9 November 2023

Mr David Westfall Bates, MD, MSc

Editor-in-Chief

Journal of Patient Safety

c/- Lippincott Williams & Wilkins

Dear David,

Re: Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511[1]

The Neuromodulation Society of Australia and New Zealand ("NSANZ") seeks the retraction of the above-named paper due to its numerous fundamental inaccuracies and false, misleading and deceptive statements regarding:

1. The content and meaning of Spinal Cord Stimulation ("SCS") surgical procedure data[2], on which the paper heavily relies.
2. A purported relationship between the SCS surgical procedure data and 520 adverse events reported to the Therapeutic Goods Administration ("TGA"), the description of which is proclaimed to be the sole aim and purpose of the paper.
3. A purported SCS device removal ratio of 40%, calculated from the surgical procedure data.

[1] https://pubmed.ncbi.nlm.nih.gov/35067619/, referred to throughout as "the paper" or "the study".

[2] Contained in the Admitted Patient Care National Minimum Dataset (APCNMD), as sourced by the paper's authors from the Australian Institute of Health and Welfare's National Hospital Morbidity Database for the period July 2012 to June 2019

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4. The claimed use of relevant National Health and Research Medical Council ("NHMRC") criteria to grade the severity of the 520 adverse events.
5. The claimed use of relevant US National Cancer Institute ("US NCI") criteria to grade the severity of the adverse events.
6. The purported opinion of the regulator to whom these events were originally reported.
7. Patient mortality associated with SCS therapy, evident from the 520 adverse event reports.

The paper also fails to disclose material commercial conflicts of interest which alone are sufficient to warrant retraction by any scientific journal.

Grounds for Retraction – Summary

Contrary to what is claimed, the study represented in the paper:

- Does not quantify the numbers of SCS devices permanently implanted and removed in Australia between 2012 and 2019, nor at any other time.
- Does not grade the severity of the 520 TGA-reported adverse events using valid, relevant NHMRC and US NCI criteria.

Instead, the paper:

- Misrepresents Medicare hospitalisation and SCS surgical procedure data, falsely asserting that it represents the numbers of devices permanently implanted and removed between 2012 and 2019.
- Overlooks or ignores the numerous routine reasons for performing a minor surgical procedure on an SCS device, such as changing its batteries or removing temporary leads after a trial.
- Fabricates a false 'device removal ratio' of 40% based on these misrepresentations.

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- Conflates the misrepresented surgical procedure data with the 520 adverse events reported to the TGA, wrongfully inferring that 40% of devices were removed due to adverse events.
- Exaggerates and embellishes the severity of the 520 adverse events through use of a self-styled, arbitrary severity grading system
    - a system which results in absurd, alarmist outcomes such as the deeming of lead repositioning as "life-threatening" if IV anti-biotics are used to manage infection risk.
- Misrepresents this self-styled grading system as accurately reflecting relevant, authoritative third-party grading criteria established and used by the NHMRC and US NCI in relation to the clinical trialling of pharmaceutical drugs and cancer therapies, respectively.
- Falsely asserts that these grading criteria are appropriate and accepted for use in relation to surgically-implanted electrical stimulation medical devices.
- Falsely attributes to SCS therapy, five patient deaths noted in the 520 adverse event reports, in direct contradiction to the actual TGA primary source material on which the paper is based.
- Makes the wholly unsubstantiated assertion that SCS patients are likely to underreport adverse events, despite no SCS patient being interviewed for the paper, and none of the authors having any clinical experience with SCS therapy.
- Misrepresents the TGA as having agreed with the paper's unsubstantiated assertion that SCS adverse events are substantially underreported, when the regulator has not.
- Falsely claims that the TGA's website cites a research paper which supports that unsubstantiated assertion, when the regulator's website does not.
- Falsely cites a particular research paper as supporting that unsubstantiated assertion, when that research paper does not; being concerned instead with pharmaceutical drug clinical trials.

Grounds for Retraction – Detail

1. **False, misleading and deceptive statements regarding the content and meaning of the SCS surgical procedure data contained in the Admitted Patient Care National Minimum Dataset/Australian Institute of Health and Welfare's National Hospital Morbidity Database**

The table below solely comprises verbatim extracts from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[3]

Methods

Data on the number of stimulators implanted and removed were sourced from the Admitted Patient Care Minimum Data Set

METHODS

Number of Spinal Cord Stimulators Implanted and Removed

Data on the number of spinal cord stimulators implanted and removed per year in Australia were sourced from the Australian Institute of Health and Welfare's National Hospital Morbidity Database (which are based on the Admitted Patient Care National Minimum Dataset)

Results

The number of spinal cord stimulators implanted and removed each year …. are shown in Table Table1.1. There were a total of 26,786 devices implanted, 10,702 devices removed

TABLE 1

Totals Per Year of Spinal Cord Stimulators Implanted and Removed and Number of TGA Reported Adverse Events

Year	Units Implanted	Units Removed	Adverse Events
2012/13	2307	897	120
2013/14	2918	1073	53
2014/15	3217	1251	29
2015/16	4280	1577	35
2016/17	4433	1788	40
2017/18	4837	1996	103
2018/19	4794	2120	140*
Total	**26,786**	**10,702**	**520**

