dietetics

MDPI

Brief Report

Clinical Trials of Vitamin Supplements: Are They Meeting the European Medicines Agency Prompt Dissemination Regulation?

Maria A. Lampropoulou [1,2], Maria G. Grammatikopoulou [3,4,*], Xenophon Theodoridis [2], Savvas Katsaridis [4], Despoina Bobora [4], Aikaterini Patsatsi [5], Anna-Bettina Haidich [6] and Dimitrios G. Goulis [3,*]

1 4th Department of Pediatrics, Papageorgiou General Hospital, Aristotle University of Thessaloniki, GR-56429 Thessaloniki, Greece
2 Medical School, Faculty of Health Sciences, Aristotle University of Thessaloniki, GR-54124 Thessaloniki, Greece
3 Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, GR-56429 Thessaloniki, Greece
4 Department of Nutritional Sciences and Dietetics, Faculty of Health Sciences, Alexander Campus, International Hellenic University, GR-57400 Thessaloniki, Greece
5 2nd Department of Dermatology, Papageorgiou General Hospital, Aristotle University of Thessaloniki, GR-56429 Thessaloniki, Greece
6 Laboratory of Hygiene, Preventive Medicine and Medical Statistics, Medical School, Aristotle University of Thessaloniki, GR-54124 Thessaloniki, Greece
* Correspondence: mariagram@auth.gr (M.G.G.); dgg@auth.gr (D.G.G.)

Citation: Lampropoulou, M.A.; Grammatikopoulou, M.G.; Theodoridis, X.; Katsaridis, S.; Bobora, D.; Patsatsi, A.; Haidich, A.-B.; Goulis, D.G. Clinical Trials of Vitamin Supplements: Are They Meeting the European Medicines Agency Prompt Dissemination Regulation? *Dietetics* **2022**, *1*, 114–123. https://doi.org/10.3390/dietetics1020012

Academic Editor: Bahram H. Arjmandi

Received: 25 June 2022
Accepted: 2 August 2022
Published: 1 September 2022

Abstract: Vitamin supplements are over-the-counter medications consumed by the majority of adults. Given that many supplements may be ineffective and/or associated with adverse events, compliance of the registered trials to the European Medicines Agency (EMA) rule for prompt reporting of the results is of crucial importance for consumers' health. The present retrospective study was designed to evaluate compliance with the European Union (EU) requirement to post the trial results to the EU Clinical Trials Database (EudraCT) and assess the trial characteristics associated with this compliance. Three independent researchers searched the EudraCT for completed trials on vitamin supplements performed on humans. A total of 144 completed trials involving 40,464 participants fulfilled the inclusion criteria. For 45.7% of these, results were due. Trials funded by the industry had approximately quadruple chances of being published, adjusting for their design, masking, comparator, and participant age group. Moreover, trials testing vitamin supplement safety are more likely to report their findings as compared to vitamin efficacy. Many vitamin supplementation trials registered in the EudraCT failed to report their results and adhere to the EMA regulations. Stricter regulations should be imposed concerning trial results reporting to increase transparency and public trust.

Keywords: trial registration; dietary supplements; medical nutrition therapy; research methodology; trial design; funding; oral nutrient supplements; research transparency; good clinical practice

1. Introduction

The dietary supplements industry has grown during the past decade, offering more than 90,000 products on the market [1]. Although supplements are often advertised claiming health benefits [2], most of these are not supported by scientific evidence [3]. In parallel, many dietary supplements are either adulterated or contaminated [4–7] and have been associated with multiple adverse events [8]. While consumers admit not trusting dietary supplement advertisements [9], they tend to consume at least one as adults [10–13], mainly in the form of multivitamins [11,13,14]. As concerns for consumer safety have been raised [9,15,16], the need for transparency in the dietary supplement industry in parallel to consumer education is imminent [17].

Dietary supplement research consists mainly of *in vivo* and animal studies, with many reaching the level of randomized controlled trials (RCTs), without always examining validated endpoints. Lesser et al. [18] were the first to report that, as far as nutrition research is concerned, the type of funding source is significantly related to the conclusions drawn, with commercial funding being associated with more positive results. Since then, this industry effect has been reported in drug and device studies concerning direct [19,20] and indirect funding [21]. Trial quality appears to be a constantly moving target [22] and the lack of adherence to good clinical practices is apparent in both the USA and the European Union (EU) [23]. Within the EU, registration of all RCTs is required on the European Union Clinical Trials Database (EudraCT) platform. The completion of the study must be followed by the prompt (within a year) publication of the results. Through this rule, the European Medicines Agency (EMA) aims to increase transparency and availability of the results, irrespectively of their publication in scientific journals. However, a review of the EudraCT entries revealed that only half (49.4%) of the completed trials reported their results promptly [24]. The same trend was identified in the clinicaltrials.gov registry [25].

Given that vitamin supplements are over-the-counter medications (i.e., available without a prescription) and consumed by most adults while often entailing various adverse events, compliance of the registered trials to the EMA rule for prompt results reporting is crucial for consumers' health. The present study was designed to evaluate the vitamin supplement trials' compliance with the EU requirement to post the results of the trials to the EudraCT and assess the trial characteristics associated with this compliance.

