CORRESPONDENCE

Comment on the “TrialsTracker: Automated ongoing monitoring of failure to share clinical trial results by all major companies and research institutions” [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

The purpose of this correspondence is to discuss the TrialsTracker, presented by Powell-Smith and Goldacre in their article ‘TrialsTracker: Automated ongoing monitoring of failure to share clinical trial results by all major companies and research institutions’ (2016) as a tool to discover publication bias in clinical trial results. The findings from one specific organization (European Organization for Research and Treatment of Cancer; EORTC) are compared with the actual publication history of the trials in question. We also present shortcomings of the method being used and suggestions for improvement to the proposed algorithm.

Keywords

TrialsTracker , publication bias , clinical trials

This article is included in the **All trials matter** collection.

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Approval Status ? ✓

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Any reports and responses or comments on the article can be found at the end of the article.

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We read with great interest the article by Drs Powell-Smith and Goldacre¹ on the incomplete reporting of clinical trial results by pharmaceutical companies and research institutions. The necessity to publish results of all clinical trials, regardless of the trial outcome, cannot be denied². Failure to do so is unethical not only towards patients who have participated in these trials but also towards the medical community at large which relies on unbiased reporting to make informed decisions both in clinical practice and research³.

The European Organization for Research and Treatment of Cancer (EORTC), as a non-profit pan European clinical research organization, very much supports this view. EORTC is driven by the mission to improve the survival and quality of life of cancer patients, and adheres to a strict policy to publish all of its completed trials in full⁴. We were therefore surprised by the results from TrialsTracker⁵ stating that 52.6% of EORTC trials are missing results (20 trials out of 38). We downloaded the full trial dataset used by the tracker via GitHub (<https://github.com/ebmdatalab/trialstracker>). After selection according to the set criteria (ie. completed since 01/01/2006, interventional phase II or III, led by EORTC) a total of 29 relevant trials were found. The tracker classified these as: 14 with successful result reporting and 15 (51.7%) without results. We identified the latter 15 trials through the NCT ID number and cross-referenced this with the EORTC internal bibliography list. This (manual) investigation yielded the following results (see Table 1):

- A total of 9 trials had been successfully published, but the NCT ID number was not listed in PubMed's Secondary Source ID field. For all of these trials the NCT ID was stated in the article itself and a link to the correct reference was provided in the publications section of ClinicalTrials.gov
- Three further trials had been recently successfully published without mention of the NCT ID number. The reference was not yet present in ClinicalTrials.gov but was scheduled to be updated soon.
- The last three trials were still undergoing analysis, and the planned publications were in various stages of development.

This would put the EORTC under-reporting "score" at 3/29 or about 10% of its trials being overdue for publication.

Our investigation revealed several shortcomings of the automated tracker algorithm:

- The decision to only accept results posted directly in ClinicalTrials.gov or with a listed NCT ID in PubMed's Secondary Source ID field is very restrictive. EORTC does not post results in ClinicalTrials.gov directly as this presents a substantial administrative burden, and does not allow results to be put into context. Other organizations may be in the same situation.
- The authors state that since 2005 "all major medical journals (through the International Committee of Medical

Journal Editors) have required trials to be registered, and all trials should include their registry ID in the text." The majority of our trials, as identified by the tracker, fulfill these criteria, yet several were incorrectly classified due to absence of a specific PubMed field provided by the medical journals. Despite this omission, these trial results could be correctly found through recognized databases such as ClinicalTrials.gov and PubMed or even a standard search engine like Google.

- For at least two studies, the NCT ID PubMed link was available for a publication that did not contain the actual study results. The EORTC 55971 study on neoadjuvant treatment in ovarian cancer was published in NEJM in 2010⁶. Yet this publication was not identified by the tracker, but two subsequent publications on exploratory subgroup analyses were considered as evidence of trial results publication^{7,8}.

