Adequacy of registration and results reporting of randomized controlled trials in ClinicalTrials.gov and publications

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ADEQUACY OF REGISTRATION AND RESULTS REPORTING OF RANDOMIZED CONTROLLED TRIALS IN CLINICALTRIALS.GOV AND PUBLICATIONS

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DEDICATION

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LIST OF ABBREVIATIONS

CI – confidence interval

ClinicalTrials.gov – Public registry of clinical trials data and results sponsored by the National Institutes of Health in the United States of America

CONSORT – Consolidated Standards of Reporting Trials

EMA – European Medicines Agency

EU – European Union

EudraCT – European Union Drug Regulatory Authorities Clinical Trials

FDAAA – Food and Drug Administration Amendments Act

ICMJE – International Committee of Medical Journal Editors

IF – Impact Factor

ISRCTN register – International Standard Randomised Controlled Trial Number Register

PLoS Medicine – An open-access, peer-reviewed medical journal by the Public Library of Science (PLoS) that covers the full spectrum of the medical sciences

NA or N/A – not applicable

NIH – National Institutes of Health

RCT – Randomized controlled trial (hrvatski, randomizirano kontrolirano ispitivanje)

SPSS – Statistical Package for Software Solutions

WHO – World Health Organization

WHO ICTRP – World Health Organization (WHO) International Clinical Trial Registry Platform

WHO MDS – World Health Organization Minimum Data Set

1. Introduction

1.1 *Discrepancies in the reporting of data from ClinicalTrials.gov*

Timely and complete reporting of clinical trials protocol and results data is mandatory in clinical research (1-3). Proponents of trial registries argue that registration promotes patient safety, design, and outcome transparency, and maintains public trust and evidence-based patient information (4, 5). Legislative bodies in the US and European Union (EU) implemented policies to create publicly accessible online trial databases, such as ClinicalTrials.gov and EU Clinical Trials Register (EU-CTR), which store sponsor added data (4-8).

In the US, The Food and Drug Administration (FDA) Amendment Act (FDAAA) of September 27, 2007, mandates that clinical trials, involving non-experimental FDA approved drugs, biologics, and devices that are over phase 1, have at least one US-based site, and include a non-experimental FDA approved drug need to be not only registered but have basic results reported within 1 year from trial completion (9). The history of changes to results or protocol data can be viewed in a study's archive of saved modifications from initial registration, found separately online at http://clinicaltrials.gov/archive/ (10). Further, registered trials remain on the site once posted. Presently, interventional trials subject to the FDAAA must report results within 21 days after the first patient is enrolled (a 90 day submission deadline was given immediately following the enactment). Trials not involving a serious or life threatening disease or condition that are over phase 1 with at least 1 U.S. site with FDA-approved drugs must report results within one year of trial completion (11). However, trials of previously approved drugs that have not been approved for a new indication do not have to report results until two years after completion (12). Penalties for failing to register or submit trial results with adverse events listed on ClinicalTrials.gov include withholding of NIH grant funding and civil monetary penalties of up to $10,000 a day. To this day, however; the FDA has not imposed any penalties on a single research entity.

As of May 2016, ClinicalTrials.gov (available at https://clinicaltrials.gov/) lists over 210,000 studies in all 50 U.S. states and 193 countries making it the largest human participants clinical trial

registry (**Figure 1**). The site was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA) requiring that the Department of Health and Human Services, through the National Institutes of Health (NIH), establish a registry of clinical trials involving experimental treatments for diseases and conditions (13). The U.S. National Library of Medicine (NLM) and NIH maintain the database and registration of trials is available to any publicly or privately supported clinical trial.

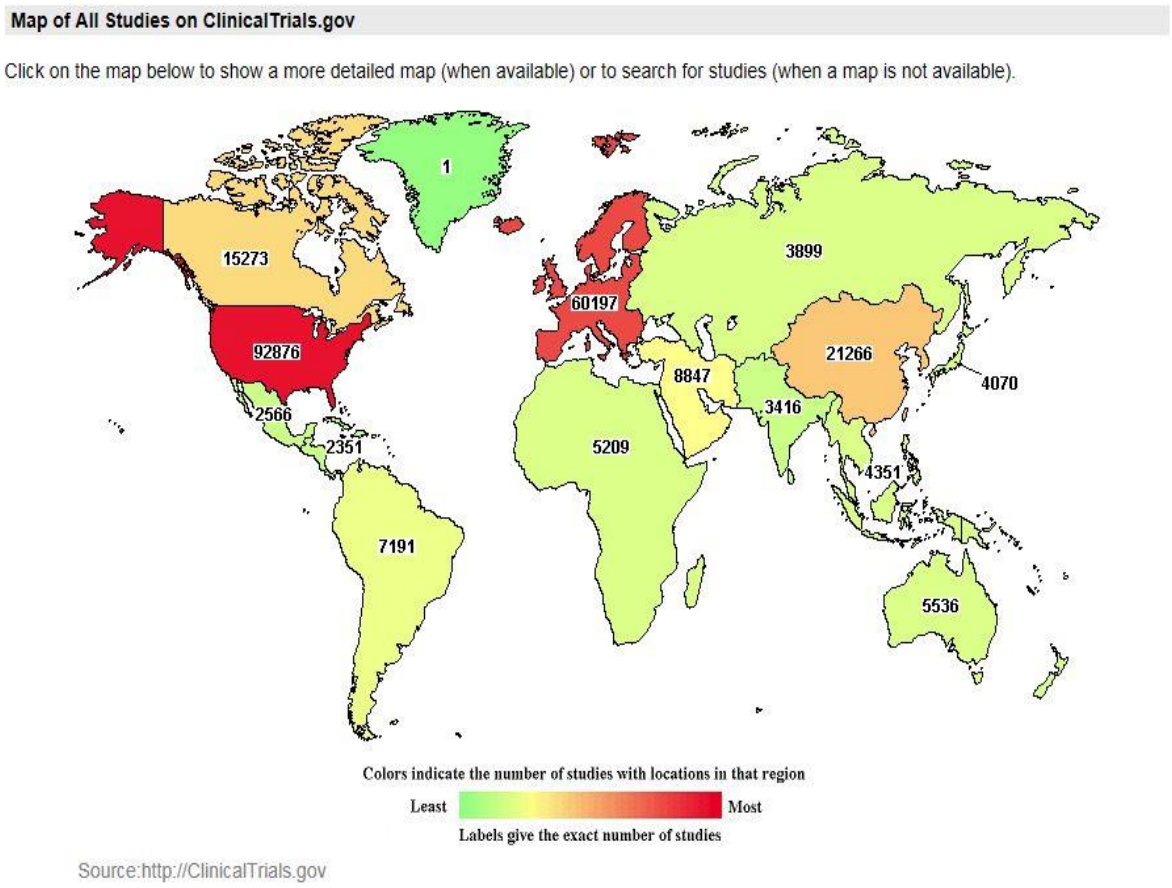

Figure 1. Worldwide distribution of clinical trials registered in ClinicalTrials.gov as of May 10, 2016. Source: http://clinicaltrials.gov

The content of the data and results is the sole responsibility of a study's sponsor or principal investigator. As stated on the ClinicalTrials.gov website, not all clinical trials conducted are registered in ClinicalTrials.gov because not all studies are required by law to be registered. However, the number of studies registered each year has increased as sponsors and investigators voluntarily register their studies due to pressure from legislators and medical journal editors (14).

Investigators may submit a certification for delayed or extended results submission. A presumptively exempt trial meets certain conditions for delayed results reporting as follows: 1) if a trial's completion date is reached before a drug, biologic, or device is initially approved or cleared by the FDA for any use, then results must be reported no later than 30 days after approval, licensing or clearance by the FDA; 2) if a new, non-label specified use for an FDA-approved drug, biologic, or device trial is awaiting approval (sponsor has or will file an FDA application within 1 year) from the FDA for that use, then results must be submitted 30 days after: FDA approval of the new use, a complete written statement from the FDA, the application or premarket notification for the new use is withdrawn without resubmission for no less than 210 days or 2 years after the certification submission date, if none of the aforementioned has occurred. Sponsors seeking an extension must submit a justifiable written request that provides an estimated results submission date.

For adequate trial registration and a pre-requisite for publication in ICMJE member journals, the WHO and ICMJE require the completion of 20 items (**Table 1**) for basic, mandatory information (1, 2, 11, 12). ClinicalTrials.gov and EU-CTR features these items (8, 12). However, despite these well-intentioned steps to promote trial registration and standardize data entry, there are still issues with the transparency of registration and reporting (15, 16). Recently, Hartung and colleagues found inconsistencies in data reporting in trials registered in ClinicalTrials.gov and corresponding publications, including inconsistent reporting of serious adverse events (SAEs) (17). Similarly, Becker et al. reported discrepancies in study and outcomes characteristics as well as results information in randomized controlled trials (RCTs) registered in ClinicalTrials.gov and published in journals with an impact factor (IF) ≥ 10 as they assumed high-quality data reporting in these journals (18).

Table 1. WHO Minimum Data Set items included in ClinicalTrials.gov.*

WHO Minimum Data Set items
1. Primary Registry and Trial Identifying Number
2. Date of Registration in Primary Registry
3. Secondary Identifying Numbers
4. Source(s) of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor(s)
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title*
11. Countries of Recruitment
12. Health Condition(s) or Problem(s) Studied*
13. Intervention(s)*
14. Key Inclusion and Exclusion Criteria*
15. Study Type*
16. Date of First Enrollment*
17. Target Sample Size*
18. Recruitment Status
19. Primary Outcome(s)*
20. Key Secondary Outcomes*

Source: http://www.who.int/ictrp/network/trds/en/. We assessed 9 items for discrepancies in the registry and publications (indicated in bold letters).

These recent studies highlight the fact that inadequate data registration and reporting in ClinicalTrials.gov demonstrated at the beginning of the registration policy (5, 10, 14, 19-21), still undermines the transparency of clinical trials. In response to the current state of clinical trials reporting, WHO recently issued a statement regarding public disclosure of trial results to streamline publishing, prospective registration, and results reporting periods, including for unreported trials (22).

1.2 ***Adverse event terminology use in ClinicalTrials.gov***

Reporting on the harms of drugs are essential to patient safety (23, 24). There are several dictionaries that exist for the coding of narrative data on adverse events before and after a drug is available on the market for electronic medical records, adverse event databases, or for product labeling (25-28). The Medical Dictionary of Regulatory Activities (MedDRA) dictionary has been used by pharmaceutical companies applying for drug approval since 1999, but its use is currently required only in the EU and Japan (29, 30) . In the US in 2013, the Food and Drug Administration (FDA) has mandated the use of MedDRA for safety reporting for marketed drug products (29, 31). Developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), MedDRA facilitates coding of adverse events or adverse drug reactions for health care practitioners, researchers, and other stakeholders in clinical research (24, 32). Several levels exist in MedDRA for the conversion of narrative or aggregate text describing adverse events into codes (24). Some other medical dictionary programs used for the coding of adverse events include the WHO Adverse Reactions Terminology (WHOART) and the Systematized Nomenclature of Medicine--Clinical Terms (SNOMED). Additionally, the Common Terminology Criteria for Adverse Events (CTCAE) once exclusively used to describe adverse events form oncology trials has become common use to describe adverse events in other clinical fields (33, 34).

Reporting of harms varies by clinical trials registry (35). For example, ClinicalTrials.gov, sponsored by the National Institutes of Health, requires that all serious adverse events that are expected or unexpected be reported in tabular format grouped by organ system and arm including the number and frequency of events while other adverse events can be reported using a frequency threshold of ≤ 5%

(36).Currently, all unanticipated or anticipated serious and other adverse events must be reported in ClincalTrials.gov with the adverse event term, number of participants at risk and affected, and affected organ system. Although the reporting of adverse events in ClinicalTrials.gov is required, there is no requirement for the use of controlled vocabulary or terminology for the definition or description of adverse event terms from trials. On the other hand, investigators posting to the European Union Clinical Trials Register (EUCTR) can state that all other adverse and serious adverse events are not reported or recorded in the protocol of the study, but suspected unexpected serious adverse events should be reported using the Clinical Trial Eudravigilance database (37).

Although medical dictionaries are intended to aid in the coding of narrative data on adverse events before and after a drug is available on the market (26) inconsistencies in the coding of identical narrative text of adverse events are documented in the literature between different medical dictionaries and within various versions of the same dictionary (25, 27, 28, 38, 39). These discrepancies can have an impact on patient safety in that harmful side effects are not recorded properly or minimized (24). Additionally, the safety profile of various drugs is evaluated using search terms derived from medical dictionaries (40).

1.2.1 Problem statement and research focus

1.2.1.1 *Discrepancies in the reporting of data from ClinicalTrials.gov*

Studies of ClinicalTrials.gov registration so far compared registered trial protocol data and results with corresponding publications in high-impact journals (10, 18). A single study (10) reported the analysis of the changes in trial registration during the conduct of the trial. Insight into the changes between registered and published data could identify specific elements in the data entry process over time that may require increased sponsor diligence to allow ClinicalTrials.gov to remain a useful tool for researchers as well as patients.

Our aim was to understand where data entry inconsistencies occur along the progression of data completion and modification in RCTs registered in ClinicalTrials.gov in the context of FDAAA and ICMJE regulations. Thus, we examined a cohort of completed trials registered on ClinicalTrials.gov after FDAAA and ICMJE reporting requirements for the completeness and changes occurring in protocol and

results data in the registry from initial to last registration as well as the completeness and changes of these data from last registration and subsequent publications.

Accordingly, we performed:

1) a cross-sectional study of WHO minimum data set registration and results reporting completeness;

2) a historical cohort study of the WHO minimum data set changes during registration as well as in subsequent publications;

3) a historical cohort study of the results reporting changes from last registration to subsequent publications; and

4) an evaluation of the completeness and changes in reporting of registered WHO minimum data set items and results in publications.

1.2.1.2 *Adverse event terminology use in ClinicalTrials.gov*

As clinicaltrials.gov is a public repository for the use of patients, clinicians, and other stakeholders in clinical research, it is important to determine if and what types of medical terminology programs are used in the reporting of adverse event data. It is essential to determine if the same inconsistencies that are present in electronic medical records, adverse event databases, or for product labeling could also be present in trials reported on ClinicalTrials.gov.

The FDA's Modernization Act of 1997 and the FDAAA 801 of 2007 both stipulate that clinical trial results must be reported in a language that patients can easily understand. Additionally, the CONSORT group revised their 2001 statement to include more comprehensive suggestions on how to improve adverse events reporting for randomized controlled trials (23).

