Characteristic distribution of peripapillary retinal nerve fibre layer oedema in acute methanol-induced optic neuropathy.

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A research report submitted to the

Faculty of Health Sciences, University of Cape Town,

in partial fulfilment of the requirements for the degree of

Master of Medicine in Ophthalmology.

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Declaration Page

I, Dr. Francois Ignatius Maritz, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree at this or any other university.

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Signature: Signed by candidate

Date: 28 November 2023

Cover letter.

Title

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Supervisor:

- Initial set-up of research and proposal
- Provision of literature
- Assisted with figures and graphs set-up and guidance
- Proof reading and academic writing guidance

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Conflicts of interest:

Nothing to disclose.

Funding:

None

Keywords:

Methanol-induced optic neuropathy, Methanol poisoning, peripapillary nerve fibre layer, OCT

Word and element counts:

Total word count: 2328

Word count – Abstract: 231

Word count – Article: 2097

Number of references: 19

Number of figures: 2

Number of tables: 1

Number of graphs: 1

Number of pages: 11

Tables:

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Abstract

Aims: To describe a characteristic distribution of peripapillary retinal nerve fibre layer oedema in acute methanol-induced optic neuropathy (Me-ION).

Methods: This retrospective case series study included four adult patients with acute Me-ION treated at Groote Schuur hospital in Cape Town during the national alcohol ban amid the COVID-19 pandemic from 27 March 2020 to 31 May 2020. Clinical examination included a best corrected visual acuity, pupillary light reflex assessment, anterior segment slit-lamp examination, and dilated fundoscopy. Fundus photography and retinal nerve fibre layer (RNFL) thickness by optical coherence tomography (OCT) was performed.

Results: All patients were examined during the acute phase of Me-ION, with a mean interval of 5.5 days between methanol exposure and ocular examination. Fundoscopy showed peripapillary retinal nerve fibre layer whitening and oedema, which extended superiorly and inferiorly from the optic disc and followed the vascular arcades but spared the nasal and temporal areas. In three cases, this correlated with a distinctive pattern of superior and inferior quadrant RNFL thickening on OCT with relative sparing of the nasal and temporal quadrants.

Conclusion: Our study is the first to associate this fundoscopic finding with the distinctive superior and inferior quadrant RNFL oedema on OCT during the acute phase of Me-ION. Recognition of this pattern can aid in early diagnosis and timely initiation of life-saving treatment, particularly in cases where patients may be unaware of their methanol exposure.

Introduction:

Methanol is a colourless liquid which is commonly used in antifreeze, industrial solvents, perfumes, washing liquids and paint removers.(1) The most common cause of methanol poisoning is the inadvertent ingestion of adulterated alcoholic beverages.(1) During the COVID-19 pandemic, several countries including Iran, India, the USA and Spain faced outbreaks of methanol poisoning (2–5). These incidents were attributed to alcohol prohibitions that prompted the circulation of illicit alcohol containing methanol as a cheap substitute for ethanol.(6)

Methanol poisoning is a severe and potentially life-threatening condition, with a mortality rate ranging from 18% to 44%.(1) In the absence of prompt medical intervention, the lethal dose of methanol is estimated to be as little as 1.2ml/kg.(1) The first symptoms, which may develop within 4 hours of ingestion, include non-specific gastrointestinal complaints such as nausea and vomiting, as well as central nervous system depression, and can be mistaken for ethanol intoxication. This is then followed by an asymptomatic latent period of about 10-12 hours, after which the typical triad of central nervous system depression, metabolic acidosis and visual loss develops. (7,8) Visual disturbances usually manifest at 12-48 hours after methanol ingestion, affect about 50% of cases of methanol poisoning, and may help to establish the diagnosis of methanol poisoning.(9)

Methanol-induced optic neuropathy (Me-ION) is a serious condition that my result in long term visual impairment and even blindness. (10,11) The main mechanism of Me-ION is thought to be the inhibition of mitochondrial oxidative phosphorylation through the binding of formic acid, which is the toxic metabolite of methanol, to cytochrome c oxidase, which is the key enzyme of this process. The retinal ganglion cells and their axons, which form the optic nerve, are particularly susceptible to this mitochondrial dysfunction, likely due to their high energy dependence.(7)