We also want to introduce two caveats to take into account when refining a tracker such as the one proposed:

- The algorithm can be easily manipulated to inflate the success rate for any trial sponsor by either not listing trials as completed or by listing them as terminated in the registry.
- Also, once the trial is completed, any publication with an adequate NCT ID PubMed link is sufficient for the TrialsTracker algorithm, which means articles on quality assurance, subgroups, translational research, prognostic models, or other data not containing actual trial results will inflate the statistics.

As a general observation, we feel that tracking publications linked to trials without checking these publications for accuracy and adequacy represents a simplistic measure of publication reporting. A substantial source of bias lies in the incorrect publication of trial results, often done with the intention to present larger treatment effects⁹. We feel such a tracking system, by increasing pressure to publish all trials on short notice, may contribute to the problem by leading to compromises on the quality of the publication.

A straightforward approach to resolve this could be to add to clinical trial registries an indicator on the publication status of final trial results. The sponsor would be responsible for updating this indicator and for providing the actual reference. Registry administrators could then check the appropriateness of the reference based on criteria already required to check online posting of results, therefore providing independent confirmation that the trial results are adequately published. Such an indicator would allow for more accurate reporting and could be used to set up an automatic alert system.

The EORTC welcomes initiatives to improve clinical trial reporting. The EORTC has an explicit data sharing policy (<http://www.eortc.org/investigators/data-sharing/>) that allows anyone to request direct access to clinical trial data from completed studies. In

addition to ClinicalTrials.gov, EORTC also registers all its clinical trials that fall under the EU clinical trial directive (Directive 2001/20/EC) by default into EudraCT (<https://eudract.ema.europa.eu>). Since January 2016, summary clinical trial results must be made publicly available through the EU Clinical Trials Register for all EudraCT registered trials. The authors may consider this as an additional source of trial results sharing.

Our conclusion is that the proposed TrialsTracker is a much needed and welcome initiative. However, in this first implementation it is too simplistic to be of real informative use and its conclusions are misleading. We hope that improvements to the algorithm will converge in a useful tool that can address the very real and serious concern of unreported clinical trial results.

Author contributions

CC prepared the first draft. JB and LC were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

All authors are employees of the EORTC.

Grant information

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Table 1. Trial overview.

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00002517	58921	Combination Chemotherapy in Treating Children With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndrome	Entz-Werle N, Suciu S, van der Werff ten Bosch J, Vilmer E, Bertrand Y, Benoit Y, Margueritte G, Plouvier E, Boutard P, Vandecruys E, Ferster A, Lutz P, Uyttebroeck A, Hoyoux C, Thyss A, Rialland X, Norton L, Pages MP, Philippe N, Otten J, Behar C; EORTC Children Leukemia Group.. Results of 58872 and 58921 trials in acute myeloblastic leukemia and relative value of chemotherapy vs allogeneic bone marrow transplantation in first complete remission: the EORTC Children Leukemia Group report. <i>Leukemia</i> . 2005 Dec;19(12):2072-81	published	TRUE	ref provided; no pubmed link
NCT00002641	62931	Surgery With or Without Chemotherapy in Treating Patients With Soft Tissue Sarcoma	Woll PJ, Reichardt P, Le Cesne A, Bonvalot S, Azzarelli A, Hoekstra HJ, Leahy M, Van Coevorden F, Verweij J, Hogendoorn PC, Ouali M, Marreaud S, Bramwell VH, Hohenberger P; EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee.. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. <i>Lancet Oncol</i> . 2012 Oct;13(10):1045-54.	published	FALSE	ref provided; pubmed linked
NCT00003636	55971	Chemotherapy Plus Surgery in Treating Patients With Stage III or Stage IV Ovarian, Peritoneal, or Fallopian Tube Cancer	Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RH, van der Burg ME, Lacave AJ, Panici PB, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GC, Pecorelli S, Reed NS; European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group.; NCIC Clinical Trials Group.. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. <i>N Engl J Med</i> . 2010 Sep 2;363(10):943-53.	published	FALSE	ref provided; pubmed linked but not to main publication

