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European non-commercial sponsors showed substantial variation in results reporting to the EU trial registry

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Abstract

Objective: To describe the trial results reporting behavior of leading European non-commercial sponsors by country and over time.

Study design and setting: Cross-sectional analysis describing results reporting rates to the European Clinical Trials Registry among the top sponsors across Europe as of May 2021 and a comparison of reporting trends for a cohort of major sponsors between January 2018 and May 2021.

Results: Fifty-nine highly active sponsors from 10 countries and 9 collaborative groups had 1,916 trials due to report, representing 14% of all due trials on the registry (n = 13,709); of these, 1,058 had reported results (55.2%). Sponsors in the UK, Belgium and Germany had the highest compliance at 94%, 69% and 58%; those in Spain, France and the Netherlands, had the lowest, ranging from 4% to 21%. Collaborative groups had a reporting rate of 50%. In the major sponsors cohort (n = 49), those with no reporting to the registry decreased from 27 (55%) in 2018 to 10 (20%) in 2021. Thirteen of these sponsors (27%) reached a 90-100% reporting rate in 2021 compared to 0 in 2018.

Conclusion: Compliance with EU regulations by non-commercial sponsors is highly variable between countries. Enforcement of EU reporting regulations should be prioritized.

Keywords: EU clinical trials regulation; Reporting of results; EudraCT; EU-CTR; Non-commercial sponsors

1. Introduction

EU regulations mandate the registration of trials of medicinal products prior to commencement [1]. For each country within the European Economic Area (EEA: EU member states plus Iceland, Liechtenstein, and Norway) in which a trial sponsor plans to enrol subjects, a clinical trial application must be filed with the national regulator via the EudraCT system [2]. Once all ethical and regulatory approvals are in place, the trial may proceed in a given country and the trial application is made public by the European Medicines Agency (EMA) as a registration on the EU Clinical Trial Register (EU-CTR). Only phase 1 trials in healthy adult volunteers are exempt from public posting. Additionally, some non-EEA trials in pediatric populations are also required to be registered. All information from a clinical trial is entered into the EudraCT, validated by the sponsor and, within 15 days, made publicly available on the EU-CTR. The sponsor is solely responsible for the completeness and accuracy of trial information. Under subsequent EU guidelines, as of December 2016 all registered trials in the EudraCT system should also have results submitted to them within 12 months of completion and six months for certain paediatric trials [3]. These results reporting requirement was retrospectively applied to all completed trials on the registry dating to its launch in 2004. Together, the EU registration and reporting requirements should be major boons to transparency in clinical research and aids in the reduction in reporting biases.

Goldacre et al. assessed compliance with these requirements as of January 2018 and found poor performance overall with just 49.5% of over 7,200 due trials reported and large discrepancies in reporting rated between commercial (68%) and non-commercial (11%) sponsors [4]. Non-commercial sponsors on the EU-CTR mainly include universities, hospitals, research foundations and teams , and individual investigators acting as sponsors.

In June 2019, the noted lack of compliance with EU results reporting regulations prompted the EU Commission, the EMA, and the Heads of Medicines Agencies (HMA) to issue a statement noting that access to summary trial results allows “patients, practitioners, policy makers and

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What is new?

Key findings:

- As of May 2021, among the five largest non-commercial sponsors of clinical trials of medicines in 10 European countries, only the UK sponsors were adequately complying with EU trial reporting regulations.
- In a 40-month period, 49 major sponsors have increased the number of reported trials from 147 (January 2018) to 1,332 (May 2021): an 806% increase, compared to just a 25% increase in the total number of registered trials. This substantial increase was mainly due to the performance of sponsors from the UK, Belgium and Germany.

What this adds to what is known?

- Comparing non-commercial sponsors in the 10 European countries with the highest clinical trial activity shows high variation in results reporting rates across countries.
- Spain, France and the Netherlands, have lower reporting among major sponsors while Belgium, and especially the UK, stand out as better at reporting results to the EU-CTR compared to their peer countries.

What is the implication, what should change now?

