Topical review

A snapshot and scorecard for analgesic clinical trials for chronic pain: The RReACT database

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1. The RReACT database

It was not long ago that public access to information about drug trials, especially for off-label uses, was almost nonexistent [21,23]. During those “dark ages,” patients with chronic pain and their physicians had difficulty learning about research studies seeking participants. The 1997 FDA Modernization Act resulted in the creation of the ClinicalTrials.gov registry website, maintained by the National Library of Medicine on behalf of the National Institutes of Health (http://www.ClinicalTrials.gov/) [2,15,25]. In 2005, the International Committee of Medical Journal Editors required clinical trials to be registered in a public trials registry in order to be considered for publication in an International Committee of Medical Journal Editors journal, though unregistered studies may still be published in journals not requiring preregistration [1,14]. The 2007 Food and Drug Administration (FDA) Amendments Act requires that all FDA phase II-IV biologic drug and device trials be registered on ClinicalTrials.gov [3,15,25].

Access to results of completed trials is equally important, with persistent concerns about publication bias and the lag time between study completion and publication in the peer-reviewed literature [25]. The FDA Amendments Act partially addresses this concern by requiring posting of summarized results on ClinicalTrials.gov within 1 year of study completion [19], but recent studies found that only 22% of applicable trials met their ClinicalTrials.gov reporting deadline, and only 8%-10% of all completed trials reported results on the registry [7,8,12].

Visualizing the entire analgesic clinical trial landscape is challenging. We present the Repository of Registered Analgesic Clinical Trials (RReACT) database, which provides a snapshot of registered analgesic clinical trials and a scorecard for public availability of results. The project is part of the Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) initiative, a public-private partnership between the FDA, the National Institutes of Health, industry, and academia. The RReACT database is freely accessible via the ACTTION website (http://www.acction.org/).

The RReACT database currently contains all analgesic clinical trials listed on ClinicalTrials.gov for “postherpetic neuralgia” (PHN), “fibromyalgia”, and “diabetic peripheral neuropathy” (DPN), 3 of the most frequently studied chronic pain disorders. For each disorder, trials meeting the search criteria are listed and linked to the ClinicalTrials.gov registration page through the unique study National Clinical Trial (NCT) code. For a trial to be included, either the primary outcome measure or a key secondary outcome measure must assess analgesic efficacy. Trials of nutritional supplements and nontraditional medications are included. Device studies are excluded. Analgesic clinical trials registered on sites other than ClinicalTrials.gov (the World Health Organization International Clinical Trials Registry Platform cross-links 14 registries, many of which are country-specific [http://www.who.int/ictrp/en/]) were not included.

Trial status (as of December 1, 2011) is listed as: not yet enrolling, actively recruiting, active but not recruiting, on hold, terminated, or completed. The investigational drug name is listed as reported on ClinicalTrials.gov, with alternate identifiers provided where applicable. Drug mechanism of action and route of administration was determined by searching the ClinicalTrials.gov website, the scientific literature, Wikipedia, and other public sources on the generic or brand name or sponsor code(s). The study sponsor is listed as reported on ClinicalTrials.gov; pharmaceutical companies listed only as collaborators are not shown. Enrollment countries, FDA study phase, start and completion dates are as reported on ClinicalTrials.gov (if the completion date has not yet passed, the date is denoted as “estimated”). The number of subjects is as listed on ClinicalTrials.gov, but whether this is the actual enrollment or the planned enrollment is often unspecified.

Design summary and comparison groups are as reported on ClinicalTrials.gov, with an added description of study controls. “Placebo” is defined as an inactive substance, and “active placebo” refers to a drug that may be active but is believed to have no benefit for the disorder under study; “positive controlled” refers to a drug of proven efficacy for the disorder under study and “active comparator” refers to a drug with possible benefit for the disorder. If comparison groups are only described in publication abstracts, sponsor results summaries, or press releases, the source is noted. The primary outcome measure is taken directly from ClinicalTrials.gov. Secondary outcome measures are not listed in the outcome measures column.
The most difficult type of information to gather is the results of completed studies. Using the NCT study code, drug name, trial name, and other identifiers, the following websites were searched for publicly available study results: (1) ClinicalTrials.gov; (2) PubMed; (3) ClinicalStudyResults.org [11]; (4) Sponsor-related websites; (5) Google; (6) Google Scholar. Sponsors and lead investigators were not contacted directly because the RReACT database project aims to gather information readily available to the public for a large number of studies. Articles published in peer-reviewed journals were considered the most accurate results. To confirm that results corresponded to the trial registered on ClinicalTrials.gov, we relied on NCT number (often unstated in the publication), drug name, dose groups, sample size, duration, principal investigator, description of comparators, and other available information. Press releases and abstracts of poster/platform presentations at scientific meetings were considered “available results” when nothing else could be found, even though such sources are unlikely to have been fully peer reviewed, and abstracts published in meeting programs may differ from the posters that appeared at the meeting [4]. When press releases or company statements regarding the status of drug development did not provide results specific to the listed study, the information gleaned is provided in the results column, but such trials were not considered to have “available results.”

Results are summarized for the outcome measure assessing analgesic efficacy. If the primary outcome measure was unrelated to analgesic efficacy, results for the secondary outcome measure assessing pain are summarized. The source and results pertaining to analgesic efficacy are quoted directly from the abstract of journal articles, press releases, and sponsor results summaries.

