Neoadjuvant endocrine therapy for estrogen receptor positive breast cancer in an African setting

by

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FACULTY OF SCIENCE

DECLARATION FORM - MASTER'S DEGREE CANDIDATES

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Acknowledgments

"Anything is possible when you have the right people to support you" Misty Copeland

A big thank you to the patients who entrusted us with their health during the COVID pandemic, when we couldn't operate or offer them the standard treatment. We all didn't lose hope but fought to try new avenues to give them hope.

Thank you to my supervisor Dr Francois Malherbe and to Prof. Lydia Cairncross for being patient with me when I struggled to juggle between work, exams, and my research.

To Dr Tselane Thebe, for the literature review and insight into Oncology.

To Daniel Nel who breathed life into this project. I didn't have to look far for statistical analysis and manuscript revision.

To my family who sacrificed their time and the cups of coffees they made to make sure that this project is complete.

And to the Almighty who gave me strength and perseverance when I wanted to give up.

Table of Contents

Neoadjuvant endocrine therapy for estrogen receptor positive breast carcinoma in an African setting

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Abstract

Background
Several studies have reported response rates for ER positive cancers on neoadjuvant endocrine therapy (NET), with lower toxicity compared to neoadjuvant chemotherapy (NCT). During the first wave of the COVID pandemic, clinician preference for NET increased significantly, buying time for hospital recovery before proceeding to surgery. To date, no studies have yet explicitly reported on the use of NET in an African context.

Methods
This study was a retrospective review, looking at breast cancer patients who received NET between 01 March 2019 to 31 December 2020 at Groote Schuur Hospital. Patients were included if they were female, older than 18 years, ER positive, and had a biopsy-proven breast cancer less than 50mm in size on clinical exam.

Results
There were 16 patients included in the study, of which all were female. The mean age was 59 years (range 41-75). When comparing the histological measurement to initial size on imaging, 7 patients had an excellent response to NET with tumours that decreased in size, whereas 9 patients had tumours that increased in size despite NET. There was no statistically significant difference between the two groups in terms of patient and pre-treatment tumour characteristics, pathological results, endocrine therapy, surgical therapy, or adjuvant oncological therapy. For the 9 patients who had progression on NET, the post resection median tumour size was more than double the pre-NET tumour size, as determined on imaging.

Conclusion
Until further studies can be performed in this setting, NET should be used with caution in situations where there will be a significant delay to surgery.

Introduction

Breast cancer is heterogeneous, with different subtypes, all needing a slightly different approach to management. Perou et al. first described the molecular subtypes of breast cancer in 2000.[1] Initially, their work was based on gene array analysis dividing breast cancer into different subtypes. Tumours that expressed surface estrogen receptors (ER) and/or progesterone receptors (PR) were called luminal breast cancers. Tumours that overexpressed Human epidermal growth factor 2 (HER2) receptors and lacked ER and PR receptors were called HER2 enriched tumours and tumours that lacked ER, PR and HER2 receptors were called triple negative tumours. Today, multidisciplinary teams involved in the treatment of breast cancer base a large part of their treatment decisions on the results of immunohistochemistry stains to detect ER, PR and HER2 receptors. In luminal breast cancers, hormonal treatment plays a significant role in adjuvant treatment. It is used either alone or as an adjunct to chemotherapy in treating these tumours. In HER2 enriched tumours, the biological monoclonal antibody to the HER2 receptor, Trastuzumab, and chemotherapy form the basis of adjuvant treatment. In triple negative cancers, chemotherapy is the only adjuvant treatment. [1,2]

Neoadjuvant chemotherapy (NCT) was initially reserved for locally advanced breast cancers and shrinking large tumours to make them amenable to breast conserving surgery (BCS).[3,4] However, NCT has become the standard of care in treating most HER2 enriched and triple negative breast cancers. We now know that the response rate of breast cancer to chemotherapy, while in situ, is associated with a better prognosis. Breast cancers that achieve a pathological complete response (pCR) after chemotherapy have a favourable long-term outcome.[5,6] Studies have shown that HER2 enriched and triple negative cancers can achieve a 50-60% pCR after NCT. The response rates in luminal cancers are much lower at 10-20%, leading researchers to consider if better response rates are possible using neoadjuvant endocrine treatment (NET).[7,8]