- Non-commercial sponsors should invest in and implement processes to train and assist investigators in order to enhance compliance of trial reporting.
- European sponsors should routinely include the cost of reporting results on EudraCT as part of publication costs when requesting funding.
- Regulations in individual countries could also be issued to penalize sponsors who fail to report the results on EudraCT, following the lead of countries like Denmark.

other economic operators to make well-informed decisions about health-care and medical research" [5]. Two years later, 18 advocacy organizations sent an open letter to the HMA management group asking regulators to ensure that sponsors comply with EU trial reporting regulations that inspired further 'joint action' from the HMA, EMA and EU Commission to address reporting to the EU-CTR [6,7].

Goldacre et al. developed the EU Trials Tracker, a live website tool aimed to monitor every clinical trial that breaches EU regulation on trial results reporting. This tool updates the information monthly. Based on the EU Trials Tracker, as of May 2021, 70.2% of over 13,500 due trials have reported results but gaps in both reporting and data quality remain [8].

This analysis aims to describe the current reporting behavior of leading non-commercial sponsors throughout the EEA. We will examine reporting by country and investigate which major non-commercial sponsors have improved their reporting behavior since the initial analysis in 2018 [4] and the extent to which non-reporting remains an issue for others. This analysis will aid in understanding the current state of compliance with EU regulations throughout the continent and where further action is needed to promote compliance with EU reporting guidelines.

2. Materials and methods

Goldacre et al. have previously described their conservative methodology for identifying trials "due" to report on the EU-CTR [4]. Briefly, the trial must be listed in a "completed" trial status in all registered locations and have a completion date at least 13 months in the past (one year from completion plus an additional month to account for administrative delays). Trial information from the results section is not considered when determining if a trial is due to report or not. As of May 2021, there were 5,621 unique sponsors listed on the EU Trials Tracker, of which 130 were major sponsors with $\geq$50 trials registered on EU-CTR. These major sponsors had between 1 and 767 trials due to report; among all sponsors, 2,998 had 0 trials due to report.

To examine reporting by country we manually reviewed all sponsors with at least five due trials on the registry. This cut-off ensures we only consider "active" sponsors with a minimum level of engagement with the EU regulatory process. From this list of active sponsors, we extracted the top five sponsors from each EEA country by number of due trials and any "collaborative group" that conduct trials through national or multinational collaborations. Ties were broken by the total number of trials on the EU-CTR and countries that did not have five sponsors in our active non-commercial population were excluded. The data for universities and their associated medical centres, even if they are legally distinct entities, were grouped at the discretion of the study team based on publicly available information in order to maintain the reputational linkages. Details on aggregated sponsors are available in the supplemental information. As a benchmark, we also include results reporting data from the 10 top commercial sponsors on the EU TrialsTracker by total number of trials.

For each included non-commercial sponsor, we extracted the total number of trials registered on the EU-CTR, the number and percentage of due trials with results, and details of data issues that obfuscate whether a trial is due to report or not using the EU TrialsTracker methodology (i.e., inconsistent data). These trials fall into four categories: 1) trials with a global completion date that are still ongoing in some locations, 2) trials completed in all locations but missing a completion date, 3) trials missing a trial status, and 4) trials with a non-EEA protocol that cannot be marked as completed due to limitations of the EU-CTR.

