regCOVID: Tracking publications of registered COVID-19 studies

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Abstract

In response to the COVID-19 pandemic many clinical studies have been initiated leading to the need for efficient ways to track and analyze study results. We expanded our previous project that tracked registered COVID-19 clinical studies to also track result articles generated from these studies. We conducted searches of ClinicalTrials.gov and PubMed to identify articles linked to COVID-19 studies, and developed criteria based on the trial phase, intervention, location, and record recency to develop a prioritized list of result publications. We found 760 articles linked to 419 interventional trials (15.7% of all 2,669 COVID-19 interventional trials as of 15 August 2021), with 418 identified via abstract-link in PubMed and 342 via registry-link in ClinicalTrials.gov. Of the 419 trials publishing at least one article, 123 (29.4%) have multiple linked publications. We used an attention score to develop a prioritized list of all publications linked to COVID-19 trials and identified 58 publications that are result articles from late phase (Phase 3) trials with at least one US site and multiple study record updates. For COVID-19 vaccine trials, we found 69 linked result articles for 40 trials (13.9% of 290 total COVID-19 vaccine trials). Our method allows for the efficient identification of important COVID-19 articles that report results of registered clinical trials and are connected via a structured article-trial link.

Introduction

The COVID-19 pandemic led to the initiation of thousands of clinical studies testing various interventions and studying the natural course of the disease. For researchers or the public, it can be difficult to navigate and organize a large number of such studies. We previously created a framework for monitoring registered COVID-19 studies using ClinicalTrials.gov (CTG) registry, known as regCOVID.\textsuperscript{1,2} The framework uses data science methods that computationally identifies COVID-19 clinical studies using a keyword search. The framework also uses a computerized code to regularly monitor and analyze key features relating to COVID-19 interventional trials, observational studies, and patient registries registered at CTG.

A study may publish three types of information: (1) registration data at study initiation (in a clinical trial registry, such as CTG), (2) basic summary results at study completion (in a clinical trial registry), or (3) an article with well commented full study results (in a journal). Prior analyses of phase-2-or-higher interventional trials indicate that only 27.8% publish a study result article.\textsuperscript{3} A completed study with one or more study results journal articles provides the most value to researchers and the public. Poor information about study status or study results may lead to reduced public trust in clinical trials enterprise.\textsuperscript{4}

In this study, we extended our regCOVID monitoring project to now identify study result articles that are linked to registered COVID-19 trials.\textsuperscript{1,3} Since the total amount of all published COVID-19 articles may be overwhelming, we propose focusing only on articles that are linked to formally registered studies to facilitate an effective review of COVID-19 scientific literature. Unlike many efforts that use predominantly manual review to provide the public with an overview of trials and their results, we use a computational clinical research informatics approach to assess which COVID-19 studies are publishing, what they are
Materials And Methods

Our project repository (available at https://github.com/lhncbc/r-snippets-bmi/tree/master/regCOVID/regCOVIDpublications) includes our computer code, supplemental files, analysis results and a detailed web-based results report. We also refer to the project using a short name of regCOVIDpub. Throughout methods and results, we reference supplemental files on the project repository by the file name. The script is written in R language. For result reports, we use R Markdown framework. For most analyses, the repository will offer monthly refreshed results.

To find result articles linked to COVID-19 clinical studies we perform three high-level steps. In the first step, we identify all COVID-19 studies. In the second step we attempt to gather all published study result articles linked to those studies, and in the third step, we retrieve additional metadata about the articles and their affiliated studies and create a prioritization scoring system to identify the most significant publications. The sections below elaborate on details of each high-level step.

COVID-19 Studies

For the first step we retrieved all COVID-19 studies (see supplemental file ‘../regCOVIDpublications_trials_all.csv’ in the study repository) using the results of our previously published work on tracking registered COVID-19 clinical studies (regCOVID). We considered eligible studies to be a COVID-19 interventional trial, observational study or registry, that was recruiting, active, or ended (completed or terminated) and registered at CTG.

Identification of COVID-19 research articles

Once we identified the eligible studies, in the second step, we searched for publications linked to each study using two different methods: registry-linked and abstract-linked. This methodology is based on prior published work by our research group. We describe each article linkage mechanism separately below.

