Access to randomized clinical trial (RCT) protocols is necessary for the interpretation and reproducibility of the study results, but protocol availability has been lacking. We determined the prevalence of protocol availability for all published cancer RCTs in January 2020. We found that only 36.1% (48/133) of RCTs had an accessible protocol and only 11.3% of RCTs (15/133) had a publicly accessible protocol that was not behind a paywall. Only 18.0% (24/133) of RCTs were published in conjunction with the protocol on the journal website. In conclusion, few cancer RCTs have an accessible research protocol. Journals should require publication of RCT protocols along with manuscripts to improve research transparency.

Keywords: Protocols, Clinical trials, Access, Cancer

Methods
Our primary aim was to determine the availability of research protocols in a contemporary cross-section of published cancer RCTs. We conducted a PubMed search of all published cancer RCTs in the month of January 2020. The search query (Additional file 1) yielded 1098 results that were assessed by two authors (CB, KZ) to determine if they were RCTs. For published RCTs that did not include a protocol in the online materials, we conducted an internet search including ClinicalTrials.gov, PubMed, and Google to determine whether a current or prior version of the protocol was available (Additional file 2). Only primary analyses of RCTs were included. Pilot RCTs and studies not written in English were excluded. Two-sided Mann-Whitney U and chi-square tests were used to compare differences between groups and the analysis was conducted in R.

Results
A total of 133 RCTs were included in the final analysis (Fig. 1). Within this cohort, the median study sample size was 128 and most studies investigated cancer-directed therapy (40.6%) or supportive care interventions (45.9%), such as symptom control, patient satisfaction,
decision-making, and health literacy (Table 1). The most common primary endpoints included symptom management (29.4%), event-free survival (21.0%), and overall survival (9.1%). Notably, 4.5% of RCTs did not specify a primary endpoint, which is consistent with a prior systematic review of cancer RCTs [8].

Most RCTs were supported by academic or public institutions (60.1%), followed by industry-sponsored RCTs (24.1%) and those without a stated funding source (15.8%). In total, 48 RCT protocols (36.1%) were identified and only 24 protocols (18.0%) were published in conjunction with the RCT manuscript. Twelve protocols (9.0%) were previously published, 5 protocols (3.8%) were accessible at ClinicalTrials.gov, and 7 protocols (5.3%) were available elsewhere online. A total of 15 protocols (11.3%) were publicly accessible without a paywall. Of the RCTs with previously published protocols, only one included a protocol update with the published results. Phase III RCTs were more likely to have an identifiable protocol compared to other RCTs (Table 1; p=0.006). The median impact factor was significantly higher among journals that published protocols in conjunction with the RCT manuscript compared to journals that did not (7.0 vs 3.5; p<0.0001). The median sample size among RCTs with an identifiable protocol was nearly double that of RCTs in which a protocol could not be found (203 vs 102; p=0.001). Median sample sizes were similar among RCTs published in conjunction with the protocol compared to those that were not (312 vs 184; p=0.56). There was no difference in protocol availability between industry sponsored and academic or publicly sponsored RCTs (43.8% vs 33.8%; p=0.32).