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00003941	30974	Combination Chemotherapy With or Without Peripheral Stem Cell Transplant in Treating Men With Previously Untreated Germ Cell Cancer	Daugaard G, Skoneczna I, Aass N, De Wit R, De Santis M, Dumez H, Marreaud S, Collette L, Lluch JR, Bokemeyer C, Schmoll HJ. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSCG, and Grupo Germinal (EORTC 30974). Ann Oncol. 2011 May;22(5):1054-61.	published	TRUE	ref provided; no pubmed link
NCT00017095	10994	Biomarker (p53 Gene) Analysis and Combination Chemotherapy Followed by Radiation Therapy and Surgery in Treating Women With Large Operable or Locally Advanced or Inflammatory Breast Cancer	Bonnefoi H, Piccart M, Bogaerts J, Mauriac L, Fumoleau P, Brain E, Petit T, Rouanet P, Jassem J, Blot E, Zaman K, Cufer T, Lortholary A, Lidbrink E, André S, Litière S, Lago LD, Becette V, Cameron DA, Bergh J, Iggo R; EORTC 10994/BIG 1-00 Study Investigators.. TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1-00): a randomised phase 3 trial. Lancet Oncol. 2011 Jun;12(6):527-39.	published	FALSE	ref provided; pubmed linked
NCT00021450	22991	Radiation Therapy With or Without Bicalutamide and Goserelin in Treating Patients With Prostate Cancer	Bolla M, Maingon P, Carrie C, Villa S, Kitsios P, Poortmans PM, Sundar S, van der Steen-Banasik EM, Armstrong J, Bosset JF, Herrera FG, Pieters B, Slot A, Bahl A, Ben-Yosef R, Boehmer D, Scrase C, Renard L, Shash E, Coens C, van den Bergh AC, Collette L. Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. J Clin Oncol. 2016 May 20;34(15):1748-56.	published	TRUE	published 2016; ref not yet provided
NCT00028756	30994	Comparison of Immediate and Delayed Adjuvant Chemotherapy in Treating Patients Who Have Undergone a Radical Cystectomy for Stage III or Stage IV Transitional Cell Carcinoma of the Bladder Urothelium	Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, Dumez H, de Santis M, Théodore C, Leahy MG, Chester JD, Verbaeys A, Daugaard G, Wood L, Witjes JA, de Wit R, Geoffrois L, Sengelov L, Thalmann G, Charpentier D, Rolland F, Mignot L, Sundar S, Symonds P, Graham J, Joly F, Marreaud S, Collette L, Sylvester R; European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group.; Groupe d'Etude des Tumeurs Urogénitales.; National Cancer Research Institute Bladder Cancer Study Group.; National Cancer Institute of Canada Clinical Trials Group.; German Association of Urologic Oncology.. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):76-86.	published	FALSE	ref provided; pubmed linked

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00052299	06012	Chemotherapy With or Without Gemtuzumab Ozogamicin in Treating Older Patients With Acute Myeloid Leukemia	Amadori S, Suci S, Stasi R, Salih HR, Selleslag D, Muus P, De Fabritiis P, Venditti A, Ho AD, Lübbert M, Thomas X, Latagliata R, Halkes CJ, Falzetti F, Magro D, Guimaraes JE, Berneman Z, Specchia G, Karrasch M, Fazi P, Vignetti M, Willemze R, de Witte T, Marie JP. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). J Clin Oncol. 2013 Dec 10;31(35):4424-30.	published	FALSE	ref provided; pubmed linked
NCT00052312	55984	Doxorubicin and Cisplatin With or Without Paclitaxel in Treating Patients With Locally Advanced, Metastatic, and/or Relapsed Endometrial Cancer		not yet published	TRUE	no publication; overdue
NCT00061984	62012	Doxorubicin With or Without Ifosfamide and Pegfilgrastim in Treating Patients With Locally Advanced or Metastatic Soft Tissue Sarcoma	Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, Suflarsky J, Whelan J, Hohenberger P, Krarup-Hansen A, Alcindor T, Marreaud S, Litière S, Hermans C, Fisher C, Hogendoorn PC, dei Tos AP, van der Graaf WT; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group.. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014 Apr;15(4):415-23.	published	FALSE	ref provided; pubmed linked
NCT00066378	10021	Anastrozole With or Without Gefitinib in Treating Postmenopausal Women With Metastatic or Locally Recurrent Breast Cancer	Tryfonidis K, Basaran G, Bogaerts J, Debled M, Dirix L, Thery JC, Tjan-Heijnen VC, Van den Weyngaert D, Cufer T, Piccart M, Cameron D; EORTC-Breast Cancer Group.. A European Organisation for Research and Treatment of Cancer randomized, double-blind, placebo-controlled, multicentre phase II trial of anastrozole in combination with gefitinib or placebo in hormone receptor-positive advanced breast cancer (NCT00066378). Eur J Cancer. 2016 Jan;53:144-54.	published	FALSE	ref provided; pubmed linked