In the acute phase, Me-ION is characterized by bilateral, symmetrical visual loss with sluggish pupillary light reflexes and dyschromatopsia. The most common fundoscopy findings are hyperaemic, swollen optic discs and peripapillary retinal oedema.(6) In some cases, a characteristic pattern of white, peripapillary retinal oedema which spreads out superiorly and inferiorly from the optic disc and extends along the vascular arcades has been described. (12,13)

We present a case series where we associate this striking clinical pattern of superior and inferior white peripapillary retinal oedema on fundoscopy with a unique pattern of superior and inferior retinal nerve fibre layer (RNFL) thickening on ocular coherence tomography (OCT) in 4 patients seen with acute methanol poisoning at Groote Schuur hospital in Cape

Town, South Africa, during the national alcohol ban of the COVID-19 pandemic.

Methods:

This is a retrospective case series of four adult patients with acute methanol toxicity who were seen at the Division of Ophthalmology, Groote Schuur hospital, Cape Town, South Africa, during the COVID-19 related national alcohol ban between 27 March 2020 and 31 May 2020. An attempt was made to locate possible other patients but according to the author's knowledge all other cases of methanol toxicity during the study period had passed away or did not present to hospital.

Patients underwent ophthalmic evaluation once their general medical condition had stabilised. History taking included demographics (e.g., gender, age), particulars of the event involving methanol ingestion, pre-existing ocular conditions, systemic comorbidities, medication, and recreational drug usage. Details about the prior medical management of the systemic manifestations of methanol toxicity was collected from patient records. Clinical examination included a best corrected visual acuity using a Snellen visual acuity chart at 6 metres, pupillary light reflex assessment, anterior segment slit-lamp examination, and dilated fundoscopy. Fundoscopy was performed by the same medical practitioner using a slit lamp with 78-dioptre lens as well as an indirect ophthalmoscope with a 20-dioptre lens. Fundus photography (Canon CF-1 Digital Retinal Camera, Retinal imaging control software MYD; version 4.5.0.8) and optical coherence tomography (OCT) using a Heidelberg SD-OCT Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany: software version V6.16.8) was performed. Summary statistics and frequencies were used to describe the data using R-Studio version 2023.09. Data was entered into an Excel spreadsheet and the mean values of the horizontal and vertical distribution of peripapillary retinal nerve fibre layer oedema were calculated and compared against the mean values of the normative database of the Heidelberg SD-OCT Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany: software version V6.16.8).

This study was approved by the Human Research Ethics Committee of the University of Cape Town. (HREC nr: 712/2021)

Results

During the national alcohol ban implemented in South Africa during the initial stages of the COVID-19 pandemic in 2020, four patients presented with acute Me-ION to the Division of Ophthalmology, Groote Schuur hospital, Cape Town.

All patients admitted to drinking an alcoholic home brew within 2 days of visual loss. All were male with a mean age of 39 years (range 33-50 years). Case 1 and 4 were admitted to the

intensive care unit for sustained low-efficiency daily diafiltration dialysis (SLEDD). All 4 cases received methylprednisolone 1g daily intravenously for 3 days and erythropoietin 20 000 IU intravenously. None of the patients had any known comorbidities or past ocular history, and none admitted to any recreational drug use. All patients were referred to ophthalmology as soon as their general medical condition allowed with a mean interval between methanol exposure to ocular examination of 5.5 days (range 3-10 days). Table 1 details the ocular findings of the patients. Case 1,2 and 3 presented with bilateral profound acute painless visual loss with visual acuities of count fingers (CF) or worse and decreased optic nerve function. In contrast, case 4 presented with left-sided visual loss and reduced optic nerve function but retained 6/6 vision and normal optic nerve function in the right eye.