The aims of this study were two-fold: 1) to determine the variability in the types and versions of medical terminology programs for trials that studied drug classes that encompass the most common diseases such as, antidepressants, analgesics or anesthetics, anti-inflammatory agents, antineoplastic agents, enzyme inhibitors, hypoglycemic agents, neuromuscular agents , antidepressants, anti-allergics, and anti-infectives by funder type in the context of the FDA's Modernization Act of 1997 and the FDAAA 801 of 2007 and 2) to determine the variability in the medical terminology used to describe adverse events

in trials in ClinicalTrials.gov for a specific condition classified by organ system within the same terminology program.

2. Objectives and hypotheses

2.1 Research Objectives

The research objectives for the discrepancies in the reporting of data from ClinicalTrials.gov are as follows:

1) to understand where data entry inconsistencies occur along the progression of data completion;
2) to elucidate where data entry inconsistencies occur in the modification of data in RCTs registered in ClinicalTrials.gov in the context of FDAAA and ICMJE regulations; and
3) to look specifically at possible differences between phase 3 and 4 clinical trials because there may be discrepancies in the data between phase 3 studies with interventions not approved by the FDA and phase 4 studies with FDA-approved interventions.

The research objectives of adverse event terminology use in ClinicalTrials.gov are as follows:

1) to determine the variability in the types and versions of medical terminology programs for trials that studied drug classes that encompassed the most common diseases such as, antidepressants, analgesics or anesthetics, anti-inflammatory agents, antineoplastic agents, enzyme inhibitors, hypoglycemic agents, neuromuscular agents, antidepressants, anti-allergics, and anti-infectives by funder type in the context of the FDA's Modernization Act of 1997 and the FDAAA 801 of 2007 and
2) to assess the variability in the medical terminology used to describe adverse events in trials in ClinicalTrials.gov for a specific condition classified by organ system within the same terminology program.

2.2 Hypotheses

2.2.1 *Discrepancies in the reporting of data from ClinicalTrials.gov*

There are no hypotheses for the main part of this study assessing completeness and changes in WHO Minimum Data items as we intended to describe and summarize data from our sample of RCTs in ClinicalTrials.gov.

The null hypothesis for the subsample of phase 3 and phase 4 trials is:

1) there is no difference between the study characteristics of phase 3 and phase 4 RCTs in our sample of RCTs in ClinicalTrials.gov.

2.2.2 *Adverse event terminology use in ClinicalTrials.gov*

There are no hypotheses for Study 2 as we intended to describe and summarize a large amount of data regarding the use of adverse events terminology in ClinicalTrials.gov

3. Research design and methodology

3.1 *Discrepancies in the reporting of data from ClinicalTrials.gov*

3.1.1 *Sample and trial inclusion*

The inclusion criteria for the RCT cohort were: 1) RCTs that were completed at the time of our search (September 2014) and were registered on or after September 27, 2009 and updated on or before September 27, 2012 subject to FDAAA with results and their corresponding published results in journals; 2) having a ClinicalTrials.gov registration number; and 3) having registration data in the ClinicalTrials.gov Archive site (from September 27, 2009). The sample excluded phase 1 trials of unknown status, still recruiting, and non-RCTs (e.g., observational trials) (**Figure 2**). The chosen period allowed at least 2 years for posting and publishing results in the registry and in a journal.

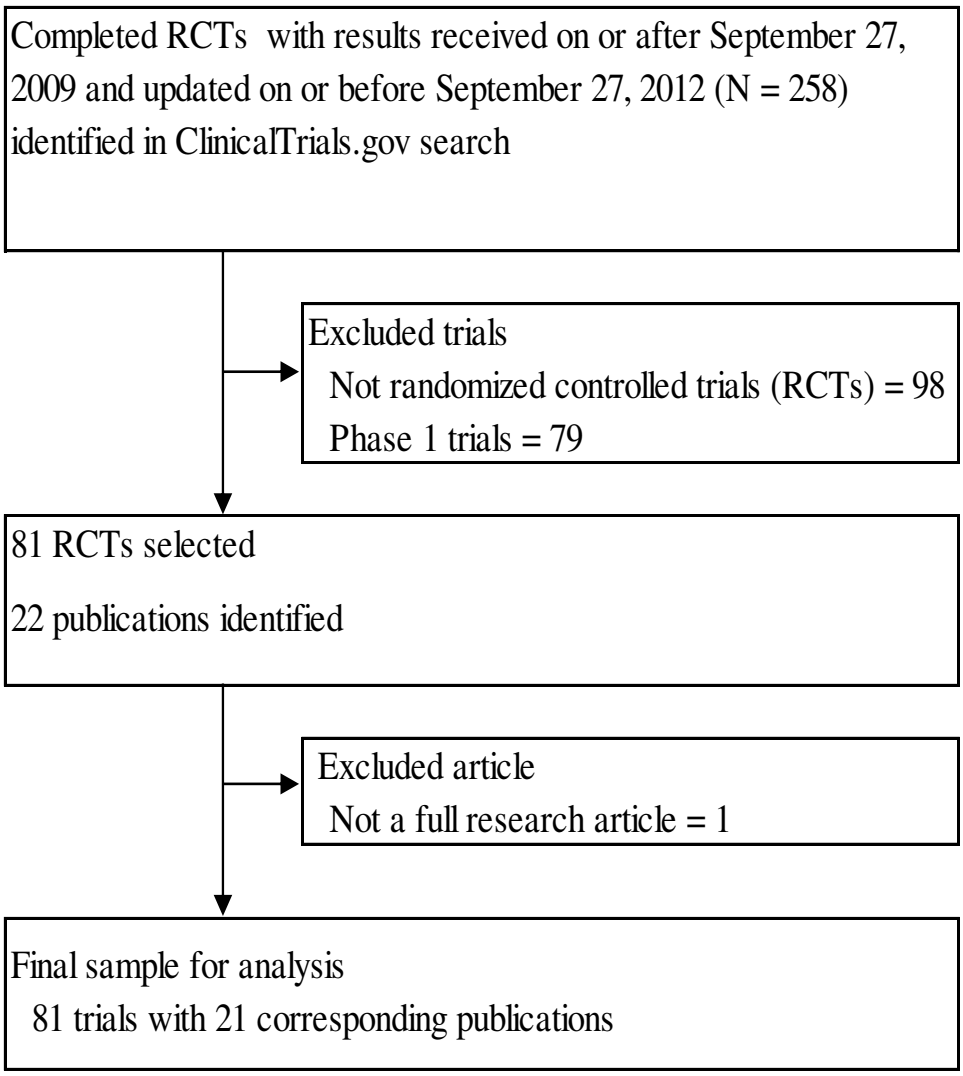

Figure 2. Study flow diagram for the selection of our sample of completed ClincalTrials.gov RCTs received on or after September 27, 2009 and updated on or before September 27, 2011.

3.1.2 *Publication search*

ClinicalTrials.gov provides links to associated publications to studies cited in MEDLINE; however, these studies may not contain pertinent trial data. To this end, we searched MEDLINE in October 2013 and again in September 2014 with the study identifier (NCT) from the ClinicalTrials.gov registry by typing an NCT number followed by the PubMed secondary source ID tag [si] (e.g., NCT01068600[si]) into the search field via PubMed (41). We performed manual searches using the first author name and study and title using Web of Knowledge (Thomson Reuters). Manual searching did not yield any additional publications over the publication links provided in ClinicalTrials.gov.

3.1.3 *ClinicalTrials.gov data extraction and comparisons*

ClinicalTrials.gov data were extracted by one investigator to compare the completeness between first and last registration before publication and history of changes in the registration data from first to last registration and changes between the last registration and a subsequent publication for 9 out of a total of 20 items from the WHO Minimum Data Set (11): Item 10 ('Scientific Title'), Item 12 ('Health Condition(s) or Problem(s) Studied'), Item 13 ('Interventions'), Item 14 (both 'Key Inclusion and Key Exclusion Criteria'), Item 15 ('Study Type'), Item 16 ('Date of First Enrollment'), Item 17 ('Target Sample Size'), Item 19 ('Primary outcome') and Item 20 ('Key secondary outcomes'). We extracted data for all 20 of the WHO Minimum Data Set items. The sample for the main completeness and changes analysis excluded eight data items (2 – 5; 8, 9, 11 and 18) because of their transient, general nature, no expectation of changing from first to last registration or their exclusion from journal articles (9). Additionally, Item 1 ('Primary registry and Trial Identifying Number') was used only to identify the randomized controlled trials (RCTs) in our study and items 7 ('Contact for Public Queries') and 8 ('Contact for Scientific Queries') were not visible in the registry as ClinicalTrials.gov does not routinely list contact information for completed trials. We identified data set items for completeness and differences by: a) missing information – data not visible in the specified registry item or b) uninformative terminology – unspecified or unclear information for the relevant registry item (e.g., a code instead of a generic name

of a drug for Item 13), both at the time of the first registration and the time of the last registration modification before publication (10).

3.1.4 *Extraction and comparison of data from publications*

To evaluate the history of changes in the registration data from first to last registration and changes between the last registration and a subsequent publication the 9 WHO Minimum Data Set items for which the information was changed, we similarly examined as Huić et al. (10) for: a) qualitative change – the difference in the meaning of the information provided in a registry field (e.g., incongruity of data items in the article compared to those in the registry, direction of change in time, uninformative entries); or b) quantitative change – difference in a numerical entry in a registry field (10).

We modified criteria developed by Chan et al. (42) to describe discrepancies between registered and published primary and secondary outcomes as:

1) the registered outcome changed to primary or secondary or vice versa in the article;

2) the registered outcome changed from primary to unspecified;

3) a new registered outcome was introduced in the publication (a newly stated outcome in the publication but not included in the registry);

4) the registered outcome was omitted in the publication;

5) the timing of assessment (time frame) different in article and registry;

6) the outcome used for power calculation in article different from registered; and

7) a combination of newly introduced or omitted outcomes and difference in power calculation.

3.1.5 *Data validation and second reviewer coding of data*

Values for particular categories were validated after data were entered into the database by sorting and filtering of data for each variable to identify any values outside of the defined range of values for a particular category. To avoid potential data collector bias from possible subjective interpretation of major changes of the WHO Minimum Data Set items and results, a second investigator (AM) independently reviewed data for completeness and changes in a 10% random sample of RCTs representative of our entire RCT cohort.

Inter-observer agreement was high (kappa range 0.80 to 1.00, 95% confidence interval (CI) 0.84–1.00).We resolved through consensus discussion differences in rating the nature of the secondary outcome statistical analysis technique, which had the lowest kappa in any single category (0.80), before the full data extraction by SP.

3.1.6 *Assessing completeness of results reporting in ClinicalTrials.gov*

Results reporting completeness from initial to last registration as well as from last registration to the publication in 5 summary groups of a trial results record were determined by the presence of a) Participant Flow elements: recruitment and pre-assignment details, reporting groups description, and overall study participant flow (including participant discontinuation); b) Baseline Characteristics elements: population descriptions, baseline characteristics, or reporting groups descriptions; c) Outcome Measures elements: population description – analysis technique (e.g., intention-to-treat), agreement of descriptive or inferential statistical analyses for primary or secondary outcomes between the data at last registration compared to the publication, and if the analysis used favored the experimental or the control; and d) Serious and e) Other Adverse Events as well as participant deaths for agreement between number and description of events reported in ClinicalTrials.gov compared to the publication.

An adverse event is any unexpected event that occurs during the course of a medicinal drug study that may be serious (results in unfavorable consequences such as hospitalization or death) or non-serious (43). According to the FDAAA 801, adverse event reporting became a reporting requirement in September 2009 for certain clinical trials that involve a drug, device, or biological agent which have either

1) one or more sites in the United States, or 2) a new, non-label specified use for an FDA-approved drug, biological agent or device, or 3) a U.S. manufactured drug, biological agent or device exported for research (4). We grouped RCTs as reporting SAEs or OAEs in the registry if the ratio (number of participants affected / at risk) listed in the SAE or OAE table reported was ≥ 1 out of the number at risk. We noted the OAE frequency reporting threshold in the registry as well as in the publication or the reporting of Treatment Related Adverse Events (TEAEs) in the publication as the absolute number of events may differ due to both of these methods to treat OAEs. Also, we compared the number or description of OAEs explicitly listed in the registry to what was listed in the publication to facilitate event recording. Occurrence of participant death was when number of deaths was ≥ 1 was listed in the Participant Flow, Outcome Measures, or SAE sections for trials in the results record of the registry or recorded in publications.

To examine any embargoes on clinical trial results disclosure, we abstracted the text from the 'More Information: Certain Agreements' field in ClinicalTrials.gov and coded them according to publication contingent on sponsor review, specification of other temporal embargoes, or the lack of any type of results release restriction.

3.1.7 *Discrepancies between phase 3 and phase 4 studies in ClinicalTrials.gov*

Under the assumption that there may be discrepancies in the data between phase 3 studies with interventions not approved by the FDA and phase 4 studies with FDA-approved interventions, we compared the completeness and changes in the WHO Minimum Data Set items and results elements in phase 3 and phase 4 trials in ClinicalTrials.gov and publications. In the current study, there were 27 (33.3%) phase 3 trials and 26 (32.1%) phase 4 trials. Out of those, 8 (38%) and 7 (33.3%) phase 3 and phase 4 trials, respectively, have associated publications.

To avoid potential data collector bias from possible subjective interpretation of drug class, matching of unsourced terminology, and the FDA indication for the trials in ClinicalTrials.gov, a second investigator independently reviewed data for completeness and changes in a 10% random sub-sample of RCTs representative of our entire RCT cohort.

Inter-observer agreement ranged from good to high (kappa range 0.72 to 0.83, 95% confidence interval (CI) 0.70- 0.84). We resolved through consensus discussion differences in rating whether a drug was used for the FDA indication, which had the lowest kappa in any single category (0.72).

3.2 *Discrepancies in the reporting of data from ClinicalTrials.gov*

3.2.1 *ClinicalTrials.gov data extraction and comparisons*

We searched for trials in July 2015 from ClinicalTrials.gov that were completed (at the time of our search) trials with results that studied analgesics or anesthetics, anti-inflammatory agents, antineoplastic agents, enzyme inhibitors, hypoglycemic agents, neuromuscular agents , antidepressants, anti-allergics, and anti-infectives. These drug classes treat a broad range of medical conditions and they were the most currently studied drug classes in ClinicalTrials.gov as of January 2016. We used the NIH Drug Information Portal database (44). We classified the studied condition as an FDA-approved or non-approved indication from information from the drug label available at the inception of the trial using the Drugs@FDA database (45). If a study uses more than 1 drug, then the study was included if at least 1 of the drugs is a part of any of the drug classes of interest.

