Clinical Trial Protocol

Full Title:	Managing chronic Myalgia Temporomandibular Disorder (M-TMD): a pragmatic phase III definitive three-arm parallel-group, co-primary outcome, individually randomised open-label controlled superiority trial comparing the clinical- and cost-effectiveness and safety of Botulinum toxin type A, Lidocaine, and Amitriptyline/Gabapentin, with internal pilot and cost-effectiveness analysis (MiTiGate)
Short Title/Acronym:	MiTiGate trial
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Statement: This protocol has regard for the HRA guidance.

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RESEARCH SPONSOR

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PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: **MiTiGate**

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I have carefully read and understood protocol version 5.0 07 October 2025. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

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TRIAL SUMMARY

Trial Title	Managing chronic Myalgia Temporomandibular Disorder (M-TMD): a pragmatic phase III definitive three-arm parallel-group, co-primary outcome, individually randomised open-label controlled superiority trial comparing the clinical- and cost-effectiveness and safety of Botulinum toxin type A, Lidocaine, and Amitriptyline/Gabapentin, with internal pilot and cost-effectiveness analysis (MiTiGate)	
Acronym	MiTiGate	
Clinical Phase	Phase III	
Summary of Trial Design	A pragmatic, phase III definitive, three-arm, co-primary outcome, parallel-group, individually randomised, open-label, controlled superiority trial with an internal pilot comparing the clinical- and cost-effectiveness and safety of Botulinum toxin (BTX) injections, lidocaine 2% injections, treatment as usual (TAU: amitriptyline and/or gabapentin)	
Summary of Participant Population	Adults with chronic (≥3months) myalgia temporomandibular disorder (M-TMD)	
Planned Sample Size	663 participants (including dropout)	
Setting	12 UK hospital sites providing recruitment and intervention. Adjunctive recruitment: self- and primary care referral, plus database searches as required	
Treatment Duration	36 weeks (3 injection cycles - weeks 0, 12 & 24; or initiation of medication and two reviews at weeks 0, 12, and 24)	
Follow Up Duration	36 weeks	
Planned Trial Period	48 months	
	Objectives	**Outcome Measures**
Primary	To determine whether BTX or lidocaine are superior to treatment as usual (TAU, amitriptyline/gabapentin) in reducing pain intensity and improving quality of life after 36 weeks of treatment comprising 3 injection cycles.	Co-primary clinical outcome measures: Disorder-specific quality of life measured by Oral Health Impact Profile-TMDs (OHIP-TMD) and Characteristic Pain Intensity (CPI) at 36 weeks.

	To assess cost-effectiveness in terms of incremental cost per QALY gained of the most effective treatment in comparison to the other treatments at 36 weeks.	Principal economic outcome: incremental cost per quality-adjusted life year gained of the most effective treatment compared to other treatments at 36 weeks
Secondary	To assess cost-effectiveness in terms of incremental cost per QALY over a lifetime horizon To evaluate whether the interventions affect generic quality of life (EQ-5D-5L)	Health Utilisation Questionnaire (HUQ) administered at screening, 12 and 36 weeks alongside time and travel questionnaire (T&TQ) administered at 24 weeks. EQ-5D-5L administered at screening, 12, 24, and 36 weeks.
	To compare the proportion of participants achieving more than 30% and more than 50% reductions in pain intensity, as well as 30% and 50% improvements in quality of life, across treatment groups at 36 weeks	Disorder-specific quality of life measured by Oral Health Impact Profile-TMDs (OHIP-TMD) and Characteristic Pain Intensity (CPI) at baseline and 36 weeks.
	To examine responder rates and adherence over time in all interventions	Routinely collected descriptive data. Longitudinal sequential qualitative data collection from purposive sub-sample of participants.
	To evaluate whether any of the interventions affect jaw function	Jaw function limitation questionnaire short-form administered at screening, 12, 24 and 36 weeks.
	To evaluate whether any of the interventions affect psychosocial distress, sleep quality, or analgesia use	PHQ-4, psychosocial distress administered at screening, 12, 24 and 36 weeks. Brief Pittsburgh Sleep Quality Index administered at screening, 12, 24 and 36 weeks. Over-the-counter (OTC) analgesia use. Data collected from patient at screening, 12, 24 and 36 weeks
	To compare the adverse effect profiles of the interventions including changes in the	Structural TMJ changes on MRI and apparent diffusion coefficient as a marker of bone density. Serum

	temporomandibular joint (TMJ) using MRI and biomarkers.	biomarkers of bone turnover (CTX and P1NP). Measured from screening visit (visit 1) up to 36 weeks.
	To explore treatment experiences and acceptability of interventions	Longitudinal sequential qualitative data collection from participants Global impression of change at 36 weeks. Liverpool adverse effects profile. AE or SAE reporting from informed consent up to 36 weeks.
Exploratory	Explore participants' reporting accuracy of pain intensity in response to a controlled pressure stimulus. Explore the influence of pain reporting accuracy on outcome in the trial.	Pain tolerance and threshold to a pressure stimulus and participant's reported pain intensity. R^2 values derived from regression of applied stimulus and reported pain intensity.
Investigational Medicinal Product(s)	Oral gabapentin Oral amitriptyline As this is a pragmatic trial any brand of the oral medication can be used Injectable therapy to bilateral masseter and temporalis muscles: - Intra-muscular lidocaine 2%, 2mls with or without preservative - Intra-muscular botulinum toxin type A as Botox (Allergan/AbbVie), 100iu in solution with 2mls 0.9% Normal saline	
Formulation, Dose & Route of Administration	Botulinum toxin type A (Botox, Allergan/AbbVie) 100iu in solution with 2mls of 0.9% Normal saline delivered bilaterally intramuscularly to masseter and temporalis in fixed site areas. Lidocaine 2% 2mls delivered bilaterally intramuscularly to masseter and temporalis in fixed site areas. Oral gabapentin or amitriptyline. Amitriptyline suggested as first-line if not trialled previously unless ≥60 years of age or epileptic where further discussion will occur with patient over which drug they would prefer to trial. Dosing titration and regimen determined by clinician's usual practice within or below/slower than NICE's stated parameters:	

	- Starting doses: 10mg amitriptyline once daily in the evening; either 100mg or 300mg of gabapentin once daily, then twice daily on day 2, and then three times daily on day 3. - Titration interval: quickest allowed for gabapentin and amitriptyline is 1 week and slowest is 4 weeks. - Titration increments: 10mg increments of amitriptyline. 100-300mg increments for gabapentin which could be applied to all of the three times daily regimen, or one- or two of the three-times daily intakes. - Ceiling total daily doses: 75mg once daily amitriptyline in evening, 3600mg gabapentin split across three doses. - Duration of therapy: trial amitriptyline or gabapentin for at least 8-12 weeks with a minimum of 2 weeks at the most effective or tolerable dose - Discontinuation: taper medication down over **at least** 4 weeks or slower for both amitriptyline and gabapentin in similar increments or smaller than upwards titration.

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GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
BPSQI	Brief Pittsburgh Sleep Quality Index
BTX	Botulinum toxin
CA	Competent Authority
CI	Chief Investigator
CIs	Confidence Intervals
CPI	Characteristic pain intensity from the graded chronic pain scale (Von Korff et al., 1992)
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTX	Serum cross-linked C-telopeptide of type I collagen
DC/TMD	Diagnostic Criteria for Temporomandibular disorders (Schiffman et al., 2014)
DLT	Dose Limiting Toxicity
IDMC	Independent Data Monitoring Committee
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GCPS	Graded Chronic Pain Scale
GDPR	General Data Protection Regulation
HRA	Health Research Authority

HTA	Human Tissue Authority
HTAct	Human Tissue Act
HUQ	Health Utilisation Questionnaire
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRMER	Ionising Radiation (Medical Exposure) Regulations
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IU	International unit
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
M-TMD	Myalgia temporomandibular disorder
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
OHIP-TMDs	Oral Health Impact Profile for Temporomandibular Disorders
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PK	Pharmacokinetic
PPIE	Patient and public involvement and engagement
PPS	Personal Social Services

P1NP	Procollagen 1 Intact N-Terminal Propeptide
QA	Quality Assurance
QALY	Quality-adjusted life year
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SM	Self-management of TMD (Durham et al., 2016a)
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as usual (Amitriptyline or Gabapentin oral medication)
TMD	Temporomandibular disorder
TMG	Trial Management Group
TMJ	Temporomandibular "jaw" joint
TMF	Trial Master File
T&TQ	Time and travel questionnaire
TSC	Trial Steering Committee

1. BACKGROUND

TMD are a group of common painful disorders affecting the temporomandibular "jaw" joint (TMJ), the muscles that move it (muscles of mastication), or associated structures. TMD are the most common cause of facial pain after toothache; 1 in 15 vs 1 in 10 people, respectively (Macfarlane et al., 2001). TMD produce daily impacts causing substantial healthcare and economic costs (Durham et al., 2021).

TMD have a nociplastic aetiology in the trigeminal sensory system. First onset of TMD is 4% per annum, peaking in the fourth decade (Slade et al., 2016). The most common TMD is myalgia (M-TMD), representing two-thirds of all cases (Slade et al., 2013).

Accepted first-line treatment of acute (<3 months' duration) M-TMD is self-management (SM). Most dentists/doctors provide this in line with guidance (Hamad et al., 2020; NICE, 2021) with or without providing some form of oral splint ("mouthguard"). Despite SM, with or without a splint, in the acute phase, many cases of M-TMD can last greater than three months, producing chronic pain (Slade et al., 2016) and are referred for further specialist-led treatment. Unfortunately, there is a lack of evidence on which treatment is most effective and should be tried first following SM with or without a splint.

Secondary care specialists mostly provide NICE and NHS England's (https://tinyurl.com/NHSE-RCS-GIRFT-TMD) standard of care as first-line treatment (Durham et al., 2016b); off-license amitriptyline or gabapentin (between 16-54% cases received over time in a recent economic modelling study (Durham et al 2021)). However, both drugs have adverse effects and a weak evidence base, as do lidocaine injections which are used intermittently by specialists (Machado et al., 2018; NICE, 2021). There is no licensed intervention for M-TMD due to the weak evidence base and a failure to translate research findings from other trigeminally-mediated conditions, e.g., management of chronic migraine. Migraine research is relevant to M-TMD as chronic M-TMD and chronic migraine share similar nociplastic mechanisms, and there is robust evidence supporting trialling up to 3 cycles of Botulinum toxin (BTX) injections to manage chronic migraine with few adverse effects (Burstein et al., 2020; Bendtsen et al., 2018; NICE, 2012; Herd et al., 2018). Given the potential for translation of management advances from chronic migraine into chronic M-TMD it is important to learn lessons from pre-existing research and examine BTX and lidocaine injections against chronic M-TMD's current standard of care (amitriptyline/gabapentin) to determine the best balance between efficacy, adverse effects, and cost.

2. RATIONALE

It is critical to generate some robust data on the effectiveness and cost-effectiveness of injectable treatments (BTX and lidocaine) given recent UK data demonstrate they are already being used as (part of) routine clinical care for M-TMD in a substantial number of secondary care settings. The lack of robust data on BTX's effectiveness, dose scheduling, and risks in M-TMD are apparent in the variability of the responses on dosing, scheduling, and administration from those clinical units in the UK utilising it (Anwar et al., 2022). Lidocaine is known to be an active comparator treatment delivered by the same

mode of administration as BTX and may offer a more effective or cost-effective treatment option (Machado et al., 2018)

2.1. Risk Assessment

All four IMPs are already used widely with M-TMD and in other trigeminally-mediated pain conditions, with detailed safety profiles available. Participants are potentially vulnerable due to the prolonged period of pain that they are experiencing, but risks are well mitigated for within the protocol.

This trial is categorised as:

- Type A = no higher than the risk of standard clinical care

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Primary Objectives

a) To determine whether BTX or lidocaine are superior to treatment as usual (TAU, amitriptyline/gabapentin) in reducing pain intensity and improving quality of life after 36 weeks of treatment comprising 3 injection cycles.
b) To assess cost-effectiveness in terms of incremental cost per QALY gained of the most effective treatment in comparison to the other treatments at 36 weeks.

3.2. Secondary Objective(s)

a) To assess cost-effectiveness in terms of incremental cost per QALY over a lifetime horizon.
b) To evaluate whether the interventions affect generic quality of life (EQ-5D-5L).
c) To examine responder rates and adherence over time in all interventions.
d) To evaluate whether any of the interventions affect jaw function.
e) To evaluate whether any of the interventions affect psychosocial distress, sleep quality, or analgesia use.
f) To compare the adverse effect profiles of the interventions including the MRI sub study examining changes in the temporomandibular joint.
g) To explore treatment experiences and acceptability of interventions.

3.3. Outcome Measures

The outcomes selected represent the most important as defined by our PPIE consultation. They address both the Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials (IMMPACT) recommendations (Dworkin et al., 2008) and the TMD core outcome recommendations soon to be published (Ferreira et al., 2022). IMMPACT's five recommended outcome domains are measured within the trial: 1) Pain intensity; 2) Physical functioning via disorder-specific quality-of-life; 3) Emotional functioning; 4) Participant global impression of change; 5)

Symptoms, side-effects, adverse events. Domains 1 and 2 are co-primary outcomes and domains 3-5 are secondary outcomes. Outcomes and costs will be collected either electronically or at distance via post or telephone at weeks 0, 12, 24, and 36 unless otherwise stated. All outcomes and costs will be measured using validated published instruments.

The following data and outcomes will be collected and reported:

3.3.1. Primary Endpoint/Outcome

The trial's two co-primary outcomes for effectiveness are:

- Characteristic pain intensity (CPI) assessed by a composite average, worst and current numerical rating scale of pain (0-100 scale (Von Korff et al., 1992)) at 36 weeks of treatment examining last 12 weeks' pain intensity.
- Disorder-specific related quality of life (the Oral Health Impact Profile for TMDs [OHIP-TMD (Yule et al., 2015)]) at 36 weeks of treatment examining the last 4 weeks' quality of life.

The trial's primary economic outcome is:

- incremental cost per quality-adjusted life year gained of the most effective treatment compared to other treatments at 36 weeks calculated using data from the Health Utilisation Questionnaire (HUQ) (administered baseline, 12, & 36 weeks), the time and travel questionnaire (T&TQ administered at census date of 24 weeks), the EQ-5D-5L (administered at baseline, 12, 24 & 36 weeks), and routine sources and study specific estimates for unit costs (Jones and Burns, 2021).

3.3.2. Secondary Endpoints/Outcomes

The secondary outcomes are:

- CPI at 12 and 24 weeks
- OHIP-TMD at 12 and 24 weeks
- 30% and 50% reduction from baseline in CPI
- 30% and 50% improvement from baseline in OHIP-TMD
- Health Utilisation Questionnaire (HUQ) alongside time and travel questionnaire (T&TQ) (Durham et al., 2016b)
- EQ-5D-5L (Herdman et al., 2011)
- Jaw function limitation questionnaire short-form (Ohrbach et al., 2008)
- PHQ-4, psychosocial distress (Kroenke et al., 2009)
- Brief Pittsburgh Sleep Quality Index (Sancho-Domingo et al., 2021)
- Over-the-counter (OTC) analgesia use (Dworkin et al., 2008)
- Structural changes and apparent diffusion coefficient (representing bone density) in the TMJ on MRI (Muraoka et al., 2021) and serum biomarkers of bone turnover CTX and P1NP (Szulc et al., 2017)
- Global impression of change in pain intensity, daily activities, emotional status, and overall status (Dworkin et al., 2008)
- Liverpool adverse effects profile (Baker, 1995; Besi et al., 2015)

- Longitudinal sequential qualitative data collection from purposive sub-sample of participants using semi-structured interviews.
- Pain reporting accuracy from the pain reporting assessment and feedback study procedure. This will be reported as pain threshold, pain tolerance, and R^2 values from applied pressure stimuli and participant's reported pain intensity.

