



Results availability for analgesic device, complex regional pain syndrome, and post-stroke pain trials: comparing the RReADS, RReACT, and RReMiT databases

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Abstract

Evidence-based medicine rests on the assumption that treatment recommendations are robust, free from bias, and include results of all randomized clinical trials. The Repository of Registered Analgesic Clinical Trials search and analysis methodology was applied to create databases of complex regional pain syndrome (CRPS) and central post-stroke pain (CPSP) trials and adapted to create the Repository of Registered Analgesic Device Studies databases for trials of spinal cord stimulation (SCS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS). We identified 34 CRPS trials, 18 CPSP trials, 72 trials of SCS, and 92 trials of rTMS/tDCS. Irrespective of time since study completion, 45% of eligible CRPS and CPSP trials and 46% of eligible SCS and rTMS/tDCS trials had available results (peer-reviewed literature, results entered on registry, or gray literature); peer-reviewed publications could be found for 38% and 39%, respectively. Examining almost 1000 trials across a spectrum of painful disorders (fibromyalgia, diabetic painful neuropathy, post-herpetic neuralgia, migraine, CRPS, CPSP) and types of treatment, no single study characteristic consistently predicts unavailability of results. Results availability is higher 12 months after study completion but remains below 60% for peer-reviewed publications. Recommendations to increase results availability include supporting organizations advocating for transparency, enforcing existing results reporting regulations, enabling all primary registries to post results, stating trial registration numbers in all publication abstracts, and reducing barriers to publishing “negative” trials. For all diseases and treatment modalities, evidence-based medicine must rigorously adjust for the sheer magnitude of missing results in formulating treatment recommendations.

Keywords: Clinical trials, Transparency in research, Registries, RReACT, RReADS, RReMiT, Global databases, Publication bias, Selective reporting

1. Introduction

The value of evidence-based medicine rests on the assumption that treatment recommendations are robust, free from bias, and include results of all randomized clinical trials. However, publication bias and other types of reporting bias remain prevalent, and selective reporting of clinical trial results has been demonstrated to produce unrealistic estimates of drug effectiveness and the risk–benefit ratio.^{5,13,27,28,35,38,44,45,47,48,50,51,54,56,59} Patients with

chronic pain, and their treatment providers, have the right to expect transparency in clinical trials research.

Clinical trial registration provides public access to basic trial information, planned outcome measures, and data analysis plans. Many registries enable links to results publications, but often the links are either missing or incorrect, and few publications include trial registration numbers.^{4,15–17,30,53,55,60} Direct posting of results is possible on the largest registry, ClinicalTrials.gov (CTG), and while not peer reviewed, can be sufficiently standardized to facilitate meta-analyses. Depositing results on CTG is required for certain types of studies, but compliance is low.^{4,7,10,12,18,23–25,30,33,36,37,49,60}

The Repository of Registered Analgesic Clinical Trials (RReACT) was developed to provide a global snapshot of registered clinical trials and a scorecard for public availability of results for post-herpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), and fibromyalgia (FM).^{12,30} The global RReACT methodology has also been applied to create the Repository of Registered Migraine Trials (RReMiT).⁴ Disorders covered in the RReACT and RReMiT databases are frequently studied in industry-sponsored clinical trials designed to test new therapies.

We hypothesized that disorders less commonly studied in new drug development efforts, and studies evaluating analgesic devices, might differ substantially in transparency. Two disorders that are associated with severe and refractory pain but with little industry drug development effort are complex regional pain syndrome ([CRPS]; type

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1 and type 2 differ by nervous system injury) and central post-stroke pain (CPSP). Described more than a century ago, both remain endlessly challenging from mechanistic and therapeutic viewpoints.

Issues of transparency and selective reporting are particularly important in invasive procedures and complex devices in the field of neuromodulation.⁴² Development of new medical devices for chronic pain is regulated very differently than new drug development.^{32,41} Spinal cord stimulation (SCS), a Food and Drug Administration (FDA)-approved class II device to relieve severe intractable pain,⁹ is usually a 2-step procedure consisting of an initial trial of percutaneous lead placement followed by permanent implantation if deemed successful. Spinal cord stimulation has been a treatment option for over 4 decades, and the technology is improving rapidly.⁴⁶ Two noninvasive techniques of brain stimulation have emerged in the past decade: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).^{31,34} Repetitive transcranial magnetic stimulation is currently a class II device approved by the FDA for the treatment of major depression⁸ but is used off-label to evaluate its effectiveness to treat chronic pain. Transcranial direct current stimulation has not yet been approved. We therefore hypothesized that analgesic device studies might also be substantially different in transparency from drug trials.

To evaluate trial transparency in CRPS, CPSP, and analgesic device research and compare the results with previous studies, creation of new RReACT-type databases was necessary.