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00066391	30992	Irinotecan and Cisplatin in Treating Patients With Locally Advanced or Metastatic Penile Cancer	Theodore C, Skoneczna I, Bodrogi I, Leahy M, Kerst JM, Collette L, Ven K, Marréaud S, Oliver RD; EORTC Genito-Urinary Tract Cancer Group.. A phase II multicentre study of irinotecan (CPT 11) in combination with cisplatin (CDDP) in metastatic or locally advanced penile carcinoma (EORTC PROTOCOL 30992). Ann Oncol. 2008 Jul;19(7):1304-7.	published	TRUE	ref provided; no pubmed link
NCT00074087	21012	Liposomal Doxorubicin in Treating Patients With Stage IIB, Stage IVA, or Stage IVB Recurrent or Refractory Mycosis Fungoides	Dummer R, Quaglini P, Becker JC, Hasan B, Karrasch M, Whittaker S, Morris S, Weichenthal M, Stadler R, Bagot M, Cozzio A, Bernengo MG, Knobler R. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol. 2012 Nov 20; 30(33):4091-7.	published	FALSE	ref provided; pubmed linked
NCT00077116	06013	Idarubicin, Cytarabine, and Gemtuzumab Ozogamicin in Treating Patients With Previously Untreated High-Risk Myelodysplastic Syndrome or Acute Myeloid Leukemia Secondary to Myelodysplastic Syndrome	de Witte T, Suci S, Meert L, Halkes C, Selleslag D, Bron D, Amadori S, Willemze R, Muus P, Baron F. Idarubicin and cytarabine in combination with gemtuzumab ozogamicin (IAGO) for untreated patients with high-risk MDS or AML evolved from MDS: a phase II study from the EORTC and GIMEMA Leukemia Groups (protocol 06013). Ann Hematol. 2015 Dec;94(12):1981-9.	published	TRUE	published 2015; ref not yet provided
NCT00079261	20021	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone With or Without Gemcitabine in Treating Patients With Previously Untreated Aggressive Non-Hodgkin's Lymphoma	Aurer I, Eghbali H, Raemaekers J, Khaled HM, Fortpied C, Baila L, van der Maazen RW; EORTC Lymphoma Group.. Gem-(R)CHOP versus (R)CHOP: a randomized phase II study of gemcitabine combined with (R)CHOP in untreated aggressive non-Hodgkin's lymphoma--EORTC lymphoma group protocol 20021 (EudraCT number 2004-004635-54). Eur J Haematol. 2011 Feb;86(2):111-6.	published	TRUE	ref provided; no pubmed link
NCT00085228	30021	Docetaxel With or Without Oblimersen in Treating Patients With Hormone-Refractory Adenocarcinoma (Cancer) of the Prostate	Sternberg CN, Dumez H, Van Poppel H, Skoneczna I, Sella A, Daugaard G, Gil T, Graham J, Carpentier P, Calabro F, Collette L, Lacombe D; EORTC Genitourinary Tract Cancer Group.. Docetaxel plus oblimersen sodium (Bcl-2 antisense oligonucleotide): an EORTC multicenter, randomized phase II study in patients with castration-resistant prostate cancer. Ann Oncol. 2009 Jul;20(7):1264-9.	published	FALSE	ref provided; pubmed linked