In all cases, fundoscopy showed a distinctive pattern of peripapillary RNFL whitening and oedema, which extended superiorly and inferiorly from the optic discs and followed the vascular arcades but spared the nasal and temporal areas (see figure 1). Additionally, the RNFL whitening and oedema in case 2 was more widespread and extended nasally and temporally from the optic disc. Case 4 had the characteristic pattern of superior and inferior whitening and oedema in the eye with normal optic nerve function, as well as the eye with visual impairment and reduced optic nerve function. (see figure 2)

	Time between methanol ingestion and ocular examination (days)	Snellen visual acuity		Pupillary light reflexes	Anterior segment	Fundoscopy
		OD	OS			
Case 1	3	NPL	NPL	Bilateral total afferent pupillary defects	Normal	Superior and inferior peripapillary retinal nerve fibre layer whitening and oedema
Case 2	5	CF	CF	Sluggish pupillary light reflexes	Normal	Global peripapillary retinal nerve fibre layer whitening and oedema

Case 3	10	CF	CF	Sluggish pupillary light reflexes	Normal	Superior and inferior peripapillary retinal nerve fibre layer whitening and oedema
Case 4	4	6/6	CF	Left afferent pupillary defect	Normal	Superior and inferior peripapillary retinal nerve fibre layer whitening and oedema

Table 1: Clinical examination of all study participants

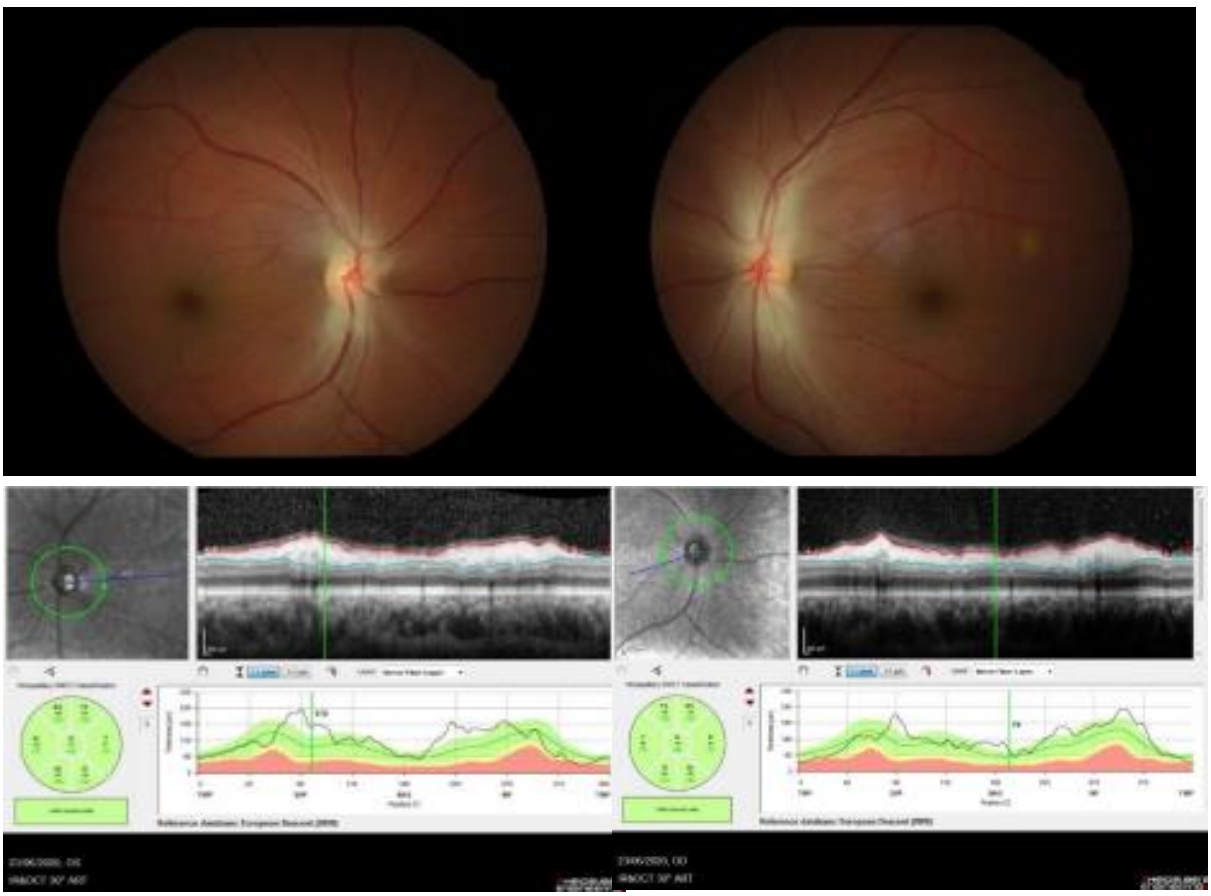


Figure 1: Fundus photos and RNFL OCT of case 1. Patient presented with bilateral NPL vision with total afferent pupillary defects. Both eyes demonstrated peripapillary retinal nerve fibre layer whitening and oedema which extended superiorly and inferiorly from the optic discs, and which corresponded to superior and inferior RNFL thickening on OCT.