2. Methods

In this study, the RReACT methodology previously developed for PHN, DPN, and FM was applied to extend RReACT by creating new databases for CRPS and CPSP. A similar methodology was applied to create 2 new databases: the Repository of Registered Analgesic Device Studies (RReADS) databases. One covers trials of SCS and the other covers 2 types of external noninvasive transcranial stimulation, rTMS and tDCS. As part of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the U.S. FDA, RReACT, RReMiT, and RReADS are freely accessible through the ACTTION Web site (<http://www.action.org/>).

Trials in RReACT are randomized and have a primary (or key secondary) outcome measure assessing drug efficacy. Trials of nutritional supplements and nontraditional medications are included. Trials in RReADS are prospective trials testing SCS, rTMS, and tDCS in patients with pain of various etiologies. Nonrandomized, observational, and/or single-group studies are included, but retrospective studies and trials including only healthy volunteers are excluded.

The RReACT and RReADS provide registry information on investigational drug/device name(s), drug route and mechanism of action or device stimulation site and parameters, secondary identifiers, study sponsor, study phase, start and completion dates, countries of enrollment, number of subjects, design summary, comparison groups, and primary/key secondary outcomes. Trial status is listed as actively recruiting, active but not recruiting, terminated, completed, unknown, or other. Trials listed as “active but not recruiting” included trials “not yet open for recruitment” and trials “active but no longer recruiting.” Trials listed as terminated included trials “withdrawn before subject enrollment” and trials “terminated after beginning enrollment.” Data collection took place in July 2013 for CRPS and CPSP and in February 2014 for SCS, rTMS, and tDCS.

The World Health Organization’s International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/Default.aspx/>) provides a single public-access search portal to 15 primary

registries, including CTG. All 15 registries follow international standards for clinical trial registries, which largely coincide with International Committee of Medical Journal Editors requirements.^{57,58} As of August 2014, CTG is global and is the largest registry, with more than 173,000 trials, and the EU Clinical Trials Register is the second largest, with more than 23,000 trials.

For this study, all 15 primary registries were searched through the ICTRP search portal, with the CTG registry also searched separately, for the 2 target disorders and the 2 types of devices. All trials found were examined manually. If the same trial was listed in 2 or more registries, it was considered to be multiply-registered and only analyzed once. Results were sought for all trials except for those shown as actively recruiting, withdrawn before subject enrollment, or not yet open for recruitment. A comprehensive search algorithm was followed. If links or citations of journal publications were provided on the registry record, they were manually checked to confirm correct pairing with the registered trial. If none was available, a manual search of PubMed using the trial name, drug name, key words from the study title, registry identifiers, principal investigator name, and other trial information was conducted. The gray literature was searched using Google, Google Scholar, and sponsor-related Web sites. To ensure accurate registry-results pairings, we relied on all available trial information, including registry data on comparison groups, sample size, principal investigator, and study dates. Available trial-specific efficacy endpoint results are categorized as peer-reviewed journal article, data entered on registry, or gray literature. Results from the highest-level source are summarized, with peer-reviewed articles ranking highest and gray literature lowest. Only journals available through PubMed were considered peer reviewed. PubMed comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books. Google Scholar and Google searches may pick up journals that are not indexed on MEDLINE. Each journal’s article review policy was not separately assessed to confirm that peer review takes place before publication. Most journals indexed for PubMed are peer reviewed or refereed, but peer review criteria and reviewer or referee qualifications vary. The U.S. National Library of Medicine does not maintain a list of peer-reviewed or refereed journals in PubMed, and PubMed searches cannot be limited to peer-reviewed journals. Separate searches of databases such as Scopus, which does not include the exact same journals as PubMed, were not conducted and could have turned up additional publications (including non-peer-reviewed and non-English language articles) from journals not indexed on PubMed.

3. Results

3.1. RReACT-CRPS and RReACT-CPSP

As of July 2013, there were 34 trials for CRPS (**Table 1**) and 18 trials for CPSP (**Table 2**) meeting criteria for inclusion. The RReACT-CRPS database and the RReACT-CPSP database are supplemental files for this article (see appendices). A total of 31 trials were registered on CTG (16 CRPS and 15 CPSP). The other 21 trials (18 CRPS and 3 CPSP) were listed exclusively on 1 or more of ICTRP’s other registries. Fourteen trials were multiply-registered; 10 for CRPS and 4 for CPSP. **Figure 1** shows the number of registered trials initiated each year for the 2 disorders. Years 2005 and 2006 brought the greatest number of new trials for CRPS, and 2012 brought the greatest number of new trials for CPSP.

For CRPS, 3 of the 34 total trials were actively recruiting participants. Results were sought for the remaining 31 trials (17 trials listed as completed, 5 trials terminated after beginning enrollment, 7 trials listed as active but not recruiting, and 2 trials of unknown status). For CPSP, 7 of the 18 total trials were actively

Table 1
Complex regional pain syndrome.

