visual acuity (BCVA) in the study eye at 24 months. To assess post-trial implementation strategies and scalability.
Study Intervention	Patients who originally presented with severe central involving (CI)-DMO (CRT ≥400µm) and then received anti-VEGF treatment will be eligible for DAME once their CRT has been reduced to <400µm. Patients who consent will be randomised to the intervention or comparator group. **Intervention** Treatment with SML, applied every 2-3 months until DMO fully clears and if it recurs after having previously dried based on Optical Coherence Tomography (OCT) scans (in the latter case, provided that CRT remains <400µm). Rescue treatment with anti-VEGFs will be allowed if CRT increases to 400µm or more and/or BCVA falls 10 ETDRS letters or more from the previous visit or from baseline (first visit in the trial) [or if there is a loss of >5 ETDRS letters, but < 10 ETDRS letters, and a clear justification from the investigator for why rescue treatment is needed]. **Comparator** Continuing with anti-VEGF monotherapy, as per current standard of care, until DMO fully clears or if it recurs after having previously dried, based on OCT scans. Anti-VEGFs will be given as per summary of product characteristics (SmPC). Rescue therapy (switching to a different anti-VEGF) will be allowed if, despite timely and appropriate treatment, DMO increases or if BCVA falls ≥10 ETDRS letters from the previous visit or from baseline (first visit in the trial) [or if there is a loss of >5 ETDRS letters,

	but <10 ETDRS letters, and there is clear justification from the investigator for why rescue treatment is needed]. If the above rescue treatments fail to rescue, rescue treatment with intravitreal steroids is allowed, as per current standard practice. In the comparator arm and in the intervention arm, if anti-VEGFs are used, participating sites will use the type of anti-VEGF they routinely use in their standard clinical practice.
Primary Outcome	Change in BCVA in the study eye from randomisation (baseline) to week 104 (24 months) (equivalence margin +/- 5 ETDRS letters).
Key Secondary Outcomes	All at week 104 (24 months) from randomisation: • CRT in the study eye • Health related and vision related quality of life • Safety • Number of treatments used (anti-VEGF injections, SML sessions) in the study eye • Number/proportion of people receiving "rescue" treatment in the study eye • Number of rescue treatments received in the study eye • Number/proportion of people discontinuing treatment (with reasons) • Number/proportion of people losing (with reasons) ≥5, ≥10 and ≥15 ETDRS letters (from baseline to week 104) in the study eye • Number/proportion of people gaining ≥5, ≥10 and ≥15 ETDRS letters (from baseline to week 104) in the study eye • Number/proportion of people with CRT ≤300µm in the study eye • Number/proportion of people with no DMO • Health and social care service use and non-health care costs • Participant experience and acceptability
Key Inclusion and Exclusion Criteria	**Inclusion criteria** Adults (≥18 years) with diabetes type 1 or type 2 who presented with severe CI-DMO (CRT ≥400µm) and are within the first year of initiating anti-VEGF therapy but who still have DMO and their CRT is below 400µm (and it remains, at the time of randomisation) following anti-VEGF therapy in either one eye or both eyes. **Exclusion criteria** • Causes of macular oedema other than DMO. • DMO with CRT ≥400µm • Receipt of anti-VEGFs before their presentation with severe DMO (previous macular laser treatment for DMO is allowed) • Use of unlicensed anti-VEGFs (e.g. bevacizumab) • Inability, for any reason, to attend study visits • Active proliferative diabetic retinopathy (PDR) (treated and inactive PDR is allowed) • Use of pioglitazone which cannot be stopped for the duration of the trial • Cataract surgery or laser panretinal photocoagulation (PRP) within the previous 6 weeks • Currently enrolled in a CTIMP (Clinical Trial of an Investigational Medical Product) • Declined consent for participation
Countries of Recruitment	United Kingdom (UK)
Study Setting	Hospital Eye Services (HES)

Target Sample Size	264 participants
Study Duration	54 months

2. STUDY TEAM

Chief Investigator	**Professor Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland *For full details of co-applicants and co-investigators please request by email from: dame@nictu.hscni.net*
Statistician	**Christina Campbell** Senior Biostatistician Northern Ireland Clinical Trials Unit (NICTU) 7 Lennoxvale Belfast, BT9 5BY Northern Ireland
Health Economist	**Dr Ashley Agus** Senior Health Economist Northern Ireland Clinical Trials Unit (NICTU) 7 Lennoxvale Belfast, BT9 5BY Northern Ireland
Clinical Trials Unit	**Northern Ireland Clinical Trials Unit (NICTU)** 7 Lennoxvale Belfast, BT9 5BY Northern Ireland
Primary Sponsor	**Belfast Health and Social Care Trust (BHSCT)** **Alison Murphy** Research Manager Research Office 2nd Floor King Edward Building The Royal Hospitals Grosvenor Road Belfast, BT12 6BA Northern Ireland Email: ResearchSponsor@belfasttrust.hscni.net
Sponsor's Reference	24014NL-UC
Contact for public queries	**Clinical Trial Manager** Northern Ireland Clinical Trials Unit (NICTU) 7 Lennoxvale Belfast, BT9 5BY Northern Ireland Email: dame@nictu.hscni.net
Contact for scientific queries	**Professor Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland

	Email: n.lois@qub.ac.uk

3. ROLES AND RESPONSIBILITIES

3.1. Funder

The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme is providing the research costs to the DAME study (Reference NIHR157427; investigator-led application HTA 22/112). Further details can be found at www.fundingawards.nihr.ac.uk/award/NIHR157427

The nested process evaluation to assess post-trial implementation and scalability will be funded through the support provided by the late Miss Elizabeth Sloan via the Queen's University of Belfast (QUB) Foundation.

The funders have no role in the study design, data acquisition, analysis and interpretation, or manuscript preparation.

3.2. Contributorship

The Chief Investigator (CI) conceived the study. The CI planned the study design, which was finalised with input from all co-investigators, including the DAME Participant and Public Involvement (PPI) Group. The statisticians determined the sample size and planned data analysis, with input from the CI. The statisticians will oversee the primary statistical analysis of the trial. The health economists planned and will conduct the cost-effectiveness evaluation. Experts on qualitative research and implementation science designed and will undertake/analyse the participant experience and acceptability evaluation and implementation strategies. The CI is the grant holder and will oversee the management and conduct of the study.

3.3. Sponsor

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation who will undertake Sponsor delegated duties in relation to the management of the study. The Sponsor will have no role in the collection, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication.

3.4. Trial Oversight Committees

3.4.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. It will comprise the CI and representatives from the Northern Ireland Clinical Trials Unit (NICTU), and any other co-investigators who provide trial specific expertise as required at the time. The TMG will meet face to face or online on a monthly basis, and will communicate between times via telephone or online meetings and emails as needed. The roles and responsibilities of the TMG will be detailed in the TMG Charter. Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All day-to-day activity will be managed by the Trial Manager, in consultation with the CI as needed, providing a streamlined approach for handling enquiries regarding the trial and disseminating communications.

3.4.2. Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened to provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. The minimum quoracy for any TSC meeting to conduct business is 67% (two thirds) of the appointed membership. An independent chair will lead the TSC. The TSC will also include the CI, at least one public member and others with clinical expertise relevant to the project. The membership, the role of the TSC and the frequency of meetings will be listed in the TSC

Charter. The TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants. Meetings will be formally minuted and will be stored in the TMF. On occasion, observers may be invited to attend TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the NICTU.

3.4.3. Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be convened, comprising two independent clinicians with experience in undertaking clinical trials and an independent statistician. The DMEC's overarching responsibility is to safeguard the interests of trial participants, in particular with regard to safety, and assist and advise the TSC so as to protect the validity and credibility of the trial. The membership, the role of the DMEC and the frequency of meetings will be listed in the DMEC Charter. The DMEC will meet to agree conduct and remit, which will be detailed in the DMEC Charter and include: monitoring the data and making recommendations to the TSC on whether there are any ethical, safety, or other reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies; and making recommendations to stop the trial for benefit on the basis of an effect estimate that is likely to influence decisions about the use of the relevant therapy by clinicians outside of the trial. Meetings will be formally minuted and will be stored in the TMF. Following recommendations from the DMEC, the TSC will decide what actions, if any, are required. It will be the responsibility of the TSC to inform the Sponsor if concerns exist about participant safety, following which the Sponsor will take appropriate action. If a trial extension and/or funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

3.4.4. User Involvement or Any Other Relevant Committees

Trial conception and design. When researchers were evaluating the results of DIAMONDS, a NIHR-HTA funded trial they had recently completed [1-4], the DIAMONDS PPI Group voiced the importance of the trial's findings for the choice of which laser to be used to undertake macular laser for people with DMO. When discussing treatment options for patients with diabetic macular oedema (DMO) more generally, they mentioned the preference of many patients for macular laser over anti-vascular endothelial growth factor therapies (anti-VEGFs) which need to be given as injections into the eye. They explained that many people are distressed and experience anticipatory responses (e.g. fear and anxiety) to intraocular injections, which may even start the day before treatment. Furthermore, some people feel uncomfortable after anti-VEGFs, finding it difficult to return to work or undertake routine activities. In parallel to these conversations, there were data showing that patients undergoing anti-VEGF therapy do not receive them in a timely manner, due to a lack of capacity of Hospital Eye Services (HES), resulting in improvement in vision and prevention of sight loss being compromised. On this basis, DAME researchers worked with the Research Partnership from Diabetes UK Northern Ireland to convene a new diverse PPI Group to support the design and conduct of DAME. Final decisions about the trial's protocol were made at a meeting with the research team and PPI Group (a separate meeting with a member of the PPI Group who felt daunted by communicating within a large group also took place).

Preparation of participant facing materials: Participant information leaflet, consent form, and posters were prepared with active input from the PPI Group. Posters will be placed in clinics/injection rooms to make potential participants aware of the trial and ensure staff at participating sites remember to inform potential participants about DAME.

Trial recruitment: Researchers and the DAME PPI Group will work together ensuring all possible strategies to recruit a diverse group of participants living with diabetes (PLWD) are used in the trial.

Retention of participants in the trial: The DAME PPI Group's input will be sought during the follow-up period to ensure adequate measures are in place to maximise retention of participants in the trial. In this regard, when designing DAME, researchers and the PPI Group planned evaluations and follow-up of participants in the simplest and most convenient way possible, to facilitate their involvement on the trial and the completion of all visits.

Interpretation of trial results, dissemination, and implementation: When data analysis is completed, results will be interpreted with input from the DAME PPI Group. The TMG will consult with the PPI Group

to identify best strategies for dissemination and implementation of trial results, which will include the evaluation of the Study Within A Trial (SWAT) embedded in DAME. The implementation strategy included in DAME will be essential for the implementation in clinic of trial results.

Identification of areas of future research: The DAME PPI Group will help the researchers to identify new areas of research, based on the results of DAME.

4. BACKGROUND AND RATIONALE

4.1. Background Information

DMO is a leading cause of sight loss in people living with diabetes (PLWD). Considering the prevalence of DMO (7%) [5, 6] and diabetes (~4.8 million) [7], around 336,000 PLWD have DMO in the UK. With its increasing incidence [8] DMO will continue to be a burden to society.

In DMO, fluid collects at the macula, the area that gives central vision, leading to sight loss. As fluid accumulates, the macula thickens; this is measured in microns (μm) with optical coherence tomography (OCT) scans. A measure of central retinal subfield thickness (CRT) is obtained with OCT scans when DMO is diagnosed, guiding treatment selection. National Institute for Health and Care Excellence (NICE) guidance advises intraocular injections of anti-VEGF for PLWD presenting with severe (CRT ≥400μm) centre involved DMO [9-11]. For PLWD presenting with milder forms of centre involved DMO (CRT <400μm) NICE advises macular laser because it is as effective as anti-VEGFs but costs less [9-11].