Discussion - The TGA received notifications of 520 adverse events in a period where 26,786 spinal cord stimulator devices were implanted

Given the relatively high number of spinal cord stimulators that are removed each year in Australia

Conclusions

…and each year in Australia, many are removed

[3] https://pubmed.ncbi.nlm.nih.gov/35067619/

NB: The paper's "Methods" summary section says that its SCS device data is sourced from the "Admitted Patient Care Minimum Data Set" (or "APCMND"), whereas the paper's more expansive "METHODS" section says that its SCS device data sourced from "the Australian Institute of Health and Welfare's National Hospital Morbidity Database (which are based on the Admitted Patient Care National Minimum Dataset)" (or "AIHW Database"). The paper uses these descriptors interchangeably throughout the paper. For ease of reference, hereafter we will refer solely to the "AIHW Database".

As evident from the verbatim excerpts above, the paper frequently and consistently asserts specific figures for the quantity of SCS devices which it claims were implanted and removed between July 2012 and June 2019. These claims are vital to every aspect of this paper, featuring heavily throughout, but particularly in the Methods, Results, Discussion and Conclusions sections.

Regarding the source of these specific figures, the paper states:

> "Data on the number of spinal cord stimulators implanted and removed per year in Australia were sourced from the Australian Institute of Health and Welfare's National Hospital Morbidity Database…We used the codes "39134-01 NEUROSTIMULATOR or RECEIVER…..for implants and the code "39135-00 NEUROSTIMULATOR or RECEIVER…. for removals".

This statement is demonstrably and unambiguously false. The specific figures recorded against these codes in the AIHW Database do not represent numbers of SCS devices. They represent numbers of surgical procedures.

This fact is readily apparent from the most cursory review of the AIHW Database, with its discernment requiring no medical nor scientific expertise.

For example:

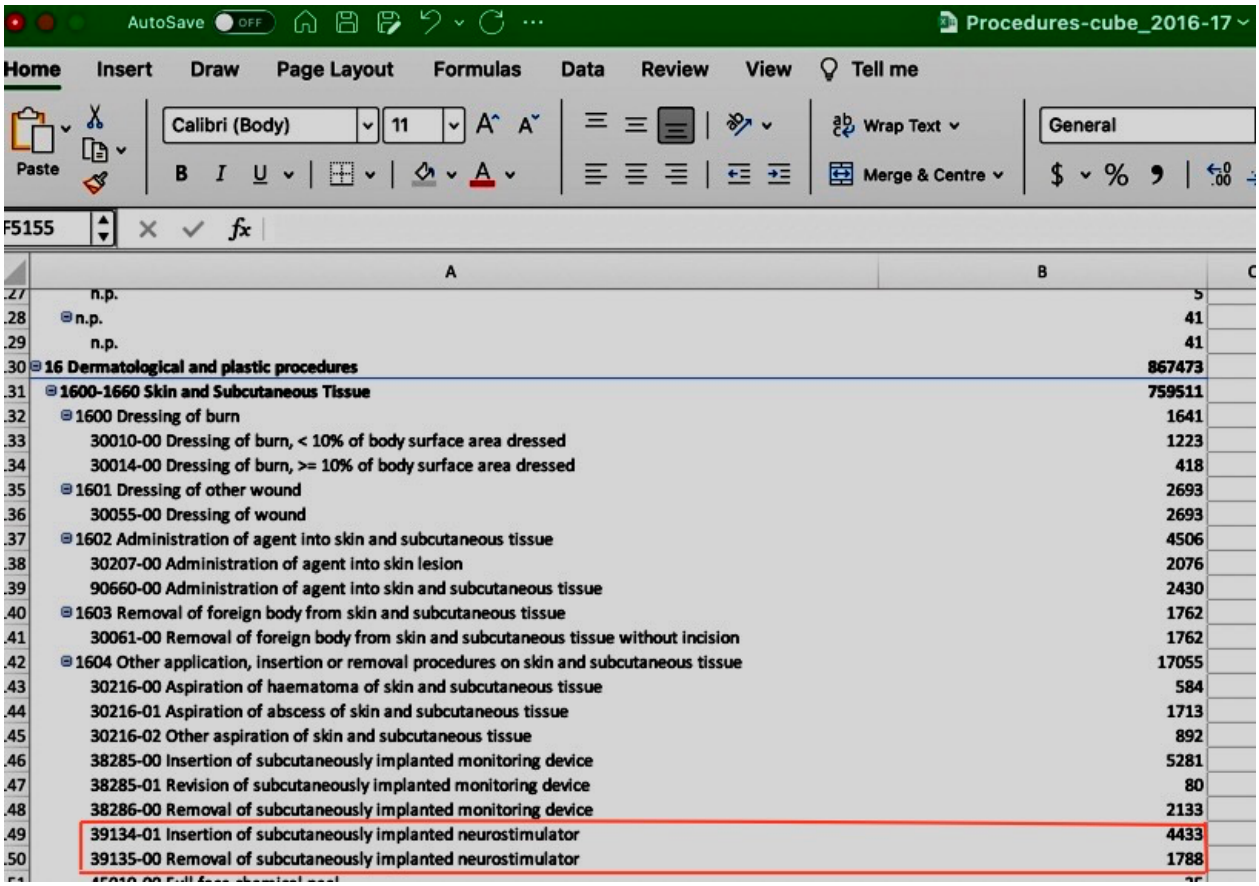
- The database is clearly labelled a "Procedures data cube".[4]
- It describes itself as comprising two spreadsheets; "Procedure Counts Data" and "Procedure Counts Summary".