CRPS	No. of trials
Total no. of trials*	34
Trial status	
Completed	17
Terminated or unknown	7
Active, not recruiting	7
Not yet open for recruitment	0
Withdrawn before subject enrollment	0
Recruiting	3
Total eligible for a results search†	31
Results	
Total results	11 (35%)
Results in peer-reviewed literature	9 (29%)
Results entered on registry	1
Results in gray literature only	1
Trial registration	
Registered on ClinicalTrials.gov	16
Eligible for a results search	16
Total results	6 (38%)
Results in peer-reviewed literature	4 (25%)
Registered exclusively on other registries	18
Eligible for a results search	15
Total results	5 (33%)
Results in peer-reviewed literature	5 (33%)
Multiply-registered	10
Time since study completion	
<1 y‡	1
Total results	0
Results in peer-reviewed literature	0
1 y or more§	15
Total results	10 (67%)
Results in peer-reviewed literature	9 (60%)
Sponsorship¶	
Industry primary sponsor	4
Total results	2 (50%)
Results in peer-reviewed literature	0
Nonindustry as primary sponsor	27
Total results	9 (33%)
Results in peer-reviewed literature	9 (33%)

* As of July 2013.

† Includes trials listed as completed, terminated after beginning enrollment, active but not recruiting, and trials of unknown status.

‡ For trials listed as completed, with a completion date within 12 months of our data collection.

§ For trials listed as completed, with a completion date 12 months or more from our data collection.

¶ Includes trials eligible for a results search with a primary sponsor listed on the registry trial record. CRPS, complex regional pain syndrome.

Table 2
Central post-stroke pain.

CPSP	No. of trials
Total no. of trials*	18
Trial status	
Completed	9
Terminated or unknown	1
Active, not recruiting	1
Not yet open for recruitment	0
Withdrawn before subject enrollment	0
Recruiting	7
Total eligible for a results search†	11
Results	
Total results	8 (73%)
Results in peer-reviewed literature	7 (64%)
Results entered on registry	1
Results in gray literature only	0
Trial registration	
Registered on ClinicalTrials.gov	15
Eligible for a results search	10
Total results	7 (70%)
Results in peer-reviewed literature	6 (60%)
Registered exclusively on other registries	3
Eligible for a results search	1
Total results	1 (100%)
Results in peer-reviewed literature	1 (100%)
Multiply-registered	4
Time since study completion	
<1 y‡	0
Total results	0
Results in peer-reviewed literature	0
1 y or more§	8
Total results	7 (88%)
Results in peer-reviewed literature	6 (75%)
Sponsorship¶	
Industry primary sponsor	6
Total results	6 (100%)
Results in peer-reviewed literature	5 (83%)
Nonindustry primary sponsor	5
Total results	2 (40%)
Results in peer-reviewed literature	2 (40%)

* As of July 2013.

† Includes trials listed as completed, terminated after beginning enrollment, active but not recruiting, and trials of unknown status.

‡ For trials listed as completed, with a completion date within 12 months of our data collection.

§ For trials listed as completed, with a completion date 12 months or more from our data collection.

¶ Includes trials eligible for a results search with a primary sponsor listed on the registry trial record. CPSP, central post-stroke pain.

recruiting participants. Results were sought for the remaining 11 trials (9 trials listed as completed, 1 trial listed as active but not recruiting, and 1 trial of unknown status).

Thirty-five percent of CRPS trials (11/31) and 73% of CPSP trials (8/11) had available results. Twenty-nine percent of CRPS trials (9/31) and 64% of CPSP trials (7/11) had results in a peer-reviewed journal. Forty-four percent (7/16) of publications for CRPS and CPSP were linked directly to the registry, and the remaining 56% were found by manually searching through PubMed. For CRPS, 1 trial had results available through direct posting on CTG and 1 had results available only in the gray literature. For CPSP, 1 trial had results available through direct posting on CTG. Central post-stroke pain was significantly more likely to have results available of any kind compared with CRPS (Fisher's exact test; $P = 0.043$), but not when considering the availability of peer-reviewed results (Fisher's exact test; $P = 0.070$).

Focusing on those CRPS trials where the registry entry showed the trial as "completed" and with a specific completion date, results could be found for 10 of the 15 trials (67%) completed at least 12

months before our data collection, of which 9 (60%) were in peer-reviewed journals. The 1 CRPS trial completed <12 months before our data collection did not have available results. For CPSP, results could be found for 7 of the 8 trials (88%) completed at least 12 months before our data collection, of which 6 (75%) were in peer-reviewed journals. No CPSP trials were completed <12 months before our data collection. Although the total number of trials with a specified completion date is very small, CRPS and CPSP were not significantly different for availability of any results or results in peer-reviewed journals.