Most patients presenting to HES in the UK have DMO with CRT ≥400μm and, thus, they are treated with anti-VEGFs. Currently, as per standard practice, anti-VEGFs are given monthly initially (loading dose) and then typically every 1-3 months until the macula dries, even if CRT falls to below 400μm at any time. In 72% of people on anti-VEGFs, the fluid remains until at least the second year of treatment [12]. Trials have shown that after five years, 38-48% of participants still require anti-VEGFs either because DMO remains or because it recurs after clearing once anti-VEGFs are stopped. Most patients on anti-VEGFs need follow-up for life. Anti-VEGFs are expensive and carry potential harms including increased intraocular pressure, retinal detachment, cataract, and infection (endophthalmitis). The latter, although rare, can lead to total blindness.

Furthermore, intraocular injections cause discomfort to many patients during administration and for hours thereafter and elicit anticipatory stress responses (communication from DAME PPI Group). Research has shown that a significant proportion of patients (25%) experience high levels of preprocedural anxiety, and nearly 10% report high levels of pain [13]. Other experiences of treatment burden, not commonly assessed in previous studies, have been found to be important including time and functional disruption associated with intravitreal injections [14]. Moreover, HES are unable to cope with the demand and, as a result, injections are not being given in a timely manner, which has a negative impact on outcomes and the cost-effectiveness of the treatment. Finding ways to reduce the number of injections to optimise patient experience and maximise adherence is a goal pursued worldwide.

Trials comparing anti-VEGFs with standard macular laser have demonstrated superiority in terms of efficacy of anti-VEGFs against laser in severe DMO. These trials included predominantly eyes with very thickened retinas (e.g. >460μm in RISE and RIDE trials [15] and >479μm in VIVID [16] and VISTA trials [17]. When anti-VEGFs were used in combination with macular laser in some of these trials, combined treatment (anti-VEGFs and macular laser) did not appear to be superior to anti-VEGFs alone. However, macular laser was not necessarily applied when CRT had gone below 400μm following anti-VEGFs [17]. It would be at this stage that macular laser would have a higher chance to be effective, as its penetration through the neurosensory retina and areas of macular oedema, and subsequently, its uptake by the retinal pigment epithelium (RPE) would be more adequate when compared with its likely reduced penetration and effect on the RPE when the macula is very thickened by marked DMO.

4.2. Rationale for the Study

DAME will be a pragmatic trial comparing clinical- and cost-effectiveness, side effects and participant experience and acceptability of combined treatment with anti-VEGFs + Subthreshold Macular Laser (SML) for participants who present with severe DMO and are treated initially with anti-VEGF, with the SML applied after CRT falls to <400μm (when laser has more chance to succeed), versus the current standard of care of continuing with anti-VEGF monotherapy even when the CRT falls below 400μm if DMO is present. We hypothesize that injections and visits to the clinic will be reduced by introducing SML at the most appropriate time.

DAME follows on from the DIAMONDS trial [1-4], which showed that SML, which does not damage the macula, is as effective to treat DMO of <400µm as standard laser, which produces a burn. Although DIAMONDS participants had poor glycaemic control (mean HbA1c 8.5%), most maintained excellent sight and fulfilled driving standards throughout their 2-year follow-up. Those treated with SML needed, on average, only two sessions of laser, with clinic visits every 3-4 months and only 18% received rescue treatment with anti-VEGFs, with an average total cost of care of £898 per participant (i.e. similar to the cost of the drug in a single anti-VEGF injection).

We hypothesize that treating people with severe DMO (CRT ≥400µm) initially with anti-VEGFs and then, when CRT goes below 400µm, continuing with SML every 2-3 months until DMO clears will be as effective but more cost-effective, have fewer side effects and be preferred by people with DMO when compared to continuing with anti-VEGF monotherapy. If SML allows people initially treated with anti-VEGFs to maintain the characteristic early vision gains that are observed following the first few anti-VEGF injections [2, 15, 16, 19] this new strategy could become the new standard of care for people with severe DMO and be implemented worldwide. Potential benefits would include fewer injections with subsequent reduction in inconvenience, stress, harms and costs, and fewer clinic visits, which will facilitate patient's compliance with the treatment and reduce costs and inconvenience to people with severe DMO.

A Cochrane review and network meta-analysis found that anti-VEGFs improve vision in DMO but concluded "evidence from RCTs may not apply to real-world practice where people are often undertreated and under-monitored" [17]. In this regard, a recently published, large cohort study from Moorfields Eye Hospital found that half of the patients with DMO treated with anti-VEGFs achieved vision of 70 ETDRS letters at 1.9 months of initiating this therapy but, in 50% of these, vision dropped below this level by 14.7 months (i.e. visual gain was not maintained) [20]. Similarly, a "real world" analysis of 28,658 eyes of participants with DMO treated with anti-VEGFs found that eyes with good vision at baseline (before initiating anti-VEGF therapy), were at risk of visual loss a year following treatment initiation, highlighting that outcomes observed in anti-VEGF trials are not reproduced in clinical practice [21].

4.3. Rationale for the Intervention

Macular laser is likely to be effective in combination with anti-VEGFs in people initially presenting with ≥400µm DMO if the macula laser is applied after the CRT has gone below 400µm following anti-VEGFs. A Single Technology Appraisal by NICE found that for people presenting with DMO and CRT of <300µm, there was no statistically significant difference in efficacy between anti-VEGFs and laser, but laser was more cost-effective [10]. When CRT was between 300µm and 400µm, there were gains in vision of 7 ETDRS letters with anti-VEGFs and 4 ETDRS letters with macular laser, a statistically significant difference but of doubtful clinical relevance; and macular laser dominated in cost-effectiveness.

A recent randomised trial conducted by the Diabetic Retinopathy Clinical Research Network (Protocol V) [22] including people presenting with DMO and good vision (median 85 ETDRS letters), with CRT of <400µm (median 290µm and 299µm in aflibercept and macular laser arms, respectively) and median HbA1c of 7.6% showed comparable efficacy between aflibercept and macular laser, with 16% and 17% of participants experiencing an improvement in BCVA of >5 ETDRS letters at two years. The recently completed NIHR-HTA funded DIAMONDS trial, showed that macular laser is effective and cost-effective for the treatment of people presenting with DMO and CRT <400µm [1-4]. In this pragmatic trial, participants who had good vision (median 82 ETDRS letters), median CRT of 331µm and median HbA1c of 8.5% (i.e. more severe disease than those included in Protocol V) maintained good sight throughout the two years of follow-up (mean change in vision of less than 3 ETDRS letters) with 18% of participants experiencing an improvement in BCVA of >5 ETDRS letters at two years [2, 3].

In clinical practice, macular laser is offered only to people presenting with new DMO with CRT <400µm but not routinely to those who have started anti-VEGFs, even if, at some point, their CRT is <400µm. The proposed strategy (initial anti-VEGF therapy for people presenting with severe DMO with CRT of ≥400µm followed by macular laser after CRT goes below 400µm) would likely allow participants to achieve visual acuity improvement (which often occurs following the first few anti-VEGF injections [15] [16] [18] [19] but is less frequently observed after macular laser monotherapy) but without the need to continue with anti-VEGF injections long-term. The DAME PPI Group felt that participants would be likely to prefer this new proposed strategy (anti-VEGF followed by SML).

Our DIAMONDS trial in people presenting with DMO of <400µm showed that SML, which does not produce any deleterious functional or structural changes in the retina, is as effective as standard laser, which produces a burn in the retina [1-4]. A recent systematic review of the literature on SML for DMO

identified five small (30-56 eyes in total in each trial) randomised trials comparing anti-VEGFs alone with anti-VEGFs + SML [23]. In four of these trials [24-27] no statistically significant differences in best-corrected visual acuity (BCVA) were found between treatment groups, whereas in one [28] a significant improvement in BCVA was observed only in the combined anti-VEGF+SML group. A statistically significantly reduced number of anti-VEGF injections was required in the anti-VEGF+SML group in three of the four trials in which this outcome was investigated [24-26]. None of the trials included other important outcomes such as health-related and visual-related quality of life, participant-reported experience, adverse events, or costs. The CRT in these trials varied (means of 494-513μm, 462-457μm, 458-470μm, 466-451μm, 433-458μm) and the SML was applied after randomisation (i.e. not when CRT had gone below 400μm following anti-VEGFs).

4.4. Rationale for Comparator

The comparator in DAME will be the current standard of care for these patients: continuing with anti-VEGF monotherapy until DMO fully clears or if it recurs after having previously dried, based on OCT scans. Participating sites will use the type of anti-VEGF they routinely use in their standard clinical practice to treat the participants.

5. STUDY AIM AND OBJECTIVES

5.1. Research Hypothesis

DAME will test whether, in people presenting with severe DMO (CRT ≥400μm) who are initially treated with anti-VEGFs, treatment with SML (intervention) after their CRT has decreased to <400μm is equivalent (equivalence margin +/- 5 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) to continuing anti-VEGF monotherapy (control, comparator = standard of care) for preserving/improving BCVA in the study eye at 104 weeks (primary outcome).

5.2. Study Aim

To conduct a pragmatic randomised equivalence trial to assess clinical- and cost-effectiveness, safety, participant experience and acceptability of SML applied after CRT is <400μm following initial anti-VEGF injections, compared to continued anti-VEGF monotherapy, in people who originally presented with severe DMO (CRT ≥400μm). DAME includes an assessment of service providers and planners of factors that enable sustainable delivery of the service to participants, assuming a positive trial result, after the study.

5.3. Study Objectives

In people initially presenting with severe DMO (CRT ≥400μm) who receive treatment with anti-VEGFs and once their macular CRT, as determined on OCT scans, has decreased to <400μm;

1. To determine if the clinical effectiveness of anti-VEGFs and SML is equivalent to anti-VEGF monotherapy.
2. To determine the cost-effectiveness of anti-VEGFs and SML compared to anti-VEGF monotherapy via an economic evaluation.
3. To evaluate the participant experience and acceptability of anti-VEGFs and SML compared to anti-VEGF monotherapy via a mixed methods evaluation.
4. To evaluate the post-trial implementation and scalability of anti-VEGFs and SML via a process evaluation.

6. STUDY DESIGN

6.1. Study Design

Pragmatic, allocation-concealed, single-masked (outcome assessors), multicentre, randomised (1:1), equivalence trial with an internal pilot to assess feasibility of recruitment.

6.2. Internal Pilot

An internal pilot will be conducted over the first six months of recruitment, with the aims of assessing feasibility of recruitment and determining if the study should continue to a full trial. The go/amend/stop criteria will be assessed six months after the first participant is randomised. The target recruitment will be an average of one participant per month/per open site. With staggered opening of sites, it is anticipated

that by six months from the time the first participant is randomised, 16% of the required sample size would be met. Therefore, the internal pilot recruitment target is 42.

We will apply a traffic light system (Table 1) to specify criteria for progression to the full trial as follows: GREEN: Progress to full trial. AMBER: Discuss feasibility with the TSC and NIHR, develop a recovery plan to reach the recruitment target and evaluate options to improve recruitment, including number of eligible participants identified, percentage of participants randomised and reasons for non-randomisation, review of site recruitment performance, and a review of recruitment procedures. RED: Discuss cessation of the trial with the TSC and NIHR.

Table 1. Traffic light system for progression criteria from the internal pilot study

	Red	Amber	Green
% Threshold	<50%	50-99%	100%
Average recruitment rate/site/month	<0.5	0.5-0.99	1
Number of sites opened	<6	6-11	12
Total number of participants recruited	<21	21-41	42

6.3. Study Schematic Diagram

The flow diagram depicting an overview of the trial is presented in Figure 1.