Registry-linked result article search

Registry linked result articles are those included in the study record on the CTG registry. We used the Aggregate Analysis of ClinicalTrials.gov (AACT) database developed by researchers at Duke University.
The AACT database is created by parsing the XML study data from CTG. We used the ‘result_reference’ XML field within the study record. Using prior knowledge that some result_reference articles are incorrectly labelled as such, we used article publication date to remove misclassified articles (that were actually of type ‘supporting_reference’). See this prior publication for details. We then linked the results publications found in the CTG study records to the PubMed abstract to identify key details about the article, such as article title and type. For context, a prior study on a set of 8,907 trials completed between 2006 and 2009 found that 7.3% of trials tend to have at least one registry-linked result article.

**Abstract-linked result article search**

Abstract linked articles are those where authors of trial result articles follow guidance of the International Committee of Medical Journal Editors and reference properly the relevant trial identifier in the article abstract. This reference is processed by PubMed and turned into searchable article metadata (called secondary identifier). We retrieved abstract linked articles by a metadata search in PubMed as articles where the article secondary identifier contained a CTG identifier (NCT ID) of a COVID-19 trial. For context, the same previously mentioned prior study found that 23.3% of trials tend to have abstract-linked result articles.

We combined the lists of publications from these two search methods to generate a master list of linked COVID-19 articles (see supplemental file ‘regCOVIDpublications_publication_list_all.csv’). The master publication list allows for an enhanced review of the resulting articles. It combines PubMed and CTG data and shows the trial NCT identifier, PubMed PMID identifier, trial intervention (e.g., convalescent plasma), article keywords using Medical Subject Headings (MeSH), trial sponsor (e.g., University of Oxford) and many other article or trial metadata. We separated the article set based on study type and performed the rest of the analysis on just interventional trials, as they are the most relevant trials (at this point in the pandemic) and the main focus of our study.

**Analysis of publications**

**Interventions**

The intervention being studied (e.g., remdesivir) in a trial and discussed in a publication contributes to how significant the publication is in the research landscape. Interventions must progress through the phases of interventional trials (phase 1/2/3) to receive regulatory approval for a given indication. Different interventions were studied for COVID-19 and advanced to different phases. Therefore, we created an intervention significance score for each intervention studied. The score was calculated by assigning phase-based numeric value based on whether an intervention has a trial in a given phase and adding 0.01 for each trial in that phase to add significance for the existence of multiple trials in that phase. For example, tocilizumab had 12 phase 3 trials so that would add 3.12 to the intervention score (3
for having a phase 3 trial and \((0.12 \times 0.01)\) for having 12 phase 3 trials). The higher the score the more significant the level of study of the intervention in the COVID-19 research landscape. For trials that combined two phases, we counted the trial as being of the higher phase (a phase 2/3 trial was considered just a phase 3 trial).

**Publication attention score**

Our goal was to generate a ranked list of publications with the most significant publications appearing on top. We used a construct of an attention score that gives the most significant publications higher values. The score is based on the recency of the publication, the phase of the trial, the intervention significance score, the number of times the trial record has been updated (high impact trials are more frequently updated), and whether the trial includes a US site. In other words, publications ranked higher if they were recent, from a later phase trial, involved a significant intervention, involved a CTG study record that had been updated multiple times and had at least one US site. For scoring purposes, if a trial was a combination of two phases, such as a phase 2/3 trial, we considered it under the higher phase (phase 3 in this example case).

We also retrieved article type from PubMed and gave publications that were not study result articles, such as protocols or editorials, less significance, and therefore lower attention scores, than study result articles.

In the final ranked publication list, we also present to the user further important publication and study metadata that are not input parameters for the calculation of the attention score. This information includes, the study sponsor, the journal where the publication was published, and whether study results were deposited on CTG as part of the trial record. This information can be seen in the supplemental material (regCovidpublications_Master.csv at the project repository).

**Subset of COVID-19 vaccine trials**

Due to the great importance and interest in vaccine trials for COVID-19, we looked specifically at a subset of COVID-19 vaccine interventional trials. The subset was developed by searching for the term vaccine in the trial's title (developed and evaluated in the previously published regCOVID study; as of 2021, CTG does not capture vaccine as a separate intervention type). Similar to, the overall set of COVID-19 studies, we analyzed the vaccine trials based on key trial and publication features and generated attention scores for each publication associated with a trial of a COVID-19 vaccine.