Four of the 31 CRPS trials eligible for a results search had an industry primary sponsor. Of these trials, 2 had results available (50%), but none in the peer-reviewed literature. The remaining 27 had a nonindustry primary sponsor, of which 9 had results available (33%), all in the peer-reviewed literature. Six of the 11 CPSP trials eligible for a results search had an industry primary sponsor. All 6 had available results, of which 5 (83%) were in the peer-reviewed literature. The remaining 5 had a nonindustry primary sponsor, of which 2 had results available (40%), all in the peer-reviewed literature.

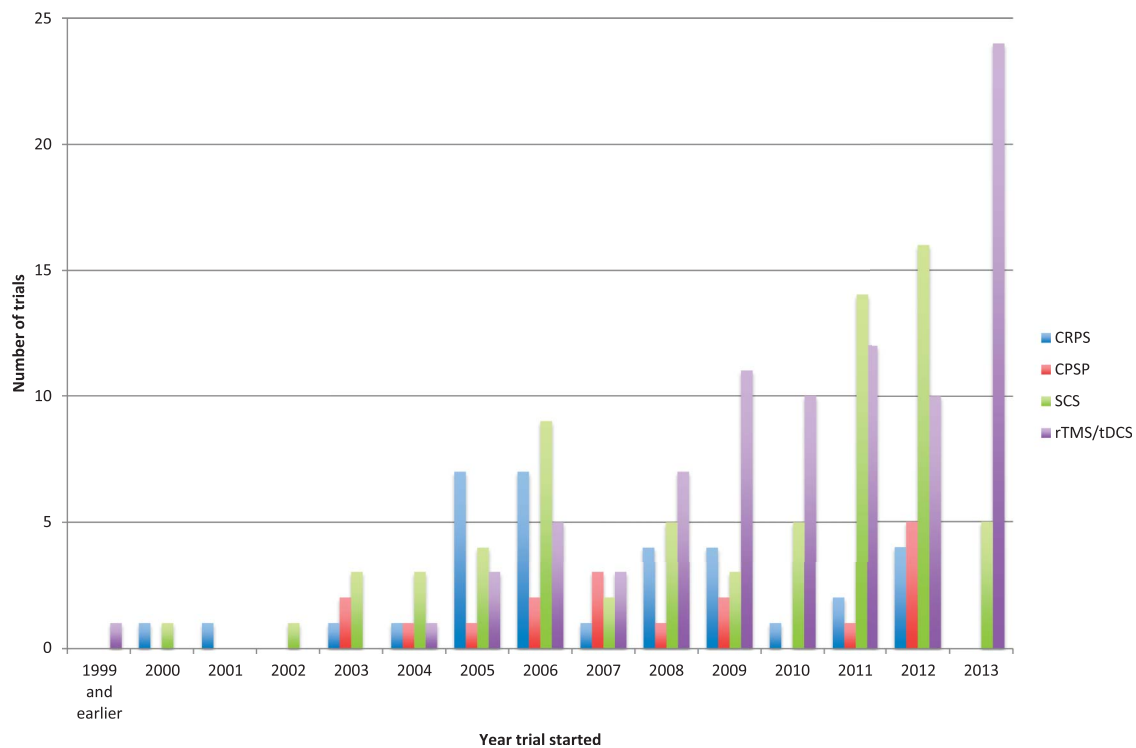


Figure 1. Number of registered trials initiated each year for the past 15 years for the 2 disorders, complex regional pain syndrome (CRPS) and central post-stroke pain (CPSP), and the 2 types of devices, spinal cord stimulation (SCS), and repetitive transcranial magnetic stimulation/transcranial direct current stimulation (rTMS/tDCS).

3.2. RReADS-SCS and RReADS-rTMS/tDCS

As of February 2014, there were 72 trials for SCS (**Table 3**) and 92 trials for rTMS/tDCS (**Table 4**) meeting criteria for inclusion in the RReADS database. The RReADS-SCS and RReADS-rTMS/tDCS databases are supplemental files for this article. A total of 131 trials were registered on CTG (55 SCS and 76 rTMS/tDCS). The other 33 trials (17 SCS and 16 rTMS/tDCS) were listed exclusively on 1 or more of ICTRP's 14 other registries. Only 3 trials were multiply-registered, all for SCS. As shown in **Figure 1**, 2012 brought the greatest number of new trials for SCS and 2013 had the greatest number of new trials for rTMS/tDCS.

For SCS, 18 of the 72 total trials were actively recruiting participants, 4 were withdrawn before subject enrollment, and 1 was not yet open for recruitment. Results were sought for the remaining 49 trials (22 trials listed as completed, 12 trials terminated after beginning enrollment, 8 trials listed as active but not recruiting, and 7 trials of unknown status). For rTMS/tDCS, 34 of the 92 total trials were actively recruiting participants, 2 were withdrawn before subject enrollment, and 12 were not yet open for recruitment. Results were sought for the remaining 44 trials (25 trials listed as completed, 1 trial terminated after beginning enrollment, 5 trials listed as active but not recruiting, and 13 trials of unknown status).