We selected all clinical trials with results that were registered on or after between September 27, 2009 and updated on or before December 31, 2012. This period allowed almost 3 years for trials to post results, which include adverse events. From information listed for the endpoint classification of each trial, we selected studies of drugs that only investigate the efficacy or the ability of a drug to ameliorate a condition and safety or when adverse events associated with treatment are summarized for the drug. Trials of unknown status, still recruiting, using drugs without comprehendible generic or brand names (i.e., code(s) used instead), without a listed start date, without a listed endpoint classification, and with a completion date after December 31, 2012 were excluded.

3.2.2 *ClinicalTrials.gov data extraction*

We identified trials with a unique trial identification number (NCT). We extracted data pertinent to our study outcomes including sponsor type, drug intervention, study start and completion dates, condition, study classification, trial phase, sample size, participant age. Additionally, we abstracted study

design characteristics including study type (interventional or observational), type of masking, purpose of the study, intervention model (parallel, etc.), and allocation (randomized or non-randomized). Regarding sponsor data, we recorded and code by type: zero= NIH, 1= other U.S. Federal Agency, 2= industry, 3= individual, four= university, 5= community-based organization. Then, we dichotomized this variable into one = industry- funded trials (including solely industry-funded trials) and two = non-industry funded trials (including trials funded by NIH, other U.S. Federal Agency, individuals, universities, or community-based organizations).

We identified the use of a medical dictionary program for adverse events from its notation in the footnote section of the summary table for serious and other adverse events in the results section of each trial record. We recorded the type and version of the medical dictionary program or other method of adverse event recording, if noted in the table. If the use of a medical dictionary was not referenced, then we found the most appropriate dictionary that contains the exact match in MedDRA, SNOMED-CT, or CTCAE databases. Since drugs can be in multiple classes, we chose the class in common as the representative class for the drugs in that particular study.

A second data extractor independently extracted trial data on the assignment of drug classes, FDA-approval for a specific indication, and matching un-sourced terminology (trial records where no source dictionary was listed for adverse events) for adverse events to a dictionary. Inter-observer agreement ranged from good to high (kappa range 0.72 to 0.83, 95% confidence interval (CI) 0.7- 0.84).

3.2.3 *Statistical analysis*

Descriptive analyses were performed using Excel 2013 (Microsoft) on coded data abstracted from ClinicalTrials.gov using frequencies, means, or medians with standard deviations (SD) or 95% confidence intervals (CI). We used the chi-square test to determine the differences in distribution of categorical variables. We used the independent samples median test to determine the difference between the sample size and maximum age in phase 3 vs. phase 4 trials. We considered statistical tests with *P*-values below 0.05 as significant. We used SPSS 22.0 (Statistical Package for Software Solutions, IBM SPSS Inc., Chicago, IL, USA).

3.2.4 Ethical Principles

There was no need for approval from an institutional review board, as both studies were cross-sectional and historical cohort database studies. We neither collected patient data nor performed experimental procedures. There are no conflicts of interest to declare.

The second study on the use of medical terminologies was funded in part by the research grant from the Croatian Science Foundation to Ana Marušić, (ProHealth, No. IP-2014-09-7672).

4. Results

4.1 *ClinicalTrials.gov trials and published articles characteristics for Study 1*

The search of the registry retrieved 258 clinical trials. We excluded 98 non-randomized trials (e.g., observational trials) (**Figure 1**). Out of the remaining 149 RCTs, we excluded 79 phase 1 trials, leaving 81 RCTs with 21 corresponding publications as the final study sample for analysis.

Among the 81 identified RCTs, most trials started recruiting participants before registering the study (93.8%) (**Table 2**). Most trials were double blind (n = 54, 66.7%) and industry sponsored (n = 55, 67.9%), without a site in the U.S. site (n = 37, 45.7%), and were primarily for treatment (n = 69, 84%). Drugs were the most common intervention (n = 62, 76.5%), mostly in parallel assignment (n = 63, 77.8%), and in phase 3 (n = 27, 33.3%). Over a third (33.1%) of the trials were multicenter, with mostly both female and male participants (87.7%). The median sample size was 83 (95% CI: 62 – 116), with a range of 12 to 2312 participants. Three trials (3.7%) were missing participant ages, all of which had a drug intervention. Most trials were classified as safety/efficacy (n = 34, 42.0%), followed by efficacy studies (n = 20, 24.7%). Serious adverse events (SAEs) were reported in 38 (46.9%) trials.

The majority (n = 60, 74.1%) of trials had no corresponding published journal article while 21 (26%) trials had one or more associated full publications (**Table 2**). Two (9.5%) RCTs reported only positive results while one (4.8%) RCT reported only negative results, while both positive and negative results were reported in 85.7% of trials. Serious adverse events (SAEs) and other adverse events (OAEs) were reported in 7 (33%) and 15 (71.4%) published trials. The funding source for half (50%) of the RCTs was not identical to the sponsor in publications. The duration of 50% of trials was shorter in the publication than registered.

Table 2. ClinicalTrials.gov randomized controlled trial (RCT) registry characteristics (n=81) and trial publication data (n=21).*

	No. Trials (%)		No. Trials (%)
Started before registration:		***Maximum participant age (years), median, range:***	
Yes	76 (93.8)	65.0 (6-95.0 years)	
No	5 (6.2)	Missing data	34 (42.0)
Study phase:		***Sample size, median (range):***	
2	25 (30.9)	83 (12-2312)	
2/3	3 (3.7)		
3	27 (33.3)		
4	26 (32.1)		
Blinding:			
Open	16 (19.8)		
Single blind	11 (13.6)		
Double blind	54 (66.7)		
Control:			
Placebo	20 (24.7)		
Active	19 (23.5)		
Missing data	42 (51.9)		

Condition:			Immune System Diseases	3 (3.7)
Bacterial and Fungal Diseases	1 (1.2)		Muscle, Bone, and Cartilage Diseases	2 (2.5)
Behaviors and Mental Disorders	4 (4.9)		Nervous System Diseases	7 (8.6)
Cancers and other Neoplasms	1 (1.2)		Nutritional and Metabolic Diseases	6 (7.4)
Digestive System Diseases	4 (4.9)		Parasitic Diseases	1 (1.2)
Diseases and Abnormalities at or before Birth	1 (1.2)		Respiratory Tract (Lung and Bronchial) Diseases	11 (13.6)
Eye Diseases	5 (6.2)		Skin and Connective Tissue Diseases	2 (2.5)
Heart and Blood Diseases	6 (7.4)		Substance Related Disorders	3 (3.7)
			Symptoms and General Pathology	4 (4.9)
			Urinary Tract, Sexual Organs, and Pregnancy Conditions	9 (11.1)
			Viral Diseases	2 (2.5)
			Wounds and Injuries	1 (1.2)
			Missing	8 (9.9)
Assignment:			***Intervention type***:	
Parallel		63 (77.8)	Drug	62 (76.5)
Cross-over		15 (18.5)	Procedure and surgery	3 (3.7)
Factorial		1 (1.2)	Behavioral	1 (1)
Single group		2 (2.5)	Device	3 (3.7)
			Biological and vaccine	7 (8.6)
			Dietary supplement	2 (2.5)
			Other	2 (2.5)
Classification:			***Intervention name:***	
N/A[†,‡]		13 (16)	Specific	70 (100)
Safety		6 (7.4)		
Efficacy		20 (24.7)		

Safety/Efficacy	34 (42.0)		
Bio-equivalence	2 (2.5)		
Bio-availability	1 (1.2)		
Pharmacodynamics	2 (2.5)		
Pharmacokinetics/dynamics	3 (3.7)		
Purpose:		***Sponsor:***	
Treatment	69 (85.2)	Non-industry	26 (32.1)
Prevention	10 (12.3)	Industry	55 (67.9)
Screening	1 (1.2)		
Missing data	1 (1.2)	***Location:***	
		Non-US only	37 (45.7)
		US only	24 (29.6)
		Both US and non-US	3 (3.7)
		Not provided	17 (21.0)
Recruitment:		***Outcome measures:***	
Completed	70 (100)	Primary outcome	70 (100)
		Primary and secondary outcomes	68 (84.0)
Center:		***Primary outcome:***	
Multicenter	26 (32.1)	Defined	76 (93.8)
Single center	55 (67.9)	Clinical	65 (80.2)
		Surrogate	2 (2.5)
Participants' gender:		***Secondary outcomes:***	
Both	71 (87.7)	Defined	63 (77.8)
Female	6 (7.4)	Clinical	58 (30.9)
Male	4 (4.9)	Surrogate	5 (6.2)

Data from published articles (n=21):

	No. Trials (%)	**No. Trials (%)**	
Studies with publication(s), n=21:		***Serious Adverse Events (SAEs):***	
None	60 (74.1)[§]	Yes	7 (33.3)
One	16 (19.8)	No	14 (66.7)
Two	5 (6.2)**		
Funding:		***Other Adverse events (OAEs):***	
Identical to sponsor	5 (31.3)	Yes	15 (71.4)
Not identical to sponsor	11 (68.8)	No	6 (28.6)
Partially identical[††]	3 (18.8)		
Missing data	2 (12.5)		
Ethics committee approval:		***Trial aim:***	
Yes	81 (100)	Superiority	2 (12.5)
		Noninferiority	1 (6.3)
		Unstated or N/A	18 (85.7)
Outcome:			
Positive results	2 (9.5)		
Negative results	1 (4.8)		
Both positive and negative results	18 (85.7)		

Duration of the study:	
Same as data in registry	7 (43.8)
Longer duration than data in registry	3 (18.8)
Shorter than data in registry (follow up was shorter)	8 (50.0)
Different data in summary, methods and results of the article	1 (6.3)
No data in article	1 (6.3)
No data in registry	1 (6.3)

*No power analysis was performed to determine the sample size needed for the current study as our study observed reporting in a sample of eligible trials in the context of FDAAA and ICMJE requirements and had no requirement for statistical power.
[†]N/A: not applicable
[‡] N/A in end point section - not applicable due to study design
[§]Even though we used 2 sources to identify published trials – searching with the NCT[si] in MEDLINE and author and study details in Web of Science – it unlikely that the use of a third electronic bibliographic database would have retrieved other publications as non-publication has been an issue with ClinicalTrials.gov RCTs for over 5 years (46).
**All publications for studies with multiple publications were reviewed; however data for our study were only extracted from single publications for the 21 published studies.
[††]Other sources of funding in addition to the sponsor.

4.1.1 *Results disclosure*

Results disclosure restrictions with a pre-specified duration were found mostly in industry funded RCTs (n = 25, 30.9%) in the 'Certain Agreements' field in ClinicalTrials.gov. RCTs that listed restrictions without a pre-specified duration that stipulated sponsor review of data or multi-site publications before single-site publications were 24 (29.6%) industry funded trials, but 0 non-industry trials. Three (3.7%) industry sponsored RCTs and 8 (9.9%) non-industry RCTs did not list any type of disclosure agreement in the registry.

4.1.2 *Completeness of WHO Minimum Data Set items*

At initial registration, 81 RCTs had 19 missing registry fields of the 9 WHO Minimum Data Set items (**Table 3**). The secondary outcome was the only item of the 9 WHO Minimum Data Set items that was missing at initial registration for 17 (20.9%) RCTs. None of the WHO items was found in another registry field at initial registration. Items missing from the appropriate field at initial registration were the key secondary outcomes (19.7%) and scientific title (3.7%).

At least 1 of the 9 WHO Minimum Data Set items were missing at last registration for 16 (19.8%) RCTs (**Table 3**). At the last registration before publication, the key secondary outcomes (16.3%) field, like at initial registration, was the most frequently missing field, while trials with a missing scientific title entry remained about the same (5%). Similar to initial registration, no data that were missing from a designated field were found in other registry fields at last registration.

Table 3. Randomized controlled trials (RCTs) with missing registration information in the fields of 9 WHO Minimum Data Set items at initial and last registration and differences between registered trials and published trial registration data.

	Trials with missing or misplaced data, no. (%)				
	Initial Registration (n= 81)		Last change before publication date (n=80)[†]		
Minimum Data Set items[*]	Missing from proper field	Found in another registry field	Missing from proper field	Found in another registry field	Changes between last registered and published data, no. (%), n=21[‡]
10. Scientific Title	3 (3.7)	0 (0.0)	4 (5.8)	0 (0.0)	10 (47.6)
12. Health Condition(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
13. Intervention(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)
14. Key Inclusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (90.5)
or Key Exclusion Criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (90.5)
15. Study Type	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (19.0)
16. Date of First Enrollment[†]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (38.1)
17. Target Sample Size	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
19. Primary Outcome(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (28.6)
20. Secondary Outcome(s)	16 (19.8)	0 (0.0)	13 (18.9)	0 (0.0)	12 (57.1)

[*]Specified trial information intended to show that a trial is adequately registered. Eleven data items not included due to their transient or general nature or their exclusion from journal articles.
[†]One trial had no recorded changes.
[‡]Difference from the last registration change for trials with at least one change recorded.

4.1.3 *Changes to Minimum Data Set items during the trial*

There were changes during the conduct of the trial to 8 out of 9 WHO Minimum Data Set items for 31 RCTs; no changes were recorded for the target sample size element from initial to last registration (**Table 4**). Only 1 trial had no changes. ClinicalTrials.gov protocol changes for both major and minor changes had a median of 4 with a range of 1 – 83 (95% CI: 4 – 5). The most frequent major changes in RCTs from initial to last registration were in the scientific title (18.8%), date of first enrollment (13.8%), key secondary outcomes (12.6%) followed by health condition(s) (8.8%), primary outcome (8.8%), key inclusion (3.8%) and exclusion (2.6%) criteria. Out of the 3 trials that had a single major change in the protocol section, most of these changes occurred with the primary outcome element.

Table 4. Major changes in ClinicalTrials.gov registry fields for 8 WHO Minimum Data Set items from initial compared to last registration in 31 out of 80 RCTs with 1 or more changes.*

WHO Dataset item	Change	No. (%) trials
Item 10 - Scientific Title	Changed after initial registration	14 (17.5)
	Added after initial registration	1 (1.3)
	Total	15 (18.8)
Item 12 - Health condition(s)	Changed after initial registration	5 (6.3)
	Added additional	2 (2.5)
	Total	7 (8.8)
Item 13 - Intervention(s)	Code changed to generic name after initial registration	1 (1.3)
	Added an additional intervention	1 (1.3)
	Total	2 (2.6)
Item 14 - Inclusion criteria	One criterion deleted	2 (2.5)
	Added at last change before publication	1 (1.3)
	Total	3 (3.8)
Item 14 - Exclusion criteria	Two or more criteria deleted	1 (1.3)

	Added at last change before publication	1 (1.3)
	Total	2 (2.6)
Item 15 -Study type	Phase changed from phase 1/2 to phase 2	1 (1.3)
	Phase changed from phase 2 to phase 3	1 (1.3)
	Total	2 (2.6)
Item 16 - Date of first enrollment	Changed after initial registration to earlier date	6 (7.5)
	Changed after initial registration to later date	5 (6.3)
	Total	11 (13.8)
Item 19 - Primary outcome	Added at last change before publication	1 (1.3)
	Existing outcome deleted	6 (7.5)
	Total	7 (8.8)
Item 20 - Key secondary outcomes	Added at last change before publication	1 (1.3)
	Existing outcome deleted	9 (11.3)
	Total	10 (12.6)

Major changes in registered data were qualitative changes–the difference in the meaning of the information provided in a registry field or a quantitative change–difference in a numerical entry in a registry field.
[†]No changes recorded for Item 17 - Target sample size from initial to last registration.
[‡]1 trial had no recorded changes.