**Observational studies and registries**

We also analyzed both observational studies and registries. Similarly, to interventional trials, we identified both abstract and registry linked publications and assigned attention scores based on the recency of the
publication, the number of study record updates and whether or not the study included a US site. Phase is not relevant for observational studies and registries.

**Results**

All analytical results presented below were based on a query date of 15 August 2021. We plan to publish refreshed results at the study repository. Repository history mechanism and formal data releases allow retrieval of any data release over time. The repository contains a report generated using an R notebook framework (computer code combined with user friendly result outputs). In addition to the report, important results are available as separate files in spreadsheet format. Such separate files are referred to in the results prefixed with ‘regCOVIDpublications_‘.

**Interventional trials**

As of the query date (15 August 2021), we identified and analyzed a total of 2 669 recruiting, active or ended (completed or terminated) COVID-19 interventional trials (see file regCOVIDpublications_trials_int.csv). On the trial level, a total of 419 trials (15.7% out of all 2 669 trials) have at least one linked result article. 123 trials have multiple publications, with 63 trials having published three or more articles.

The total number of trial-article-link-type combinations was 760, with 418 (55.0%) articles identified via abstract link and 342 (45.0%) identified via registry link. 11 (1.5 %) articles overlapped and were identified via both link types. Since the same article can be linked to multiple trials (e.g., meta-analysis or an editorial about multiple trials), we found that there were 679 distinct publications linked to all included COVID-19 interventional trials.

It is important to consider the level of effort (of the principal investigator or other study officials) to link a publication to a trial. Abstract linking is easier and faster because the article author can simply state the NCT ID in the abstract and the article-study linkage is auto-generated thanks to the automated processing of PubMed abstracts. The majority of result articles (55.0%) were abstract-linked. On the other hand, registry linking requires update of the record in CTG by either XML file submission though their application protocol interface or by using CTG’s web-based data entry system (called Protocol Registration and Results System; PRS). Per our methodology, 964 registry-linked articles were removed as incorrect, misclassified result articles (articles that had a publication date prior to the start of the trial).

**Interventions**

Using our computerized approach, we identified 3 295 interventions used in COVID-19 interventional trials. Of these 3 295 interventions, 549 had at least one publication connected to a trial. Table 1 shows the top 10 interventions based on intervention score, and includes the number of total trials, the count of
trials by phase, the number of sponsors testing a given intervention, and the number of publications resulting from these trials. Data for all interventions (beyond those top 10 shown in Table 1) are available in file regCovid_intervention-phase_cnts_int2.csv as well as in the regCOVIDpub report at the project repository.

Table 1. Counts of interventional trials by phase, publications and sponsors aggregated by COVID-19 intervention studied.

| Intervention    | Count | 1 | 2 | 3 | 4 | N/A | Intervention Significance Score | Number of Sponsors | Number of Publications |
|-----------------|-------|---|---|---|---|-----|-------------------------------|-------------------|-----------------------|
| Hydroxychloroquine | 120   | 3 | 36| 54| 16| 11  | 12.2                          | 100               | 81                    |
| Ivermectin      | 43    | 2 | 14| 16| 4 | 7   | 11.43                         | 39                | 16                    |
| Remdesivir      | 43    | 1 | 10| 26| 3 | 3   | 11.43                         | 28                | 24                    |
| Azithromycin    | 41    | 1 | 16| 17| 2 | 5   | 11.41                         | 38                | 37                    |
| Tocilizumab     | 40    | 1 | 18| 12| 3 | 6   | 11.4                           | 36                | 22                    |
| Ritonavir       | 28    | 1 | 7 | 8 | 8 | 4   | 11.28                         | 24                | 22                    |
| Vitamin D       | 23    | 1 | 6 | 6 | 2 | 8   | 11.23                         | 21                | 5                     |
| Dexamethasone   | 24    | 0 | 2 | 13| 7 | 2   | 10.24                         | 22                | 18                    |
| Lopinavir       | 24    | 0 | 6 | 8 | 6 | 4   | 10.24                         | 20                | 21                    |
| Colchicine      | 22    | 0 | 9 | 11| 1 | 1   | 10.22                         | 22                | 11                    |