A longer-term economic model will also be explored extrapolating costs and outcomes over a lifetime horizon.

4. TRIAL DESIGN

The trial is a pragmatic, phase III definitive three-arm parallel-group, co-primary outcome, individually randomised, open-label controlled superiority trial with a 12-month internal pilot comparing the clinical- and cost-effectiveness and safety of: 1) Botulinum toxin type A injections; 2) Lidocaine 2% injections; 3) TAU: amitriptyline and/or gabapentin. The participants will be suffering from Myalgia Temporomandibular disorder (M-TMD) diagnosed using criteria derived from the Diagnostic Criteria for TMD (DC/TMD (Schiffman et al., 2014)) for ≥3months. Unilateral or bilateral M-TMD is eligible for inclusion. M-TMD comorbid with another sub-type of TMD that is not the primary familiar pain is also eligible. Participants must have trialled self-management (SM, (Durham et al., 2016a)) for ≥6weeks and not found it to have controlled the pain to their satisfaction. They can have experienced physiotherapy, splint (orthotic) therapy, or psychological treatments and still be eligible. They must not have had any of the trial's IMPs within the 12 weeks prior to consent.

Participants will be randomised 1:1:1 between TAU (NICE's standard of care amitriptyline and/or gabapentin (NICE, 2021)) and the two injectable therapies stratified by psychosocial distress (PHQ-4 score ≥6 (Penlington et al., 2020)) and site. The trial includes a qualitative and economic evaluation. The trial's flow is demonstrated by Figure 1.

4.1. Internal pilot

An internal pilot will be conducted in the first 12 months of recruitment to assess site opening, recruitment rates, and completeness/quality of outcome data. Table 1 shows the progression criteria against the parameters measured. After 12 months all sites should be open.

Table 1: Progression criteria for internal pilot's parameters

Parameter	**Progression criteria at 12 months of recruitment**		
	Red	**Amber**	**Green**
% sites open (n of sites)	≤50 (≤6)	50-75 (7-9)	76-100 (10-12)

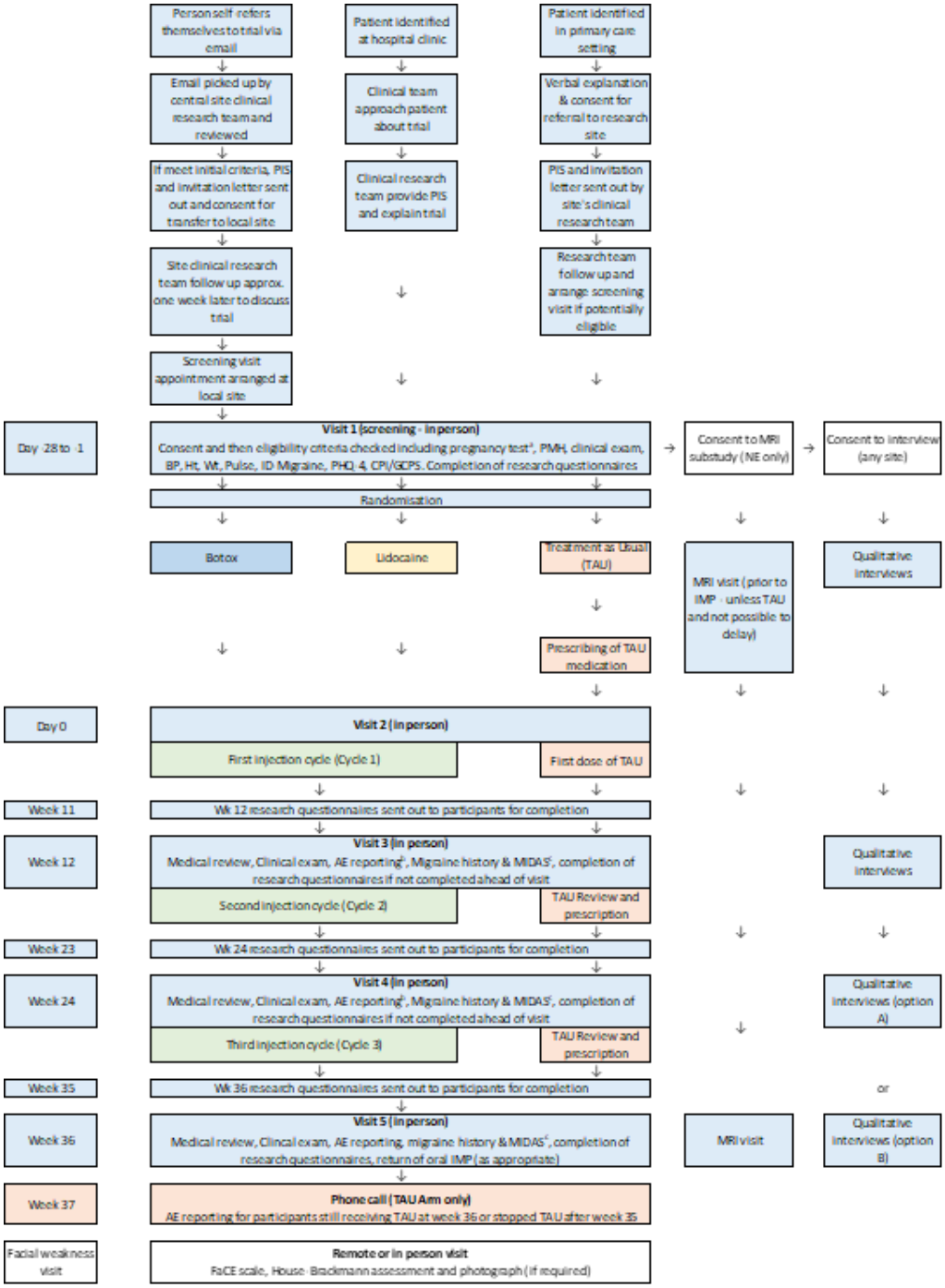
Patient recruitment rate per site-month	≤1	1.1-2.9	≥3
% of total recruitment (n of patients)	<20 (≤132)	20-35.1 (133-233)	>35.2 (≥234)
% patient attrition across all sites	≥40	28-39	≤27
Outcome data	Given the variety of outcomes we will conduct a review of completeness and quality of outcome data rather than use quantitative metrics		

If trial progress meets all the green criteria, then the trial will transition to the full trial.

Should a majority of progression criteria be within the amber range then a time-bounded mitigation plan will be constructed with the Trial Steering Committee (TSC) for consideration by funder.

If any criterion falls within the red range, then discussions will be held with the TSC and funder about expediting recruitment or study closure.

Figure 1 - Trial and research activity flow diagram



a If person of child bearing potential
b if headache reported as Adverse Event then ID-Migraine should be completed
c if ID-Migraine positive at screening visit or if has reported headaches at any visit
d only applicable if participant contacts site reporting facial weakness following start of treatment

AE - Adverse events, **BP** - Blood pressure, **CPI/GCPS** - Characteristic Pain Intensity as part of Graded Chronic Pain Scale, **FaCE scale** - Facial Clinimetric Evaluation Scale assessing patient's perceived impact of facial weakness, **MIDAS** Migraine Disability Assessment Test - headache quality of life measure, **Ht** - Height, **ID-Migraine** - migraine screening instrument, **MH** - Migraine history, **PHQ-4** - Patient health questionnaire 4 for anxiety/depression screening, **PMH** - Past medical history, **TAU** - Treatment As Usual, **Wt** - Weight

5. STUDY SETTING

This is a multicentre trial in the United Kingdom with secondary care delivery of intervention. Recruitment will occur from both the secondary care sites, the allied primary dental and medical care networks, and self-referral to draw on a diverse population, as well as database searches as required and where available.

6. ELIGIBILITY CRITERIA

Only personnel formally delegated by the Principal Investigator to assess eligibility may perform this task and **this assessment must be documented in the participant's clinical notes**.

NB: Enrolling a patient onto the trial who **does not meet** the inclusion/exclusion criteria is **considered** a **protocol waiver** and **is in breach** of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004 as protocol waivers **ARE NOT PERMITTED.**

6.1. Inclusion Criteria

1. Adults ≥18 years old
2. Willing and able to give informed consent prior to trial procedures occurring.
3. DC/TMD (Schiffman et al., 2014) derived diagnosis of M-TMD with pain for ≥3months identified as the primary complaint of familiar pain.
4. Self-management trialled for ≥6 weeks and not controlled the pain to the patient's satisfaction*
5. Minimum pain intensity of 30 on CPI over last 3 months (Dworkin et al., 2010; Von Korff et al., 1992)
6. For people of childbearing potential: an agreement to use a highly effective method of contraception or to practise sexual abstinence to avoid pregnancy for the duration of trial involvement. Refer to section 6.3.

* Self-management is defined as comprising any, or a combination of the following international agreed components: education, self-exercise therapy, thermal modalities, self-massage therapy, dietary/nutrition advice, or parafunctional activity identification, monitoring, and avoidance (Durham et al., 2016a). If a patient has yet to complete 6 weeks but is eligible on all other criteria for the trial it is permissible, to arrange to rescreen them following the completion of self-management. In self-referrals to the trial who have yet to complete 6 weeks and require further information: these patients can be signposted to the freely available standardised self-management information produced in collaboration with the lead site and co-produced with patients for ease of understanding (https://www.tims.nhs.uk/wp-content/uploads/2020/06/4.5-TIMS-TMD.pdf and https://www.newcastle-hospitals.nhs.uk/services/facial-pain/#temporomandibular-disorder-tmd and asked to discuss with their general dental practitioner). They can then be re-screened for the trial pending their review at 6 weeks.

6.2. Exclusion Criteria

A documented diagnosis, or the patient reports any, of the following:

1. Current use of any of the trial interventions or has used any within the last 12 weeks*#. Patients can continue any other treatment modality they currently find helpful for their TMD subject to no absolute contraindications to its use alongside the interventions under investigation.
2. Any other subtype of TMD that is the primary cause of familiar pain detected on clinical examination; familiar pain is pain provoked by clinical exam or testing/movement of a structure that matches the patient's primary complaint e.g., for M-TMD familiar pain is provoked from examination or use of the muscles of mastication. Patients can have other forms of (painful) TMD comorbid with M-TMD, but these should not be the primary cause of familiar pain determined by DC/TMD derived diagnostic procedures.
3. Enrolled in another interventional research trial which could affect the outcome of this trial.
4. People who are pregnant, planning pregnancy, or breast-feeding during the time of the trial participation*.
5. Current or planned acupuncture within trial period or 3 months prior to trial period*.
6. Formal diagnosis of lactose intolerance or lactose allergy and unable / unwilling to receive oral capsules of lactose free gabapentin if randomised to the treatment as usual arm**.
7. Fibromyalgia
8. Neuropathic pain
9. Coagulopathy
10. Uncontrolled hyperthyroidism
11. Renal failure
12. Severe liver disease
13. Connective tissue disorders e.g. Ehlers-Danlos syndrome, Epidermolysis bullosa, Marfan syndrome, Osteogenesis imperfecta, Rheumatoid arthritis, Poly/dermatomyositis, Scleroderma, Sjogren's syndrome, Systemic lupus erythematosus, Vasculitis
14. Any (previous) substance use disorder
15. Concerns from the research or clinical team over patient safety due to psychosocial distress, previous or current mental health illness*
16. Taking any of the following groups of medications:
    a. Aminoglycoside antibiotics
    b. Anticholinesterases
    c. Non-depolarising and depolarising muscle relaxants
    d. Opiates other than codeine. If taking codeine (including co-codamol), please see footnote†
    e. Monoamine oxidase inhibitors (MAOIs)
17. Allergy or intolerance to any trial intervention, or any contraindication as per each IMP SmPC
18. For the MRI sub study group:

a. cardiac pacemaker, defibrillator or pacing wires.
b. cochlear implant, an aneurysm clip or a hydrocephalus shunt.
c. sustained injuries involving metal fragments to the eye.
d. Pregnancy.
e. any other non-MRI-compatible implant or device.

For participants who would receive amitriptyline as treatment as usual, were they to be randomised to this arm, the following exclusions (19-25) also apply, and they would therefore be offered gabapentin instead:

19. Significant cardiovascular history as indicated by recent (less than 12 calendar months) myocardial infarction, any cardiac rhythm disorder, degree of heart block, prolonged QT interval, or coronary artery insufficiency.
20. Personal or family history of repeated syncope outside of stressful situations; family history of long QT syndrome or sudden unexplained cardiac death in immediate family
21. Ileus
22. Urinary retention
23. Glaucoma
24. Orthostatic hypotension
25. Taking any of the following groups of medications:
    a. Selective serotonin and or norepinephrine uptake inhibitors
    b. Triptans

*If the chronology of events allows, the potentially eligible patient can be booked to be rescreened for a place on the trial at an appropriate point in the future.

If a participant is taking pregabalin or nortriptyline for **non-TMD** reasons on trial entry, the following must apply:

- If taking nortriptyline, they must be able and prepared to receive gabapentin if randomised to TAU
- If taking pregabalin, they must be able and prepared to receive gabapentin if randomised to TAU

** Lactose free amitriptyline **tablets** are not available and participants with a diagnosed lactose intolerance or allergy must be willing / able to use oral **capsules** of lactose free gabapentin if randomised to the treatment as usual arm. They will not be able to receive oral amitriptyline.

† If the patient is taking codeine containing preparations, the following criteria apply:

- Co-codamol up to a single ingestion dose of 30mg of codeine up to every 4 hours (up to a maximum intake of co-codamol of four times daily) is acceptable.
- For any other formulation of codeine, if its dosage ≥ 30mg in a singular ingestion or more frequently than every 4 hours, a principal investigator led risk assessment should be conducted and recorded, to ensure that if the patient was to receive Treatment As Usual there are no other are no other sedative drugs e.g. benzodiazepines, z-drugs etc or other comorbidities that might place the patient at greater risk of respiratory depression or challenges e.g. diminished respiratory function or sleep apnoea. If there are any concerns, the patient will not be eligible for the trial
- No other type of opiate, other than codeine dosing as referred to above, is allowed on trial entry

- All codeine use, at trial entry and during the trial, must be recorded in medications section of CRF

6.3. Effective Methods of Contraception

As per the MHRA's Clinical Trials Facilitation Group, for the purposes of the protocol a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. The protocol also acknowledges that a person of child-bearing potential is defined as either a cis-female or trans-male. Individuals able to help achieve conception are defined as either cis-male or trans-female.

For the purpose of this protocol, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

To be eligible for the trial, participants of child-bearing potential who are sexually active must confirm that they understand the need to use a highly effective method of contraception (failure rate of <1%) for the duration of their involvement of the trial. Participants of child-bearing potential must also confirm that they understand that any sexual partner capable of helping them conceive should also use a highly effective method of contraception during involvement in the trial. Those sexual partners must also confirm that they understand they need to use a highly effective method of contraception for the duration of the trial. Barrier methods are not considered highly effective and female partners of male participants are also advised to use a highly effective method of contraception additionally. Similarly, the reverse is true for any participant who can help achieve conception with sexual partner(s) of childbearing potential.