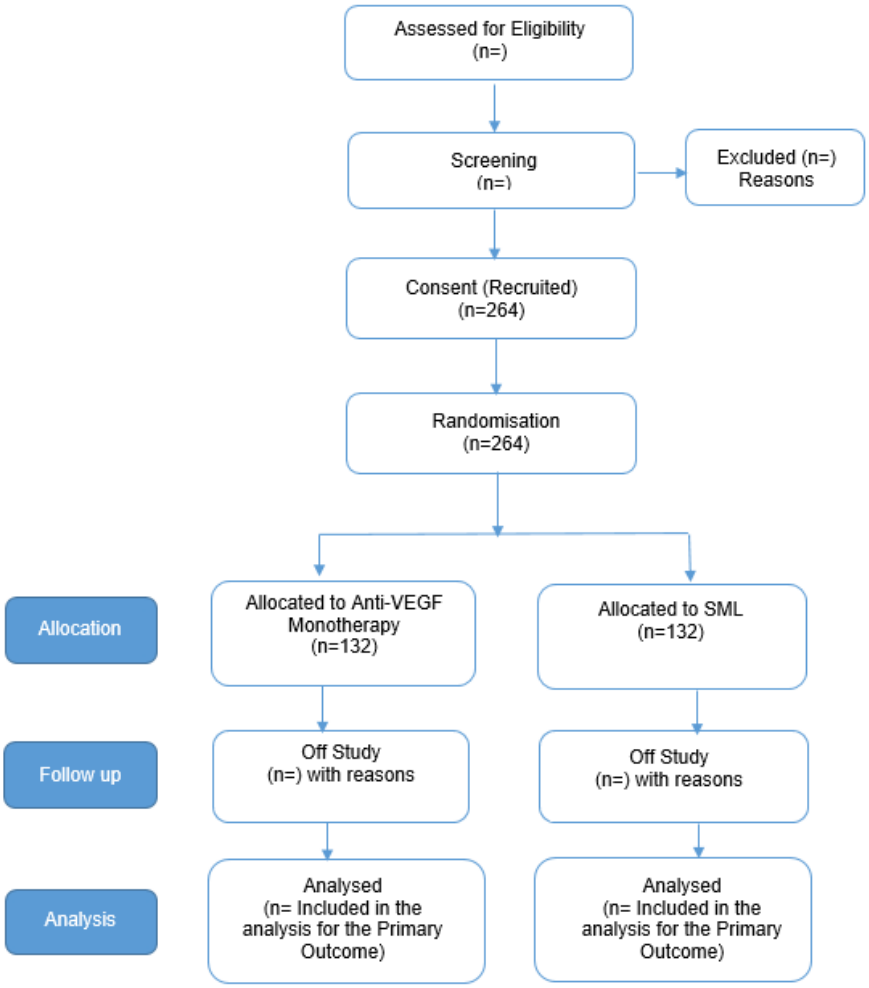

Figure 1. Flow Diagram for DAME

6.4. End of Study

For the purposes of submitting the end of trial notification to the Sponsor and the Research Ethics Committee (REC), the end of trial will be considered to be when database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by the REC
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Mandated by the Sponsor (e.g. following recommendations from the DMEC and TSC
- Funding for the trial ceases

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the clinical trial authorisation will be notified in writing when the trial has been concluded or if it is terminated early.

7. TRIAL SETTING AND PARTICIPANT ELIGIBILITY CRITERIA

7.1. Study Setting

Recruitment for DAME will take place in at least 20 HES across the four UK nations, with catchment areas that cover diverse populations. A list of study sites will be maintained in the TMF.

7.2. Eligibility Criteria

Eligibility to participate in the trial will be confirmed by an ophthalmologist delegated to undertake this task on the delegation log. Patients will be eligible to participate in the study if they fulfil the following criteria:

7.2.1. Inclusion Criteria

Adults (≥18 years) with diabetes type 1 or type 2 who presented with severe CI-DMO (CRT ≥400µm) and are within the first year of initiating anti-VEGF therapy but who still have DMO and their CRT is below 400µm (and it remains, at the time of randomisation) following anti-VEGF therapy in either one eye or both eyes.

7.2.2. Exclusion Criteria

1. Causes of macular oedema other than DMO.
2. DMO with CRT ≥400µm.
3. Receipt of anti-VEGFs before their presentation with severe DMO (previous macular laser treatment for DMO is allowed).
4. Use of unlicensed anti-VEGFs (e.g. bevacizumab)
5. Inability, for any reason, to attend study visits.
6. Active proliferative diabetic retinopathy (PDR) (treated and inactive PDR is allowed).
7. Use of pioglitazone which cannot be stopped for the duration of the trial.
8. Cataract surgery or laser panretinal photocoagulation (PRP) within the previous 6 weeks.
9. Currently enrolled in a CTIMP (Clinical Trial of an Investigational Medical Product).
10. Declined consent for participation.

7.3. Co-enrolment Guidelines

Participants enrolled in investigational drug studies are not candidates for this study. Participants enrolled in other observational studies can take part in DAME provided that their participation in the study will not jeopardise their participation in DAME. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

8. Trial Treatment

8.1. Trial Intervention and Comparator

Patients who originally presented with severe DMO (CRT ≥400µm) and then received anti-VEGF treatment will be eligible for DAME once their CRT has been reduced to <400µm. Patients who consent will be randomised to the intervention or comparator group.

8.1.1. Comparator Arm: Anti-VEGF Monotherapy (standard care)

In this arm of DAME, anti-VEGFs including ranibizumab and biosimilars, aflibercept, faricimab, and brolucizumab will be used, as per the standard of care at participating sites. The anti-VEGF should be administered in line with the summary of product characteristics (SmPC) and follow the DAME participant pathway, as shown in Figure 2.
As the safety profile and efficacy of anti-VEGFs are well established and as they will be used in accordance with their marketing authorisations, the DAME study has been categorised as a Type A Clinical Trial of an Investigational Medicinal Product (CTIMP) study. As the risks are no higher than standard care, a risk-adapted approach to the management of the anti-VEGFs as investigational medicinal products has been adopted.

Anti -VEGFs will be stored in accordance with manufacturer's recommendations and local practice. Anti-VEGFs will be prescribed and dispensed in accordance with usual local site prescription practice. There will be no additional labelling outside the usual practice at local sites. There will be no additional records of accountability for supply, administration or destruction of study drug outside the standard clinical practice for these products at the local hospital site.

8.1.2. Intervention Arm: Subthreshold Micropulse Laser (SML)

In this arm of DAME, SML will be applied in line with the DAME Guideline and follow the DAME participant pathway, as shown in Figure 2. The same guideline was also used in the DIAMONDS trial [14-16].

8.2. Rescue Treatment

Rescue treatment will be allowed for each arm as outlined below.

8.2.1. Rescue Treatment Comparator Arm: Anti-VEGF Monotherapy (standard care)

Switching to a different anti-VEGF will be allowed if, despite timely and appropriate treatment with one type of anti-VEGF:

- DMO increases (rather than progressively declines while treatment is being given)

AND/OR

- BCVA falls ≥10 ETDRS letters from the previous visit or from baseline (first visit in the trial)

OR

- There is a loss of >5 ETDRS letters [but <10 ETDRS letters] and clear justification from the investigator (this should be appropriately recorded in the Case Report Form [CRF])

8.2.2. Rescue Treatment Intervention Arm: Subthreshold Micropulse Laser (SML)

Rescue therapy with anti-VEGFs will be allowed if:

- CRT increases to ≥400µm

AND/OR

- If BCVA falls ≥10 ETDRS letters from the previous visit or from baseline (first visit in the trial)

OR

- If there is a loss of >5 ETDRS letters [but <10 ETDRS letters] and clear justification from the investigator (this should be appropriately recorded in the Case Report Form [CRF]).

IMPORTANT: If a rescue injection(s) restores vision and reduces the DMO again to a CRT of <400 µm, SML should then be continued.

8.2.3. Rescue Treatment Comparator and Intervention Arms

In either arm, **rescue treatment with intravitreal steroids** is allowed if the above rescue therapies fail to rescue (i.e. CRT continues to increase and/or vision continues to decrease). Intravitreal steroids will be

given as per standard of care. If the investigator feels that steroids should be the first rescue treatment for any specific reason this will be permitted and the reason will need to be specified and recorded in the pertinent CRF.

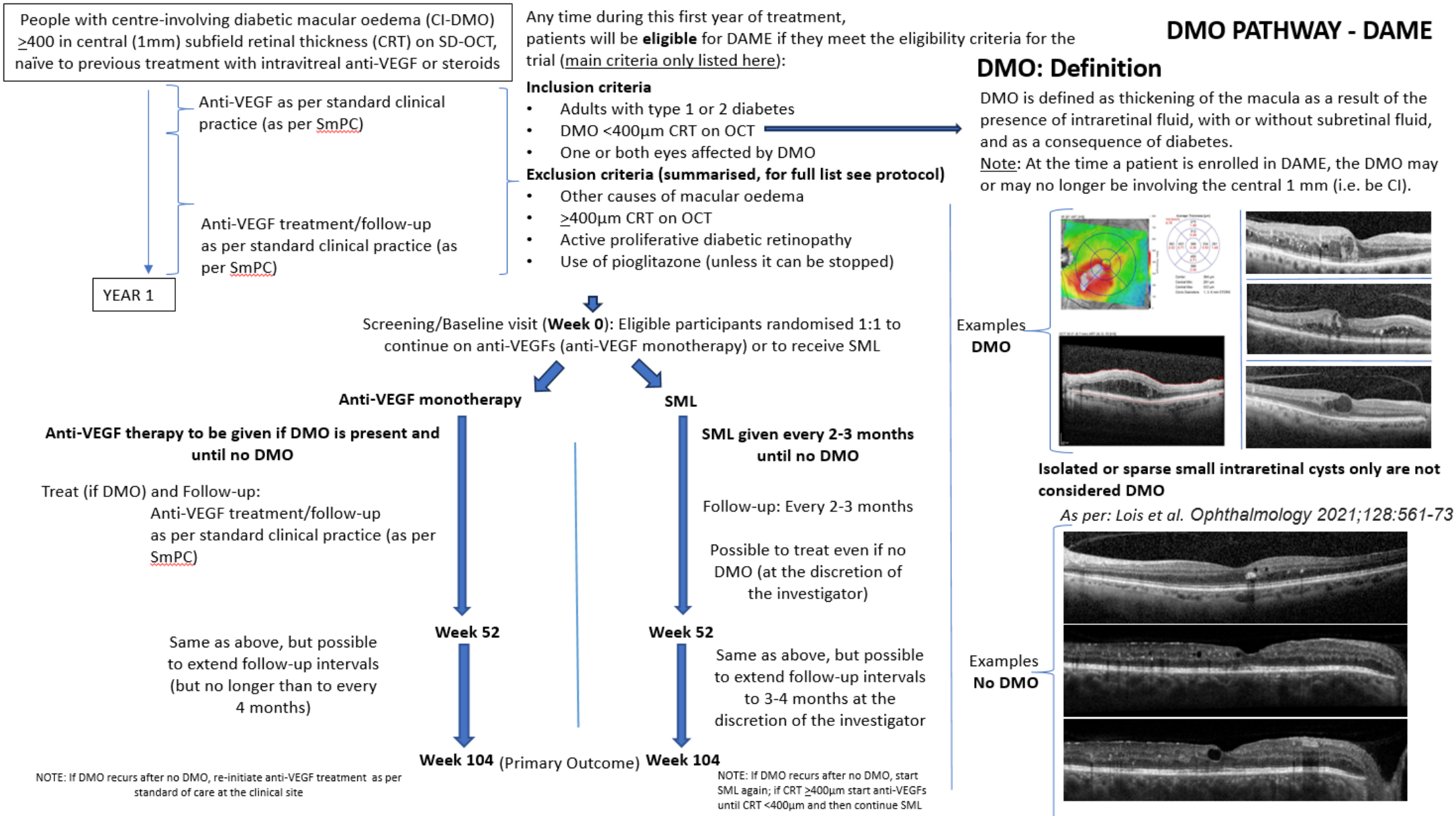

Figure 2 DAME Pathway for anti-VEGF monotherapy and SML arms, including criteria for establishing presence/absence of DMO.