[4] Australian Institute of Health and Welfare. *Procedure Data Cubes*. Canberra: AIHW; 2020. Available at: https://www.aihw.gov.au/reports/hospitals/procedures-data-cubes/contents/data-cubes.

- The data is structured under a "Procedures" taxonomy consisting of:
  - "Procedure chapters", followed by
  - "Procedure sub-chapters" ("Skin and Subcutaneous Tissue") followed by
  - "Procedure blocks ("Other application, insertion or removal procedures on skin and subcutaneous tissue"), followed by
  - "Procedure codes" ("39134-01 Insertion" and "39135-00 Removal"), followed by
  - "Procedures", under which are listed the specific figures associated with these insertion and removal procedures.

IMAGE A, below, is a screenshot taken from the 2016/17 AIHW Database[5]. It illustrates the clarity and certainty with which the database communicates the nature of its contents.

IMAGE A.



[5] Ibid.

NB: The number of procedures logged against the codes 39134-01 and 39135-00 in the above table (outlined in red) match the 2016/17 numbers for "Units Implanted" and "Units Removed" in Table 1 of the paper.

The AIHW Database is not a medical device registry. It contains information on hundreds of medical procedures because it's "a collection of electronic confidentialised summary records for separations (that is, episodes of care) in public and private hospitals in Australia"[6]

The type of information to be collected about "episodes of care" for admitted patients is determined by The Admitted Patient Care National Minimum Dataset[7] ("APCNMD") which the AIHW describes as "a core set of data elements…for mandatory collection and reporting at a national level", including demographic, medical and financial information, such as Medicare eligibility status[8].

Indeed, Medicare eligibility is the reason why the codes 39134-01 and 39135-00 are used in the AIHW Database; they're the Medicare Benefits Schedule (MBS) item numbers for SCS device insertion and removal procedures.

Instead of reflecting actual SCS device numbers, the AIHW Database contains the numbers of a surgical procedures claimed through Medicare by surgeons for their patients. It's a record of professional medical services associated with SCS therapy, logged with the Department of Health for the purpose of calculating Medicare benefits payable to the patient receiving these services.

Further, the AIHW Database does not identify the devices in relation to which the surgical procedures were performed, nor do they indicate whether they were performed for permanent, temporary or transitory reasons, the range of which may include the following:

[6] https://meteor.aihw.gov.au/content/394352
[7] https://www.aihw.gov.au/getmedia/a80cbfd4-2601-472f-942b-9bd2c90bca1d/apc.pdf?v=20230605180438&inline=true
[8] https://www.aihw.gov.au/reports/hospitals/admitted-patient-care-nmds/summary

- trial electrode implantation
- post-trial removal of trial electrodes
- post-trial implantation of permanent electrodes
- post-trial implantation of battery pack/generator
- transitory removal of permanent device to renew batteries
- re-implantation of the re-powered device
- removal of permanent device for the purpose of upgrading device technology
- implantation of the upgraded device
- temporary removal of permanent device to facilitate the medical treatment of an unrelated condition, in or adjacent to the implant area
- permanent removal of a device to facilitate the medical treatment of an unrelated condition, in or adjacent to the implant area
- permanent removal of a device causing or contributing to, or suspected of causing or contributing to, a serious adverse event
- permanent removal of a device causing or contributing to, or suspected of causing or contributing to, a non-serious adverse event.

Moreover, as known by any clinician with first-hand experience of SCS therapy, in any given period:

- the number of surgical implanting procedures logged under the MBS would *exceed* the number of permanently implanted devices, and
- the number of surgical removal procedures would likely *exceed* the number of permanently removed devices.

This is because:

- The permanent implanting of a single device involves a minimum of two surgical procedures, both covered by the MBS item 39134-01.
- The temporary implanting of just the electrodes for trial purposes involves a minimum of two surgical procedures, regardless of whether the trial is successful, with all

implantations logged against MBS item 39134-01 and the removal of trial electrodes logged against MBS item 39135-00.

- The transitory removal and re-implantation of devices for the purpose of renewing batteries every 2.5 (rechargeable) to 10 years (non-rechargeable) involves a minimum of two surgical procedures, covered by MBS item numbers 39135-00 and 39134-01, respectively.
- The elective upgrading from an older device to a newer device containing the latest advanced technology like real-time neural sensing and modulation involves a minimum of two surgical procedures, covered by MBS item numbers 39135-00 and 39134-01, respectively.
- The temporary or permanent removal or repositioning of a device solely to facilitate surgical and/or non-surgical treatment of unrelated medical conditions in or around the implant area involves one to two surgical procedures, covered by item numbers 39135-00 and 39134-01.

