# Look and LEEP: How are we doing? A 5-year audit of the colposcopy clinic at Groote Schuur Hospital, from 01 January 2017 to 31 December 2021

A minor dissertation in fulfillment for the requirements of the degree Master of Medicine (MMED) in Obstetrics and Gynaecology.



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**Supervisor**: Prof. Nomonde Mbatani

Faculty of Health Sciences

Department of Obstetrics and Gynaecology

Groote Schuur Hospital

University of Cape Town

**Declaration**

I, Marlene Whelpton, declare that the submitted dissertation is my original work. The dissertation forms an integral component of my specialized Master's degree in Obstetrics and Gynaecology at the University of Cape Town. The work is genuine and has not been submitted nor presented for any other academic degree or institution. The research was carried out under the guidance and supervision of an academic mentor within the Department of Obstetrics and Gynaecology. The study adhered to academic protocols, and I secured ethical approval before commencing my research.

I further declare that this research complies with all relevant ethical standards and guidelines.

I have not plagiarized any content, and I have properly cited all sources used in this study.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Name :

Signature: Signed by candidate

Date: 29/1/24

**Acknowledgements:**

Firstly, I would like to thank my husband Drew Gaskell for his love and support and help with this research project. I would also like to thank Ms Moleen Zunza and Dr Abbaas Allie for the excellent statistical analyses and the help with interpretation thereof. Lastly, I would also like to express my sincere gratitude to Professors Mbatani and Petro for their invaluable input into this research project.

**Table Of Content:**

Western Cape Government

**GROOTE SCHUUR HOSPITAL**
**Enquiries**: Dr Bernadette Eick
**e-mail**: GSHReserach.Request@westerncape.gov.za

**Dr N. Mbatani**
Division of Obstetrics and Gynaecology

E-mail: nomonde.mbatani@uct.ac.za

**Dear Dr Mbatani**

**RESEARCH PROJECT: Look and Leep: How are we doing? An Audit of the GSH Colposcopy Clinic from 1st Jan 2017 – 31st Dec 2021**

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 October 2023**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
**c) Confidentiality must always be maintained.**
**d)** No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
**g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
**n) Kindly submit a copy of the publication or report to this office on completion of the research.**
**o) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
**p) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

**DR BERNADETTE EICK**
**CHIEF OPERATIONAL OFFICER**
**Date:** 04 January 2023
C.C. Mr. L. Naidoo, Mr. A. Mohamed, Professor M. Matjila, Dr S. Murray

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

# FHS016: Annual Progress Report / Renewal

| 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 \| 10 \| 24 |
| ☐ Not approved | See attached comments | | |
| Signature Chairperson of the HREC/ Designee | | Date Signed | 15/10/2023 |

**Note:** 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.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

| Comments to PI from the HREC |
|---|
| |

## Principal Investigator to complete the following:

## 1. Protocol information

| | | | |
|---|---|---|---|
| Date (when submitting this form) | 11\|10\|23 | | |
| HREC REF Number | 677 \| 2022 | Current Ethics Approval was granted until | 30\|10\|2023 |
| Protocol title | LOOK AND LEEP: HOW ARE WE DOING? AN AUDIT OF THE GROOTE SCHUUR HOSPITAL COLPOSCOPY CLINIC FROM 01 JANUARY 2017 - 31 DECEMBER 2021 | | |
| Protocol number (if applicable) | | | |
| Are there any sub-studies linked to this study? | ☐ Yes | ☒ No | |
| If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study. | | | |
| Principal Investigator | DR NOMONDE MBATANI | | |

HUMAN RESEARCH
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13 OCT 2023
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UNIVERSITY OF CAPE TOWN



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval p

| | |
|---|---|
| Department / Office Internal Mail Address | Nomonde.Mbatani@uct.ac.za |

| | | |
|---|---|---|
| 1.1 Does this protocol receive US Federal funding? | ☐ Yes | ☒ No |
| 1.2 If the study receives US Federal Funding, does the annual report require full committee approval?<br><br>**Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates.<br><br>(Please send electronic copy for full committee review to hrec-submission@uct.ac.za) | ☐ Yes | ☒ No |

**If yes in 1.2 please complete section 1.3 below for invoicing purposes**

## 1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

| ***Submission Type*** | ***Description*** | ***New fee (Vat Incl.)*** | ***tick ✓*** |
|---|---|---|---|
| ***Research funded solely from UCT departmental/ divisional/group budget*** | Annual evaluation of research progress report for re-certification | **R0,00** | ☐ |
| ***Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges*** | Annual evaluation of research progress report for re-certification | **R0,00** | ☑ |
| ***Annual re-certification / Progress report (FHS016 Form)*** | Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval | **R7000,00** | ☐ |
| ***Annual re-certification / Progress report (FHS016 Form)*** | Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review | **R3 710.00** | ☐ |
| ***Annual re-certification / Progress report (FHS016 Form)*** | National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval | **R6000.00** | ☐ |
| ***Annual re-certification / Progress report (FHS016 Form)*** | National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review | **R1 500,00** | ☐ |

***NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.***

**Please provide details for Invoicing, either complete section 1 or 2 :**

**1. Invoice billing – Directly to Sponsor**

| | |
|---|---|
| Sponsor's name | N/A |
| Billing Address of Sponsor: | |
| Vat Number: | |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

| | |
|---|---|
| Contact person | |
| Telephone number | |
| Email Address | |
| 2. **Internal Journal Billing:** | |
| Fund Number: | N/A |
| Cost Centre Number: | |
| Account Holder Name: | |
| Division of Account Holder: | |

## 2. List of documentation for approval

## 3. Protocol status (tick ✓)

| | |
|---|---|
| ☐ | Open Enrolment |
| ☐ | Closed to enrolment (tick ✓) |
| ☐ | Research-related activities are ongoing |
| ☐ | Research-related activities are complete, long-term follow-up only |
| ☑ | Research-related activities are complete, data analysis only |
| ☐ | Main study is complete but sub-study research-related activities are ongoing |
| ☐ | Study is closed → Please submit a Study Closure Form (FHS010) |

## 4. Enrolment

| | |
|---|---|
| Number of participants enrolled to date | N/A |
| Number of participants enrolled, since last HREC Progress report (continuing review) | N/A |
| Additional number of participants still required | N/A |

## 5. Refusals

| | |
|---|---|
| Total number of refusals (participants invited to join the study, but refused to take part) | N/A. |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

## 6. Cumulative summary of participants

| | |
|---|---|
| Total number of participants who provided consent | |
| Number of participants determined to be ineligible (i.e. after screening) | |
| Number of participants currently active on the study | |
| Number of participants completed study (without events leading to withdrawal) | |
| Number of participants withdrawn at participants' request (i.e. changed their mind) | |
| Number of participants withdrawn by PI due to toxicity or adverse events | |
| Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance) | |
| Number of participants lost to follow-up.<br>Please comment below on reasons for loss of follow-up. | N/A |
| | |

| | |
|---|---|
| Number of participants no longer taking part for reasons not listed above.<br>Please provide reasons below: | N/A |
| | |

## 7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:

Literature review, concept note and protocol done
Data retrieved from database
Data filtered
Data provided to statistician.

## 8. Protocol violations and exceptions (tick ✓ all that apply)

| | |
|---|---|
| ☑ | No prior violations or exceptions have occurred since the original approval |
| ☐ | Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved |
| ☐ | Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review |

## 9. Amendments (tick ✓ all that apply)

| | |
|---|---|
| ☑ | No Prior amendments have been made since the original approval |

| | |
|---|---|
| ☐ | Prior amendments have been reported since the last review and have already been approved |
| ☐ | New protocol changes/ amendments are requested as part of this continuing review (See note below) |

**Note:** If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

## 10. Adverse events

| |
|---|
| 10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established. |
| N\A |

| | | |
|---|---|---|
| 10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)? | | |
| ☐ Yes | ☐ No | ☑ Not applicable |
| If yes, please describe: | | |
| | | |

## 11. Summary of Monitoring and Audit Activities (tick ✓)

| | | |
|---|---|---|
| 11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)? | | |
| ☐ Yes | ☐ No | ☑ Not applicable |

| | | |
|---|---|---|
| 11.2 Did a Data and Safety Monitoring Board publish a report? | | |
| ☐ Yes | ☐ No | ☑ Not applicable |

| | | | | | |
|---|---|---|---|---|---|
| 11.3 If yes, please identify the agency and attach a summary of the findings. | | | | | |
| Agency Name | | Report attached | ☐ Yes | ☐ No | ☐ Not applicable |
| | | DSMB report attached | ☐ Yes | ☐ No | ☐ Not applicable |

| | |
|---|---|
| 11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team? | |
| ☐ Yes | ☑ No |
| If yes, please explain: | |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

## 12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:

| | |
|---|---|
| ☐ | Increased |
| ☐ | Decreased |
| ☐ | Shown no change |

If there has been a change, please explain:

