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Reporting of design features and analysis details in randomized clinical trials of procedural treatments for cancer pain: an ACTION systematic review

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Abstract

Background and objectives: The objective of this study was to assess the reporting of randomized clinical trials (RCTs) investigating procedural treatments (e.g., nerve blocks, targeted drug delivery) for cancer pain, with a focus on aspects that are particularly challenging in these trials.

Methods: This article presents results from a systematic review of reporting of RCTs of procedural interventions for cancer pain. Articles were identified by searching PubMed from 1966 to June 2014. Data related to quality of reporting are presented for early (1985 – 2004) and late periods (2005–2014).

Results: A total of 35 published trials were included. Approximately two-thirds of the articles clearly indicated the level of blinding. Only 26% reported a primary outcome measure. Less than half explicitly reported the number of patients who completed the trial, and only 1 reported a method that was used to accommodate missing data. Almost one-third of articles included a responder analysis, all of which specified the definition of a responder.

Conclusions: The goal of highlighting these deficiencies in reporting is to promote transparent reporting of details affecting the completion and interpretation of procedural cancer pain trials so that their quality can be more easily evaluated.

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Introduction

Analgesic treatments provide sufficient relief for many people with cancer pain, but may provide inadequate relief for many others.¹ Procedural therapies (e.g., epidural or spinal drug delivery, peripheral nerve or plexus block/ablation, percutaneous vertebral augmentation) may be useful in providing improved pain relief.^{2,3} When evaluating trials of procedural interventions for cancer pain, it is important to consider the methodological challenges inherent to analgesic trials (e.g., dependence on subjective measures of outcome), procedural trials (e.g., difficulty blinding), and trials with cancer patients (e.g., co-morbid conditions and potential for increased dropout and mortality) and how the combination of these challenges can affect completion and interpretation of trials of procedural treatments for cancer pain.

An important methodologic issue central to all clinical trials is pre-specification of the primary outcome measure to ensure an unbiased interpretation of the results.⁴⁻⁶ In pain trials, specification of the primary outcome measure requires a clear definition of the type of pain and the time frame the participants should consider when rating their pain. Research has shown that patients experiencing pain often consider other factors (e.g., interference in sleep and physical activity) when rating their pain intensity.⁷ This can lead to increased variability in ratings, especially if patients are not consistent in the factors they consider when rating their pain over the course of the study.^{8,9} Ratings may not reflect the pain intensity of particular interest when a patient experiences pain from many sources, not all of which are targeted by the specific treatment, as may be the case for cancer patients. Therefore, when communicating with clinical trial participants, it is important for researchers to describe the type and location of pain that they would like the participants to focus on and rate.⁸

Blinding patients and investigators in procedural trials can be difficult. A sham procedure that completely blinds participants and researchers who perform follow-up assessments might be ideal methodologically, but may be unethical with high risk procedures,¹⁰ and blinding providers may be particularly difficult. Use of an active control group may be a viable alternative strategy; however, it is only possible to blind assessors and sometimes patients in such trials. Additionally, it is difficult to show that a new treatment is more effective than an existing treatment and demonstrating that 2 treatments have equivalent efficacy requires larger sample sizes than demonstrating that one treatment is superior to another.¹¹

Recruitment and retention may be particularly difficult in trials that include cancer patients due to the presence of both physiological and psychiatric comorbidities and high mortality rates. Cancer patients are often enrolled in oncologic treatment trials, which could interfere with their eligibility for participation in trials of procedural pain treatments; moreover, patients and their families may be reluctant to participate in a cancer pain trial in which they could be randomized to a more conservative treatment arm. Furthermore, many oncologists tend to prefer treating patients with opioid analgesics and may be reluctant to refer their patients to RCTs for procedural pain treatments. These barriers can make it difficult to maintain sufficient statistical power to detect treatment effects in clinical trials.^{12,13} Cancer

pain may increase during the study along with disease progression or ongoing cancer treatments. Potentially unstable pain levels can increase variability in pain intensity ratings and decrease assay sensitivity (i.e., the ability to detect a true treatment effect). Furthermore, studies that investigate treatments for pain and other symptoms related to cancer, as opposed to treatments to cure cancer, may not be as high of a priority to clinicians and patients, leading to additional difficulties with recruitment and retention.¹⁴ The challenges outlined highlight the importance of clearly reporting participant flow as well as methods to accommodate missing data when evaluating procedural treatments for cancer pain.