Indeed, with permanent implantation and removal comprising only two of the several reasons for surgeries among the large number of SCS devices implanted over the last few decades, it is possible, that during any given year:

- *none* of the implanting procedures logged in the AIHW Database were carried out for the purpose of permanently implanting devices
- *none* of the logged removal procedures logged in the AIHW Database were carried out for the purpose of permanently removing devices
- *none* of the logged removal procedures logged in the AIHW Database were carried out on devices implanted that year.

Finally, it should be noted that the total numbers of permanent implants and removals cannot be discerned from any known and reliable data source.

With no centralised database tracking the devices since their introduction in Australia more than 40 years ago, the size of the installed base was unknowable at the time of the study.

NSANZ's best estimate, based on long-term growth rates, is a minimum average of 50,000 devices.

For the sake of comparison, this estimate is less than double the total number of surgical implanting procedures recorded by AIHW Database over the 6.5 year review period (26,786).

Assuming a conservative minimum base of 50,000 devices yields an adverse event rate of 1:100, or 1%, during the review period.

Remarkably, the study decries the absence of a centralised register of SCS devices, yet doesn't concede that ignorance of the size of the total installed base is a major impediment to putting the 520 adverse events in proper context.

It is conspicuously silent on this fundamental issue, preferring instead to obfuscate and distract through conflation of the surgical procedure data with the adverse event data, when no evident relationship exists between the two.

2. False, misleading and deceptive inferences of relativity between the disparate AIHW Database's surgical procedure and the TGA adverse event data sets

The table below solely comprises verbatim extracts from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[9]

Methods - Adverse events were coded by seriousness, severity, body system affected, type of event, action taken, and attribution of fault. Data on the number of stimulators implanted and removed were sourced from the Admitted Patient Care Minimum Data Set.

Reports of adverse events associated with spinal cord stimulators were sourced from the TGA. To provide a context for the safety data, we sourced information on the number of spinal cord stimulators implanted each year in Australian hospitals.

Number of Spinal Cord Stimulators Implanted and Removed - Data on the number of spinal cord stimulators implanted and removed per year in Australia were sourced from the Australian Institute of Health and Welfare's National Hospital Morbidity Database (which are based on the Admitted Patient Care National Minimum Dataset) …the TGA has a searchable log of reported adverse events associated with devices from posttrial use, created in July 2012.[14]

Results - The number of spinal cord stimulators implanted and removed each year and TGA reported events for the period 2012–2019 are shown in Table 1. There were a total of 26,786 devices implanted, 10,702 devices removed, and 520 reported adverse events.

TABLE 1

Totals Per Year of Spinal Cord Stimulators Implanted and Removed and Number of TGA Reported Adverse Events

Year	Units Implanted	Units Removed	Adverse Events
2012/13	2307	897	120
2013/14	2918	1073	53
2014/15	3217	1251	29
2015/16	4280	1577	35
2016/17	4433	1788	40
2017/18	4837	1996	103
2018/19	4794	2120	140*
Total	**26,786**	**10,702**	**520**

Discussion - … The TGA received notifications of 520 adverse events in a period where 26,786 spinal cord stimulator devices were implanted…We also for the first time highlight the issue that devices are being removed in Australia at a rate of 4 for every 10 implanted. Other than the high number of adverse events reported, the TGA data do not provide details about why these were removed.

Conclusions - Spinal cords stimulators have the potential for serious harm, and each year in Australia, many are removed

[9] https://pubmed.ncbi.nlm.nih.gov/35067619/

Under the section titled "Aim", the paper states a *singular* aim "to describe the adverse events relating to spinal cord stimulators reported to the Therapeutic Goods Administration of Australia between July 2012 and January 2019"[10].

Yet it repeatedly juxtaposes all discussion and description of these events against the misrepresented AIHW surgical data, for the apparent reason of implying a relationship between the two.

The conclusion that this conflation was deliberate and intended to mislead readers is borne out by two examples that go beyond juxtaposition to ascribe a direct relationship between them.

Firstly, the study explicitly describes the misrepresented AIHW data *as a context* for understanding the 520 adverse events reported to the TGA –

> "Reports of adverse events associated with spinal cord stimulators were sourced from the TGA. *To provide a context for the safety data,* we sourced information on the number of spinal cord stimulators implanted each year in Australian hospitals".

Secondly, the study at one point describes the AIHW data as "TGA data" when conflating its fabricated device removal ratio of 4/10 with the 520 adverse events –

> "We… highlight the issue that devices are being removed in Australia at a rate of 4 for every 10 implanted. Other than the high number of adverse events reported, the TGA data do not provide details about why these were removed".

Individually and cumulatively, these conflations create the dominant impression that many devices had to be removed because of adverse events, when no such inference can be drawn from the data on which the study relies.

Another example of the deceitful conflation of the AIHW data and TGA data is found in the paper's Table 1, which actively misguides the reader from the outset with the introductory

[10] p 507

statement – “There were a total of 26,786 devices implanted, 10,702 devices removed, and 520 reported adverse events”.

These numbers are the cumulative totals of three eponymous columns. These columns intersect seven rows labelled for the seven years from 2012/13 to 2018/19, inclusive.

When reading from left to right, the reader is clearly invited to infer that in any given year, the “Adverse events” relate to the (false) implant and removal numbers. This pattern recurs, and the lie is repeated, eight times (seven years plus a cumulative total).