Several studies have reported similar clinical and biological response rates for ER positive cancers on NET, with lower toxicity, compared to NCT.[9-12] NET may also be an effective strategy for tumour downsizing and could facilitate BCS. The optimal axillary management for patients who have undergone NET remains an area of investigation.[10] Aromatase inhibitors (AI's) are more effective than Tamoxifen in terms of response. Thus NET is often preferred for postmenopausal women.[9,11] Ovarian suppression, however, may be added to Tamoxifen to improve its efficacy in premenopausal women.[10] Despite its proven effectiveness in the reduction of the T/N stage as well as achieving a pathological complete response, some still consider NET to be less effective than NCT.[11,12] However, the perceived increased efficacy of NCT comes at the cost of a significantly greater incidence of major adverse events.[9,11] This makes NET a more attractive option for patients with significant comorbidities and advanced age. Conversely, NCT is generally preferred for fit, premenopausal women where the potential gains in oncological outcomes justify the risk.

The arrival of the COVID pandemic challenged many treatment paradigms, including the role of NET. With hospital resources depleted by the demands of providing care for patients affected by COVID, many surgical procedures had to be delayed. Clinician preference for NET increased significantly during the first wave, buying time for the hospital to recover before proceeding to surgery.[13-15] As of yet, no long-term data is available to evaluate the true impact of this drastic practice change on outcomes.

Africa has a higher age-standardised breast cancer mortality rate than high-income countries. In addition, the highest breast cancer incidence rates are from sub-Saharan Africa.[16] Despite the high incidence and mortality in the region, breast cancer has not been extensively studied in this population. To date, no studies have yet explicitly reported on the use of NET in an

African context. Like the rest of the world, the COVID pandemic forced us to change our early-stage ER positive breast cancer management strategy. This study aims to assess the characteristics, workup, decision-making and outcomes of patients treated with NET in this setting.

Methods

This study was a retrospective review, looking at breast cancer patients who received NET between 01 March 2019 to 31 December 2020 at Groote Schuur Hospital. Patients were included if they were female, older than 18 years, ER positive, and had a biopsy-proven breast cancer less than 50mm in size on clinical exam. Patients were excluded if they had HER2 positive tumours, had metastatic or advanced loco-regional tumours or met the inclusion criteria but did not undergo surgery. Ethical approval for the study was received from the human research ethics committee at the University of Cape Town [HREC: 075/2022]. All patients were anonymised before statistical analysis.

Initial tumour size was based on radiological measurement at diagnosis, which was then compared to the maximum tumour diameter in the resected specimen, as reported by the pathologist. Tumour grading was reported according to the Nottingham Histologic Score system (the Elston-Ellis modification of Scarff-Bloom-Richardson grading system). ER, PR, HER2 and Ki67 were studied through immunohistochemistry (IHC). ER and PR were recorded according to the Allred score between 0 and 8 and the Ki67 index was expressed as a percentage of positive cells. Trastuzumab is not available at our hospital and therefore, routine fluorescent *in situ* hybridisation (FISH) was not performed for equivocal HER2 results.

Numerical variables were analysed for normality using the Shapiro-Wilk test, with central tendency and dispersion represented as appropriate. Analysis of continuous data was done using the T-test and Mann-Whitney test. Fisher's exact test analysed categorical variables. A confidence interval of 95% was used, with a two-tail test hypothesis using an alpha-value of 0.05 as a discriminator for rejection of the null hypothesis.

Results

Patient and tumour characteristics

There were 16 patients included in the study, of which all were female. The mean age was 59 years (range 41-75). When comparing the histological measurement to initial size on imaging, 7 patients had an excellent response to NET with tumours that decreased in size, whereas 9 patients had tumours that increased in size despite NET. All patients had tumours that were ER 8/8, and none were Her2-enriched. Further patient and tumour characteristics are shown in table 1.

Table 1: Patient and pre-treatment tumour characteristics

	Progression (n=9)	No Progression (n=7)	Overall (n=16)	P
Age (years)	59 (± 9)	59 (± 14)	59 (± 11)	NS
Postmenopausal	7 (78%)	5 (71%)	12 (75%)	NS

Median tumour size on initial imaging (mm)	16 (13-20)	15 (9-20)	15 (11-20)	NS
Ultrasound done	6 (67%)	7 (100%)	13 (81%)	NS
T2 disease	4 (45%)	4 (57%)	8 (50%)	NS
N1 disease	3 (33%)	2 (29%)	5 (31%)	NS
Ductal subtype	7 (78%)	7 (100%)	14 (88%)	NS
Ki-67 (%)	15 (± 10)	17 (± 11)	16 (± 10)	NS
Her2 indeterminate	3 (33%)	4 (57%)	7 (44%)	NS

Endocrine and surgical treatment

Hormonal therapy was initiated with a SERM (Tamoxifen) in 13 and an aromatase inhibitor (Arimidex) in 3 patients. Only 1 patient complained of side effects, reporting hot flushes on Tamoxifen. The difference in interval between initiation of NET and surgery and the type of surgical procedure is shown in table 2.

