Study Protocol

TAMS: Topical Azithromycin Meibomian Gland Dysfunction Survey

Study Acronym	**TAMS**
Sponsor	**Tayside Health Board**
Sponsor Ref Number	3-020-19
Funder	
Chief Investigator	Ian Jarvis
REC Number	
ISRCTN Number	ISRTCN(registration pending)
Version Number and Date	1.0 12/05/2019

PROTOCOL APPROVAL

Topical Azithromycin Meibomian Gland Dysfunction Survey

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Ian Jarvis Chief Investigator	Signature	Date
John Jarvis Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IF	Incidental Findings
ISF	Investigator Site File
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SMF	Study Master File
SMG	Study Management Group

SUMMARY/SYNOPSIS

Study Title	**Topical Azithromycin Meibomian Gland Dysfunction Survey**	
Study Design	Post treatment patient survey	
Study Population	NHS Tayside Patients with symptomatic MGD who underwent treatment with topical azithromycin at *Jarvis Optometrist,* Dundee within the time period January 2016 and May 2019	
Sample Size	40	
Planned study Period	8 months	
Clinical phase duration	This is a retrospective patient data analysis linked to the pre- and post-treatment survey data. The study participants were on one month treatment between 01/01/2016 and 01/04/2019	
Follow up phase duration	N/A	
Primary	Objectives to assess the impact of treatment on patient symptoms and management of MGD	Outcome Measures improved patient symptoms of MGD
Secondary	Objectives assess clinical signs of MGD	Outcome Measures improved clinical signs
Inclusion Criteria	NHS Tayside patients aged 18 and over, able to consent, who have chronic MGD where previous treatment has been ineffective	
Exclusion Criteria	Asymptomatic or no MGD	

1 INTRODUCTION

Meibomian gland dysfunction is caused by chronic inflammation of the Meibomian glands which affects the quality of secretion from those glands. This results in rapid evaporation of the tear film leading to symptoms of dry eye. Current treatment regimens mainly address only the symptoms and not the underlying cause of dry eye.

2 BACKGROUND & RATIONALE

Meibomian gland dysfunction (MGD) can have a significant impact on patient lifestyle, Mertzanis et al (1). There are many documented strategies for treating MGD, however there are few papers in the literature with regard to topical azithromycin. Foulks et.al (2) has shown the effect of topical azithythromycin on Meibominan Gland Dysfunction was as effective as oral doxycycline and in some areas better. With oral doxycycline, antibiotic allergy is often a problem. Other possible effects such as GI upset >1/10and UV sensitivity 1/100-1/100 (3) are often encountered. However there are no recorded systemic issues with topical azithromycin (4). Also, the course is much shorter, one month compared to three months for oral doxycycline. This helps with compliance and the likelihood of completing the course of treatment. Foulks et al (5) have shown that topical azithromycin can improve both symptoms and signs of MGD

This study hopes to show that topical azithromycin has a correlated effect on patient symptoms and management of Meibomian gland dysfunction and has a lasting impact.

Topical azithromycin is only licensed in the UK for 3 days use in acute bacterial conjunctivitis. However as an Independent prescribing Optometrist the CI has the remit to prescribe off - licence medication where deemed appropriate.

3 STUDY OBJECTIVES & OUTCOMES

To assess the impact of treatment on patient symptoms and management of MGD by analysis of a post treatment survey. A reduction in symptoms and reduced management regime will be a measure of the success of the treatment. Also, collation of clinical signs will be analysed to look for any statistically significant change post-treatment.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To assess the impact of treatment on patient symptoms and management of MGD	*Reduced symptoms and management regime*	*1 year*

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To assess clinical signs of MGD	*Reduced clinical signs of MGD*	*1 year*

4 STUDY DESIGN

This is a retrospective review/analysis of patients' examination data linked to pre- and post-treatment survey.

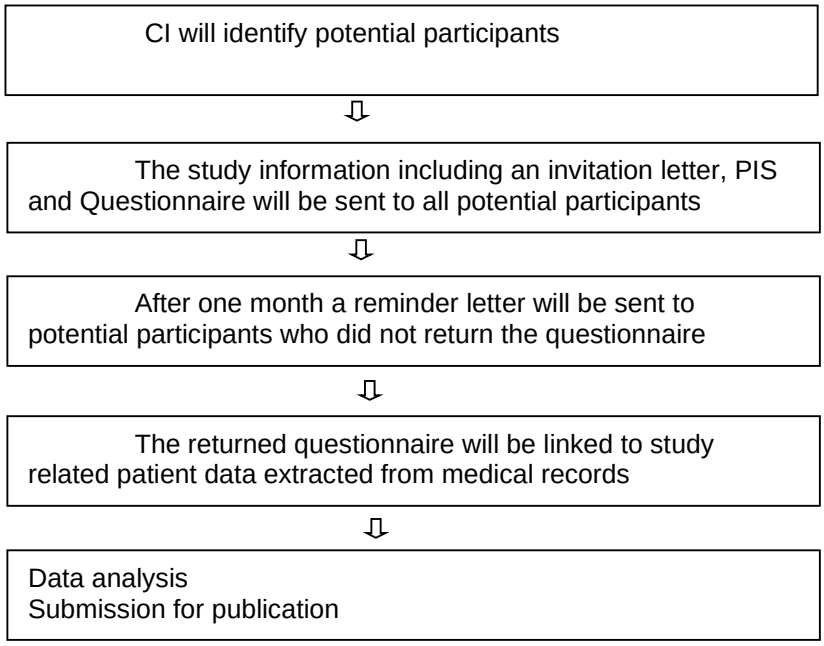
The study will comprise of:

1. A post-treatment survey of patient symptoms and management pre and post treatment.
2. Separate collation of pre- and post-treatment clinical signs of MGD.

