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Supporting Information

Supplementary methods and results

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Appendix to: Greenwell C, Webster A, Harris IA, et al. Surgical clinical trial activity in Australia, 2010–20, by specialty: analysis of trial registration data. *Med J Aust* 2025; doi: 10.5694/mja2.52555.

Supplementary methods

Data sources and eligibility criteria for trials

The Australian New Zealand Clinical Trials Registry (ANZCTR) is an online register of clinical trials conducted in Australia and elsewhere; ClinicalTrials.gov is a United States-based trials registry. Both are endorsed by the World Health Organization (WHO) International Clinical Trials Registry Platform (3). Trial registration has been required for publication in journals endorsed by the International Committee of Medical Journal Editors (ICMJE) since 2005 (4) and as a condition of ethics approval for clinical trials undertaken in Australia since 2014 (5). Trial registration records include a set of mandatory data items required by the WHO Trial Registration Data Set, including study type, health conditions studied, intervention details, funding, and sponsor details (6). Information is entered by the trial sponsor or a delegate, such as the trial investigator. It is estimated that trials registered with ANZCTR and ClinicalTrials.gov capture more than 95% of trials recruiting participants in Australia (7).

We extracted data from trial registration records in the ANZCTR on 21 October 2022 and in ClinicalTrials.gov on 27 October 2022. We extracted ANZCTR trial data from the ANZCTR online search facility (1) and accessed ClinicalTrials.gov trial data through a connection to the PostgreSQL Access to Aggregate Content of ClinicalTrials.gov (AACT) database in R Studio (2). We used the following eligibility criteria to select trials: date of registration between 1 January 2010 and 29 February 2020, trial type interventional, recruitment in Australia (including multinational trials with recruitment in Australia), and recruitment not restricted to people under 18 years of age. All registered trials were included, regardless of completion status.

Criteria for identifying surgical trials

We defined surgical trials as those in which any component of the intervention was delivered by a surgeon, and the intervention was proposed to improve surgical patient outcomes. We broadly defined "delivered by a surgeon" to include trials of non-surgical interventions, such as pre-operative medicines or diet programs, intended to be prescribed by surgeons prior to surgery to improve patient outcomes.

For each eligible trial, we searched intervention and condition fields in the trial registration record to identify surgical trials. For ANZCTR-registered trials, we used the intervention code "Treatment: Surgery" or condition category "Surgery". For ClinicalTrials.gov-registered trials, we used the intervention type "Procedure" or condition name containing the string "surg". For each potential surgical trial, we also examined additional trial registration record fields to identify whether it met our definition of a surgical trial (study intervention delivered by a surgeon and proposed to improve surgical patient outcomes). In the ANZCTR, these fields were: Trial ID, Scientific title, Interventions, Comparator, Inclusive criteria, Brief summary, Health condition, Condition category. In the ClinicalTrials.gov, these fields were: NCT ID, Official title, Intervention, Inclusion criteria, Brief summary, Intervention names, Condition names, Keywords.

We classified surgical trials under ten surgical specialty areas: cardio-thoracic; otolaryngology, head and neck surgery; general (including colorectal); neurosurgery; orthopaedic; plastic and reconstructive; urology; vascular; ophthalmology; and transplantation surgery. These specialty classifications match the surgical divisions accredited by the Royal Australasian College of Surgeons, with the addition of ophthalmology (accredited by

the Royal Australian and New Zealand College of Ophthalmologists) and a separate classification for transplantation surgery as a highly specialised cross-disciplinary field with specialty post-fellowship education and training. Paediatric surgery trials were not eligible because the study was of trials with adult participants. We did not include obstetrics and gynaecology trials because we considered the trial activity of this specialist group would be more appropriately assessed separately to include trials of medical and surgical interventions. We did not include oral and maxillofacial trials because of the potential cross-over with the dental profession.

Trials that met the following criteria did not meet our definition of surgical trials and were classified as non-surgical: non-surgical procedures (e.g., stem cell transplantation, biopsies other than sentinel lymph node biopsies), procedures delivered by non-surgical specialists (cardiologists, interventional radiologists, gastroenterologists, neurologists, pulmonologists), trials not specific to a surgical specialty included in this study (e.g., gynaecology, oral and maxillofacial) or trial inclusion criteria that was specific to multiple surgical specialties (e.g., "all elective surgery"), anaesthesia (unless anaesthesia was partly or solely delivered by the surgeon), neoadjuvant therapies, pre-surgery education and consent, interventions outside the peri-operative period (e.g., rehabilitation, drugs for pain management), generic hospital care and safety (e.g., nursing care, ventilation), trials with healthy participants, and trials in which the outcomes were non-surgical (e.g., sleep quality after surgery).