2. Materials and Methods

2.1. Search Strategy

The EudraCT was searched for completed trials on vitamin supplements by three independent researchers (M.L., S.K., D.B.). Trials were considered eligible when (1) performed on humans of any age and health status, (2) were completed, (3) involved an intervention with any vitamin supplement without concomitant medication, and (4) did not include vitamin supplements in the placebo comparator.

2.2. Data Extraction

For each trial, data were extracted by three reviewers (M.L., S.K., D.B.) in a predefined Microsoft Excel® (Microsoft, Redmond, Washington, WA, USA) form, including (1) the planned sample size, (2) comparators, (3) country of origin, (4) funding source, (5) population (age group, health status), (6) scope of the trial (diagnosis, prophylaxis, safety, therapy, efficacy), (7) masking, and (8) design.

2.3. Statistical Analyses

To test the normality assumption of the data, the Kolmogorov–Smirnoff test was used. Non-normally distributed continuous data were presented as medians and interquartile range (IQR), and categorical data were expressed as frequencies. A binary logistic regression was applied to assess the association between protocols that had published their results within a year after completion and explanatory variables. In the univariate model, explanatory variables with a $p < 0.2$ were selected for inclusion in the multivariable model. Explanatory variables with a $p > 0.2$ in the univariate model considered methodological interest were also included in the multivariable model. Effects of the risk factors were expressed as odds ratios (OR) with their 95% confidence intervals (95% CI) and respective p values. The area under the receiver operating characteristic (ROC) curve was calculated for the multivariable model. The level of significance was set at $p < 0.05$. All analyses were performed in SPSS version 25.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Characteristics of the Included Trials

Out of the 360 trials identified, 95 consisted of duplicate entries and were removed. Of the remaining, 144 involved completed trials, including 40,464 participants. For 45.7% of identified registered trials, results were due. The characteristics of the completed trials are presented in Table 1. Identification of trials with positive findings was not possible, as the majority reported mean and standard deviation characteristics per intervention arm.

Table 1. Characteristics of the trials included in the analysis (*n*).

Sponsor:	Commercial	34
	Academic	72
	Non-commercial	38
Scope of the trial:	Diagnosis (Yes/No/NR)	7/128/9
	Prophylaxis (Yes/No/NR)	36/96/9
	Safety (Yes/No/NR)	78/60/6
	Therapy (Yes/No/NR)	93/48/3
	Efficacy (Yes/No/NR)	105/38/1
Design:	RCT (Yes/No/NR)	127/16/1
Masking:	Double-blind (Yes/No/NR)	98/41/5
Participants:	Newborns (Yes/No)	2/140
	Infant and toddlers (Yes/No)	1/143
	Children (Yes/No)	8/136
	Adolescents (Yes/No)	11/133
	Adults (Yes/No)	126/18
	Aging (Yes/No)	108/36
Population health status:	Healthy	14
	Patients	120
	Healthy participants and patients	8
	Vulnerable population	2
Sample size:	*n* *	86 (57–200)
Country of origin:	UK	42
	Austria	20
	Multicenter	14
	Other	68

* expressed as median (IQR); IQR, inter-quantile range; NR, not reported; RCT, randomized controlled trial; UK, United Kingdom.

3.2. Factors Associated with Prompt Results Reporting in Trials

The univariate regression analysis (Table 2) revealed that trial results were more likely to be reported when assessing vitamin safety and being sponsored by the industry. Based on the multivariate regression analysis results, trials funded by the industry had approximately quadrupled the chances of being published, taking into account their design, masking, comparator, and participant age group.

Table 2. Multivariate regression analysis explaining prompt results reporting.

Variables	Univariate Model			Multivariable Model		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Safety scope (Yes/No)	2.35	1.18 to 4.70	0.016	1.66	0.76 to 3.58	0.201
RCT design (Yes/No)	1.66	0.55 to 5.01	0.365	1.98	0.61 to 6.45	0.257

Table 2. *Cont.*

Variables		Univariate Model			Multivariable Model		
		OR	95% CI	*p* Value	OR	95% CI	*p* Value
Sponsor:	-Commercial vs. non-commercial	5.13	1.88 to 14.01	0.001	4.42	1.53 to 12.75	0.006
	-Academic vs. non-commercial	1.15	0.49 to 2.72	0.746	1.23	0.52 to 2.93	0.643
Adult participants (Yes/No)		1.36	0.48 to 3.86	0.563	0.96	0.32 to 2.85	0.937

CI, confidence intervals; OR, Odds ratio; RCT, randomized controlled trial; ROC, receiver operator curve; Area under the ROC curve: 0.69 (95% CI 0.61–0.78), $p \leq 0.001$.

4. Discussion

The present study revealed that the scope of the vitamin supplement trials (safety assessment) and the sponsor type are independent factors affecting prompt publication of the results. On the other hand, when all the key trial characteristics were accounted for, commercially funded trials were more likely to report their findings in the registry within the one-year deadline suggested by the EMA.