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00085475	62027	Imatinib Mesylate in Treating Patients With Locally Advanced or Metastatic Dermatofibrosarcoma Protuberans or Giant Cell Fibroblastoma	Rutkowski P, Van Glabbeke M, Rankin CJ, Ruka W, Rubin BP, Debiec-Rychter M, Lazar A, Gelderblom H, Sciot R, Lopez-Terrada D, Hohenberger P, van Oosterom AT, Schuetze SM; European Organisation for Research and Treatment of Cancer Soft Tissue/Bone Sarcoma Group.; Southwest Oncology Group.. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol. 2010 Apr 1;28(10):1772-9.	published	TRUE	ref provided; no pubmed link
NCT00086879	26034	Erlotinib Compared With Temozolomide or Carmustine in Treating Patients With Recurrent Glioblastoma Multiforme	van den Bent MJ, Brandes AA, Rampling R, Kouwenhoven MC, Kros JM, Carpentier AF, Clement PM, Frenay M, Campone M, Baurain JF, Armand JP, Taphoorn MJ, Tosoni A, Kletzl H, Klughammer B, Lacombe D, Gorlia T. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. J Clin Oncol. 2009 Mar 10;27(8):1268-74.	published	TRUE	ref provided; no pubmed link
NCT00110045	65041	Caspofungin Acetate in Treating Aspergillosis in Patients With Hematologic Cancer or in Patients Who Have Undergone a Stem Cell Transplant	Viscoli C, Herbrecht R, Akan H, Baila L, Sonet A, Gallamini A, Giagounidis A, Marchetti O, Martino R, Meert L, Paesmans M, Ameye L, Shivaprakash M, Ullmann AJ, Maertens J; Infectious Disease Group of the EORTC.. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. J Antimicrob Chemother. 2009 Dec;64(6):1274-81.	published	TRUE	ref provided; no pubmed link
NCT00182819	22033	Radiation Therapy or Temozolomide in Treating Patients With Gliomas	Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, Brandes AA, Kantor G, Taphoorn MJ, Hassel MB, Hartmann C, Ryan G, Capper D, Kros JM, Kurscheid S, Wick W, Enting R, Reni M, Thiessen B, Dhermain F, Bromberg JE, Feuvret L, Reijneveld JC, Chinot O, Gijtenbeek JM, Rossiter JP, Dif N, Balana C, Bravo-Marques J, Clement PM, Marosi C, Tzuk-Shina T, Nordal RA, Rees J, Lacombe D, Mason WP, Stupp R. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2016 Nov;17(11):1521-1532.	published	FALSE	published 2016; ref not yet provided; pubmed link to QA articles