In addition to optimizing the validity of the trial results, maximizing the clinical interpretation is also important. A “responder” analysis that compares the percentage of participants in each treatment group that achieved a specific response (e.g., 30% or 50% reduction in pain from baseline) may help clinicians evaluate the clinical meaningfulness of a treatment effect.^{15,16} Another important factor when evaluating the clinical benefit of a treatment is understanding and weighing its associated risks against the benefits; therefore, it is necessary for articles to adequately report adverse events (AEs).¹⁷

The objective of this systematic review was to investigate the reporting of randomized clinical trials (RCTs) that evaluated procedural treatments for cancer pain, focusing on how the challenges described above have been addressed. As part of the activities of the Analgesic, Anesthetic and Addiction Trials, Translations, Innovations, and Opportunities Network (ACTION) public-private partnership focused on improving clinical trial methods, we provide recommendations for the execution and reporting of the results of procedural treatment trials for cancer pain with the hope of facilitating progress in identifying efficacious treatments for refractory cancer pain.

Methods

Article Selection

In this systematic review, we evaluated reports of RCTs for procedural interventions to treat cancer pain that were published between the start of PubMed (1966) and June 2014 (see Appendix 1 for search strategy). Trials evaluating post-cancer surgery-related pain were excluded. Procedural interventions were defined as percutaneous, minimally invasive procedures for the purpose of pain relief (e.g., epidural or spinal drug delivery, peripheral nerve or plexus block/ablation, percutaneous vertebral augmentation). Surgical procedures such as open spinal surgery, cordotomy, tumor debulking, and palliative radiation, were excluded. Eligible trials could use any measure to record pain data, did not have to be blinded, could include either adult or pediatric patients, and required a procedural intervention in at least one arm of the trial. The articles were each screened for inclusion by DR and RAK independently.

Data Extraction

A coding manual was developed to evaluate the reporting of trial design details in procedural cancer pain trials, as well as the fulfillment of the 10 CONSolidated Standards of Reporting Trials (CONSORT) harms reporting recommendations¹⁷ (Appendix 2). The CONSORT

group publishes various guidelines to promote improved reporting of clinical trials (<http://www.consort-statement.org/>). The manual was pre-tested and modified for content and clarity by JSG, DR, and SMS in 3 rounds, which comprised 2 rounds of 3 articles each and a third round of 2 articles. RAK was then trained on the procedures and definitions included in the coding manual using the same set of articles that were used during the pre-test rounds. The final list of included articles was organized into 2 randomized lists, and each article was coded by 2 independent coders (DR and RAK). After all of the articles had been independently coded, RAK reviewed the data and corrected all discrepancies due to obvious oversight. Discrepancies that were due to differences in interpretation were adjudicated by RAK, with input from JSG and SMS. In the case of trials with a medication management group, we categorized this as protocol defined if the specific medications to be used were defined in the protocol or the protocol instructed investigators to follow the WHO cancer pain treatment guidelines.¹ In the articles that reported trials that were designed to test the hypothesis that one active treatment was better than another (i.e., superiority design) and reported a non-significant result, we identified whether the authors made any claims of comparable efficacy between groups (e.g., both treatments “provided an equivalent extent of pain relief”; “both 1-injection and 2-injection methods were equally safe and efficacious”).

Statistical Analyses

Descriptive statistics were used to analyze all trial characteristics and trial design details, including pain assessment and CONSORT harms reporting recommendations. Statistical comparisons of reporting quality between subgroups were not performed due to the small number of trials identified. We did, however, compare the percentages of articles that clearly reported design and statistical details between early (i.e., articles published between 1985 and 2004) and late (i.e., articles published between 2005 and 2014) periods using descriptive statistics. A pre-specified cut-off of a difference of 10 percentage points between periods was considered noteworthy and reported and discussed in the manuscript. We chose this date because it split the sample approximately in half and yielded a later set of articles that was published in a similar time frame to those covered in previous reviews, allowing for comparison.