Table 2: Endocrine and surgical treatment

	Progression (n=9)	No Progression (n=7)	Overall (n=16)	P
Tamoxifen: AI	6:3	7:0	13:3	NS
Duration NET (weeks)	12 (12-20)	16 (14-34)	16 (12-22)	NS
Mastectomy vs WLE	7:2	2:5	9:7	NS
ALND vs SLNB	5:4	2:5	7:9	NS

There were no significant postoperative complications, 2 patients had seromas and one had a superficial surgical site infection.

Pathology, adjuvant treatment and outcomes

There were no cases of complete pathological response and all subjects had clear resection margins. Pathological tumour size and nodal status is shown in table 3. Only one patient who was initially N0 clinically was up-staged to N1 disease at pathological examination. There were no reported cases of local recurrence during follow-up.

Table 3: Pathological results and adjuvant oncological therapy

	Progression (n=9)	No Progression (n=7)	Overall (n=16)	P
Tumour size (mm)	33 (14)	9 (4)	22 (16)	NS
Number of involved nodes	0 (0-1)	0 (0-1)	0 (0-1)	NS
High-risk features	3 (33%)	2 (29%)	5 (31%)	NS

on histology*				
RT	5 (56%)	5 (71%)	10 (63%)	NS
Chemo	1 (11%)	1 (14%)	2 (13%)	NS

*including Extracapsular extension, Lymphovascular invasion.

Discussion

While there is good evidence for the use of NET for hormone positive tumours, studies from the African continent are lacking. This study evaluated a cohort of patients placed on NET while awaiting surgery, which was delayed due to the covid pandemic. The main finding from this study was that, out of the 16 patients included in the study, only 7 had tumours that did not progress on NET. This is in contrast to many other studies where NET was shown to have a favourable response rate, deeming it to be not only appropriate for use as a bridge to surgery but also as a longer-term strategy to facilitate BCS.[9-12]

There may be several reasons for the lower response rate in this study. Due to the small numbers in this cohort, the statistical comparisons were likely underpowered to detect significant differences in the two groups. Despite this, and considering the findings from other studies, possible reasons for the poor response rate can be suggested. The first is that, while all patients who had a good response had a preoperative ultrasound to determine the size of the tumour, only two-thirds of the group that progressed had an initial ultrasound. A mammogram is inferior in determining tumour size when compared to ultrasound.[17] Therefore, it is possible that the three patients who did not have a mammogram had an underestimation of their tumour size, especially considering that 2 out of the 3 patients had lesions less than 10mm in size on initial imaging.

A second reason for the overall low response rate might be the relatively low use of AI's for NET. A meta-analysis has shown a highly significant benefit for AI's vs Tamoxifen in terms of clinical and radiological response rates when explicitly used as NET.[9] Even though most of the patients in this study were postmenopausal, Tamoxifen was still most commonly used. The reason for this is resource related. Due to their cost, AI's are not available as first line endocrine therapy for state sector patients. They are reserved for use with a clear contraindication to Tamoxifen use, e.g., history of thromboembolism.

A third factor that may have affected the results is the high number of Her2-indeterminate tumours. Although there was otherwise very little difference in tumour biology between the two groups, Her2 status may have affected the results in either direction. In our resource-limited setting, FISH is not done for every Her2-indeterminate tumour. Thus, it is possible that some of the patients in the group that had progression on NET may have had Her2-enriched tumours and would have benefited from NACT rather than NET.

Although not statistically significant, patients who had progression on NET were treated for 4 weeks shorter (12 vs 16 weeks) than those who had a good response. Although it is generally believed that 12-16 weeks should be the desired duration of therapy, there have been studies that have shown the median time to maximal response is between 6-8 months, with no discernible benefit seen beyond 12 months.[18] Adequate treatment duration is vital to allow maximal response, which may facilitate BCS.[19] Although not statistically significant, the patients in this study who had an excellent response to NET had higher rates of BCS and SLNB than the progression group with higher rates of mastectomy and ALND.