4.1.4 ***Completeness of WHO Minimum Data Set items in publications***

At initial registration unpublished and published trials had, just like at initial registration for all studies combined, the scientific title and secondary outcome fields were missing for 2 (2.5%) and 13

(16%) RCTs, respectively. Both unpublished and published trials were missing the scientific title field for 2.5% of RCTs while 14.8% of unpublished RCTs had omitted secondary outcomes at last registration.

4.1.5 *Changes to WHO Minimum Data Set items in publications*

Similar to WHO Minimum Data Set changes from first registration to last, where omissions and additions were common, omitted criteria for the key inclusion (90.5%) and exclusion (90.5%) criteria items were the most common changes in the publication compared to last registration for published RCTs (**Table 5**). Trials that had omitted registered secondary outcomes stated in publications were 19% along with other secondary outcome changes occurred in 12 (57.1%) published trials. Sixteen (76.2%) and 8 (38.1%) trials out of the 21 published RCTs that had a subsequent publication reported all registered primary and secondary outcomes, respectively.

When compared, unpublished studies had more changes than published trials to the scientific title (16.3% vs. 2.5%), date of enrollment (10.0% vs. 3.8%), secondary outcome(s) (8.8% vs. 3.8%), and primary outcomes (7.5% vs. 1.3%) Minimum Data Set items.

Table 5. Major changes in ClinicalTrials.gov RCT registry data found in published articles (n=21) compared to last registration.[*]

ICMJE/WHO Dataset item/change	Change	No. (%) of trials
Item 10 - Scientific Title	More informative[†] in article than in registry	9 (42.9)
	More informative in registry than in article	1 (4.8)
	Missing in registry	1 (4.8)
	Total	11 (52.3)
Item 13 - Intervention(s)	More informative in article	2 (9.5)
	Total	2 (9.5)
Item 14 - Inclusion criteria	New criteria added in article	6 (28.6)
	Criteria/on omitted in article	4 (19.0)
	More informative in article than in registry	6 (28.6)
	Added at last change before publication	3 (14.3)
	Total	19 (90.5)
Item 14 - Exclusion criteria	New criteria added in article	6 (28.6)
	Criteria/on omitted in article	9 (42.9)

	More informative in article than in registry	3 (14.3)
	Added at last change before publication	1 (4.8)
	Total	19 (90.5)
Item 15 -Study type	More informative in registry than article	1 (4.8)
	More informative in article than in registry	2 (9.5)
	Study design change	1 (4.8)
	Total	4 (19.0)
Item 16 - Date of first enrollment	Changed to later date (according to date in article vs. in registry)	2 (9.5)
	Changed to earlier date (according to date in article vs. in registry)	2 (9.5)
	Missing in registry or article	4 (19.0)
	Total	8 (38.1)
Item 17 - Target sample size	Smaller in article than in registry	1 (4.8)
	Total	1 (4.8)
Item 19 - Primary outcome	New outcomes introduced in article	1 (4.8)
	Registered outcomes omitted in article	1 (4.8)
	Outcomes switched, i.e., primary changed to secondary outcome in article	1 (4.8)
	Not reported separately from secondary outcomes (merged primary with secondary)	2 (9.5)
	New outcomes added at last change before publication	1 (4.8)
	Total	6 (28.6)
Item 20 - Key secondary outcomes	New outcomes introduced in article	3 (14.3)
	Secondary outcome changed to primary in article	1 (4.8)
	Stated in article but missing in registry	4 (19.0)
	Registered outcomes omitted in article	3 (14.3)
	Combo of newly introduced or omitted outcomes and difference in power calculation	1 (4.8)
	Total	12 (57.1)

[*]Major changes based on modified classification checklist from Chan et al. (42).
[†]More informative data in publications refers to more specific or clearer information (e.g., time frame adequately described for an outcome) than in ClinicalTrials.gov for the relevant registry item.

4.1.6 *Completeness of ClinicalTrials.gov results*

All 81 trials (100%) had a missing population description in the Baseline characteristics section at last registration in ClinicalTrials.gov, followed by 36 (44.4%) RCTs missing the study location country (**Table 6).** Sample size between the registry and publication was in 100% agreement, while agreement was 88% for participant gender, 75% for age and 44% for study location country (**Table 6**). The pre-assignment details field in the Participant flow section was the predominantly missing item in that results section for 42 (51.9%) trials. Eighty-six percent of participant trial completion flow data was congruent between registered and published data. Of the RCTs with different flow data between the registry and the publication (14%), participant discontinuation was noted solely in the publication or a fewer number of discontinued participants were listed in the registry for 2 (9.5%). Participant completion information was solely in the registry for 1 (4.8%) RCT (**Table 6**). Agreement between registered and published inferential statistical methods was 53.4% and 28.6% for primary and secondary outcomes, respectively. A comparison of registered versus published results revealed that for 1 (3%) trial (NCT01009619) the treatment was favored over placebo in the corresponding publication.

The median time from trial completion to publication for the 16 published trials was 19 months (6 – 56 months), 95% CI: 15 - 30. The time delay between trial completion and the search for the 21 publications included in the current study (September 2014) was 34.7 ± 20.9 months (mean ± SD).

Table 6. ClinicalTrials.gov participant flow, baseline measures, deaths, and participant discontinuation data in registered RCTs (n=81) and corresponding publications (n=21).

Results record element	No. RCTs (%)
Participant Flow	
ClinicalTrials.gov omitted recruitment details	40 (49.4)
ClinicalTrials.gov omitted pre-assignment details	42 (51.9)
ClinicalTrials.gov omitted reporting groups description	7 (8.6)
ClinicalTrials.gov omitted overall study flow	0 (0.0)
Trials with matching participant completion data in a publication compared to ClinicalTrials.gov	16 (76.2)
Baseline Measures	
ClinicalTrials.gov omitted population description	81 (100.0)
ClinicalTrials.gov omitted enrollment	0 (0.0)
Trials with matching enrollment in a publication compared to ClinicalTrials.gov	19 (90.5)
ClinicalTrials.gov omitted participant age	0 (0.0)
Trials with matching ages in a publication compared to ClinicalTrials.gov	14 (87.5)
ClinicalTrials.gov omitted participant gender	0 (0.0)
Trials with matching genders in a publication compared to ClinicalTrials.gov	17 (81.0)
ClinicalTrials.gov omitted location countries	36 (44.4)
Trials with matching location countries in a publication compared to ClinicalTrials.gov	10 (47.6)
Deaths	
Not reported in publication	0 (0)
Reported as zero or not occurring	5 (23.8)
Different absolute number and/or frequencies	0 (0)
More in publication	0 (0)
More in ClinicalTrials.gov	0 (0)
ClinicalTrials.gov participant deaths description compared to publication differs	0 (0)
Discontinuation due to an AE	
Different number in publication than in ClinicalTrials.gov	3 (14.3)
More in publication	2 (9.5)
More in ClinicalTrials.gov	1 (4.8)

4.1.7 *Adverse events reporting in ClinicalTrials.gov and publications*

One or more serious adverse events (SAEs) were reported for 38 (47%) RCTs in ClinicalTrials.gov and for 7 (33%) published trials whereas 54 (66.7%) and 15 (71.4%) other adverse events were reported in the registry and publication, respectively (**Table 7**). All 21 (100%) published RCTs reported SAEs in a corresponding publication and in ClinicalTrials.gov, but 1 (4.8%) trial had an incongruent number of SAEs when registry and publication data were compared. Of the 43 (53.1%) of RCTs that explicitly recorded the zero or non-occurrence of SAEs in the registry, only 5 (23.8%) of RCTs specified the zero or non-occurrence of SAEs in publications. Out of the trials, involving a drug intervention 4 (19%) reported the zero or non-occurrence of SAEs in publications. Descriptions of SAEs in ClinicalTrials.gov differed from published descriptions for 3 (14.3%) RCTs.

Trials with registered OAEs reported similarly in publications for all 21 (100%) RCTs with corresponding publications, however the registered number of OAEs disagreed for 13 (61.9%) RCTs (**Table 7**). Of these, the number of OAEs were greater in ClinicalTrials.gov for 2 (9.5%) and greater in publications for 11 (52.4) RCTs. Trials explicitly recorded other adverse events (OAEs) as zero for 32% of RCTs in the registry while only 4.8% of RCTs explicitly stated the zero or non-occurrence of OAEs in the publication. Out of the published trials involving a drug intervention, 5% reported the zero or non-occurrence of OAEs. Of the 13 (61.9%) trials with incongruent OAEs reporting, 10 (47.6%) and 3 (14.3%) in the registry and publication, respectively, reported a frequency threshold from 1% to 10%.

RCTs that explicitly stated that zero or no deaths occurred in the registry were 23.8% (**Table 7**). One publication (NCT01014013) reported only Treatment Emergent Adverse Events (TEAEs) for both SAEs and OAEs while another reported TEAEs for OAEs only as opposed to the total OAEs from the study. Two studies (NCT01068600 & NCT01072448) had combined SAE and AE descriptions in the corresponding publications.

Industry funded trials reported SAEs more often (n = 33, 40.7%) than non-industry funders (n = 3, 3.7%) in ClinicalTrials.gov. Industry funded trials reported OAEs for 43 (53.1%) RCTs while non-industry for 4 (4.9%) RCTs in the registry. Three (3.7%) trials had a single registry entry without further

changes and 32 (39.5%) underwent at least 1 change in the 8 WHO Minimum Data Set items from initial to last registration.

Overall for 81 trials, the median results reporting time was 12 months (range -1 to 158 months), 95% CI 11 – 12 (results were posted before the end date for 2 studies). Similarly, the median time for reporting results with OAEs was 12 months (range 1 – 158 months), 95% CI: 12 – 15 while it took a median of 12 months (95% CI: 11 – 14, range 1 – 158 months) for trials reporting SAEs to post results. Thirty-eight (46.9%) trials that reported both serious and other adverse events posted results over 12 months after initial registration.

Table 7. ClinicalTrials.gov results record summary of reporting completeness in registered RCTs (n=81) and corresponding publications (n=21).*

Results record element	No. RCTs (%)
Study results	
Population description	
ClinicalTrials.gov omitted primary outcome analysis inclusion type (intention-to-treat, per-protocol, other)	17 (21.0)
Trials with matching primary analysis inclusion type in a publication compared to ClinicalTrials.gov	
Intention-to-treat	4 (19.0)
Per-protocol	2 (9.5)
Other	2 (9.5)
ClinicalTrials.gov omitted secondary outcome analysis inclusion type	12 (14.8)
Trials with matching secondary analysis inclusion type in a publication compared to ClinicalTrials.gov	
Intention-to-treat	2 (9.5)
Per-protocol	1 (4.8)
Other	2 (9.5)
Primary outcome results	
Agreement between descriptive statistics used in registry vs. publication	0 (0) 0 (0)

Agreement between inferential statistics used in registry vs. publication	11 (53.4)
Larger treatment effect in publication	0 (0)
Larger treatment effect in ClinicalTrials.gov	0 (0)
Cannot be compared to heterogeneous statistical analysis	2 (9.5)
Secondary outcome results	
Agreement between descriptive statistics used in registry vs. publication	2 (9.5)
Agreement between inferential statistics used in registry vs. publication	6 (28.6)
Larger treatment effect in publication	1 (4.8)
Larger treatment effect in ClinicalTrials.gov	0
Cannot be compared to heterogeneous statistical analysis	0
Adverse Events	
Serious adverse events, registry vs. publication SAEs ≥ 1	
Not reported in publication	0
Reported as zero or not occurring	5 (23.8)
Different absolute number and/or frequencies	1 (4.8)
More in publication	0
More in ClinicalTrials.gov	1 (4.8)
ClinicalTrials.gov SAE description compared to publication differs	3 (14.3)
Other adverse events, registry vs. publication	
ClinicalTrials.gov omitted frequency threshold for which AEs are reported	0 (0)
Omitted frequency threshold for which AEs are reported in a publication	18 (85.7)
Not reported in publication	0
Reported as zero or not occurring	1 (4.8)
Different absolute number and/or frequencies	13 (61.9)
More in publication	11 (52.4)
More in ClinicalTrials.gov	2 (9.5)
ClinicalTrials.gov AE description compared to publication differs	9 (42.9)

*One publication was not a full article and thus was excluded. One publication (NCT01014013) reported Treatment Emergent Adverse Events (TEAEs) for both SAEs and OAEs while another (NCT01014585) reported TEAEs for OAEs only. Two studies (NCT01068600 and NCT01072448) combined SAE and AE descriptions in the publication.

4.1.8 *Characteristics of phase 3 and 4 trials in ClinicalTrials.gov and publications*

Out of the 81 trials that comprised our main study, 27 were phase 3 (32%) while 26 (32.1%) were phase 4 trials. Similar proportions of phase 3 compared with phase 4 trials started recruiting participants before registering the study (96% vs. 85%, *P*=.66) and had a parallel design (85.2% vs. 81%, *P*=.57) (**Table 8**). Our data show that phase 3 trials did not differ significantly from phase 4 trials for other various study characteristics. Phase 3 and phase 4 trials similarly were industry-sponsored (85% vs. 50%, *P*=.51), double blind (82% vs. 46%, *P*=.409) trials for treatment (89% vs. 85%, *P*=.22) conducted both in and outside the U.S. (20% vs. 23%, *P*=.29). The classification of safety/efficacy described both phase 3 and 4 trials almost equally (12% vs. 10%, *P*=.71). Drugs were the equally common intervention (81.5% vs. 81%, *P*=.24) for phase 3 and 4 trials. Over a third (n = 12, 44%) of phase 3 and over a quarter (n = 7, 26.9%) of phase 4 trials were multicenter, with a similar proportion of both female and male participants (93% vs. 89%, *P*=.87). The median sample size was 223 (95% CI: 89 – 511) for phase 3 trials, with a range of 12 to 2312 participants. Phase 3 trials reported SAEs in 19 (70.3%) trials. The median sample size was 75 (95% CI: 50 – 111), with a range of 16 to 340 participants. Eight (30.8%) phase 4 trials reported SAEs.