Results

Coder Discrepancies

We coded a total 1,340 survey questions for the entire sample of articles, and 333 (25%) discrepancies occurred. Of the 333 discrepancies, 213 (64%) were due to obvious oversights by one of the coders, and the remaining 120 (36%) were due to differences in interpretation.

Trial Characteristics

A total of 755 records were identified through the database search; 697 were eliminated by screening the titles or abstracts. We eliminated an additional 23 articles after screening the full text because they were not RCTs or the treatment was not specific for cancer pain, leaving 35 articles that met the eligibility criteria (Figure 1; Appendix 3). Almost half (43%) of these articles were published between 2005 and 2014. Most (83%) had a parallel group study design. The median number of participants randomized was 47 (interquartile range

[IQR] 21–71). The most common types of interventions studied were peripheral nerve blocks, including sympathetic/plexus blocks (46%); drugs delivered via epidural administration (23%); drugs delivered via intrathecal injection (20%); and percutaneous vertebral augmentation (9%). More than half (69%) of the articles used another active procedural treatment as the comparison group, followed by non-invasive medication management defined by the trial protocol (17%). Three articles reported using a sham procedure control (Table 1).

Twenty-five (71%) of the reports described pain-related eligibility criteria, of which previous failure of conservative treatment ($n=15$, 60%) and minimum baseline pain were most common ($n = 11$, 44%). Those with mental health disorders were excluded in 8 (32%) trials (Table 1). Twenty-two (63%) articles stated that pre-intervention pain medications were allowed to continue during the trial. Eleven (50%) permitted any concomitant pain medication, 14 (64%) permitted any rescue pain medication, and 8 (36%) allowed specific concomitant or rescue pain medications.

Although only 12 (34%) articles reported the eligibility criteria pertaining to types of cancer, the primary cancer types of the enrolled patients were specified in 30 (86%) of the articles. Within those 30 articles, 20 (67%) included 2 or more cancer types and 10 (33%) included only a single cancer type. Almost three-quarters (71%) of reports did not state whether metastatic or non-metastatic cancer types were included and of the remaining 10 articles, 8 (80%) reported that both metastatic and non-metastatic cancer types were included.

About half of the articles (48%) did not report sponsorship for the trial; of the 18 articles that did, 9 indicated industry sponsorship. Approximately two-thirds (63%) of the articles clearly indicated the level of blinding in the trial; 26% of the trials were double-blind, 9% were single-blind (i.e., participant-blinded), 11% were assessor only-blinded, and 9% of the articles reported that the participant and all study staff except the person performing the intervention were blind (Table 1). The percentage of articles that clearly indicated the level of blinding increased in the late period (55% early period vs. 73% late period).

Primary Outcome Measure and Assessments

Most (83%) of the articles did not specify a primary outcome measure. Six articles defined a primary outcome measure, including the time at which the primary outcome measure would be analyzed; all of these also specified the primary method for statistical analysis. However, only 1 indicated that the primary outcome measure was pre-specified or protocol defined (Table 2). The primary outcome measures varied, including the following: (1) 100mm visual analogue scale for pain, (2) 0 – 10 numeric pain rating scale (NRS), (3) Roland Morris Disability Questionnaire, (4) % change in pain intensity, (5) achievement of pain relief (defined as < 20 on a 0 – 100 NRS), and (6) achievement of a 20% improvement in pain of composite drug related toxicity score using the National Cancer Institute – Common Toxicity Criteria. The majority of articles (86%) did not state that the participants were given any specific instructions on how to assess their pain. The reported instructions included asking participants to rate their (1) pain at rest and nighttime pain, (2) average daily pain, (3) “global pain” at 9:00am and 9:00pm, and (4) back pain specifically (2 articles). Six articles reported the type of pain that was assessed (i.e., average, least, worst, current, or multiple of