Highly effective methods include:

Persons of child-bearing potential	Partners of trial participants able to help achieve conception
- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) - Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) - Bilateral tube occlusion or hysterectomy - Vasectomised partner (>3 months earlier) - Sexual abstinence	- Condom - Sexual abstinence - Vasectomy or vaginoplasty/genital reconstruction - permanently sterile by bilateral orchidectomy

Abstinence is defined as refraining from sexual intercourse with the potential for conception. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual

lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), assumption of no conceptive potential (excepting amenorrhea detailed below), and withdrawal are not acceptable methods of highly effective contraception for the purposes of the trial.

Participants are postmenopausal, when they have had no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient and a second measurement must confirm this.

Applicable contraceptive methods should be recorded in the participant's medical record.

7. TRIAL PROCEDURES

7.1. Recruitment

This is a multicentre trial recruiting from at least 12 secondary care centres in the United Kingdom. 663 participants will be recruited for this trial from one of three entry points:

a) Secondary care identification of patient under their care who fits the criteria.
b) Primary care referral of patient to trial who they believe fits the criteria.
c) Self-referral following public advertisement of the trial.

7.1.1. Patient Identification

Primary care and secondary care participants will be identified by either attendance at routine clinics (including outreach dental screening clinics), records/database search, or self-referral to the trial in response to public advertisements, including those on social media at its email address (nuth.mitigate@nhs.net). Patients may also self-refer to local sites if appropriate.

The trial will use a short verbal explanation of the trial and/or a standard letter of invitation as appropriate, followed by a participant information sheet (PIS) to approach those potentially eligible for the trial. This may be in person at a routine clinic appointment, or by post, phone, videoconference, or email as appropriate to the method of identification of the potential participant.

For all identification methods except self-referral the patient's regular clinical care team will request permission from the potentially eligible participant for the research team to contact them (where the regular clinical care team is not the same as the research team). Where the patient is in primary care, permission will be sought from the patient to refer them to the research team at the local trial site.

Self-referral to the trial will be encouraged through public advertisements, word of mouth, social media and use of other public fora and media. The advertised self-referral process will explain people may be eligible to self-refer if they:

- can answer yes to both of the two most sensitive and specific screening questions for TMD (Lövgren et al., 2016; Nilsson et al., 2006) – 1) Do you have pain in your temple, face, jaw or

jaw joint once a week or more, and 2) Do you have pain once a week or more when you open your mouth or chew?;
- have had the pain for 3 months or greater; and
- have tried self-management for at least 6 weeks.

Those then self-referring to the trial will do so through its email address (nuth.mitigate@nhs.net), or via a local secure site email address, when appropriate, by confirming they can answer in the affirmative to the specific two screening TMD questions (Nilsson 2006; Lovgren et al 2016). An initial contact will then be made by clinical members of the Newcastle research team, or the local research team, by sending a standard email/letter of invitation and PIS to them. A follow-up expression of interest call will be scheduled with clinical members of the research team (Newcastle team or local site) approximately a week later to answer any questions patients have and confirm their demographics and TMD status, including treatment. If they are interested in participating, have a high likelihood of being eligible for the trial, and have a site near them, then they can be invited to attend a screening visit at their nearest site. If at any point during the self-referral process a potential participant's details need to be transferred to their local site, they will be asked for permission to securely send their details to that site so they can be invited to attend a screening visit at their nearest site

7.1.2. Consent

Those potentially eligible for the trial will be invited to a screening visit (visit 1) where informed consent will be taken. Screening will occur at the secondary care site either within a normal scheduled clinic visit or at a research specific visit. Potential participants will have had sufficient time to review the trial documentation at this visit; this will likely be at least 24 hours but may be less in some circumstances. For example, a potential participant would like to be screened at same routine clinic visit as the approach is made to participate in the trial once they have considered the information on the trial and have had any questions that they may have had answered to their satisfaction. During, and prior to, the screening visit (visit 1) potential participants will be given opportunity, and encouraged, to ask questions about the trial given they will have received the PIS and a description of the trial. At the screening visit the following will be re-explained:

a) How the trial will run and its duration.
b) Their right to withdraw at any time by revoking their consent without any detriment to them.
c) For people of childbearing potential, the need for an acceptable effective method of contraception or to practise sexual abstinence (see section 6.3).
d) The common adverse effects associated with the trial interventions.
e) The likelihood of Botulinum toxin not immediately being available through routine NHS treatment at the end of the trial.

Informed consent will be sought by an appropriately trained and clinically qualified member of the research team who is delegated to do so at that site. For non-English language speakers or those with additional communication needs there will be appropriate professional interpretation or technical

services employed in line with the local site's policies and protocols. Relatives **are not to be used** to interpret for the potential participant.

Written informed consent will be taken before any of the screening activities are undertaken as part of the screening visit (Visit 1). Consent will be documented in the individual's clinical notes and include *confirmation of a-e above* and the following details:

- Date the potential participant received the PIS.
- Date and version of PIS used, and consent form used.
- A brief summary of any questions asked by the potential participant and the answer(s) given.

The original copy of the signed consent form will be retained in the Investigator Site file (ISF) with additional copies being provided to the participant and a copy scanned or placed into their clinical notes in secondary care. Participants will give specific permission for their GP and general dental practitioner/referring clinician and relevant consultant (where applicable) being informed of their trial participation.

In the event of protocol amendments or information becoming available that might affect the participant's willingness to continue in the trial it may become necessary to re-consent the participant. This would be completed on an updated consent form after all necessary approvals are obtained.

7.1.3. Screening and eligibility assessment

Screening will occur following written informed consent and before randomisation. All potential participants will be screened and clinically reviewed and examined to assess eligibility and ensure compliance with trial inclusion and exclusion criteria (sections 6.1 & 6.2).

Each potential participant will be assigned a unique Subject ID number to identify them, which at the point of randomisation will then become their Subject ID for the trial. Everyone considered for the trial, including those who fail screening, must be recorded on the electronic trial screening database. The Subject ID number will be a six-digit code and used within the trial database and all other relevant documents. If a potential participant does not go on to be randomised the Subject ID will not be reused.

Eligibility will be assessed at the site by a clinician appropriately delegated to do so by the site PI and the assessment will be documented in the participant's clinical (e-) notes, which includes a statement of eligibility. An eligibility checklist will be completed in the clinical data management system (CDMS) for all patients screened for the trial.

The patient will be informed whether they meet eligibility criteria and treatment arranged as necessary. Patients who do not meet the eligibility criteria will continue with their standard treatment pathway with their original care team and will be considered as 'screen failures'. These 'screen failures' will be recorded on the screening log with reasons for not participating in the trial documented wherever possible. Screen failures **do not** count towards recruitment targets. An

electronic screening log, integrated into the Sealed Envelope Redpill database will capture anonymised screening data, when available, including:

- Patient referral method to trial: NHS clinic, self-referral, primary care dental, primary care medical
- Number of patients referred to, or approached, by trial sites and provided with a PIS.
- The number of patients eligible/not eligible and reasons (e.g. not diagnosed with M-TMD).
- Potentially eligible patients approached for consent.
- Patients declined/not consented and the reasons why (if known).
- Patients deemed ineligible at screening may be rescreened at a later date if there is a change in circumstances and the trial has not closed to recruitment.

The other data collection at the screening and eligibility assessment are described in section 7.4.

7.1.4. Payment

Participants will be offered reasonable travel expense reimbursement for trial visits.

7.1.5. Randomisation

Those who provide informed consent and fulfil eligibility criteria will be randomly allocated stratified by psychosocial status (PHQ-4 score≥6 (Penlington et al., 2020)) and site in a ratio of 1:1:1 to one of the three arms of the study: TAU, lidocaine injections, or Botulinum toxin type A injections 3 monthly for 3 cycles (weeks 0, 12, 24). The randomisation process will use the Sealed Envelope (SE) system (a central, secure, 24-hour web-based randomisation system with concealed allocation). The SE system will use random permuted blocks within strata. Those who have been delegated the randomisation task at local sites will be provided with personal login IDs and passwords. The study is open label. Those participating in the trial north-east of England (Newcastle, Sunderland, Middlesbrough sites) will be offered the opportunity to participate in the optional MRI sub-study. Seventeen participants from each arm of the trial will be sequentially selected from those who opt-in to the sub-study making a total of 51 participants in the sub-study.

7.2. Blinding

As the treatments have differing modes of delivery and differing adverse effects that would identify them easily the trial is designed as an open label trial. As a result, therefore blinding of the participant, clinical team, Health Economics and the TMG is not possible.

The trial statisticians (senior statistician and trial statistician) will be unblinded to produce and review reports to the Independent Data Monitoring Committee (IDMC). Unblinded reports will be kept confidential and will only be viewed by the IDMC members and the trial statisticians. The statistical analysis plan will be written and approved by the trial statisticians prior to any access to unblinded outcome data. The statistical methodology lead will remain blinded to outcome data until data lock for the final analysis. Should any amendments to the statistical analysis plan be required after the

senior and trial statisticians have accessed unblinded outcome data these can be reviewed and approved by the blinded statistical methodology lead.

7.3. Out of hours contact

Due to the low risk and unblinded nature of the trial and the fact it involves commonly used medications with a substantial body of evidence for their safety, there will be no out of hours contact for the central trial team. At each secondary care site participants will be able to access the usual NHS out-of-hours system for that site for any clinical problems.

As this is an unblinded, open label trial participants will be able to inform any clinician managing them in a medical emergency of the treatment they have had. To further enhance safety, they will be issued with a trial information card with all the trial's details on including the treatments and the local team's in hours contact details for quick and easy reference. They will be advised to always carry this on their person. Local sites' on call arrangements for any urgent problems with a trial participant will apply.

Any out of hours contacts will be recorded, via the HUQ or, if related to an adverse effect, through routine study visit procedures.

7.4. Trial Assessments

After written informed consent is given, a variety of assessments will be used to capture the data required from participants as they progress through the trial.

7.4.1. Pregnancy test

Where indicated a urine dip stick test will be carried out at visit 1 (Face-to-face screening visit). This will be conducted prior to any other assessments. If positive the patient will be a screen failure and no further data will be collected. If the chronology allows, the patient may be rescreened post-partum if they are not breastfeeding the child.

7.4.2. Visit 1 – Face to face screening visit (day -28 up to -1)

Following informed consent, a negative pregnancy test, and confirmation of eligibility, data will be captured at visit 1 (screening) prior to randomisation within the clinical data management system (CDMS), including the following:

- Sex at birth
- Age
- Ethnicity
- Home postcode to calculate index of multiple deprivation
- Current employment details, or reason for not working.
- Income, or details of benefits received.
- Highest level of education

- Relevant past medical history including: systems enquiry; allergies; current treatment and medications; any non-drug therapies; analgesia use in the last month and reason.
- TMD history including: duration of M-TMD to nearest month; other (known) TMD diagnoses; TMD treatment history and dates of treatment to nearest month.
- Migraine history using ID Migraine to screen. A positive screen will result in collection of details on: number of headache days per month categorised into <10days, 10-15 days, >15 days, any accompanying symptoms to the headache, and a MIDAS questionnaire.

The CRF will also capture the diagnoses elicited from the clinical review and examination derived from the Diagnostic Criteria for TMD (Schiffman et al., 2014). A routine extra and intra-oral examination will be conducted examining: cranial nerves V and VII, temporomandibular joint including pain-free opening and maximum unassisted opening, masseter and temporalis, cervical lymph nodes, salivary glands, screening of intra-oral soft and hard tissues to note any gross and relevant mimicking or serious pathology and not including periodontal examination. Vital signs will be recorded including weight, height, blood pressure, and pulse.

Research assessments as detailed in the schedule of events will be conducted prior to randomisation following confirmation of eligibility.

Eligible participants will be randomised at the end of the screening visit (visit 1). A follow up visit (visit 2) will be scheduled following randomisation to start treatment for those participants randomised to Botox or lidocaine. This should ideally be within 14 days of screening but may be up to 28 days. Administration of IMP may occur on the same date as the screening visit, following randomisation, should the participant and investigator both agree to this.

For participants randomised to TAU, they may receive a prescription to obtain their medication at the screening visit, or their GP will be contacted to ask them to prescribe it. For those participants who agree to undergo an MRI, the participant should be advised not to start their medication until after the completion of the MRI, if possible.

7.4.3. Visit 2 – Day 0

Participants will commence treatment at visit 2. For those randomised to receive an injectable, this will be their first cycle of treatment. For those participants allocated to TAU, this will be the start date of their medication, but does not need to be an in-person visit. The start date of the medication will be reported on ePro by the participant or reported to the trial team by telephone who will record this date in the eCRF. Further visit dates will be calculated from this Day 0 timepoint.

7.4.4. Further visits (3, 4, and 5)

All participants will have completed the research assessments ahead of the follow-up visit as described in 7.4.6 and if not, further copies will be issued for completion prior to commencing the follow-up visit. Consent will be reconfirmed at each follow-up visit. Follow up and or further treatment will occur at visits 3 (week 12 +/- 7 days), 4 (week 24 +/- 7 days) and 5 (week 36 +/- 7 days).

Follow up visit 3 at week 12 (+/- 7 days), visit 4 at week 24 (+/- 7 days) and follow up visit 5 at week 36 (+/- 7 days), will be conducted in person for all treatment arms. A clinical assessment will take place here, as well as a vital signs assessment. Participants allocated to Botox or Lidocaine will also receive their next cycle of injections at visits 3 and 4. Participants allocated to TAU will have their medication reviewed by the trial investigator and changes made, if required, at visits 3 and 4. Their GP will be written to, if necessary, to ask them to alter their prescription, based on the decision of the trial investigator. Treatment may also be provided by the site pharmacy, depending on local processes.

At the 36 weeks, patients will be returned to the care of their GP as per usual standard of care practice. The GP will discuss and agree with the patient how their care will be conducted after the trial. The research team will contact the patient by telephone 7 days after the 36 week visit to identify any adverse events in that time period. Two attempts will be made to contact the participant.

Case report forms will be completed as required at each trial visit to capture any changes in the medical history, migraine history (if relevant), and if receiving injectable therapy examination status of any facial nerve weakness using the House-Brackmann regional and global scores (Reitzen et al., 2009).

7.4.5. Facial Weakness visit

If participants perceive any facial weakness in between scheduled visits, they will be able to contact their local team to arrange an ad hoc visit. During this visit they will be clinically reviewed either face-to-face or by videoconference using the House-Brackmann regional and global scores (Reitzen et al., 2009). They will also be asked to complete the FaCE scale to capture any effects of the weakness on their everyday lives (Kahn et al., 2001).

7.4.6. Research assessments using self-report symptom-based questionnaires

The questionnaire administration schedule is detailed in the schedule of events (section 7.4.10, 'research assessments' in table). Administration will be electronic with links sent to participants via Sealed Envelope. Paper based questionnaires will be available for any participants with computer ability/access issues or for people who haven't completed by the time of their follow-up visit. Postage paid envelopes will be provided for return of questionnaires for those who lack computer access or competence. A verbal data completion option by telephone will also be possible if required.

7.4.6.1. Patient health questionnaire-4 (PHQ-4)

The PHQ-4 is a validated 4-item self-report instrument used to screen for psychosocial distress. It contains two items on depression and two on anxiety and is in widespread use in both primary and secondary care in the NHS. The instrument's minimum additive score is 0 and maximum is 12. Scores ≥9 indicate a substantial level of psychosocial distress and will be highlighted to both the patient and their GP for further investigation and management as appropriate alongside continuing in the trial unless there are concerns over patient safety (Kroenke et al., 2009).