Forty-five percent of SCS trials (22/49) and 48% of rTMS/tDCS trials (21/44) had available results. Thirty-three percent of SCS trials (16/49) and 45% of rTMS/tDCS trials (20/44) had results in a peer-reviewed journal. Fourteen percent (5/36) of publications for rTMS, tDCS, and SCS trials were linked directly to the registry, and the remaining 86% (31/36) were found by manually searching through PubMed. For SCS, 2 trials had results available through direct posting on CTG and 4 had results available only in the gray literature. For rTMS/tDCS, 1 trial had results available through direct posting on CTG. There was no significant association between the type of device and the availability of results.

Focusing on those SCS trials where the registry entry showed the trial as "completed" and with a specific completion date, results could be found for 10 of the 18 trials (56%) completed at least 12 months before our data collection, of which 8 (44%) were in peer-reviewed journals. There were 3 SCS trials completed <12 months before our data collection, and only 1 had any available results (not peer reviewed). For rTMS/tDCS, results could be found for 14 of the 21 trials (67%) completed at least 12 months before our data collection, of which 13 (62%) were in peer-reviewed journals. Two rTMS/tDCS trials were completed <12 months before our data collection, and none had any available results. There was no significant association between the type of device and the availability of results for completed trials with a specified completion date.

Twenty-two of the 49 SCS trials eligible for a results search had an industry primary sponsor. Of these trials, 10 had results available (45%), of which 8 (36%) were in the peer-reviewed literature. The remaining 27 had a nonindustry primary sponsor, of which 12 (44%) had any available results, with 8 (30%) in the peer-reviewed literature. Only 2 of the 44 rTMS/tDCS trials eligible for a results search had an industry primary sponsor, and both had results available in the peer-reviewed literature. The remaining 42 had a nonindustry primary sponsor, of which 19 (45%) had any available results, with 18 (43%) in the peer-reviewed literature.

3.3. Comparison of RReADS, RReACT-CRPS, and RReACT-CPSP with RReACT and RReMiT

A total of 763 trials were eligible for a results search (391 PHN/DPN/FM, 237 migraine, 42 CRPS/CPSP, and 93 SCS/rTMS/tDCS). Irrespective of time since study completion, **Figure 2** shows the number of trials eligible for a results search, the number with available results, and the number with results in the peer-reviewed literature for all 6 disorders (PHN, DPN, FM,

Table 3
Spinal cord stimulation.

SCS	No. of trials
Total no. of trials*	72
Trial status	
Completed	22
Terminated or unknown	23
Active, not recruiting	9
Not yet open for recruitment	1
Withdrawn before subject enrollment	4
Recruiting	18
Total eligible for a results search†	49
Results	
Total results	22 (45%)
Results in peer-reviewed literature	16 (33%)
Results entered on registry	2
Results in gray literature only	4
Trial registration	
Registered on ClinicalTrials.gov	55
Eligible for a results search	35
Total results	15 (43%)
Results in peer-reviewed literature	12 (34%)
Registered exclusively on other registries	17
Eligible for a results search	14
Total results	7 (50%)
Results in peer-reviewed literature	4 (29%)
Multiply-registered	3
Time since study completion	
<1 y‡	3
Total results	1 (33%)
Results in peer-reviewed literature	0
1 y or more§	18
Total results	10 (56%)
Results in peer-reviewed literature	8 (44%)
Sponsorship¶	
Industry primary sponsor	22
Total results	10 (45%)
Results in peer-reviewed literature	8 (36%)
Nonindustry primary sponsor	27
Total results	12 (44%)
Results in peer-reviewed literature	8 (30%)

* As of February 2014.

† Includes trials listed as completed, terminated after beginning enrollment, active but not recruiting, and trials of unknown status.

‡ For trials listed as completed, with a completion date within 12 months of our data collection.

§ For trials listed as completed, with a completion date 12 months or more from our data collection.

¶ Includes trials eligible for a results search with a primary sponsor listed on the registry trial record. SCS, spinal cord stimulation.

migraine, CRPS, and CPSP) and both types of devices (SCS and rTMS/tDCS). In the RReMiT database, 55% of 237 eligible trials had any results available and 45% had peer-reviewed results available, irrespective of time since study completion.⁴ In the RReACT databases for PHN, DPN, and FM, 46% of 391 eligible trials had any results available and 30% had peer-reviewed results available, irrespective of time since study completion.³⁰ In the RReACT databases for CRPS and CPSP, 45% of 42 eligible trials had any results available and 38% had peer-reviewed results available. In the RReADS databases for SCS, rTMS, and tDCS, 46% of 93 eligible trials had any results available and 39% had peer-reviewed results available.