these). The most common maximum frequencies of pain ratings throughout the studies were daily or multiple times daily ($n = 12$, 34%), and weekly or every other week ($n = 11$; 31%). The duration of follow-up was highly variable between studies, ranging from as short as 1 day to until the participants died (Table 2). Fifteen (43%) articles stated where the follow-up assessments were performed. The most frequently reported follow-up assessment locations were at home ($n = 9$, 60%) and the clinic, hospital, or study site ($n = 7$, 47%). Only 11 (31%) articles reported the total number of times the participant was required to return to the clinic for a visit. This percentage improved in the more recent set of articles (20% early vs. 47% late). Three articles (9%) stated that there were no follow-up visits, and the 32 remaining articles did not specify whether the follow-up visits were scheduled with non-trial clinic visits.

Participant flow, data analyses, accommodation of missing data, and interpretation

The number of trial completers was reported in 14 (40%) articles, with a median of 88% (IQR 69–97%) of participants completing the studies that reported this information. The number of participants included in the analyses was stated in 20 (57%) articles. Only 1 article reported a method to accommodate missing data (i.e., mixed effects ANOVA).

Eleven (31%) articles provided a responder analysis. All 11 articles that reported a responder analysis defined the criteria used to establish who qualified as a responder. The following definitions for responders were used: (1) Those who reached a pre-specified low level pain score (e.g., pain decreased to less than 20 on a 0–100 NRS) ($n = 5$), (2) A participant with complete pain relief ($n = 3$), (3) 20% pain relief ($n = 1$), (4) 30% pain relief ($n = 1$), (4) any reduction in pain or morphine consumption ($n = 1$).

Of the 30 articles using either another active procedural treatment or a defined non-invasive medication management protocol as the control arm, 22 (73%) did not find a statistically significant difference between treatments. Eight (36%) articles went on to imply that the treatments were “equally efficacious” based on non-significant results of trials designed to test superiority. Furthermore, none of these articles provided a confidence interval for the treatment effect to support implications of equivalent efficacy.

CONSORT Harms Reporting Recommendations

The 10 CONSORT harms reporting recommendations were fulfilled to varying degrees, with only 1 item (i.e., reporting the denominators for harms data) reported more frequently in the late time period, which occurred after the harms reporting guidelines were published. See Table 4 for the detailed results on CONSORT harms reporting recommendations.

Discussion

This review identified significant deficiencies in reporting and interpretation of RCTs of procedural treatments for cancer pain, only a few of which appear to have substantially improved in the past decade compared to the previous 2 decades. When comparing the cancer pain articles published between 2005 and 2014 to available reviews of analgesic trials for any pain condition published between 2006 and 2012, the cancer pain articles reported the following detail less frequently: (1) primary analysis (20% vs 68%⁵), (2) methods to

accommodate missing data (0% vs. 45%¹⁸), (3) withdrawals due to harms (20% vs. 58%¹⁹), and (4) reporting of instructions provided to patients about the type of pain to be assessed (e.g., worst vs. average) (26% vs. 57%²⁰).

Clear and unambiguous reporting of the design and statistical details described above and others is essential for readers to critically evaluate trial results. We summarize the concepts that are particularly challenging or pertinent when designing, reporting, and reading reports of RCTs of procedural interventions for cancer pain below and in (Table 4). It is beyond the scope of this review to cover, in detail, all important issues related to design, analysis, and reporting of RCTs. Our suggestions should be used to highlight unique considerations for procedural cancer pain trials in combination with general guidelines such as the CONSORT statement.²¹

Blinding of group assignments is important to minimize bias in all clinical trial outcomes; this is especially true when the outcomes are subjective, as with participant-reported pain.²² Furthermore, when it is not feasible to blind participants and clinicians to the treatment assignments, premature drop out may occur when participants are assigned to the obvious control group, which can lead to a form of selection bias. Although it may be challenging to blind procedural trials, it is important to make and clearly describe any and all attempts that were made to blind participants, investigators, non-study physicians, procedural physicians, and outcome assessors so that readers can evaluate the potential bias from lack of blinding in these trials.