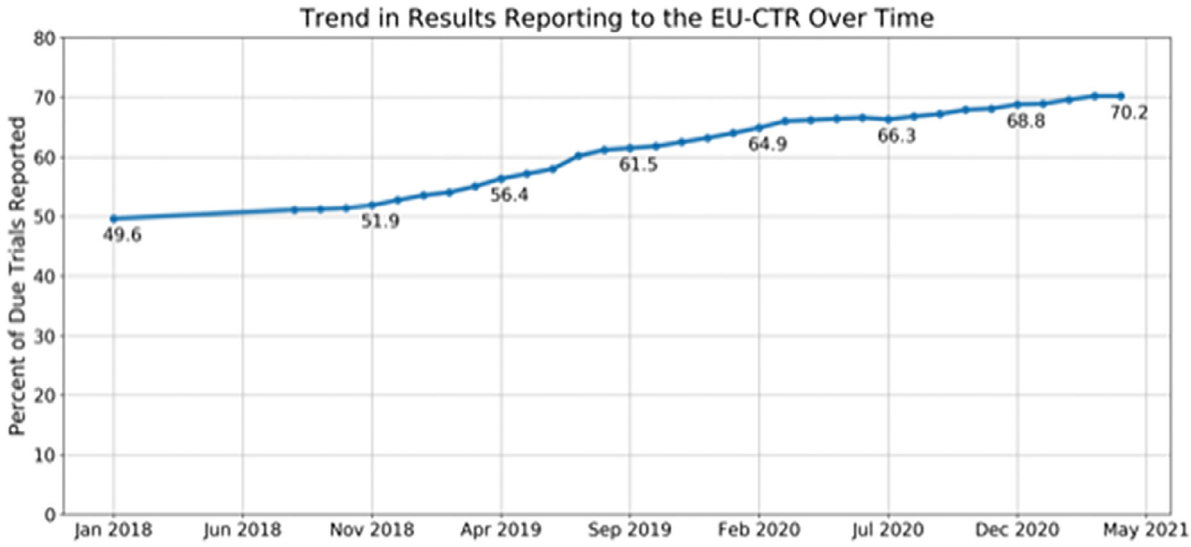

Fig. 1. The percent of trials confirmed as due reported to the EU-CTR including data from January 2018 from Goldacre et al. [4], then monthly from August 2018 onward following the launch of the EU Trials Tracker.

Lastly, in order to track reporting performance of large non-commercial sponsors over time, we compared data from the original analysis in January 2018 [4] on the reporting performance of major non-commercial sponsors to those same sponsor's reporting rates as of May 2021. Major sponsors are defined as those with at least 50 trials registered on the EU-CTR. Sponsors did not have to be included in our active non-commercial population to be considered for this analysis. Some sponsors from the original Goldacre et al. analysis have since been disaggregated into separate records on the EU TrialsTracker at the request of the sponsors as they are legally separate entities for purposes of trial reporting (e.g., Heidelberg University and Heidelberg University Hospital or the various hospitals in the Copenhagen University Hospital system). In order to maintain consistency with the original analysis, the constituent sponsors have been re-aggregated according to the 2018 groupings.

As we had complete data for each grouping of interest across the entire EU-CTR, it is inappropriate to present confidence intervals or conduct comparative statistical tests as if these were point estimates randomly sampled from a larger population. Including confidence intervals and comparing point estimates using statistical tests presupposes that these were random samples drawn from a distribution of values and subject to sampling variation. In reality, we had the complete population of trials of interest for each sponsor across all analyses. As such, any comparisons can be taken at face value without the need to describe variation that doesn't exist. While we considered using comparative measures, like odds ratios, to show differences between countries, we felt this was also inappropriate as reporting is clustered by country. In order to properly calculate these figures, we would require more clusters than countries that exist in the EU to have adequate power. We therefore limited our analysis to descriptive proportions to convey the trends and variation of interest.

The full code for the EU TrialsTracker is available and the results of this analysis can be fully replicated from EU TrialsTracker data via a Jupyter Notebook. All data and code are available on GitHub [9,10].

3. Results

As of 1 May 2021, there were 39,487 trials registered on the EU-CTR. Overall, 13,709 trials were assessed as due and 9,620 (70.2%) of these had a results report posted to the EU-CTR. The overall trend in reporting from January 2018 to May 2021 is shown in Fig. 1. Our active non-commercial population included 50 sponsors from 10 countries and nine collaborative groups (n = 59) with 6,072 sponsored trials. This population of sponsors had 1,058 of 1,916 (55.2%) due trials reported representing 14.0% of all due trials and 11.0% of all reported trials identified on the EU TrialsTracker (Table 1). The 10 largest commercial sponsors had 2,989 of 3,024 (98.8%) due trials reported (Supplemental information).

Reporting of active non-commercial sponsors by country shows substantial variation ranging from 3.9% to 93.6%. The median reporting percent among all 11 groupings (10 countries + the collaborative groups) was 39.5%. The included sponsors from the UK led all countries with 93.6% of due trials reported followed by Belgium (68.6%) and Germany (57.8%). Conversely, sponsors from France (3.9%), Spain (10.3%), the Netherlands (20.9%) all finished >10 percentage points away from the median country (Austria, 39.5%) (Table 1). The 9 collaborative groups reported 50% of due trials. Fifteen included sponsors had no due trials reported. These sponsors were located in Bel-

Table 1. Total number of clinical trials on the EU-CTR, those due to report results and actually reported. Non-commercial sponsors by country and collaborative groups