Table 8. ClinicalTrials.gov characteristics and trial publication data from phase 3 (n=27) and 4 (n=26) randomized controlled trials (RCTs).

	Phase 3 studies (No. trials, %)	**Phase 4 studies (No. trials, %)**	***P* value**
Study characteristics			
Pre-registered			
Yes	1 (3.7)	4 (15.4)	0.664
No	26 (96)	22 (84.6)	
Gender			
Female	0 (0)	1 (3.8)	
Male	2 (7.4)	2 (7.7)	0.868
Both	25 (93)	23 (88.5)	

Blinding			
None (open label)	4 (14.8)	5 (19.2)	
Double	22 (81.5)	12 (46.2)	0.409
Single	1 (3.7)	9 (34.6)	
Maximum participant age, median (range), years	65 (12 - 95)	70 (17 - 85)	0.121
Outcome measures			
Primary	27 (100)	26 (100)	
Defined	25 (93)	25 (96.2)	
Clinical	25 (93)	21 (80.8)	
Surrogate	1 (3.7)	0 (0)	
Secondary	24 (89)	21 (80.8)	
Defined	23 (85.2)	22 (80.8)	
Clinical	21 (77.8)	23 (80.8)	
Surrogate	1 (3.7)	24 (80.8)	
Mixture of both primary and secondary outcomes	24 (89)	25 (80.8)	
Center			
Single	15 (55.6)	19 (73.1)	
Multicenter	12 (44.4)	7 (26.9)	
Sample size, median (range)	223 (12 - 2312)	75 (16 - 340)	0.74
Control			
Open	16 (59.3)	16 (61.5)	0.659
Active	11 (40.7)	15 (57.7)	
Condition			
Bacterial and Fungal Diseases	0 (0)	1 (3.8)	
Behaviors and Mental Disorders	1 (3.7)	1 (3.8)	
Cancers and other Neoplasms	1 (3.7)	0 (0)	
Digestive System Diseases	1 (3.7)	0 (0)	
Diseases and Abnormalities at or before Birth	1 (3.7)	0 (0)	
Eye Diseases	1 (3.7)	3 (11.5)	
Heart and Blood Diseases	2 (7.4)	3 (11.5)	
Immune System Diseases	1 (3.7)	1 (3.8)	
Muscle, Bone, and Cartilage Diseases	0 (0)	1 (3.8)	

Nervous System Diseases	4 (14.8)	2 (7.7)	
Nutritional and Metabolic Diseases	2 (7.4)	2 (7.7)	
Respiratory Tract (Lung and Bronchial) Diseases	6 (22.2)	1 (3.8)	
Skin and Connective Tissue Diseases	1 (3.7)	1 (3.8)	
Substance Related Disorders	1 (3.7)	0 (0)	
Symptoms and General Pathology	1 (3.7)	3 (11.5)	
Urinary Tract, Sexual Organs, and Pregnancy Conditions	2 (7.4)	1 (3.8)	
Viral Diseases	0 (0)	0 (0)	
Wounds and Injuries	0 (0)	0 (0)	
Missing	2 (7.4)	6 (23.1)	
Design			
Single group	0 (0)	1 (3.8)	
Parallel	23 (85.2)	21 (80.8)	0.57
Cross-over	4 (14.8)	4 (15.4)	
Intervention name			
Specific	27 (100)	26 (100)	
Intervention type			
Drug	22 (81.5)	21 (80.8)	
Device	0 (0)	2 (7.7)	
Procedure/surgery	0 (0)	1 (3.8)	0.236
Biological and vaccine	3 (11.1)	1 (3.8)	
Other	2 (7.4)	0 (0)	
Classification			
N/A	5 (18.5)	3 (11.5)	
Safety	1 (3.7)	4 (15.4)	
Efficacy	7 (25.9)	5 (19.2)	
Safety/Efficacy	12 (44.4)	10 (37.0)	0.71
Bio-equivalence	1 (3.7)	1 (3.8)	
Pharmacodynamics	1 (3.7)		
Pharmacokinetics/dynamics	0 (0)	3 (11.5)	
Purpose			
Treatment	24 (89)	23 (85.2)	
Prevention	3 (11.1)	2 (7.7)	0.22
Screening	0 (0)	1 (3.8)	
Sponsor			
Non-industry	4 (14.8)	13 (50)	0.505
Industry	23 (85.2)	13 (50)	

Location			
Non-US only	11 (40.7)	16 (61.5)	
US only	8 (29.6)	7 (26.9)	0.29
Both US and non-US	20 (74.1)	23 (85.2)	
Not provided	7 (25.9)	3 (11.5)	
Study characteristics from published articles			
Number of published studies			
0	19 (70.3)	19 (70.3)	
1	5 (62.5)	6 (23.1)	
2	3 (11.1)	1 (3.8)	
Funding			
Identical to sponsor	1 (12.5)	2 (28.6)	
Not identical to sponsor	5 (62.5)	4 (57.1)	
Partially identical	2 (25)	1 (14.3)	
Ethics committee approval	27 (100)	26 (100)	
Adverse events			
Serious	4 (50)	0 (0)	
Other	4 (50)	4 (57.1)	
Trial aim			
Superiority	0 (0)	2 (28.6)	
Noninferiority	1 (12.5)	0 (0)	
Unstated or N/A	7 (87.5)	4 (57.1)	
Direction of outcome			
Negative	0 (0)	1 (14.3)	
Positive	1 (12.5)	0 (0)	
Both positive and negative	7 (87.5)	6 (85.7)	
Duration of the study			
Same as data in registry	2 (25)	3 (42.9)	
Longer duration than data in registry	1 (12.5)	1 (14.3)	
Shorter than data in registry (follow up was shorter)	4 (50)	2 (28.6)	
Different data in summary, methods and results of the article	1 (12.5)	1 (14.3)	

4.1.9 *Completeness of WHO Minimum Data Set items for phase 3 and 4 trials in ClinicalTrials.gov*

At initial registration in ClinicalTrials.gov, two (7.4%) phase 3 trials had a missing study country and one (3.7%) did not list secondary outcomes (3.7%). Initially in the registry phase 4 trials were missing data where 1 (3.8%) trial had a missing study country while 1 (3.8%) had at least one missing secondary outcome. At last registration, the number and type of missing data remained the same as at initial registration for phase 3 trials whereas no data were missing for phase 4 trials.

Nineteen studies remained unpublished for both phase 3 (70.3%) and 4 (73%) trials while 8 (29.6%) phase 3 and 5 (19.2%) phase 4 trials had one or more associated full publications (**Table 9**). The majority of phase 3 (n = 7, 25.9%) and 4 (15.4%) studies reported both positive and negative results. One (3.7%) phase 3 trial reported only positive results while 1 (3.8%) phase 4 trial reported only negative results. Phase 3 and phase 4 trials reported 19 (70.3%) and 7 (26.9%) serious adverse events (SAEs), respectively.

Regarding published SAEs, 5 (18.5%) phase 3 trials and 1 (3.8%) phase 4 trial reported them. Other adverse events (OAEs) were reported in 7 (25.9%) and 5 (19.2%) phase 3 and 4 trials, respectively. The funding source for half (50%) of the RCTs was not identical to the sponsor in publications for both phase 3 and 4 trials. Also for both phase 3 and 4 trials, the duration of 50% of trials was shorter in the publication than registered.

Table 9. ClinicalTrials.gov phase 3 (n=27) and phase 4 (n=26) randomized controlled trial (RCT) registry characteristics and trial publication data.

	No. RCTs (%)	
	Phase 3 trials	**Phase 4 trials**
Study results		
Population description		
ClinicalTrials.gov omitted primary outcome analysis inclusion type (intention-to-treat, per-protocol, other)	2 (7.4)	8 (30.8)
Trials with matching primary analysis inclusion type in a publication compared to ClinicalTrials.gov		
Intention-to-treat	1 (12.5)	2 (28.5)
Per-protocol	1 (12.5)	0 (0)
Other	2 (25)	0 (0)
ClinicalTrials.gov omitted secondary outcome analysis inclusion type	4 (50)	3 (43)
Trials with matching secondary analysis inclusion type in a publication compared to ClinicalTrials.gov		
Intention-to-treat	0 (0)	1 (14.3)
Per-protocol	0 (0)	0 (0)
Other	2 (25)	0 (0)
Primary outcome results		
Agreement between descriptive statistics used in registry vs. publication	0 (0)	0 (0)
Agreement between inferential statistics used in registry vs. publication	5 (62.5)	4 (57.1)
Larger treatment effect in publication	0 (0)	0 (0)
Larger treatment effect in ClinicalTrials.gov	0 (0)	0 (0)
Cannot be compared to heterogeneous statistical analysis	0 (0)	0 (0)
Secondary outcome results		
Agreement between descriptive statistics used in registry vs. publication	0 (0)	1 (14.3)
Agreement between inferential statistics used in registry vs. publication	2 (25)	3 (43)
Larger treatment effect in publication	0 (0)	1 (14.3)

Larger treatment effect in ClinicalTrials.gov	0 (0)	0 (0)
Cannot be compared to heterogeneous statistical analysis	0 (0)	0 (0)
Adverse Events		
Serious adverse events, registry vs. publication, n=19		
SAEs ≥ 1		
Not reported in publication	0 (0)	0 (0)
Reported as zero or not occurring	2 (25)	1 (14.3)
Different absolute number and/or frequencies	1 (12.5)	1 (14.3)
More in publication	1 (12.5)	
More in ClinicalTrials.gov	0 (0)	1 (14.3)
ClinicalTrials.gov SAE description compared to publication differs	2 (25)	1 (14.3)
Other adverse events, registry vs. publication, n=22		
ClinicalTrials.gov omitted frequency threshold for which AEs are reported	0 (0)	0 (0)
Omitted frequency threshold for which AEs are reported in a publication	5 (62.5)	7 (100)
Not reported in publication	0 (0)	0 (0)
Reported as zero or not occurring	5 (62.5)	1 (14.3)
Different absolute number and/or frequencies	6 (75)	4 (57.1)
More in publication	5 (62.5)	3 (43)
More in ClinicalTrials.gov	1 (12.5)	1 (14.3)
ClinicalTrials.gov AE description compared to publication differs	5 (62.5)	3 (43)

4.1.10 *Results disclosure for phase 3 and 4 trials*

Phase 3 (n = 10, 37.0%) and 4 (n = 16, 61.5%) trials had an embargo on the reporting of results. Trials without any restriction on the reporting of data included 14 (51.9%) phase 3 and 3 (11.5%) phase 4 trials. Phase 3 and phase 4 trials that had no agreement were 2 (7.4%) and 5 (19.2%). Almost a quarter (n = 6, 23%) of phase 3 industry-sponsored trials had an embargo on the publication results. Of the 13 (50%) industry-sponsored phase 4 RCTs, the majority (n = 9, 34.6%) had an embargo on the reporting of results.

4.1.11 *Changes to Minimum Data Set items during the trial for phase 3 and phase 4 trials*

There were changes during the conduct of the trial to 7 out of 9 WHO Minimum Data Set items to all phase 3 (n = 27) and 4 (n = 26) RCTs; no changes were recorded for the health conditions element from initial to last registration (**Table 10**). The most frequent major changes occurred in phase 4 RCTs from initial to last registration with changes to the study design and the addition of new secondary outcomes (both at n = 4, 15.4%) for phase 4 trials (**Table 10**). Other changes that followed involved the deletion of existing secondary outcomes (n = 3, 11.1%) for phase 3 trials and the addition of new primary outcomes (n = 3, 11.5%) for phase 4 trials.

Table 10. Major changes in ClinicalTrials.gov registry fields for 7 WHO Minimum Data Set items from initial compared to last registration in phase 3 (n = 27) and phase 4 (n = 26) trials.

WHO Minimum Dataset item	Change	Phase 3	Phase 4
Item 9 – Brief title	Changed after initial registration	1 (3.7)	1 (3.8)
Item 10 – Scientific Title	Changed after initial registration	1 (3.7)	0 (0)
Item 15 – Study type	Study design change	0 (0)	4 (15.4)
Item 17 – Target Sample Size	Smaller at last registration	2 (7.4)	0 (0)

Item 16 – Date of first enrollment	Changed after initial registration to earlier date	1 (3.7)	1 (3.8)
Item 19 – Primary outcome			
	Added at last change before publication	0 (0)	1 (3.8)
	New outcome added	0 (0)	3 (11.5)
	Changed to secondary	2 (7.4)	0 (0)
Item 20 – Key secondary outcomes	New outcome added	0 (0)	4 (15.4)
	Added at last change before publication	0 (0)	1 (3.8)
	Existing secondary outcome deleted	3 (11.1)	0 (0)

4.1.12 *Changes to WHO Minimum Data Set items in publications for phase 3 and 4 trials*

The most common changes in the publication compared to last registration for published phase 3 RCTs involved the scientific title (n = 5, 62.5%) and the introduction of new secondary outcomes (n = 6, 75%) (**Table 11**). As the predominant change in phase 4 trials, four (57.1%) trials had introduced new secondary outcomes in an article.

Table 11. Major changes in ClinicalTrials.gov RCT registry data compared to last registration in published phase 3 (n = 8) and 4 (n = 7) studies.

		No. (%) of trials	
ICMJE/WHO Dataset item/change	**Change**	**Phase 3**	**Phase 4**
Item 10 - Scientific Title	More informative in article than in registry	5 (62.5)	0 (0)
Item 12 - Health Condition(s)	Changed in article	0 (0)	1 (14.3)
Item 14 - Inclusion criteria	New criteria added in article	2 (25)	2 (28.6)
	Criteria/on omitted in article	3 (37.5)	1 (14.3)
	More informative in article than in registry	3 (37.5)	1 (14.3)
	Added at last change before publication	3 (37.5)	0 (0)
Item 14 - Exclusion criteria	New criteria added in article	2 (25)	2 (28.6)
	Criteria/on omitted in article	7 (87.5)	1 (14.3)
	More informative in article than in registry	1 (12.5)	1 (14.3)
	Added at last change before publication	1 (12.5)	0 (0)
Item 15 -Study type	More informative in registry than article	0 (0)	1 (14.3)
	Study design change	1 (12.5)	0 (0)
Item 16 - Date of first enrollment	Changed to later date (according to date in article vs. in registry)	2 (25)	0 (0)

Changed to earlier date (according to date in article vs. in registry)	1 (12.5)	0 (0)

	Missing in registry or article	1 (12.5)	1 (14.3)
Item 17 - Target sample size	Smaller in article than in registry	1 (12.5)	0 (0)
Item 19 - Primary outcome	New outcomes introduced in article	0 (0)	1 (14.3)
	Registered outcomes omitted in article	1 (12.5)	0 (0)
	Outcomes switched, i.e., primary changed to secondary outcome in article	0 (0)	0 (0)
	Not reported separately from secondary outcomes (merged primary with secondary)	0 (0)	1 (14.3)
	New outcomes added at last change before publication	0 (0)	0 (0)
Item 20 - Key secondary outcomes	New outcomes introduced in article	6 (75)	4 (57.1)
	Registered outcomes omitted in article	1 (12.5)	1 (14.3)
	Combo of newly introduced or omitted outcomes	1 (12.5)	0 (0)

4.1.13 *Completeness of ClinicalTrials.gov results for phase 3 and 4 trials*

All phase 3 and 4 trials (100%) had a missing population description in the Baseline characteristics section at last registration in ClinicalTrials.gov, followed by 4 (14.8%) phase 3 and 8 (30.7%) phase 4 trials with omitted location countries (**Table 12**). Sample size between the registry and publication was in 100% agreement for phase 3 trials, while 5 (71.4%) of phase 4 trials agreed. Regarding participant gender, 6 (75 %) phase 3 and 2 (28.6%) phase 4 trials agreed between the two sources. Two trials each for both phase 3 and 4 trials had matching location countries for 25% and 28.6% of trials, respectively.

