Sentinel Lymph Node Biopsy in a Resource Limited Setting: A Retrospective Comparison of Sentinel Lymph Node Biopsy before and after the introduction of SentiMag at an Academic Breast Unit

by

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Master of Medicine (Surgery)

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Acknowledgments

I would like to thank my father, mother and wife who have tolerated me and supporting me during this journey away from them and home to pursue my career.

A big thank you to my supervisors: Dr F. Malherbe who assisted in bring this project to life and gave me a chance after I lost the first one

A big thank you to Dr Mohamed Almoslemany whose helped me with stats and final touches and refinement in this project
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Title: Sentinel Lymph Node Biopsy in a Resource Limited Setting: A Retrospective Comparison of Sentinel Lymph Node Biopsy before and after the introduction of SentiMag at an Academic Breast Unit

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Abstract

**Background**: Sentinel lymph node biopsy (SLNB) is performed for the staging and prognostication of breast cancer in cases with a clinically and radiologically negative axilla. Using blue dye and a radioactive colloid injection is considered the gold standard for SLNB. This study aims to evaluate the SLNB outcomes before and after the introduction of SentiMag at an academic breast unit.

**Methods**: A retrospective cohort study was performed comparing SLNBs done from (1 January 2017 to 31 December 2017) and (1 January 2018 to 31 December 2018). During 2017 all SLNBs were done with a nuclear medicine technique and in 2018 the SentiMag system was used.

**Results**: There was no difference between the 2 groups comparing age, T-stage, size of tumour, grade of tumour and molecular status. The only statistically significant difference found was more higher-grade tumours in the group where a nuclear medicine technique was used (2017) p=0.04. There was no difference in the type of surgery performed comparing mastectomy and breast conserving surgery rates between the 2 groups. There was an 11% increase in the number of patients who had a SLNB done with the SentiMag technique (2018). In 2017 42% (58/139) had a SLNB and in 2018 53% (59/112) had a SLNB.

**Conclusion**: This result demonstrates the feasibility of the magnetic technique for SLNB in a resource constrained low- and middle-income country. This new method has none of the disadvantages of the standard technique and is promising as a safe and effective alternative in the absence of nuclear medicine facilities.
Introduction

Cancer is increasing worldwide with low-and middle-income countries (LMIC) the worst affected. The rate of new cancers diagnosed as well as the mortality rate of cancer in LMICs is disproportionately higher compared to high-income countries.\(^1\) Studies estimate that in by 2035 developing countries will harbor two thirds of the new cancer cases.\(^2\) This projected increased burden of disease in LMIC demands that breast units position themselves to provide up-to-date surgical treatment of the axilla in women with early breast cancer.

Sentinel lymph node biopsy (SLNB) is a tool that is widely used for the staging and prognostication of breast cancer in patients who have a clinically and radiologically negative axilla. Using blue dye and a radioactive colloid injection is considered the gold standard for SLNB.\(^3,4\) Using either blue dye or radioactive colloid injection individually leads to a detection rate of 85.6%, while using them together achieves a 96% detection rate.\(^5\) Nuclear medicine techniques have several drawbacks including radiation exposure, nuclear medicine unit dependency and legislative control accompanying the use of radiopharmaceuticals. Hence, it is mostly used in centres with an active nuclear medicine department. An injectable magnetic tracer has become available, and it can be used as an alternative to SLNB. The magnetic tracer is a sterile aqueous suspension of superparamagnetic iron oxide (SPIO) particles with brownish colour that accumulate in the sentinel lymph nodes. This build-up is then identified using a handheld magnetometer (SentiMag\(^\text{®}\)).\(^6\) The main advantage of
SentiMag is that it is now possible to provide a sentinel node service away from nuclear medicine departments. In South Africa, access to nuclear medicine departments is limited as they are mostly situated in large academic hospitals making SLNB inaccessible to many women with breast cancer.