Among published trials, the funding of RCTs by the industry is quite common [26]. The same trend has been reported to prevail in nutrition research [27–30]. Industry trials are more likely to adhere to dissemination regulations compared with non-commercial trials and are more likely to publish their findings on time [19–21,24,31–33]. When the pharmaceutical industry has spent funds on a trial, results are expected to be disseminated. Gordon et al. [33] reported that trial costs were positively associated with timely publication. In parallel, when a commercial sponsor finances several trials, prompt result dissemination is more likely to occur [24], as frequent funders tend to comply with transparency rules [34]. Interestingly, even academic-led trials often fail to disseminate their results promptly [35–37].

Overall, the compliance of vitamin intervention trials to the requirement for results publication appears poor [24]. Goldacre [24] reported that many trials remain on an "ongoing" status to bypass the dissemination problem, although they have, in fact, been completed. Indeed, in the present study, many trials were registered as ongoing, although in some cases, 10 years had passed from the reported trial initiation date. According to Chen [35], results dissemination is gradually increasing following the completion of the study, with the majority of trials publishing their findings sometime after the suggested 12-month period, at a median time of 26.1 months.

Trial transparency is an important issue [38,39], pledged by the World Health Organization [40] and the European Commission (EC). According to the Helsinki declaration for research conducted in humans, not only positive, but negative and inconclusive results must also be published, or made publicly available. On some occasions, research appears to be conducted based on inertia and convention instead of evidence-based medicine [41]. Although mandatory trial registration was an important milestone towards transparency [42,43], selective reporting bias remains an issue of concern, especially among commercially funded research [31,44–48]. The research appears unanimous on the fact that trials with positive findings are more likely to be published or report their findings [33,49–51]. Table 3 details the primary studies investigating the timely reporting of results in various research areas. Most studies indicate a suboptimal reporting rate, dependent on several factors and trial characteristics [24,25,31–33,52–54].

Table 3. Characteristics of primary studies investigating results reporting in trial registries.

First Author	Study Design	Registry Searched	Interventions Included in Analyses	Completed Trials (*n*)	Registry Reported Results (%)	Factors Associated with Results Reporting															
						Sponsor			More Recent Trials	Frequent-Funder Sponsor	Industry Collaborator	Trial Phase	RCT	Trial Origin		Terminated Trial	Sample		Trial Aim		
						Industry	US State	Academic						Outside the US	With US Partner		*n*	Adult	Drug	Vaccine/BA	Device/DTA
Al-Durra [48]	CS	CTG	Digital health	556	11	↓	↑					↑ II		↑							
Chen [35]	CS	CTG	All Œ	4347	26.8 † 12.6 Ž																
DeVito [25]	Cohort	CTG	All	4209	40.9 * 63.8 †	↑	↑†			↑	↑	↓ I/III		↓	↑	↑			↑	↑	↓
Gill [32]	Retrospe-ctive cohort	CTG	US-based	3360	28	↑						↑ III/IV						↑			
Goldacre [24]	Retrospe-ctive cohort	EudraCT	All	7274	49.5	↑			↑	↑											
Gopal [53]	CS	CTG	All	1097 ^ 2231 ‡ 2923 Š	6.8 ^ 19.1 ‡ 10.8 Š	↑	↓		↑			↓ IV									
Jones [49]	CS	CTG, EudraCT, BCTR, ICTRP, CPRCT, etc.	Zika, Ebola, H1N1	333	5 * 18 Ž 47 †							↓ III									
Law [52]	CS	CTG	All	337	12	↑	↓					↑ III/IV					↑				
Liu [36]	Cohort	CTG	Oncology	12,240	37.8		↑	↓								↑	↑				
Prayer [45]	CS	CTG	All	5642	22	↑						↑ III/IV									
Saito [46]	CS	CTG	Random sample	400	29.5	↓						↓ II/III	↓				↑	↓			
Turner [37]	CS	CTG	Neurology	4719	32.2	↑	↑	↓											↑		↑
Van Hereten [47]	CS	CTG	Otology	419	8.6	↓														↑	
Viteri-García [55]	CS	Trials Tracker	Dentistry-related	20	40	↑															
Present study	CS	EudraCT	ONS-related	144	45.7	↑							↑								

BA, biological agent; BCTR, Brazilian Clinical Trials Registry; CPRCT, Cuban Public Registry of Clinical Trials; CS, cross-sectional; CTG, https://clinicaltrials.gov/ (accessed on 3 August 2022); DTA, diagnostic test accuracy; EudraCT, European Union Clinical Trials Database; H1N1, ICTRP, International Clinical Trials Registry Platform; ONS, oral nutrient supplementation; US, United States; * at one-year post-completion data, in compliance with the law; † at any time after trial completion (often exceeding the one year); Ž at two-year post-trial completion; ^ 2006–2007 period; ‡ 2007–2008 period; Š 2008–2009 period; I phase 1 trial; II phase 2 trial; III phase 3 trial; IV phase 4 trial; Œ conducted by an academic medical center; ↑ increased; ↓: decreased.

Concerning trial characteristics, the adoption of an RCT design is associated with less likelihood of adhering to the reporting timeframe [46], although the opposite was shown herein with regard to vitamin supplements. As for the age of the participating sample, trials with a children target population have been suggested to be more likely to disseminate results [32,46]. However, in the present analysis, no difference was recorded in the dissemination rate between trials with participants of different age groups. Regarding the type of funding source and prompt results reporting, the existing evidence appears contradicting (Table 3).