Focusing on just those trials with a specified completion date at least 12 months before data collection, the percentages rise as follows (any results/peer-reviewed results): CRPS 67/60, CPSP 88/75, SCS 56/44, and rTMS-tDCS 67/62. Comparison data are available from the RReMiT database, where the percentages (irrespective of study completion date) rise from 55% for any results and 45% for peer-reviewed results to 70% for any results

Table 4
Repetitive transcranial magnetic stimulation and transcranial direct current stimulation.

rTMS/tDCS	No. of trials
Total no. of trials*	92
Trial status	
Completed	25
Terminated or unknown	16
Active, not recruiting	17
Not yet open for recruitment	12
Withdrawn before subject enrollment	2
Recruiting	34
Total eligible for a results search†	44
Results	
Total results	21 (48%)
Results in peer-reviewed literature	20 (45%)
Results entered on registry	1
Results in gray literature only	0
Trial registration	
Registered on ClinicalTrials.gov	76
Eligible for a results search	39
Total results	19 (49%)
Results in peer-reviewed literature	18 (46%)
Registered exclusively on other registries	16
Eligible for a results search	5
Total results	2 (40%)
Results in peer-reviewed literature	2 (40%)
Multiply-registered	0
Time since study completion	
<1 y‡	2
Total results	0
Results in peer-reviewed literature	0
1 y or more§	21
Total results	14 (67%)
Results in peer-reviewed literature	13 (62%)
Sponsorship¶	
Industry primary sponsor	2
Total results	2 (100%)
Results in peer-reviewed literature	2 (100%)
Nonindustry primary sponsor	42
Total results	19 (45%)
Results in peer-reviewed literature	18 (43%)

* As of February 2014.

† Includes trials listed as completed, terminated after beginning enrollment, active but not recruiting, and trials of unknown status.

‡ For trials listed as completed, with a completion date within 12 months of our data collection.

§ For trials listed as completed, with a completion date 12 months or more from our data collection.

¶ Includes trials eligible for a results search with a primary sponsor listed on the registry trial record. rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

and 57% for peer-reviewed results at 12 months after study completion.⁴ Pooling the data sets yields 225 total trials with a specified completion date at least 12 months before data collection, and the percentage with any results is 69% and with peer-reviewed results is 57%. Extending the time window to studies with a specified completion date at least 2 years before data collection, the proportions show little further change for CRPS, CPSP, SCS, rTMS/tDCS, and migraine. Comparing the RReADS databases, all RReACT databases, and the RReMiT database, there were no significant differences in terms of results availability or proportion with peer-reviewed publications.

4. Discussion

In evidence-based medicine, randomized controlled trials are the gold standard for establishing the safety and efficacy of an intervention. However, the current infrastructure of evidence-based medicine—the levels of evidence and grades of