We checked the dataset to ensure there were no surgical trial records included in both ANZCTR and ClinicalTrials.gov by inspecting the linked study field in ANZCTR, which records the identifying numbers of any trials linked to the registered trial, and trial scientific titles. No duplicate records were identified.

Classification of trial characteristics

We extracted the following trial characteristics: source registry (ANZCTR, ClinicalTrials.gov); recruitment country (Australia only, Australia and other); planned recruitment size (1-100, 101-1000, more than 1000); allocation to intervention (randomised, non-randomised); purpose (treatment, prevention, diagnosis, other); masking (masked, open); primary sponsor (responsible for initiating, managing, or financing the trial, as defined by the ANZCTR under "primary sponsor" and by ClinicalTrials.gov under "lead sponsor" and categorised as government, industry, and other which includes hospital, university, charities/societies/foundations). We categorised trials as having industry involvement if commercial bodies or industry were involved as primary sponsor, secondary sponsor, collaborator, funding source, or a combination of those roles (see ANZCTR for role definitions (1)). For trials meeting the study criteria for surgical trials, we also used the registration record to map the trial to one of the ten surgical specialties.

If the trial intervention could be performed in more than one specialty, we classified it under one specialty for the primary analysis, and then remapped it for a sensitivity analysis. These interventions were: amputations, classified as vascular (primary analysis) or orthopaedic (sensitivity analysis); hand surgery, classified as plastic surgery (primary analysis) or orthopaedic (sensitivity analysis); and spinal surgery (excluding spinal cord stimulation implantation), classified as neurosurgery (primary analysis) or orthopaedic (sensitivity analysis).

A list of the included surgical trials by surgical specialty is included in the Supporting Information, file 2.

Data sources and eligibility criteria for surgical procedures

To estimate surgical activity by specialty, we used Australian Institute of Health and Welfare (AIHW) procedures data cubes (8) to estimate the number of surgical procedures performed for persons aged 19 years or older during 1 July 2010 – 30 June 2020. These data cubes record all procedures undertaken in Australian public or private hospitals by financial year. The AIHW defines a procedure as "a clinical intervention that is surgical in nature, carries a procedural risk, carries an anaesthetic risk, requires specialised training, and/or requires special facilities or equipment only available in an acute care setting" (9). As a result, the AIHW procedure data captures both surgical and non-surgical procedures. We completed the initial identification of surgical procedures in the AIHW data using the Medicare Benefits Schedule (MBS) (10). The AIHW procedure data cubes are coded using the Australian Classification of Health Interventions (ACHI), which is based on the MBS with extra codes (90000 series) capturing additional procedural components or concepts not included in the MBS (11). For procedures with MBS codes, we identified surgical procedures as those in the MBS Group T8– Surgical Operations. For the 90000 series, we manually inspected and classified procedures as surgical or non-surgical. We excluded the following procedure types that were classified as surgery in the MBS dataset: biopsies (apart from sentinel lymph node biopsies) and procedures generally performed by non-surgical specialists (cardiologists, interventional radiologists, gastroenterologists, neurologists, and pulmonologists).

We classified surgical procedures according to the ten surgical specialties used for the trial data. First, we based this classification on the MBS subgroup or manual classification for the 90000 series. Second, we made the following changes to ensure consistency between trial and procedure data: colorectal were reclassified as general, amputations reclassified as vascular, hand surgery reclassified as plastic, spinal surgery reclassified as neurosurgery, and transplantation procedures reclassified as transplantation. Further, we reclassified sacral nerve stimulation procedures as general, female stress incontinence procedures as urological, and multiple general procedures were reclassified to other specialties.