STUDY DESCRIPTION

Patients with symptomatic MGD who underwent treatment with topical azithromycin at *Jarvisoptometrist,* Dundee will be invited to take part in the study. An invitation letter along with a PIS, Questionnaire and pre-paid envelope will be sent to all eligible potential participants via post.
The participants will be provided with the study information including questionnaire for them to make an informed decision about whether or not to participate, this will be sufficient for consent to be implied by the questionnaire being completed and returned.

STUDY FLOWCHART



INCIDENTAL FINDINGS

Any incidental findings (IF: previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI, with the consent of the participant.

STUDY POPULATION

NHS Tayside patients with symptomatic MGD who have attended a community optometric practice *Jarvisoptometrist* in Dundee between 01/01/2016 and 01/04/2019.

NUMBER OF PARTICIPANTS**:**

40 participants who are all NHS Tayside patients

INCLUSION CRITERIA**:**

SYMPTOMATIC MGD

NHS Tayside patients who attended a community Optometric practice with chronic MGD, where previous treatment has been ineffective.
All participants are aged over 18 years and able to consent to participation

EXCLUSION CRITERIA

ASYMPTOMATIC OR NO MGD

5 PARTICIPANT SELECTION AND ENROLMENT

Patient records will be assessed by CI for selection of potential study participants as suitable if they have chronic MGD which has not resolved with other treatments

IDENTIFYING PARTICIPANTS

Patients will be recruited from a community Optometric practice, *Jarvisoptometrist*, Dundee. They will be identified by the clinician who is the CI. An invitation letter, PIS and Questionnaire will be sent to all potential participants. A unique study identifier will be allocated to each participant. Completed questionnaires will be linked to clinical data using the unique identifier.

CONSENTING PARTICIPANTS

Consent will be implied by return of completed study questionnaire

6 DATA COLLECTION & MANAGEMENT

DATA COLLECTION

Data collected will be from
1. Returned Patient survey responses
2. Clinical data: tear break-up time and Meibomian gland dysfunction grading (collected from clinical records).
3. The Questionnaire data will be linked with MGD grading of the patient.

Anonymised data collected from completed questionnaires and medical records will be collated for statistical analysis.
The clinical data required for research data analysis include:
Tear Break-up time (TBUT)
Meibomian gland dysfunction (MGD) grading

DATA MANAGEMENT SYSTEM

Electronic CRF will be used to store all data related to the study. Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP53 Data Management Systems in Clinical Research.
The data management system (DMS) will be an Excel spreadsheet as approved by Sponsor. The DMS will be based on the protocol and CRF for the study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial/study and to ensure the eligibility and safety of the participant. The trial/study database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.

The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be **CI**.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the study team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases.

7 STATISTICS AND DATA ANALYSIS

This is a pilot study.
Patient survey will use a Likert scale with opportunity for open responses
Examination data will be collated and appropriate statistical analysis will be applied

PROPOSED ANALYSES

Primary objective variables will be change in:

1. Symptoms
2. Effect on lifestyle
3. Management of MGD

Secondary objective variables will be change in:

1. Tear break-up time
2. Meibomian gland dysfunction

This data will be collected from clinical records. The statistical analyses will be a paired sample t test

There will be data linkage between data from primary and secondary objectives data

MISSING DATA

Only completed data sets will be used

TRANSFER OF DATA

No data transfer out of site

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

STUDY MANAGEMENT GROUP

The study will be co-ordinated by a Study Management Group (SMG), consisting of Chief Investigator (CI) statistician and consultant reviewers

INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS Tayside R&D approval will be obtained prior to commencement of the study.

CONFIDENTIALITY AND DATA PROTECTION

The CI and trial staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

INSURANCE AND INDEMNITY

Tayside Health Board is Sponsoring the study.

Insurance – NHS Tayside will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study].

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (“CNORIS”) which covers the legal liability of Tayside in relation to the study.

Indemnity The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

10 ADVERSE EVENTS

N/A

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12 STUDY CONDUCT RESPONSIBILITIES

PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the individual CRF for that patient documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study.

END OF STUDY

The end of study is defined as when all data collected and last CRF completed. There will be no additional clinical assessments as a result of the study. The data will be collected from pre-existing clinical records. The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

PEER REVIEW

Peer review of the protocol will occur via the resulting publication by the referees of the journal to which the paper and its protocol will be submitted

14 REFERENCES

1. Mertzanis P, Abetz L, Rajagopalan K, et al. The relative burden of dry eye in patients' lives: comparisons to a US normative sample. *Invest Ophthalmol Vis Sci* 2005;46:46-50

2. Topical azithromycin and oral doxycycline therapy of meibomian gland dysfunction: a comparative clinical and spectroscopic pilot study.
Foulks GN[1], Borchman D, Yappert M, Kakar S.
Cornea. 2013 Jan;32(1):44-53. doi: 10.1097/ICO.0b013e318254205f.

3. https://www.medicines.org.uk/emc/product/8663

4. https://www.mims.co.uk/

5. Topical Azithromycin Therapy of Meibomian Gland Dysfunction: Clinical response and lipid alterations Gary N Foulks, MD,[1] Douglas Borchman, PhD,[1] Marta Yappert, PhD,[2] Kim Sung-Hye,[1] and John W McKay[1]Cornea. 2010 Jul; 29(7): 781–788.