While Hydroxychloroquine was the intervention with the most publications (81) and highest intervention score (8.301) based on the number of trials and the breadth of the phases the trials covered, Convalescent Plasma was the intervention with the most distinct sponsors studying it (103). 708 interventions had at least one phase 3 (or phase2/3) trial. While multiple vaccine candidates have progressed through each phase, the intervention significance score is lower than most other interventions that progressed to a similar phase since the volume of trials studying the vaccine candidate is usually limited by the fact that only the developer (and select co-sponsors) are studying the vaccine candidate. For example, the vaccine candidate mrna-1273 from Moderna has 9 total trials (three Phase 1, two Phase 2 and four Phase 3) with an intervention significance score of 6.09, which is lower than most other interventions that also proceed to phase 3 (as seen in Table 1) which have a much higher volume of total trials.

**Publication significance**

Using the attention score to rank publications, we generated a ranked list of all 760 publications and a short list of 58 prioritized publications (publications that were not protocols, were from late phase trials (phase 3) with at least one US site and had multiple study record updates). Of the 760 trial-publication combinations, 234 (30.8%) were phase 3, 186 (24.5%) had at least one US site, and 528 (69.5%) had multiple study record updates.
Table 2 shows the top 10 articles from the ranked list. For brevity, the table shows only a subset of available table columns. For the full list of 760 result article and trial combinations for COVID-19 interventional trials and full spectrum of metadata (table columns), see supplemental file regCOVIDpublications_publication_list_int.csv (master article list). The master article list aggregates metadata from both PubMed and CTG.

Table 2. Top 10 publications based on publication attention score.
| PMID     | Article Title                                                                 | Publication Date | NCT ID             | Intervention*                  | Attention Score |
|----------|------------------------------------------------------------------------------|------------------|--------------------|--------------------------------|-----------------|
| 33624010 | Patients With Uncomplicated Coronavirus Disease 2019 (COVID-19) Have Long-Term Persistent Symptoms and Functional Impairment Similar to Patients with Severe COVID-19: A Cautionary Tale During a Global Pandemic. | 8/9/2021         | NCT04292899        | Remdesivir                   | 4.128           |
| 33972949 | LENZILUMAB EFFICACY AND SAFETY IN NEWLY HOSPITALIZED COVID-19 SUBJECTS: RESULTS FROM THE LIVE-AIR PHASE 3 RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL. | 5/15/2021        | NCT04351152        | Lenzilumab                    | 4.123           |
| 33204764 | Safety of Hydroxychloroquine Among Outpatient Clinical Trial Participants for COVID19 | 6/22/2021        | NCT04328467        | Hydroxychloroquine            | 4.119           |
| 33068425 | Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial. | 6/4/2021         | NCT04328467        | Hydroxychloroquine            | 4.118           |
| 31282542 | A Randomized, Placebo-Controlled, Pilot Clinical Trial of Dipyridamole to Decrease Human Immunodeficiency Virus-Associated Chronic Inflammation. | 2/5/2021         | NCT04410328        | Dipyridamole ER Aspirin       | 4.117           |
| 33681731 | Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: A randomized clinical trial. | 4/2/2021         | NCT04354428        | Ascorbic Acid Hydroxychloroquine Azithromycin Folic Acid Lopinavir/Ritonavir | 4.114           |
| 33153629 | GM-CSF Neutralization With Lenzilumab in Severe COVID-19 Pneumonia: A Case-Cohort Study. | 12/8/2020        | NCT04351152        | Lenzilumab                    | 4.114           |
| 34269813 | Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection: A Randomized Clinical Trial. | 8/11/2021        | NCT04332107        | Azithromycin                  | 4.114           |
| 33284679 | Hydroxychloroquine as Postexposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Randomized Trial. | 3/23/2021        | NCT04328961        | Hydroxychloroquine Ascorbic Acid | 4.114           |
| 32459919 | Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. | 12/1/2020        | NCT04292899        | Remdesivir                     | 4.114           |
* For presentation purposes, the following interventions are omitted in table (but present in full report): Placebo, Standard of Care and control

The use of the attention score and prioritizing certain facts about a trial and publication greatly reduces the list of all publications to a manageable list of publications for readers to review (58 publications compared to 760 publications). Assuming a researcher may spend two minutes on each abstract, reviewing the full list versus the prioritized short-list results in a difference of 23.1 hours in terms of total review time.