Sponsor or sponsors' country (N)	Clinical trials on the EU-CTR (n)	Clinical trials due to report results (n)	Clinical trials reported n (%)
Collaborative groups (9)	282	100	50 (50.0)
Austria (5)	624	324	128 (39.5)
Belgium (5)	605	140	96 (68.6)
Denmark (5)	685	300	120 (40)
France (5)	586	78	3 (3.9)
Germany (5)	504	230	133 (57.8)
Italy (5)	399	50	17 (34.0)
Netherlands (5)	923	91	19 (20.9)
Spain (5)	267	39	4 (10.3)
Sweden (5)	433	69	24 (34.8)
UK (5)	764	495	464 (93.6)

N, number of sponsors: the top five having at least five trials due to report; n, number of clinical trials

gium (n=1), France (n=3), Italy (n = 3), Netherlands (n = 1), Spain (n = 4) and the Collaborative groups (n = 3). (Supplemental information).

Among all (n = 6,072) registered trials in our active non-commercial population, 940 (15.5%) had inconsistent data that prevented them from being identified as due to report. Sponsors from Italy (48.9%) and Spain (29.2%) had the highest rates of inconsistencies across their trial portfolio while the UK (3.3%) and Austria (8.8%) had the lowest. The median percent of inconsistent trials was 14.5% from Germany (Table 2). Missing completion date information was the most common issue causing 78.5% of all inconsistencies in our population followed by trials containing contradictory information on completion status (16.4%), missing a trial status in the appropriate field (4.9%) and including a non-EEA protocol (0.2%). Sponsors with very low numbers of inconsistent data also had relatively low numbers of sponsored trials. Of the eight sponsors with less than three inconsistent trials, only two sponsored more than 25 trials overall. Some trials with inconsistent data also had results available. Overall, 228 (24%) of all inconsistent data trials had results available however it is unclear how these would impact reporting rates without more information about the majority of inconsistent data trials without results.

The 2018 manuscript by Goldacre et al. [4] identified 49 major non-commercial sponsors. From January 2018 to May 2021 these sponsors increased in the number of registered trials by 25.2% (5,201 to 6,511), the number of due trials by 117.1% (983 to 2,134), and the number of due trials reported by 806% (147 to 1,332). In 2018, 27 (55%) of these sponsors had no due trials reported; in 2021 just 10 (20%) had failed to report any results. Similarly, the number of sponsors that reported >90% of their due trials increased from 0 in 2018 to 13 in 2021. Sponsors with no reporting in 2021 are from Belgium (n = 1), France (n = 2), Italy (n = 3), the Netherlands (n = 2) and Spain (n = 2) (Table 3 and Supplemental Information). There were seven very highly active sponsors with more than 200 trials posted on the EU-CTR in 2021. Among these, KU Leuven (Belgium) reported 98% of all due trials – an increase of 82 trials over 2018 (Table 4) while Hospitals of Paris - AP-HP (France) reported just a single due trial (3%) between 2018 and 2021. The other five highly active sponsors (Copenhagen University and Hospitals, Denmark; Erasmus University and Radboud University, the Netherlands; Karolinska Institutet, Sweden; Medical University of Vienna, Austria) reported between 33% and 43% of due trials.

The large increase in reporting was primarily driven by sponsors in the UK. In 2018, just two UK sponsors exceeded 75% reporting while in 2021 all 14 UK sponsors exceeded that mark including the only five sponsors with 100% reporting (Table 4). Major UK sponsors reported 94.4% of their trials in 2021, an increase of 564 new trials reported since 2018. Only the 3 Belgian and 3 German sponsors had collectively reported more than 50% of their due trials in 2021. Belgian sponsors added 100 and German sponsors 79 results to the registry in that time period. Major sponsors from Spain (0%), France (1.8%) and Italy (10%) had the worst reporting rates in 2021 (Table 5).

4. Discussion

4.1. Summary of results

This study uses data from the EU Trials Tracker to holistically track how top non-commercial sponsors are complying with EU regulations on trial reporting. Overall, we report large gains in the total number of results appearing on the registry between 2018 and 2021 but with major gaps among some large sponsors and countries.