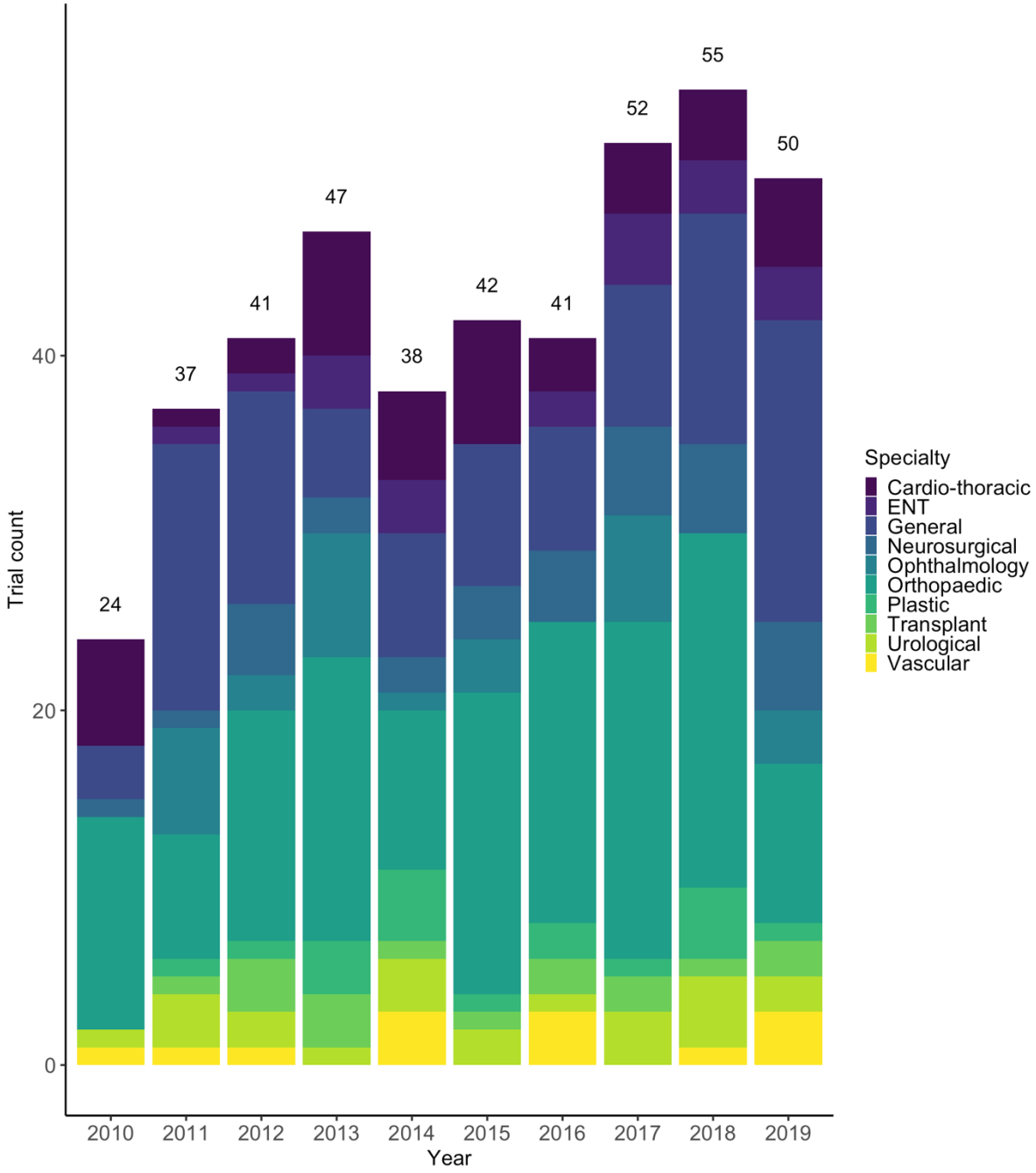
If a procedure could be performed in more than one specialty, we classified it under one specialty for the primary analysis, and then remapped it for a sensitivity analysis. These procedures were: amputations, classified as vascular (primary analysis) or orthopaedic (sensitivity analysis); hand surgery, classified as plastics (primary analysis) or orthopaedic (sensitivity analysis); and spinal surgery (excluding spinal cord stimulation implants), classified as neurosurgery (primary analysis) or orthopaedic (sensitivity analysis). The classification of included and excluded surgical procedures codes by surgical specialty is outlined in the Supporting Information, file 2.

Review of surgical trial and procedure datasets

The surgical trial and procedure datasets were prepared in a three stage review process. In the first stage, one investigator (Claire Greenwell) extracted and identified trials and procedures that met the inclusion criteria and classified them according to specialty. Second, three investigators (Claire Greenwell, Angela Webster, Sarah Lord) reviewed each surgical specialty to discuss key procedure types and exclusion criteria. A detailed review of the trial record was undertaken if inclusion or classification was uncertain, and the issue was reviewed by a surgical research specialist (David Beard) if a decision could not be made. The final stage was an overall review of the study methodology and resolution of outstanding classification questions by a surgical research specialist (David Beard) and practising surgeon (Ian Harris).