This misleading outcome might be considered incidental if the paper’s inclusion of such a granular table served a clear purpose beyond the creation of a misleading impression of relativity between the (false) device data and the adverse event data.
However, no such purpose is apparent, and indeed, the existence of one is contra-indicated by the paper’s abject failure to reference the vast majority of Table 1’s data.

Of the 24 specific figures contained in Table 1 , 21 are ignored in the commentary.
Of the 3 specific figures mentioned in the commentary, only one is germane to the paper’s aim of describing the adverse events, which explains why it’s also the only number that truly and accurately depicts what it’s supposed to.

3. False, misleading and deceptive use of an irrelevant, fabricated "device removal ratio" based on the AIHW Database surgical procedure data

The table below solely comprises verbatim extracts from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[11]

Results - the ratio of removals to implants was 4 per every 10 implanted
Conclusions - Each year in Australia, for every 100 spinal cord stimulators implanted, approximately 40 are removed
Discussion - devices are being removed in Australia at a rate of 4 for every 10 implanted

Despite the study's sole stated aim of describing the 520 events reported to the TGA, its "Results" section additionally makes the wholly unsubstantiated assertion that "the ratio of removals to implants was 4 per every 10 implanted".

This number appears to have been calculated by dividing the total number of surgical implanting procedures (26,786) logged in the AIHW Database by the total number of surgical removal procedures (10,702)) logged in the AIHW Database.

The clear implication of the text of the "Results" summary is that 40% of devices were removed due to adverse events reported to the TGA.

Cumulatively, the repeated juxtaposition of the misrepresented AIHW data against the TGA adverse event data egregiously misleads and deceives the reader.

Firstly, as discussed above, the SCS surgical implanting and removal procedure numbers are misrepresented as device numbers.

[11] https://pubmed.ncbi.nlm.nih.gov/35067619/

Secondly, they're combined in a simple fraction as numerator and denominator; the very act of which effectively fabricates a relationship that does not exist, and makes no sense when considering that removal procedures can be performed on any device in the larger installed base.

Thirdly, as is the case with the raw AIHW numbers, frequent juxtaposition of 4/10 against the evidently unrelated TGA data is used to conflate the two, fabricating a further relativity which does not exist.

In summary – the 4/10 ratio is a false and misleading concept that does not measure any rate of device removal, let alone the rate of device removal among the 520 adverse events reported to the TGA.

NB: the rate of device removal over the review period, and the rate of device removal among the 520 adverse events, are incapable of calculation from these data sets, because they don't contain the following critical information:

- the number of devices on which the surgical removal procedures were performed
- the average size of the installed base during the review period
- the reasons for the performance surgical removal procedures, which could be for permanent, temporary, transitory or device-unrelated purposes as outline above.

4. False, misleading and deceptive statement regarding NHMRC grading criteria and its purported use to grade the severity of the adverse events

The table below solely comprises a verbatim extract from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[12]

Seriousness - Adverse events were coded as "serious" or "not serious" according to the Australian National Health and Medical Research Council (NHMRC) safety monitoring and reporting in clinical trials involving therapeutic goods guidelines.[16] A serious adverse event is any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Adverse events requiring surgical intervention were classified as serious as the patient would require hospitalization.

Of the paper's various deceptions, those relating to the NHMNC grading criteria are among the most blatant.

Although the above definition of "serious" adverse event appears in the NHRMC guidelines for therapeutic goods undergoing clinical trials, those same guidelines make clear that they apply to pharmaceutical medicines, not medical devices.

According to the NHRMC guidelines for therapeutic goods undergoing clinical trials, the definition of a serious adverse event applying to a medical device is as follows:

"An adverse event that: led to death

1. *led to serious deterioration in the health of the participant, that either resulted in:*
    - *a life-threatening illness or injury, or*
    - *a permanent impairment of a body structure or a body function, or*
    - *in-patient or prolonged hospitalisation, or*

[12] https://pubmed.ncbi.nlm.nih.gov/35067619/

- *medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function*

2. *led to fetal distress, fetal death or a congenital abnormality or birth defect.*

Note: Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event."

It is difficult to conceive that the study's misapplication of drug guidelines to a medical device was inadvertent, because the NHRMC guidelines for therapeutic goods undergoing clinical trials:

- delineate two discrete categories of therapeutic goods, being either pharmaceutical drugs or medical devices
- commence with this delineation and an observation that different guidelines apply to each
- devote separate, consecutive chapters detailing each set of guidelines.

The study's surreptitious misapplication of incorrect NHMRC guidelines is highly consequential, because it substantially expands the types of adverse events described as 'serious' versus 'not serious'.

Whereas the NHMRC's guidelines for drugs specify any admission to hospital as 'serious', those applying to devices only deem admission to be serious if due to a serious deterioration in health.

The NHMRC guidelines further distinguish device-related adverse events from drug-related adverse events by expressly clarifying that hospital admission for a procedure required by a Clinical Investigation Plan (eg to reposition a SCS lead) is not deemed a serious adverse event

Exacerbating the study's deception regarding its claimed use of relevant NHMRC guidelines is the fact that it does not actually apply the NHMRC drug guidelines.