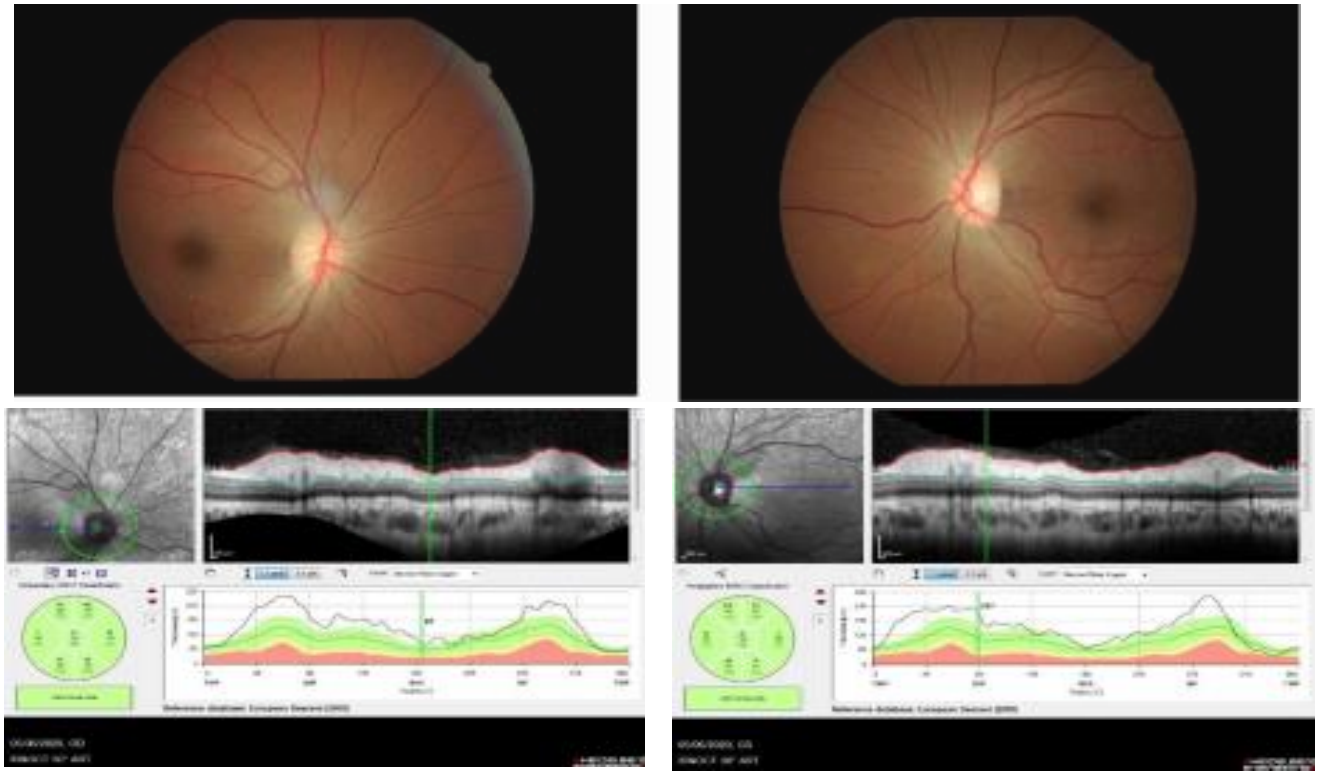
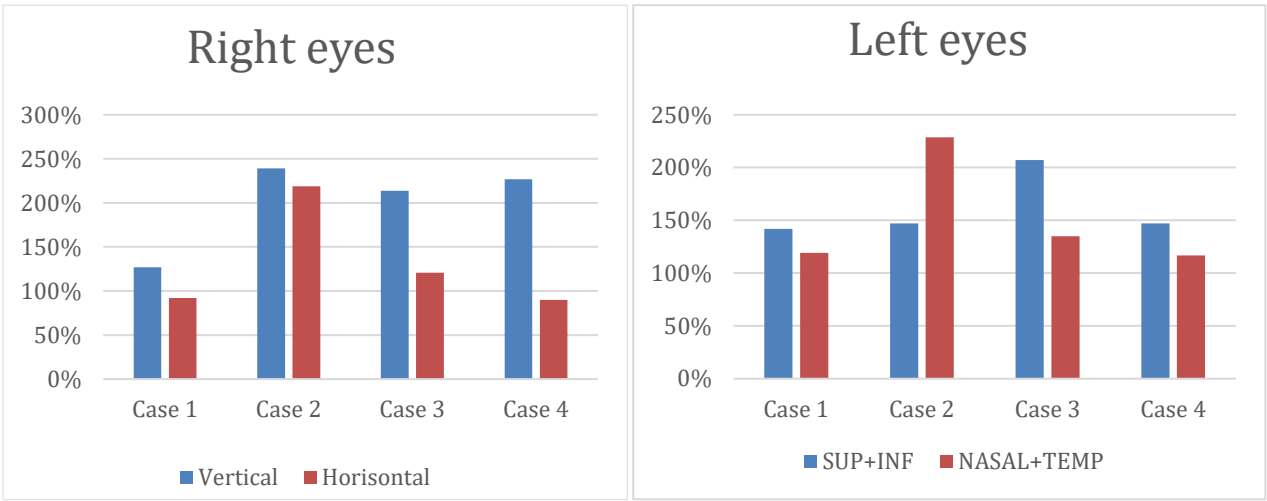