Supplementary results

Figure 1. Number of surgical trials by year, by specialty



ENT = ear, nose, and throat surgery (otolaryngology, head and neck surgery).

Table 1. Characteristics of 435 surgical trials with planned recruitment of adults in Australia, by specialty, registered 1 January 2010 – 29 February 2020

	Orthopaedic	General	Cardio-thoracic	Neurosurgery	Ophthalmology
Clinical trials	142 (33%)	97 (22%)	45 (10%)	32 (7%)	29 (7%)
Registry					
ANZCTR	134	87	33	27	15
ClinicalTrials.gov	8	10	12	5	14
Purpose					
Treatment	128	79	32	29	28
Prevention	9	14	11	1	1
Diagnosis	1	4	1	2	0
Other	4	0	1	0	0
Recruitment					
Australia only	131	86	35	28	16
Australia and overseas	11	11	10	4	13
Planned recruitment size					
1-100	95	54	22	23	16
101-1000	46	42	17	9	13
More than 1000	1	1	6	0	0
Randomisation					
Yes	103	74	30	17	20
No	39	23	15	15	9
Masking (for randomised trials)					
Masked	60	35	14	12	17
Open	36	37	16	4	2
Missing information	7	2	0	1	1
Primary sponsor					
Government	2	5	3	0	0
Industry	36	6	8	8	13
Other	104	86	34	24	16
Industry involvement					
Yes	56	14	13	14	16
No	86	83	32	18	13

	Urological	Otolaryng-ology, Head and Neck	Plastic	Transplantation	Vascular
Clinical trials	22 (5%)	21 (5%)	18 (4%)	16 (4%)	13 (3%)
Registry					
ANZCTR	20	19	18	14	9
ClinicalTrials.gov	2	2	0	2	4
Purpose					
Treatment	20	19	16	10	10
Prevention	2	2	2	5	2
Diagnosis	0	0	0	0	1
Other	0	0	0	1	0
Recruitment					
Australia only	18	19	17	13	9
Australia and overseas	4	2	1	3	4
Planned recruitment size					
1-100	11	17	13	12	8
101-1000	10	4	5	4	4
More than 1000	1	0	0	0	1
Randomisation					
Yes	16	17	12	14	8
No	6	4	6	2	5
Masking (for randomised trials)					
Masked	6	11	9	9	2
Open	8	5	1	5	6
Missing information	2	1	2	0	0
Primary sponsor					
Government	3	1	0	0	0
Industry	2	3	1	1	4
Other	17	17	17	15	9
Industry involvement					
Yes	2	3	3	2	5
No	20	18	15	14	8

Table 2. Numbers of registered trials and procedures, by surgical specialty

	Procedures		Registered trials			
Surgical Specialty	**Rank**	**Observed**	**Rank**	**Observed**	**Expected***	**Observed / Expected ratio**
General	1	9,804,429 (26%)	2	97 (22%)	115	0.85
Orthopaedic	2	7,092,232 (19%)	1	142 (33%)	83	1.71
Ophthalmology	3	5,082,402 (14%)	5	29 (7%)	59	0.49
Urological	4	4,433,541 (12%)	6	22 (5%)	52	0.42
Plastics	5	3,695,633 (10%)	8	18 (4%)	43	0.42
Neurosurgery	6	3,122,491 (8%)	4	32 (7%)	37	0.88
Otolaryngology, head and neck	7	2,031,279 (5%)	7	21 (5%)	24	0.88
Cardio-thoracic	8	1,110,470 (3%)	3	45 (10%)	13	3.47
Vascular	9	808,538 (2%)	10	13 (3%)	9	1.37
Transplantation	10	16,133 (<1%)	9	16 (4%)	0	84.8
Total		37,197,148		435	435	

* Number of trials expected were the numbers of trials correlated with those of procedures.