N/A
No Risk → Retrospective analysis of database

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

## 13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**

| | | |
|---|---|---|
| ☐ Yes | ☐ No | ☑ Not Applicable – N/A |

**If yes, please complete the following:**

| | | | |
|---|---|---|---|
| Insurer's name: | | | |
| Policy no. | | *Coverage Period: | |

***For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.***

## 14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)

| | |
|---|---|
| ☐ Yes | ☑ No |

If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

## 15. Signature

| My signature certifies that the above is complete and correct. | | | |
|---|---|---|---|
| Signature of PI | | Date | 11/10/23 |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

**2.1 Tables**

Table 1 Baseline characteristics of the 715 participants

| Characteristic | N (%) or mean (standard deviation |
|---|---|
| Age, years | 39.085 (9.081) |
| Parity median (IQR) | 2 (1 to 3) |
| CD4 count, median (IQR) | 337.5 (195 to 540) |
| Current smoker | |
| No | 554 (77.81) |
| Yes | 158 (22.19) |
| HIV diagnosis | |
| yes | 249 (34.83) |
| No | 451 (63.08) |
| Unknown | 15 (2.10) |
| CD4 count | |
| <200 | 86 (26.71) |
| 201-499 | 140 (43.48) |
| >500 | 96 (29.81) |
| HIV viral load | |
| Unsuppressed | 77 (17.19) |
| Suppressed | 299 (66.74) |
| Unknown | 72 (16.07) |
| HIV treatment | |
| None | 11 (1.58) |
| Yes | 410 (58.74) |
| Not applicable | 277 (39.68) |

Table 2 Factors associated with overtreatment among patients attending colposcopy clinic between 2017-2021: Logistic regression model

| | Univariate logistic regression | | Multiple logistic regression | |
|---|---|---|---|---|
| Characteristic | Crude odds ratio (95% CI) | p-value | *Adjusted odds ratio (95% CI) | p-value |
| Age, years | 1.058 (1.035 to 1.080 | <0.001 | 1.058 (1.035 to 1.083) | <0.001 |
| Parity | 1.005 (0.863 to 1.169) | 0.954 | 0.888 (0.749 to 1.053) | 0.172 |
| Current smoker | | | | |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.067 (0.656 to 1.736) | 0.795 | 0.852 (0.498 to 1.455) | 0.557 |
| HIV diagnosis | | | | |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.688 (0.449 to 1.054) | 0.085 | 0.752 (0.474 to 1.193) | 0.226 |
| Unknown | 4.077 (1.405 to 11.830) | 0.010 | 3.452 (1.098 to 10.856) | 0.034 |
| CD4 count | | | | |
| <200 | 1 (reference) | | | |
| 201 -499 | 0.758 (0.327 to 1.755) | 0.517 | | |
| >500 | 1.068 (0.451 to 2.527) | 0.881 | | |
| HIV viral load | | | | |
| Unsuppressed | 1 (reference) | | | |
| Suppressed | 1.775 (0.723 to 4.360) | 0.211 | | |
| Unknown | 2.134 (0.745 to 6.110) | 0.158 | | |

*Adjustment was done for the variables in the multiple logistic regression model

Table 3 Association between over treatment and selected characteristics in patients attending colposcopy clinic: Univariate chi-squared test

| Characteristic | No overtreatment n (%) | Overtreatment n (%) | p-value |
|---|---|---|---|
| Referral pap smear<br>Normal<br>Abnormal | 25 (71)<br>581 (85) | 10 (29)<br>99 (15) | 0.025 |
| Final Histological diagnosis<br>Normal<br>Abnormal | 56 (71)<br>515 (87) | 23 (29)<br>79 (13) | <0.001 |
| Final Histological diagnosis<br>Normal<br>Abnormal<br>cancer | 56 (71)<br>485 (87)<br>30 (88) | 23 (29)<br>75 (13)<br>4 (12) | 0.001 |

## 2.2 Figures

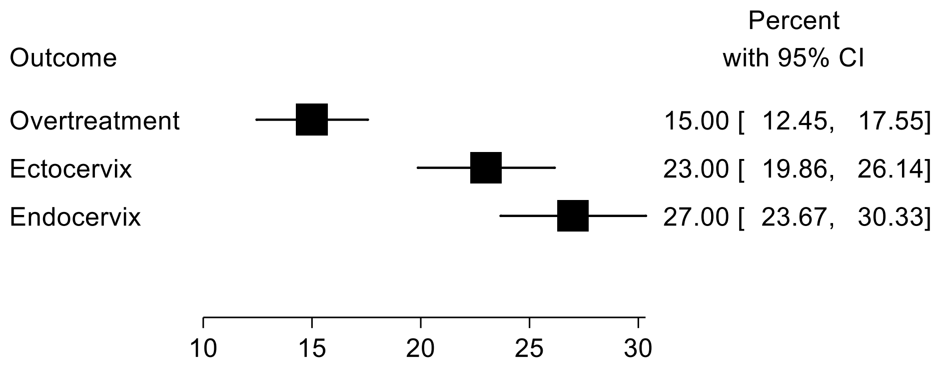


Figure 1 Clinical outcome estimates with 95% CI

Endocervix and ectocervix refers to the margins of the histology specimen.

Note overtreatment is >10%, p-value <0.001

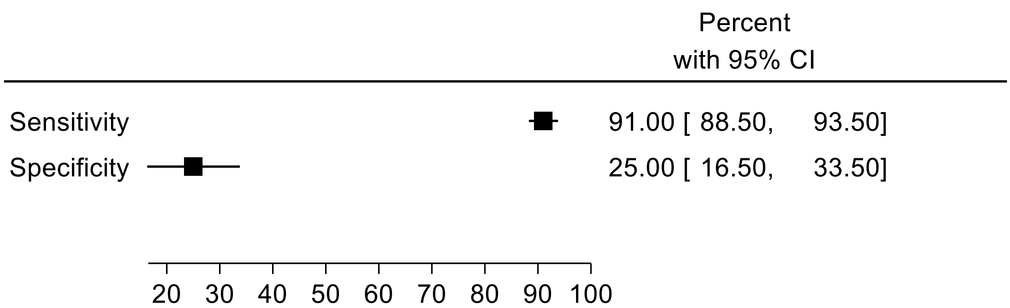


Figure 2 Diagnostic accuracy for Colposcopy Diagnosis

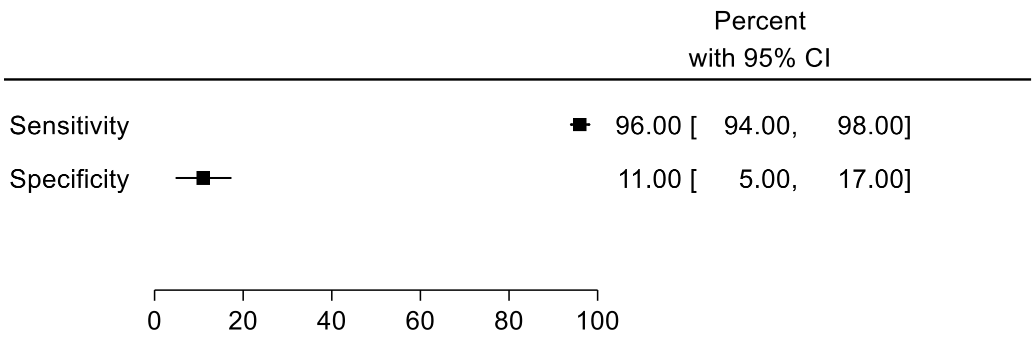


Figure 3 Diagnostic accuracy for referral Pap smear

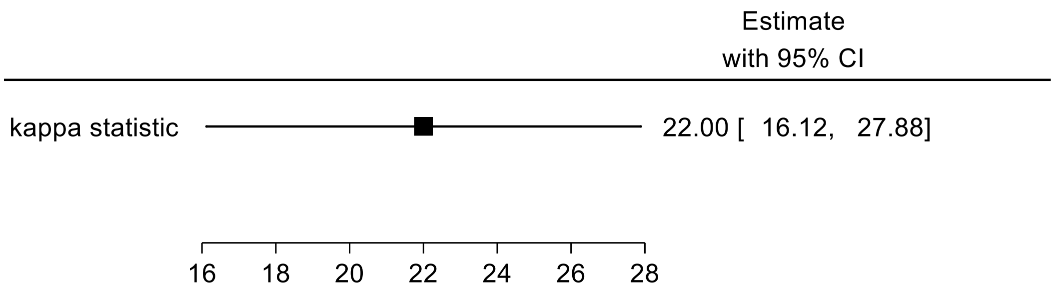


Figure 4 Agreement between colposcopic diagnosis and outcome: **Fair agreement**

## 3. List of Abbreviations

| | | |
|---|---|---|
| HPV | - | Human Papillomavirus |
| WHO | - | World Health Organization |
| HIV | - | Human Immunodeficiency Virus |
| CIN | - | Cervical Intraepithelial Neoplasia |
| VIA | - | Visual Inspection with Acetic acid |
| LEEP | - | Loop Electrosurgical Excision Procedure |
| TZ | - | Transformation zone |
| ASCCP | - | The American Society for Colposcopy and Cervical Pathology |
| ASCUS | - | Atypical squamous cells of undetermined significance |
| ASC-H | - | Atypical Squamous cells High grade lesion cannot be excluded. |
| HSIL | - | High Grade Squamous Intraepithelial Lesion |
| LSIL | - | Low Grade Squamous Intraepithelial Lesion |

## 4. Abstract

**Background**: Cervical cancer persists as the second most common cancer in women in developing countries. The prevalence of cervical cancer has markedly decreased in well developed nations, primarily attributed to the implementation of efficacious screening services. Such screening services pose formidable challenges in developing countries. Therefore, the 'See-and-Treat' strategy has been adopted in South Africa and other developing countries to reduce loss to follow up and prevent patients from presenting with advanced disease, thereby reducing the morbidity and mortality associated with cervical cancer. The main limitation of this approach is the risk of overtreatment, identified as final histopathology without high grade lesion (HSIL). The objective of our study was to determine the rate of overtreatment at a colposcopy clinic in a tertiary centre with extensive experience in colposcopy and to detect possible factors associated with this rate.