**Vaccine trial subset**

For the subset of 290 total COVID-19 vaccine trials (as of the query date), we found at least one publication for 40 (13.9%). For those 40 trials, we identified 69 trial and publication combinations, with 55 (79.7%) being abstract linked. Due to the urgency and significant public interest in COVID-19, we observed significant result articles published for trials that are formally ongoing, such as the Pfizer phase 2/3 trial for its vaccine candidates BNT162b1 and BNT162b2, which has already published four result articles, but does not have a listed completion date until 2 May 2023.

As of the query date, no vaccine trial has formally deposited basic summary results to the CTG registry. Legal mandate allows for one year to do so for applicable US trials after the formal completion of the trial. This shows that vaccine trial sponsors may prefer publishing a result article in an academic journal as opposed to registry result deposition to communicate the results to the public. Although, this imbalance is also impacted by legal rules (for US-based trials) governing registry result deposition, namely, the official primary completion date and one year allowed legal time window after this date greatly influence when registry result deposition is performed.

**Observational studies and registries**

Because of the mostly computerized nature of our analysis, we executed the same analyses on COVID-19 observational studies and registries. We found 485 result articles for observational studies. In contrast to interventional trials, more publications were registry linked (280 articles, 57.7%) than abstract linked (205 publications). On the study level, 246 COVID-19 observational studies (12.4% of all 1 990 COVID-19 registered observational studies) had at least one result publication.

We found 111 result articles for registries and similarly to observational studies, the majority were registry linked (63 articles, 56.8% of the 111 publications). On a study level, 53 COVID-19 registries (16.6% of 319 total COVID-19 registered registries) had at least one linked study result article.

Unlike applicable interventional trials, US law does not mandate registration of observational studies or registries. A lack of a registration mandate does not allow for the determination of the proper
denominator (to know the totality of COVID-19 observational studies or registries). The whole method of using abstract link or registry link (relying on NCT ID) naturally fails for unregistered studies. Researchers must rely on traditional PubMed searches to discover result articles of unregistered studies.

**Discussion**

There are several prior analyses that report on how many studies provide results to the public. Huser et al. analysis from 2013 reported that 27.8% of analyzed interventional trials had published a linked result article.\(^3\) A systematic review by Bashir et al. from 2017 found that a median of 23% (ranging from 13% to 42%) were linked to a result article.\(^8\) With much increased public attention during the COVID-19 pandemic, we were motivated to find out what would be the percentage for COVID-19 studies. Our results, as of the query date, show that only 15.7% of COVID-19 interventional trials have a linked result article. However, it is too early to arrive at a formal number due to the relatively recent completion date (or formal ongoing status) of many trials.

Our methodology quickly identified result publications for prominent trials, such as trials involving vaccines approved in the US. Targeted review of those studies shows that such studies updated their CTG record frequently, which gives more confidence in the study metadata and study status (completed, terminated, or ongoing). In terms of paring trials with their result-reporting journal articles, the majority of linked result articles for interventional COVID-19 trials were found via abstract-link (55.0%), perhaps due to the easier practice of including the NCT ID in the article abstract.

The main advantage of our approach is offering researchers and the public a structured overview of literature with valuable metadata that combines information from scientific literature (PubMed) and clinical trial registry (CTG). It allows researchers to sort or aggregate articles based on various useful parameters (trial phase, sponsor, intervention and many others). Such capability is not possible with existing tools. Neither PubMed search nor clinical trial registry allow for review that would combine data from both sources. It allows for an overview of the clinical research in a given disease generated through automated computer script. For example, a review of all articles for a given intervention (such as hydroxychloroquine) could reveal if there is a consensus opinion on its efficacy or if there is a divide and more research is needed. In the case of hydroxychloroquine, a review of five results articles from four clinical trials in the US (on the prioritized short list) all expressed that the intervention was ineffective. A review of a full article master list (worldwide scope; not restricted to trials with at least 1 US site) would show a total of 81 articles from 38 trials studying hydroxychloroquine (see supplemental file for the master article list called ‘regCOVIDpublications_publication_list_int.csv’).