**Discussion**

In summary, we found only a very small number of RCTs were published along with the protocol with only one published manuscript that included a protocol update. Journals with a higher impact factor were more likely to include RCT protocols. Access to RCT protocols is critical for transparency, reproducibility, and interpretation of the study results. More journals should require publication of RCT protocols in conjunction with the study results.
| Study characteristics for randomized cancer clinical trials | RCTs with protocols, n=48 | RCTs without protocols, n=85 |
|-----------------------------------------------------------|---------------------------|-------------------------------|
| Sample size, median (range)                              | 203 (7–13,195)            | 102 (6–3864)                  |
| Type of cancer, n (%)                                     |                           |                               |
| Central nervous system                                   | 0                         | 3 (3.5)                      |
| Head and neck                                            | 3 (6.2)                   | 5 (5.9)                      |
| Gastrointestinal                                         | 7 (14.6)                  | 21 (24.7)                    |
| Lung                                                      | 6 (12.5)                  | 6 (7.1)                      |
| Genitourinary                                             | 11 (22.9)                 | 13 (15.3)                    |
| Breast                                                    | 9 (18.8)                  | 20 (23.5)                    |
| Leukemia/lymphoma                                        | 5 (10.4)                  | 6 (7.1)                      |
| Melanoma                                                  | 1 (2.1)                   | 2 (2.3)                      |
| Soft tissue sarcoma                                       | 1 (2.1)                   | 1 (1.2)                      |
| Thyroid                                                   | 0                         | 1 (1.2)                      |
| Multiple                                                  | 5 (10.4)                  | 7 (8.2)                      |
| Study type, n(%)                                          |                           |                               |
| Cancer-directed therapy                                   | 25 (52.1)                 | 29 (34.1)                    |
| Supportive care                                           | 17 (35.4)                 | 44 (51.8)                    |
| Imaging                                                   | 1 (2.1)                   | 2 (2.4)                      |
| Preventative/screening                                   | 2 (4.2)                   | 6 (7.0)                      |
| Surgical/anesthesia                                       | 1 (2.1)                   | 4 (4.7)                      |
| Other                                                     | 2 (4.2)                   | 0                            |
| Primary endpoint*, n(%)                                    |                           |                               |
| Overall survival                                          | 4 (7.4)                   | 9 (10.1)                     |
| Event-free survival                                       | 15 (27.8)                 | 15 (16.9)                    |
| Response rate                                             | 4 (7.4)                   | 6 (6.7)                      |
| Symptom management                                        | 14 (25.9)                 | 28 (31.5)                    |
| Other                                                     | 17 (31.5)                 | 25 (28.1)                    |
| Not specified                                             | 0                         | 6 (6.7)                      |
| Single primary endpoint                                   | 42 (87.5)                 | 75 (88.2)                    |
| Co-primary endpoints                                      | 6 (12.5)                  | 4 (4.7)                      |
| Trial phase, n (%)                                        |                           |                               |
| III                                                       | 21 (43.8)                 | 18 (21.2)                    |
| II                                                        | 10 (20.8)                 | 26 (30.6)                    |
| Not specified                                             | 17 (35.4)                 | 41 (48.2)                    |
| Source of funding                                         |                           |                               |
| Industry                                                  | 14 (29.2)                 | 18 (21.2)                    |
| Academic/public                                           | 27 (56.2)                 | 53 (62.3)                    |
| None listed                                               | 7 (14.6)                  | 14 (16.5)                    |

*Co-primary endpoints were counted twice
Abbreviations
RCT: Randomized clinical trial

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05382-7.

Additional file 1. PubMed Search Query. Description: This additional file contains the complete original PubMed search query used to generate the initial study cohort of 1098 results, which were then reviewed to identify randomized clinical trials.

Additional file 2. Journal and Protocol Availability Status for All Included Trials. Description: This additional file contains the PubMed ID, journal and protocol availability status for all 133 studies included in this analysis.

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Authors’ contributions
CB and KZ designed the initial search query and reviewed the results. CB and KZ performed the statistical analyses. CB, LM, NL, and KZ contributed to the data interpretation and writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. Additional file 1 contains the complete PubMed search query used to generate the initial study dataset. Additional file 2 contains the PubMed ID, journal, and protocol availability for the included randomized clinical trials.

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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References
1. Chan A, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to published articles. JAMA. 2004;291:20.
2. Boutron I, Dutton S, Ravaud P, Altman DG. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. JAMA. 2010;303:20.
3. Lucey M, Clark J, Glaziov P. Public availability of trial protocols. Lancet. 2017;390:1013.
4. Zakeri K, Noticewala S, Vitzthum L, Sojourner E, Shen H, Mell L. ‘Optimism bias’ in contemporary national clinical trial network phase III trials: Are we improving? Ann Oncol. 2018;29:10.
5. Altman DG, Furberg CD, Grimshaw JM, Rothwell PM. Lead editorial: Trials - using the opportunities of electronic publishing to improve the reporting of randomized trials. Trials. 2006;7(1):6. https://doi.org/10.1186/1745-6215-7-6.
6. Raghav KP, Mahajan S, Yao JC, Hobbs BP, Berry DA, Pentz RD, et al. From protocols to publications: A study in selective reporting of outcomes in randomized trials in oncology. J Clin Oncol. 2015;33:31.
7. Spence O, Hong K, Onwuchekwa Uba R, Doshi P. Availability of study protocols for randomized trials published in high-impact medical journals: A cross-sectional analysis. Clin Trials. 2020;17(1):99–105. https://doi.org/10.1177/1740774519868310.
8. Mell LK, Lau SK, Rose BS, Jeong JH. Reporting of cause-specific treatment effects in cancer clinical trials with competing risks: A systematic review. Contemp Clin Trials. 2012;33:5.

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