**Methods:** This was a retrospective, descriptive cohort study that analysed data from 715 women who had undergone the 'See-and-Treat' treatment approach from 2017 to 2021 at Groote Schuur Hospital Colposcopy clinic. Overtreatment was defined as final histopathology results of Cervical Intraepithelial Neoplasia grade 1 (CIN 1) or less.

**Results:** Of the 715 women, there were 109 (15.24%, 95% CI 0.13 – 0.18) with a histopathology result of CIN 1 or less. There was a statistically significant association between age and the odds of overtreatment as well as between HIV negative women, when compared to HIV positive women on treatment, and the odds of overtreatment. No statistically significant association was found between smoking status, HIV viral load, CD4 count or parity.

**Conclusion**: The overtreatment rate in this study can be considered acceptable and comparable with rates reported in the literature. HIV negative women should be considered for a biopsy prior to LEEP to decrease risk of overtreatment, but the risk should be weighed against the risk of loss to follow up.

**Keywords**: Cervical intraepithelial neoplasia, Colposcopy, See-and-Treat, Overtreatment, Negative histology.

## 5. Chapter 1: Introduction and Literature review.

Cancer of the cervix is a preventable and largely curable disease; however, it remains the 4th most common cancer in women in the world [1,3] and the second most common cancer in developing countries. [2] Each year approximately 570 000 new cases of cervical cancer are diagnosed, and more than 311 000 die due to cervical cancer. Nine out of ten cervical cancer related deaths occur in low-income countries. [2,3] These countries have access to less than 5% of the global cancer resources. It is estimated that the lifetime risk for a woman in a low resource country to develop cervical cancer is between 2-4%. [1]

Cervical cancer reflects the global inequity of health care clearly. [3] The incidence of cervical cancer has decreased profoundly in well developed countries, largely due to effective screening services. These services include cytology-based screening with or without HPV DNA testing followed by colposcopy, biopsy and treatment of precancerous lesion, or referral for management of invasive cancer. These programs are too expensive, materially and on an organizational level, to maintain in low-resource countries. [4,5] These underdeveloped countries have an incidence of cervical cancer twice as high as the developed countries with cervical death rates as high as 90%. [1,2,3]

In May 2018 the director-general of the WHO announced a global call to action towards the elimination of cervical cancer. In 2019 a global strategy towards the elimination of cervical cancer as a public health problem was developed. This strategy outlines key goals and targets to be reached by 2030 and set the world on track to eliminate cervical cancer. According to Dr TA Ghebreyesus, director-general of WHO, cost effective, evidence-based interventions which include HPV vaccination, screening and appropriate treatment of precancerous lesions and improving access to management of invasive cancers would make cervical cancer a disease of the past. The global strategy for 2030 are the following: 90% of girls must be fully vaccinated with the HPV vaccine at the age of 15 years. Ninety percent of women must be screened with high performance test by the age of 35 and again by the age of 45, and 90% of women identified with cervical disease must receive treatment. This includes treatment of precancerous lesions as well as management of invasive cancer (the 90-70-90 initiative) [3]

Almost all cases of cervical cancer are caused by high-risk human papilloma virus (HPV). HPV is one of the most common sexually transmitted diseases. It is estimated that the incidence of new HPV infections in the USA ranges from 1 million to 5.5 million/year and the prevalence is as high as 20 million. However, as HPV is not a reportable disease the actual incidence and prevalence is unknown and is likely much higher. There are over 200 HPV types identified. The high-risk types that are involved in cervical cancer include type 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70. HPV 16 accounts for more than 50% of cervical lesions. HPV 16 has a stronger propensity to persist and lead to neoplastic changes than other high-risk types. [6,7] HPV is implicated in 99.7% of squamous cell carcinoma of the cervix. Adenocarcinoma of the cervix is also related to HPV, but the correlation is less profound. [7]

HIV and HPV:
HIV also plays an important role in HPV infection and cervical cancer. In 2018 it was estimated that 40 million people worldwide were living with HIV and more than half of those were female. In the same year 570 000 new cases of cervical cancer were diagnosed, which represents 6.6% of all female cancers. [8] Women living with HIV have a higher susceptibility to become infected with high-risk HPV, having persistent high risk HPV infection with subsequent development of CIN, and/or invasive cervical cancer. It is estimated that HIV positive women have a 3-fold increased risk to develop cervical lesions compared to HIV negative patients. [8] Women who are HIV positive are 2,5 times more likely to have recurrence after treatment for precancerous lesions of the cervix, due to persistence of disease. [8, 4] HIV and HPV infection rates in South Africa are among the highest globally. [9] HPV infection in HIV positive women in SA has been documented as 61%. [9]

Since the development of cervical cancer occurs over several years, it may permit early diagnosis and treatment of precancerous lesions if feasible and effective screening programs are in place. [10]

Cervical intraepithelial neoplasia (CIN) is a condition of the cervix that may exist in one of three stages: CIN 1, CIN 2, or CIN 3. The diagnosis of CIN is made by histopathological examination of biopsy or excision specimen of the cervix. A judgement of whether a cervical tissue specimen reveals CIN, and to what degree, is dependent on the histological features concerned with differentiation, maturation and stratification of cells and nuclear abnormalities. The proportion of the thickness of the epithelium showing mature and differentiated cells is used for grading CIN. More severe degrees of CIN are likely to have a greater proportion of the thickness of epithelium composed of undifferentiated cells, with only a narrow layer of mature differentiated cells on the surface. If left untreated CIN 2 or CIN 3 (collectively known as $CIN2^+$) can progress to invasive cervical cancer and is therefore a premalignant condition. [11]

The conventional screening method used involves a 3-step treatment plan. This includes the initial abnormal cervical cytology result, referral for a colposcopically guided cervical biopsy, followed by treatment if CIN $2^+$ is diagnosed on histology. [12]
This traditional screening method requires highly trained human resources and a substantial amount of laboratory equipment. In low- and middle-income countries, because of the high cost of setting up screening programs based on cytology, coverage of screening is very low and alternative screening methods are needed. In addition, follow-up of a positive cytology test with colposcopy and biopsy requires resources and skilled personnel that are largely lacking in many countries. Other bottlenecks in cytology-based screening programs include the need for referral to distant health facilities for diagnostic and treatment services, and the long waiting times before cytology results are available. [11]

Many low-income countries have developed alternative screening strategies to overcome difficulties faced with conventional screening strategies. The ‘Screen and Treat’ programs that are used in some countries are non-cytology based and includes HPV DNA testing or visual inspection with acetic acid (VIA) followed by treatment with ablative therapy in women who screen positive. According to Denny et al [1] both HPV testing and VIA perform as well as or better than cytology-based screening for identifying high- grade cervical cancer precursor lesions. Thermo-ablation and cryotherapy are relatively low- technology treatment methods that are highly efficacious with minimal adverse effects and morbidity. [1] These ‘Screen-and-Treat’ methods overcome two of the biggest barriers to cervical cancer prevention in low resource countries: cytology-based screening and colposcopy, which are expensive and largely unavailable. Several studies have confirmed the efficacy and safety of such screen and treat methods to prevent cervical cancer. [1,13]