4.2. Research in context

In May 2021, our population of the 5 largest non-commercial sponsors, by country, reported 55% of due

Table 2. Total number of clinical trials on the EU-CTR and those with inconsistent data. Non-commercial sponsors by country andcollaborative groups

Sponsor or sponsors' country (N)	Clinical trials on the EU-CTR (n)	Clinical trials with inconsistent data n (%)	Types of Inconsistent Data				Inconsistent with Results n (%) of inconsistent data
			Ongoing with Completion dates n (%) of inconsistent data	Missing Completion Date	Contains Non-EEA Country	Missing Trial Status	
Collaborative groups (9)	282	66 (23.4)	36 (54.6)	29 (43.9)	1 (1.5)	0	40 (60.6)
Austria (5)	624	55 (8.8)	8 (14.6)	44 (80)	0	3 (5.5)	7 (12.7)
Belgium (5)	605	93 (15.4)	13 (14)	73 (78.5)	0	7 (7.5)	24 (25.8)
Denmark (5)	685	96 (14.0)	11 (11.5)	85 (88.5)	0	0	27 (28.1)
France (5)	586	73 (12.5)	8 (11.0)	42 (57.5)	0	23 (31.5)	3 (4.1)
Germany (5)	504	73 (14.5)	22 (30.1)	48 (65.8)	0	3 (4.1)	32 (43.8)
Italy (5)	399	195 (48.9)	5 (2.6)	188 (96.4)	0	2 (1.0)	39 (20)
Netherlands (5)	923	135 (14.6)	19 (14.1)	113 (83.7)	0	3 (2.2)	27 (20)
Spain (5)	267	78 (29.2)	5 (6.4)	73 (93.6)	0	0	8 (10.3)
Sweden (5)	433	51 (11.8)	11 (21.6)	36 (70.6)	0	4 (7.8)	4 (7.8)
UK (5)	764	25 (3.3)	16 (64)	7 (28)	1 (4)	1 (4)	17 (68)

N, number of sponsors: the top having at least 5 trials due to report; n, number of clinical trials

trials. Past studies have looked at reporting among the entire population of non-commercial sponsors. In the original study by Goldacre et al., just 11% of all due trials sponsored by non-commercial funders were reported [4]. In a recent study examining required reporting to ClinicalTrials.gov, the compliance rate for non-industry trials was 35% reported within one year of primary completion and 69% reported at any time after becoming due [11]. US law requires reporting within one year of the completion of primary data collection rather than one year from full study completion as required by EU guidelines [12]. Recent efforts by transparency advocates further confirm major advances among reporting from major non-commercial sponsors throughout the EU while highlighting similar gaps [13]. Major commercial sponsors maintained high reporting rates on the EU-CTR from 2018 into 2021 as observed in this analysis.

The reporting rates of major non-commercial sponsors increased substantially from 2018 compared to 2021 driven largely by British sponsors. Improvements were not limited to UK sponsors though, as the rest of Europe also had a reporting rate increase from 8% in 2018 to 43% in 2021. The particularly high rates of compliance by UK non-commercial sponsors could be based on campaigning and political interest in enhancing clinical trials reporting compared to their counterparts in the rest of Europe. Key events in the UK include: a) the founding of civil society campaigns such as AllTrials (an international initiative born in the UK) [14]; b) the setup of the Trials Tracker project including the launch of the EU Trials Tracker [8] and the publication of the first results [4]; c) specific focus on the issues of research integrity and trial reporting from the UK Parliament House of Commons' Science and Technology Committee [15]; and d) the ongoing work of transparency advocates in generating reports on reporting compliance of UK institutions [16]. The results of this latter report, and interest from the UK Parliament following the launch of the EU TrialsTracker, seemed to have triggered an energetic response from the UK universities as observed in our analysis. A similarly notable increase in Germany may also have been influenced by advocacy reports drawing attention to the low 7% compliance rate among universities in late 2019 [17]. These large and rapid improvements in trial reporting, apparently associated with interventions from policymakers, campaigners, and the media, suggest that public advocacy can increase trial reporting.

In both of our analysis populations, sponsors from Spain, France, and the Netherlands showed very little reporting effort. A prior analysis of the top 25 sponsors with due trials in Spain showed a reporting rate of 25% (19 of 75 trials) in 2021, with 72% (13 of 18) among collaborative groups but only 11% (6 of 57) among the rest of non-commercial sponsors [18], this is similar to the 10% found in this study with just 5 sponsors. In France, just 7% (10 of 159) of due trials from 27 non-commercial sponsors were reported as of February 2021 [19], similar to

Table 3. Sponsors with highest proportion of non-commercial clinical trials[a] unreported in January 2018 and in May 2021. The 25 major sponsors reporting at the median or less in 2021. (The complete list of sponsors is included in Supplemental information).