The study was conducted at Groote Schuur Hospital (GSH), an academic hospital in South Africa. Groote Schuur Hospital provides a centralized diagnostic breast cancer clinic and multidisciplinary team management for all patients diagnosed with breast cancer in the western part of Cape Town. An average of 550 new patients with breast cancer have been diagnosed between 2014 to 2017 with about 60% of patients presenting with early breast cancer. The unit has been using a nuclear medicine technique to identify sentinel lymph nodes since 2001. In January 2018, the nuclear medicine technique was replaced by SentiMag for all SLNBs.

The study aimed to evaluate the SLNB outcomes of the newly introduced SentiMag technique in comparison to the standard nuclear medicine technique.

**Methods**

A retrospective cohort study, which included all patients meeting the inclusion criteria managed by the Groote Schuur Hospital/University of Cape Town Breast Surgery Unit multidisciplinary team, from 1 January 2017 to 31 December 2018, was undertaken. The sample population was divided into 2 groups for comparison. The first group, named “nuclear medicine”, consisted of all patients who had surgery in 2017 and had an SLNB using a radioisotope, while the second group, named “SentiMag”, consisted of patients who had surgery in 2018 and had a SLNB using SPIO.

The data were retrospectively collected from patient notes, digital and paper records. All information was collected on a password-protected database. The
inclusion criteria were female patients, age 18 or older, who had breast surgery and axillary surgery for breast cancer at Groote Schuur Hospital and surrounding referral hospitals (New Somerset Hospital, Mitchells Plain Hospital and Victoria Hospital). Patients with ductal carcinoma in situ were included if they had axillary surgery. Patients were excluded from the study if they received neoadjuvant chemotherapy, had no axillary surgery, had non-epithelial breast cancer, or had incomplete records.

For sentinel node localization, patients receiving a nuclear medicine SLNB were injected with a radioactive tracer (99mTc), the day before surgery. The injection was made subareolar in patients with non-palpable tumours and subcutaneously above the tumor in patients with palpable tumours. Lymphoscintigraphy was routinely performed, and the hottest node was marked on the skin of the axilla in the nuclear medicine department the day before surgery, as per local protocol. The timing and mode of administration of radioisotope were documented in the clinical records. Sentinel nodes were detected intraoperatively using a gamma probe. The magnetic technique was standardized for patients receiving a SentiMag SLNB. The operating surgeon injected a 5-ml solution, consisting of 2 ml of the magnetic tracer Sienna+ (Sysmex Europe GmBH, Hamburg, Germany) diluted with 3 ml of normal saline, into the retroareolar subcutaneous space. The solution was injected pre-operatively the day before surgery. During surgery, the surgeon used a handheld magnetometer SentiMag®, (Sysmex Europe GmBH, Hamburg, Germany) for skin localization of the sentinel lymph node. After incision, the surgeon removed all metal instruments from the operative field and replaced them with plastic retractors and forceps before the handheld magnetometer was used for sentinel node localization. Excision of nodes with the handheld magnetometer was undertaken by using the same cut-off as used for the gamma probe. Any node with a count of 10 % or more of the node with the
highest count was excised. Beyond four sentinel nodes, surgeons noted the background count and excised additional nodes only at their discretion. Any palpable nodes were also removed. All nodes were examined with hematoxylin-eosin staining on paraffin-embedded specimens.

Ethical approval for the study was received from the Human Research and Ethics Committee of the University of Cape Town (HREC number 199\2019). The data were analysed using STATA v14. Numerical data were summarized as means and medians and categorical data were summarized as proportions. A t-test was used to compare means and a Wilcoxon Ranksum test was performed to compare medians. For categorical data, a Fisher’s exact test or a Chi-squared test was used as appropriate. A level of significance was set at a two-sided p-value of 0.05

**Results**

After excluding patients not meeting the inclusion criteria and, considering patients that had bilateral surgery, 140 axillary procedures were performed in 2017 and 112 in 2018. Bilateral breast patients are having their axillae counted separately