**Levels of trial visibility**

Our results show various levels of trial result reporting ranging from zero to multiple result articles. We found 96 COVID-19 interventional trials that had multiple study result articles, as well as multiple registry
record updates. On the next level are trials with exactly one result article. Considering trials with at least one linked journal article, 70.6% of those have exactly one article. Within the set of trials with exactly one article, 26.9% only had a publication of publication type protocol and not of publication type study result article, which is most valuable. Finally, the vast majority of COVID-19 trials do not have any linked result publications (2 250 studies, 84.3%), making it difficult for interested parties to know the outcome of the trial. An even more extreme case of minimal trial information are trials with no linked result articles and zero updates (besides the initial registration) to the CTG study record (459 interventional trials, 17.2% of 2 669 total interventional trials). Our project, regCOVID, is the first to utilize number of registry record updates (and the type of this update) as a novel, computed study metadata construct to further categorize studies by level of activity. This can be helpful in comparing studies with identical official study status and improve the prioritization of result publications stemming from these studies.

*Result deposition:* As an alternative to publishing study results through an article, many studies chose to distribute study results by depositing them on CTG. A total of 61 trials deposited basic summary results. Within those, 35 trials only did registry result deposition and have no study result article and the remaining 26 trials did both result deposition and published a result article.

**Trial registration timing**

As part of our analysis, we found that trials register at three different points in time: (1) *prior* to trial initiation, (2) after trial initiation and prior to completion (*during*), and (3) *after* trial completion. For the set of all COVID-19 trials the breakdown was 2 237 (44.9%) prior to trial initiation, 2 157 (43.3%) during the trial, and 584 (11.7%) after the trial completion. In comparison, when considering all studies initiated in 2020 (not restricted to COVID-19), 59.3% registered prior to starting, 27.1% registered during the study and 13.6% registered after the study was completed. The comparison shows that COVID-19 studies are more likely to register late (during the study; proportion of 43.3% for COVID-19 studies versus 27.1% for general studies).

**Publication timing**

Publication of study results, including peer review, can be a complex and lengthy process. Prior studies indicate that it can take 21 months. In Supplemental S1 we review where trials stand in this ‘writing phase’. In a pandemic, like COVID-19, the quick publication of trial results is important for understanding which interventions are effective. Prior approval of COVID-19 vaccines and in the context of hospital staff and intensive bed shortages, clinicians were keen to learn about the efficacy of numerous tested interventions. A shorter publication timeline was targeted. Using our set of registered COVID-19 studies, on average, articles, that are not protocols, were published 149 days after the start of the trial. We used trial start date as an anchor since many trials list on CTG anticipated completion dates in the future.
Publishing prior to formal study completion: While primarily clinical trials publish study results articles after the formal trial completion date, for high profile trials it is not uncommon to see the opposite situation. During an ongoing pandemic, timely publication of results is important. For example, for the widely known trial regarding the Moderna COVID-19 vaccine (NCT04470427) which has an official primary completion date of 27 October 2022, the study result article was published in December 2020 (PMID: 33378609). This situation is, in fact, quite common. We found 364 trial result articles linked to 164 COVID-19 trials that are not formally completed as of the query date.

Other considerations

Termination reason: The updating of the study registry record can be very important to the public and researchers. An especially important update is change of study status to terminated. Namely, the reason for termination can provide a highly valuable insight. Such type of update is unlikely to be published as a separate article in a medical journal and the trial registry is the most suitable platform to communicate such an update. Of note is the fact that not all registries support record update and some may only focus on initial registration. To complement our intervention and publication prioritization, we also briefly analyzed the termination reason metadata supported by CTG registry. Most terminated trials (103, 87.3% of 118 terminated COVID-19 studies) specified a termination reason that helped explain why the trial was terminated. Most often, COVID-19 trials were terminated due to the inability to recruit and enroll participants. Other termination reasons were: intervention safety concerns, futility of the intervention, or availability of results from other trials making trial continuation unnecessary.