8.3. Treatment Adherence

DAME is a pragmatic trial. As such, treatment would be suggested and applied as per current standard of care (i.e. anti-VEGFs will be given as per standard of care; SML will be applied as per standard of care). In both arms, adherence to the DAME care pathway will be determined by the collection of pertinent data in the CRF (e.g. when was the visit scheduled and whether it occurred at the time planned; criteria for rescue treatment were met just prior to rescue treatment being given; pertinent treatment was provided when DMO was present). At all participating sites, investigators should ensure timely follow-up and treatment, when required, for all trial participants.

8.4. Treatment Discontinuation

Treatment should continue throughout the duration of the trial unless clear harm has occurred, or the treating ophthalmologist feels further treatment should not be performed (e.g. endophthalmitis has occurred after an intravitreal injection). If a participant discontinues treatment, they will continue to be followed to 104 weeks, unless they withdraw their consent for their ongoing participation in the DAME trial. The reason for discontinuation of treatment will be recorded in the CRF.

8.5. Post-Trial Care

After participants have completed the trial, arrangements for their future continued care will be as per standard practice within the NHS.

9. Assignment of Treatment

9.1. Sequence Generation

Eligible participants who provide consent will be randomised 1:1 to receive SML or to continue with anti-VEGF monotherapy. A minimisation algorithm will be used to ensure balanced allocation of participants across trial arms for potentially important factors including centre, duration of DMO (≤1year, >1year), number of doses of anti-VEGFs received up to the time of randomisation (1-6; 7-12), type of anti-VEGF used (ranibizumab, ranibizumab-biosimilar, Brolucizumab, aflibercept, or faricimab) up to the time of randomisation, which will be continued throughout the trial unless lack of efficacy is observed and rescue treatment is needed, presenting BCVA [BCVA ≥ 69 ETDRS letters (Snellen equivalent ≥ 20/40; logMAR ≥ 0.3), 24–68 ETDRS letters (Snellen equivalent ≤20/50-20/320; logMAR 0.4–1.2) and CI-DMO (Yes, No). Minimising randomisation by these variables will ensure both trial arms will be balanced with regard to these potentially important baseline characteristics.

9.2. Allocation Concealment Mechanism

An automated system with the allocation concealed to the ophthalmologist or designee randomising the participant will be used to generate the random allocation sequence.

9.3. Allocation Implementation

After informed consent, participants will be randomised via an automated web-based system. Sites will be provided with trial specific randomisation guidelines. Randomisation will be completed by an appropriately trained and delegated member of the research team. Each participant will be allocated their own unique trial identifier during the randomisation process, which will be used throughout the study for participant identification on all data collection forms and questionnaires.

9.4. Masking

Optometrists obtaining the primary outcome measure will be masked to treatment allocation. Photographers/Imaging technicians obtaining the measures of CRT will be masked to treatment allocation. Masked assessors will not have access to clinical information about the participant and only to blank worksheets, which they will be given to record pertinent data. The trial statistician, who has no role in decision-making with regard to the conduct of the trial, will be unmasked. This will also facilitate linkage with the DMEC. The remainder of the trial team at the NICTU will also be unmasked for the purposes of managing data collection, reviewing cases to assess protocol deviations, and safety reporting. Staff delivering treatments and participants receiving the treatments will not be masked to treatment allocation.

10. Outcome Measures

10.1. Primary Outcome Measure

Change in BCVA in the study eye from randomisation (baseline) to 104 weeks (24 months) (equivalence margin +/- 5 ETDRS letters).

10.2. Secondary Outcome Measures

All at 104 weeks (24 months) from randomisation:

1. CRT in the study eye.
2. Health related and vision related quality of life.
3. Safety
4. Number of treatments used (anti-VEGF injections, SML sessions) in the study eye.
5. Number/proportion of people receiving "rescue" treatment in the study eye.
6. Number of rescue treatments received in the study eye.
7. Number/proportion of people discontinuing treatment (with reasons).
8. Number/proportion of people losing (with reasons) ≥5, ≥10 and ≥15 ETDRS letters (from baseline to week 104) in the study eye.
9. Number/proportion of people gaining ≥5, ≥10 and ≥15 ETDRS letters (from baseline to week 104) in the study eye.
10. Number/proportion of people with CRT ≤300µm in the study eye.
11. Number/proportion of people with no DMO*
12. Health and social care service use and non-health care costs.
13. Participant experience and acceptability.

*DMO is defined as thickening of the macula as a result of the presence of intraretinal fluid, with or without subretinal fluid, and as a consequence of diabetes. Isolated or sparse small intraretinal cysts only are not considered DMO (see Figure 2)

10.3. Safety Outcomes

Participants will be assessed/asked at each visit, specifically about each of the following safety outcomes. These events may be associated with the administration of anti-VEGF, SML and intravitreal steroids and are most relevant to DAME, as such these will be reported as safety outcomes. A "new" occurrence of any of the following safety outcomes during the trial should be recorded on the Safety Outcome eCRF. These events will not be reported separately as adverse events (AE)/serious adverse events (SAE). See section 15 for AE and SAE reporting requirements.

- Self-reported central/paracentral scotomas
- Self-reported reduced colour vision
- Self-reported metamorphopsia
- Corneal epithelial erosion
- Corneal ulcer
- Endophthalmitis
- Intraocular inflammation (anterior, posterior or panuveitis)
- Intraocular pressure elevation (over 21mmHg)
- Intraocular haemorrhage (suprachoroidal/vitreous/pre-retinal haemorrhage)
- Retinal tear
- Retinal detachment
- Retinal vasculitis
- Retinal vascular occlusion (retinal vein or retinal artery occlusion)
- Lens touch (which may occur at the time of an intravitreal injection and may be seen only post-administration in the form of a focal cataract)
- Allergic reaction to any treatments given, including eye drops

- Angina
- Myocardial infarction
- Stroke
- Transient ischaemic attack (TIA)
- Kidney disease

10.4. Definition of Study Eye

The unit of randomisation will be the participant, not the eye. In participants with DMO in both eyes, if both eyes become eligible at the same time, the eye with better BCVA will be the "study eye" (as it is known that the better seeing eye more strongly determines quality of life than the worse seeing eye). If both eyes have the same BCVA, the study eye will be that with lower CRT. If one eye becomes eligible for the trial before the other eye, the participant would be randomised for treatment on that eye. Future treatment of their fellow eye (if it also becomes eligible at a later time) would be the same as that for the study eye (e.g. if the participant is randomised to SML in the study eye, their fellow eye would receive SML also, provided DMO develops and CRT is ≥400µm and only after the CRT goes below 400µm following initial anti-VEGF therapy, just as in the study eye).

11. SCREENING, CONSENT and RECRUITMENT

11.1. Recruitment Strategy

People that may become a potential participant in this trial (i.e. people with DMO ≥400µm eligible for anti-VEGFs and being started on this treatment) will be identified by a member of the clinical assessment team through referrals to HES, through electronic databases or logbooks, or whilst in clinic. A member of the care team will introduce the study to the potential participant at any time during their first year of anti-VEGF therapy, which might be before their CRT has gone below 400µm. Participants expressing interest in taking part in the trial will be given further verbal and written details by a member of the research team, including the DAME Participant Information Leaflet (PIL). After anti-VEGF treatment is initiated and when the CRT is below 400µm the participant, if eligible based on the DAME eligibility criteria, could be enrolled and randomised (once consented appropriately). When a participant consents to join DAME, they will be asked if they agree to be approached at a later date to be invited to take part in a focus group discussion, so that they can be approached and consented when these focus groups are organised. Participants will also be asked if following completion of the DAME trial, data collected as part of their standard care, can be reviewed for future follow-up studies. As explained above, participants will be randomised only when their DMO has improved and the CRT is <400µm following treatment with anti-VEGFs. Enrolment can happen at any time after the CRT has gone below 400µm provided that it is still within one year of initiating anti-VEGF therapy (see Figure 2).

11.2. Screening Procedure

Participants attending clinic for a routine appointment will be screened to check for eligibility based on the eligibility criteria as specified in this protocol. All screening data must be recorded via electronic data capture (EDC) which must be completed by the Principal Investigator (PI) or designee to document all participants screened for the study and all participants recruited. Participants screened and not recruited to the study will be documented via EDC, including the reason(s) for not being enrolled. A minimal dataset will be recorded on these patients which will include age, sex at birth, sexual orientation, ethnicity and partial postcode (with the exception of non-recruited patients in Scotland), to determine if there are differences with those willing to participate. The PI or designee will be required to submit screening data to the NICTU at set time points. .

11.3. Informed Consent Procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible participants may only be included in the trial after written informed consent is obtained. Informed consent must be obtained prior to conducting any trial specific procedures

A DAME PIL will be produced by the DAME PPI Group and research team. This will contain brief and clear information, in plain English, about the purpose of DAME and what will happen if they wish to take part in the trial. The NICTU will provide DAME PILs approved by the REC, to all sites. The PI or designee will be responsible for ensuring that all participants are given a copy of the PIL and are allowed adequate time to review it and the opportunity to ask any study related questions. All participants should have the capacity to self-consent. This should be judged by the PI or the designated member of the study team who will have the responsibility for taking consent. PILs in languages other than English will be available so that, even if potential participants do not understand English and come with interpreters to clinic, they will be able to read about DAME and to join the study if they wish. This will be highlighted to all sites to ensure diversity of recruitment.

Informed Consent Forms (ICF) approved by the REC will be provided to all sites by the NICTU. The PI or designee is responsible for ensuring that informed consent for trial participation is given by each participant before any trial procedures are undertaken and before any treatment is administered. This requires that the ICF be signed and personally dated by the participant before any trial procedures/treatments. If consent is not given, a participant cannot be screened or recruited into the trial.

Two copies of the ICF must be signed and personally dated by the participant and the individual taking consent. The signed informed consent will either be uploaded in the electronic case records (if the site works with electronic records) or filed in the patient's medical notes (if the site works with paper medical records). One of the original signed informed consent forms will be retained by the participant and the other will be kept by the site in the Investigator Site File (ISF).

Following the recruitment of a participant onto the study, the PI or designee will issue a letter to the participant's General Practitioner (GP) to inform them that their patient is participating in the DAME trial, if this is approved by the participant.

11.4. Withdrawal of Consent

Participants may withdraw their consent from the trial at any time without prejudice. If consent is withdrawn this will be documented in the participant's medical notes and in the CRF.

In the event of a request to withdraw from the study, anonymised data recorded up to the point of withdrawal will be included in the study analysis unless requested otherwise by the participant.

The participant may request to discontinue treatment at any point. Should the participant request discontinuation of treatment, they will continue to be followed to 104 weeks, unless they withdraw their consent for their ongoing participation in the DAME trial.

12. SCHEDULE OF ASSESSMENTS

12.1. Participant Schedule

The frequency of assessments and follow up specifically for the trial are detailed in the schedule of assessments below (Table 2). The schedule defines the timing of assessments necessary for data collection. Participants will be followed until the final follow up assessment at week 104 (24 months).