Three-quarters of phase 3 trials had matching participant completion data in a publication compared to ClinicalTrials.gov. Eighty-six percent of participant trial completion flow data was congruent between registered and published data for phase 4 trials. Of the RCTs with different flow data between the registry and the publication 1 phase 3 trial (12.5%) and 2 (28.5%) phase 4 trials, 1 (12.5% vs. 28.5%) of each had more participants recorded in ClinicalTrials.gov. Additionally, 1 (14.3%) phase 4 trial had more participants recorded in the publication (**Table 12**).

Table 12. Characteristics of results about participants from phase 3 (n = 27) and phase 4 (n = 26) trials in ClinicalTrials.gov.

Results record element	No. RCTs (%)	
	Phase 3	Phase 4
Participant Flow		
ClinicalTrials.gov omitted recruitment details	16 (59.2)	9 (34.6)
ClinicalTrials.gov omitted pre-assignment details	13 (48.1)	13 (50)
ClinicalTrials.gov omitted reporting groups description	2 (7.4)	2 (7.7)
ClinicalTrials.gov omitted overall study flow	0 (0)	0 (0)
Trials with matching participant completion data in a publication compared to ClinicalTrials.gov	6 (75)	6 (85.7)
Baseline Measures		
ClinicalTrials.gov omitted population description	27 (100)	26 (100)

ClinicalTrials.gov omitted enrollment	0 (0)	0 (0)
Trials with matching enrollment in a publication compared to ClinicalTrials.gov (n=21)	8 (100)	5 (71.4)
ClinicalTrials.gov omitted participant age	0 (0)	0 (0)
Trials with matching ages in a publication compared to ClinicalTrials.gov (n=16)	2 (25)	4 (57.1)
ClinicalTrials.gov omitted participant gender	0 (0)	0 (0)
Trials with matching genders in a publication compared to ClinicalTrials.gov	6 (75)	2 (28.6)
ClinicalTrials.gov omitted location countries	4 (14.8)	8 (30.8)
Trials with matching location countries in a publication compared to ClinicalTrials.gov	2 (25)	2 (28.6)
Deaths		
Not reported in publication	0 (0)	0 (0)
Reported as zero or not occurring	3 (11.1)	1 (3.8)
Different absolute number and/or frequencies	0 (0)	0 (0)
More in publication	0 (0)	0 (0)
More in ClinicalTrials.gov	0 (0)	0 (0)
ClinicalTrials.gov participant deaths description compared to publication differs	0 (0)	0 (0)
Discontinuation due to an AE		
Different number in publication than in ClinicalTrials.gov	1 (12.5)	2 (28.5)
More in publication	0 (0)	1 (14.3)
More in ClinicalTrials.gov	1 (12.5)	1 (14.3)

Agreement between registered and published inferential statistical methods was 62.5% and 57.1% for phase 3 and phase 4 trials, respectively (**Table 13**). None of the descriptive analyses for the primary outcome for either phase 3 or phase 4 trials matched between the two sources. A comparison of registered versus published results revealed that for 1 phase 4 (14.3%) trial (NCT01009619) the treatment was favored over placebo in the corresponding publication.

4.1.14 *Adverse events reporting in ClinicalTrials.gov and publications for phase 3 and 4 trials*

One or more serious adverse events (SAEs) were reported for 19 (70.3%) phase 3 and 7 (26.9%) phase 4 RCTs in ClinicalTrials.gov. As for published SAEs, there were 5 (62.5%) phase 3 trials and 1 (14.3%) phase 4 trial. (**Table 13**). In ClinicalTrials.gov, 22 (81.4%) phase 3 and 15 (57.7%) phase 4 trials reported other adverse events (OAEs). There were 7 (87.5%) and 5 (71.4%) (OAEs) reported in publications. All phase 3 and 4 (100%) published RCTs reported SAEs in a corresponding publication and in ClinicalTrials.gov, but 2 trials had an incongruent number of SAEs when registry and publication data were compared (1 each of phase 3 (37.5%) and phase 4 (57.1%) trials). In trials without recorded SAEs in the registry, 2 (25%) and 1 (14.3%) reported them as explicitly not occurring.

Out of the 5 (62.5%) published industry-sponsored phase 3 RCTs, 2 (40%) explicitly stated the non-occurrence of SAEs while 1 (7.7%) RCT noted the explicit non-occurrence of SAEs out of the 13 (48.1%) industry-funded phase 4 RCTs. Trials with registered OAEs reported similarly in publications for all phase 3 and 4 trials (100%) RCTs with corresponding publications, however the registered number of OAEs disagreed for 6 (75%) phase 3 RCTs and 4 (57.1%) phase 3 RCTs (**Table 13**). Of these, the number of OAEs were greater in ClinicalTrials.gov for 1 (12.5% and 14.3%) of each phase 3 and phase 4 trials and greater in publications for 5 (62.5%) and 3 (43%) phase 3 and 4 RCTs, respectively. Other adverse events (OAEs) were explicitly recorded as zero for 5 (62.5%) phase 3 RCTs and 1 (14.3%) phase 4 RCT. RCTs that explicitly stated that zero or no deaths occurred in the registry were 3 (11.1%) phase 3 and 1 (3.8%) phase 4 trials (**Table 13**). One each phase 3 (12.5%) and phase 4 (14.3%) publication

(NCT01014013 and NCT 01014585) reported only Treatment Emergent Adverse Events (TEAEs) as OAEs only as opposed to the total OAEs from the study.

Table 13. ClinicalTrials.gov results record summary of reporting completeness in registered RCTs and corresponding publications in phase 3 and 4 trials (n=8 and n=7).

	No. RCTs (%)	
	Phase 3 trials	**Phase 4 trials**
Study results		
Population description		
ClinicalTrials.gov omitted primary outcome analysis inclusion type (intention-to-treat, per-protocol, other)	2 (7.4)	8 (30.8)
Trials with matching primary analysis inclusion type in a publication compared to ClinicalTrials.gov		
Intention-to-treat	1 (12.5)	2 (28.5)
Per-protocol	1 (12.5)	0 (0)
Other	2 (25)	0 (0)
ClinicalTrials.gov omitted secondary outcome analysis inclusion type	4 (50)	3 (43)
Trials with matching secondary analysis inclusion type in a publication compared to ClinicalTrials.gov		
Intention-to-treat	0 (0)	1 (14.3)
Per-protocol	0 (0)	0 (0)
Other	2 (25)	0 (0)
Primary outcome results		
Agreement between descriptive statistics used in registry vs. publication	0 (0)	0 (0)
Agreement between inferential statistics used in registry vs. publication	5 (62.5)	4 (57.1)
Larger treatment effect in publication	0 (0)	0 (0)
Larger treatment effect in ClinicalTrials.gov	0 (0)	0 (0)
	0 (0)	0 (0)
Cannot be compared to heterogeneous statistical analysis		
Secondary outcome results		
Agreement between descriptive statistics used in registry vs. publication	0 (0)	1 (14.3)
Agreement between inferential statistics used in registry vs. publication	2 (25)	3 (43)
Larger treatment effect in publication	0 (0)	1 (14.3)
Larger treatment effect in ClinicalTrials.gov	0 (0)	0 (0)

Adverse Events

Serious adverse events, registry vs. Publication	**Phase 3 trials**	**Phase 4 trials**
SAEs ≥ 1		
Not reported in publication	0 (0)	0 (0)
Reported as zero or not occurring	2 (25)	1 (14.3)
Different absolute number and/or frequencies	1 (12.5)	1 (14.3)
More in publication	1 (12.5)	
More in ClinicalTrials.gov	0 (0)	1 (14.3)
ClinicalTrials.gov SAE description compared to publication differs	2 (25)	1 (14.3)
Other adverse events, registry vs. Publication		
ClinicalTrials.gov omitted frequency threshold for which AEs are reported	0 (0)	0 (0)
Omitted frequency threshold for which AEs are reported in a publication	5 (62.5)	7 (100)
Not reported in publication	0 (0)	0 (0)
Reported as zero or not occurring	5 (62.5)	1 (14.3)
	6 (75)	4 (57.1)
Different absolute number and/or frequencies		
More in publication	5 (62.5)	3 (43)
More in ClinicalTrials.gov	1 (12.5)	1 (14.3)
ClinicalTrials.gov AE description compared to publication differs	5 (62.5)	3 (43)

The median time from trial completion to publication for the 8 published phase 3 trials was 20 months (17 – 1349 months), 95% CI: 17 – 1349, while it took phase 4 studies a median of 30 months (range 7 – 96 months), 95% CI: 7 - 96) to publish. For the 27 phase 3 trials the median results reporting time was 13 months (range 10 to 35 months), 95% CI 10 – 35. Phase 4 studies reported results similarly at a median of 13 months (range 1 – 91 months), 95% CI: 9 – 16. The median time for phase 3 studies reporting results with OAEs was 13 months (range 9 – 1333 months), 95% CI: 24 – 86, while it took a median of 12 months (95% CI: 13 – 158, range 9 – 1333 months) for phase 3 trials reporting SAEs to post results. Likewise, phase 4 trials posted results with OAEs at a median of 12 months (range

24 months), 95% CI: 9 – 17 and it took a median of 14 months (range 9 – 18 months), 95% CI: 9 – 17 for trials with SAEs.

4.2 *Characteristics of studies describing adverse events in ClinicalTrials.gov*

Out of 100 trials that studied a drug intervention, pain was the most studied (n = 5, 5%) followed by major depressive disorder and acne vulgaris, (both n = 4, 4%) (**Table 14**). Most trials were randomized (n = 69, 69%). MedDRA was the most commonly used (n = 33, 33% and n = 50, 50%) dictionary to describe serious and other adverse events (SAEs and OAEs, respectively). Mostly, version 14 of MedDRA described adverse events in 9 trials each that recorded SAEs (33.3%) and OAEs (34.6%). Predominantly, 74 (74%) trials reported OAEs, whereas 47 (47%) reported SAEs. The majority (n = 58, 58%) of drugs were used for an FDA indication. Omitted medical terminology sources were 12 (12%) for trials with SAEs and 20 (20%) for OAEs. Of the 236 lay terms SAEs and 381 for OAEs, the same lay term defined up to 3 different adverse events in 8 (8%) and 69 (69%) trials, respectively.

Sixty-four studies (64%) were parallel studies for treatment (n = 80, 80%) and double blind (n = 43, 43%). Most were safety/efficacy studies, n = 46, 46%. Of these, 31 (67.4%) trials reported all SAEs in a systematic matter while 45 (97.8%) trials that reported OAEs recorded all OAEs in a systematic manner.

Table 14. Characteristics of trials in ClinicalTrials.gov reporting adverse events (n = 100).

Conditions	No. of trials (%)
Acne vulgaris	5 (5)
Post inflammatory hyperpigmentation	1 (1)
Acute back strain	1 (1)
Advanced solid tumor	1 (1)
Allergic conjunctivitis	1 (1)
Alzheimer's disease	1 (1)
Asthma	3 (3)
Bronchial hyperresponsiveness	1 (1)

Attention deficit disorder with hyperactivity	2 (2)
Insomnia	1 (1)
Breast cancer	1 (1)
Brittle nail syndrome	1 (1)
Chemotherapy-Induced Nausea and Vomiting	1 (1)
Chronic kidney disease	1 (1)
Chronic lymphocytic leukemia	1 (1)
Chronic myelogenous leukemia	1 (1)
Philadelphia chromosome positive acute lymphoblastic leukemia	1 (1)
Chronic obstructive pulmonary disease	3 (3)
Conjunctivitis	1 (1)
Keratitis	1 (1)
Blepharitis	1 (1)
Diabetes	3 (3)
Diabetes mellitus, type 1	1 (1)
Hypertension	2 (2)
Dry eye syndromes	1 (1)
Keratoconjunctivitis sicca	1 (1)
Epilepsy	2 (2)
Erectile dysfunction	2 (2)
Essential hypertension	1 (1)
Exercise induced asthma	1 (1)
Falciparum malaria	1 (1)
Fibromyalgia	1 (1)
Gastric motility disorder	1 (1)
Glaucoma	1 (1)
Ocular hypertension	1 (1)
Head lice	3 (3)
Healthy volunteers	1 (1)
Helicobacter pylori infection	1 (1)
Hepatitis C	1 (1)
HIV infections	2 (2)
Dyslipidemia	1 (1)
Endothelial dysfunction	1 (1)

Hypertriglyceridemia	1 (1)
Impaired fasting glucose	1 (1)
Inflammation	2 (2)
Liver dysfunction	1 (1)
Liver transplantation	1 (1)
Major depressive disorder	4 (4)
Non erosive reflux disease	1 (1)
Chronic gastritis	1 (1)
Osteoarthritis knee pain	1 (1)
Pain	7 (7)
Perennial allergic rhinitis	4 (4)
Plaque psoriasis	1 (1)
Pneumonia, bacterial	1 (1)
Post operative anterior chamber inflammation (flare)	1 (1)
Post operative pain	1 (1)
Prevention	1 (1)
Pterygium	1 (1)
Pulmonary arterial hypertension	2 (2)
Recurrent abortion	1 (1)
Recurrent respiratory papillomatosis	1 (1)
Restless legs syndrome	1 (1)
Rheumatoid arthritis	2 (2)
Seasonal allergic rhinitis	5 (5)
Secondary hyperparathyroidism	1 (1)
Sedation	1 (1)
Skin and soft tissue infections	1 (1)
Skin manifestations	3 (3)
Smoking	1 (1)
Sore throat	1 (1)
Stable plaque psoriasis	1 (1)
Urogential chlamydia trachomatis infection	1 (1)
Vulvovaginal candidiasis	1 (1)
Wrinkles	2 (2)

End Point Classification	
Efficacy	30 (30)
Safety	8 (8)
Efficacy/Saftey	46 (46)
Unlisted	16 (16)
Allocation	
Non-randomized	3 (3)
Randomized	70 (70
Model	
Crossover	5 (5)
Factorial assignment	1 (1)
Parallel assignment	64 (64)
Single group assignment	14 (14)
Purpose	
Basic science	1 (1)
Prevention	3 (3)
Treatment	80 (80)
Drug class	
Antidepressants	1 (1)
Analgesics or anesthetics	22 (22)
Anti-inflammatory agents	17 (17)
Antineoplastic agents	9 (9)
Enzyme inhibitors	13 (13)
Hypoglycemic agents	2 (2)
Neuromuscular agents	2 (2)
Antidepressants	6 (6)
Anti-allergics	6 (6)
Anti-infectives	22 (22)

4.2.1 *Finding unsourced adverse event terms from ClinicalTrials.gov*

Five (5%) studies that reported SAEs did not list a specific version of the dictionary used (**Table 15**). One (1%) study reporting SAEs did not list the name of the dictionary but listed a version number. Six (6%) trials listed MedDRA as the source of the vocabulary for the OAEs, but trials did not list a specified version. An unspecified version of SNOMED CT was used in 1 (1%) trial. Similar to SAEs, 1 (1%) trial that reported OAEs stated the version of the dictionary used without explicitly stating the dictionary.

