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RESEARCH

Sample-size determination and adherence in randomised controlled trials published in anaesthetic journals

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Background: Sample-size calculations are critical to ensure that randomised control trials return robust and reliable results. The estimated treatment effects used in these calculations is often significantly different from the actual treatment effect and can dramatically impact trial validity.
Methods: This study examined sample-size calculations in randomised controlled trials designed to show superiority between two-arm parallel groups with a single primary outcome that were published in the top five anaesthetic journals for 2014 (as per Thomson Reuters impact factors). In particular, it sought to determine treatment effect estimations used in a priori sample-size calculations and compare them with actual treatment effects.
Results: A PubMed search identified 209 possible articles; 52 were drawn for full text review; and 28 were included in the final analysis. The relative difference between expected and actual event rates was greater than 20% in 80% of trials and greater than 50% in 44% of trials.
Conclusions: Unrealistic assumptions of treatment effects in randomised controlled trials published in anaesthesia journals are common. Trial sample sizes should be calculated thoughtfully and realistically and should be fully reported in both trial protocols and publications. Researchers should be aware of the opportunity cost as well as the possible dangers to patients when unrealistic assumptions are made. Where possible researchers should collaborate to achieve meaningful trial sample sizes to ensure robust clinical findings.

Keywords: anaesthesia, clinical trial, power calculations, sample size, treatment effect, type II error

Introduction

Sample-size calculations are critical to ensure that randomised control trials return robust and reliable results. According to the CONSORT statement for the reporting of parallel-group randomised trials, these calculations should be reported and justified in the methods section.[1] Sample-size calculations establish the patient numbers required to detect clinically relevant differences between interventions. Where trials are underpowered they run the risk of failing to identify a true difference between groups, and increase the likelihood of false-positive trials—particularly when the null hypothesis is true.[2] In contradistinction, excessively large sample sizes run the risk of unnecessarily exposing trial subjects to risk of a new intervention.[3]

The primary parameters used in calculating samples sizes are: (1) the threshold chosen for the type I error (also call the level of significance or the *p*-value—commonly set at 5%); (2) the study power (commonly set at 80% or 90%); (3) the assumed event rate in the control group, together with some assumed standard deviation; and (4) the expected treatment effect. Assumed event rate and its standard deviation are commonly based on previously reported results, while expected treatment effect should be based on what a clinically meaningful treatment effect would be considering the clinical study environment. These assumptions are often significantly different from actual trial findings and can dramatically impact the intended power of a trial.[4]

In this study we aimed to examine sample-size calculations in randomised controlled trials designed to show superiority between two-arm parallel groups with a single primary outcome that were published in the top five anaesthetic journals for 2014 (as per Thomson Reuters impact factors). In particular, we sought to determine treatment effect estimations used in a priori sample-size calculations and compare them with the actual treatment effects identified by the trial.

Methodology

We systematically reviewed PubMed using the search terms 'randomized controlled trials' and 'randomised controlled trials' to identify all 2014 clinical randomised controlled trials published in the five anaesthetic journals with the highest impact factor as reported by Thomson Reuters. Pain-specific journals were excluded. MN screened titles and abstracts to identify candidate articles. Articles were excluded if they were not randomised, were cluster trials, included a factorial design, were non-inferiority trials, were pilot trials, made use of more than two trial arms, or reported more than one primary outcome. Articles were selected for full text review if either screener deemed them possibly eligible. Chance corrected inter-observer agreement for trial eligibility was tested using the kappa statistic.

A full text review of all candidate articles was conducted to identify eligible trials. From these eligible trials we systematically extracted the following data using a standardised data-collection sheet: author, year of publication, journal, *p*-value, power, expected control event rate, expected treatment effect, required sample size, actual number of recruited participants, actual control event rate, actual treatment effect, and intention-to-treat analysis. Full text screening and data extraction was conducted in duplicate by two teams, MN, SK and TM, BM, with the final data

being checked by RR. As no meta-analysis of study data was planned we did not assess trial quality or risk of bias.

For each trial the following were reported: sample-size calculation, power, alpha, two-sided testing assumption, calculated sample size, number of patients randomised, number of patients analysed, significance of trial findings, expected treatment effect, actual treatment effect, and the percentage relative difference between the estimated and actual event rates (estimated event rate minus actual event rate divided by estimated event rate). Where required, expected treatment effects reported in trial measurement units were converted to a percentage to facilitate comparison.