Cervical cancer, along with maternal deaths, has been identified as a national priority in South Africa as well as other Sub-Saharan countries. [14] In order to mitigate the impact of cervical cancer on health and socio-economic development, the country needs to implement a comprehensive cervical cancer prevention and management program. This entails implementation of three interdependent strategies, namely: (i) reducing oncogenic HPV infections, (ii) detecting and treating cervical pre-cancer, and (iii) providing timely treatment and palliative care for invasive cancer.
Cervical cancer ranks as the leading cause of female cancer deaths in South Africa and particularly affects women in the reproductive age group. Recent estimates suggest that given a population of 19.35 million women aged 15 and older who are at risk of developing cervical cancer, 7 735 women are diagnosed annually with cervical cancer and 4 248 would die from the disease. This means more than 50% of women diagnosed with cervical cancer die from the disease, a similar occurrence as found in other low-income countries.
The number of diagnosed cases is still on the increase and the morbidity and mortality pattern in many women may be compounded by late presentation, with advanced disease (in over 75% of cases) which is more difficult and more expensive to treat effectively.
Despite the existence of a national cervical screening program implemented in 2002, the incidence of new cases of cervical cancer is unchanged in South Africa, due to lack of adequate screening coverage, especially for populations at risk.
The mean age of diagnosis of cervical cancer is about 45 years, with many cases occurring before the age of 35. Black women and women living with HIV bear a disproportionate burden of cervical cancer disease, reflecting lack of access to comprehensive and effective integrated care. [14]

Cancer control methods implemented in South Africa include a two-tiered approach - primary and secondary prevention strategies.
Primary prevention includes safer sexual practices, smoking cessation, and HPV vaccination against oncogenic HPV 16 and 18. The HPV vaccination program was started in SA in 2014 for prepubertal girls (i.e., before the onset of sexual activity.) Studies have shown that if 70% of girls aged 9-12 years of age are vaccinated against HPV there will be a 43% reduction in the lifetime risk of cervical cancer. (22) Unfortunately, the uptake of the vaccine has been inadequate in low- and middle-income countries due to cost, service delivery, lack of political commitment and a global vaccine shortage. (2,14,15)
Secondary prevention includes screening and treatment of precancerous lesions in asymptomatic women.
This is done with a cytology-based screening program with or without HPV DNA testing, or visual methods. HPV DNA testing is recognized as the ideal cervical cancer screening method because of its high sensitivity, positive and negative predictive value, objectivity, and reproducibility. Randomized controlled trials (RCTs) have shown that HPV testing not only detects more CIN $2^+$ lesions at screening, but also leads to their substantial reduction in subsequent screening intervals and a 70 per cent reduction in subsequent invasive cancer. Despite its promising performance, the costs, logistics and technology requirements for successful implementation of a current commercially available HPV test are challenges for under-resourced health systems. (14)
The South African National cervical screening program offers three free pap-smears in a woman's lifetime; at ages of 30, 40 and 50. For HIV positive women allows for the first pap smear to be done at the time of HIV diagnosis and then every 3 years if Pap smear is normal. (14)

Once an abnormal cytology result is obtained the patient is then referred to a colposcopy clinic.
~~This procedure is usually carried out to treat the patient's condition.~~
The psychological stress and financial costs of multiple visits following the conventional management strategy for abnormal cervical cytology has been a great concern on management of patients, therefor the 'See and Treat' strategy was developed. (16)
The See and treat strategy was included in the updated ASCCP and WHO recommendations for prevention of cervical cancer and has been implemented in most institutions in South Africa. (11,17)

See and treat using Loop Excision (LEEP) of the cervical transformation zone (TZ) is an excisional surgical procedure that enables simultaneous histological diagnosis and treatment of cervical precursor lesions at a single visit, therefore eliminating the need for a 2 or 3 step management approach with cervical biopsy and avoids an additional clinic/hospital visit. (18) The latest WHO guidelines recommend a See and Treat program in countries where an appropriate strategy with cytology followed by colposcopy is present for women diagnosed with an abnormal cytology (abnormal is considered as ASCUS or worse). In this instance the See and Treat approach followed by LEEP (otherwise known as Look and LEEP) is a safe and feasible option. (10,11)
Ablation therapy can also be used in see and treat management.

The See and Treat strategy can help decrease the cost of treating a patient's condition and improve their quality of life. It can also help minimize the number of patients who are lost to follow up. One-visit diagnosis and management can help decrease the anxiety of patients. (19,20)
Excision can decrease the false negative histology that can occur with colposcopic directed biopsies. (20) The biggest concern for See and treat approach is overtreatment. (18,22,23) See and Treat with LEEP can lead to unnecessary potential adverse events of the procedure, some occurring immediately, like post procedure pain, bleeding, and cervical infection, which are mostly mild and self-limiting. However, the potential long-term consequences of LEEP procedures include the risk of preterm birth in subsequent pregnancies. (24,25,26) There is strong observational (but no experimental) evidence suggesting a causal link between treatment for CIN with LEEP and subsequent preterm delivery (defined as birth before 37 completed weeks). (25) Evidence regarding this is still controversial and more recent studies have suggested that the increased preterm birth is related to the depth of excisional procedure, or the cervical dysplasia itself. (25, 26) Regardless of the potential adverse effects, LEEP is STILL a safe, easy to learn method, which can be performed on

an outpatient basis, with local anesthesia. Furthermore, in areas with high disease prevalence, the risk of overtreatment is correspondingly low. (28)

The ASCCP defines overtreatment as a final histological diagnosis of CIN 1 or less. (17,21) The recommended rate of overtreatment following the see and treat management program is <10% as a standard requirement according to the Cochrane Colposcopy and Cervical Cytopathology collaborative group. (28)

Potential reasons for discrepancy between a high-grade cytology result and neg LEEP include diagnostic error, complete excision of dysplastic focus during targeted biopsies, spontaneous regression of the lesion and secondary destruction of dysplasia by post biopsy inflammation. (19)

The colposcopy clinic at Groote Schuur hospital accepts patients referred with the following Pap smear criteria:

- High grade squamous intraepithelial lesion (HSIL)
- Atypical squamous cells where high-grade lesion cannot be excluded (ASC-H)
- 3 consecutive smears with atypical squamous cells of undetermined significance (ASCUS) repeated 3-6months apart.
- 2 consecutive smears with low grade squamous intraepithelial lesion (LSIL)
- Any glandular abnormality
- Suspicion of microinvasion

If a high-grade precursor lesion (CIN $2^+$) is observed during colposcopy the patient is counselled and offered a choice of either immediate excision or colposcopically directed biopsies.

The See and treat with LEEP is used if:

- There is parity between cytology and colposcopic findings (i.e., high grade lesion on Pap smear and colposcopy)
- The upper limit of the lesion is seen.
- There is no evidence of glandular abnormality.
- No evidence of micro-invasive cancer

If a LEEP is not possible a cone biopsy is done. A cone is indicated in the following circumstances:

- Marked disparity between cytology and colposcopy finding, e.g., HSIL Pap smear but normal colposcopy.
- Upper limit of the lesion is not visualized.
- Evidence of glandular abnormality
- evidence of micro-invasion

In the context of South Africa being a low resource setting with a high incidence of cervical cancer and cancer related deaths it is vital to offer our patients a good quality screening and treatment program without causing any further harm secondary to overtreatment.
With this objective in mind our study aims to audit the outcome of patients attending the colposcopy clinic at Groote Schuur Hospital.
In doing so we will have a better idea of the spectrum of disease, rate of overtreatment and factors contributing to these outcomes, and we will be able to offer recommendations for improvement of our service.

## ***3. Research Question***

What is the rate of overtreatment of women receiving see and treat LEEP management at GSH colposcopy clinic?

### 3.1) **Aims**

1. Review indications for See and Treat LEEP
2. Demographics of women referred to colposcopy clinic for examination.
3. Colposcopy findings
4. Final histopathological diagnosis of specimen
5. Comparison of abnormal cytology, colposcopic findings and final histology to determine rate of overtreatment.

## ***4. METHOD***

### 4.1) **Study design**

A retrospective, descriptive cohort study

### 4.2) **Study population and sampling**

All women referred to GSH colposcopy clinic who HAVE undergone the see and treat approach from 1st Jan 2017 until 31st Dec 2021. All the data will be extracted from the colposcopy database and included in the analysis.

**Inclusion criteria:**
All patients that received LEEP treatment at initial colposcopy examination

Exclusion criteria

- Any patient with incomplete dataset
- Patients who undergone biopsy prior to excision treatment.

### 4.3) **Objectives**

Primary objective

- To assess the agreement of pre-treatment cytological and colposcopic findings with the final histopathological result.
- To determine the percentage of over-treatment that occurs in the colposcopy clinic when using the See and Treat approach. Over-treatment will be defined as histological diagnosis of CIN I or less. The recommended over-treatment rate is <10% as standard requirement by the Cochrane Colposcopy and Cervical Cytopathology collaborative.

Secondary Objectives

- Demographic particulars of participants,
- Review excision margins
- Rate of recurrence
- Correlate outcomes in HIV positive vs HIV negative patients
- Operator related factors influencing treatment.

4.4) **Data management and statistical analysis**

**Database**

The Anogenital-tract clinical database (HREC ref = 344/2011) was established in April 2010 at the colposcopy clinic at Groote Schuur Hospital. Every patient that attends this clinic has the following captured on the system:

- Demographic details
- Medical history (including HIV status)
- Clinical complaints
- Results

This database will be assessed, and the relevant cohort and their details will be extracted for analysis.