7.4.6.2. Characteristic pain intensity (CPI) and Graded Chronic Pain Scale

The CPI is a validated three-item self-report instrument derived from the Graded Chronic Pain Scale examining current, average and worst pain intensity on a numerical rating scale of 0 (no pain) to 10 (worst pain imaginable) in the last three months. The instrument's total minimum score is 0 and maximum is 100 which are derived by taking the mean of the three responses and multiplying by 10.

The Graded Chronic Pain Scale will be used in full at screening and consists of 7 items. Three of the items are the CPI and the remaining four are related to disability experienced because of the persisting pain. Three of the disability items use the same numerical rating scale as the CPI and the other uses a four-choice categorical response. The GCPS produces five ordinal outcomes via an algorithm: I (lowest pain-related disability), IIa, IIb, III, IV (highest pain related disability).

7.4.6.3. Oral Health Impact profile for TMD (OHIP-TMDs)

This is a validated 22-item self-report instrument examining disorder specific quality of life in TMD. The instrument's minimum additive score is 0 and its maximum is 88 with higher scores equating to worse disorder specific quality of life. Its minimum clinically important difference has been determined as 6.0 (Yule et al., 2015).

7.4.6.4. EQ-5D-5L

This is a validated 5-item self-report instrument examining generic quality of life from which health utilities can be derived. The minimum health utility is -0.59 (a state worse than death), rising to 0 (death) and a maximum utility of 1.0 (state of perfect health).

7.4.6.5. Brief Pittsburgh Sleep Quality Index (BPSQI)

This is a validated 6-item self-report measure examining five features of sleep: quality, latency, duration, efficiency, and disturbance. Item scores are calculated using a mixture of algorithms and addition but can be summed to give a total minimum score of 0 and a maximum score of 15 with higher scores indicating more problems with sleep. A threshold of >5 has been determined as the threshold for poor sleep (Sancho-Domingo et al., 2021).

7.4.6.6. Short-form jaw functional limitation scale (SF-JFLS)

This is a validated 8-item self-report instrument examining functional limitation in TMD. The instrument's total minimum score is 0 and maximum is 10 which are derived by taking the mean of the eight responses. Higher scores indicate increased functional limitation (Ohrbach et al., 2008).

7.4.6.7. Global impression of change (GIC)

The validated Patient Global Impression of Change scale (Dworkin et al., 2005; Guy, 1976) asks the patient to compare a construct following treatment to prior to treatment and employs a seven-point response scale (scoring in parentheses): very much improved (3) through no change (0) to very much worse (-3). The constructs examined through four items will be: pain intensity; ability to conduct daily

activities; emotional state; overall status. Patients will be asked to select a level of change from the seven-point scale in response to the prompt, "*Since the start of the study my [insert construct] is*".

7.4.6.8. Liverpool adverse events profile (LAEP)

This is a validated instrument examining the frequency of 25 adverse events whilst taking medications over the last month (Baker, 1993; Baker et al., 1994; Baker, 1994; Baker, 1995; Jasionis et al., 2021; Romoli et al., 2018). It does not ascribe causality and is simply a measure of frequency and quantity of adverse outcomes whilst taking medication(s) (Dang et al., 2021). Its minimum additive score is 25 and its maximum is 100 with higher scores equating to more adverse outcomes experienced at a greater frequency. A threshold value in an Italian population has been established of 36.5 which is predictive of likelihood of terminating use of anti-epileptic medication (Romoli et al., 2018).

7.4.6.9. The Migraine Disability Assessment Test (MIDAS)

This is a validated instrument with five items that examine the impact of headache-related disability on three domains over the last 3 months: school, work or paid (self-) employment; household work or chores; and family, social and leisure activities. It employs an open, but guided, response option for respondents to estimate the number of days (0-90) affected by headache in each of the five items. Scores are calculated by summing the response to each item. Higher scores indicate higher levels of headache-related disability with severe disability (IV) defined >20, moderate (III) defined as 11-20, mild (II) defined as 6-10, and little to no disability (I) defined as 0-5. Its minimum additive score is 0 and its maximum is 450 (Stewart et al 2000). Its minimally important clinical difference has been determined as a change in ≥5 total score (Lipton et al 2017, 2019, 2020).

7.4.6.10. Facial Clinimetric Evaluation (FaCE) scale

This is a validated 15-item instrument examining 6 domains related to facial nerve paralysis: facial movement, facial comfort, oral function, eye comfort, lacrimal control, social function (Kahn et al., 2001). It employs a five-point response scale: strongly agree (1) through don't know (3) to strongly disagree (5). Its total score ranges from 0 (most affected) to 100 (not affected) and is calculated by an algorithm. The scale will only be used if patients opt into its use due to their perception of a facial weakness after an injectable therapy has been applied.

7.4.6.11. Health Utilisation Questionnaire (HUQ)

This is a validated instrument examining two areas (Breckons et al., 2018; Durham et al., 2016b; Durham et al., 2021; Wordsworth and Thompson, 2001): 1) healthcare utilisation in past 3-6 months including visits to clinicians, out-of-pocket expenditure on over-the-counter medication, prescription costs, NHS and private healthcare treatment; 2) productivity in the last 3-6 months including employment status, number of days contracted, number of days absent and present with pain at work, the quantity and quality of work completed (Brouwer et al., 1999) and the work attendance with health problems scale (van Roijen et al., 1996). A reference period of 3 months will be used at Screening (visit 1) and at 12 weeks (visit 3). A reference period of 6 months will be used at 36 weeks (visit 4).

7.4.6.12. Time and travel questionnaire (T&T)

This validated instrument collects data on all healthcare visits (Breckons et al., 2018; Durham et al., 2016b; Durham et al., 2021; Wordsworth and Thompson, 2001): the distance, duration, and usual mode of transport, in addition to any childcare or accompanying person required and any activities foregone for the visit.

7.4.7. Pain reporting assessment & feedback

All participants will undergo an assessment of their pain reporting and be given feedback on this at visit 1 (screening) and visit 3 (week 12), based on methods reported by Treister *et al* (2018) which have been shown to diminish the placebo response in pharmacological trials (Treister et al., 2018). Pain threshold (lowest stimulus intensity that is perceived as painful, corresponding to 1 on a 0–10 numerical rating scale [NRS]) and pain tolerance (maximal tolerable stimulus intensity, corresponding to 10 on a 0–10 NRS) will be measured at the thumbnail of the dominant hand using an algometer (FPN 100; Wagner Instruments, USA). The measurement can still be taken if the participant has false / acrylic nails, and the wearing of false / acrylic nails will be recorded in the database. Three stimulus levels (threshold, 75% of tolerance, and a stimulus equidistant to the prior two) will each be applied for 3 seconds, each on four occasions in a random order with a 20-second interstimulus period. Participants will rate each stimulus immediately following application on a 0–10 NRS. Feedback will be given to participants after the first six stimuli, and again after all 12 stimuli, on how accurately their reported pain scores reflect the applied stimulus intensities by plotting responses on a scatter chart to identify outliers and by calculating R^2.

7.4.8. MRI sub-study assessments

Each of the 51 participants recruited into the MRI sub-study (17 from each arm of the study in the North East of England) will undergo two MRI scans of their temporomandibular joints, and temporalis and masseter muscles. The first scan will take place between trial visit 1 and visit 2 (day -28 to -1) and must be prior to commencement of trial intervention, where possible. The second MRI visit will occur within +/- 7 days of the week 36 visit. MRI scans will take place at the Centre for In Vivo Imaging, Newcastle University. Each MRI scan will take approximately 1 hour. If for any reason an MRI scan is of insufficient quality for research assessments, if appropriate, a repeat scan may be arranged with the participant's consent.

Any incidental findings during the MRI procedure will be identified by the radiologist reviewing the scan, who will report to the Newcastle clinical team, who will contact the patient to discuss the finding and inform the local site team and GP/Dentist/Consultant as appropriate. Further monitoring, investigation, or treatment, as appropriate, would then be conducted in the usual NHS care pathways for the finding identified. If the finding clearly and unambiguously nullifies the M-TMD diagnosis or meets another exclusion criteria, the patient would be withdrawn from the trial and informed of this whilst discussing the finding with the clinical team. Otherwise, as long as the patient was happy to continue in the trial, this would be possible.

A venous blood sample totalling approximately 4 – 6 mL in an EDTA tube will be taken at each of the two MRI visits. Each sample will be used to measure serum biomarkers of bone turnover CTX and P1NP at screening and at 36 weeks. Samples will be labelled in accordance with the Sponsor's usual requirements and will be transported, stored, accessed, and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act. Once blood samples have been analysed, they will be disposed of in accordance with local site protocols. Analysis will take place in the Sponsor's clinical laboratories (Newcastle Laboratories) or via Newcastle Laboratories as part of a service level agreement with an external laboratory in compliance with the UK Data Protection Act 2018, the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, and the 2004 Human Tissue Act. If it is not possible to perform analysis on the blood sample for any reason (e.g., degraded sample, insufficient sample), if appropriate, a repeat sample will be obtained with the participant's consent.

7.4.9. Qualitative evaluation

A qualitative evaluation will explore barriers and facilitators to study participation and trial progress with those sampled at the screening visit. Thereafter an embedded piece of longitudinal qualitative research will explore participants' perspectives of the treatment received.

Participants will be recruited from all treatment arms, including those who withdraw or choose not to participate despite meeting eligibility criteria (apart from agreeing to consent to the trial). Up to 30 participants will be recruited for semi-structured interviews across all sites in the pilot. Up to 20 of these participants will then go on to have sequential interviews at 12 and 24 or 36 weeks to explore treatment experiences. Interviews will be conducted by a trained interviewer from the research team over Zoom; however, a contingency will be available for participants who may not have access to Zoom to ensure a diverse range of participants will be included. This may include either Microsoft Teams, a telephone or face-to-face interview. Live interpretation will be possible for non-English speakers. Recruitment will be via purposive, maximum variation sampling stratified by age band, sex, decile of index of multiple deprivation and ethnic group to ensure a diverse range of participants are included. A summary table of pseudonymised characteristics from the research database will be provided by NCTU to the qualitative team for the purpose of sample selection for the qualitative research.

Recruitment and analysis will follow the principles of the constant comparative method (Glaser, 1965), occurring concurrently until data saturation is achieved. Interviews will be informed by interview topic guides, which will be collaboratively constructed with PPIE input, and reviewed and refined as data collection and analysis progresses.

7.4.10. Schedule of Events

		Day -28 to -1[a] (Visit 1)	**Day 0 (Visit 2)**	**Week 12 (Visit 3)** **+/- 7 days**	**Week 24 (Visit 4)** **+/- 7 days**	**Week 36 (Visit 5) [c]** **+/- 7 days**	**Week 37 (+3 days)**	**Unscheduled Visit - Facial Weakness, medication concern, or other**
Activity	Identification potential participants	Face-to-face screening	1st dose of IMP [a]	Research Assessment IMP review and/ or provision[b]	Research Assessment IMP review and/ or provision[b]	Research Assessment	Phone call	Research Assessment (**As/If required**)
	Potential participant identification							
Clinical team providing care review clinical notes or databases	x							
Self-referring individual self-screens and makes email contact[1]	x							
Provide PIS +/- invitation letter/email as appropriate	x							
	Consent & eligibility							
Informed Consent		x		x[d]	x[d]	x[d]		
Dipstick pregnancy Test		x				x[e]		
Confirmation of eligibility		x						
	Routine Data Collection[2]							
Sociodemographics		x						
PMH (systems, meds, allergies, daily analgesia use, non-drug therapies)		x						
Medical review (systems, con meds, allergies, daily analgesia use, non-drug therapies)				x	x	x		
Clinical examination inc CN V & VII		x		x	x	x		
Blood pressure, Pulse, Weight, & Height. Height only at day screening		x		x	x	x		
Diagnosis & TMD history		x						
ID-Migraine +/- Migraine history & MIDAS[2]		x		x[f]	x[f]	x[f]		
	Research assessments (occur prior to randomisation and re-administration or review of IMP)							
Pain reporting assessment & feedback		x		x				

		Day -28 to -1[a] (Visit 1)	**Day 0 (Visit 2)**	**Week 12 (Visit 3) +/- 7 days**	**Week 24 (Visit 4) +/- 7 days**	**Week 36 (Visit 5) [c] +/- 7 days**	**Week 37 (+3 days)**	**Unscheduled Visit - Facial Weakness, medication concern, or other**
Activity	Identification potential participants	Face-to-face screening	1st dose of IMP [a]	Research Assessment IMP review and/ or provision[b]	Research Assessment IMP review and/ or provision[b]	Research Assessment	Phone call	Research Assessment (**As/If required**)
PHQ-4 & red flag assessment		x		x	x	x		
GCPS		x						
CPI (within GCPS[3])		x		x	x	x		
OHIP-TMDs		x		x	x	x		
EQ-5D-5L		x		x	x	x		
BPSQI		x		x	x	x		
SF-JFLS		x		x	x	x		
GIC				x	x	x		
LAEP				x	x	x		
FaCE scale and facial weakness exam				Optional, as determined by patient				x
AE & SAE Reporting		x	x	x	x	x	x[g]	x
HUQ		x		x		x		
T&TQ					x			
MRI sub-study assessments: MRI & bone biomarkers[4]		x (prior to IMP – TAU IMP may be started prior to MRI if it is not possible to delay)				x		
Qualitative interviews purposive subsample		x[h] (inc declines)		x	Either 24 or 36 weeks not both			
	Randomisation							
Randomisation – **after** all questionnaires & main study research assessments		x						
	Treatment							
Dosage schedule (dose and tapers) prescribed or reviewed for TAU arm		X[i]	X[i]	x	x	x[j]		
Botox injections (Botox arm only)			x	x	x			
Lidocaine injections (Lidocaine arm only)			x	x	x			

		Day -28 to -1[a] (Visit 1)	Day 0 (Visit 2)	Week 12 (Visit 3) +/- 7 days	Week 24 (Visit 4) +/- 7 days	Week 36 (Visit 5) [c] +/- 7 days	Week 37 (+3 days)	Unscheduled Visit - Facial Weakness, medication concern, or other
Activity	Identification potential participants	Face-to-face screening	1st dose of IMP [a]	Research Assessment IMP review and/ or provision[b]	Research Assessment IMP review and/ or provision[b]	Research Assessment	Phone call	Research Assessment (**As/If required**)

[1] Self-screens by checking self-assessment questions on duration and M-TMD (section 7.1.3) on the advert, and then emails clinical study team who send PIS and invitation letter requesting a telephone call. Telephone call to explain study and confirm demographics and TMD status including treatment. Individual then enters study as normal via screening visit at site local to them with GP and GDP informed if screens as eligible and gives consent to participate.
[2] If ID-Migraine positive then migraine history and MIDAS are completed and updated at that visit and at each subsequent visit, but ID-Migraine is not.
[3] CPI forms part of Graded Chronic Pain scale which will be completed at screening in full, following this CPI will be completed on its own at all other visits
[4] Only for subsample in North-East England (section 7.4.7)

[a] Ideally IMP should be provided within 14 days of the screening (either prescription received or injectable delivered), but this can be up to 28 days from screening. If >28 days, it should be recorded as a protocol deviation. IMP administration may also occur on the same date as screening following randomisation if the participant and investigator wish to start then.
[b] All research assessments will be collected up to 7 days ahead of any IMP administration at these visits and prior to administration of any further IMP. New local prescriptions will be issued by the GP following instruction from the site teams at weeks 12 and week 24, or by sites for their pharmacy at 12 weeks and at 24 weeks for the patient to collect in the TAU arm.
[c] All research assessments will be collected up to 7 days ahead of any IMP administration at these visits and the CRF updated at the visit.
[d] Confirmed in writing in the clinical notes at each study visit.
[e] Pregnancy test required at 36 weeks for all participants of childbearing potential or 7 days after this point if participants are still on TAU week 36[e]
[f] Migraine history and MIDAS only repeated if positive at any of the previous visits. If reporting a new headache then ID-Migraine, migraine history and MIDAS are completed at that visit and the migraine history and MIDAS are repeated at subsequent visits.
[g] Phone call to collect AE data in 7 days since week 36 visit. Only required if participant still receiving TAU IMP at week 36 or stopped IMP after week 35.
[h] Qualitative interview will ideally take place during screening but may be up to 4 weeks after consent to the interview. This may be after the start of the IMP in some cases.
[i] TAU prescription may be issued at any point during screening or at Day 0 as appropriate. Day 0 is the first dose of IMP.
[j] Review of medication only at week 36

IMPORTANT: If participants who discontinue trial treatment plan to begin a new therapy for TMD (NHS or private) within the remainder of the trial monitoring period, they should be asked if they will complete the next set of research assessments prior to beginning a new treatment in routine clinical care and then go back on schedule to the next scheduled set of research assessments following this.