Table 2. Schedule of Assessments

	Screening / Baseline	Assessments/ Treatment[@] from baseline to week 52	Week 52	Assessments /Treatment[@] from week 52 to week 104	Week 104
Informed Consent	✓				
Demographics	✓				
Medical / Ophthalmic History	✓				
HbA1c[*]	✓[*]				✓
BCVA in study eye and fellow eye	✓	✓	✓	✓	✓
SD-OCT	✓	✓	✓	✓	✓
Cataract grading[$]	✓[$]				✓[$]
NEI VFQ-25	✓		✓		✓
EQ-5D-5L	✓		✓		✓
Health Service Use Questionnaire[µ]		✓[µ]	✓[µ]	✓[µ]	✓[µ]
Patient Cost Questionnaire	See Footnote[∝]				
Randomisation	✓[#]				
SML[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]
Intravitreal Anti-VEGF[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]
Safety Outcomes	✓	✓	✓	✓	✓
Adverse Events/Serious Adverse Events	✓	✓	✓	✓	✓
Treatment Adherence		✓	✓	✓	✓
Treatment Experience (VAS)[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]
Acceptability Questionnaire (TFA)					✓

* = HbA1c does not need to be obtained if there is a result within the previous 12 wks. If so, this value will be recorded in the corresponding CRF. If no HbA1c has been obtained within the previous 12 weeks, HbA1c should be obtained and the result recorded in the corresponding CRF.

+ = SML and Anti-VEGFs to be given as per Figure 2 throughout the trial.

= Randomisation and treatment should occur within 2 weeks of the baseline visit. The first treatment given can be done at the screening/baseline visit (i.e. a separate visit for this purpose is not required).

µ=Health Service Use Questionnaire will be completed at every visit, regardless of whether the participant received treatment or not.

∝ = Patient Cost Questionnaire to be completed at approximately 26 weeks and 78 weeks.

@ = Assessments/Treatment will be done throughout the trial in both arms (as stated above and as shown in Figure 2). All participants will be followed as per standard care and as per Figure 2. At baseline, week 52 and week 104 evaluations will be performed as indicated in the table above. At all other visits (visits taking place between screening/baseline and week 52, and between week 52 and week 104) participants will be assessed as shown in the above table and, if and when treatment is undertaken (SML or anti-VEGFs), the VAS questionnaires will be filled in (these will not be required if the participant receives no treatment). $= Cataract grading would be done as per the pertinent working guideline.

All participants will be followed as per standard care. Participating sites are advised to ensure that visits take place within the study windows outlined below, that follow-up appointments are scheduled in a timely manner and that treatment, if required, is provided timely to participants.

Participants in the anti-VEGF arm will be seen, depending on the anti-VEGF used, at 4–16-week intervals throughout the trial.

Participants in the SML arm will be followed up at 8–16-week intervals.
When participants are receiving active treatment with anti-VEGFs and if they require injections every 4 weeks, the advised window is + 1 week for visits/treatments to occur. In all other circumstances the advised window is ±2 weeks for appointments to take place (i.e. if the participant was due in 8 weeks, the visit could be scheduled any time between 6 and 10 weeks).

As a minimum, participants should be followed up no longer than every 16 weeks since their last visit (i.e. intervals longer than 16 weeks between follow-up visits are not allowed in either arm at any point throughout the trial). Intervals longer than 16 weeks, will be recorded as protocol deviations in the CRF.

12.2. Demographics

Demographics including date of birth (DOB), sex at birth, sexual orientation, ethnicity, employment status and postcode will be recorded for recruited participants. The proportion of participants in each group will be monitored throughout the study to try to ensure a diverse population is recruited into DAME.

12.3. Previous Medical and Ophthalmic History

Use of insulin in people with type 2 diabetes at baseline (or if started during the trial) will be recorded in the CRF. Similarly, if patients with type 1 or 2 diabetes are using (or are prescribed during the trial) medications that may quickly reduce levels of glycaemia (e.g. Glucagon-like peptide 1 [GLP-1] receptor agonists such as Semaglutide; sodium-glucose co-transporter 2 [SGLT2] inhibitors such as Canagliflozin, Empagliflozin, Dapagliflozin); and/or if they are on (or are put on) an insulin pump; and/or if they are on (or are started on during the trial) continuous glucose monitoring (CGM); or if they receive a pancreatic/islet cell transplant, this should be recorded in the CRF.

Previously diagnosed systemic diseases and medications will be recorded at baseline. Previous diagnosis of PDR, if established, will be recorded at baseline, as well as previous treatment for it with PRP or anti-VEGFs. If a participant develops PDR during the trial, and whether or not they receive treatment for it (and the type of treatment) will be recorded in the CRF and updated throughout the trial. In addition, diagnosis of other ocular diseases affecting vision that develop during the trial will be recorded, as well as any information with regard to undergoing any type of intraocular eye surgery(s).

12.4. HbA1c

HbA1c will be obtained at baseline and at the 104 week visit, unless a measure of HbA1c from the previous 12 weeks is available, in which case this value will be recorded and used for subsequent analysis.

12.5. Clinical Outcomes

12.5.1. Best-Corrected Visual Acuity (BCVA)

The primary outcome will be change in BCVA from randomisation to week 104 in the study eye. There is no consensus on the core outcomes to be measured in trials for DMO but BCVA is routinely measured in the standard care of people with DMO and it is the primary clinical measure, together with the anatomical presence of DMO as evidenced by OCT, on which management decisions including treatment initiation, discontinuation, and re-treatment, are made. BCVA has been used as a primary outcome in previous trials on treatments for DMO and is closely related to participant-reported quality of life. Full-refracted distance BCVA will be measured in both eyes using the Early Treatment Diabetic Retinopathy Study (ETDRS) Visual Acuity charts by masked optometrists using the ETDRS visual acuity charts at four metres at baseline and at 52 weeks and 104 weeks in accordance with the DAME guideline Fully refracted BCVA will be obtained if a 10-ETDRS letter drop (from baseline and/or from visit to visit) is determined in the study eye at any of the other time points, or in both eyes if both eyes are on the study, to confirm the drop in vision (because, if related to DMO, this would indicate that rescue treatment should be considered). Masked optometrists at participating sites will be available, if required, for these additional evaluations. BCVA will be obtained at all other time points using the refraction determined at baseline for the visits taking place in year 1 of the trial, or that determined at week 52, for the visits taking place in the second year of the trial.

If at any point during the trial a ≥10 ETDRS letter loss occurs, the reason for the drop in vision should be specified by the ophthalmologist evaluating the participant and documented in the CRF (e.g. if the

drop in vision is thought to relate to progression of cataract, this should be stated; if the drop in vision is thought to occur as a result of recurrence of DMO, once DMO had cleared, this should be stated and actioned accordingly, etc.), as well as whether or not the ophthalmologists thinks that the loss is likely to be reversible or irreversible (e.g. if related to progression of cataract, it would likely be reversible; if related to recurrence of DMO it would still be reversible; if loss of outer retina is observed on OCT [i.e. foveal atrophy has developed] the loss in BCVA would be likely irreversible, etc.).

12.5.2. Central Retinal Thickness (CRT)

CRT, as determined by using spectral domain OCT (SD-OCT) will be obtained at baseline and at each follow-up visit, as per current standard clinical practice. SD-OCT will be obtained by masked technicians, photographers, or nurses, as per standard practice at each of the participating sites. The measure of CRT obtained in the central 1mm as well as the measure of macular volume will be recorded in the CRF by the masked staff obtaining the OCT and used for the analysis.

In addition, presence/absence of intraretinal and subretinal fluid indicating DMO, as per DAME definition (see Figure 2), will be determined and recorded in the CRF at each of the follow-up visits. CRT and evaluation of the presence/absence of intraretinal and subretinal fluid and presence/absence of DMO (small isolated/sparse cysts will not be considered DMO), as determined by SD-OCT, is routinely done in clinical practice on the evaluation of patients with DMO and used to guide treatment.

Presence/absence of DMO and presence/absence of intraretinal and/or subretinal fluid will be determined by the clinician evaluating/treating the patient (as treatment will be guided by these findings).

12.5.3. Trial Treatment

For the purpose of the trial, all participants will complete visits at screening/baseline, week 52 and week 104. All other visits will take place as per standard of care, and as indicated in Figure 2 and should be recorded in the CRF.

Number of Trial Treatments (Anti-VEGF Injections, SML Sessions) and Rescue Treatment:
The number of anti-VEGF injections given to the participant before they enter the trial (i.e. from initiating anti-VEGF therapy up to the point they are randomised) and the number of months from initiating anti-VEGFs to entering the trial will be recorded in the CRF at the baseline visit. The number of anti-VEGF injections received from baseline to week 52 and to week 104 will also be recorded in the CRF for all participants (those in the anti-VEGF monotherapy arm and those in the SML arm who receive rescue treatment with anti-VEGFs).

The number of laser treatments given throughout the trial period will also be recorded for participants in the SML arm. In addition, the number of intravitreal injections of steroids (if used to rescue) in either arm will be recorded.

12.5.4. Safety Outcomes and Adverse Events

Participants will be checked for the occurrence of any of the safety outcomes, AEs and SAEs at each visit. If a safety outcome or an AE occurs these should be recorded in the relevant eCRF. If a SAE occurs this should be reported on the SAE Report Form. See section 15 for the recording and reporting of AEs and SAEs.

12.6. Study Instruments for Participant Follow Up

12.6.1. EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The EQ-5D-5L [29] is a generic preference-based measure of health, which provides a description of health using five dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) each with five levels of severity. Responses can be converted to an overall utility score and used for the calculation of quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale where 0 represents the worst imaginable health state and 100 the best imaginable health state.

12.6.2. National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

The NEI VFQ-25 [30] is a validated vision-specific questionnaire that is used to evaluate visual outcomes in participants with eye diseases including diabetic retinopathy and DMO. In addition to eliciting information about general health and vision, it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision. A subset of the questions from the NEI VFQ-25 comprise the Visual Function Questionnaire-Utility Index (VFQ-UI) [31] and responses on the VFQ-UI can be used to calculate QALYs.

12.6.3. Health Service Use Questionnaire

A study specific questionnaire will measure a participant's use of healthcare relating to their eyes. To avoid double counting of outpatient visits, participants will not be asked to report these in this questionnaire as all visits for treatment or assessment will be recorded prospectively in the CRF.

12.6.4. Patient Cost Questionnaire

A questionnaire will measure the out-of-pocket costs to the participant when they attend hospital appointments relating to their eyes and the impact on their ability to work/ undertake usual activities.

12.6.5. Participant Treatment Experience Visual Analogue Score (VAS)

All participants (in both arms of the trial) will be asked to rate the following parameters of their experience by completing a Visual Analogue Score (0-10) and brief qualitative comments within 1 hour prior to the procedure (anti-VEGF injection/SML or steroid injection if this were to be done)] (items 1-5), immediately after the procedure (items 6-7), and at 24 hours post-procedure (items 8-12). All VAS (0-10) ratings will be accompanied by brief qualitative comments about each parameter. The items that will be evaluated include:

(1) Anxiety/fear (associated with the procedure) experienced over the past 24 hours prior to the procedure
(2) Disruption to normal activities experienced over the past 24 hours prior to the procedure
(3) Disruption to usual sleep quality over the past 24 hours prior to the procedure
(4) Current anxiety / fear associated with the procedure prior to the procedure
(5) Current anticipated pain / discomfort associated with the procedure prior to the procedure

(6) Pain/discomfort experienced during the procedure
(7) Anxiety /fear experienced during the procedure

(8) Experienced anxiety / fear during the past 24 hours post procedure
(9) Disruption to normal activities over the past 24 hours post procedure
(10) Disruption to usual sleep quality over the past 24 hours post procedure
(11) Pain / discomfort experienced (intensity and duration) over the past 24 hours post procedure
(12) Side effects experienced (description and duration) over the past 24 hours post procedure

The above data collection was designed to address important aspects but minimising the burden to participants, following the input from the DAME PPI Group. These data will be collected at each visit (if treatment is given).