The literature indicates that an industry-funded trial is more likely to adhere to the results reporting regulations [24,25,32,37,45,52,53,55], whereas few studies suggest the opposite [46–48]. Moreover, several government-funded trials fail to report their results in a timely manner [52,53]. The frequency of funding is also important with sponsors conducting several trials having greater chances for timely results publication [24,53]. On the other hand, academic funding is associated with reduced results reporting [36,37]. As expected, more recent trials exhibit greater chances of reporting their results promptly [24,53]. Trials terminated early [25,36], or those with more participants [36,46,52] are more likely to report their findings.

The present retrospective study revealed that even trials with vitamin interventions, seemingly encompassing fewer adverse effects compared with medication or vaccine interventions, are often failing to report their results on time. This might be due to negative findings concerning the efficacy, adverse events, or factors associated with participant recruitment and the overall quality of the trial. Trials of dietary supplements often have negative findings [15] and an increased rate of adverse events. The evidence of harm appears to be accumulating [8]. Although a "food-first" policy [56,57] is the approach for all micronutrient inadequacies, considering that vitamin supplementation inevitably increases dietary intake [58,59], the majority of dietitians tend to prescribe vitamin supplements [56]. However, the present study revealed that publication of relevant clinical trials is often arbitrary, lacking compliance with regulatory rules, limiting the ability to aid the development of evidence-based clinical decisions [3,60].

Dietary supplements are key players in the health arena, and the recent EMA approval of icosapent ethyl/eicosapentaenoic acid for reducing the risk for cardiovascular disease [61] indicates that the road for lifestyle medicine has been paved. Undoubtfully, a careful balance of all nutrient requirements is important for health attainment [62]. In this manner, unhealthy nutritional habits and lifestyle effects often have a negative effect in nutrient homeostasis, in which case, dietary supplements are required to restore nutrient balance [63]. Additionally, in several chronic diseases, pharmacotherapy often interacts with individual nutrient requirements, augmenting the needs of patients in order to improve quality of life, medication tolerance, disease-specific endpoints, or tamper down adverse events associated with chronic medication prescription [64–67]. In all the aforementioned cases, the use of dietary supplements can be beneficial, however, response greatly varies according to the genetic make-up of each patient [68,69] (pharmacogenetics) and the degree of observed nutrient deficiency.

The need for robust, transparent, and independent trials in nutrition research consists of a public health priority, and for this, specific guidelines have recently been developed by the NOURISH working group [70–73]. Recently, the science of nutrition has been criticized for using inaccurate assessment methods and weak study designs [72,74–76], all of which undermine its integrity and usefulness for public health. Industry is a key factor contributing to nutrition research. As a result, the food and pharmaceutical industries will always be linked to the science of nutrition. Nevertheless, research integrity and transparency through a collective effort are required to improve medical practice and medical nutrition therapy. According to Feehan [77], apart from the production of high-quality scientific research, investigators and sponsors are also responsible for maintaining public trust. Although in their majority, vitamin supplementation trials do not appear to adhere to the EMA reporting guidelines and standards, the case may be worse with regard

to herbal medicine supplement trials. Recent research in the area revealed that trialists fail to adhere to the formula elaborations suggested by the CONSORT statement for RCTs incorporating herbal medicine interventions, including standardization information, data on the purity, quality, etc. [67].

Recently, the joint letter issued by the EC, EMA, and the Head of Medicines Agencies (HMA) [78], reminded sponsors who were not compliant with the EC guideline, on their legal requirement to disseminate their results in a timely manner. Through these reminders, the percentage of posted results increased substantially, although for some trials, the reminders were not deemed successful. Similar efforts were also conducted in the USA, revealing that email reminders of the requirement to post findings improved results reporting [79].

Limitations of the present study include the search in one registry only and the inability to identify trials with positive findings. However, it should be noted that the arbitrary publication of findings in the registry, with many failing to answer the main hypothesis tested, is an important issue identified. Moreover, we did not manage to use the quality checklist for clinical trials submission proposed recently, as our search preceded its publication [80].

Selective publication of a trial's findings endangers the fields of evidence-based medicine and nutrition and reduces the public's trust to the industry [81]. These fields are of critical importance to public health; thus, a collective approach is required to increase trial transparency. Moreover, the future calls for shared clinical data on the individual patient level, aiming to increase the application, aggregation, and reuse of clinical trial findings [81,82]. At the moment however, trial data sharing appears inadequate in the EU, despite the fact that trial results affect the health of millions of people across the continent [83].

5. Conclusions

According to Goldacre [24], the higher rate of disseminated findings among commercially financed trials indicates that compliance is, in fact, feasible. It appears that more recently conducted trials will likely adhere to trial transparency rules more adequately [24], suggesting that compliance is a learning procedure for all actors involved. Although research appears consistent concerning the lack of prompt dissemination of the findings of clinical trials, related consequences remain vague, allowing for a breach of the statutory obligations of trialists and funders [38]. Moreover, the fact that trials assessing over-the-counter substances, like simple vitamins, still fail to comply, leaves ample space for speculations over their efficacy and possible harms. Thus, stricter regulations should be imposed concerning trial results reporting.