Key

AE & SAE - Adverse Event & Serious Adverse Event
BPSQI - Brief Pittsburgh Sleep Quality Index
CN V & VII - 5th Cranial Nerve and 7th Cranial Nerve
CPI (within GCPS) - Characteristic Pain Intensity (Graded Chronic Pain Scale)
EQ-5D-5L - See section 7.4.6.4
FaCE - Facial Clinimetric Evaluation
GIC - Global impression of change
HUQ – Health Utilisation Questionnaire
MIDAS – Migraine Disability Assessment Test
LAEP - Liverpool adverse events profile
OHIP-TMDs - Oral Health Impact profile for TMD
PHQ-4 - Patient Health Questionnaire-4
PMH – Past Medical History
SF-JFLS - Short-form jaw functional limitation scale
T&TQ – Time and travel questionnaire

7.5. Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason along with the withdrawal itself within both the CRF/CDMS, on a trial withdrawal form and participant's clinical notes in order ensure that information relevant to the trial design, medication tolerability and efficacy is collected where possible.

Please note there is **no requirement** to withdraw from the trial due to participants electing to discontinue trial treatment or investigator-led treatment discontinuation, please see section 7.6. Participants who discontinue trial treatment can continue to complete all remaining assessments at distance, however, if this is not possible all efforts should be made to ensure that the research assessments at 36 weeks are completed as a minimum.

If participants who discontinue trial treatment plan to begin a new therapy for TMD (NHS or private) within the remainder of the trial monitoring period, they should be asked if they will complete the next set of research assessments prior to beginning a new treatment in routine clinical care and then go back on schedule to the next scheduled set of research assessments following this.

The PI, CI, or other delegated individual may withdraw a participant from the trial at any time if they consider it necessary for any reason including (but not limited to) the following reasons:

- Loss of capacity
- Pregnancy
- Symptomatic deterioration
- Unacceptable toxicity
- Sustained and significant issues with tolerance of any of the IMPs used
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw them. As examples this might include, but is not limited to, the following situations: continued participation in the trial would place unreasonable demands on the participant's physical or psychological health; participant loses capacity for a prolonged period; participant experiences an adverse event, which in the opinion of the investigator results in the inability to continue to comply with the trial. The participant would be informed of the decision and return to their routine care pathway in the NHS.
- Notification of an adverse event using the IMP in another trial; or with any of the interventions in routine clinical practice, which in the interpretation of the investigators, may potentially put trial participants at risk.
- Termination of the clinical trial by the sponsor

The PI or their delegate will record the withdrawal status and reason on the CRF.

If a trial participant withdraws/is withdrawn from the trial, all data collected to the point of withdrawal will be retained and included in analysis. This point is included in the consent for the trial.

Those who withdraw/are withdrawn from the trial will return to having their M-TMD managed by their referring/treating clinician as per routine care in the NHS. For those on medications in the TAU arm a suitable taper off schedule will be suggested to the patient's GP within the letter explaining they have withdrawn.

7.6. Discontinuation of trial treatment

Participants may elect (or investigators may elect for participants) to stop receiving any of the IMPs and remain on the trial. Participants will continue to take part in trial assessments as per the schedule of events except for the MRI sub-study if they are enrolled in this. After discontinuation, if they elect to begin a new therapy for TMD within routine clinical care (NHS or private), they will be asked to complete the next set of research assessments that are due prior to beginning the new treatment and then go back to the regular schedule following this and the new treatment details recorded in their clinical notes and CRF.

Discontinuation of treatment along with a reason, if possible, will be recorded in the clinical notes and the CRF. A discontinuation from treatment form will also be completed and stored in the ISF.

7.7. Storage and Analysis of Samples

Samples will be labelled in accordance with the Sponsor's usual requirements and relevant legislation (e.g., GDPR) and will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and 2006 Human Tissue (Scotland) Act. Once blood samples have been analysed for bone biomarkers they will be securely and appropriately disposed of in accordance with local site protocols. Once blood samples have been analysed, they will be disposed of in accordance with local site protocols. Analysis will take place in the Sponsor's clinical laboratories (Newcastle Laboratories) or via Newcastle Laboratories as part of a service level agreement with an external laboratory in compliance with the UK Data Protection Act 2018, the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, and the 2004 Human Tissue Act.

7.8. End of Trial

The end of the trial is defined as the last 36-week follow-up visit (or the last follow up safety phone call) of the last participant to reach this point, or the date of the last data gathered from questionnaires, blood samples or MRI analysis, whichever is the later. The sponsor, CI, and TSC have the right to terminate the trial at any point for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, Research Ethics Committee (REC), Human Regulatory Authority (HRA) and NHS R&D Office(s) within 90 days, or 15 days if the study is terminated prematurely. It is the CI's responsibility to ensure that any appropriate follow-up is arranged for all participants; this will be delegated to the site PIs.

A final report will be provided to the Sponsor, REC, MHRA and Funder within their specified time frames. A lay summary will be made available to all participants via the trial's varying media.

Subject to further successful funding a substantial amendment may be submitted to HRA, Ethics, R&D and MHRA to cover longer term follow of participants beyond the stated end point above.

7.9. Post-trial care

At 36 weeks participants will return to routine NHS standard clinical care with the referrer/treating clinician. If the patient wishes to continue TAU, this can occur at the discretion of the referrer/treating clinician but suggested taper off regimens will also be provided for these clinicians.

Continuation of any injectable therapy will be reliant on the local NHS formulary funding arrangements for these interventions and may not be possible following completion of the trial until any positive outcomes from the trial that support changes in local formularies take effect which may be some time. This is pre-specified in the consent and PIS for the study. No provision for continuation of trial medication will be made by the trial team or Sponsor.

8. TRIAL MEDICATION

8.1. Name and Description of IMPs

Four IMPs are used within three arms in this trial: oral amitriptyline hydrochloride, oral gabapentin, lidocaine hydrochloride injection B.P. 2%, Botulinum toxin type A injections. Amitriptyline and gabapentin are within the same arm as 'treatment as usual' (TAU). The other two injectable IMPs form individual and separate arms. Participants will be randomised using three stratification variables (7.1.5) 1:1:1 to one of the three arms: TAU, Botulinum toxin type A injections, or Lidocaine 2% injections.

Amitriptyline 10mg and 25mg tablets (any brand) for oral administration will be used.

Gabapentin 100mg, 300mg, and 400mg capsules (any brand, unless lactose is flagged as a problem to the patient in which case a lactose free capsule will be selected using NHS SPS preferred method through the EMC database to exclude Lactose as an excipient) for oral administration will be used.

Botulinum toxin A will be provided as a 100 Allergan unit vial of Botox™ (AbbVie Ltd, Maidenhead, UK) for reconstitution with 0.9% Normal saline and injection intramuscularly.

Lidocaine 2% solution (any brand) will be provided as a 2ml ampoule for injection intramuscularly.

The following SmPCs will be used for the trial:

Medication	SmPC
Gabapentin	Neurontin 100mg Hard Capsules
Amitriptyline	Amitriptyline 10mg Film-Coated Tablets
Lidocaine 2%	Lidocaine Hydrochloride Injection BP 2% w/v
Botox	BOTOX 100 Allergan Units Powder for solution for injection

Serious adverse reactions (SARs) that are thought to have a causal relationship with the IMP must be assessed for expectedness against the current, approved version of the RSI. Market authorisation holders may update the SmPC over the trial's duration. The CI/Sponsor/NCTU will monitor and review any changes to SmPCs, considering the impact on the trial and then revise any relevant documentation as required.

8.2. Drug Storage and Supply

All IMPs will be sourced by each individual site's local pharmacy via standard NHS routes and kept in accordance with UK legislation, local protocols, and the products' Summary of Product Characteristics (SmPC).

Amitriptyline (any brand) requires no special storage conditions.

Gabapentin (any brand) needs to be stored at <25 degrees Celsius and as a Schedule 3 controlled drug (CD no Register Exempt Safe Custody) in the UK, it must comply with current UK controlled drugs regulations.

Botox should be stored at 2-8 degrees Celsius in a refrigerator prior to constitution. Any Botox that has not been reconstituted and is surplus to requirements should be disposed of in line with local trust policies/protocols. Any reconstituted Botox that is left over after patient administration should be disposed of in line with local trust policies/protocols.

Lidocaine 2% needs to be stored away from light at <25 degrees Celsius. Any residual lidocaine should be disposed of in line with local trust clinical policies/protocols.

Returned and unused injectable IMP will be disposed of at site in accordance with local trust requirements. Vials or similar containment vessels for the injectable IMPs, including packaging, will not be returned to pharmacy. Records of IMP disposal must be kept in line with GCP requirements.

8.3. Preparation and Labelling of IMPs

The use of the four IMPs is routine within clinical practice for TMD and therefore pose no greater risk than routine clinical care. The IMPs in use are licensed, marketed products with one (Botox) requiring reconstitution. There is therefore no requirement for accountability, segregated storage, temperature monitoring or labelling compliant with annex 13 for this trial. All IMPs will be provided in the standard approved manufacturer's packing with their labelling and patient information leaflets. For oral amitriptyline and gabapentin as prescribed medications for self-administration the pharmacy applied label will comply with current UK regulations.

8.4. Dosage Schedule & Modifications

This is a pragmatic trial in respect of the use of the oral medications in the TAU arm. Broad guidance is given but clinicians can follow their routine clinical practice subject to ceiling and safety thresholds. It is therefore important that dosages and tapering regimen are fully documented in the eCRF.

Trial investigators must therefore pay careful attention to the relevant SmPCs for guidance regarding posology, contraindications, special warnings and precautions for use, interactions, fertility, pregnancy and lactation, and effects on ability to drive and operate machinery for use of each of the

four IMPs which includes appropriate dose reductions as appropriate due to age or renal function. SmPCs will be provided to each site prior to the site commencing recruitment and the relevant sections are 4.2-4.7.

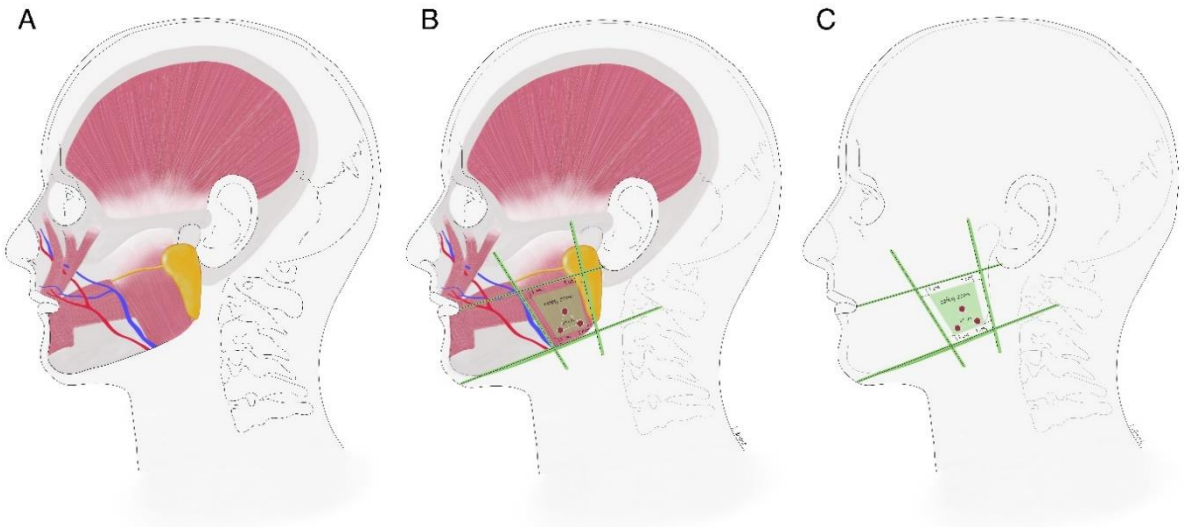
In TAU amitriptyline is recommended as first-line if not trialled previously unless the participant is epileptic, or ≥60 years of age, or is on another serotonergic agent for example SNRI, SSRI, Triptan. In the first two incidences (epilepsy diagnosis or age), due to amitriptyline's adverse effect profile further discussion will occur with patient over which drug, they would prefer to trial in the TAU arm (amitriptyline or gabapentin). Those patients meeting an exclusion criterion for amitriptyline (see exclusion criteria 19-24 which includes use of other serotonergic agents) will be offered gabapentin instead. Amitriptyline and gabapentin dosing titration and regimen are determined by clinician's usual practice but should lie within or below/slower than NICE's stated parameters (NICE, 2021):

- Starting doses: 10mg amitriptyline once daily in the evening; either 100mg or 300mg of gabapentin once daily, then twice daily on day 2, and then three times daily on day 3.
- Titration interval: quickest allowed for gabapentin and amitriptyline is 1 week and slowest is 4 weeks.
- Titration increments: 10mg increments of amitriptyline. 100-300mg increments for gabapentin which could be applied to all the three times daily regimen or one- or two of the three-times daily intakes.
- Ceiling doses: 75mg amitriptyline, 3600mg gabapentin
- Duration of therapy: trial amitriptyline or gabapentin for at least 8-12 weeks with a minimum of 2 weeks at the most effective or tolerable dose
- Issues of tolerability will be discussed with the patient and recorded in the CRF with a possible step back to the previous dose to see if a longer duration at this dose is either more effective or allows upward titration due to accommodation of any adverse effects.
- Discontinuation: unless an emergency the *quickest* allowed discontinuation would be spread over 4 weeks or slower for amitriptyline and gabapentin in similar increments or smaller than upwards titration dose steps. Much slower tapering off over a number of months of either drug is permissible and often required/desirable.

The same standardised sites and doses for the injectable IMPs will be used for both injectable IMPs and all patients. These are based on data suggesting they are the sites with the widest safety margins for adverse effects from the injectable IMPs (Hu et al., 2010; Lee et al., 2017; Peng and Peng, 2018). Bilateral masseter and temporalis will be injected for all patients.