Results

In 2014 the five anaesthetic journals with the highest impact factor for 2014 were Anesthesiology, Anesthesia and Analgesia, British Journal of Anaesthesia, Anaesthesia, and the Canadian Journal of Anesthesia. The PubMed search identified 209 possible articles from which 52 were drawn for full paper review. Chance corrected inter-observer agreement for trial eligibility was excellent (kappa = 0.82). Twenty-four trials were subsequently excluded for the following reasons: Not randomized (2),[5,6] pilot trial (4),[7–10] cross-over trial (2),[11,12] factorial (2),[13,14] multiple outcomes (5),[15–19] secondary analysis (4),[20–23] using dynamic sample size calculations (1),[24] non-inferiority trial (2),[25,26] and trial stopped early (2).[27,28] Trial selection process is shown in 0 1, sample-size calculation details of the 28 included trials are reported in Table 1, and a comparison of expected and actual treatment effects are provided in Table 2.

All trials reported a sample size calculation. Two trials explicitly used one-sided assumptions when calculating the sample size[36,54] while 13 trials did not explicitly report two-sided assumptions.[33,35,37–39,42,46,48–53] All studies (for brevity hereafter name of first author only given) made use of an alpha of 0.05 and power of 80%, except for Caperellei, Cheung and Yates, who used 90% power,[30,31,54] and Liu who used 95% power and an alpha of 0.001.[43] Three trials did not achieved their planned sample size.[39,48,51] Of note Saporito,[46] Stein,[49] and Cheung[31] recruited between 50% and 100% more patients than required by their sample-size calculations. In addition, Saporito *et al*. powered their trial to show superiority between two interventions but conducted a non-inferiority trial.[46]

All trials except for Ju reported an expected treatment effect; in addition Ju did not use the outcome that the trial was powered on as the primary reported trial outcome.[38] Justification for the expected treatment effect was provided for 16 trials (57%): 12 from prior trials; 2 from pilot studies; 1 from observational data; 1 from clinical relevance. For the remaining 12 trials (43%) no justification was provided.

The relative difference between the expected and actual event rates was greater than 20% in 80% of trials and greater than 50% in 44% of trials. In six trials the actual treatment effect was in the opposite direction to that expected,[34,37,40,41,51,4] of which one trial had explicitly made use of a one-sided power calculation.[54] Eleven trials were designed using expected treatment effects greater than 20% of actual reported non-significant results,[30,32,34,40,41,43,47,51,52,54,55] of which seven used expected treatment results greater than 50% of actual reported.[30,41,43,47,51,54,55]

Discussion

Sample-size calculations form the basis of robust evidence-based medicine. Randomised controlled trials need to be of high quality and so require, among other things, a published a priori sample size and power calculation.[57] This allows the trial to be reproduced and explains the researchers' underlying assumptions in designing the trial. An appropriate sample size is determined by the following design parameters: minimum expected difference (also known as the effect size), estimated measurement variability, desired statistical power, significance criterion (*p*-value), and whether a one- or two-tailed statistical analysis is planned.[58] Factors resulting in the need for a large sample size are: the desire for a highly powered study, small treatment effect, smaller *p*-values, the desire for narrower confidence intervals, two-tailed design of the study and increasing variability/standard difference.

Several studies in the recent past have examined power and sample-size calculations and have noted that a large percentage of randomised controlled trials are either underpowered or have no record of an a priori sample-size calculation. Further, many trials were found to have low statistical power thereby increasing the probability of a type II error.[2,57] Christley *et al*., in a review of the surgical literature, noted that of 127 randomised controlled trials only half were sufficiently powered to detect large differences between treatment groups.[2] These underpowered studies may even have affected meta-analyses where low-powered studies with significant results have been included, especially when they have negative results. Muncer *et al*. note that by ignoring power the single-study researcher makes it

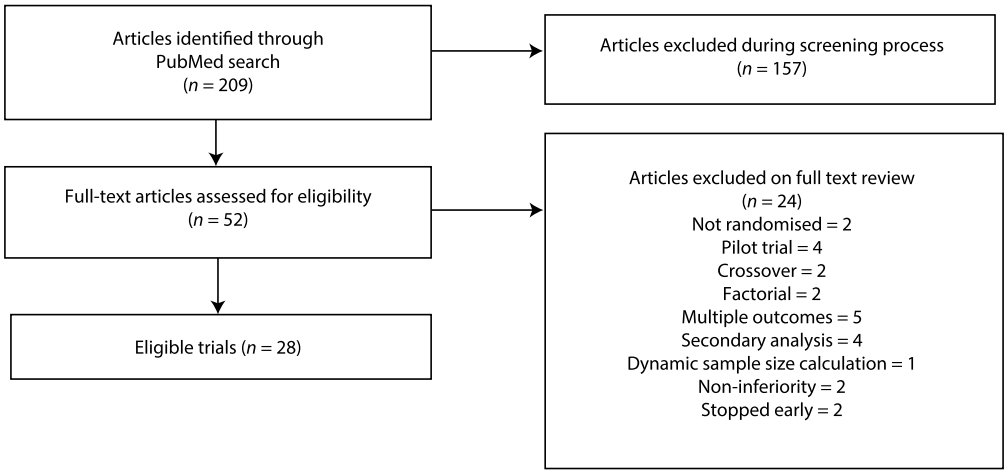

Figure 1: Trial selection process.