Publication bias: While manual review of abstracts of result publications was out of scope, we understand the potential presence of publication bias that may lead some trials to not formally publish results in a medical journal. For example, with reports of clearly terminated plans for further vaccine developments by some sponsors, a lack of result articles for certain trials and vaccine candidates hints at possible publication bias in vaccine trials.

Other manual trial trackers: Besides computational methods to obtain the most relevant COVID-19 journal articles, alternatively, it is possible to rely on websites (and research teams) that provide manually reviewed lists of completed studies with reported results. For example, The New York Times maintains a vaccine and therapy tracker. Another study tracker is published by the NIH. While it was out of scope to manually curate a sophisticated list of COVID-19 studies, or do a comprehensive review and comparison of our results to manual COVID-19 study trackers, we did compare the vaccine subset of COVID-19 studies identified through our methodology with those identified by the New York Times and NIH COVID-19 vaccine study trackers. Our motivation was to see how inclusive our methodology was. Our computerized approach study identification methods identified 25 of 32 phase 3 vaccine trials included in the New York Times vaccine tracker and included 5 of 6 trials present in the NIH study tracker.

Generalization to other diseases: regCTGpublications
Due to the computerized nature of our methodology, the method and developed script can be applied to other conditions to achieve an analogous overview of interventions and ranked list of publications. Our project called regCTG\textsuperscript{11} finds a list of studies for a given condition (generalization of regCOVID).\textsuperscript{1} A second project called regCTGpublications (or regCTGpub for short) generates a ranked list of result articles for trials in a given condition (generalization of regCOVIDpub). The regCTGpub project repository\textsuperscript{12} contains web-based result reports (analogous to table 1 and table 2) for select medical conditions (such as Age-Related Macular Degeneration, Alzheimer, etc.).

Limitations

Our study has several limitations. First, we rely on structured links between a registered study and the result article. A prior study for trials completed from 2004 to 2008 indicates that the negative predictive value of such a link may be as low as 56\%.\textsuperscript{13} In other words, an unlinked result article may exist for a trial. However, in recent years, journal requirements to include NCT trial identifiers in an abstract may now be better enforced. Second, researchers have no obligation to publish result articles in a medical journal. Our study uses indexed medical journal publications, though sponsors may make study results public via a press release, instead. Third, our study uses only a single, US-based, clinical trial registry: ClinicalTrials.gov, though, on the other hand, other registries often do not allow linking of a result publication in a registry record, don’t support basic summary result deposition and have limited or no API access options. Also, the CTG registry has a significant number of non-US studies: as of March 2021, 60\% of studies in the recruiting status were non-US only. Fourth, one part of our algorithm, that can be turned off or re-configured for a different country, focused on trials with at least one US site. We chose this because some legal mandates are tied to this factor. Also, approval in the US (by Food and Drug Administration) is a significant factor in world-wide regulatory context (with some exceptions). Fifth, interventions are entered into CTG as free text and proper linkage of identical interventions (expressed using similar intervention strings, such as ‘anti-sars-cov-2 convalescent plasma’ and ‘convalescent covid 19 plasma’) depends on a computational algorithm that can miss some linkage of identical interventions.

Conclusion

We developed a data science driven approach to quickly identify and track linked articles for COVID-19 clinical studies. We characterize which studies are publishing, what type of trial-article link is used, and design a ranking score to prioritize the most significant publications for understanding clinical research for COVID-19. For a set of 2 669 active or ended interventional trials, we found 760 published study result articles, including a short list of 58 key articles from late phase, US based trials with multiple study updates. We separately analyzed trials for COVID-19 vaccines and found 69 linked result articles (including the Pfizer/BioNTech, Moderna and Johnson and Johnson vaccine trials). The computerized nature of our many analyses allows for the publication of monthly refreshed data at our GitHub
repository and the development of a generalized format that can be used to perform similar analysis for other conditions.

Declarations

Data Availability

The datasets generated and analysed during the study are available in the regCOVIDpublications repository: https://github.com/lhncbc/r-snippets-bmi/tree/master/regCOVID/regCOVIDpublications

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Author Contributions

CM and VH conceived of the project. CM performed the code development and data retrieval. VH and CM analyzed the results. VH and CM reviewed the manuscript.

Additional Information

Competing Interests

The authors declare no competing interests.

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