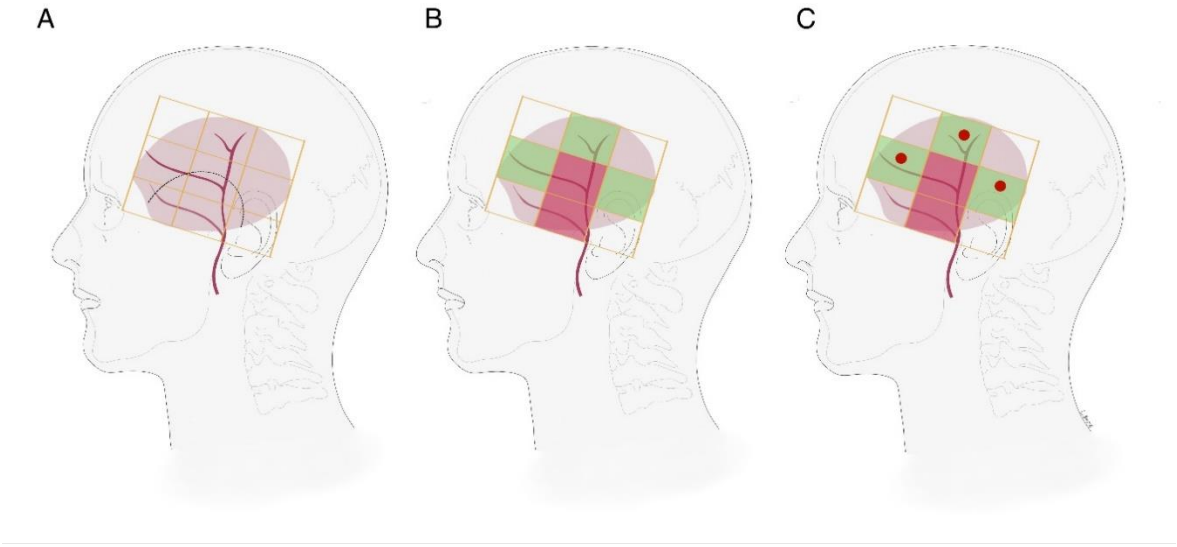
The sites for injection are detailed in figures 1 and 2. All injections should be provided bilaterally using a 27-30 gauge 12.7-13mm detachable needle with a graduated 1.0ml syringe following skin cleaning in accordance with local aseptic non touch technique policy. The needle ideally can be replaced after one side has been injected. Figure 3 demonstrates the injection sites without penetration of skin in a volunteer.

Figure 1 Masseter – a) Anatomical structures; b) Positioning of injection sites with anatomy; c) Positioning of injection sites without anatomy



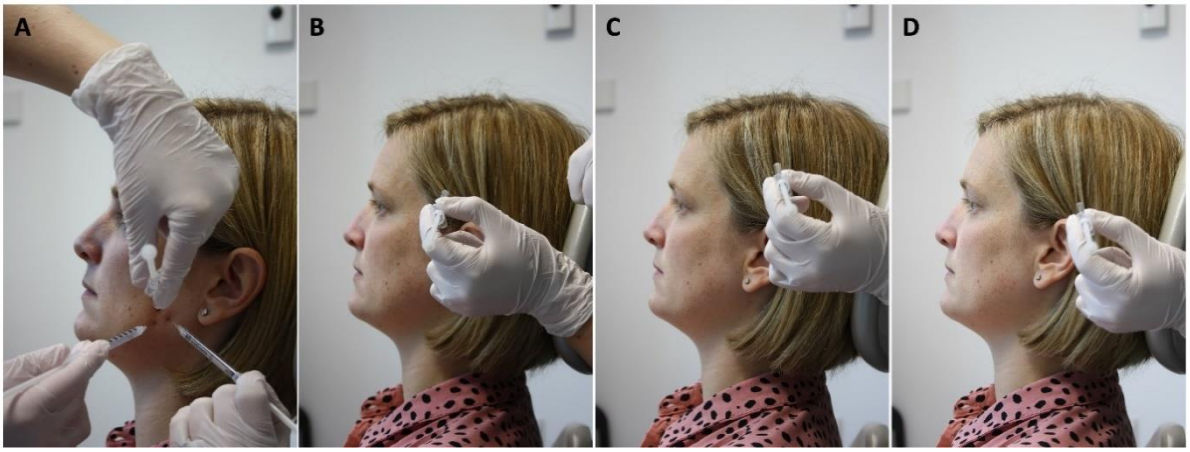
a) Safest zones in masseter are estimated using four anatomical lines – superior line, ear lobe to commissure; inferior line, mandibular angle to chin along inferior border of mandible; anterior line, anterior border of masseter; posterior line, posterior border of masseter. These four lines create a parallelogram. The boundaries of the safe zone within the parallelogram lie 1cm from each of the lines (area of darker blue shading). They therefore stay away from the facial artery and vein and parotid gland as well as the major branches of the facial nerve
b) The three injection sites are indicated (red dots) and should be a minimum of 1cm apart and at least 1cm from the edges of the parallelogram. The inferior two sites should be injected by angling the needle tip away from the facial artery/vein and parotid at the anterior and posterior boundaries respectively and the needle should contact bone before withdrawing ~2-3mm and aspirating before administering the Botox or 2% Lidocaine. The superior site may not touch bone but if at ~12mm depth with a negative aspiration the Botox or 2% Lidocaine can be administered.
Image redrawn from (Peng and Peng, 2018)

Figure 2 Temporalis – a) Anatomical structures and identifying zones; b) Safest zones for injection; c) Positioning of injection sites



a) Dotted curved line indicates the most superior extension of temporalis tendon; vessels are superficial temporal artery and vein. Four anatomical lines and grid in yellow are created for safest zones for injection described under (b)
b) Safest zones in temporalis (green shaded boxes) are estimated using four anatomical lines (in yellow) – superior line parallel to most superiorly palpable part of Temporalis; inferior line runs along tragal canthal line; anterior line is the posterior border of the zygomatic-frontal process; posterior line runs parallel to most posterior part of the convexity of the pinna. These four lines then create a square which is divided into an equally spaced 3x3 grid (in yellow) with the three safest zones within this grid for deposition of Botox or 2% Lidocaine demonstrated in green whereas the higher risk zones are demonstrated in red.
c) The three injection sites are indicated (red dots) and should be a minimum of 1cm apart. All sites should ideally be ***within the hair*** *(unless bald) to avoid visible anterior temporal fossa atrophy and inadvertently weakening frontalis and causing brow changes. Bone should be contacted in all sites before withdrawing ~2-5mm and aspirating before administering the Botox or 2% Lidocaine.*
Image adapted and redrawn from (Lee et al., 2017)

Figure 3 Injection sites on a volunteer: a) all three sites simultaneously demonstrated within safest zones of masseter (would be injected individually); b-d) three sites demonstrated individually (anterior to posterior [left to right]) within safest zones of temporalis on a volunteer.



100 units of Botox should be reconstituted with 2mls of 0.9% normal saline once the participant attends and confirms is going ahead with treatment. The vial's diaphragm should be wiped prior to reconstitution with a cleaning wipe. Brand of cleaning wipe will be determined by local aseptic non touch technique policy. Dosages per injection site are then:

- Masseter 10 units (0.2mls) per injection site = total 30 units per muscle
- Temporalis 5 units (0.1mls) per injection site = total 15 units per muscle
- Total dose per patient = 90 units. Maximum ceiling dose 100 units.

2mls of 2% Lidocaine will be used in same sites and volumes as for Botox. Volumes of Lidocaine per injection site are then:

- Masseter 0.2mls (4mg) per injection site = total 0.6ml per muscle
- Temporalis 0.1mls (2mg) per injection site = total 0.3ml per muscle
- Total dose per patient = 36mg. Maximum ceiling dose 40mg.

The cycles of injections provided will follow the schedule of events in section 7.4.10: day 0; week 12 +/- 7 days; week 24 +/- 7 days.

Doses selected for the injectable IMPs are based on the best quality evidence currently available for BTX and local anaesthetic injection therapy in M-TMD balancing risk of adverse effects against effectiveness (Al-Moraissi et al., 2020; Chan et al., 2016; De la Torre Canales et al., 2020; Machado et al., 2018; Nouged et al., 2019). The doses chosen provide the maximum chance of effectiveness and lowest chance of adverse effects, with the ceiling doses positioned well within the safety margin for the drug (≤25% of the total possible dose in one administration) and at the lowest end of the range of doses given to these muscles (Thambar et al., 2020). The BTX dosing scheduling is contemporary with current practice in the UK (Anwar et al., 2022) and consistent with the NICE recommendations for injectable (intramuscular) treatment of another trigeminally mediated pain (chronic migraine) which completes after the third cycle if no therapeutic effect is felt by the patient (Bendtsen et al., 2018; NICE, 2012). The Lidocaine dosing schedule is within the parameters within the published literature at the conservative end of repeated injections and mirrors the BTX scheduling given Lidocaine is an active comparator within the trial (Al-Moraissi et al., 2020; De la Torre Canales et al., 2020; Nouged et al., 2019).

Please note participants can elect to stop receiving any of the IMPs and can continue within the trial (details in section 7.6).

8.5. Known Drug Reactions and Interactions

The Summary of Product Characteristics (SmPC) for the four trial IMPs will be referenced for the safety information for sites in this trial. Specifically, the investigators should be aware of the following potential interactions:

Amitriptyline is contraindicated with monoamine oxidase inhibitors (exclusion criteria) and severe interactions have been observed with sympathomimetic agents, bupropion, cinacalcet, clozapine, dronedarone, fluoxetine, lithium, ozanimod, paroxetine and terbinafine.

Gabapentin requires caution around co-prescription with any other medication known to exert respiratory depression or CNS depression and if being prescribed in older adults, and any patient who may have compromised respiratory, renal, or neurological function (MHRA 2017)

Participants receiving lidocaine should be clinically observed as per usual practice.

No interactions of clinical significance have been noted for gabapentin or Botox.

8.6. Concomitant Medications

Simple analgesia (Ibuprofen, Aspirin, Paracetamol, co-codamol) are permitted and will be recorded via the database at screening (Visit 1) and throughout the trial. Use of prescribed opiates for a non TMD event should be reported in the database and a risk assessment considered if the participants are receiving Treatment As Usual, to determine if there are any risks associated with contraindicated medications. All repeat medications will also be recorded in the clinical notes and database.

8.7. Assessment of Compliance

Participants' compliance on the TAU (oral medication) arm will be assessed by the trial team at each research assessment through verbal enquiry as part of the e-CRF: used medication (y/n and why not if no); used as per dosing regimen (y/n and why not and at what regimen if no). Following prescription of trial medication, the participant will be contacted via an ePRO form or telephone to check they have commenced taking the medication and the date it started.

As the oral IMPs represent no higher risk than the standard of care participants will return their unused oral trial medication to their local pharmacy for disposal unless they are discussing with their GP continuation of the medication. At visit 5 (week 36) participants will be asked if they used all the trial medication and at what dosing regimen and why they took this/these decision(s).

Injectable IMP packaging will not be returned to the pharmacy, but unused injectable IMP will be returned, if appropriate, or disposed of locally in line with local Trust procedures. Clinicians will document the administration of the injection in the participant's clinical record.

Compliance in the TAU arm of the trial is potentially difficult to assess, as participants may take varying amounts of medication to treat their condition. Despite this variation they may still be considered compliant for trial purposes as the variation may be the best method, they have identified to relieve symptom burden whilst managing any adverse effect profile. To provide an objective decision on compliance for the trial for participants in the TAU arm, an assessment of compliance will be made following the completion of the week 36 visit for each participant. The IMP data collected across the 36 weeks will be looked at independently by three clinicians, each with a special interest in the field of facial pain, who will each record their assessment on whether each participant in the TAU arm has been compliant with their prescribed treatment based on their CPI data and responses to the e-CRF data points on use of medication. Each clinician will independently report their findings, and if there are any inconsistencies between the findings for individual participants, the clinicians will discuss these and come to a consensus. Participants who are not considered to have been compliant with their treatment will be identified to the statistics team for analysis purposes.

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences. * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

9.1.1. Assessment of severity of AEs

The PI, or delegated clinician, should make an assessment of severity for each AE according to the following criteria:

Grade 1: Minor adverse event, not requiring medical intervention. May be asymptomatic and is likely to be a clinical or diagnostic observation only; or may be a symptomatic but minor, or transient event, with no necessity for medical intervention. This might include asymptomatic laboratory or radiographic findings. A minor adverse event is likely to have only marginal clinical relevance.

Grade 2: An adverse event which may require some medical intervention (local/non-invasive) and which is symptomatic to patient. May affect activities of daily living.

Grade 3: Significant symptoms reported, requiring medical intervention, and possibly requiring hospitalisation. Medically significant and likely to be significantly affecting activities of daily living.

Grade 4: An adverse event that requires urgent intervention or may have life-threatening consequences.

Grade 5: Death related to the adverse event.

9.1.2. Assessment of seriousness of AEs

The PI, or delegated clinician, should make an assessment of seriousness against the standard definition in the Safety Reporting Definitions section 9.1

9.1.3. Assessment of causality of AEs

The relationship between the use of IMP and the occurrence of each AE must be assessed and categorised by the PI or delegated clinician using clinical judgement to determine the causal relationship. Other factors such as medical history of underlying diseases, concomitant therapy and any other relevant risk factors should be considered. The PI should also consult the current version of the Reference Safety Information as per section 8.1 and make a determination according to the definitions below:

Yes (related)	Event considered related to IMP
Probable	It is probable the event is related to IMP
Possible	It is possible the event is related to IMP
Unlikely	It is unlikely the event is related to IMP
No (unrelated)	Event considered unrelated to IMP
Unable to determine	After review of information available the PI/delegated clinician is unable to determine if event is related to IMP or not

9.2. Recording and Reporting AEs and SAEs

All AEs occurring from point of consent to end of trial participation must be recorded in the AE eCRF page as well as the participant's clinical notes.

For all AEs the following will be recorded: severity, seriousness, causality, and any concomitant medication used.

All SAEs occurring from point of consent to end of trial participation must be reported to NCTU on an SAE form and also recorded in the AE eCRF page and recorded as serious.

All SARs occurring from the 1st dose of IMP to the time periods specified in table 2 must be reported to NCTU on an SAE form and also recorded in the AE eCRF page.

Table 2 – Half-lives of IMPs and time period from last dose to end of SAR monitoring

Medication	**Half life /hrs**	**Cleared (5 half lives) /hrs**	**Source**	**Time period from last trial dose (including any tapering dose) for end of SAR monitoring/days***
Oral amitriptyline	25	155	https://www.medicines.org.uk/emc/product/14334/smpc	7
Oral gabapentin	7	35	https://www.medicines.org.uk/emc/product/158/smpc	7
IM Lidocaine 2%	1.68	8.4	https://pubmed.ncbi.nlm.nih.gov/7439378/	7
IM Botox	10	50	https://www.ema.europa.eu/en/documents/referral/botox-article-29-referral-annex-i-ii-iii_en.pdf	7

**Rounded up to nearest week. If pregnancy falls outside of this time period, it would not need to be reported for the trial or monitored for adverse effects*

Following this defined active monitoring period for SARs, investigators are still required to report any SARs or SUSARs they become aware of.

All SAEs/SARs must be reported to NCTU on an SAE Form via secure email to nctu.mitigate.sae@nhs.net as soon as possible and within 24 hours of research staff becoming aware of the event.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken

- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator

In addition, for each SAR an assessment of whether the event is considered expected or unexpected in the opinion of the chief investigator (or delegate if unavailable), in accordance with the approved reference safety information (section 8.1), is required.

Any change of condition or other follow-up information should be submitted to NCTU at nctu.mitigate.sae@nhs.net as soon as it is available or at least within 24 hours of the information becoming available via the SAE Follow-up form. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3. Pre-specified AEs

As part of the trial, a number of adverse events of interest relating to Botox and Amitriptyline and Gabapentin will be collected as part of routine data collection. The events below are the pre-specified adverse events of interest and will therefore be collected:

- New onset headache
- Facial weakness following Botox (see section 7.4.5 for assessment/recording details).
- Other adverse effects listed within the Liverpool adverse events profile.