Author Contributions: Conceptualization, D.G.G. and M.G.G.; methodology, D.G.G., M.G.G. and A.-B.H.; formal analysis, X.T., A.-B.H.; investigation, M.A.L., S.K., D.B., M.G.G. and X.T.; resources, D.G.G. and M.G.G.; data curation, M.A.L., S.K., M.G.G., D.B. and X.T.; writing—original draft preparation, M.A.L. and M.G.G.; writing—review and editing, M.A.L., M.G.G., X.T., S.K., D.B., A.P., A.-B.H. and D.G.G.; visualization, X.T. and M.G.G.; supervision, D.G.G., A.-B.H., A.P. and M.G.G.; project administration, D.G.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study as it does not involve patients.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are available upon request to the corresponding authors.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Manson, J.E.; Bassuk, S.S. Vitamin and Mineral Supplements. *JAMA* **2018**, *319*, 859. [CrossRef] [PubMed]
2. Molin, T.R.D.; Leal, G.C.; Muratt, D.T.; Marcon, G.Z.; de Carvalho, L.M.; Viana, C.; Viana, C. Regulatory framework for dietary supplements and the public health challenge. *Rev. Saude Publica* **2019**, *53*, 90. [CrossRef] [PubMed]
3. Incze, M. Vitamins and Nutritional Supplements. *JAMA Intern. Med.* **2019**, *179*, 460. [CrossRef] [PubMed]
4. Tucker, J.; Fischer, T.; Upjohn, L.; Mazzera, D.; Kumar, M. Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. *JAMA Netw. Open* **2018**, *1*, e183337. [CrossRef] [PubMed]
5. Cohen, P.A. American Roulette—Contaminated Dietary Supplements. *N. Engl. J. Med.* **2009**, *361*, 1523–1525. [CrossRef] [PubMed]
6. Cohen, P.A.; Bass, S. Injecting Safety into Supplements—Modernizing the Dietary Supplement Law. *N. Engl. J. Med.* **2019**, *381*, 2387–2389. [CrossRef]
7. Cohen, P.A.; Wen, A.; Gerona, R. Prohibited Stimulants in Dietary Supplements After Enforcement Action by the US Food and Drug Administration. *JAMA Intern. Med.* **2018**, *178*, 1721. [CrossRef]
8. Carroll, A.E. Given Their Potential for Harm, It's Time to Focus on the Safety of Supplements. *JAMA* **2018**, *320*, 1306. [CrossRef]
9. Karbownik, M.S.; Paul, E.; Nowicka, M.; Nowicka, Z.; Kowalczyk, R.P.; Kowalczyk, E.; Pietras, T. Knowledge about dietary supplements and trust in advertising them: Development and validation of the questionnaires and preliminary results of the association between the constructs. *PLoS ONE* **2019**, *14*, e0218398. [CrossRef]
10. Gahche, J.J.; Bailey, R.L.; Potischman, N.; Ershow, A.G.; Herrick, K.A.; Ahluwalia, N.; Dwyer, J.T. Federal Monitoring of Dietary Supplement Use in the Resident, Civilian, Noninstitutionalized US Population: National Health and Nutrition Examination Survey. *J. Nutr.* **2018**, *148*, 1436S–1444S. [CrossRef]
11. Kantor, E.D.; Rehm, C.D.; Du, M.; White, E.; Giovannucci, E.L. Trends in Dietary Supplement Use Among US Adults from 1999–2012. *JAMA* **2016**, *316*, 1464. [CrossRef]
12. Li, J.; Li, X.; Gathirua-Mwangi, W.; Song, Y. Prevalence and trends in dietary supplement use among US adults with diabetes: The National Health and Nutrition Examination Surveys, 1999–2014. *BMJ Open Diabetes Res. Care* **2020**, *8*, e000925. [CrossRef] [PubMed]
13. Kamangar, F.; Emadi, A. Vitamin and mineral supplements: Do we really need them? *Int. J. Prev. Med.* **2012**, *3*, 221–226. [PubMed]