2. Snapshots

As of December 1, 2011, there were 373 trials for PHN, fibromyalgia, and DPN meeting criteria for inclusion in the RReACT database. There were no obvious trends in the number of new trials registered on ClinicalTrials.gov each year. For each disorder, 2006 brought the greatest number of new trials. No studies registered before 2006 were still listed as actively recruiting subjects. The only studies registered before 2008 still open for enrollment were for fibromyalgia. For each disorder, the percentage of studies listed as terminated ranged from 8.6% to 11.8%. Few studies registered in 2010 and 2011 have been terminated. The percentage of studies listed as “unknown status” ranged from 4.3% to 5.2%. Fig. 1 shows the number of new trials registered each year for the 3 disorders. Fig. 2 shows for each disorder the number of completed trials, the number with available results, and the number with results in the peer-reviewed literature.

The database contains 93 analgesic clinical trials for PHN. Twelve trials were registered in 2011. Thirteen are actively recruiting participants and 56 are listed as completed (60%). Results could be found for 35 of all 56 completed trials (63%) and for 31 of 46 trials completed before 2010 (67%). Of 35 trials with available results, 22 (63%) had results published in peer-reviewed publications. The total proportion of all completed trials with results in a peer-reviewed journal was 39% (22/56).

The database contains 116 analgesic clinical trials for fibromyalgia. Twelve trials were registered in 2011. Twenty trials are actively recruiting and 66 trials (57%) are listed as completed. Results were available for 44 of 66 completed trials (67%) and for 38 of the 51 trials completed before 2010 (75%). Publication in peer-reviewed journals accounted for 29/44 (66%) of the studies with results available. The total proportion of all completed trials with results in a peer-reviewed journal was 44% (29/66).

The database contains 164 analgesic clinical trials in painful DPN. Ten trials were registered in 2011. Twenty-one trials are actively recruiting and 106 (65%) are listed as completed. Seventy-two of all 106 completed trials (68%) have results available, with results available for 66/87 trials completed before 2010 (76%). Publication in peer-reviewed journals accounted for 41/72 (57%) of the studies with results available. The proportion of all completed trials with results in a peer-reviewed journal was 39% (41/106).

3. Scorecard: progress?

Trial registration on a public database is now nearly universal, especially for pivotal phase 3 trials. As 2012 dawned, the 119,073
trials registered on ClinicalTrials.gov represent a 150% increase from September 2010 [26], and a 524% increase from October 2005 [24].

Reporting of study results lags behind. Only 39%-44% of completed studies in the RReACT database were published in peer-reviewed journals. Even including the so-called “grey literature” (publicly available meeting abstracts, posters, press releases, and sponsor summaries), results were found for 63%-68% of all completed trials in the RReACT database. Zarin and colleagues examined whether time since study completion impacts reporting or publication of results [26]. Of a sample of 150 trials listed on ClinicalTrials.gov as having results available, only 25% had associated publications retrievable via PubMed; 1 year later, associated publications had risen to 52% for the same trial sample [26]. Ross and colleagues also found that publication rates in peer-reviewed journals increased as more time elapsed after trial completion [16]. For RReACT database studies completed at least 2 years ago, 68%-76% have results available in any format.

A more worrisome explanation for the unavailability of trial results would be publication bias [9,10,17]. Several resources are available to investigate such a possibility. After a new drug is approved, the FDA makes publicly available its Summary Basis of Approval documents containing detailed analyses of all clinical studies conducted by the applicant. The European Medicines Agency publishes its dossier as well. Turner and colleagues compared the published literature with Summary Basis of Approval documents for 74 pivotal trials conducted during 13 successful antidepressant drug development programs and found 63% were published in full format by a peer-reviewed journal [20]. Positive results and full publication were strongly correlated. Only 3% of positive trials went unpublished, while 67% of negative trials were unpublished. Furthermore, negative trials may be described in journal publications in a way that conveys a positive outcome [20].

A Cochrane review of the impact of “grey” literature on meta-analyses found that published trials reported a 9% greater treatment effect, suggesting that negative trials were less likely to progress from grey literature to full journal publication [5,6]. Several groups of investigators have examined complete protocols and other study documents (some obtained via legal action) and found evidence suggesting publication bias in reporting of primary outcome measures [9,21] and mortality [13]. Song and colleagues endorse systematically searching for and including results of relevant, but difficult to access, studies as one method to minimize dissemination bias [18].

The public has little ability to cross-check results or determine whether a results source is reliable. Independent FDA assessments are publicly available for only a few RReACT database trials. Compared with study reports submitted to regulatory agencies like the FDA, Wieseler and colleagues found significantly poorer reporting quality in both registry reports and journal publications [22]. ClinicalStudyResults.org provided a disclaimer about the lack of independent review and the limited applications of the results; others state results without qualification. It is beyond the current scope of the RReACT database project to assess the reliability of available results. Presentation of all available results in RReACT, free of judgment about the source, is consistent with the recommendation of Song and colleagues [18]. Furthermore, the grey literature is not reliably indexed and archived the way peer-reviewed journals are; results may be posted and then taken down, or a URL may no longer work. Websites can change from being freely accessible to operating on a paid or subscription basis. Highlighting the importance of gathering results into a database like RReACT, ClinicalStudyResults.org has recently gone offline altogether.

Going forward, the database of analgesic trials for PHN, DPN, and fibromyalgia will be updated regularly and all major registries accessible through the World Health Organization platform will be searched. There are hundreds of registered trials to be added for other painful conditions such as postoperative pain and low back pain. The ultimate goal is to provide the scientific community, industry, regulators, and the public at large with an unbiased and searchable database of the current landscape of analgesic trials and set benchmarks for measuring progress.

Conflict of interest statement
The views expressed in this article are those of the authors, none of whom have financial conflicts of interest related to the issues examined in this article.

Acknowledgements
No official endorsement by the US Food and Drug Administration or the pharmaceutical companies that provided unrestricted grants to support the activities of ACTTION should be inferred. Financial support for this project was provided by the ACTTION public-private partnership, which has received research grants or other revenue from the FDA, various pharmaceutical companies, and other sources.

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