Table 15. Description of the sources of the adverse events terminology in ClinicalTrials.gov.

	No. of trials (%)
Adverse Events	
Serious	46 (46)
Other	74 (74)
Reported frequency threshold	
0%	22 (22)
1%	9 (9)
2%	11 (11)
3%	2 (2)
5%	56 (56)
Medical Terminology Source and Version	
Serious adverse events	
MedDRA	
Version 10.0	4 (4)
Version 12.0	7 (7)
Version 12.1	5 (5)
Version 13.0	3 (3)
Version 13.1	2 (2)
Version 14.0	8 (8)
Unstated version	4 (4)
SNOMED CT	
Versions 2008AA - 2012AB	0 (0)
CTCAE	
Version 3	1 (1)
Other adverse events	
MedDRA	
Version 10.0	4 (4)

Version 10.1	1 (1)
Version 11.0	3 (3)
Version 12.0	6 (6)
Version 12.1	5 (5)
Version 13.0	9 (9)
Version 13.1	4 (4)
Version 14.0	8 (8)
Unstated version	6 (6)
SNOMED CT	
Versions 2008AA - 2012AB	1 (1)
Unstated version	1 (1)
CTCAE	
Version 3	1 (1)

4.2.2 *Matching adverse event terminology with lay terms from ClinicalTrials.gov*

Of the 236 lay terms for SAEs and 381 for OAEs, the same lay term defined up to 3 different adverse events in 11 (11.%) and 57 (66%) trials, respectively. Specifically, the same type of SAEs that 2 terms described included infections/infections and infestations, heart/cardiac failure, fever/pyrexia, ovarian cancer/ovarian adenoma, each of the paired terms were used in a total of 8 (8%) trials. Three different lay terms defined the same OAE describing a feeling of tiredness as fatigue, asthenia, and lethargy for 16 (16%) trials and 3 terms described a cold as a common cold, an upper respiratory tract infection, and a head cold in 24 (24%) trials. The same type of OAEs that were described by 2 terms were for eye itching (eye pruritus/eye irritation), ear infection (otitis media/ear infection), and sore throat (oropharyngeal pain/sore throat) for 17 (17%) trials.

5. Discussion

Our study demonstrated that discrepancies continue to exist in the reporting of data in ClinicalTrials.gov registered RCTs, despite more than 10 years of ICMJE mandatory registration policy and 7 years of FDAAA legislation. Our assessment of registered and published WHO Minimum Data Set item completeness and changes in addition to results completeness is unique in providing a comprehensive view of data reporting in both the registry and subsequent publications. Only one study (10) to date evaluated 9 WHO Minimum Data Set changes from the initial to latest registered data at the time when the registration of results was not mandatory. Other studies that assessed essential WHO Minimum Data Set items in ClinicalTrials.gov either assessed only the latest registered WHO Minimum Data Set items or registered results completeness, but not changes during the conduct of the trial (17, 18). Furthermore, only selected Minimum Data Set items and results elements or other study characteristics considered important were reported in those studies (10, 17, 18, 21, 42, 47), whereas we completed a global assessment of completeness and changes in 9 WHO Minimum Data Set items registration and completeness of results elements essential to the determination of data reporting quality. Out of those, the secondary outcome and scientific title were the only missing items at initial and last registration. At last registration, 17% of RCTs had missing secondary outcomes while changes to the scientific title were most common, followed by changes to the date of enrollment element to an earlier date. Changes to primary and secondary outcomes mostly involved the deletion of existing outcomes. The most common last registration to publication changes were new criteria for the exclusion and inclusion criteria items added in a publication, followed by secondary outcome changes where the outcome was omitted in the registry but stated in the article. The number of both SAEs and OAEs disagreed with published data and explicit statements describing non-occurrence were absent in publications.

Similar to discrepancies surrounding the reporting of trial and participant data in ClinicalTrials.gov, our study found a deficiency in how adverse events are recorded in ClinicalTrials.gov. Our study of the source of adverse events in ClinicalTrials.gov was the first to assess the use of medical

terminology dictionaries in the registry. MedDRA defined most of the terms in trials with adverse events, but many trials failed to list the source of the terminology used. Users chose up to 3 different terms to describe the same adverse event, which leaves those terms unclear for lay people and a lack of consistency for comparison to other adverse events across studies. One recent systematic review observed the challenges in coding patient level data (48). Other studies analyzed the variability between versions of (27, 29, 48), the lack of specificity in locating adverse event terminology between dictionaries (25), or issues with coding patient level data (49), but no study to date has assessed the use of medical terminology in ClinicalTrials.gov. Trials omitted medical terminology sources for OAEs for 20% of trials without any notation of the source. Further, we found inconsistencies in the entry of the data in the adverse event tables where versions of the utilized dictionary remained unlisted (5% and 6%) or users failed to list the name of the dictionary (1% for both) SAEs and OAEs.

5.1 *Limitations*

We discuss several limitations in the current studies. The use of a single registry may question the external validity of the results, but ClinicalTrials.gov is the largest trials registry, with more than 180,000 registered trials as of February 2015. Second, the accuracy of data in the registry is the responsibility of the study investigator and it is difficult to assess it without the study's protocol. This may be addressed by recently proposed changes for the modification of section 801 of the FDAAA of 2007 (50), based on public referendum, for mandatory inclusion of original study protocols along with trial registry data for all clinical trials (50). Third, due to the retrospective design of the study where we assessed changes during the trial and in publications, data interpretation may be subjective, particularly for qualitative data regarding major changes in the WHO Minimum Data Set and results due to data collector characteristics and bias. Characterizing the drugs and adverse events in our study was also subject to bias. In this regard, a second reviewer independently extracted data in pilot studies to establish inter-rater agreement, determine clear rules for data entry and minimize subjective data collection. Fourth, we may have overlooked existing study publications, despite different search methods. Fifth, our sample sizes were

small for both studies thus; the changes or discrepancies recorded should be viewed with caution. Despite these limitations, we observed how data were reported in a transparent manner over the course of a clinical trial. Also, we evaluated the agreement in statistical analysis methods between registered and published results in the context of selective reporting as past research has shown favorable outcomes selection in clinical trials (47, 51, 52). Further, we highlighted the use of medical terminologies to describe adverse events in ClinicalTrials.gov, an important issue that stakeholders neglect.

5.1.1 *Completeness of registered and published data*

While previous studies reported prevalent omission of primary and secondary outcomes (34% and 40%, respectively for articles published in ICMJE journals (10) from 2005 to 2008, and 34% and 44% for registered trials in ClinicalTrials.gov (46) from 1999 to 2007) we found that primary outcomes in registered trials and any matching publications from 2009 to 2012 were not omitted at last registration, and that secondary outcomes were omitted for 19% of RCTs. Most omissions of registered and published data were of registered outcomes that appeared in the publication for 40% of RCTs for primary and 65% of RCTs for secondary outcomes. The differences may reflect an improvement in adherence to section 801 or ICMJE policy requirements for the registration of at least 1 primary outcome. The decrease in the number of registered secondary outcomes could be due to the lack of secondary outcomes or reporting for later reporting.

5.1.2 *Changes in published data*

At the publication level, we observed 38% of trials mostly involved a changed primary outcome to a secondary outcome while changes to 57% of RCTs mostly involved secondary outcome omissions in a publication. This contrasts the studies that found published outcome discrepancies between registered and published primary outcomes for 16% of RCTs and secondary outcomes for 9% of RCTs (18) and for 15% and 80% of RCTs in publications, respectively (17). Hannink and colleagues reported registered vs. published primary outcome differences that included published primary outcomes for 28% of RCTs, which also reported statistically favorable outcomes and primary outcome omissions for 21% of RCTs

(51). Our study also confirmed two previous reports that primary outcomes for 30% of RCTs were discrepant between the registry and publication, mostly to favor statistically significant results for RCTs that had disease-specific or focused interventions (21, 53).

Inconsistencies between the current study and these others in terms of outcome discrepancies indicate that selective reporting remains an issue regardless of the condition, intervention, or reporting in journals with a high-IF (17, 18, 47).Further, perhaps assessing the quality of data reporting in low-IF journals would contribute new information about the quality of reporting compared to high-IF journals, which represent higher quality research, are subjected to stricter peer-review, and are mainly members of the ICMJE (47, 54, 55).

The criteria used to determine primary outcome discrepancies could have played a role in the differences between our study and others. Becker et al. and Hartung et al. labeled outcomes as discrepant based on registered and published outcome descriptions and numerical differences (17, 18). We determined discrepant reporting in outcomes between the two sources using criteria that were more detailed as used by Chan et al. (42). Nonetheless, data reporting incongruence between registered and published data remained rather high.

5.1.3 *Adverse event reporting*

Adverse events were underreported in publications from most recent RCTs. All 21 (100%) published RCTs reported registered SAEs and OAEs in subsequent publications but an explicit statement describing the non-occurrence of SAEs or OAEs in publications to clearly discern the absence of both was missing for 76% of trials. This finding concurs with the omission or underreporting of the occurrence of adverse events (AEs) of more than a third of RCTs recently reported for FDAAA-covered RCTs completed almost 1.5 years after the results reporting mandate (17). Withholding or underreporting adverse events may betray clinical trial participants in that data from their contribution and experiences go undisclosed, which may affect future participation for clinical research studies in general (56-58). The number of OAEs was incongruent for over half of RCTs, but this could be attributed to frequency

threshold reporting. Regarding explicit death statements, 5 (24%) studies explicitly reported the non-occurrence of participant death. Over a third of trials with AEs reported results past the FDAAA results reporting deadline for trials with AEs.

5.1.4 *Nature of statistical analysis technique*

Discordance between registered and published descriptive and inferential statistical analysis technique was high. None of the registered primary outcome descriptive statistical methods used for the 21 (100%) published studies were used in subsequent publications. Only in 2 published trials (NCT01218958 & NCT01486615) the registered secondary outcome descriptive analysis matched the published analysis. Concerning inferential statistics, registered RCTs had a primary outcome discordance of 53% while secondary outcomes for 29% of RCTs were in disagreement. This prevalence is higher than reported for published RCTs between 2010 and 2011 where 16% of RCTs had primary outcome discordance between registered and published data (18). In 1 trial (NCT01009619) a larger treatment effect was reported in the publication. Incongruent statistical analyses between registered and published data is an alarming finding because sponsors or investigators may select and disclose favorable outcomes while concealing other comparisons that may better reflect how an intervention affects participants (5, 14, 46).

5.1.5 *Discrepancies in phase 3 and phase 4 trial data*

The same discrepancies that afflict studies in the main study also occur in these subsamples. Discrepancies in the reporting of data in mostly phase 3 trials underwent registry and publication level changes. Similar to the characteristics of the trials from the main study, the secondary outcome was mostly missing for both phase 3 and 4 trials at initial (n = 1 for both, 3.7% and 3.8%) and last registration. In addition, changes to the secondary outcome for both phase 3 and 4 studies during registration were the most common where 3 (11.1%) phase 3 trials omitted a previously registered outcome and 4 (15.4%) phase 4 trials added a new outcome after registration. At the publication level similar to findings from the main study, the most changes occurred for the scientific title (n = 5, 62.5%) and newly added secondary outcomes (n = 6, 75%)

for phase 3 studies. Similarly, many (n = 4, 57%) published phase 4 studies had newly added secondary outcomes.

Like the studies overall, many (75%) studies reporting SAEs did not explicitly report their non-occurrence in publications. Mirroring our main study findings regarding the nature of the statistical analysis, any descriptive analyses used in the registry were underreported in publications for phase 3 and phase 4. We found that the same type of omissions, changes, and underreporting that plagued the data from the main study occurred in both phase 3 and 4 studies. Phase 4 studies use an FDA approved drug, so it was surprising to observe similar discrepancies to phase 3 studies, which study non-approved drugs. However, the fact remains that discrepancies are rampant in the main trials as well as these subsamples.

5.2 *Prompting ClinicalTrials.gov to mandate the use of a source for medical terminology*

MedDRA was the predominant medical terminology used in 33% and 50% of trials describing SAEs and OAEs, respectively. Although consumers of MedDRA note several pitfalls regarding its use such as a lack of specificity (39) and unavailability in certain languages (30), it was the choice medical terminology in our study. Many studies reporting either SAEs (12%) or OAEs (20%) did not record a medical terminology in the adverse event table in ClinicalTrials.gov. Lay terms defined up to 3 adverse events in our study. With these issues in mind, perhaps the use of MedDRA, despite its drawbacks, or lay terms should be obligatory by ClinicalTrials.gov. The FDA may one day require industry-funded studies to use MedDRA, but until then studies describing adverse events, including those in ClinicalTrials.gov, may lack comparability.