14. Blumberg, J.B.; Bailey, R.L.; Sesso, H.D.; Ulrich, C.M. The Evolving Role of Multivitamin/Multimineral Supplement Use among Adults in the Age of Personalized Nutrition. *Nutrients* **2018**, *10*, 248. [CrossRef] [PubMed]
15. Cohen, P.A. The Supplement Paradox: Negligible Benefits, Robust Consumption. *JAMA* **2016**, *316*, 1453–1454. [CrossRef]
16. Sancar, F. Oversight of Supplements. *JAMA* **2019**, *321*, 1042. [CrossRef]
17. Dwyer, J.T.; Coates, P.M. Why Americans Need Information on Dietary Supplements. *J. Nutr.* **2018**, *148*, 1401S–1405S. [CrossRef]
18. Lesser, L.I.; Ebbeling, C.B.; Goozner, M.; Wypij, D.; Ludwig, D.S. Relationship between Funding Source and Conclusion among Nutrition-Related Scientific Articles. *PLoS Med.* **2007**, *4*, e5. [CrossRef]
19. Lundh, A.; Lexchin, J.; Mintzes, B.; Schroll, J.B.; Bero, L. Industry sponsorship and research outcome: Systematic review with meta-analysis. *Intensive Care Med.* **2018**, *44*, 1603–1612. [CrossRef]
20. Lundh, A.; Lexchin, J.; Mintzes, B.; Schroll, J.B.; Bero, L. Industry sponsorship and research outcome. *Cochrane Database Syst. Rev.* **2017**, *2*, MR000033. [CrossRef]
21. Ahn, R.; Woodbridge, A.; Abraham, A.; Saba, S.; Korenstein, D.; Madden, E.; Boscardin, W.J.; Keyhani, S. Financial ties of principal investigators and randomized controlled trial outcomes: Cross sectional study. *BMJ* **2017**, *356*, i6770. [CrossRef] [PubMed]
22. Bhatt, A. Quality of clinical trials: A moving target. *Perspect. Clin. Res.* **2011**, *2*, 124. [CrossRef] [PubMed]
23. Sellers, J.W.; Mihaescu, C.M.; Pharm, M.; Ayalew, K.; Kronstein, P.D.; Yu, B.; Ning, Y.-M.; Rodriguez, M.; Williams, L.; Khin, N.A. Descriptive Analysis of Good Clinical Practice Inspection Findings from U.S. Food and Drug Administration and European Medicines Agency. *Ther. Innov. Regul. Sci.* **2022**. [CrossRef]
24. Goldacre, B.; DeVito, N.J.; Heneghan, C.; Irving, F.; Bacon, S.; Fleminger, J.; Curtis, H. Compliance with requirement to report results on the EU Clinical Trials Register: Cohort study and web resource. *BMJ* **2018**, *362*, k3218. [CrossRef] [PubMed]
25. DeVito, N.J.; Bacon, S.; Goldacre, B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: A cohort study. *Lancet* **2020**, *395*, 361–369. [CrossRef]
26. Buchkowsky, S.S.; Jewesson, P.J. Industry Sponsorship and Authorship of Clinical Trials Over 20 Years. *Ann. Pharmacother.* **2004**, *38*, 579–585. [CrossRef]
27. Chartres, N.; Fabbri, A.; Bero, L.A. Association of Industry Sponsorship With Outcomes of Nutrition Studies. *JAMA Intern. Med.* **2016**, *176*, 1769. [CrossRef]
28. Navarrete-Muñoz, E.M.; Tardón, A.; Romaguera, D.; Martínez-González, M.Á.; Vioque, J. La financiación de la industria alimentaria y la investigación epidemiológica sobre nutrición y salud. *Gac. Sanit.* **2018**, *32*, 168–171. [CrossRef]
29. Fabbri, A.; Holland, T.J.; Bero, L.A. Food industry sponsorship of academic research: Investigating commercial bias in the research agenda. *Public Health Nutr.* **2018**, *21*, 3422–3430. [CrossRef]
30. Rey-López, J.P.; Gonzalez, C.A. Research partnerships between Coca-Cola and health organizations in Spain. *Eur. J. Public Health* **2019**, *29*, 810–815. [CrossRef]
31. Anderson, M.L.; Chiswell, K.; Peterson, E.D.; Tasneem, A.; Topping, J.; Califf, R.M. Compliance with Results Reporting at ClinicalTrials.gov. *N. Engl. J. Med.* **2015**, *372*, 1031–1039. [CrossRef] [PubMed]