Sponsor, country	2018			2021		
	Trials on the EU-CTR, N	Trials due to report results, N	N (%) reported	Trials on the EU-CTR, N	Trials due to report results, N	N (%) reported
Hospitals of Paris, France	194	7	0 (0)	305	31	1 (3.2)
Karolinska Institutes, Sweden	189	21	0 (0)	224	30	13 (43.3)
Radboud University, Netherlands	178	3	0 (0)	238	34	14 (41.2)
Erasmus University, Netherlands	161	3	0 (0)	213	5	2 (40)
University of Amsterdam, Netherlands	153	4	0 (0)	196	14	0 (0)
Agostino Gemelli University Policlinic, Italy	142	11	0 (0)	156	11	0 (0)
Ghent University, Belgium	126	19	0 (0)	141	39	8 (20.5)
VU University Medical Centre, Netherlands	126	3	0 (0)	174	18	1 (5.6)
Utrecht University, Netherlands	122	6	0 (0)	154	17	3 (17.7)
AOU di Bologna, Policlinico S Orsola-Malpigi, Italy	120	1	0 (0)	127	1	0 (0)
Helsinki University, Finland	101	12	0 (0)	120	18	4 (22.2)
Université Libre de Bruxelles, Belgium	85	3	0 (0)	99	7	0 (0)
Vita-Salute San Raffaele University, Italy	83	5	0 (0)	130	7	2 (28.6)
Hospices Civils de Lyon, France	81	3	0 (0)	103	15	0 (0)
University of Oslo, Norway	72	1	0 (0)	102	6	1 (16.7)
University of Munich (Ludwig-Maximilians), Germany	71	26	0 (0)	78	40	5 (12.5)
Maastrich University, Netherlands	61	2	0 (0)	75	7	0 (0)
Fundació Clínic per a la Recerca Biomédica, Spain	60	1	0 (0)	76	5	0 (0)
Gothenburg University, Sweden	56	6	0 (0)	54	8	1 (12.5)
Uppsala University/Uppsala County Council, Sweden[b]	55	6	0 (0)	73	11	4 (36.4)
European Institute of Oncology, Italy	54	1	0 (0)	61	1	0 (0)
Blaise Pascal Université, France[c]	53	4	0 (0)	62	11	0 (0)
Hospital de la Santa Creu i Sant Pau, Spain	53	3	0 (0)	61	10	0 (0)
Medical University of Vienna, Austria	354	166	8 (4.8)	405	221	72 (32.6)
Copenhagen University and Hospitals, Denmark[d]	395	133	9 (6.8)	527	228	79 (34.6)

N, number of trials

[a] Only the sponsors included in Goldacre et al. [4] analysis was eligible for inclusion in this analysis; these were sponsors with more than 50 trials registered on the EU-CTR in January 2018. To make a logical comparison between 2018 and 2021, only the specific sponsors' names included in Goldacre et al. analysis is considered in both 2018 and 2021, unless otherwise stated.

[b] In 2021, this combined 6 sponsors: Uppsala University, Uppsala University Hospital, Uppsala Clinical Research Center, Uppsala University & Uppsala County Council, Region Uppsala, and Uppsala County Council.

[c] In 2021, this is CHU Clermont-Ferrand.

[d] In 2021, this combined 13 sponsors: Bispebjerg Hospital, Copenhagen University and Hospital, Frederiksberg Hospital, Herlev and Gentofte Hospital, Holbæk Hospital, Hvidovre Hospital, Nordsjællands Hospital, Næstved Hospital, Rigshospitalet, Roskilde Hospital, Slagelse Hospital, University of Copenhagen, and Zealand University Hospital.