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00227630	08031	Pemetrexed Disodium and Cisplatin Followed By Surgery and Radiation Therapy in Treating Patients With Malignant Pleural Mesothelioma	Van Schil PE, Baas P, Gaafar R, Maat AP, Van de Pol M, Hasan B, Klomp HM, Abdelrahman AM, Welch J, van Meerbeeck JP; European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group.. Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial. Eur Respir J. 2010 Dec;36(6):1362-9.	published	FALSE	ref provided; pubmed linked
NCT00263822	55041	Erlotinib or Observation in Treating Patients Who Have Undergone First-Line Chemotherapy for Ovarian Cancer, Peritoneal Cancer, or Fallopian Tube Cancer	Vergote IB, Jimeno A, Joly F, Katsaros D, Coens C, Despierre E, Marth C, Hall M, Steer CB, Colombo N, Lesoin A, Casado A, Reinthaller A, Green J, Buck M, Ray-Coquard I, Ferrero A, Favier L, Reed NS, Curé H, Pujade-Lauraine E. Randomized phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platin-based chemotherapy for ovarian carcinoma: a European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup study. J Clin Oncol. 2014 Feb 1;32(4):320-6.	published	FALSE	ref provided; pubmed linked
NCT00424060	26061	Epothilone ZK-219477 in Treating Patients With Recurrent Glioblastoma	Stupp R, Tosoni A, Bromberg JE, Hau P, Campone M, Gijtenbeek J, Frenay M, Breimer L, Wiesinger H, Allgeier A, van den Bent MJ, Bogdahn U, van der Graaf W, Yun HJ, Gorlia T, Lacombe D, Brandes AA. Sagopilone (ZK-EPO, ZK 219477) for recurrent glioblastoma. A phase II multicenter trial by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group. Ann Oncol. 2011 Sep;22(9):2144-9.	published	TRUE	ref provided; no pubmed link
NCT00433433	20051	Fludeoxyglucose F 18 PET Scan-Guided Therapy or Standard Therapy in Treating Patients With Previously Untreated Stage I or Stage II Hodgkin's Lymphoma	Raemaekers JM, André MP, Federico M, Girinsky T, Oumedaly R, Brusamolino E, Brice P, Fermé C, van der Maazen R, Gotti M, Bouabdallah R, Sebban CJ, Lievens Y, Re A, Stamatoullas A, Morschhauser F, Lugtenburg PJ, Abruzzese E, Olivier P, Casasnovas RO, van Imhoff G, Raveloarivahy T, Bellei M, van der Borgh T, Bardet S, Versari A, Hutchings M, Meignan M, Fortpied C. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2014 Apr 20;32(12):1188-94.	published	FALSE	ref provided; pubmed linked but not to main publication

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT00458913	08052	Bortezomib and Cisplatin as First-Line Therapy in Treating Patients With Malignant Mesothelioma	O'Brien ME, Gaafar RM, Popat S, Grossi F, Price A, Talbot DC, Cufer T, Ottensmeier C, Danson S, Pallis A, Hasan B, Van Meerbeeck JP, Baas P. Phase II study of first-line bortezomib and cisplatin in malignant pleural mesothelioma and prospective validation of progression free survival rate as a primary end-point for mesothelioma clinical trials (European Organisation for Research and Treatment of Cancer 08052). Eur J Cancer. 2013 Sep;49(13):2815-22.	published	FALSE	ref provided; pubmed linked
NCT00526149	90061	BI 2536 in Treating Patients With Recurrent or Metastatic Solid Tumors	Schöffski P, Blay JY, De Greve J, Brain E, Machiels JP, Soria JC, Sleijfer S, Wolter P, Ray-Coquard I, Fontaine C, Munzert G, Fritsch H, Hanft G, Aerts C, Raponi J, Allgeier A, Bogaerts J, Lacombe D. Multicentric parallel phase II trial of the polo-like kinase 1 inhibitor BI 2536 in patients with advanced head and neck cancer, breast cancer, ovarian cancer, soft tissue sarcoma and melanoma. The first protocol of the European Organization for Research and Treatment of Cancer (EORTC) Network Of Core Institutes (NOCI). Eur J Cancer. 2010 Aug;46(12):2206-15.	published	TRUE	ref provided; no pubmed link
NCT00766155	40054	Chemotherapy and Radiation Therapy Before Surgery Followed by Capecitabine With or Without Oxaliplatin in Treating Patients With Locally Advanced Rectal Cancer		not yet published	TRUE	no publication; overdue
NCT01019434	26082	Radiation Therapy and Temozolimus or Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma	Wick W, Gorlia T, Bady P, Platten M, van den Bent MJ, Taphoorn MJ, Steuve J, Brandes AA, Hamou MF, Wick A, Kosch M, Weller M, Stupp R, Roth P, Golfopoulos V, Frenel JS, Campone M, Ricard D, Marosi C, Villa S, Weyerbrock A, Hopkins K, Homicsko K, Lhermitte B, Pesce G, Hegi ME. Phase II Study of Radiotherapy and Temozolimus versus Radiochemotherapy with Temozolomide in Patients with Newly Diagnosed Glioblastoma without MGMT Promoter Hypermethylation (EORTC 26082). Clin Cancer Res. 2016 Oct 1;22(19):4797-4806.	published	TRUE	published 2016; ref not yet provided; pubmed link to QA articles

NCT ID number	EORTC ID number	Study title	Reference	Publication status	Trialstracker overdue status	Reason trialstracker in/exclusion
NCT01538381	90111	Neoadjuvant Afatinib Window Study in Squamous Cell Carcinoma of the Head and Neck		not yet published	FALSE	no publication; study listed as not completed by TrialsTracker.