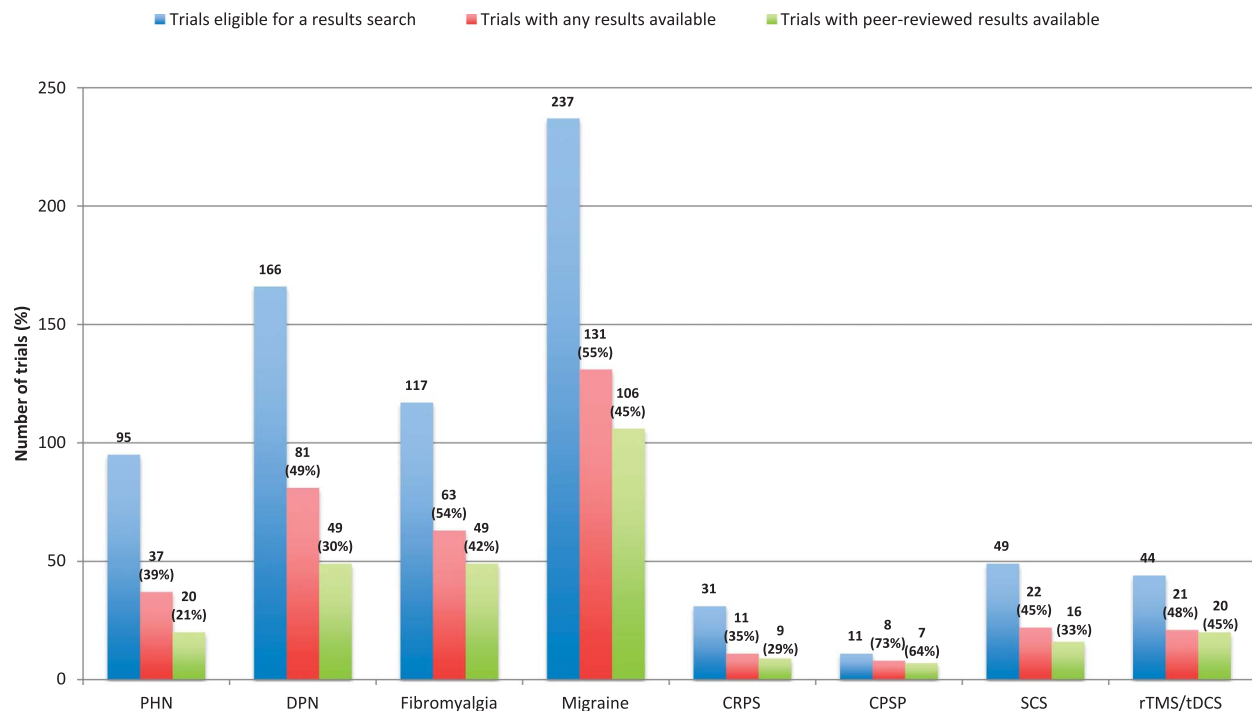


Figure 2. Number of trials eligible for results search and results availability. Shown in the figure are the number of trials eligible for a results search (trials listed as completed, terminated after beginning enrollment, active but not recruiting, and trials of unknown status), the number of trials with results available of any type (peer-reviewed literature, results entered on registry, and gray literature), and the number of trials with results in the peer-reviewed literature only. The 6 disorders studied in the Repository of Registered Analgesic Clinical Trials and Repository of Registered Migraine Trials databases, post-herpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), fibromyalgia, migraine, complex regional pain syndrome (CRPS), and central post-stroke pain (CPSP), are shown alongside the 2 types of devices studied in the Repository of Registered Analgesic Device Studies databases, spinal cord stimulation (SCS), and repetitive transcranial magnetic stimulation/transcranial direct current stimulation (rTMS/tDCS).^{4,28}

recommendation—is not necessarily generalizable to evaluating invasive interventions such as SCS. When performing research on non-pharmacological interventions, challenges related to randomization procedures and the use of blinding arise, and randomized controlled trials are not always feasible.^{1,6,22,26,29,40,43} Despite the expense of new technologies, rigorously controlled trial designs assessing basic efficacy have not been required for SCS device approvals after the advent of clinical trial registries. Spinal cord stimulation trial designs providing an appropriate double-blind control are problematic because the induction of paresthesias in the area of pain is part of the therapeutic assessment, but the absence of masking can lead to several types of bias.^{6,14} Device studies of rTMS and tDCS can be more rigorously controlled because the devices are noninvasively applied to the skull, and masking noises, in combination with mimicking the cutaneous sensation and muscular discomfort caused by these types of devices, can effectively blind the wearer to whether or not the device has been turned on.^{1,40,43} Full double-blinding may be possible if all assessments are made by an independent person not involved in operating the device.

Because of the methodological and practical constraints associated with device-based research, we included in the RReADS databases prospective studies that were nonrandomized or observational, as these types of studies are often used when a randomized controlled trial is not feasible. In non-randomized trials, a rigorous prospective design and focused data collection can reduce bias caused by incomplete data or unmasked outcome assessment.⁶ Although beyond the scope of this project, our impression of the trials in the RReADS database suggests that many registry trial records contain vaguely described study designs, multiple exploratory endpoints without

a clearly specified primary outcome, and non-standard measures only indirectly assessing pain. Pre-specified statistical analysis plans were often either missing or minimal. An ACTTION systematic review comparing registered and published primary outcome specifications in the analgesic trials contained in the initial version of RReACT found many discrepancies.⁴⁴ In the RReADS database, for some trials, the lack of clarity in design description on the registry was such that we were unable to confirm the accuracy of the trial-publication pairing (eg, SCS trials ACTRN12612000350820 and ISRCTN33292457).

Kessler et al.²¹ suggest that off-label use of an approved medical device allows clinicians to uncover new uses in an experiential manner, but cautions that therapeutic procedures using established devices for new indications do not always receive systematic rigorous evaluation. The threat of publication bias and selective outcome reporting is particularly great in the field of neuromodulation and intervention-based research, where advances in the field have historically relied on case reports or case series, and issues revolving around study design, blinding, and bias may be unresolvable.^{6,14,29,42} Ergina et al.⁶ suggest that for procedure-based interventions, a distinction should be made between explanatory trials, which evaluate the efficacy of the intervention, and pragmatic trials, which assess how the procedure is administered in clinical practice and seek to inform clinical decision-making. Many trials in the RReADS databases, especially of SCS, had primary outcomes other than analgesia, and seemed to be directed toward how best to deliver the intervention or were evaluating the technical performance of new technologies. The decision to permanently implant an SCS device is made based on the clinical response to temporary lead placement. Spinal cord stimulation trials either recruit patients

who have already had a device implanted, or provide efficacy analyses only on the patients progressing to full implantation, and thus are comparable to enriched enrollment trials of new drugs, but are not comparable with the more classic parallel-design, placebo-controlled drug trial or any type of crossover trial.