Figure 2: Fundus photos and RNFL OCT of case 4. The right eye had 6/6 vision with normal optic nerve function, whilst the left eye had CF vision and a relative afferent pupillary defect. Both eyes demonstrated peripapillary retinal nerve fibre layer whitening and oedema which extended superiorly and inferiorly from the optic discs, and which corresponded to superior and inferior RNFL thickening on OCT.

RNFL OCT of case 1,3 and 4 demonstrated RNFL thickening with a distribution that corresponded to the fundoscopy findings, affecting predominantly the superior and inferior quadrants, whilst the nasal and temporal quadrants were relatively spared (see figure 1 and 2). Case 2 demonstrated more diffuse RNFL thickening, which corresponded to the more diffuse peripapillary retinal whitening and oedema visible on fundoscopy. Graph 1 shows RNFL percentage thickening compared to normative data both in the vertical meridian (mean of the superior and inferior quadrants) and horizontal meridian (mean of the nasal and temporal quadrants) for each eye of all cases. It demonstrates the pattern of predominantly vertical RNFL thickening with horizontal sparing in case 1,3 and 4, but global thickening in case 2.



Graph 1: Retinal nerve fibre layer percentage thickening compared to normative data of the Heidelberg SD-OCT Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany: software version V6.16.8) both in the vertical meridian (mean of the superior and inferior quadrants) and horizontal meridian (mean of the nasal and temporal quadrants) for each eye of all cases. It demonstrates the pattern of predominantly vertical retinal nerve fibre layer thickening with horizontal sparing in case 1,3 and 4, but global thickening in case 2.

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Discussion

Methanol-induced optic neuropathy (Me-ION) is a potentially sight-threatening condition. During the COVID-19 pandemic and the associated alcohol prohibition, we observed four cases of Me-ION due to inadvertent consumption of tainted liquor. All patients were examined in the acute phase, with a mean interval between methanol exposure and ocular assessment of 5.5 days (range 3-10 days). Notably, three patients demonstrated distinct fundoscopic findings of white retinal oedema affecting only the superior and inferior peripapillary areas. This correlated with an increased peripapillary RNFL thickness on OCT in the superior and inferior quadrants, with relative sparing of the nasal quadrant and the maculopapular bundle.