When assessing pain it is important to provide instructions pertaining to which type of pain the participants are expected to rate.²⁰ Provision of such instructions may decrease the variability in pain assessments by focusing participants' attention on the type, timing, and location (e.g., specific body part, or worst site) of the pain of interest rather than having participants assume what pain to rate.^{8,20} Decreasing the variability in outcome measures may increase the assay sensitivity of a trial²³ as long as it does not decrease the magnitude of the signal. Additionally, such instructions may increase the validity of the trial because the outcome measure will more likely reflect true ratings of the pain of interest. Focusing participants' attention on specific types of pain can be especially important for cancer patients who may have multiple sources and locations of pain. Any special instructions provided to patients for pain rating outcomes should be described in the publications of all clinical trials.

A high percentage of missing outcome data can negatively affect the validity of the trial results.^{18,24–28} Missing data are likely to be an issue in cancer pain trials because cancer patients have increased rates of morbidity and mortality.^{12,13} When data are missing, pre-specified statistical approaches to accommodate missing data should be used. It is impossible to recommend a single method to accommodate missing data because all of the methods depend on assumptions about the missingness mechanism. Statisticians and regulatory agencies suggest specifying a primary method (e.g., direct likelihood, multiple imputation, inverse probability weighting) that assumes a particular missingness mechanism (e.g., missing at random), and adding sensitivity analyses that vary the assumptions regarding the missingness mechanism to see how strongly the results depend on the

assumptions that are made. Additionally, they discourage use of single imputation methods such as last (or baseline) observation carried forward that make unrealistic assumptions and artificially increase the precision of the estimates of interest.^{18, 24–28} The number of participants who are randomized, complete the trial, and are included in the analyses, as well as the methods used to accommodate missing data and whether they were pre-specified should be clearly outlined in peer-reviewed publications.

A responder analysis can provide additional information for clinicians to interpret the clinical meaningfulness of a treatment effect.^{15,16} However, it is important that the definition and criteria used to designate a responder is pre-specified in the design of the trial and clearly reported in articles. A complimentary option for displaying the data is a cumulative proportion of responders (CPR) curve, which plots the percentage of responders over a comprehensive range of response definitions (e.g., 0% to 100% decrease in pain)²⁹ The CPRs for the treatment groups can be compared using a rank test. This analysis eliminates the requirement to pre-specify a specific response definition and allows for interpretation over the entire range of response definitions.

Many of the trials we reviewed compared 2 active treatment groups, possibly because it is often difficult to create a placebo for procedural interventions, oncologists may hesitate to refer cancer patients, or the patients and their families may be reluctant to be randomized to an inactive treatment. It is important to note that conclusions of comparable efficacy based a non-significant statistical test of superiority may not be valid.¹¹ Reporting the confidence interval for the between-group difference (i.e., treatment effect) allows readers to evaluate whether or not the data remain consistent with a clinically meaningful difference between groups despite the absence of statistical significance. However, it is important to note that even when the confidence intervals support a conclusion of no clinical difference between treatment groups, such conclusions should be evaluated using sufficiently powered and designed non-inferiority studies.^{11,30, 31} In a correctly executed non-inferiority study, the maximum observed difference between the new treatment and the standard treatment that would not be considered clinically meaningful is determined *a priori* and used to set a non-inferiority margin. The lower confidence bound for the difference in, say, mean response between the new treatment and the standard treatment must fall above this non-inferiority margin for the new treatment to be declared “non-inferior.”^{11,30, 31} The limitations of concluding comparable efficacy from superiority trials should be acknowledged in manuscripts and considered by readers when interpreting the results of clinical trials.