Device-based investigation faces financial, regulatory, and insurance barriers combined with limited funding.^{2,20} Only 3% of total neuroscience research funding in 2005 was directed toward medical devices.³ Only 2 rTMS/tDCS trials were registered with an industry primary sponsor. Both rTMS and tDCS are still early in their development, with tDCS not yet approved by the FDA, and rTMS only approved for depression. Many questions remain, such as whether to target deep or superficial structures, how to best apply “sham” stimulation, and the optimum frequency and duration of stimulation sessions to achieve an enduring effect.^{1,22,26,40,43,52} The market potential of rTMS and tDCS, an important incentive for large-scale industry partnership, is not certain. Spinal cord stimulation, which has been FDA-approved for more than 20 years, has a much larger proportion of industry-funded trials. In the RReADS-SCS database, almost half (45%) of trials eligible for a results search had been registered with an industry primary sponsor.

The new RReACT databases and the RReADS databases suggest a different industry role than in PHN, DPN, FM, and migraine, which all have multiple approved drugs and are frequently targeted in phase 2/3 new compound development programs. Only 2 CRPS trials (of AV-411 and lenalidomide), and no CPSP trials, appeared to represent a pharma new oral drug registration effort. Patients with CRPS may be involved in litigation or disability claims, and many CPSP sufferers have too much neurological impairment to serve as trial subjects. Regulatory approval pathways for therapeutic devices are different from those governing new drug development, and might explain the role of industry in the SCS and rTMS/tDCS trials.^{32,41}

We found the proportion of trials without available results to be similar across a diverse range of pain disorders and treatment strategies, as has been shown to be true in psychiatric disorders and other medical conditions.^{10,11,13,17,19,23,24,33,36,48,50,51} Results are rarely available within a year of trial completion, as would be expected, but the effect of time is similar across all conditions for which this analysis could be conducted. For studies providing a specified completion date of at least 12 months before data collection, the percentage only rises to 69% for any results and to 57% for peer-reviewed results. Extending the window to 24 months for results to become available only slightly increases these percentages. In migraine, studies with primary industry sponsorship were more likely to be published, but industry sponsorship had no apparent effect in CRPS, CPSP, and device trials.⁴ For disorders difficult to study using a typical randomized controlled trial design (such as CRPS and CPSP), there may be many fewer trials, but the ones that are conducted are no less likely to have available results. Device trials have substantial design and blinding issues, but not a distinct publication issue.

For all disease areas, what can be done to increase the proportion of registered trials with available results? First, groups advocating for increased transparency in clinical trials research deserve support. For example, AllTrials (<http://www.alltrials.net>) is an initiative that includes BMJ, the Cochrane Collaboration, PLOS, and the Dartmouth Institute for Health Policy & Clinical Practice.¹¹ Second, existing regulations require posting of study results within 12 months of study completion for certain categories of trials. Compliance is poor and enforcement could

be better.^{10,24,25,33} Third, large registries besides CTG could enable direct posting of study results and better support investigators who wish to do so. Fourth, far too much manual searching was required to create RReACT, RReMiT, and RReADS. For CRPS and CPSP, 17% of trials had 1 or more published article(s) linked to the trial record, a proportion that increased to 38% when PubMed was manually searched. For rTMS, tDCS, and SCS, the proportion increased from 5% of trials to 39%; and in RReMiT, the proportion increased from 20% to 45% through manual searches. If all journals would provide the trial registration number, preferably in the abstract, accurate links could become automatic on all registries.⁴ Fifth, the apparent barriers to publishing negative trials must be reduced, a focus of Project OPEN (<http://www.open-project.eu/welcome>).^{4,30,39,55} “Negative” clinical trials have lower publication rates and take longer to be published, although it remains uncertain whether the impact factor of the journal they eventually appear in is lower.^{19,48} Peer-reviewed journals welcoming unexpected, controversial, provocative, and/or negative results such as the *Journal of Negative Results in Biomedicine* are a step forward but not necessarily feasible for investigator-initiated trials with insufficient funds to pay publication costs. Could a narrowly focused, peer-reviewed clinical trials “brief communications” journal using a standardized results-reporting format and offering authors’ limited statistical assistance succeed?

The RReACT, RReMiT, and RReADS databases are not designed to delve deeper into issues of publication bias and selective reporting of results. However, by spanning almost 1000 trials in 6 disorders and 2 types of devices, a universal problem is clearly apparent. Irrespective of time since completion, more than half of all registered clinical trials do not have publicly available results. Evidence-based medicine must more rigorously take into account the sheer magnitude of missing results in formulating treatment recommendations.

Conflict of interest statement

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at <http://links.lww.com/PAIN/A6>, <http://links.lww.com/PAIN/A7>, <http://links.lww.com/PAIN/A8> and <http://links.lww.com/PAIN/A9>.

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