Caption:

NCT ID number: Identification number according to ClinicalTrials.gov registry.

EORTC ID number: Identification number according to EORTC.

Study title: Title of the study protocol.

Reference: the reference to the publication of the main results if available.

Publication status: Status of the publication of the main results according to the EORTC bibliography listing.

Trialstracker overdue status: Status of the publication of the main results according to the TrialsTracker algorithm. TRUE = overdue (ie. not published) / FALSE = not overdue (ie published).

Reason trialstracker in/exclusion: Main reason for discrepancy or accordance between EORTC and TrialsTracker publication status.

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Adam Jacobs

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This article is necessarily limited in scope as it presents results for just one trial sponsor, and we do not know if that sponsor is representative. However, as the authors are from just one institution, it is of course perfectly reasonable that they have focused on their own institution, so this is not intended as a criticism, merely as an observation.

Coens *et al* have done a good job of presenting a more detailed analysis of the studies from their institution, and have shown convincingly that the estimate of their publication rate from the automated Trial Tracker was substantially inaccurate for their institution, by means of the gold standard of a manual search. They provide a sensible and balanced discussion of the limitations of the automated search algorithm more generally, pointing to some possible unintended consequences. While those unintended consequences are at this stage purely speculative, it does no harm to bear in mind what the risks are of an automated process such as the Trials Tracker.

I have 2 suggestions for improving the paper. First, Coen *et al* state that only 29 of the 38 trials identified by the Trials tracker were "eligible studies", which they define as "completed since 01/01/2006, interventional phase II or III, led by EORTC". When I applied those criteria myself to the EORTC trials identified by the Trials Tracker, I found 30 eligible studies. As far as I could tell from the Trials Tracker data, all 38 studies were completed since 01/01/2016 and were led by EORTC, and 8 studies were not drug interventions. It would be helpful if Coen *et al* could be more explicit about why they excluded 9 trials from their analysis.

Second, I think the finding that some trials were not identified as published by the Trials Tracker despite a publication that was clearly linked in the clinicaltrials.gov record deserves more emphasis. Although this is mentioned in the paper, a casual reader might miss it, and this is perhaps the most important finding in terms of a way in which the Trial Tracker could easily be improved.

Competing Interests: I have previously blogged about the Trials Tracker and found similar results

to Coen et al, namely that the Trials Tracker seriously underestimates publication rates. See <http://www.statsguy.co.uk/the-trials-tracker-and-post-truth-politics/>

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 08 February 2017

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Tamas Ferenci

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This paper from Coens *et al* discusses an important aspect of the recently published TrialsTracker database/analysis of the EBM Data Lab (University of Oxford). The paper introducing it from Drs. Powell-Smith and Goldacre ¹ initiated exciting comments ¹, press statements ² and even tweet exchanges with pharmaceutical companies ³, raising similar concerns; the present article is the first however to formalize such criticisms through the detailed analysis of a particular institute's trials.

I welcome this investigation as a systematic substantiation of the concerns raised in the aforementioned sources. Albeit pertaining to a single institute, the results are at least illustrative – even if not representative – for the entire TrialsTracker project. (A notable – and important – exception that is not discussed in the present manuscript is the question of results posted to company websites.)

The presentation of the findings from Coens *et al* is almost flawless in my opinion, with the following minor remarks:

1. I don't see how 38 changed to 29 (number of relevant EORTC studies). The said criteria – completed, has completion_date and it is later than 1 Jan 2006, interventional, phase 2 or 3 – results indeed in 38 records. Yet, Coens *et al* reports only 29, saying that these are "relevant", but how they define relevance (ie. what 9 studies were excluded and why) is not discussed at all.
2. Table 1 should be improved by clearly marking which trial belongs to which category: has results or not, in the latter case the reason from the three listed (NCT ID not in SI field, no NCT ID given in the publication, really not published). In the current form it is difficult to match the concrete trials to the authors' statements (e.g. what are the trials that have a publication but not NCT ID given?).