32. Gill, C.J. How often do US-based human subjects research studies register on time, and how often do they post their results? A statistical analysis of the Clinicaltrials.gov database. *BMJ Open* **2012**, *2*, e001186. [CrossRef] [PubMed]
33. Gordon, D.; Taddei-Peters, W.; Mascette, A.; Antman, M.; Kaufmann, P.G.; Lauer, M.S. Publication of Trials Funded by the National Heart, Lung, and Blood Institute. *N. Engl. J. Med.* **2013**, *369*, 1926–1934. [CrossRef] [PubMed]
34. Whitlock, E.P.; Dunham, K.M.; DiGioia, K.; Lazowick, E.; Gleason, T.C.; Atkins, D. Noncommercial US Funders' Policies on Trial Registration, Access to Summary Results, and Individual Patient Data Availability. *JAMA Netw. Open* **2019**, *2*, e187498. [CrossRef]
35. Chen, R.; Desai, N.R.; Ross, J.S.; Zhang, W.; Chau, K.H.; Wayda, B.; Murugiah, K.; Lu, D.Y.; Mittal, A.; Krumholz, H.M. Publication and reporting of clinical trial results: Cross sectional analysis across academic medical centers. *BMJ* **2016**, *352*, i637. [CrossRef]
36. Liu, X.; Zhang, Y.; Li, W.F.; Vokes, E.; Sun, Y.; Le, Q.T.; Ma, J. Evaluation of Oncology Trial Results Reporting over a 10-Year Period. *JAMA Netw. Open* **2021**, *4*, 2110438. [CrossRef]
37. Turner, B.E.; Magnani, C.J.; Frolov, A.; Weeks, B.T.; Steinberg, J.R.; Huda, N.; Shah, L.M.; Zuroff, L.; Gu, B.J.; Rasmussen, H.; et al. Neurology trial registrations on ClinicalTrials.gov between 2007 and 2018: A cross-sectional analysis of characteristics, early discontinuation, and results reporting. *J. Neurol. Sci.* **2021**, *428*, 117579. [CrossRef]
38. Hudson, K.L.; Collins, F.S. Sharing and Reporting the Results of Clinical Trials. *JAMA* **2015**, *313*, 355. [CrossRef]
39. Groves, T. Big strides in Europe towards clinical trial transparency. *BMJ* **2014**, *349*, g6276. [CrossRef]
40. World Health Organization. *Joint Statement on Public Disclosure of Results from Clinical Trials*; WHO: Geneva, Switzerland, 2017.
41. Ioannidis, J.P.A. How to Make More Published Research True. *PLoS Med.* **2014**, *11*, e1001747. [CrossRef]
42. Zarin, D.A.; Ide, N.C.; Tse, T.; Harlan, W.R.; West, J.C.; Lindberg, D.A.B. Issues in the Registration of Clinical Trials. *JAMA* **2007**, *297*, 2112. [CrossRef] [PubMed]
43. Zarin, D.A.; Tse, T.; Williams, R.J.; Califf, R.M.; Ide, N.C. The ClinicalTrials.gov Results Database—Update and Key Issues. *N. Engl. J. Med.* **2011**, *364*, 852–860. [CrossRef] [PubMed]
44. Chan, A.-W.; Song, F.; Vickers, A.; Jefferson, T.; Dickersin, K.; Gøtzsche, P.C.; Krumholz, H.M.; Ghersi, D.; van der Worp, H.B. Increasing value and reducing waste: Addressing inaccessible research. *Lancet* **2014**, *383*, 257–266. [CrossRef]
45. Prayle, A.P.; Hurley, M.N.; Smyth, A.R. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: Cross sectional study. *BMJ* **2012**, *344*, d7373. [CrossRef]
46. Saito, H.; Gill, C.J. How Frequently Do the Results from Completed US Clinical Trials Enter the Public Domain?—A Statistical Analysis of the ClinicalTrials.gov Database. *PLoS ONE* **2014**, *9*, e101826. [CrossRef]
47. van Heteren, J.A.A.; van Beurden, I.; Peters, J.P.M.; Smit, A.L.; Stegeman, I. Trial registration, publication rate and characteristics in the research field of otology: A cross-sectional study. *PLoS ONE* **2019**, *14*, e0219458. [CrossRef]
48. Al-Durra, M.; Nolan, R.P.; Seto, E.; Cafazzo, J.A.; Eysenbach, G. Nonpublication rates and characteristics of registered randomized clinical trials in digital health: Cross-sectional analysis. *J. Med. Internet Res.* **2018**, *20*, e11924. [CrossRef]
49. Jones, C.W.; Adams, A.C.; Murphy, E.; King, R.P.; Saracco, B.; Stesis, K.R.; Cavanaugh, S.; Roberts, B.W.; Platts-Mills, T.F. Delays in reporting and publishing trial results during pandemics: Cross sectional analysis of 2009 H1N1, 2014 Ebola, and 2016 Zika clinical trials. *BMC Med. Res. Methodol.* **2021**, *21*, 120. [CrossRef]
50. McGauran, N.; Wieseler, B.; Kreis, J.; Schüler, Y.B.; Kölsch, H.; Kaiser, T. Reporting bias in medical research—A narrative review. *Trials* **2010**, *11*, 37. [CrossRef]
51. Hopewell, S.; Loudon, K.; Clarke, M.J.; Oxman, A.D.; Dickersin, K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst. Rev.* **2009**, *2009*, MR000006. [CrossRef]
52. Law, M.R.; Kawasumi, Y.; Morgan, S.G. Despite Law, Fewer Than One In Eight Completed Studies Of Drugs And Biologics Are Reported On Time On ClinicalTrials.gov. *Health Aff.* **2011**, *30*, 2338–2345. [CrossRef] [PubMed]
53. Gopal, R.K.; Yamashita, T.E.; Prochazka, A.V. Research without results: Inadequate public reporting of clinical trial results. *Contemp. Clin. Trials* **2012**, *33*, 486–491. [CrossRef] [PubMed]
54. Fleminger, J.; Goldacre, B. Prevalence of clinical trial status discrepancies: A cross-sectional study of 10,492 trials registered on both ClinicalTrials.gov and the European Union Clinical Trials Register. *PLoS ONE* **2018**, *13*, e0193088. [CrossRef] [PubMed]
55. Viteri-García, A.; DeVito, N.J.; Goldacre, B. Too few trials or too few reported trials? *Evid. Based. Dent.* **2018**, *19*, 67–68. [CrossRef]
56. Dickinson, A.; Bonci, L.; Boyon, N.; Franco, J.C. Dietitians use and recommend dietary supplements: Report of a survey. *Nutr. J.* **2012**, *11*, 14. [CrossRef]
57. Ventura Marra, M.; Boyar, A.P. Position of the American Dietetic Association: Nutrient Supplementation. *J. Acad. Nutr. Diet.* **2009**, *109*, 2073–2085. [CrossRef]
58. Blumberg, J.; Frei, B.; Fulgoni, V.; Weaver, C.; Zeisel, S. Impact of Frequency of Multi-Vitamin/Multi-Mineral Supplement Intake on Nutritional Adequacy and Nutrient Deficiencies in U.S. Adults. *Nutrients* **2017**, *9*, 849. [CrossRef]
59. Hatzopoulou, K.; Filis, V.; Grammatikopoulou, M.G.; Kotzamanidis, C.; Tsigga, M. Greek Pregnant Women Demonstrate Inadequate Micronutrient Intake Despite Supplement Use. *J. Diet. Suppl.* **2014**, *11*, 155–165. [CrossRef]
60. Schneider, L.S. The risks and uses of dietary supplements. *Lancet Neurol.* **2019**, *18*, 814. [CrossRef]
61. Chapman, M.J.; Zamorano, J.L.; Parhofer, K.G. Reducing residual cardiovascular risk in Europe: Therapeutic implications of European medicines agency approval of icosapent ethyl/eicosapentaenoic acid. *Pharmacol. Ther.* **2022**, *237*, 108172. [CrossRef]
62. National Research Council (US). Committee on Diet and Health Dietary Intake and Nutritional Status: Trends and Assessment. In *Diet and Health: Implications for Reducing Chronic Disease Risk*; National Academies Press: Washington, DC, USA, 1989.