The following data will be extracted (for each patient)

- Age
- Parity
- Smoking status
- Contraception
- HIV status
- ART status if HIV positive
- Referral Pap smear result
- Colposcopy result
- Histology result
- Complication
- Operator of colposcopy and LEEP

**Statistical Analysis**

All statistical analyses will be performed using Stata version 18 (StataCorp, College Station, TX, USA). We will be summarizing the variables using mean (standard deviation) and median (interquartile range). If categorical variables are used, they will be categorized using count (percentage).
When comparing means between variable we will be using the t-test.
Sensitivity and Specificity will be used to measure diagnostic accuracy.
Estimates will be reported using 95% confidence intervals with a significance level at $p<0.05$.

4.5) **Data collection and management**

All data extracted will be secured in an excel file and will be password protected. All patients will have a unique study number to protect patient confidentiality.

4.6) **Timeline of study**

| | |
|---|---|
| Ethics approval | September - Novemeber 2022 |
| Data collection | November - March 2023 |
| Analysis | March – May 2023 |
| Write up and submission | May 2023 – Jan 2024 |

## ***5.) Ethical considerations***

This is a retrospective study analyzing data from an established database with ethics approval. There will be no patient contact and patient management and outcomes cannot be altered, therefore posing no risk to patients.
Patient names will be replaced by a study number to ensure confidentiality and no identifying data will be reported.

Ethics approval was obtained from Health Science Human Research Ethics Committee (HREC Ref 677/2022)

## ***6.) Study limitations***

The retrospective nature of the study depends on adequately collected data. There may be certain aspects of the structured perfoma missing or incomplete.

## ***7.) Budget***

| Expenses | Cost |
|---|---|
| Stationary, printing and sundries | R 2500 |
| Statistician | R 5000 |
| Minor equipment and software | R 5000 |

## ***8.) Reporting and implementing of results.***

The study findings will be made known to the department of Obstetrics and Gynaecology and all collaborating partners. Presentations will be delivered at relevant departmental forums. A manuscript will be prepared for publication, and the dissertation will be submitted for examination as an MMed.

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# 6. Chapter 2: Publication-ready Manuscript

## Title page:

## Look and LEEP: How are we doing? Outcomes of women undergoing Look and LEEP during a 5-year audit of the colposcopy clinic at Groote Schuur Hospital.

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**Conflict of interest**

The authors declare no conflict of interest.

**Funding source**

None

**Ethical approval**

Ethical approval was obtained from the University of Cape Town Institutional Research Ethics Committee for study and the use of the Anogenital tract clinical database. (HREC ref = 344/2011)

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**Abstract:**

**Background**: Cervical cancer persists as the second most common cancer in women in developing countries. The prevalence of cervical cancer has markedly decreased in well developed nations, primarily attributed to the implementation of efficacious screening services. Such screening services pose formidable challenges in developing countries. Therefore, the 'See-and-Treat' strategy has been adopted in South Africa and other developing countries to reduce loss to follow up and prevent patients to present with advanced disease, thereby reducing the morbidity and mortality associated with cervical cancer. The main limitation of this approach is the risk of overtreatment, identified as final histopathology without preinvasive cervical lesion. The objective of our study is to identify the rate of overtreatment at a colposcopy clinic in a tertiary center with extensive experience in colposcopy and to detect possible factors associated with this rate.

**Methods:** This was a retrospective, descriptive cohort study that analyzed data from 715 women who had undergone the 'See-and-Treat' treatment approach from 2017 to 2021 at Groote Schuur Hospital Colposcopy clinic. Overtreatment was defined as final histopathology results of Cervical Intraepithelial Neoplasia grade 1 (CIN 1) or less.

**Results:** Of the 715 women, there 109 (15.24%, 95% CI 0.13 – 0.18) with a histopathology result of CIN 1 or less. There was a statistically significant association between age and the odds of overtreatment as well as between HIV negative women, when compared to HIV positive women on treatment, and the odds of overtreatment. No statistically significant association was found between smoking status, HIV viral load, CD4 count or parity.

**Conclusion**: The overtreatment rate in this study can be considered acceptable and comparable with rates reported in the literature. HIV negative women should be considered for a biopsy prior to LEEP to decrease risk of overtreatment, but the risk should be weighed against the risk of loss to follow up.

**Keywords**: Cervical intraepithelial neoplasia, Colposcopy, See-and-Treat, Overtreatment, Negative histology.

**Introduction:**

Despite being a preventable and largely curable disease, cervical cancer persists as the 4th most common cancer in women worldwide, and the second most common cancer in developing countries. [1] The unfortunate reality is that 90% of cervical cancer related deaths occur in developing countries, where access to less than 5% of the global cancer resources underscores the stark manifestation of global health care inequity. [1,2]

The prevalence of cervical cancer has markedly decreased in well developed nations, primarily attributed to the implementation of efficacious screening services. Regrettably, the financial and organizational exigencies associated with maintaining such services pose formidable challenges in developing countries. [3,4] These nations exhibit an incidence of cervical cancer that is twofold greater than that observed in developed countries and is accompanied by cervical cancer related mortality rates as high as 90%. [1,2,5]
Hence, it is evident that developing countries necessitate the adoption of alternative screening strategies.

The incidence of cervical cancer in South Africa ranges between 23 and 27 per 100 000, notably higher than the global incidence of 15 per 100 000. On an annual basis, 5743 new cases are reported, and 3027 deaths are attributed to cervical cancer.
Cervical cancer, alongside maternal deaths, has been formally designated as a national priority in SA, as well as in other Sub-Saharan countries. [6,7]

Given the gradual progression of cervical cancer development over several years, the implementation of feasible and effective screening programs holds the potential to enable early diagnosis and treatment of precancerous lesions.
One such initiative is the 'See-and-Treat' screening program, which involves diagnosis of precancerous lesions followed by subsequent treatment with ablation therapy and/or excision.

Cervical intraepithelial neoplasia (CIN) manifests in three stages: CIN 1, CIN 2 and CIN 3. The definitive diagnosis relies on a histopathological examination of cervical biopsy or excision specimens. Accurate characterization of CIN hinges on assessing histopathological features related to cell differentiation, maturation, stratification and nuclear abnormalities. Grading is determined by the proportion of epithelial thickness exhibiting mature and differentiated cells. [8]
Neglecting recognition and treatment for the more advanced stages of CIN, specifically CIN 2 and CIN 3 (collectively denoted as CIN2+), may lead to the development of invasive cervical cancer, categorizing them as premalignant lesions. [9]

Traditionally, women that have abnormal Pap smear results are referred for a colposcopic examination and directed biopsies, with subsequent treatment contingent upon the biopsy's outcome, particularly if identified as cervical intraepithelial neoplasia grade 2 or higher (CIN2+). [10]

The 'See-and-Treat' management strategy facilitates the concurrent histopathological diagnosis and treatment of precursor lesions leading to cervical cancer. The objective of this strategy is to reduce instances of loss to follow-up and optimize the utilization of medical resources. [11] The most recent guidelines from the World Health Organization (WHO) advocate for the implementation of the 'See-and-Treat' program in countries where a suitable screening strategy is already in place, involving screening with cytology, followed by colposcopy for women identified with abnormal cervical cytology. In this context, the 'See-and-Treat' approach, followed by a Loop Electrosurgical Excision Procedure (LEEP) is a safe and viable option. This approach is therefore also referred to as 'Look-and-LEEP'. [8,9] The WHO recommends screen followed by triage and then treatment in women living with HIV.

The 'See-and-Treat' strategy does not only result in cost savings but also diminishes the frequency of clinic visits, non-compliance issues, and patient anxiety. [12,13]

The primary concern associated with this management strategy is the risk of overtreatment, leading to potentially avoidable adverse events. Complications of LEEP include immediate post-procedure issues such as bleeding, pain, visceral injuries (bladder or bowel), and infection, while long-term consequences may involve cervical incompetence, potentially leading to preterm labor and delivery, as well as cervical stenosis. [11,15,16]

Recently, strategies have used 'See-and-Treat' protocols to women exclusively with High-Grade Squamous Intraepithelial Lesion (HSIL) Pap smears, aiming to mitigate the risk of overtreatment and enhance precision in medical interventions. Certain studies indicate that the implementation of these strategies can result in an overtreatment rate as low as 4%. [17,18]

Different countries have variations in overtreatment rates due to factors such as diverse laboratory quality, screening methods and the design disparities between their respective national screening programs. The overtreatment rate is influenced by divergent frequencies of abnormal Pap smear results and referral criteria. Furthermore, there is recognized correlation wherein narrowing the screening interval is associated with an increased likelihood of unnecessary treatment. [19]

Human Immunodeficiency Virus (HIV) significantly contributes to Human Papilloma Virus (HPV) infection, and consequently, it plays a crucial role in the development of cervical cancer. South Africa experiences some of the highest rates of HIV and HPV infections globally, contributing to an increased burden as more women are referred to colposcopy clinics for the treatment of abnormal Pap smears. While HIV positive women with abnormal cytology demonstrate a higher likelihood of presenting colposcopic abnormalities, the performance of colposcopy seems comparable to that in HIV negative women. [3,20,21]

Our study aimed to determine the overtreatment rate among women undergoing ‘See-and-Treat’ approach in cervical cancer prevention at a colposcopy clinic at a tertiary level institution with extensive experience in the method. Additionally, it sought to identify potential predictors associated with the overtreatment rate. The American Society for Colposcopy and Cervical Pathology (ASCCP) defines overtreatment as a final histopathological diagnosis of CIN 1 or less. [14,22] The Cochrane Colposcopy and Cervical Cytopathology collaborative group recommends that institutions employing the ‘See-and-Treat’ approach should maintain an overtreatment rate of less than 10%. [23]

**Aim and Study Objectives:**

The principle aim of this study was to evaluate the percentage of overtreatment that occurs in a colposcopy clinic that employs the ‘See-and-Treat’ approach, by evaluating the concordance between the pre-treatment cytological and colposcopic diagnosis and the final histopathological result.