My major comments are therefore rather about missing details and potential further improvements:

1. TrialsTracker looks up results from clinicaltrials.gov (results section) and Pubmed (only

through NCT ID as SI). While non-publication in Pubmed might have several – not necessarily malicious or negligent – reasons, such as the publication being rejected or a long review process, clinicaltrials.gov has no such limitation, so non-disclosure there seems to be much more inexcusable at first glance. Coens *et al* touches this issue, but only extremely briefly, stating that "[uploading results to clinicaltrials.gov] presents a substantial administrative burden, and does not allow results to be put into context". I'd really welcome a more detailed discussion of the first part: how large is this burden, is it in fact prohibitive...? (Especially for organizations with tens of thousands of employees and clinical trials with a budget in excess to ten million US dollars.) As far as the second part is concerned, I disagree: the aim of the deposition of results in repositories is not its presentation "in context", but simply making them available. Not that the presentation of the context is not important, but it is a *separate* issue. (Actually, availability of raw results might even be beneficial, avoiding potential biases introduced by a biased context ⁴.) Thus, this sentence of the authors should be elaborated in more detail.

2. Coens *et al* very instructively point out that the decision on where to look for NCT ID in a publication is a specificity/sensitivity trade-off. Ironically, the restriction of search to SI, which was originally meant to exclude studies not reporting main results does sometimes include false results (as exemplified by EORTC 55971), and more importantly, the reverse can also be true. Extending the search to the whole abstract, however, might allow even more false results to enter. Interestingly, Powell-Smith is somewhat vague about this issue stating that "in our experience approximately 1.5% of PubMed records include a valid nct_id list in the abstract, but not the Secondary Source ID field" without further details. I am positive that additional research into this topic would be beneficial.
3. Coens *et al* are quoting Powell-Smith *et al* to justify that EORTC was acting correctly when NCT IDs were published in the text, regardless of where it appears ("The authors state that since 2005 >>all major medical journals (through the International Committee of Medical Journal Editors) have required trials to be registered, and all trials should include their registry ID in the text.<< The majority of our trials, as identified by the tracker, fulfill these criteria".) This quotation is somewhat misleading to suggest that the ID can be anywhere in the text (and not necessarily in SI – as is the case for many EORTC publication) and it is completely correct this way: MEDLINE's guideline explicitly requires NCT ID to be recorded in that particular field, i.e. the secondary source ID field ⁵ (as also cited by Powell-Smith *et al*). Thus, TrialsTracker's requirement is not arbitrary, as one might believe based on the description of Coens *et al*: "several were incorrectly classified due to absence of a specific PubMed field provided by the medical journals" – SI is not just "a specific PubMed field".
4. More importantly, in some cases, NCT ID is given not only outside the SI field, but outside the abstract. (E.g. NCT00003941. An even more problematic example is NCT00021450, where the NCT IDs location is behind the paywall.) We can argue whether the script should look for the abstract or only the SI field, but obviously there is no realistic way to scan the full text of the articles, so these cases are clearly invisible to any automated algorithm, no matter how elaborate.

Finally, let me note that the authors – quite rightly – summarize the drawbacks of the automation, but to be balanced, its strengths should have been mentioned: first, that the automated nature allows investigation on a scale in quantity that cannot be achieved – or only through extreme

measures – with manual checking, and second, perhaps even more importantly, that the automated algorithm is totally transparent and surely free of any subjective decisions. Finally, even if the algorithm is imperfect, at least it is uniformly imperfect, thus the results are likely comparable in spite of this. As far as the distribution of these false results is similar among sponsors, their TrialsTracker score can still be compared. (That's the reason why one cannot simply correct EORTC's results, for example based on this paper, because that would mean that even this comparability is lost.)

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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