Table 4. High performing sponsors from 2018 to 2021

2021 Highest Reporting Percent		2021 Most Reported Trials		Biggest Change in Reporting Percent		Biggest Change in Trials Reported	
Sponsor	**Percent**	**Sponsor**	**N trials**	**Sponsor**	**Delta in Reporting Percent**	**Sponsor**	**Delta of Reported Trials**
King's College London, UK	100	Imperial College London, UK	93	Manchester University NHS Foundation Trust, UK	+100	Imperial College London, UK	+88
Guy's and St Thomas' NHS Foundation Trust, UK	100	KU Leuven, Belgium	82	NHS Greater Glasgow and Clyde, UK	+92	KU Leuven, Belgium	+81
NHS Greater Glasgow and Clyde, UK	100	Copenhagen University and Hospitals, Denmark	79	Technical University of Munich, Germany	+90	Copenhagen University and Hospitals, Denmark	+70
Manchester University NHS Foundation Trust, UK	100	University College London, UK	79	University of Nottingham, UK	+89	University College London, UK	+70
University of Birmingham, UK	100	Medical University Vienna, Austria	72	Guy's and St Thomas' NHS Foundation Trust, UK	+88	King's College London, UK	+67

Table 5. Number of clinical trials from major non-commercial unreported as of January 2018 and May 2021 by country. Clinical trials[a] unreported in 2018 [4] were considered.

Country (N)	January 2018		May 2021	
	Trials due to report results, n	**n (%) reported**	**Trials due to report results, n**	**n (%) reported**
Collaborative group (1)	14	10 (71.4)	29	28 (96.6)
Austria (3)	234	13 (5.6)	312	125 (40.1)
Belgium (3)	30	1 (3.3)	130	90 (69.2)
Denmark (3)	201	17 (8.5)	359	142 (39.6)
Finland (1)	12	0 (0)	18	4 (22.2)
France (3)	14	0 (0)	57	1 (1.8)
Germany (5)	151	1 (0.7)	230	133 (57.8)
Italy (4)	18	0 (0)	20	2 (10.0)
Netherlands (6)	21	0 (0)	95	20 (21.1)
Norway (1)	1	0 (0)	6	1 (16.7)
Spain (2)	4	0 (0)	15	0 (0)
Sweden (3)	33	0 (0)	49	18 (36.7)
UK (14)	250	105 (42.0)	814	768 (94.4)
Total	*983*	*147 (15.0)*	*2134*	*1332 (62.4)*

N, number of non-commercial sponsors; n, number of trials.

[a] Only the sponsors included in Goldacre et al. [4] analysis is included here; these were sponsors with more than 50 trials registered on the EU-CTR in January 2018.

the 4% observed in our analysis of the top 5 active French sponsors conducted just a few months later.

A recent analysis on 7,175 journals in Scopus found that only 22% of all articles in the field of Medicine are open access [20]. Although this percentage will increase with the implementation of Plan S [21], an open access initiative fully supported by the EU Commission and many funders, this will take years to begin to show an impact. Fulfilling the EU regulations ensures the timely free access to trial results independent of the delays or shortcomings of the journal publication process. Increased compliance with EU reporting regulations would also aid in addressing long

standing issues with publication bias [22,23]. Furthermore, trial registries are important sources of studies for consideration in evidence synthesis [24]. Despite the presence of inconsistencies on registries, these registrations were valid surrogates of the primary outcome in the trial protocol for 79% of trials examined in one analysis [25] and usually provide more safety information –especially important when dealing with serious adverse events and deaths– than articles [26,27].

The presence of errors and omissions in different types of entry is common and has been previously identified in the EU-CTR [4] and other registries [28–30]. In our population of 59 highly active non-commercial sponsors, 16% of registered trials had inconsistencies, most commonly missing completion dates. It is noteworthy that the UK sponsors (3% of trials with inconsistencies) had the highest overall data quality, whereas the sponsors from Italy (49%) and Spain (29%) were the worst. The confluence of strong data quality and high reporting rates suggest a strong engagement with the regulatory process by UK sponsors.

4.3. Limitations

This analysis has limitations. Firstly, the analysis populations were defined as a specific, non-random subsets of all non-commercial sponsors running clinical trials with medicines in Europe. We picked our populations to include the leaders in clinical research across Europe and to provide comparable data across countries and sponsors. As such, these results are indicative of how very large non-commercial sponsors are performing but may not necessarily generalize to smaller non-commercial sponsors. Goldacre et al. found that the number of trials registered on the EU-CTR was highly associated with increased reporting rates, however this relationship was likely influenced by the high reporting rates of very large commercial sponsors [4].