The secondary objectives encompassed gathering demographic details of participants, scrutinizing excision margins of specimens, examining outcome correlations between HIV positive and HIV negative women and assessing operator related factors influencing the treatment of women at the colposcopy clinic.

**Method:**

A retrospective, descriptive cohort study that included all women referred to Groote Schuur Hospital colposcopy clinic who have undergone the ‘See-and-Treat’ approach from the 1st of January 2017 to the 31st of December 2021.

Patient data was extracted from the existing Anogenital tract clinical database and incorporated into the analysis. (HREC ref = 344/2011)

Information extracted from the database included patient demographics (age), personal behaviors (smoking status, method of contraception), reproductive history (parity), medical history including (HIV status, CD4 count, HIVVL, on antiretroviral treatment or not), referral cytology (classified according to the Bathesda system) and colposcopic diagnosis (HSIL/LSIL)

The final histopathological results and excision margin status were obtained from the National Health Laboratory Service (NHLS) database.

During the study period, inclusion criteria included all patients who underwent LEEP at their initial colposcopic examination. Individuals who had a cervical biopsy before LEEP, as well as those referred to LEEP necessitating theater services or scheduled for LEEP at a subsequent visit, were excluded.

Overtreatment is defined as procedures leading to a histopathological diagnosis of CIN1/LSIL/HPV and inflammatory changes. i.e. lacking confirmed evidence of preinvasive lesions diagnosed on the referral cytology and colposcopic examination.

**Data analysis:**

Baseline demographic and clinical characteristics were summarized using appropriate summary statistic for distribution. These included measures such as mean and standard deviation, alongside median and interquartile range for numerical variables. Categorical variables were summarized using frequencies and percentages.

To compare the overtreatment proportion in our sample a One Sample Test of Proportions was conducted using 10% as the reference proportion. This proportion of 10% is the recommendation of overtreatment specified by the Cochrane Colposcopy and Cervical Cytopathology collaborative group.
The Pearson Chi-squared test was used to test for the differences between referral cytology (Pap smear) and colposcopic categories and their associated occurrence of overtreatment. Cohen's Kappa test for agreement was used to assess the agreement between colposcopic diagnosis and the histological diagnosis of our sample.

Univariable and multivariable logistic regression modeling was performed to determine the strength and significance of associations of predictors when regressed on overtreatment status. Based on expert opinion specific to our sample demographic the following variables were chosen to be included in our multivariable regressions a priori: Age, Parity, Current smoking status, and HIV status. A separate multivariable model was necessary to model the associations of clinical predictors specific to HIV prognostication and: CD4 count, HIV viral load (VL) status and HIV Treatment status.

Missing data was assumed to be missing completely at random and complete case analysis was performed during all forms of statistical analyses.

All statistical analyses were performed using Stata version 18 (StataCorp, College Station, TX, USA)

**Results:**

Between January 1, 2017, and December 31, 2021, a total of 715 women underwent the 'See-and-Treat' approach at the colposcopy clinic at Groote Schuur Hospital.

The characteristics of the study sample is summarized in Table I.

Of the 715 women the mean age in years was 39 (SD 9.08).

Eighty seven percent of the women were parous (i.e. had between 1-4 children), and 5.3% of women were grand-multiparous (i.e. 5 or more children).

There were 54 nulliparous women, of whom 23 were under 30 years of age. Of these patients 21 had HSIL diagnosis on colposcopy, 1 had LSIL and 1 had no documented colposcopy finding.

Of all the women involved in the study, 77.8% were nonsmokers.

In terms of HIV status, 63% of the women were HIV positive. Of these women the majority (66.74%) were virally suppressed with only 17.19% unsuppressed. The CD4 count of these women was categorized into the following groups: those with a CD4 of <200, CD4 of 201-499 and those with CD4 of >500. Most of the women (43.5%) had a CD4 of 201-499 with almost equal occurrence in the <200 and >500 category (26.7% and 29.8% respectively.)

Table I also summarizes the referral cytology results and the colposcopic findings.

Ninety five percent of referral pap smears were abnormal. This indicates that 5% of women referred to the colposcopy clinic in fact had normal/low risk cytology results.

Normal cytology included both normal and low risk cytology and comprised of 7 patients with Negative for Intraepithelial Neoplasia (NILM), 14 patients with LSIL and 14 patients with cytology results referred to as other, including Pap smears that were not able to be analyzed due to excess blood and debris, those that had no cells to evaluate or those that just showed inflammation or infection.

In keeping with similar studies, the most common cytological abnormality referred to the colposcopy clinic was HSIL. In our study this comprised 607 (84.9%) of all referral cytology. Ten patients were referred with a Pap smear result suspicious of cancer.

Of the 715 patients had 673 had a documented colposcopy finding, and 88.26% of the findings were abnormal (i.e. HSIL or more)

Seventy-nine of the women had a documented normal colposcopy (i.e. LSIL/CIN 1 or less).
Forty-two patients had no documented colposcopy diagnosis.

The ectocervix and endocervix margin status is also demonstrated in table 1.
The ectocervix margin was clear in 77.3% and involved in 22.7% of cases and endocervix margin was clear in 72.9% and involved in 27.1% of cases. The total number of ecto- and endocervical margins is 697, indicating that the margin status was omitted in the pathologist report in 18 cases.

Table II refers to the frequency and percentage of overtreatment in the referral cytology results and colposcopic findings groups with corresponding chi$^2$ test for difference within each group.
The final histopathological diagnosis of the 715 women who received an excision treatment were abnormal in 606 patients (84.8%) and 109 patients had a histopathological diagnosis of CIN 1 or less. On tabulation of the overtreatment rate across the entire sample (n=715) the sample overtreated was 15.24% (95% CI 0.13-0,18). This value was statistically significantly different from the nul reference value used in the one sample test.

Table III refers to the referral cytology result and colposcopy diagnosis compared to the outcome of overtreatment.
The overtreatment percentage amongst those with a normal referral cytology was 28.57%, and the percentage of overtreatment amongst those with abnormal results was 14.56%. Indications for treatment, despite a normal or LSIL colposcopic reporting were: inability to clearly visualize the squamo-columnar junction during colposcopy (44%), genital atrophy (18%). The reasons for treatment in the remaining cases were not specified, indicating a lack of detailed information on why treatment was pursued in those instances. This demonstrates the complexity and subjectivity involved in making treatment decisions based on colposcopy results. Furthermore, the difference between the two groups were statistically significant as the calculated p-value of Pearsons Chi-squared test is $<0.05$.

Similarly, the overtreatment percentage amongst those with a normal colposcopy was 29.11% and amongst those with an abnormal colposcopy was 13.30%. The difference in overtreatment between these two groups of patients were statistically significant as the calculated Pearson Chi squared test is$<0.001$.

Table IV refers to the Univariable logistic regression model used to determine factors influencing the rate of over treatment. This model suggests that there is a statistically significant positive association between age and the odds of overtreatment. Specifically, for each additional unit increase in age the odds of experiencing overtreatment increase by a factor of 1.06, and this effect is considered statistically significant based on the narrow 95% confidence interval and the low p value ($p<0.001$)

In addition, HIV negative women have significantly higher odds of experiencing overtreatment compared to HIV positive patients on treatment. The odds ratio of 1,78 (95% CI 1.17-2.73) and the p-value of 0.008 supports this statistically significant difference in the odds of overtreatment between the two groups.

Univariable logistical regression analysis does not reveal any significant associations between the odds of overtreatment and the remaining predictors, including Current smoking status, HIV status, CD4 count and HIV viral load status.