Something of concern in this cohort is the doubling in median tumour size in the group that had progression on NET while awaiting surgery. Whether this is related to Her2-indeterminate status, as described above, is unknown. Regardless, this finding means that NET should be used with caution in this resource-limited setting, where routine FISH is not performed. A NACT or surgery-upfront approach may still be the wisest strategy, should surgical waiting times be reasonable. If a new Covid wave results in limited theatre availability, then NET use can be considered, but with close follow up to ensure that patients are not progressing. Due to the inaccuracy of a clinical exam, this should, ideally, be done with imaging follow up. Although biopsy of the tumour to monitor Ki-67 expression while on NET is the best method to monitor treatment response, this may not be feasible in our setting.[9] Genomic studies may be used to predict the in-vivo response to NET. However, these tests are also not available in our environment.[9,20] Another thing to consider in terms of follow up, is compliance to therapy, as this clearly will impact the tumour response to NET. Although patients were thoroughly counselled on the importance of NET and potential side effects, treatment adherence was not followed up on at the time of surgery.

The main limitation to this study was the small sample size, which meant a high risk of type 2 error to any statistical comparison. Another limitation was the lack of standardisation in how the initial tumour size was recorded. Despite the limitations, this study does raise some concerns about the use of NET in this setting. Given the ongoing limitations in theatre availability for timely upfront surgery, it is likely that NET will become an even more popular option for hormone receptor positive patients. To adequately establish the role of NET in a resource-limited environment, further studies are required. This is especially true before a more prolonged course of NET can be considered an option to facilitate BCS. Given that in vivo response to therapy predicts adjuvant treatment outcomes, it would be even more important to accurately establish the response to NET in this setting, as adjuvant endocrine therapy (AET) is widely used.[21] The ability to predict which hormone receptor positive patients will benefit from AET could be based, for example, on their response to NET. This has important implications for long term management after surgical resection. Given the limitations and potential errors that may have been introduced, as explained above, further studies are needed to investigate the effect of NET in this setting more thoroughly. This may include evaluating the Ki-67 index on the resected specimens from this cohort, which would reveal the actual biological response. Larger patient numbers are also needed to allow for more accurate statistical comparisons.

Conclusion

Although many studies have described the efficacy of NET, this study found that the majority of patients' tumours increased in size while on NET. Until further studies can be performed in this setting, NET should be used with caution in situations where there will be a significant delay to surgery.

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11 April 2022
HREC REF: 075/2022

Dr F Malherbe
Division of General Surgery
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Dear Dr Malherbe

PROJECT TITLE : EFFICACY OF NEOADJUVANT ENDOCRINE THERAPY IN EARLY LUMINAL BREAST CANCER DURING THE COVID 19 PANDEMIC: A POTENTIAL CHANGE IN STRATEGY FOR THE MANAGEMENT OF BREAST CANCER IN LOW- AND MIDDLE-INCOME COUNTRIES (MMED DEGREE – DR HUNADI MOLABE)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

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, our letter dated 02 February 2022 provides guidance found on our website:
htt : www.health.uct.ac.za fhs research humanethics forms

Approval is granted for one year until the 30 April 2023.

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 Hunadi Molabe will also be involved in this study.

Please quote the HREC REF 075/2022 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

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.

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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.

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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.

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Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or

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

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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 surgery 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.

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Short reports should not exceed 1 500 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words.

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Case reports should not exceed 1 500 words with no more than 10 references. Figures are limited to 2 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.

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Video case reports should not exceed 1 500 words with 10 references and 6 figures. Heading should include Summary (not exceeding 100 words) and Case description (with three subheadings: Introduction, Case presentation and Discussion). The video file format must be only MP4 or MOV and should not exceed 300 MB and 8 minutes. Video case reports will be published online only. The summary and the URL will appear in the printed version.

How to do it

How to do it submissions should address a practical aspect of surgical or interventional (endoscopic or radiological) patient management in which a best practice technique or method to advance optimal patient management is presented in a standardised format. The submission should be structured with a short contextual introduction focussing on the indications for the procedure, followed by numbered sequential points that explain and illustrate the procedure and its complications. The total word count should not exceed 1500 words with a maximum of 10 references and 6 figures. Five keywords should be included.

Editorials

Opinions, etc. should not exceed 1 000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles

Review articles relevant to surgery should not exceed 5 000 words, with a maximum of 50 references and no more than 6 tables or figures. A summary of 250 words or less is required.

Letters to the editor

Letters to the editor should be 400 words or less with only one image or table.

Obituaries

Obituaries should be 900 words or less and should be accompanied by a photograph.

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 or RTF document 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 Arabic numerals (1,2,3…) and referred to consecutively in the text (e.g. 'Table 1'). 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 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 as superscript, 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 and PubMed ID (PMID)/PubMed Central ID (PMCID).** 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. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

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).

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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

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

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