Table 1: Sample-size calculation characteristics of included trials

Author	Sample size calculation	Power	Alpha	Two-sided?	Sample size			
					Calculated	Randomised	Analysed	Sample size achieved?
Arab[29]	Yes	80%	5%	Yes	96	96	96	Yes
Cappelleri[30]	Yes	90%	5%	Yes	76	90	83	Yes
Cheung[31]	Yes	90%	5%	Yes	50	100	96	Yes
Cho[32]	Yes	80%	5%	Yes	78	78	78	Yes
Ferrando[33]	Yes	80%	5%	NS	30	30	30	Yes
Kuruba[34]	Yes	80%	5%	Yes	54	54	51	Yes
Horn[35]	Yes	80%	5%	NS	40	40	40	Yes
Hwang[36]	Yes	80%	5%	One-sided	62	68	66	Yes
Ilyas[37]	Yes	80%	5%	NS	128	128	128	Yes
Ju[38]	Yes	80%	5%	NS	84	100	84	Yes
Kim[39]	Yes	80%	5%	NS	166	184	181	Yes
Kim[40]	Yes	80%	5%	Yes	46	55	53	No
Landoni[41]	Yes	80%	5%	Yes	186	200	200	Yes
Lim[42]	Yes	80%	5%	NS	56	62	60	Yes
Liu[43]	Yes	95%	1%	Yes	288	680	601	Yes
Murphy[44]	Yes	80%	5%	Yes	62	70	70	Yes
Paul[45]	Yes	NR	5%	NR	NR	40	40	NA
Saporito[46]	Yes	80%	5%	NS	60	122	120	Yes
Sharma[47]	Yes	80%	5%	Yes	400	400	302	Yes
Sng[48]	Yes	80%	5%	NS	216	216	213	No
Stein[49]	Yes	80%	5%	NS	86	116	109	Yes
Ueki[50]	Yes	80%	5%	NS	34	42	37	Yes
van Loon[51]	Yes	80%	5%	NS	440	427	415	No
Westergaard[52]	No	NR	NR	NS	52	60	59	Yes
Yamamoto[53]	Yes	80%	5%	NS	78	90	86	Yes
Yates[54]	Yes	90%	5%	One-sided	202	206	202	Yes
Yoshida[55]	Yes	80%	5%	Yes	44	60	54	Yes
Zhang[56]	Yes	80%	5%	Yes	46	72	65	Yes

Note: NR—not reported; NS—not specified.

difficult to get negative results published and therefore affects meta-analysis through publication bias.[59]

In this analysis more than 80% of trials overestimated the treatment effect by more than 20% and 44% of trials by more than 50%. Similarly, in an analysis of internal medicine trials Charles *et al*. found significant discrepancies between expected and observed treatment effects.[57] The reason for these findings is unclear. It may possibly be due to overzealous estimation of the estimated parameters with a desire to lower the required sample size. This is done by first choosing a convenient study period (e.g. six months) or attainable study sample size (e.g. 100/200/300 etc. participants) and then plugging in a treatment effect that provides the desired sample size. While it is not formally necessary that the actual treatment effect should resemble the estimated treatment effect, studies designed using unrealistic treatment effects expose patients to trial risks and waste resources without the benefit of achieving a meaningful result.[60,61]

In this analysis 11 trials with estimated treatment effects greater than 20% of actual reported non-significant results, of which seven used expected treatment results greater than 50% of actual.

One of these trials assumed a 66% reduction in the composite of death and prolonged ICU stay but reported a 13% increase in the primary outcome,[41] while a second assumed a 60% decrease in the incidence of gastrointestinal morbidity but reported a 7% increase.[54] We would argue that the treatment effects assumed in many of these trials are unrealistic, especially considering the nature of some of the outcomes being studied. Many of these trials are therefore practically underpowered and would likely necessitate a second larger trial. It is worth noting that Yates *et al*.[54] made use of one-sided assumptions when calculating their sample size, but found a treatment effect in the opposite direction than expected. This highlights the danger of using one-sided sample-size assumptions in clinical research.

Trial designers do not only err by making sample sizes too small. In this analysis Saporito and Cheung doubled their sample size,[31,46] and Stein recruited 68% more patients than required without providing a clear motivation for doing so.[49] While it is appropriate to increase sample size to account for patient dropout these considerations should be made explicit in the trial protocol. Recruiting excessive patients without a reasoned rational unnecessarily exposes them to possible harm.