Instead, the authors arbitrarily and additionally deem any adverse event involving a surgical procedure to constitute a 'serious adverse event', due to a simple presumption that hospitalisation is always required for any surgical intervention.

The irrelevant NHMRC *drug* guidelines don't make this presumption, nor do they deem a surgical procedure to evince a 'serious adverse event' for any other reason .
Moreover, for the avoidance of doubt in their interpretation, the relevant NHMRC medical device guidelines expressly disagree with this deeming.

Hence at this point it's salient to question the knowledge and authority relied on by the authors when making this decision.

We observe the following:

- None of the seven authors has any clinical experience with SCS therapy.
- None of the seven authors are specialist pain medicine physicians trained and recognised by the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. In fact, only one author holds one of the specialist medical qualifications deemed a prerequisite to study pain medicine (eg anaesthesia, medicine, surgery, psychiatry).
- Only two authors hold a primary medical degree, with the remainder holding undergraduate academic qualifications in journalism, international studies, occupational therapy, physiotherapy, and pharmacy.
- Ignorance of the multiplicity of purposes for which a device can be subject to a removal procedure is evident throughout the study; they're incorrectly assumed to all comprise the permanent removal of devices due to either adverse events, device faults or lack of efficacy.
- The study extensively mispresents surgical procedure data as device data.

5. False, misleading and deceptive statement regarding the suitability of US NCI grading criteria and its purported use to grade the 520 adverse events

The table below solely comprises a verbatim extract from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[13]

Adverse Events Coding
Seriousness - The severity of each event was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE is a grading scale originally developed for grading the toxicity of cancer treatments *but is now commonly used as a standardized way to report adverse events from any clinical trial.*

The CTCAE, or "common toxicity criteria", is a taxonomy designed to aid clinicians in the detection and documentation of an array of adverse events commonly encountered in oncology; specifically, the side-effects which may arise during the clinical trialling of cancer therapies like chemotherapy and radiation therapy. The most current version of the CTCAE is version 5.0, published in 2017[14].

According to the CTCAE, an adverse event (AE) is defined as any abnormal clinical finding *temporally associated* with the use of a therapy for cancer; *causality is not required*.

The CTCAE is now commonly used outside of clinical trials in the routine care of cancer patients to guide treatment decisions such as drug dosing.[15]

Further iterations of the CTCAE have expanded its scope of potential applicability and adaptation to clinical trials involving pharmaceuticals and biologies unrelated to oncology.

[13] https://pubmed.ncbi.nlm.nih.gov/35067619/

[14] https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932726/#:~:text=It%20was%20designed%20to%20aid,interventions%20%5B3%2C%209%5D.

For example, treatments for blood disorders, infectious diseases, vaccines, cardiac medications, autoimmune diseases, and dermatological conditions.

However, contrary to the study's claim, the CTCAE is not commonly used to categorise adverse events relating to any medical device, whether during clinical trials or post-market. Certainly, it cannot be said to comprise a standard or benchmark for grading adverse events relating to any medical device.

Indeed, it's difficult to conceive a more inappropriate basis from which to devise a grading system for adverse events relating to spinal cord stimulators.

Again, a question is begged – why apply a cancer drug clinical trial grading system to post-market spinal cord stimulators?

Presumably, we posit, because it deems any adverse event requiring admission to hospital a 'severe adverse event'.

Notably, the US NCI CTCAE shares this definition in common with the NHMRC pharmaceutical drug guidelines misused by the study.

Also in common is the fact that the study does not faithfully apply either grading system.

Instead, the study arbitrarily expands the upper echelons of severity in the CTCAE ("serious" and "life-threatening"), by presuming:

- that all surgical procedures relating to adverse events require hospitalisation, hence deeming them 'serious adverse events'
- that any hospital admission involving the use of antibiotics against infection or the risk of infection to be 'life threatening'.

As was the case with the study's arbitrary changes to the NHMRC drug guidelines: the modifications to the US NCI's CTCAE constitute an effective re-engineering of the system for the apparent purpose of exaggerating the severity of adverse events.

Co-opting the CTCAE for this purpose appears to serve no credible purpose beyond imbuing the study's "DIY" grading system with undeserved institutional legitimacy.

The scale of embellishment achieved through the study's use of a thinly-veiled, self-styled "DIY" grading system is exemplified in the rare adverse event example of SCS electrode migration within the epidural space – particularly when a surgeon follows recommended clinical practice and administers perioperative antibiotics to reduce the risk of post-operative infection.

Properly reported to the TGA as an adverse event involving a medical device, in the hands of the study's authors, this event is:

- initially sorted into the 'serious' category courtesy of the wrong NHRMC guidelines (hospitalisation is required, but not due to a serious deterioration in the patient's health), then
- escalated into the category of 'life threatening', courtesy of self-styled changes to the irrelevant CTCAE.

To summarise – contrary to the study's repeated assertions, none of the 520 unique adverse events were rated according to the relevant NHMRC criteria. They were rated according to a self-styled "DIY" pharmaceutical drug-based grading system which the study misrepresented as the relevant NHMRC criteria.

Similarly, contrary to the study's repeated assertions, none of the 520 unique adverse events were coded using the irrelevant US NCI CTCAE. They were coded by an arbitrarily expanded notion of that criteria.