Secondly, data quality on the EU-CTR remains an issue. Similar to recorded issues in other registries [28,29], there are inconsistencies, errors and omissions. These inconsistencies may even persist for the same trial in different registries [30]. In addition to the "inconsistent data" issues noted in our analysis and tracked on the EU Trials Tracker, there are also issues with trials remaining in an "ongoing" status long after they should have reasonably been listed as completed [31]. This would lead to due trials being missed and therefore cause an overestimation of reporting rates in some instances. Incorrect registry data could be due to lack of time or skills by the individuals entering the data or administrative issues at national authorities [32]. Dedicated staff –administrators are usually in charge of monitoring compliance with results reporting– and software to support trial reporting may help to increase reporting rates [33]. Resources like the EU Trials Tracker can also aid sponsors as they begin to examine their portfolio of registered trials and identifying which trials are missing results.

Lastly, due to the UK leaving the EU in January 2021, trials that were ongoing as of that date can no longer become "due" to report. Overall, however, with the extremely high performance of most UK sponsors analyzed, the impact of any new trials becoming due between January and May 2021 would be unlikely to substantially alter our results.

4.4. Policy Implications

The situation described in the UK conveys a clear message: non-commercial sponsors can comply with the EU regulation on clinical trials reporting. Institutions and organizations across Europe should urgently put in place processes to train and assist investigators in this regard. Sponsors should include the cost of reporting results on EudraCT as part of dissemination costs when requesting funding and set up training and internal processes to support these efforts. Research ethics committees could request investigators to report whether trial results have been posted on the EudraCT when examining ongoing studies or considering approvals for new studies. Reminders, such as personalized emails, have been shown to improve reporting rates on ClinicalTrials.gov [34]. Regulations in individual countries could also be issued to penalize sponsors who fail to report the results on EudraCT, as Denmark announced in 2019 [35]. New European trial regulations are set to completely enter into force in early 2022 and empower countries to further monitor and sanction sponsors who fail to report to the Clinical Trial Information System that will eventually replace the EudraCT and EU-CTR [36]. The US Food and Drug Administration has recently acted against a company that failed to submit the summary trial results under US law [37]; the impact this will have on trial reporting in the US, and whether further action will be taken against non-commercial sponsors, remains to be seen. Lastly, all those involved in the clinical trials enterprise should reflect that their objective is to provide clinicians and patients with accurate estimates of the benefits and hazards of interventions: this objective is substantially undermined when the ethical obligation to timely report all trial results is not met.

5. Conclusions

The timely reporting of trial results benefits patients, investigators, clinicians, and policymakers across the world. European clinical investigators must ensure that trial results are accessible to citizens by submitting them to the EudraCT system for posting on the EU-CTR. Additional resources from non-commercial sponsors, and increased attention from national regulators, could make a huge difference in the completeness of the evidence-base generated from clinical trials in Europe covering many treat-

ments in wide use today. The marked increase in reporting among many sponsors over the past three years shows that progress is possible.

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Author contributions

R. Dal-Ré: conceptualization, investigation, methodology, data curation, visualization, writing – original draft, writing – review and editing. B. Goldacre: resources, writing – review and editing. I Mahillo-Fernández: formal analysis, writing – review and editing. N DeVito: methodology, data curation, resources, visualization, writing – review and editing

Study data

A full archive of data from the EU Trials Tracker, including all data that informed this analysis, is available on GitHub: https://github.com/ebmdatalab/euctr-tracker-data. The notebook for the analysis is available at: https://github.com/ebmdatalab/euctr_reporting_progress

Conflict of interest

N DeVito reported being employed on grants from the Laura and John Arnold Foundation (original TrialsTracker funder) and the Good Thinking Society (TrialsTracker funder) during the conduct of the study; and grants from Fetzer Franklin Fund and doctoral funding from Naji Foundation outside the submitted work. He also declares working as a member of the AllTrials Campaign. B Goldacre reported receiving grants from the Laura and John Arnold Foundation (Original TrialsTracker funder) and grants from Good Thinking Society (TrialsTracker funder); and grants from Wellcome Trust, National Institute for Health Research (NIHR), NIHR School of Primary Care Research, Oxford Biomedical Research Centre, Mohn-Westlake Foundation, Health Foundation, and the World Health Organization outside the submitted work; receiving personal income from speaking and writing for lay audiences on the misuse of science; and being a cofounder of the AllTrials Campaign. R Dal-Ré and I Mahillo-Fernández reported none.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.11.005.

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