Table 3. Total planned recruitment number for registered trials by surgical specialty to expected, based on number of procedures

	Planned recruitment			
Surgical Specialty	**Rank**	**Observed (%)**	**Expected***	**Observed / Expected ratio**
General	3	17,406 (18%)	25,248	0.69
Orthopaedic	1	33,268 (35%)	18,264	1.82
Ophthalmology	5	4,400 (5%)	13,088	0.34
Urological	4	4,927 (5%)	11,417	0.43
Plastic	9	2,009 (2%)	9,517	0.21
Neurosurgery	7	2,906 (3%)	8,041	0.36
Otolaryngology, head and neck	10	1,434 (1%)	5,231	0.27
Cardio-thoracic	2	23,273 (24%)	2,860	8.14
Vascular	6	4,017 (4%)	2,082	1.93
Transplantation	8	2,149 (2%)	42	51.7
Total		95,789	95,790	

* Total planned recruitment number expected were the planned recruitment numbers correlated with those of procedures.

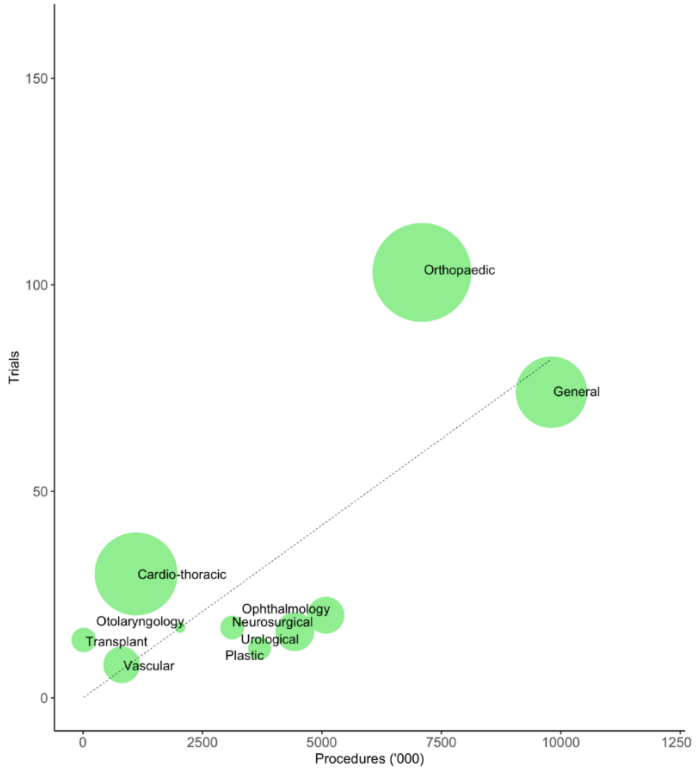
Table 4. Sensitivity analysis: numbers of registered trials and procedures by surgical specialty after reclassification of trials and procedures associated with two specialties*

	Procedures		Registered trials			
Surgical Specialty	**Rank**	**Observed**	**Rank**	**Observed**	**Expected****	**Observed / Expected ratio**
General	1	9,804,429 (26%)	2	97 (22%)	115	0.85
Orthopaedic	2	9,386,149 (25%)	1	156 (36%)	110	1.42
Ophthalmology	3	5,082,402 (14%)	4	29 (7%)	59	0.49
Urological	4	4,433,541 (12%)	5	22 (5%)	52	0.42
Plastics	5	2,823,601 (8%)	9	15 (3%)	33	0.45
Neurosurgery	7	1,798,061 (5%)	6	21 (5%)	21	1.00
Otolaryngology, Head and Neck	6	2,031,279 (5%)	6	21 (5%)	24	0.88
Cardio-thoracic	8	1,110,470 (3%)	3	45 (10%)	13	3.47
Vascular	9	711,083 (2%)	10	13 (3%)	8	1.56
Transplantation	10	16,133 (<1%)	9	16 (4%)	0	84.8
Total		37,197,148		435	435	

* These interventions were: amputations, classified as vascular (Table 2) or orthopaedic (Table 4); hand surgery, classified as plastic surgery (Table 2) or orthopaedic (Table 4); and spinal surgery (excluding spinal cord stimulation implantation), classified as neurosurgery (Table 2) or orthopaedic (Table 4).

** Number of trials expected were the numbers of trials correlated with those of procedures.

Figure 2. Relationship between surgical trial activity and number of procedures, by surgical specialty, for randomised controlled trials only



The size of the bubbles are proportionate to the planned trial recruitment number. The dashed diagonal line represents the expected number of surgical RCTs if the distribution of trial activity by surgical specialty was the same as the distribution of number of surgical procedures undertaken in Australia by specialty.

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