This review has limitations that should be acknowledged. We were only able to evaluate what was reported in published articles and not what was actually done by the investigators. Because our objective was to examine the adequacy of the reporting of clinical trials and we made no attempt to evaluate the efficacy of the interventional procedures studied within the trials, our results should not be used as justification to deny care or payment for care to cancer patients who might benefit from procedural treatments. Furthermore, we recommend that healthcare providers and payers not draw conclusions on treatment efficacy based on our results. Clearly, a multimodal approach (inclusive of procedural interventions as indicated) is optimal for the treatment of cancer pain. We only examined RCTs of interventional techniques used to treat cancer pain, and thus these results may not be

generalizable to trials of interventional treatments for other types of pain or for non-interventional techniques evaluated for cancer pain. Finally, we have not evaluated reporting of all important study details that could affect the validity of the study results. We did not consider those that we felt were not uniquely challenging in the setting of procedural interventions for cancer pain studies (e.g., process of generating randomization assignments).

RCTs of procedural treatments for cancer pain tend to have many challenges, including identifying appropriate control groups, limitations in blinding, recruiting sufficient numbers of participants, minimizing participant dropout during a medically challenging time in participants' lives, and rates of mortality for advanced metastatic disease. Clearly reporting details regarding study design, methods for statistical analysis, and results is necessary for readers to be able to evaluate the level of evidence provided by these clinical trials. We believe that highlighting areas in need of improvement will lead to clearer reporting and therefore allow for critical interpretation of cancer pain trials and the determination of the validity of their results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest statement

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Figure 1.
PRISMA diagram

Table 1.

Trial Characteristics

Characteristic	n (%) or Median (IQR) (N=35)
Study Design	
Parallel	29 (83)
Crossover	5 (14)
Unclear	1 (3)
Number Randomized*	47 (21–71)
Type of Intervention	
Peripheral (including sympathetic/plexus) nerve block	16 (46)
Epidural	8 (23)
Intrathecal/spinal	7 (20)
Vertebral augmentation	3 (9)
Other	1 (3)
Type of Control	
Different active procedure	24 (69)
Trial-defined non-invasive medication management	6 (17)
Non-defined non-invasive medication management	2 (6)
Sham procedure	3 (9)
Eligibility Criteria (of the 25 that reported eligibility criteria)	
Failure of conservative treatment	15 (60)
Minimum baseline pain intensity	11 (44)
No mental health condition	8 (32)
Life expectancy	4 (16)
No concurrent cancer treatment	4 (16)
Previous use of studied intervention	4 (16)
No drug/alcohol abuse/dependence	1 (4)
Minimum age	1 (4)
Maximum age	1 (4)
Trial Length (in days)	56 (15–129)
Sponsor	
Industry	9 (26)
Other	9 (26)
Not reported	17 (48)
Blinding	
Double-blind	9 (26)
Assessor only blinded	4 (11)
Single-blind	3 (9)

Characteristic	n (%) or Median (IQR) (N=35)
Modified double-blind [‡]	3 (9)
No blinding (defined as open-label)	3 (9)
Unclear	13 (37)

* Based on best guess if unclear (e.g., author gave number 'enrolled')

[‡] Participants and study personnel were blind, but the person performing the intervention was not (e.g., doctor performing nerve block was not blind, but the patient, investigators, and assessors were)

IQR = interquartile range

Table 2.

Reporting of Primary Outcome Measure and Assessments

Reporting characteristic	n (%) or Median (IQR)		
	1985–2014 (N=35)	1985–2004 (N=20)	2005–2014 (N=15)
Primary outcome measure identified			
No	29 (83)	17 (85)	12 (80)
Yes	6 (17)	3 (15)	3 (20)
Primary outcome pre-specified/protocol defined (of the 6 that identified a primary outcome measure)	N = 6	N= 3	N=3
No	5 (83)	2 (67)	3 (100)
Yes	1 (17)	1 (33)	0 (0)
Patient given instructions on assessing pain			
No	30 (86)	19 (95)	11 (73)
Yes	5 (14)	1 (5)	4 (27)
Specified type of pain assessed (of the 6 that identified the type of pain assessed)		N=2	N=4
Average	4 (67)	2 (100)	2 (50)
Worst	3 (50)	1 (50)	2 (50)
Least	2 (33)	1 (50)	1 (25)
Current	1 (17)	---	1 (25)
Highest frequency with which pain was assessed during the study			
Multiple times on day of procedure only	2 (6)	2 (10)	---
Daily or multiple times daily	12 (34)	7 (35)	5 (33)
Weekly or every other week	11 (31)	7 (35)	4 (27)
Monthly or less	4 (11)	1 (5)	3 (20)
Not specified	1 (3)	1 (5)	---
Other [‡]	5 (14)	2 (10)	3 (20)
Length of follow up			
1 day	2 (6)	2 (10)	
1–2 weeks	4 (11)	4 (20)	
3–4 weeks	4 (11)	1 (5)	3 (20)
2–3 months	6 (17)	2 (10)	4 (27)
6 months	2 (6)	2 (10)	---
1 year	3 (9)	---	3 (20)
Until return to baseline	3 (9)	1 (5)	2 (13)
Until death of patient	5 (14)	5 (25)	---
Until treatment failure	1 (3)	---	1 (7)
Not specified	6 (17)	3 (15)	2 (13)