All adverse events that are considered as possibly related to any of the trial IMPs must be reported for the trial on the Adverse Event CRF.

9.4. Protocol Specific Reporting Exclusions

The following condition will not need to be reported on an SAE form, but should be recorded in the database on the Adverse Event CRF page:

- Pre-planned hospitalisations (e.g. elective surgery) or scheduled treatment for pre-existing conditions that are not associated with clinical deterioration.

Worsening of pre-existing persistent pain conditions affecting the head and face are not reportable as AEs for the purpose of the trial, because of the natural chronological fluctuation of the pain intensity of all persistent head and face pain conditions (9.3). However, any event which is considered worse than usual and considered as possibly related to the trial IMP, must be reported as an AE / SAE and reported on an SAE form if appropriate.

ARs detailed in the RSI for the four trial IMPs (detailed in section 8.1) are not reportable as SUSARs

9.5. Recording and Reporting SUSARs

All SARs or suspected SARs occurring during this trial must be reported by site to NCTU immediately (and no later than 24 hours of the site becoming aware of the event), through the provided SAE/SAR reporting method. This will automatically be distributed to the Sponsor and CI.

The assessment of expectedness will be performed by the CI on behalf of the Sponsor against the approved Reference Safety Information (RSI) for the trial. The RSI is contained within the approved SMPCs for the trial's IMPs (see section 8.1) and is detailed here.

Medication	Section 4.8 of the SmPC
Gabapentin	Neurontin 100mg Hard Capsules
Amitriptyline	Amitriptyline 10mg Film-Coated Tablets
Lidocaine 2%	Lidocaine Hydrochloride Injection BP 2% w/v
Botox	BOTOX 100 Allergan Units Powder for solution for injection

Where the CI is unavailable, another medically or dentally qualified individual may be delegated this task via the trial delegation log.

All SUSARs occurring during the trial must be reported to the MHRA and REC. The Sponsor will perform this reporting. Fatal and life-threatening SUSARS must be reported no later than 7 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-life threatening SUSARs must be reported to the MHRA no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

NCTU will be responsible for ensuring that the CI undertakes the expectedness assessment to determine if a SAR is unexpected and requires reporting as a SUSAR. The reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Patient trial number
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date of the onset of the event (including time of onset and end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided on a SUSAR Reporting Form. The site is expected to fully cooperate with the NCTU in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

PIs will be informed of all SUSARs by NCTU.

9.6. Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up.
- Using clinical judgement in assigning seriousness and causality of adverse events.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
- Ensuring all AEs are recorded in eCRF.

Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using clinical judgement in assigning seriousness and causality assessments for SAEs where it has not been possible to obtain local medical assessment.
- Provide review of assessment of causality of all SAEs on behalf of Sponsor (where the assessment was not originally performed by the CI).
- Using clinical judgement in assigning expectedness to SARs in line with the RSI and following the principals of GCP.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs.
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to CTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the MHRA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs (may be
- delegated to NCTU)
- Reviewing RSI at least annually and notification of PIs of any required updates (may be delegated to NCTU).

- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuing timely submission to the MHRA and REC (may be delegated to NCTU)

TSC/DMC/TOC

- Review of safety data collected to date to identify any concerns

9.7. Notification of Deaths

Fatal SUSARs will be reported within 7 days to REC and MHRA. Monitoring of all other deaths will occur via the TMG, IDMC and the TSC.

All participant deaths will need to be reported as SAEs, with the reason for death identified on the SAE form and recorded in the eCRF.

9.8. Pregnancy Reporting

In the event of a trial participant or the partner of a trial participant becoming pregnant on the trial, the site must notify NCTU, the Chief Investigator and the sponsor representative within 24 hours of becoming aware of the pregnancy. This is by completion of a pregnancy reporting form which should be sent to nctu.mitigate.sae@nhs.net.

Site must approach the trial participant or the partner of a trial participant to obtain consent to follow the pregnancy to completion. The outcome of the pregnancy will then be obtained when available.

Pregnancy in itself is not an SAE. In the event that a congenital anomaly or birth defect does occur, this must be reported as an SAE.

9.9. Overdose

A toxic overdose, whether intentional or accidental must be reported immediately to NCTU and patients should be directed or escorted (if on premises) to their local emergency department. Toxbase can be consulted on toxic doses in adults: ≥3mg/kg of amitriptyline or symptomatic at a lower overdose; ≥150mg/kg Gabapentin or symptomatic at a lower overdose; ≥6mg/kg lidocaine or symptomatic at a lower overdose; Botox overdose is a relative term and is described in section 4.9 of its SmPC. Whilst it is not in itself an adverse event or serious adverse event, any untoward medical occurrence as a result of an overdose, or any condition that leads to an overdose being taken is considered an AE or SAE and should be reported as per section 9.2. Details of the event must be recorded in the eCRF and participant's medical records.

9.10. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU] must be notified immediately and details of the USM given. The Sponsor must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the Sponsor's standard operating procedures.

The MHRA may alert the trial team to any new safety signals identified for the trial IMPs. In the event of this occurring, the IMP may need to be discontinued with immediate effect.

9.11. Development Safety Update Reports

The following reports will be submitted each year as a condition of the authorisation to undertake a clinical trial or as a condition of a favourable opinion from a REC.

In the UK, a Development Safety Update Report (DSUR) will be submitted to the MHRA and NHS REC once a year on the date of CTA approval of the trial. NCTU must ensure that the report is submitted within 60 days of the end of the reporting period. The Trial Management Group must contribute to the compilation of the DSUR with the CI being involved in completion of the relevant sections requiring medical input and assessment of any newly identified risks and the summary of benefit-risk considerations. The CI must review and authorise the final report before it is ready for submission. The DSUR should also be reviewed by the NCTU QA Manager and Sponsor Representative prior to submission. NCTU staff will prepare and submit DSURs for the trial, in accordance with NCTU SOPs.

An NRES CTIMP Safety Report Form will be sent to REC along with the DSUR. Reports of SUSARs in the UK, urgent safety measures and any other safety reports submitted, for example, reports of an independent data monitoring committee (IDMC), will also be accompanied by a Safety Report Form.

A NRES Annual Progress Report for CTIMPs will be prepared and submitted by the CI to REC, and copied to Sponsor, on the anniversary date of the REC favourable opinion.

10. STATISTICAL CONSIDERATIONS

10.1. Analysis Populations

Intention-to-treat (ITT): This population contains all participants randomised into the trial who participated in at least one post-baseline assessment, analysed according to randomised treatment allocation.

Safety Population (SP): This population contains all participants who received **any** trial treatment, analysed according to randomised treatment allocation.

10.2. Statistical Analyses

The analysis of all outcome measures will be described in detail in a pre-specified Statistical Analysis Plan (SAP) that will be reviewed by the trial's oversight committees and signed off by the CI prior to any comparative analyses being undertaken. Any changes to the statistical analysis plan made afterwards will be documented and reviewed by the senior methodological lead who has not had access to the results of the comparative analyses. Throughout the statistical section (section 10.2), baseline refers to data collected before randomisation at the screening visit.

10.2.1. Analysis of the Co-primary Outcome Measures

The main co-primary objective is to estimate the mean difference in disorder specific quality of life measured by OHIP-TMD and pain intensity measured by CPI at 36 weeks in adults with chronic (≥3months) myalgia temporomandibular disorder (M-TMD) treated with BTX compared to TAU and Lidocaine injections compared to TAU, regardless of deviations from the allocated treatment for any reason. The estimand is described by the following attributes:

Estimand attribute	Description
Population	Adults with chronic (≥3months) myalgia temporomandibular disorder (M-TMD)
Treatment conditions	1. BTX injections (intervention) 2. Lidocaine injections (intervention) 3. TAU, amitriptyline/gabapentin (control)
Outcome measures	1. Disorder specific quality of life measured by OHIP-TMD at 36 weeks 2. Pain intensity measured by CPI at 36 weeks
Strategies used to handle intercurrent events	1. Deviation from treatment for any reason – treatment policy[1] 2. Initiation of alternative treatments – treatment policy[1] 3. Death – hypothetical[2]
Population-level summary measures	1. Mean difference in OHIP-TMD at 36 weeks (adjusted for baseline) between each intervention and control 2. Mean difference in CPI at 36 weeks (adjusted for baseline) between each intervention and control

[1]The treatment policy strategy targets the treatment effect regardless of the occurrence of intercurrent event.

[2]The hypothetical strategy targets the treatment effect in the hypothetical setting where the intercurrent event would not occur.

The co-primary outcomes of disorder specific quality of life measured by OHIP-TMD, and pain intensity measured by CPI at 36wks will each be compared between treatment groups using separate linear mixed effects regression models with nested random effects for site and participant and fixed effects for treatment, timepoint, treatment by timepoint interaction, baseline score and the stratification factor of psychosocial status. These models will each include the outcome data at all timepoints which will help account for missing data (under a missing at random assumption). These models will each be used to calculate mean differences at 36 weeks (BTX - TAU and Lidocaine injections - TAU) and associated two-sided 95% confidence intervals (CIs) for each coprimary outcome to test the superiority of BTX and Lidocaine injections compared to TAU. Superiority will be concluded if the upper limit of the two-sided 95% CIs are both less than 0. To conclude that BTX or Lidocaine are effective, statistically significant differences in both co-primary outcomes compared to TAU will be needed. This analysis will be conducted in the ITT population.

These models will also each be used to estimate the mean differences (BTX - TAU and Lidocaine injections - TAU) and associated two-sided 95% CIs for the secondary outcomes of disorder specific quality of life measured by OHIP-TMD, and pain intensity measured by CPI at 12 and 24 weeks.

A secondary analysis will additionally adjust the estimates for OHIP-TMD by including fixed effects for the baseline covariates of GCPS and duration of pain that are known to be strongly related to outcome. This will also be done for CPI. However, as CPI is a component of the GCPS, baseline GCPS will not be included. We will consider alternative strategies to deal with the intercurrent events of treatment discontinuation and alternative treatments in the SAP.

10.2.2. Analysis of Secondary Outcome Measures

Secondary outcomes will be analysed for superiority of each intervention against TAU. All analyses will be in the ITT population i.e. following a treatment policy approach. Estimated differences between treatment groups will be reported with two-sided 95% confidence intervals.

Secondary patient-reported outcomes (PHQ-4, BPSQI, SF-JFLS, GIC, Liverpool adverse effects profile, FaCE) will be analysed using linear mixed effects regression models similar to the co-primary outcomes above, but with the baseline value of the corresponding outcome included as a fixed effect. Domains or individual items may also be reported and analysed using appropriate regression techniques as described in the SAP. Analgesia use at any time during the trial will be analysed as a binary outcome using mixed effects logistic regression with a random effect for site and fixed effects for treatment and the stratification factor of psychosocial status. The secondary outcomes of 30% and 50% reduction from baseline in CPI and OHIP-TMD will be analysed separately at each timepoint using mixed effects logistic regression with a random effect for site and fixed effects for treatment, baseline score and the stratification factor of psychosocial status.

10.2.3. Missing data

Scores from the instruments used to measure primary and secondary outcomes will be calculated according to the relevant instruments published guidance. From our longitudinal six-monthly data capture experience in the 24-month duration DEEP study we expect low levels of missing outcome data at an item level (2-6% (Durham et al., 2021)). Where item level data are missing in the instruments used this will be handled according to the instruments' published guidance. In the case where there is no scoring manual, appropriate imputation methods will be specified in the SAP.

10.2.4. Subgroup Analyses

Exploratory analysis of the co-primary outcomes at 36 weeks will be carried out for the following subgroups:

- Baseline psychosocial status (split at PHQ-4 score≥6) (Penlington et al., 2020)
- Duration of pain at baseline (spilt at duration≥60 months)
- Baseline OHIP-TMD (split at ≥40, (Cao et al., 2022))
- Baseline CPI (split at ≥50) (Von Korff et al., 1992)
- Baseline report of migraine (Yes/No)
- Baseline MIDAS split at ≥11 (category III or higher) (Xu et al 2020)(Buse et al., 2012)

Where subgroups have been defined from continuous variables, we will also perform an analysis using the continuous version of the variable. Full details will be pre-specified in the SAP.

10.3. Sample Size Calculations

The sample size will be 663 which has been chosen to provide high power for both the OHIP-TMD and CPI co-primary outcomes (Durham et al., 2021; Dworkin et al., 2008; Yule et al., 2015; Collignon et al., 2020).

From Yule et al, the standard deviation (SD) of OHIP-TMD is 20.7 at 12 weeks (Yule et al., 2015), which we expect to be consistent at subsequent measurement times. The correlation with baseline was 0.6. To have 90% power (two-sided 5% type I error rate) to detect a difference between arms equal to the minimally important clinical difference (MICD) of 6.0 would require 251 per arm; taking the correlation into account would reduce this to $(1-0.6^2)*251 = 161$ per arm. We have inflated this by 27% to account for worst-case scenario loss-to-follow up identified between two large research studies we have conducted involving treatment and M-TMD (Durham et al., 2021; Yule et al., 2015). This gives a required sample size of 663.

This sample size provides extremely high power (>99%) to detect differences between arms in the CPI, which we assume has an SD of 20 based on the DEEP study (Durham et al., 2021) and MICD of 10 (Dworkin et al., 2008). To conclude superiority, statistically significant differences in both OHIP-TMD and CPI will be needed, meaning that an adjustment for multiple testing is not required and that the overall power is approximately 90% for each separate comparison (BTX vs TAU and Lidocaine vs TAU). As per consensus on multi-arm trials with distinct interventions, we do not formally adjust for multiple intervention arms (Collignon et al., 2020), but the total chance of recommending an ineffective intervention as superior to TAU is <5%. The quantity and timing of attrition will be monitored. If the attrition rate by 36 weeks increases above the estimated 27%, we may increase the sample size to maintain the power of the trial in agreement with the trial's oversight committees and subject to funding and time constraints.

11. Economic Analysis

11.1. Overview

The economic analysis will consist of two parts: a within-trial analysis estimating the cost-effectiveness of BTX or lidocaine or treatment as usual (TAU, amitriptyline/gabapentin) in for the treatment of patients with chronic M-TMD at 36-weeks and a model based analysis extrapolating the within-trial results to estimate the cost-effectiveness of those treatment options over the patients' life course. Details of both the within trial and economic model will be fully specified in a Health Economics Analysis Plan (HEAP) which will be developed by the trial health economists and reviewed by the CI and trial management group prior to data analysis.

11.2. Costs

The perspective of the analysis will be the NHS and personal social services (PSS). Additional analyses will widen the perspective to considered costs borne by participants and their families. Intervention costs will be micro-costed and primarily based on the costs of the medications and their administration. Additionally, the costs of managing chronic M-TMD, including the management of adverse events, will also be considered. A bespoke questionnaire, based on the Health Utilisation Questionnaire (HUQ), validated for use in M-TMD, will capture the frequency of participants' primary

and secondary healthcare contacts. The HUQ will be administered at baseline, 12, and 36-weeks post-randomisation. The HUQ will be designed to minimise participant burden while maintaining the accuracy of data as there will potentially be differences in healthcare resource use and hence costs associated with managing M-TMD between the interventions. A broader, societal perspective will also consider direct and indirect costs to participants such as costs to access care and time off work and usual activities due to M-TMD and attending healthcare appointments. This will be measured by the HUQ and a bespoke Time and Travel Questionnaire completed at 24-weeks. Unit costs will be derived using routine data sources and study-specific estimates. Data on the interventions costs and subsequent use of healthcare services will be combined with unit costs to produce a total cost for each trial participant.