5.3 *Implications of misconduct in the reporting of data from clinical trials*

Failure to report complete and quality results bears consequences, not only in the form of monetary fines and the restriction of NIH funds (9) but may lead to inappropriate conclusions about the effectiveness of drugs or treatments in the medical literature (16, 42, 59). Federal mandates for reporting increased clinical trial registration thus more studies are visible to the public, however, the quality of registered data and the availability and publication of results are lacking. In response, the NIH is working

with the FDA on new rules surrounding clinical trials registration (50), which aim to expand clinical trial registration to more than just FDAAA-covered trials. The rules prompt for protocols with full or non-proprietary study results, more comprehensive primary and secondary outcome descriptions, increased clarity in the reporting of adverse events and death, and an extension of the results reporting deadline from 12 to 18 months (50). Such renewed efforts are required to ensure the transparency of data reporting from clinical trials. Two recent studies reported that researchers have varying interpretations of the FDAAA, institutional policies that may impede compliance, and a disregard of the law in the face of non-enforcement, which may explain the reasons for low compliance with the FDAAA and the additional need to augment laws surrounding data reporting (60, 61).

With these current proposed changes and the WHO statement (62), the potential for ClinicalTrials.gov to provide unambiguous and transparent data reporting may help limit selective reporting. In regard to ICMJE requirement for registration as a stipulation for publication to reduce possible selection bias (12), evidence shows that completed trials with positive results get submitted faster than trials with negative results leading to "lag-time bias" where studies with positive or significantly significant results are available before trials that may have more clinically meaningful results (47, 52, 63-68). Notably, the majority (94%) of the RCTs in the current study were not prospectively registered which potentially precludes these studies from transparent reporting. Whether researchers withhold non-significant or negative outcomes from ClinicalTrials.gov or publications remains unclear. However, without a full study protocol available for comparison with registered data, patients, researchers, and allied health professionals must accept the data in ClinicalTrials.gov at face value. Protocol inclusion is already a stipulation for the publication of RCTs in several ICMJE member medical journals such as the *BMJ*, *Lancet*, and *PLOS Medicine* (47).

In the background of federal and international mandates regarding clinical trials registration and results reporting, this study showed that some minor improvements in data completion occurred over time, as compared to previous studies (10, 53). Aligned with basic results reporting mandated by the FDAAA,

all trials in our study reported at least 1 primary outcome at last registration and reported participant age, gender, and adverse events but 3 (3.7%) trials involving a drug intervention failed to report the age of the participants. Of note, all of the studies in our sample had an omitted population description for Baseline Characteristics in the ClinicalTrials.gov results section at last registration. Possibly the field is optional by ClinicalTrials.gov and FDAAA or researchers view the field as redundant. Additionally, Clinicaltrials.gov does not provide a field to record participant deaths, which leaves room for sponsors to omit or underreport deaths, which may cause doubt surrounding drug safety (69).

The majority (74%) of the studies in our sample remained unpublished after a median of 19 months (95% CI 15–30), comparable to a reported third of clinical trials in a ClinicalTrials.gov sample remaining unpublished after 4 years (69). Another study noted that over a quarter of registered vaccine clinical trials remained unpublished after 2 years (70). Perhaps the potential public release of proprietary drug information or other results release restrictions (30% of RCTs in our study) impede subsequent trial data publication. In addition, the results of clinical trials registered in ClinicalTrials.gov may also be reported solely as conference abstracts, which are sporadically available in many electronic bibliographic databases. For the current study, we chose not to attempt to search for conference abstracts, as electronic bibliographic databases may not contain a comprehensive listing. Consequently, many conference abstracts may be missed which may introduce bias.

6. Conclusions

We found discrepancies were quite high, despite FDAAA mandate and ICMJE registration requirements that both directly enforce registration and influence how that same data are disseminated in publications. Specifically,

1) primary and secondary outcome disagreements were high between registered and published outcomes regarding omissions;
2) the nature (descriptive or inferential) of the statistical analysis technique between registered and published primary outcomes did not match for all 21 published trials;
3) the scientific title and secondary outcome were most commonly omitted items in the registry;
4) changes to the inclusion criteria at the publication level were frequent; and
5) the majority of studies was not pre-registered and remains unpublished.

Perhaps with recent proposed legislative reforms requiring more complete and transparent trial registration and results reporting, data reporting practices will further improve for the benefit of patients, clinicians, and researchers [37]. Additionally, advocates or organizations that observe trial registration, such as the Ottawa Statement group [46], could further follow the development of and predict trends in changes or discrepancies in data reporting for trials in an objective manner as a way to promote transparency [47]. Further improvements in ClinicalTrials.gov registration requirements with protocol inclusion and more stringent medical journal editor imposed requirements for publishing unambiguous data are needed to encourage transparent, complete, and quality data in order reduce the overestimation of drug effectiveness and selective reporting. Moreover, registries, medical journal editors, and governments should work in tandem to enforce trial registration before publication and congruent results reporting to monitor data reporting progression and quality as these strategies may reduce detriments to patient safety and data used for clinical decisions.

Administrators at ClinicalTrials.gov should stipulate the use of MedDRA or lay terms for describing adverse events.

1) MedDRA was the most commonly used adverse event terminology;
2) Studies omitted the source of adverse event terminology; and
3) Lay terms defined multiple adverse event terms.

MedDRA facilitates coding of adverse events or adverse drug reactions for health care practitioners, researchers, and other stakeholders in clinical research (24, 32). Although the most used medical terminology worldwide for coding of adverse events in electronic patient records, adverse event databases, or for product labeling (25-28), the deficiencies of MedDRA are noted in the literature (24, 25, 29, 38, 39, 48). With the patient-centered approach that embodies ClinicalTrials.gov, administrators should keep in mind that the use of lay terms may help patients and families meander through health information. Our study showed that data are discrepant in both ClinicalTrials.gov and published reports and stakeholders should enforce requirements for clear and quality data reporting in the registry.

7. Abstract

Aim: To assess effectiveness of legislative initiatives to stimulate registration of trial results by adherence to protocol and results reporting, changes to registry and publication data, and characteristics of adverse event reporting in randomized controlled trials (RCT) after introduction of the Food and Drug Administration Amendment Act (FDAAA).

Study Design and Setting: Study 1: observational cohort of registered FDAAA-covered RCTs in ClinicalTrials.gov between 2009 and 2012 and publications. Study 2: trials of antidepressants, analgesics/anesthetics, anti-inflammatories, antineoplastics, enzyme inhibitors, hypoglycemics, neuromusculars, antidepressants, anti-allergics, and anti-infectives.

Results: Secondary outcomes at initial and last registration were often omitted during registration. RCT registration changes mostly involved scientific title. Inclusion criteria omission was most common in publications. Inferential statistical methods for primary and secondary outcomes mismatched between registry and publication for many RCTs. Few trials with zero serious adverse events (SAEs) in registry published them as non-occurring. MedDRA was mostly used for SAEs and other adverse events. We found omitted medical terminology sources. A same lay term defined up to 3 different adverse events.

Conclusions: Discrepancies remain relatively high between registered and published outcomes as well as in the reporting adverse events even after 10 years after registration policy implementation. Underreporting and inconsistencies in the reporting of data from RCTs seriously undermine transparency of clinical trials and need immediate attention of all stakeholders in health research.

8. Sažetak

Cilj: U svrhu procjene učinkovitosti donošenja dodatnog protokola Američke agencije za hranu i lijekove (FDAAA, od engl. Food and Drug Administration Amendment Act) na javnu objavu rezultata kliničkih pokusa, ocijenili smo pridržavanje protokolu i objavu rezultata u repozitoriju, promjene u zapisu repozitorija i onih objavljenih u rukopisu, te opis i prijavu nuspojava u randomiziranim kliničkim pokusima (RCT, od engl. randomized clinical trials).

Tvoriva i ispitanici: Istraživanje 1.: opservacijska kohortna studija randomiziranih kliničkih pokusa koje je legalno pokrio FDAAA, a koji su bili registrirani u ClinicalTrials.gov repozitoriju od 2009. do 2012. godine. Istraživanje 2.: presječna studija kliničkih pokusa utvrđivanja učinkovitosti i sigurnosti antidepresiva, analgetika, anestetika, protuupalnih lijekova, protutumorskih lijekova, inhibitora enzima, hipoglikemika, neuromuskulatornih lijekova, lijekova protiv alergije, te antimikrobnih lijekova.

Rezultati: Zamjenske mjere ishoda su većinom bile ispuštene u prvoj ili posljednjoj verziji zapisa u repozitoriju, dok je najčešća promjena u repozitoriju bila promjena naslova istraživanja. U objavljenim člancima najčešće su nedostajali kriteriji uključenja ispitanika, ali su postojale i razlike u predviđenim i upotrijjebljenim statističkim metodama. Samo nekoliko istraživanja je i u registru i objavljenom rukopisu naglasilo izostanak nuspojava. Rječnik MedDRA je najčešće korišten za opis teških i svih drugihnuspojava, ali je bilo istraživanja koja nisu navela korišteni rječnik. Nekoliko istih laičkih izraza upotrijbljeno je za opis i do triju različitih nuspojava.

Zaključci: I nakon donošenja dodatnog protokola, razlike u repozitoriju i objavljenim rukopisima ostale su još uvijek velike, uključujući i navođenje nuspojava. Takve razlike i nedosljednosti ozbiljno narušavaju transparentnost kliničkih pokusa i zahtijevaju hitnu reakciju svih dionika uključenih u zdravlje ljudi.

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10. Curriculum Vitae

EDUCATION

- Doctor of Philosophy (2011 – present), **University of Split School of Medicine**, Split, Croatia
- Master of Science in Public Health (2003 – 2008), **Thomas Jefferson University, Jefferson School of Population Health**, Philadelphia, Pennsylvania, USA
- Bachelor of Arts in Biology (1997 – 2001), **Ithaca College**, Ithaca, New York, USA

RESEARCH AND WORK EXPERIENCE

- Lecturer, **University of Split School of Medicine**, Split, Croatia, 2009 - present
- Laboratory Manager, **Mediterranean Institute for Life Sciences (MedILS)**, Split, Croatia, May 2007 – January 2010
- Laboratory Manager, **Thomas Jefferson University**, **Jefferson Medical College**, Department of Pathology, Anatomy and Cell Biology, Philadelphia, Pennsylvania, USA, October 2001 – March 2007

INTERNSHIP AND VOLUNTEER EXPERIENCE

- Fellow, **Elsevier Publishing Company**, **European Cooperation in Science and Technology (COST), New Frontiers of Peer Review (PEERE)**, Amsterdam, Netherlands, February – March 2016
- Clinical Research Assistant, **Children's Hospital of Philadelphia**, **Philadelphia Department of Public Health**, Varicella Active Surveillance Project, St. Leonard's Court Clinic, Philadelphia, Pennsylvania, USA, October 2005 – January 2006

- Youth Counselor, **Thomas Jefferson University**, **Jefferson Medical College**, Jeff Elect (student organization), Philadelphia, Pennsylvania, USA, April 2004
- Research Assistant, **University of Pennsylvania Perelman School of Medicine**, Division of Endocrinology, Diabetes, and Metabolism, Biomedical Graduate Studies Summer Internship Program, Philadelphia, Pennsylvania, USA, June 2000 – August 2000

PUBLICATIONS

- **Pranic S**, Marusic A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. *J Clin Epidemiol*. 2016; 70:26-37.
- Rakovac M, Pedisic Z, **Pranic S**, *et al*. Sociodemographic and lifestyle correlates of health-related quality of life in Croatian university students. *Appl Res Qual Life*. 2013 Dec;8(4): 493-509.
- Pedisic Z, **Pranic S**, *et al*. Relationship of back and neck pain with quality of life in the Croatian general population. *J Manipulative Physiol Ther*. 2013 Jun; 36(5):267-75.
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- Stojanović-Špehar S, Blažeković-Milaković S, Jokić-Begić N, **Pranić SM**, *et al*. Unaided general practitioners' clinical diagnosis in evaluation of depressive patients: a pilot study. *Psychiatr Danub*. 2010 Dec;22(4):535-9.
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CONFERENCES AND POSTER PRESENTATIONS

- **Pranić S**, Mahmić-Kaknjo M, Marušić A. Use of medical terminologies to describe adverse event terms in ClinicalTrials.gov. Poster session presented at: The 13th European Association of Science Editors (EASE) Conference. 2016 June 12; Strasbourg, France.
- **Pranić S**, Mahmić-Kaknjo M, Marušić A. Use of medical terminologies to describe adverse event terms in ClinicalTrials.gov. Poster session presented at: The Eighth Croatian Cochrane Symposium. 2016 May 9; Split, Croatia.
- **Pranic S**, Marusic A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. Poster session presented at: The Eighth Croatian Cochrane Symposium. 2016 May 9; Split, Croatia.
- Jerončić Tomić I, **Pranic S**, Vučica I, Smoljanović M. Some characteristics of mental illness and behavioral disorders in people aged 65 years and above in Split-Dalmatia County. Poster session presented at: The 4th Health for All Professional and Scientific Symposium. 2016 May 6; Rijeka, Croatia.
- **Pranic S**, Marusic A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. Paper presented at: The World Association of Medical Editors (WAME) International Conference for Medical Journal Editors. 2015 October 1 – 4; New Delhi, India.
- **Pranic S**, Marusic A. Changes to registration elements and results in a cohort of Clinicaltrials.gov trials were not reflected in published articles. Paper presented at: Research Waste/EQUATOR

Conference. Increasing value and reducing waste in biomedical research conference. 2015 September 28 – 30; Edinburgh, Scotland.

- Jerončić Tomić I, Mulić R, **Pranić S**. Lifestyle or heritage: historical context of gout and incidence specificity on the Dalmatian Islands. Health and Culture Symposium. Paper presented at: The 24th Symposium of Frane Petrić. 2015 September 22; Cres, Croatia.

ADDITIONAL CAREER DEVELOPMENT ACTIVITIES

2007: Workshop Instructor, Mediterranean Institute for Life Sciences (MedILS) Summer School, Split, Croatia, July, 2007.

2009: Attendee, MedILS Molecular Biology Conference, Split, Croatia, July, 2009.

Attendee, First Croatian Cochrane Symposium, Split, Croatia, May, 2009.

2010: Textbook Lector, *Geriatric Pharmacotherapy - the Use of Drugs in the Elderly*, CT-poslovne informacije LLC, Zagreb, Croatia, March, 2010.

2013: Attendee, Fifth Croatian Cochrane Symposium, Split, Croatia, May, 2013.

2015: Attendee, European Cooperation in Science and Technology (COST) "Disaster Bioethics" Workshop, April 27 – 28, 2015.

2015: Attendee, Seventh Croatian Cochrane Symposium, Split, Croatia, May 2015.

2015: Attendee, European Cooperation in Science and Technology (COST), New Frontiers of Peer Review (PEERE) Workshop, University of Split, Split, Croatia, June 16 – 18, 2015.

2016: Attendee, 'How to Assess a Meta-analysis' lecture, Prof. Will G. Hopkins, University of Split, Split, Croatia, March 16, 2016.

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