Reporting characteristic	n (%) or Median (IQR)		
	1985–2014 (N=35)	1985–2004 (N=20)	2005–2014 (N=15)
Specified where follow-up assessments were done (of the 15 that identified where the follow-up assessments were done)	N=15	N=9	N=4
Clinic, hospital, or study site			
Home	7 (47)	4 (44)	3 (75)
Daily diary – location not specified	9 (60)	6 (67)	3 (75)
Hospice	2 (13)	---	2 (50)
Daily visits from nurse (location not specified)	1 (7) 1 (7)	1 (11) 1 (11)	--- ---
Number of study visits to clinic reported	11 (31)	4 (20)	7 (47)
Number if specified	2 (1–5)	1 (1–6)	4 (2–5)

[‡] Did not assess pain at a regular interval (e.g., assessed pain at 1, 3, 6, and 12 months)

^{*} Specified location of baseline visit, but not follow-up

IQR=Interquartile range

Table 3.

Reporting of items from the CONSORT harms recommendations.

	N (%)		
	1985–2014 (N=35)	1985–2004 (N=20)	2005–2014 (N=15)
If the study collected data on harms and benefits, the title or abstract should so state	28 (80)	16 (80)	12 (80)
If the trial addresses both harms and benefits, the introduction should so state	13 (37)	9 (45)	4 (27)
List addressed adverse events with definitions for each (with attention, when relevant, to grading expected vs. unexpected events in reference to standardized and validated definitions and description of new definitions)	15 (43)	9 (45)	6 (40)
Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)	24 (69)	16 (80)	8 (53)
Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses).	10 (29)	5 (25)	5 (33)
Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment	7 (20)	4 (20)	3 (20)
Provide the denominators for the analyses on harms	24 (69)	12 (60)	12 (80)
Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent.	32 (91)	19 (95)	13 (87)
Describe any subgroup analyses and exploratory analyses for harms.	1 (3)	1 (5)	0 (0)
Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms.	28 (80)	16 (80)	12 (80)

Table 4.**Design Considerations and Reporting Recommendations**

Design Considerations	<ul style="list-style-type: none"> • Make attempts to blind participants, investigators, and assessors to the treatment groups to the extent possible • Pre-specify primary outcome measures and analyses • Pre-specify a definition for a “responder” if a responder analysis will be performed • Pre-specify methods to accommodate missing data that make realistic assumptions about the missingness mechanism • Provide instructions to participants on which types, characteristics, and locations of pain to assess • Use a non-inferiority or equivalence trial design if the experimental treatment will be compared to another active treatment and the goal of the study is to demonstrate that the experimental treatment has comparable efficacy to that of the other treatment
Reporting Recommendations	<ul style="list-style-type: none"> • Provide details regarding blinding of participants, investigators, and assessors • Clearly describe important clinical trial design considerations • Explicitly state the number of participants who completed the trial • Explicitly state the number of participants included in the analyses • Provide reasons for participant withdrawal • Indicate the method that was used to accommodate missing data in the statistical analyses • Report harms according to the CONSORT recommendations¹⁷ • Do not conclude comparable efficacy of 2 treatments based on a non-significant treatment difference in a superiority trial