12.6.6. The Theoretical Framework of Acceptability (TFA) Questionnaire

The focus group data will inform the adaptation of the generic Theoretical Framework of Acceptability (TFA) questionnaire [32], to generate a study specific acceptability questionnaire as recommended by the TFA authors. This questionnaire will be administered to all participants at their final clinic visit at 104 weeks and will allow comparison, on the basis of key domains of acceptability and patient-reported experience of treatments for all participants.

12.6.7. Participant Focus Groups

Focus groups will be completed to explore participant experiences of, and acceptability of treatment. Ten focus groups are planned to be conducted with participants from both arms of the trial and different locations in England, Northern Ireland, Wales and Scotland. Participants will be purposefully selected for recruitment to the focus groups on the basis of key demographic variables (including age, sex at birth, sexual orientation, ethnicity, socioeconomic background and employment status) to ensure a diverse voice with regard to patient experience and preference of those affected by DMO is obtained. Consistent with the characteristics of mixed methods approaches [33], the focus group schedule will be informed by preliminary analysis of the existing quantitative data, as obtained in the trial.

12.6.8. Participant Follow Up and Retention

Participants will be followed as per the DAME participant pathway as summarised in Figure 2. In order to ensure timely follow-up and treatment of participants, site staff may contact trial participants to remind them of scheduled visits.

The protocol of DAME was developed with the help of the DAME PPI group; study procedures and study visits have been simplified as much as possible to ensure that participation in this pragmatic trial will not represent a burden to participants or sites, increasing the chance that participants will attend all follow-up visits and that as high a number as possible of participants will be retained during the104 week period of the trial.

13. DATA COLLECTION and MANAGEMENT

13.1. Data Collection

Data collection forms (“trial worksheets”), will be provided to sites by the NICTU to collect all data required for the trial. These trial worksheets will be considered the data source for the trial. Trial worksheets can be uploaded (if the site works with electronic records) or filed (if the site works with paper medical records) in the participant medical record. All data will be transferred to the NICTU via a bespoke web based electronic case report form (eCRF).

Participant identification on the eCRF will be through their unique participant study number, allocated at the time of randomisation. Questionnaires will be given to participants by site research staff at visits for self-completion and returned to the NICTU for entry into the eCRF.

Ophthalmic images will be anonymised and uploaded electronically by each local PI or designee to the Central Administrative Research Facility (CARF), Queen’s University Belfast. CARF is only accessible by a username/password combination unique to the site. Once uploaded, the images will be downloaded by CARF personnel and stored on secure servers housed by Queen’s University Belfast. This resource of stored images may be used in future research studies (for further analysis of DAME data or for other studies). All necessary ethical approval will be secured and in place where applicable for any future studies.

13.2. Data Quality

To ensure accurate, complete, and reliable data are collected, the NICTU and CI will provide training to site staff. Source data verification (SDV) will be completed by the NICTU and will check the accuracy of entries on the electronic CRF against the source documents (i.e. worksheets) and adherence to the protocol. The extent of SDV to be completed is detailed in the Monitoring Plan.

Quality control is implemented by the NICTU in the form of Standard Operating Procedures (SOPs), which are defined to encompass aspects of the clinical data management process and to ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements [34]. Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

A DMEC will be convened for the study to carry out reviews of the study data at staged intervals during the study.

13.3. Data Management

Trial data will be entered onto the eCRF by site staff, except for questionnaire data which will be entered by NICTU staff. All data will be processed electronically as per NICTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries within an agreed time period. All queries will be responded to/ resolved within the study database. Any amended information will then be entered in the study database.

14. STATISTICAL CONSIDERATIONS

14.1. Sample Size

DAME is powered to demonstrate equivalence of treatment strategies for the primary outcome, which will be assessed 104 weeks after randomisation. Based on two one-sided t-tests at the 2.5% significance level, a 10 ETDRS letter standard deviation (SD)[2, 3, 16, 18] and an equivalence margin of +/- 5 ETDRS letters, with a significance level of 2.5% and power of 90%, a total of 210 participants would be required. Allowing for 20% dropout [15, 35] we will require 264 participants. The proposed sample size of 132 per group will also be sufficient to detect a mean difference between groups of 39.5µm in CRT (based on a SD of 86.8 [2, 3]) and 6.85 in NEI-VFQ-25 (based on a SD of 15.1[2, 3]) at 104 weeks, which are important secondary outcomes on this study. These differences in CRT and NEI-VFQ scores are both clinically relevant differences [2, 3]. An equivalence margin of +/- 5 ETDRS letters was chosen because a difference of this size or less would not be considered clinically relevant or meaningful to participants and it could represent test/re-test variability [9, 10, 11, 36, 37].

14.2. Data Analysis

14.2.1. Statistical Methods

As this is an equivalence trial, the primary statistical analysis will be per protocol, although an intention-to treat (ITT) analysis will also be undertaken [38]. The difference between treatment arms for change in BCVA (using 95% confidence interval [CI]) from randomisation [baseline] to week 104) will be compared to the permitted maximum difference of $\pm$5 ETDRS letters using an analysis of covariance model adjusting for baseline BCVA and minimisation factors. If the 95% CI of the treatment difference lies wholly within both upper and lower margins of the permitted maximum difference, the SML arm could be deemed equivalent to the anti-VEGF monotherapy arm.

A secondary analysis for change in BCVA from baseline to week 104 will use two one sided 2-sample t-tests with $p<0.025$ as the criterion for statistical significance.. The primary analysis will be based on data from the study eye only. When performing a secondary analysis on the subset of participants with both eyes treated (“study eye” and “fellow eye in the study”), study eye will be included as a random effect within the mixed model. Statistical significance for the secondary outcomes will be based on two-sided tests with $p<0.05$ as the criterion for statistical significance. The principal analysis will be based on available data. Sensitivity analyses will assess the impact of missing data by imputing extreme values (lowest and highest). We will also conduct sensitivity analyses to assess the impact of development of cataract or having cataract surgery during the trial and also to assess the impact of using treatments for diabetes that may produce rapid changes in glycaemic levels (as per section 12.3 above) . Additionally, the primary outcome will be analysed according to pre-specified subgroups (e.g. based on HbA1c, duration of DMO, type of anti-VEGF used, number of anti-VEGF injections given prior to randomisation, time from initiation of anti-VEGF treatment to randomisation, baseline vision, CI-DMO (Yes/No), loading dose completed (Y/N)) including the corresponding interaction term in the regression model using 99% CI.

Analyses of categorical secondary outcomes will use general linear models (GLM) with adjustment for minimisation covariates. Relative risk, risk difference and odds ratio will be reported where possible. Analyses of continuous secondary outcomes will use ANCOVA adjusting for corresponding baseline and minimisation factors, as appropriate. Subgroup analyses will be performed for important secondary outcomes based on ethnicity and socioeconomic status. Baseline characteristics, follow-up measurements and safety data will be described graphically and in tables using appropriate descriptive summary measures depending on scale of measurement and distribution.

14.2.2. Missing Data

Every effort will be made to minimise missing baseline and outcome data and data queries will be generated for site staff as required to request missing information.

Standard approaches will be used to detect patterns in missing data. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. We plan for the principal analysis to be based upon available case data with no imputation of missing values. Sensitivity analyses will also be undertaken to assess the impact of missing data by imputing extreme values (lowest and highest), as stated above.

A detailed Statistical Analysis Plan (SAP) will be prepared and made publicly available before undertaking final analysis.

14.2.3. Analysis of Quality of Life Data

We will take the opportunity to explore the relationships between the QoL data (obtained using the NEI-VFQ-25[30] and EQ-5D-5L [29] questionnaires) and BCVA data collected in the trial, to help develop a better understanding of how changes in QoL are related to changes in BCVA. We will firstly examine the correlation between QoL and BCVA scores at each point in time using Pearson's correlation coefficient and scatterplots. We will repeat these analyses to examine the relationship between change scores (between 2 time points) in QoL and BCVA. We will then regress each QoL subscale at the 104 week follow-up on BCVA score, to allow calculation of a minimal important difference in QoL by multiplying regression slope estimates by the prespecified clinically relevant difference for BCVA, assuming at least a moderate relationship between BCVA and QoL. We will repeat these analyses for the change scores. Other analyses may be undertaken, if considered appropriate.

14.2.4. Health Economics Evaluation

A within-trial cost-utility analysis will estimate the short-term (104 weeks) cost-effectiveness of SML compared to anti-VEGF monotherapy. Current guidelines for conducting [39-40] and reporting [42] economic evaluations will be followed. NHS and Personal Social Services (PSS) perspective will be adopted for the base-case analysis; a secondary analysis will be undertaken from a societal perspective to include non-healthcare costs (e.g. productivity losses, out of pocket costs). QALYs will be calculated using health utilities derived from the generic EQ-5D-5L [29] (primary measure) and the VFQ-UI [31] (secondary measure); Health and social service resource use and non-healthcare costs will be measured from randomisation until 104 weeks using both the CRF and a brief questionnaire and will include e.g. intervention resource (anti-VEGF injections / laser sessions), rescue treatments, ophthalmology visits, optometrist visits, other outpatient attendances, GP consultations, nurse consultations. Unit costs from publicly available sources will be used (e.g. NHS Reference Costs, Unit costs of health and social care). An annual 3.5% discount rate will be applied for future costs and QALYs. Missing data will be summarised, and patterns analysed. Sensitivity analysis will be performed to explore impact on cost-effectiveness of variations in key parameters. Probabilistic sensitivity analysis will assess uncertainty around the incremental cost-effectiveness ratio (cost per QALY) and facilitate the presentation of cost-effectiveness acceptability curves. A Markov decision model will be used to estimate long-term cost-effectiveness by extrapolating outcomes beyond the trial period. We will use existing models where appropriate and populate the model with data from the trial supplemented with data from the literature and expert opinion. Since this is an equivalence trial, there may be similar health benefits between arms, but costs may differ, and a long-term cost-comparison may be the most appropriate analysis. Participants will be consented for data from their medical records to be collected for the evaluation of longer-term outcomes after the trial has been completed. If available, these data will be incorporated into an updated economic model.

A detailed health economic analyses plan (HEAP) will be prepared and made publicly available before undertaking final analysis.

14.2.5. Participant Experience and Acceptability

The following will be undertaken to assess participant experience and acceptability in DAME.

For the VAS data, median and inter-quartile range scores will be charted on a series of line graphs to display the trajectory of any change across time for both groups and to highlight any points of divergence between the groups on all parameters of participant experience (e.g. pain/discomfort, sleep disruption etc.). Mann-Whitney U tests will be used to examine differences between groups statistically at the following key points - baseline, 12, 24, 52 and 104 weeks post-randomisation. Qualitative comments collected alongside the visual analogue scores will be subject to content analysis and will be used to provide a preliminary explanation of patterns in the quantitative scores. These data will also be used to inform the conduct of the focus groups including the purposeful selection of participants.
Qualitative data from focus groups will be transcribed verbatim, and thematic analysis carried out as specified by Braun and Clarke [43] to identify, analyse and report patterns/themes within data. These qualitative data will also be used to provide study-specific items relevant to the seven components of acceptability defined by the TFA questionnaire. Scores on this questionnaire will be calculated and compared between trial arms. Subsequently, we will use 'Pillar Integration Process' (PIP) [44] to integrate the findings from the qualitative and quantitative data sets. PIP is a systematic, analytical method created to integrate quantitative and qualitative data in a transparent manner that have undergone an initial separate analysis. PIP will help to describe and account for patterns in the quantitative assessments of participant experience, identify nuances and sub-group differences, and enhance our understanding of important contextual mechanisms at work.

14.2.6. Nested Process Evaluation to Assess Implementation and Scalability Aspects Post-Trial

The process evaluation in DAME will collect qualitative data from service providers and managers across intervention sites using:

(i) *Focus groups or individual interviews* with clinical, nursing and service management leads (or their representatives) across participating sites. Focus groups (analogous to those described above) or 1:1 interviews will be offered to participants, and applied depending on feasibility, preference and timeliness. They will be carried out when sites/participants have had experience with the new proposed intervention. We will aim to recruit a minimum of two participants per site for these focus groups/interviews, purposefully selected to have an overview of how the novel service was introduced and implemented within their hospital and wider knowledge of service setup and funding considerations for eye care.