While this fundoscopy finding has been previously documented in older studies, its association with the characteristic vertical RNFL thickening on OCT in the acute phase of Me-ION is a novel observation. (12,13)

Most publications that include peripapillary RNFL thickness measurements are performed in the subacute or chronic phase of Me-ION, often because the patients are systemically too unwell in the acute phase to receive the test. (14–16) Typically, the subacute phase (after acute systemic features have resolved) of Me-ION is associated with generalised RNFL swelling or normal RNFL measurements, while the chronic phase exhibits diffuse RNFL atrophy. (14–16) Interestingly, in a case report comprising two patients who underwent RNFL measurements at 4- and 10-months post exposure, the RNFL was atrophic in the superior and inferior quadrants, and normal in the nasal and temporal quadrants.(17) It would be of interest to know whether the atrophic quadrants were thickened in the acute phase, as observed in our case series. The cause of vertical RNFL swelling with horizontal sparing, as observed in our case series, remains uncertain. In a recent publication featuring multimodal imaging of a case of subacute Me-ION, a similar fundoscopy appearance to our cases were observed. RNFL measurements were not performed, but OCT showed thickened, hyper-reflective inner retinal layers in the superior and inferior peripapillary areas, with normal macular OCT, mirroring our cases. The authors of this study proposed that this may signify ischaemic retinal nerve fibre layer oedema due to accumulation of formic acid with mitochondrial dysfunction, predominantly in the para-optic short posterior ciliary arteries and their smaller branches, as opposed to the central retinal artery.(18)

Compared to other disease entities causing bilateral optic disc swelling or papilledema, such as idiopathic intracranial hypertension and vascular papillopathy, a previous study makes conclusions. The study suggests that OCT features of optic disc oedema usually follow the normative pattern of RNFL thickness (Inferior>Superior>Nasal>Temporal). Exceptions are

noted in uveitis and compressive aetiologies (Superior>Inferior>Nasal>Temporal).(19) Interestingly, in our study, there was a difference in the distribution of oedema between the left and right eye. Oedema in the right eye was most severe inferiorly (Inferior>Superior>Nasal>Temporal) and in the left eye superiorly (Superior>Inferior>Nasal>Temporal), however not all eyes followed these patterns of distribution. This shows that Me-ION does not follow a specific pattern of optic disc oedema compared to other disease entities, but the vertical meridian is significantly more affected than the horizontal meridian.

This study has several limitations. The limited sample size and lack of a control group posed challenges in conducting a statistical evaluation to determine whether Me-ION adheres to the normative pattern of RNFL oedema. Larger studies to compare RNFL swelling patterns in acute Me-ION to other causes of acute visual loss and RNFL swelling, such as optic neuritis, are necessary to validate our observations. Additionally, investigating the connection between RNFL measurements during the acute phase of Me-ION and alterations in retinal ganglion cell layer analysis would be beneficial. This study describes a distinct pattern of superior and inferior quadrant peripapillary RNFL swelling on fundoscopy and RNFL OCT in acute Me-ION. Recognition of this pattern may facilitate early diagnosis and timely initiation of life-saving treatment, particularly in cases where patients may be unaware of their methanol exposure.

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Addendum 1: Original ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45, E-52- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 November 2021

HREC REF: 712/2021

Dr J Steffen
Division of Ophthalmology
Ward D4, NGSH
Email: j.steffen@uct.ac.za
Student: francoismaritz28@gmail.com

Dear Dr Steffen

PROJECT TITLE: 2021/238-NOVEL DISTRIBUTION OF PERIPAPILLARY RETINAL NERVE FIBER LAYER OEDEMA IN ACUTE METHANOL TOXICITY: A CASE SERIES OF 5 PATIENTS AT GROOTE SCHUUR HOSPITAL (MMED DEGREE - DR FRANCOIS IGNATIUS MARITZ)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020: 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 November 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Francois Maritz will also be involved in this study.

Please quote the HREC REF 712/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Addendum 2: Extension of ethics approval

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/04/24
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate	Date Signed	23/4/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za. Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	12 April 2023		
HREC REF Number	712/2021	Current Ethics Approval was granted until	30 Nov 22
Protocol title	Novel distribution of peripapillary retinal nerve fiber layer oedema in acute methanol toxicity: A case series of 5 patients at Groote Schuur Hospital		
Principal Investigator	Dr. Jonel Steffen		
Department / Office Internal Mail Address	j.steffen@uct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository

HUMAN RESEARCH ETHICS COMMITTEE
21 APR 2023
HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		5
Total number of records or specimens collected, reviewed or stored since last progress report		5
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI	Signed by candidate	Date	11/04/2023

16 February 2022 Page 1 of 1 FHS017
(Note: Please complete the Closure form (FHS018) if the study is completed within this approval period)