The multivariable logistic regression models are included as tables V and VI.
The multivariable regression model (Table V) for our entire cohort reveals that the positive association between age and the odds of overtreatment remain statistically significant (OR=1.06, 95% CI 1.03 – 1.08; p-value <0.001) when adjusting for all other variables included in this model. Furthermore, despite the adjustment for other effects, this model reveals no other significant associations between the other variables (Parity, Current smoking status and HIV status) and the odds of overtreatment.
Table VI refers to the multivariable logistic regression model showing the association between the effects and the outcome of overtreatment (defined as CIN1 or less) amongst HIV positive patients in our study. This model reveals that the positive association between age and the odds of overtreatment remains statistically significant (OR=1.05, 95% CI 1.00 – 1,10; p-value 0.043) when adjusting for all the variables included in this model. Interestingly the effect of parity amongst HIV positive patients demonstrates a protective effect in that for each additional unit increase in parity, odds of experiencing overtreatment decreases by a factor of 0.65 (95% CI 0.47 – 0.91) and this effect is statistically significant based on the CI and the p-value of 0.011.

In terms of agreement between colposcopy and final Histopathology results we expected a 69.17% agreement based on a Kappa test. In fact, the agreement reached between both modalities was 75.75% with a Kappa value of 22.00, indicating a fair agreement.

**Discussion:**

Within our study of 715 women who underwent the 'See-and-Treat' treatment approach, 15.24% of patients did not have a tissue diagnosis of CIN2+, indicating that treatment was unnecessary for this subgroup.
As anticipated, the highest rates of overtreatment were observed among patients with normal or low risk cytology and colposcopy outcomes.
Numnum et al. in their study 'A prospective Evaluation of "See and Treat' in Women with HSIL pap smear results: Is This an Appropriate Strategy?' evaluated 51 patients with HSIL pap smear results. Their study found that 84% of these patients had a high-grade lesion on pap smear, resulting in an overtreatment rate of

16%. The overtreatment rate in our study for patients with HSIL pap smear was 12.36%. This was significantly lower than in Numnum's study. [17]

Patients who were referred with a NILM (negative for intraepithelial malignancy) had the highest rate of overtreatment at 42.86%, and patients with LSIL had a rate of 28.57%.
Notably, women referred with a Pap smear result of AGC-NOS displayed a remarkably high overtreatment rate of 42.11%. This is likely associated with the fact that this specific abnormality is more commonly linked to pathology that affects both the endocervix and/or the endometrium, both of which is difficult to assess on colposcopy. Despite the high overtreatment rate, a Pap smear result of AGC-NOS is an indication for LEEP, especially if there is no evidence of endometrial pathology.

Likewise, patients with HSIL on colposcopy experienced a notably lower overtreatment rate of 13.00%.
Our findings indicate that patients with a normal colposcopy, where no lesion was observed exhibited the highest overtreatment rate at 37.04%. In cases where LSIL was diagnosed on colposcopy, the overtreatment rate stood at 25.00%.

Regarding cervical cancer, 10 cytology results were suspicious of cancer. Of those, 4 patients had a colposcopic diagnosis of cancer and 3 patients had invasive cervical cancer diagnosed on final histology. For the remaining 6 patients, there were 3 that were diagnosed with HSIL on colposcopy, 1 with LSIL, 1 with no lesion seen and 1 where no diagnosis was entered into the database.

During colposcopy examination, 31 of the 715 women were perceived to have cervical cancer. Of those women 6 had histologically confirmed invasive cervical cancer, 21 had HSIL, and 4 (13%) had CIN 1 or less. This group of patients highlights not only overtreatment but a discrepancy between the colposcopic suspicion and the actual final histological findings. Age and presence or absence of HIV did not influence the likelihood of colposcopic suspicion aligning with histological findings.

Study limitations included the absence of information on the operator's proficiency in colposcopy and LEEP (i.e. registrar, fellow, gynae-oncologist), preventing the assessment of potential associations between overtreatment and the operator's expertise level. Another limitation of the study was the absence of information concerning the women referred with normal or low risk Pap smears, as this is a deviation from typical protocols.

Age emerged as a factor associated with overtreatment in both univariable and multivariable regression models. This could be attributed to the inclination of older women towards a reduced desire for future fertility, thus diminishing concerns about pregnancy complications associated with LEEP.

HIV negative women exhibited an elevated risk of overtreatment, likely stemming from the higher likelihood of HPV co-infection and persistence in HIV positive women, making them more at risk for cervical dysplasia and CIN. [24] Based on our study findings, we therefore recommend that individuals who are HIV negative undergo a comprehensive risk factor assessment and be evaluated for a cervical biopsy before undergoing LEEP. This consideration should be balanced against the potential risks associated with loss to follow-up.

There was no statistically significant association between the outcome of overtreatment and any of the other variables, including CD4 count, HIV viral load, Smoking and parity.

**Conclusion:**

Our study indicates a relatively low overtreatment rate, comparable to acceptable rates in similar studies conducted in developing countries. This can be attributed to the experience of the colposcopists performing the procedure. We suggest promoting colposcopy training to improve overtreatment rates. It would also be advisable to include operator information to the database used to assist in identifying and correct operator related factors that may lead to overtreatment. Additionally, for HIV negative women, a biopsy before LEEP following risk factor assessment is advisable.

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## 6.2 Tables:

**Demographics**

**Table I.** Summary statistics of characteristics of the cohort separated by general characteristics and HIV specific characteristics.

| Characteristic | Total Sample (n=715) |
|---|---|
| **Age (years)** Mean (SD) | 39.09 (9.08) |
| **Parity**, n (%) | |
| 0 | 54 (7.55%) |
| 1-4 | 623 (87.14%) |
| ≥5 | 38 (5.31%) |
| **Current Smoker**, n (%) | |
| No | 554 (77.81%) |
| Yes | 158 (22.19%) |
| Unknown | 3 (0.12%) |
| **Referral Papsmear Results**, n (%) | |
| Normal | 35 (4.90%) |
| Other | 14 (1.96%) |
| NILM | 7 0.98%) |
| LSIL | 14 1.96%) |
| Abnormal | 680 (95.10%) |
| HSIL | 607 (84.90%) |
| ASC-H | 40 (5.59%) |
| ASC-US | 4 (0.56%) |
| Cancer | 10 (1.40%) |
| AGC-NOS | 19 (2.66%) |
| **Colposcopy Diagnosis**, n (%) | |
| Normal | 79 (11.74%) |
| Other | 8 (1.19%) |
| No Lesion | 27 (4.01%) |
| LSIL | 44 (6.54%) |
| Abnormal | 594 (88.26%) |
| HSIL | 546 (81.13%) |
| Microinvasive Cancer | 23 (3.42%) |
| Obvious Cancer | 5 (0.74%) |
| Squamous Metaplasia | 1 (0.15%) |
| Non-specific Acetowhite lesion | 2 (0.30%) |
| Combination of abnormal | 17 (2.53%) |
| **Histological Diagnosis**, n (%) | |
| Normal | 79 (11.74%) |
| Abnormal | 560 (83.21%) |
| Cancer | 34 (5.05%) |
| **Ectocervix**, n (%) | |
| Clear | 537 (77.27%) |
| Involved | 158 (22.73%) |
| **Endocervix**, n (%) | |

| | |
|---|---|
| Clear | 508 (72.88%) |
| Involved | 189 (27.12%) |
| **Overtreatment**, n (%) | |
| No | 606 (85.76%) |
| Yes | 109 (15.24%) |
| **HIV Status**, n (%) | |
| No | 249 (34.83%) |
| Yes | 451 (63.08%) |
| Unknown | 15 (2.10%) |

| Summary statistics of HIV positive cohort | HIV cohort (n=451) |
|---|---|
| **CD4 count (cells/mm$^3$)**, n (%) | |
| <200 | 86 (27.71%) |
| 201 – 499 | 140 (43.48%) |
| >500 | 96 (29.81%) |
| **Viral Load Status**, n (%) | |
| Unsuppressed | 77 (17.19%) |
| Suppressed | 299 (66.74%) |
| Unknown | 72 (16.07%) |
| **HIV Treatment**, n (%) | |
| No | 11 (1.58%) |
| Yes | 410 (58.74%) |

Missing information not represented in the above table

**Table II**: Frequency and percentage of overtreatment in the referral cytology results and colposcopic findings groups with corresponding chi$^2$ test for difference within each group

| | Overtreatment Frequency | Overtreatment Percentage | Pearsons Chi$^2$ test p-value |
|---|---|---|---|
| **Referral cytology** | | | |
| Normal | 10 | 28.57% | 0.025 |
| Abnormal | 99 | 14.56% | |
| **Colposcopic findings** | | | |
| Normal | 23 | 29.11% | <0.001 |
| Abnormal | 102 | 13.30% | |

**Table III**. One Sample Test of Proportions comparing the overtreatment rate in the sample with the (globally accepted) reference value set by the Cochrane Colposcopy and Cervical Cytopathology collaborative group.

| Variable | Positive Response | Reference Probability | Response Rate (95% CI) | P-value |
|---|---|---|---|---|
| Overtreatment (n=715)* | 109 | 0.10 | 0.15 (0.13 – 0.18) | <0.001 |

*One sample proportion test with continuity correction

**Table IV**: Univariable logistic regression models showing the association with each predictor and the outcome of overtreatment (defined as a final histology of CIN 1 or less). The crude odds ratio (OR) has been presented with the 95% confidence interval (CI) in brackets.