Table 2: Comparison of assumed and actual treatment effect in included trials

Author	Primary outcome used for sample size calculation	Treatment effect				Significant finding?
		Estimated	Estimate justification	Actual	Relative difference	
Arab[29]	Proportion of satisfactory sensory block	50% improvement	Pilot study	36% improvement	28%	Yes
Cappelleri[30]	Duration of sciatic nerve block	12.5% improvement	NR	2% improvement	84%	No
Cheung[31]	Change in pain score (area under the curve)	30% reduction	Previous trial	17% reduction	43%	Yes
Cho[32]	Forced expiratory volume on the third postoperative day	10% improvement	Previous trial	7.5% improvement	25%	No
Ferrando[33]	Oxygenation at the end of one-lung ventilation period	10% improvement	Previous trial	18% improvement	−80%	Yes
Kuruba[34]	Morphine consumption in the first 24 h after surgery	2.7% reduction	Observational data	2.3% increase*	15%	No
Horn[35]	Neonatal core temperature	1.4% increase	Previous trial	3% increase	−114%	Yes
Hwang[36]	Incidence of spinal hypotension	35% reduction	Previous trial	43% reduction	−23%	Yes
Ilyas[37]	Time taken for successful intubation	20% reduction	Previous trial	65% increase*	−225%	Yes
Ju[38]	Oxygen index 30 min after one lung ventilation	NR	Pilot study	NR	NR	Yes
Kim[39]	First-attempt I-gel insertion success rate	15% increase	Previous trial	13% increase	13%	Yes
Kim[40]	Oropharyngeal leak pressure	20% reduction	Previous trial	5% increase*	75%	No
Landoni[41]	Composite of death and prolonged ICU stay	66% reduction	NR	13% increase*	80%	No
Lim[42]	Incidence of improper placement of tracheal tube	40% reduction	Previous trial	45% reduction	−13%	Yes
Liu[43]	Propofol or remifentanil consumption	20% reduction	NR	6% reduction	70%	No
Murphy[44]	Cerebral tissue oxygenation	4.5% increase	Previous trial	5.3% increase	−18%	Yes
Paul[45]	Depth of bougie insertion	NR	NR	NR	NR	Yes
Saporito[46]	Incidence of unscheduled outpatient visits or readmissions	NA	NR	NA	NR	No
Sharma[47]	Incidence of intrapartum fever	50% reduction	NR	5% reduction	90%	No
Sng[48]	Incidence of reactive hypertension	20% reduction	Previous trial	59% reduction	−195%	Yes
Stein[49]	Incidence of post-dural puncture headache	57% reduction	NR	77% reduction	−35%	Yes
Ueki[50]	Plasma HMGB1 level	30% reduction	NR	35% reduction	−17%	Yes
van Loon[51]	Incidence of hypoxemia	50% reduction	NR	0.8% increase*	98%	No
Westergaard[52]	Two-point difference in average pain score over 24 h	60% reduction	NR	40% reduction	33%	No
Yamamoto[53]	Complete sensory block of all sciatic nerve components	62% increase	Previous trial	69% increase	−11%	Yes
Yates[54]	Gastrointestinal morbidity	60% decrease	NR	7% increase*	88%	No
Yoshida[55]	Number of anaesthetised dermatomes 24 h after surgery	30% increase	Clinical relevance	0% increase	100%	No
Zhang[56]	Length of recovery room stay	30% decrease	NR	20% decrease	33%	Yes

Notes: NA—not applicable; NR—not reported.
*Direction of treatment effect opposite of expected.

Traditionally sample-size calculations are performed during the design phase of a trial and are rarely revisited. A trial excluded during full text review provides a different perspective on this approach. Mercier *et al*. initially assumed a 35% event rate in the baseline group with a 20% treatment effect.[24] The authors planned a sample-size recalculation once 50% of patients had been randomised to ensure that adequate power was achieved—the trial *p*-value was adjusted to correct for multiple testing. Adopting this model of trial design ensures that that the trial is adequately powered and provides reliable results.

Clinical medicine faces the challenge of dealing with a flood of inconclusive research and questions being asked of how we go about improving the reliability of our research.[62,63] Locally, South African clinical trainees are producing a multitude of small underpowered studies in an attempt to fulfil regulator training requirements.[64] To address these problems researchers should be aware of the opportunity cost as well as the possible dangers to patients when robust research methodology is not followed. Trial sample sizes should be calculated thoughtfully and realistically and should be fully reported in both trial protocols and publications. Where possible researchers should aim to collaborate so as to achieve meaningful trial sample sizes and so ensure robust clinical findings.

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