(ii) *Implementation strategy analysis* will be conducted following the focus groups/interviews above. This will be driven by the ERIC framework (Expert Recommendations for Implementing Change) [45]. We will do this in order to produce a DAME implementation toolkit as one of the trial deliverables, assuming a positive result (i.e. new tested SML pathway is shown to be beneficial).

Data from the nested process evaluation will be analysed as follows. Participants' data from focus groups and/or interviews will be subjected to a framework analysis, guided by the Consolidated Framework for Implementation Research (CFIR) [46]. CFIR allows formal categorisation of emerging barriers or drivers into specific categories – broadly including external and internal context of the service, people involved and the process of implementation and also the actual clinical intervention itself [47]. To ensure representativeness and local relevance, the analysis will create and include new codes for data that do not fit into existing CFIR categories. For the implementation strategy analysis, we will deductively match the CFIR (and any further) categories of barriers to implementation that participants report to, firstly, the reported strategies they used to implement the new intervention and also further potential strategies as per the ERIC framework [48]. These, combined, will formulate the DAME implementation toolkit, which will articulate explicitly barriers to be expected in setting up and delivering the service and what activities and initiatives could be undertaken to mitigate them and sustain DAME delivery in a NHS setting. The toolkit will also include a section on how to select what strategies might be relevant for each NHS adopting site (i.e. how to appraise local barriers and match those to implementation strategies as revealed by the trial's process evaluation).

14.2.7. Study Within A Trial (SWAT)

We will prepare a variety of summaries of the results of DAME and assess the understanding and potential impact of these with a variety of stakeholders. The findings will inform our dissemination plans for the results of DAME and provide evidence for dissemination plans in other trials. The format of these summaries will be determined when the results of DAME and their potential implications are known. However, they may include a plain language summary, scientific summary, short abstract, infographic, podcast, and its associated script. We will use methods adapted from a Study Within A Review (SWAR) to test different summaries for a systematic review [49, 50].

We will test the summaries with a variety of stakeholders. These will include participants in DAME who will be asked about their willingness to participate in the SWAT at their final (2-year) follow-up visit, when their consent will be sought to be contacted about the SWAT in the future. Others who we intend to include in the SWAT are members of the public, ophthalmologists, policy makers (e.g. those engaged in guideline production) and medical students. These participants will be drawn from within the wider DAME team and from the networks of the DAME co-applicants. They will be sought using, for example, word of mouth and social media and will be required to give consent before taking part in the SWAT.

15. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

15.1. Definitions of Adverse Events

An **adverse event (AE)** is defined as any untoward medical occurrence in a participant to whom the interventions or research procedures have been administered, including occurrences which are not necessarily caused by or related to that product.
An **adverse reaction (AR)** is defined as an AE that is deemed to be possibly, probably or definitely related (see table 3, section 15.3, below) to the study procedures (e.g. obtaining BCVA, performing OCT scans, result of the administration of an intravitreal injection, result of the action of the anti-VEGF injected, result of the SML). If serious, as per the definition below, it would be considered a **serious adverse reaction** (SAR).

A **serious** adverse event (or reaction) (SAE/SAR) is defined as an untoward medical occurrence that:
- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity; or
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator

Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, however, do not constitute a SAE.

15.2. Adverse Event Recording and Reporting

The AE reporting period for the trial begins upon consent and ends at week 104 (the last follow up visit).

The PI or designee should record all directly observed AEs/ARs and those spontaneously reported by the participant in the data collection worksheets (which constitute the data source for the trial) which will then be filed/uploaded in the medical records of the participant, in accordance with GCP.

It is expected that many of the participants will experience events that are in keeping with pre-existing medical conditions rather than being related to the trial. Events associated with any pre-existing medical condition that the participant has (including those related to diabetes), **do not** need to be reported.
The exception to this will be Death. Death, even if occurring as a result of the participants pre-existing condition, **should be** reported as a SAE.

Minor events (e.g. subconjunctival haemorrhage, temporary visual disturbances, temporary blurred vision, small floaters) which are known to be very common but innocuous occurrences in people undergoing intravitreal injections / or laser **do not** need to be reported.

Events that are collected as safety outcomes for the DAME study (as per section 10.3) **do not** need to be reported as an adverse event. These should be recorded on the Safety Outcome Form within the eCRF.

Events that are collected as outcomes for the DAME study or reported by participants on the study questionnaires **do not** need to be reported as an adverse event (decreased vision, pain/discomfort, stress/anxiety, disturbances in sleep,).

Occurrence of cataract **does not** need to be reported either as an adverse event (as grading of the cataract will be obtained already at baseline and at week 104). However, if it is a traumatic cataract (i.e. lens touch and clearly related to the injection procedure itself), this **should be** reported on the Safety Outcome Form as per section 10.3.

All other events should be assessed for causality (as per section 15.3), severity (as per section 15.4), seriousness (as per section 15.5) and expectedness (as per section 15.6). Events which are deemed to be related (AR) or related and serious (SAR) should be reported as outlined below.

ARs are to be reported on the Adverse Event Form within the eCRF; the corresponding Adverse Event worksheet should be filled also and filed/uploaded in the participant's medical records. SAEs/SARs are to be reported on the Serious Adverse Event Form. SAEs/SARs should be reported to the NICTU within 24 hours of the investigator becoming aware of the event, by email to clinicaltrials@nictu.hscni.net . The site should not wait until all information about the event is available before notifying the NICTU of the SAE. The NICTU will acknowledge receipt of the SAE Form by email. Information not available at the time of the initial report must be sought and submitted to the NICTU as it becomes available. The NICTU will notify the CI of all SAEs reported.

All reportable events as outlined above (AR/SAEs/SARs) should be followed until they are resolved. Once a participant has completed their 104 week visit if the event has not been resolved this will be recorded as ongoing.

15.3. Assessment of Causality

The PI or designee should make an assessment of causality i.e. the extent to which it is believed that the event may be related to any of the research procedures (Table 3).

Table 3. Categories of Causality for Adverse Events

Category	Definition
Definitely*	There is clear evidence to suggest a causal relationship with administration of the interventions or research procedures, and other possible contributing factors can be ruled out.
Probably*	There is evidence to suggest a causal relationship with administration of the interventions or research procedures, and the influence of other factors is unlikely.
Possibly*	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the interventions or research procedures). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the interventions or research procedures). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not Related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

15.4. Assessment of Severity

The PI or designee should make an assessment of severity according to the following categories (Table 4).

Table 4. Categories of Severity for Adverse Events

Category (Severity)	Definition
Mild (Grade 1)	The adverse event is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
Moderate (Grade 2)	The adverse event is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3)	The adverse event prevents normal everyday activities.
Life Threatening (Grade 4)	The adverse event has life threatening consequences; urgent intervention indicated.
Death (Grade 5)	The adverse event results in death.

15.5. Assessment of Seriousness

The PI or designee should make an assessment of seriousness i.e. does the event fulfil any of the following criteria:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

15.6. Assessment of Expectedness

The PI or designee should make an assessment of expectedness for ARs or SARs. The evaluation should be performed using the associated events listed in section 10.3 of the protocol and/or the reference safety information (RSI). The RSI is the Summary of Product Characteristics (SmPC) for the anti VEGF as approved by the MHRA.

ARs/SARs may be classed as either expected or unexpected as per Table 5.

Table 5. Categories of Expectedness for Adverse Reactions (ARs)/Serious Adverse Reactions (SARs)

Expectedness	Definition
Expected	The AR/SAR is listed in the protocol (section 10.3) or in the SmPC of the anti-VEGF as an expected AR.
Unexpected	The AR/SAR is not listed in the protocol (section 10.3) or not in the SmPC of the anti-VEGF as an AR.

15.7. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be related to the intervention and are unexpected, i.e. their nature or severity is not consistent with the RSI or associated events as listed in section 10.3.

The CTU is responsible for reporting SUSARs to the Sponsor, REC and MHRA within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the CTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported to MHRA and REC within 15 days after the knowledge of such an event.

15.8. Recording and Reporting of Urgent Safety Measures

The Sponsor and investigator may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. The investigator may implement urgent safety measures without prior approval from the REC or MHRA.

When a PI becomes aware of information that necessitates an urgent safety measure, they should phone the MHRA Clinical Trials helpline (020 3080 6456) and discuss the issue with a safety scientist or medical assessor immediately after an urgent safety measure has been implemented. The PI or designee should report the urgent safety measure to the CTU immediately, by email to clinicaltrials@nictu.hscni.net.

The CTU will report the urgent safety measure to the Chief Investigator and to the Sponsor immediately, using the dedicated email address: clinical.trials@belfasttrust.hscni.net. The CI will notify the MHRA and the REC providing full details of the information they have received and the decision-making process leading to the implementation of the urgent safety measure within 3 days.

The PI or designee should respond to queries from the Sponsor or Chief Investigator immediately to ensure the adherence to reporting requirements to REC and MHRA.

16. Data Monitoring

16.1. Data Access

The agreement with each PI will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Each participant's confidentiality will be maintained, and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

16.1. Monitoring Arrangements

The NICTU will be responsible for trial monitoring. The frequency and type of monitoring (on site and/or remote) will be detailed in the monitoring plan and agreed by the Sponsor.

Before the trial starts at a participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of participant recruitment and follow up.

The PI or designee should ensure that the monitor can access all trial related documents (including source documents (i.e. data collection worksheets)) that are required to facilitate the monitoring process. The extent of source data verification (SDV) will be documented in the monitoring plan.

17. REGULATIONS, ETHICS AND GOVERNANCE

17.1. Regulatory and Ethical Approvals

The trial will comply with the principles of GCP and the requirements and standards set out in the UK policy framework for health and social care research and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee (REC) and clinical trial authorisation (CTA) will be obtained from the MHRA under the notification scheme for Type A CTIMPs before the start of the trial. The trial will be registered at https://www.isrctn.com before randomisation of the first participant.

17.2. Protocol Amendments

All protocol amendments will be undertaken in accordance with the regulatory requirements. Substantial changes to the protocol will require REC and MHRA approval prior to implementation, except when modification is needed to eliminate an immediate hazard to participants.

17.3. Good Clinical Practice

The trial will be carried out in accordance with the principles of the ICH-GCP guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

17.4. Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval by the REC and the MHRA. A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants in the trial; or
(b) the scientific value of the trial.

The PI or designee is responsible for ensuring that serious breaches are reported directly to the NICTU using the dedicated email address (clinicaltrials@nictu.hscni.net) within one working day of becoming aware of the breach. The NICTU will notify the Sponsor and CI immediately to ensure adherence to reporting requirements to REC and the MHRA where a serious breach has occurred.

Protocol compliance will be monitored by the NICTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs, participant consent forms) is being completed appropriately.

17.5. Participant Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the participants by their assigned unique trial identifier and initials only. Participant confidentiality will be maintained at every stage and participant details will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.6. Indemnity

The BHSCT will provide indemnity for any negligent harm caused to participants through the Clinical Negligence Fund in Northern Ireland. Queen's University Belfast will provide indemnity for negligent and non-negligent harm caused to participants by the design of the research protocol and conduct of the Focus Groups by staff at Queen's University Belfast.

17.7. Record Retention

The PI will be provided with an ISF by the NICTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for the archiving of essential documents at their sites in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor on request. Following confirmation from the Sponsor, the NICTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the NICTU and Sponsor.