| Effect/Variable | OR (95% CI) | p-value |
|---|---|---|
| Age (years) | 1.06 (1.04 – 1.08) | <0.001 |
| Parity (n) | 1.00 (0.86 –1.17) | 0.954 |
| Current Smoker | | |
| No (reference) | - | - |
| Yes | 1.07 (0.66 – 1.74) | 0.795 |
| HIV Status | | |
| Negative (reference) | - | - |
| Positive | 0.69 (0.45 – 1.05) | 0.085 |
| Unknown | 4.08 (1.40 – 11.83) | 0.010 |
| CD4 count (cells/mm$^3$) | | |
| 0 – 200 (reference) | - | - |
| 201 – 499 | 0.76 (0.33 – 1.75) | 0.517 |
| > 500 | 1.07 ( 0.45 – 2.53) | 0.881 |
| HIVVL | | |
| Suppressed (reference) | - | - |
| Unsuppressed | 1.78 (0.72 – 4.36) | 0.211 |
| Unknown | 2.13 (0.75 – 6.11) | 0.158 |
| HIV Treatment | | |
| Yes (reference) | - | - |
| HIV Negative | 1.78 (1.17 – 2.73) | 0.008* |

**Table V**: Multivariable logistic regression model showing the association between the effects and the outcome of overtreatment (defined as a final histology of CIN 1 or less). The adjusted odds ratio (OR) has been presented with the 95% confidence interval (CI) in brackets.

| Effect | OR (95% CI) | p-value |
|---|---|---|
| Age (years) | 1.06 (1.03 – 1.08) | <0.001* |
| Parity (n) | 0.89 (0.75 – 1.05) | 0.172 |
| Current Smoker | | |
| No (reference) | - | - |
| Yes | 0.85 (0.50 – 1.46) | 0.557 |
| HIV status | | |
| Negative (reference) | - | - |
| Positive | 0.75 (0.47 – 1.19) | 0.226 |
| Unknown | 3.45 (1.10 – 10.86) | 0.034 |

Total number of observations used in model = 712

**Table VI**: Multivariable logistic regression model showing the association between the effects and the outcome of overtreatment (defined as a final histology of CIN 1 or less) amongst HIV positive patients. The adjusted odds ratio (OR) has been presented with the 95% confidence interval (CI) in brackets.

| Effect | OR (95% CI) | p-value |
|---|---|---|
| Age (years) | 1.05 (1.00 – 1.10) | 0.043* |
| Parity (n) | 0.65 (0.47 – 0.91) | 0.011* |
| Current Smoker | | |
| No (reference) | - | - |
| Yes | 1.10 (0.35 – 3.50) | 0.868 |
| CD4 count (cells/mm$^3$) | | |
| 0-200 (reference) | - | - |
| 201-499 | 0.67 (0.26 – 1.75) | 0.417 |
| ≥500 | 1.02 (0.37 – 2.82) | 0.977 |
| HIV Viral Load | | |
| Unsuppressed | - | - |
| (reference) | 1.62 (0.50 – 5.25) | 0.423 |
| Suppressed | 2.28 (0.50 – 10.29) | 0.284 |
| Unknown | | |
| HIV Treatment | | |
| No (reference) | - | - |
| Yes | 1.29 (0.13 – 12.51) | 0.828 |

Total number of observations used in model = 298

# Authors Guidelines

**Authors' Guidelines**

The Journal aims to be the prime journal on women's cancer for local health care workers and gynaecologists, focusing on all aspects of cancer prevention, detection, diagnosis and treatment. The SAJGO is also a specialist journal catering for sub-specialist gynaecologic oncologists, for other specialists with a specific interest in breast and gynaecologic cancer, including medical oncologists, radiation oncologists, surgeons, radiologists, pathologists, geneticists, specialised nurses and research scientists.

The Journal includes all aspects of female cancer prevention, diagnosis and treatment and aims to serve a broad readership. As such it should be of interest to the clinical, scientific and academic community, policy makers, government and non-government stakeholders and industry.

Cancer control programmes include primary and secondary prevention, early detection and effective treatment. These aspects form part of public health, general and specialist services and together form the important priorities of the journal.

HIV and AIDS remain problematic in the region with a severe impact on gynaecologic oncology. Papers focusing on gynaecological malignancies in HIV infected women will be prioritised. Research in this field needs to be encouraged.

The Journal encourages articles from all investigators in the fields of gynaecological and breast cancer. In particular young researchers and researchers from historically disadvantaged backgrounds will be encouraged and supported to submit their research work for publication.

Contributions from all African countries are especially welcomed. Manuscripts describing research performed at Southern African institutions and in African or developing settings will enjoy priority.

**Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.**

**AUTHORSHIP**

Named authors must consent to publication **by signing a covering letter** which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and

(iv) exact contribution of each author must be stated.

## DECLARATION OF CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute a conflict of interest. If there is no conflict of interest to declare please include the following: The authors declare no conflict of interest.

## FUNDING SOURCE

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

## RESEARCH ETHICS COMMITTEE APPROVAL

The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included. Please provide the Ethics Committee approval letter.

## STATISTICAL ANALYSIS

Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

## PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

## ETHNIC CLASSIFICATION

The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

## CATEGORIES OF SUBMISSIONS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

***Original articles***

Original articles on research relevant to gynaecological oncology should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 250 words. Five keywords should be included.

***Review articles***

Review articles that are of high quality and of relevance to the field will be published. Reviews will often be invited and unsolicited reviews are also considered. Reviews should not exceed 2 500 words, with a maximum of 25 references and no more than 6 tables or figures. A summary of 250 words or less is required. Five keywords should be included.

***Brief Report/Case reports***

Case reports should not exceed 1 500 words with no more than 15 references. Figures are limited to 4 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version. Five keywords should be included.

***Pathologist's, Radiologist's* and *Surgeon's Corners***

*Pathologist's, Radiologist's* and *Surgeon's Corners* intend to describe a specific issue, finding or technique that is new, of special interest or modified. This section is limited to 1000 words and up to 5 references and will be peer reviewed. A summary of 250 words or less is required. Five keywords should be included.

***Editorials and Commentaries***

*Editorials* and *Commentaries* are generally invited by the Editor and are overviews of articles of other research or of issues of special interest to the subspeciality. Unsolicited commentaries are also considered. These should not exceed 1 000 words.

***Correspondence or Letters to the editor***

*Correspondence or Letters to the editor* should be short and concise, commenting on a recently published article in the Journal or a controversial or topical issue of concern to the readership. Please prepare the letter in manuscript format, including a title page. The letter must not exceed 500 words, 3 authors, 1 insert (table or figure) and 5 references. A statement of potential sources of conflict of interest must accompany the letter.

**ARTICLE PROCESSING CHARGES**

Article processing charges (APCs) are not currently charged.

## MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

The manuscript should contain the title, abstract, keywords, article text and references.

The title page should be submitted as a supplementary file and should include:

- Qualification, affiliation and contact details of ALL the authors.
- Email addresses of all author must be provided.
- ORCID number of ALL authors must be provided – if authors do not have ORCID, please register at https://orcid.org/.
- Disclaimers: Acknowledgements, Declaration of conflict of interest, Funding declaration, Ethics declaration and ORCID.
- *A signed copy of the title page including the declarations must be provided in PDF format. An unsigned copy of the title page MUST be submitted in MSWord format.*

### Abbreviations

All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

### Scientific measurements

Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

**Numbers** should be written as grouped per thousand-units, i.e. 4 000, 22 160...

**Quotes** should be placed in single quotation marks: i.e. The respondent stated: '...'
Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

### General formatting

The manuscript must be in Microsoft Word. *Please DO NOT provide the manuscript in PDF format.* Text must be 1,5-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, except for Tables). *The manuscript must be free of track changes.*

## ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

**Tables** may be embedded in the manuscript file **and** provided as **'supplementary files'**. They must be numbered in Roman numerals (I, II, III, ...) and referred to consecutively in the text (e.g. 'Table I'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

**Figures** must be numbered in Arabic numerals (1,2,3, …) and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title...'. All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

## REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text in numerical order as superscript numbers, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] The superscript reference number should come after the punctuation mark.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link.** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

**Journal references:** Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med. 1998;289(1):350-355. https://doi.org/10.1000/hgjr.182.

**Book references:** Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

**Internet references:** World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002. Accessed 16 January 2010.

**Other references (e.g. reports)** should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

## COVERING LETTER

A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings. The letter must declare if any of the authors have a conflict of interest and that the requirements for submission, including ethics approval and patient permission for case reports have been fulfilled. All authors must sign the covering letter.

Please provide the names and email addresses of three possible reviewers for this manuscript.

## REVIEW PROCESS

Manuscripts, after vetting by the editorial team, are assigned for peer-review to 2 reviewers, conversant with the particular field of research. The reviewers and the authors are blinded to each other's identity. The turn-around time for review and initial editorial decision notification aims to be within 6 weeks of submission.

## PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

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