The dearth of relevant SCS knowledge, expertise and authority among the authors further underscores the illegitimacy of the paper's self-styled "DIY" severity grading process.

6. False, misleading and deceptive claim that the TGA expressed a view in relation to the 520 adverse events, has cited research supporting that view, and that this research reported 90%-95% underreporting of such events

The table below solely comprises a verbatim extract from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[16]

Seriousness - A limitation of our study is that we likely underestimate the true number of adverse events as we used data that were voluntarily reported to the TGA rather than data obtained by prospectively monitoring all implanted devices. The TGA has acknowledged this issue on their website by citing a review that reports that 90% to 95% of adverse events go unreported.

Contrary to the study's assertions, the TGA's website does not:

- Acknowledge that the true number of SCS adverse events likely exceeded 520.
- Acknowledge that SCS adverse events in general are likely to be underreported.
- Cite a review that reports that 90% to 95% of SCS adverse events go unreported.

Indeed, the TGA website makes no comment on the potential for underreporting SCS adverse events, restricting its commentary on medical device underreporting to transvaginal mesh implants, since these devices were the subject of a highly-publicised Senate Inquiry in 2017.

Further and similarly, the adverse event review referenced by the paper does not relate to medical devices, let alone spinal cord stimulators. Titled "Under-reporting of adverse drug reactions : a systematic review", its stated purpose is the investigation of differences between adverse *drug* reactions and their under-reporting.

The paper's unrelenting negative bias and predilection for exaggeration and fabrication is further evidenced in the following gratuitous claim:

[16] https://pubmed.ncbi.nlm.nih.gov/35067619/

> *"there may be a particular underrepresentation of minor adverse events. It is possible that consumers may see minor adverse events as less important and therefore not take the time to lodge a report"*

It's worth dwelling for a moment on the condescension, hubris and bias inherent in this unfalsifiable non-sequitur. It not only imagines SCS patients as naïve and misguided, it presupposes that all adverse events of are of equal importance. This is especially remarkable when it's considered that:

- no SCS patient has been interviewed for the paper
- none of the authors having any clinical experience with SCS therapy
- there's apparent ignorance of the range and purpose of both routine, as well as remedial, SCS surgical procedures.

7. False, misleading and deceptive statement that the five adverse events noting the death of a patient attributed those deaths to either the SCS device or related surgical procedures

The table below solely comprises verbatim extracts from "Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration. J Patient Saf. 2022;18:507–511"[17]

Seriousness and Severity of Reported Adverse Events Relating to Spinal Cord Stimulators - Of the 520 unique adverse events logged with the TGA, 484 (93%) were rated as serious according to the NHMRC criteria. *Based on the CTCAE coding of event seriousness, 5 (1%) resulted in death.*
Previous reviews of adverse events relating to spinal cord stimulators have concluded that the devices are safe and have downplayed the potential for serious adverse events.[11] *In contrast, our study shows that many events reported to the TGA are neither minor nor easily resolved. There were 5 reports of death, an outcome that has not been identified in trials or considered in narrative reviews of spinal cord stimulators.*

Contrary to the study's assertions, the TGA adverse event reports did not attribute five patient deaths to SCS therapy. They attributed two deaths, both of sepsis consequential to surgeries, with none related to the devices themselves**.**

The three deaths wrongly attributed by the study to SCS therapy are described verbatim in the adverse reports[18] as follows:

i. "A report was received that the patient will be undergoing palliative radiation therapy for a large tumor located in the IPG pocket …The tumor was assessed as being unrelated to the device… Additional information was received that the patient's death was not device related."

[17] https://pubmed.ncbi.nlm.nih.gov/35067619/
[18] Ref. Appendix 4, http://links.lww.com/JPS/A450 for all 5 reports

ii. "It was reported the patient experienced loss of sensation in their left leg following an SCS implant … the patient passed away on 20 July 2018 due to Deep Vein Thrombosis leading to a Pulmonary Embolism. The patient had co morbidities and the death was a result of these co morbidities…. the issue was not related to the device.

iii. "There were no reports of device-related issues from the patient prior to the passing and the patient had been receiving effective pain relief while using the device. Follow-up indicated that the physician believes the patient's death was not related to the device…a review of the complaint history record shows no reported issues from the patient prior to the patient's death ..the device diagnostic data shows the patient was regularly using stimulation and charging the device since implant."

Failure to disclose certain authors' potential conflicts of interest

Financial conflict of interest - The Age/Sydney Morning Herald (Nine Entertainment Co.) journalist/co-author

The study fails to disclose that one of the authors:

- is a tabloid journalist, not an academic researcher
- played a pivotal role in the study
- was, in fact, the instigator of the study
- is clearly financially conflicted.

While journalists commonly write about the content of academic papers after their publication in journals, it is highly unusual for them to be involved in the conception and preparation of such papers.

In this case, the originating investigation into the TGA adverse event data was instigated by a journalist working for a major media organisation[19], who then collaborated with academic researchers from the allied health professions.

It is remarkable and concerning that this highly salient fact was not disclosed in the paper.

Readers are entitled to know when a purportedly scientific study has been instigated at the behest of a journalist working for a popular tabloid media organisation.