The TMF will be held by the NICTU within the BHSCT and the essential documents that make up the file will be listed in a SOP. On completion of the study, the TMF and study data will be archived by the NICTU according to the applicable regulatory requirements and as required by the BHSCT as Sponsor. Images stored in CARF will be archived at Queen's University, Belfast, as required by the BHSCT as Sponsor. The study data and images may be used in future research studies, and participants will be consented accordingly to allow this. All necessary ethical approval will be secured and in place where applicable for any future research studies.

17.8. Competing Interests

The Chief Investigator of DAME, Prof Noemi Lois, has no conflicts of interest to declare. The members of the TMG have no financial or non-financial competing interests and the members of the DMEC and TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC or TSC member reports a conflict of interest, advice will be sought from the Sponsor. The research costs are funded by the NIHR Health Technology Assessment Programme.

18. DISSEMINATION/PUBLICATIONS

18.1. Publication Policy

The study will be used to inform participants and public, clinicians and policy makers of the best options available to treat people who present with severe DMO. It is anticipated that the study results will be used to refine current guidelines on the management of diabetic retinopathy by providing a more robust evidence base for justifying either monotherapy with anti-VEGF or combined anti-VEGF and SML for people who present with severe DMO.

The results of DAME will be disseminated widely through presentations at national and international ophthalmic/diabetes meetings and at invited speaker's lectures. The results will be presented at participant group meetings. Diabetes UK Northern Ireland has agreed to contribute to the dissemination efforts to ensure the results are available to participants, their families, and the public.

The research team includes lead clinicians and researchers with contacts across the globe. They will use these international contacts to ensure trial results are disseminated widely and incorporated into future guidelines on diabetic retinopathy.

DAME will be reported in accordance with the CONSORT guideline [51]. If necessary, the CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) statement [52] will also be applied in the event that extenuating circumstances require major modifications to the trial during its course. The trial protocol, statistical analysis plan and health economic analysis plan will be made publicly available to ensure transparency in our methodology.

In accordance with the open access policies proposed by the NIHR we plan to publish the clinical findings of the trial as well as a separate paper describing the health economic findings of the trial in high quality, high impact, peer reviewed open access journals. Other manuscripts are planned (e.g. a manuscript presenting data on patient experience and acceptability of the treatments; a manuscript with the results of the SWAT; others).

We will actively promote the findings of the study to journal editors and opinion leaders in ophthalmology and diabetes to ensure findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. The most significant results will be communicated to the wider public through media releases. An ongoing update of the study will also be provided on the NICTU website.

18.2. Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

18.3. Data Sharing Statement

Following publication of the primary and secondary outcomes and once data has been fully exploited by the DAME research team, there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI via the NICTU. If there are requests for data sharing, these will be reviewed on a case by case basis by the CI/NICTU with approval by the Sponsor.

19. REFERENCES

1. Lois N, Gardner E, Waugh N, Azuara-Blanco A, et al. Diabetic macular oedema and diode subthreshold micropulse laser (DIAMONDS): study protocol for a randomised controlled trial. Trials. 2019 Feb 12;20(1):122.

2. Lois N, Campbell C, Waugh N, Azuara-Blanco A, et al. Diabetic Macular Edema and Diode Subthreshold Micropulse Laser: A Randomised Double-Masked Noninferiority Clinical Trial. Ophthalmology. 2023 Jan;130(1):14-27.

3. Lois N, Campbell C, Waugh N, Azuara-Blanco A, et al. Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS noninferiority RCT. Health Technol Assess. 2022 Dec;26(50):1-86.

4. Mistry H, Maredza M, Campbell C, Lois N; DIAMONDS study group. Subthreshold micropulse laser versus standard laser for the treatment of central-involving diabetic macular oedema with central retinal thickness of <400µ: a cost-effectiveness analysis from the DIAMONDS trial. BMJ Open. 2023 Oct 18;13(10):e067684.

5. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. Br J Ophthalmol. 2012;96(3):345-9.

6. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Diabetes Care. 2012;35(3):556-64.

7. Diabetes UK [Internet] How many people in the UK have diabetes? Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/statistics

8. Li JQ, Welchowski T, Schmid M, Letow J, et al. Prevalence, incidence and future projection of diabetic eye disease in Europe: a systematic review and metaanalysis. Eur J Epidemiol. 2020;35(1):11-23

9. National Institute for Health and Care Excellence. Aflibercept for treating diabetic macular oedema. 2015. Available from: htttps://www.nice.org.uk/guidance/ta346

10. National Institute for Health and Care Excellence. Ranibizumab for treating diabetic macular oedema. 2013. Available from: htttps://www.nice.org.uk/guidance/ta274

11. National Institute for Health and Care Excellence. Faricimab for treating diabetic macular oedema. Available from: https://www.nice.org.uk/guidance/TA799/chapter/1-Recommendations

12. Vilà González M, Eleftheriadou M, Kelaini S, Naderi-Meshkin H, et al. Endothelial Cells Derived From Participants With Diabetic Macular Edema Recapitulate Clinical Evaluations of Anti-VEGF Responsiveness Through the Neuronal Pentraxin 2 Pathway. Diabetes. 2020 Oct;69(10):2170-85.

13. Segal O, Segal-Trivitz Y, Nemet AY, Cohen P, et al. Anxiety levels and perceived pain intensity during intravitreal injections. Acta Ophthalmol. 2016 Mar;94(2):203-4.

14. Wang R, McClard CK, Laswell S, Mahmoudzadeh R, et al. Quantifying burden of intravitreal injections: questionnaire assessment of life impact of treatment by intravitreal injections (QUALITII). BMJ Open Ophthalmol. 2022 Dec;7(1):e001188.

15. Nguyen QD, Brown DM, Marcus DM, Boyer DS, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomised trials: RISE and RIDE. Ophthalmology. 2012 Apr;119(4):789-801.

16. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014 Nov;121(11):2247-54.

17. Virgili G, Parravano M, Evans JR, Gordon I, et al. Anti-vascular endothelial growth factor fordiabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev. 2018;(10):CD007419

18. Wykoff CC, Abreu F, Adamis AP, Basu K, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in participants with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet. 2022 Feb 19;399(10326):741-55.

19. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011 Apr;118(4):615-25.

20. Kern C, Fu DJ, Huemer J, Faes L, et al. An open-source data set of anti-VEGF therapy in diabetic macular oedema participants over 4 years and their visual acuity outcomes. Eye (London). 2021 May;35(5):1354-64.

21. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 participant eyes. Br J Ophthalmol. 2021 Feb;105(2):216-21.

22. Baker CW, Glassman AR, Beaulieu WT, Antoszyk AN, et al.. Effect of Initial Management With Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss Among Patients With Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity: A Randomized Clinical Trial. JAMA. 2019 May 21;321(19):1880-1894.

23. Sabal B, Teper S, Wylęgała E. Subthreshold Micropulse Laser for Diabetic Macular Edema: A Review. J Clin Med. 2022 Dec 29;12(1):274.

24. Khattab AM, Hagras SM, AbdElhamid AH, Torky MA, et al. Aflibercept with Adjuvant Micropulsed Yellow Laser versus Aflibercept Monotherapy in Diabetic Macular Edema. Graefe's Arch. Clin. Exp. Ophthalmol. 2019;257:1373-80.

25. Abouhussein, M.A.; Gomaa, A.R. Aflibercept plus Micropulse Laser versus Aflibercept Monotherapy for Diabetic Macular Edema: 1-Year Results of a Randomised Clinical Trial. Int. Ophthalmol. 2020;40:1147-54.

26. Koushan K, Eshtiaghi A, Fung P, Berger AR, et al. Treatment of Diabetic Macular Edema with Aflibercept and Micropulse Laser (DAM Study). Clin. Ophthalmol. 2022;16:1109-15.

27. Kanar H, Arsan A, Altun A, Aki S, et al. Can Subthreshold Micropulse Yellow Laser Treatment Change the AntiVascular Endothelial Growth Factor Algorithm in Diabetic Macular Edema? A Randomised Clinical Trial. Indian J. Ophthalmol. 2020;68:145-51.

28. Akhlaghi M, Dehghani A, Pourmohammadi R, Asadpour L, et al. Effects of Subthreshold Diode Micropulse Laser Photocoagulation on Treating Participants with Refractory Diabetic Macular Edema. J. Curr. Ophthalmol. 2019;31:157-60.

29. Herdman M, Gudex C, Lloyd A, Janssen M, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.

30. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, et al. National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001 Jul;119(7):1050-8. doi: 10.1001/archopht.119.7.1050. PMID: 11448327.

31. Rentz AM, Kowalski JW, Walt JG, Hays RD, et al. Development of a preference-based index from the National Eye Institute Visual Function Questionnaire-25. JAMA Ophthalmol. 2014 Mar;132(3):310-8

32. Sekhon M, Cartwright M, Francis JJ. Development of a theory-informed questionnaire to assess the acceptability of healthcare interventions. BMC Health Serv Res. 2022 Mar 1;22(1):279.

33. Creswell W, Plano Clark VL. Designing and Conducting Mixed Methods Research. United Kingdom: SAGE Publications, 2011.

34. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2). Current Step 4 version, 9 November 2016. Available from : https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

35. Gillies MC, Sutter FK, Simpson JM, Larsson J, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomised clinical trial. Ophthalmology. 2006 Sep;113(9):1533-8.

36. Burian G. Visual function endpoints. Industry view. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-day-1-visual-function-endpoints-industry-view_en.pdf

37. Ritchie A, Atamian S, Shah N, Laidlaw A, et al. Can Visual Acuity Be Reliably Measured at Home? Validation of Telemedicine Remote Computerised Visual Acuity Measurements. Br Ir Orthopt J. 2021 Jun 16;17(1):119-26.

38. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, et al. Reporting of noninferiority and equivalence randomised trials: an extension of the CONSORT statement. JAMA. 2006 Mar 8;295(10):1152-60.

39. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual.2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technologyevaluation.

40. Drummond MF, Schulper MJ, Claxton K, Stoddart GL, et al. Methods for the economic evaluation of health care programmes. Fourth Edition. Oxford: Oxford University Press, 2015.

41. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. Second Edition. Oxford: Oxford University Press OUP, 2014.

42. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Value Health. 2022 Jan;25(1):3-9.

43. Braun V, Clarke V. Thematic Analysis: A Practical Guide. 2022 Sage Publications.

44. Johnson RE, Grove AL, Clarke A. Pillar Integration Process: A Joint Display Technique to Integrate Data in Mixed Methods Research. Journal of Mixed Methods Research. 2019;13(3):301-20.

45. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci. 2015 Feb 12;10:21.

46. Damschroder LJ, Reardon CM, Widerquist MAO, Lowery J. The updated Consolidated Framework for Implementation Research based on user feedback. Implement Sci. 2022 Oct 29;17(1):75.

47. Nevedal AL, Reardon CM, Opra Widerquist MA, Jackson GL, et al. Rapid versus traditional qualitative analysis using the Consolidated Framework for Implementation Research (CFIR). Implement Sci. 2021 Jul 2;16(1):67.

48. Waltz TJ, Powell BJ, Fernández ME, Abadie B, et al. Choosing implementation strategies to address contextual barriers: diversity in recommendations and future directions. Implement Sci. 2019 Apr 29;14(1):42.

49. SWAR 02: Effects of reading a written summary or listening to a summary podcast on knowledge and understanding of the findings of a systematic review. Available from: https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/SWARFileStore/Filetoupload,695595,en.pdf

50. Maguire L, Clarke M. How much do you need: a randomised experiment of whether readers can understand the key messages from summaries of Cochrane Reviews, without reading the full review? J R Soc Med. 2014;104:444-9.

51. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. PLOS Medicine. 2010;7(3):e1000251.

52. Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for Reporting Trial Protocols and Completed Trials Modified Due to the COVID-19 Pandemic and Other Extenuating Circumstances: The CONSERVE 2021 Statement. JAMA 2021;326(3): 257-65.