Figure 1 represents the numbers of patients included.
The description of the 2 groups of patients is represented in Table 1. The analysis found no statistical difference between the 2 groups comparing age, T-stage of tumours, size of an invasive tumor or molecular status of the cancers. However, there was a statistical difference in the grade of the tumours, with more high-grade tumours in the Nuclear Medicine group ($p=0.04$).
* In situ carcinoma was excluded from size, grade, and hormone receptor status data

**Table 1: Patient and tumour data**

The 2 groups were also compared in terms of surgical data (Table 2). There was no difference in the type of breast or axillary surgery between the two groups. Although there was an 11% difference in the number of patients receiving an SLNB, with more patients receiving SLNBs in 2018, the results did not reach statistical significance. The results did not show a statistically significant difference between the 2 groups comparing the number of nodes removed when doing a SLNB (p=0.17)
Variable | 2017 (Nuclear Medicine) n=139 | 2018 (SentiMag) n=112 | P-value
---|---|---|---
Breast Surgery Mastectomy BCS | 110 29 | 80 32 | 0.16
Axillary Surgery ANC SLNB | 81 (58%) 58 (42%) | 53 (47%) 59 (53%) | 0.08
SLNB Mean number of nodes removed | 3.9 | 4.7 | 0.17
Node Positive Node negative | 16/58 (28%) 41/58 (72%) | 9/59 (15%) 50/59 (85%) | 0.09

Table 2: Surgical data

Discussion

Sentinel node biopsy was first reported in the 1990s as an attempt to decrease the number of patients with no axillary metastasis receiving an axillary lymph node dissection (ALND).\(^8\) This is referred to as overtreatment of the axilla and needs to be limited to try and decrease complications such as lymphoedema of the arm and sensory nerve deficit of the axilla and upper arm after an ALND.\(^9\) Unfortunately, the current gold standard technique in SLNB, using a nuclear medicine tracer and a gamma probe, is not widely available due to resource constraints in low- and middle-income countries.\(^10\) Therefore, new technologies with equivalent efficacy are constantly being researched to offer SLNB without the dependence on a nuclear medicine department. SentiMag is the most promising of the new technologies available and is already widely used around the world.

Several non-inferiority trials have been published in Europe comparing SPIO to a radioisotope. In 2013 a study by Douek M \textit{et al} \(^3\) on 160 women with breast cancer scheduled for SLNB, who were clinically and radiologically node negative found that
the identification rate was 95.0% (152 of 160) with the standard technique and 94.4% (151 of 160) with the magnetic technique. Of the 404 lymph nodes removed, 297 (74%) were true sentinel nodes. In the Central-European SentiMag study, Thill M et al. compared (99m) Technetium (Tc) with the magnetic technique, using SPIO (Sienna+) for localization of SLNs. The results showed a detection rate per patient of 97.3% (146/150) for (99m) Tc vs. 98.0% (147/150) for SPIO. Their results indicate that SLNB using the magnetic technique can be performed easily, safely and equivalently in comparison to the radiotracer method. Pinero-Madrona A et al. also compared the magnetic to a nuclear medicine technique for the detection of SLNs. They found that transcutaneous and intraoperative detection rates were 95.5% vs 97.2%, and 97.2% vs 97.8% for Sentimag and Gama Probe respectively (concordance rates > 97%). At the node level, intraoperative and ex-vivo detection rates were 92.5% vs 89.3% and 91.0% vs 86.3% for SM and GP respectively. Non-inferiority was proven comparing SentiMag to the Gamma probe. The French Sentimag feasibility trial evaluated the localization of breast cancer SLN using superparamagnetic iron oxide particles in comparison to the standard technique (isotopes ± blue dye). They reported a SLN identification rate of 98.1% for both methods, 97.2% for Sienna+ and 95.4% for the standard technique. The concordance rate was 99.0% per patient and 97.4% per node. Forty-six patients (43.4%) had nodal involvement. Among involved SLNs, the concordance rate was 97.7% per patient and 98.1% per node. Rubio IT et al. assessed the concordance between SPIO and the Tc 99 radiotracer. The detection rate by Tc 99 was successful in 113 (95.7%) of patients and by SPIO in 116 (98.3%). Concordance rates per patient between the techniques was 98.2%. The SLN was positive in 36 (30%) of patients. Of this, SLN positivity was detected by both techniques in 32 patients which indicates that detection of SLNs with SPIO allows for easy
identification of axillary nodes, at a frequency not inferior to the radiotracer.\textsuperscript{15} Karakatsanis A \textit{et al}\textsuperscript{16}, in the Nordic SentiMag trial, compared the efficacy of SPIO as a tracer with Tc and patent blue and reported that SN detection rates were similar between standard technique and SPIO both per patient (97.1 vs. 97.6 \%, \( p = 0.76 \)) as well as per node (91.3 vs. 93.3 \%, \( p = 0.34 \)), something which was not affected by the presence of malignancy. Concordance rates were also consistently high (98.0 \% per patient and 95.9 \% per node).\textsuperscript{16}