This matters because the purposes and aims of journalism markedly differ from the purposes and aims of medicine, surgery and related data analysis.
Journalism is concerned with subjective narrative exposition through the reporting and framing of select facts. Medicine and surgery are concerned with rigorous scientific investigation, analysis and objective determination of the truth.

They are not "two sides of the same coin", and their commingling risks producing a paper which tells a great story but is not true or accurate.

Tellingly, the paper's authors waited until *after* the paper was published in the Journal of Patient Safety to proactively disclose the central, instigating role played by journalist Mr Liam Mannix. This occurred via the following boast in an article he authored, based on the study:[20]

> "An investigation by *The Age* and *The Sydney Morning Herald* reveals spinal cord stimulators, or the operations to install them, have led to 520 serious complications"

While the paper itself omits any express disclosure of the fact that it was instigated and co-authored by a journalist, a newspaper article he wrote about the study several months later takes the diametrically opposite approach – boldly proclaiming his central role as instigator of a study with the sole stated aim "describe the adverse events relating to spinal cord

[19] "An investigation by *The Age* and *The Sydney Morning Herald* reveals spinal cord stimulators, or the operations to install them, have led to 520 serious complications" https://www.smh.com.au/national/to-hell-and-back-devices-meant-to-ease-pain-are-causing-trauma-20220203-p59tf3.html

[20] https://www.smh.com.au/national/to-hell-and-back-devices-meant-to-ease-pain-are-causing-trauma-20220203-p59tf3.html

stimulators reported to the Therapeutic Goods Administration of Australia between July 2012 and January 2019".

Mannix's two additional articles based on the study, and his very recently published book, confirm that it was effectively a joint project between the IMH and the media, undertaken for the apparent purpose of perpetuating an anti-SCS narrative and/or deriving book royalty payments.

The project was undeniably:

- Undertaken at least in part to generate income for the journalist's media employer (and which subsequently featured in three separate articles only available to paying subscribers and which also attract advertising revenue).
- Further monetised via prominent inclusion in a book authored by him, in relation to which he receives royalties, and which is cross promoted in his employer's newspapers[21] and on his co-authors' employer's website[22], accruing incremental revenue to the benefit of these parties.

Possible financial conflicts of interest - Institute for Musculoskeletal Health author cohort

According to the IMH's website[23], certain of its funding partners are private health insurers and workers compensation insurers.

The majority of the study's authors work at the IMH, hence may be direct or indirect beneficiaries of the funding provided by these insurers.

Private health insurers and workers compensation insurers have an obvious vested financial interest in reducing the use of SCS therapy among patient populations.

The paper does not declare the IMH author cohort's possible conflict of interest.

[21] https://www.smh.com.au/healthcare/we-re-in-a-back-pain-epidemic-and-most-treatments-don-t-work-20230731-p5dsjx.html
[22] https://shop.msk.org.au/products/back-up-why-back-pain-treatments-aren-t-working-and-the-new-science-offering-hope-1
[23] https://imh.org.au/

When assessing whether this possible conflict of interest is an actual conflict of interest, it's relevant to note:

- The study's recommendation that, in view of its findings, insurers may wish to sponsor future research.
- Its speculation that, as a result of this research, "funders may need to disinvest from spinal cord stimulators".
- The lead researcher's post-publication disclosure of receipt of a sponsorship from the private health insurance peak body, Private Health Australia (PHA), to research SCS among the customers of the PHA's corporate members.
- Her co-author/journalist's interviewing of the CEO of PHA for an article in the Sydney Morning Herald and The Age[24] entitled "Insurers call for ban on spinal cord stimulator subsidies", in which the PHA called upon the Government to "stop funding the procedure".
- The conspicuous omission from that article of any:
  - disclosure of the author's co-authorship of a study suggesting that funding for SCS be withdrawn[25]
  - mention of the PHA's financial conflict of interest in calling for an SCS ban[26].
  - mention of the PHA's sponsorship of new research by his study co-author and colleague.

To recap - because the IMH is part-funded by private health insurers and workers compensation insurers, its author cohort had a possible financial conflict of interest that went undisclosed.

[24] ; https://www.smh.com.au/national/insurers-call-for-ban-on-spinal-cord-stimulator-subsidies-after-new-trial-20221024-p5bs9m.html
[25] ibid
[26] ibid

That this conflict of interest existed, and likely biased the majority of the study's authors, is further evidenced by:

- the study's overt solicitation of further research sponsorship from the private health insurance industry
- the lead researcher's subsequent professed receipt of such sponsorship
- the journalist/co-author's decision to write a follow-up article entitled "Insurers call for ban on spinal cord stimulator subsidies".

Conclusion and request for action

This paper is replete with profoundly and demonstrably false, misleading and deceptive statements.

Publication by the Journal of Patient Safety has granted it undeserved legitimacy and enabled the achievement of undisclosed commercial benefits to certain of the authors.

Continued endorsement by the Journal will inevitably lead to the deceit of more readers and the general public.

Having detailed numerous compelling grounds for retraction of the paper, we respectfully request that you, as Editor, critically review it, and per the Committee on Publishing Ethics (COPE) guidelines, instigate an investigations committee for this purpose.

Please advise us of your response to, and actions arising from, this letter.

Regards

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On behalf of NSANZ Executive Committee

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