11.3. Health-related quality of life

Participants' health-related quality of life will be measured using the EQ-5D-5L, administered at baseline, 12, 24 and 36-weeks post-randomisation. Responses will be combined with the recommended UK tariff, at the time of the analysis, to derive utility values at each scheduled assessment. These EQ-5D-5L values will then be mapped to EQ-5D-3L values using the algorithm developed by the Decision Support Unit (Hernández Alava et al. 2017), as per NICE reference case/manual (NICE manual). QALYs will be estimated using the area under the curve approach.

11.4. Within-trial analysis

For the primary economic analysis, no discounting of costs and QALYs will be performed as the time horizon is 36 weeks. The economic analysis will compare the 3 interventions in terms of mean costs and QALYs. To estimate cost-effectiveness the interventions will be ranked based on mean costs with the least costly intervention being compared to the next least costly intervention.

An adjusted analysis will estimate point estimates of mean incremental costs, QALYs and cost-effectiveness using seemingly unrelated regression (SUR), accounting for baseline costs and QALYs and stratification factors. The results will be presented as point estimates of incremental costs, QALYs and cost-effectiveness. To display the statistical imprecision in estimates of cost-effectiveness we will use stochastic sensitivity analysis, the bootstrapping technique, to produce cost-effectiveness acceptability curves (CEACs) and cost-effectiveness planes. Sensitivity analysis will be undertaken to address any uncertainty in the analysis, including the impact of missing data and replicating the comparisons used in the effectiveness analysis (e.g., BTX or lidocaine versus TAU).

11.5. Model-based analysis

A longer-term impact of interventions on costs and benefits for the NHS and patient will be explored using a lifetime economic model. The structure of the economic model will be informed by previous models conducted in this area (e.g., DEEP study and the HTA evidence synthesis on oral splints for TMD), which the team led or were involved with. The economic model will be co-designed with stakeholders; especially those who have been affected by M-TMD (PPIE members), to ensure that the model reflects their lived experience. The model will be developed in accordance with NICE's reference case and guidelines for good practice. To make the best use of the trial data these data will be used to populate the model parameters and individual patient-level simulation models will be considered alongside other frameworks. Similar to the within-trial analysis results will be presented as mean costs and QALYs for each of the interventions, as well as incremental versions. Deterministic sensitivity analysis will explore key uncertainties in the model structure and/or model parameters. All

analyses will be combined with probabilistic sensitivity analysis (PSA). The PSA will likely be a Monte Carlo simulation which requires all model parameters to be assigned a distribution, which represents the uncertainty surrounding them. The PSA results will be presented on CEACs to show the probability of each of the interventions being considered cost-effective over a range of possible threshold values for an additional QALY.

12. DATA HANDLING

12.1. Data Collection Tools and Source Document Identification

All data for an individual participant will be collected by each PI or their delegated nominees and recorded in the electronic case report form (eCRF) for the study. The study-specific eCRF will be set up using Redpill, Sealed Envelope's eCRF system. Participant identification on the eCRF will be through a unique trial identifier, known as the Subject ID. Participants will not be identifiable from eCRFs or paper data collection tools. The participant's name will be linked to their unique trial Subject ID via a record filed within each site's ISF, which will be stored in a locked room at site.

A Source Data Agreement will be completed prior to each site opening to screening and recruitment activity; this will document agreed sources of data.

12.2. Data Handling and Record Keeping

The CI has overarching responsibility for collection, quality, and retention of data. Data will be collected by an appropriately qualified and delegated member of site personnel. Data will be handled, computerised, and stored in accordance with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, to reflect the UK's status outside the EU, the latest GCP Directive (2005/28/EC) and local site policy. Paper copies of trial-related documentation will be annotated, signed, dated and filed in the Investigator Site File. Copies of the Summary PIS, PIS, completed written consent form, eligibility forms and letters to GP will be filed in the participant's medical notes.

The CI or designated nominees will continuously monitor completeness and quality of data collected on the trial database. Monitoring will include regular correspondence with site staff to ensure missing data is collected wherever possible and ensuring continuous high quality of data capture. Data completeness and progress reports will be generated for regular review at TMG meetings.

12.3. Access to Data

The site PI and staff formally delegated to do so will have access to source data and the ISF to conduct the trial.

Access to the trial database will be password-limited, with task-specific restrictions (e.g. data entry/randomisation). The site PI will formally delegate database tasks to site staff, by way of dated signatures on the Site Delegation Log.

NCTU trial management staff, representatives of the host institution, Sponsor and the MHRA will be granted access to the source data, ISF and trial database for the purposes of monitoring, audit and

inspection respectively. Consent will be sought from the participant for access to their medical records and trial data for the purposes of monitoring, audit and inspection.

Data may be securely downloaded from the trial database and released to the Trial Statistician for analysis, including, as needed, for reports to the IDMC. Data release will only take place after documented agreement from key members of the TMG.

Site staff, including the PI may not disclose or use for any purpose other than conduct of the trial any data, record or other unpublished confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said information to other parties.

12.4. Archiving

Trial documents and data will be archived in accordance with UK GCP legislation and as specified in Sponsor and NCTU SOPs. All trial documentation and data will be archived for 5 years as per Sponsor SOP: NJRO-GEN-SOP-012, as support may be required for a marketing application.

13. MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be developed, based upon the trial risk assessment, and agreed by the Trial Management Group, NCTU QA representative and the Sponsor.

All monitoring activity will be detailed in the monitoring plan. Monitoring of trial conduct and data collected will be performed by a combination of central review and off- and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and appropriate regulations. Trial site monitoring will be undertaken by NCTU trial personnel as indicated in the monitoring plan.

The trial may be subject to audit by representatives of the Sponsor or inspection by the MHRA. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

13.1. Trial Oversight

13.1.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the day-to-day progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit. The Trial Management Group will be chaired by the CI and consist of members of NCTU, statistician(s), Sponsor, and other members of the co-applicant team.

13.1.2. Trial Steering Committee (TSC)

The TSC will consist of an independent chair, the CI, two independent professional members and up to four lay members. The TSC will oversee and supervise the progress of the trial and ensure it is being conducted in accordance with applicable guidance and regulations. The TSC will review recommendations from the IDMC and provide advice regarding trial progress, to maximise the chances of completion within the proposed time scale. The TSC will usually meet following IDMC meetings.

13.1.3. Independent Data Monitoring Committee (IDMC)

The IDMC will consist of an Independent Chair, an Independent Statistician and two Independent Clinicians, one of whom will have experience of Botox. The IDMC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial, including stopping early for futility. The IDMC will aim to meet at least biannually.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

14.2. Peer Review

The study was peer reviewed as part of the funding application. The protocol has been reviewed and authorised by the Sponsor, CI, NCTU and the Trial Senior Statistician.

14.3. Public and Patient Involvement

Seven PPIE groups, individual consultation and two clinician surveys have directed development of the proposed trial. The application was also reviewed by a PPIE co-applicant and a TMD specific patient advocacy group.

The study has its own PPIE advisory panel involving patients with M-TMD and public members who will provide ongoing input throughout the study. All PPIE members will be provided with support and training by designated PPIE co-leads and through the local clinical research network.

14.4. Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

NCTU will obtain a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by NCTU until the end of the trial.

NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

14.5. Protocol Compliance

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team, but the CI will retain overall responsibility.

Protocol deviations, non-compliances and breaches are departures from the approved protocol. Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events should be documented on the deviation tracking log and will be reported to Sponsor. NCTU will ask the site to provide copies of their deviation tracking log at intervals throughout the trial. If no deviations have been identified during a particular interval, site are required to confirm this in writing to the NCTU.

It is Sponsor policy that waivers to the protocol will not be allowed.

14.6. Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The sponsor will notify the MHRA and the NHS REC within the required timelines in accordance with the sponsor and NCTU SOP.

14.7. Data Protection and Patient Confidentiality

All investigators and trial site staff will comply with the UK Data Protection Act 2018 and the UK GDPR as amended on 01 January 2021 by regulations under the European Union (Withdrawal) Act 2018, to reflect the UK's status outside the EU, with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation.

Trial data held on computers will be accessible only by authorised study personnel and will be password protected. Paper records containing personal information will only be accessible by trial

personnel at each site, central trial personnel, monitors from NCTU and auditors/inspectors from the Sponsor or regulatory authorities.

14.8. Indemnity

NHS indemnity for clinical trials conducted with NHS permission will apply for clinical negligence that harms individuals towards whom the NHS has a duty of care. Indemnity in respect of protocol authorship will be provided through a combination of NHS schemes (for those protocol authors who have substantive NHS employment contracts) and through Newcastle University's public liability insurance (for those who have their substantive contracts of employment with the University).

There is no provision for indemnity in respect of non-negligent harm.

14.9. Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by NCTU.

14.10. Post-Trial Care

See 7.9 for details of post-trial care.

14.11. Access to the Final Trial Dataset

Until publication of the trial results, access to the dataset will be limited to the Trial Management Group and to authors of the publication.

15. DISSEMINATION POLICY

The full trial dataset will be created and uploaded for publishing through the ISRCTN registry within 12 months of the end of the trial.

The PPIE advisory panel will be utilised to inform and guide dissemination. Outputs will include:

- Full final report to funder
- Presentation of results at conferences and publication within peer-reviewed open access papers
- Dissemination of results to patients, participants and the public via a range of media

Authorship eligibility for manuscripts arising from the trial will be determined by the Trial Management Group in line with ICMJE recommendations and will include site PIs in alphabetical order whose sites recruited appropriately for the trial in between other lead and senior authors.

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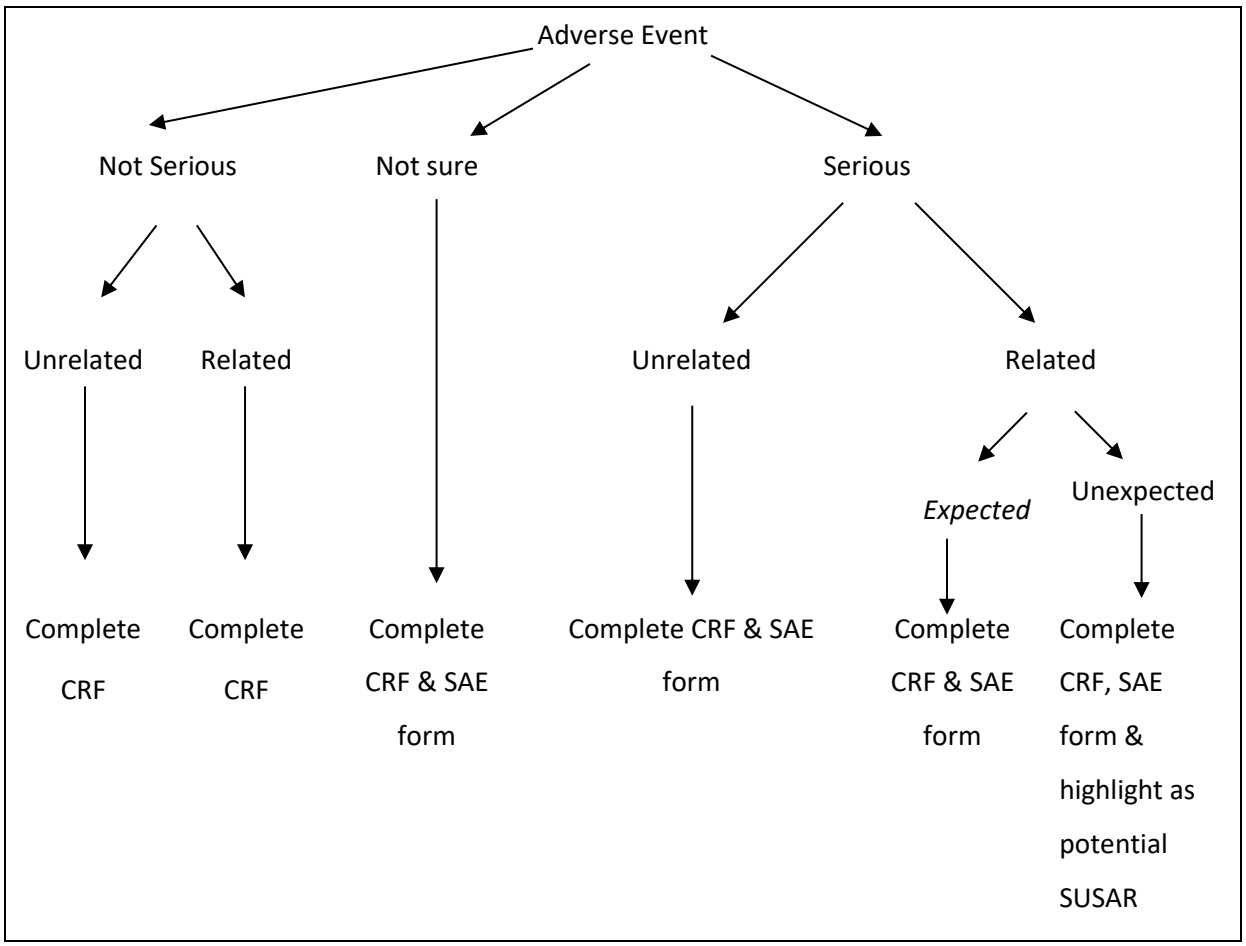
17. APPENDICES

17.1. Appendix 1 - Safety Reporting Diagram



Contact details for reporting SAEs and SUSARs

Please send SAE forms and follow up forms to nctu.mitigate.sae@nhs.net

17.2. Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
01 (Non substantial amendment 02)	V3.0	11 Jun 2024	Karen Nicholson – trial manager	Correction to the name of the chair of the IDMC. Update to remove sending of consent and eligibility proformas to Newcastle trials unit. Information is captured directly into the database. Clarification that the Patient Use of Services and Productivity (USPQ) is not being used for this trial. Instead, the Health Utilisation Questionnaire is being used. The HUQ has approval – the title in the protocol was incorrect. Clarification of the window within which the qualitative interview can occur. Updated to up to 4 weeks after written consent is given. Clarification of archive period of 5 years.
SA02	V4.0	17 Feb 2025	Karen Nicholson – trial manager	Update to addresses and names for trial team members Update to background section to provide additional information Update to exclusion criterion 6 to be explicit about the use of lactose free gabapentin Clarification that IMP can be given on the same day as the screening visit if appropriate. Already possible within the protocol but this addition was made to make it clearer and reduce the risk of inadvertent systematic ethnic group bias occurring.

				Additional field to collect whether participants have false nails in the database Clarification that MRI and / or blood sample for the MRI can be repeated if the scan or blood sample readings are not valid. This would require consent from the participant. Again, this was already possible within the protocol, but this statement was added to make it clearer. Clarification of the secondary end points and update to the statistics section to detail their analysis Correction of the figures in the table in section 4.1 which detail the internal pilot study. Correction to bring the figures in line with those agreed in the grant Clarification of protocol reporting exclusions for AE and SAE reporting Update to how the data from the EQ-5D-5L questionnaire will be analysed Clarification of the self-referral process
NSA07	5.0	07 Oct 2025	Karen Nicholson – Trial Manager	Addition of secondary analysis relating to pain intensity (CPI) and Quality of Life (OHIP-TMD) and change from baseline Addition of exploratory outcome of reporting of pain tolerance and influence on outcomes within the trial Clarification of exclusion criteria 1 relating to use of medications on trial entry Updating information on use of opiate use and codeine containing products on trial entry and during the trial Clarification of the use of analgesia during the trial and the subsequent analysis