Although, not statistically significantly different, this study did demonstrate an increase in the number of patients who had an SLNB after the introduction of SentiMag. There was an 11\% increase in the number of patients who had an SLNB done, from 42\% before to 53\% after the introduction of SentiMag. The increase in access can be explained because of the nuclear medicine department limiting the amount of SLNBs that can be performed on a surgery list to a maximum of two. This limitation of cases is due to the time available on the gamma cameras available at GSH to perform lymphoscintigraphy. The limitation in access to SLNB using nuclear medicine forced surgeons at GSH to perform an ALND, on patients with a clinically node negative axilla, at referring hospitals where more surgery lists are available, to manage waiting times. The SentiMag technique allowed the surgeons to increase the number of SLNB cases done on an operating list increasing the amount of SLNB cases that can be done at GSH. It would thus seem that technology that is not constrained by the access problems of a nuclear medicine technique, i.e., availability of nuclear medicine facilities and availability of radiopharmaceuticals, increases access to SLNB. Grigoryan \textit{et al}\textsuperscript{17} recently reported that only 29 out of 54 (53\%) of African countries had access to nuclear medicine imaging with 16 countries having a single department for the whole country. Only 13 (24\%) countries, mainly in the north and south of Africa.
had more than one facility.\textsuperscript{17} This lack of access to nuclear medicine facilities makes new techniques of doing SLNB without the use of radiopharmaceuticals very attractive. This study, therefore, confirms findings from the literature that SPIO can be easier to use without the restrictions in availability, use, manipulation, and disposal of radiopharmaceuticals.\textsuperscript{12,13,18,19}

Other than access to a nuclear department the cost of the equipment needed to implement an SLNB service is one of the main factors hampering the establishment of an SLNB service in developing countries. To the best of our knowledge, no cost analysis has been done to compare SentiMag to a nuclear medicine technique. There is initial capital that needs to be spent to acquire the detection equipment for both procedures. The cost of SPIO and radiopharmaceuticals is similar. Man et al\textsuperscript{20} reported that the following all need to be accounted for in calculating the cost of a nuclear medicine SLNB service; day admission for injection of the radiopharmaceutical, specially arranged specimen transportation as per local risk management protocol, annual on-site contamination tests and monthly calibration of pocket dosimeters all at extra cost. They estimated that by using SPIO alone $22,300 per year can be saved using SPIO compared to radiopharmaceuticals.\textsuperscript{20}

The study did not show a higher nodal retrieval rate between the Nuclear medicine and Sentimag groups. The mean number of nodes removed using the nuclear medicine technique was 3.9 compared to 4.7 (p=0.17) in the patients who had the magnetic procedure. The results agree with current literature, many authors found that SLNB using SPIO resulted in a similar number of nodes retrieved compared to Tc. However, Rubio I et al\textsuperscript{14}, retrieved more nodes in the SPIO group.
It is currently not known why some surgeons harvest more nodes using the SentiMag procedure. Rubio et al\textsuperscript{14} speculated that it could be explained by a learning curve in using the new tracer agent. The SentiMag technique is different from the nuclear medicine technique in that plastic instruments need to be used during the time the magnetometer is used to prevent interference. Another reason for the increase in the number of lymph nodes removed could be due to the difference in the size of the tracer particles leading to the tracer being taken up differently by the axillary lymph nodes.

The major limitation of this study is the retrospective nature of data collection which can lead to selection bias. A strength is that it not just reports on the results of the SentiMag procedure in isolation but rather compares the new technique to the previous standard of care. Further studies are needed to add to the already considerable amount of data supporting SentiMag as a viable alternative to conventional methods.

<table>
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<tr>
<th>Study (Ref.)</th>
<th>Number of nodes removed using Tc (mean)</th>
<th>Number if nodes removed using SPIO (mean)</th>
<th>P-Value</th>
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<tr>
<td>Douek et al (2013)\textsuperscript{3}</td>
<td>1.9</td>
<td>2.0</td>
<td>NS</td>
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<td>Thill et al (2015)\textsuperscript{11}</td>
<td>1.8</td>
<td>1.9</td>
<td>NS</td>
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<td>Rubio et al (2015)\textsuperscript{14}</td>
<td>1.77</td>
<td>2.2</td>
<td>p = 0.001</td>
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<td>Houpeau et al (2016)\textsuperscript{13}</td>
<td>1.8</td>
<td>1.9</td>
<td>NS</td>
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</table>
Conclusion

This study demonstrated the feasibility of the magnetic technique for SLNB in a resource limited setting. The results from this study, along with the accumulating evidence from the literature, are practice changing. This new method has none of the disadvantages of the standard technique and is promising as a safe and effective alternative in the absence of nuclear medicine facilities, making it ideal for SLNB in resource-constrained settings.
References


05 April 2019

HREC REF: 199/2019

Dr F Malherbe
Surgery
J-Floor, OMB

Dear Dr Malherbe

PROJECT TITLE: REDUCING THE NUMBER OF UNNECESSARY AXILLARY LYMPH NODE DISSECTIONS THROUGH THE USE OF SENTIMAG

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

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

Approval is granted for one year until 30 April 2020.

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)

Please quote the HREC REF 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, FHS 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

HREC 199/2019
# FHS017: Annual Progress Report / Renewal

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

<table>
<thead>
<tr>
<th>Approved</th>
<th>Annual progress report</th>
<th>Approved until/next renewal date</th>
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[ ] Not approved

See attached comments

Signature Chairperson of the HREC/Designee
Date Signed

**Note:** Please note that incomplete submissions will not be reviewed. Please email this form and supporting documents (if applicable) in a combined pdf file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown.

**Principal Investigator to complete the following:**

## 1. Protocol Information

- **Date (when submitting this form):** 10/08/2021
- **HREC REF Number:** 198/2019
- **Current Ethics Approval was granted until:** 30/04/2020
- **Protocol title:** REDUCING THE NUMBER OF UNNECESSARY AXILLARY LYMPH NODE DISSECTIONS THROUGH THE USE OF SENTIMAG
- **Principal Investigator:** F Malherbe
- **Department / Office:** Department of Surgery
- **Internal Mail Address:** J Floor, OMB, Groote Schuur Hospital

1.1 Does this protocol receive US Federal funding? [ ] Yes [ ] No

## 2. Protocol status (tick ✓)

- [ ] Research-related activities are ongoing
- [x] Data collection is complete, data analysis only

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

## 3. Protocol summary

- Total number of records or specimens collected, reviewed or stored since the original approval
- Total number of records or specimens collected, reviewed or stored since last progress report

Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report. [ ] Yes [ ] No

## 4. Signature

25 March 2020

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)
Author Guidelines for the South African Journal of Surgery

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.

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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.

**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.

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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 parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to [www.icmje.org](http://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 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.

**Scientific letters/short reports**

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.

**Case reports**

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.

**Video case reports (SAJS-VIDEO)**

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](http://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/](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.

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