63. Lentjes, M.A.H. The balance between food and dietary supplements in the general population. *Proc. Nutr. Soc.* **2019**, *78*, 97–109. [CrossRef] [PubMed]
64. Valsamidou, E.; Gioxari, A.; Amerikanou, C.; Zoumpoulakis, P.; Skarpas, G.; Kaliora, A.C. Dietary Interventions with Polyphenols in Osteoarthritis: A Systematic Review Directed from the Preclinical Data to Randomized Clinical Studies. *Nutrients* **2021**, *13*, 1420. [CrossRef] [PubMed]
65. Grammatikopoulou, M.G.; Gkiouras, K.; Nigdelis, M.P.; Bogdanos, D.P.; Goulis, D.G. Efficacy of Vitamin D3 Buccal Spray Supplementation Compared to Other Delivery Methods: A Systematic Review of Superiority Randomized Controlled Trials. *Nutrients* **2020**, *12*, 691. [CrossRef] [PubMed]
66. Tsiogkas, S.G.; Grammatikopoulou, M.G.; Gkiouras, K.; Zafiriou, E.; Papadopoulos, I.; Liaskos, C.; Dardiotis, E.; Sakkas, L.I.; Bogdanos, D.P. Effect of Crocus sativus (Saffron) Intake on Top of Standard Treatment, on Disease Outcomes and Comorbidities in Patients with Rheumatic Diseases: Synthesis without Meta-Analysis (SWiM) and Level of Adherence to the CONSORT Statement for Randomized Controlled Trials Delivering Herbal Medicine Interventions. *Nutrients* **2021**, *13*, 4274. [CrossRef]
67. Valsamidou, E.; Amerikanou, C.; Tzavara, C.; Zoumpoulakis, P.; Mariolis-Sapsakos, T.D.; Skarpas, G.; Kaliora, A.C. Nutraceuticals for Knee Osteoarthritis Pain Relief. Results from a Preliminary Randomised Clinical Trial. *Dietetics* **2021**, *1*, 2–14. [CrossRef]
68. Gkouskou, K.K.; Grammatikopoulou, M.G.; Vlastos, I.; Sanoudou, D.; Eliopoulos, A.G. Genotype-guided dietary supplementation in precision nutrition. *Nutr. Rev.* **2021**, *79*, 1225–1235. [CrossRef]
69. Gkouskou, K.K.; Grammatikopoulou, M.G.; Lazou, E.; Sanoudou, D.; Goulis, D.G.; Eliopoulos, A.G. Genetically-guided medical nutrition therapy in type 2 diabetes mellitus and prediabetes: A series of n-of-1 superiority trials. *Front. Nutr.* **2022**, *9*, 772243. [CrossRef]
70. Weaver, C.M.; Lichtenstein, A.H.; Kris-Etherton, P.M. Perspective: Guidelines Needed for the Conduct of Human Nutrition Randomized Controlled Trials. *Adv. Nutr.* **2021**, *12*, 1–3. [CrossRef]
71. Lichtenstein, A.H.; Petersen, K.; Barger, K.; Hansen, K.E.; Anderson, C.A.M.; Baer, D.J.; Lampe, J.W.; Rasmussen, H.; Matthan, N.R. Perspective: Design and Conduct of Human Nutrition Randomized Controlled Trials. *Adv. Nutr.* **2021**, *12*, 4–20. [CrossRef]
72. Grammatikopoulou, M.G.; Nigdelis, M.P.; Theodoridis, X.; Gkiouras, K.; Tranidou, A.; Papamitsou, T.; Bogdanos, D.P.; Goulis, D.G. How fragile are Mediterranean diet interventions? A research-on-research study of randomized controlled trials. *BMJ Nutr. Prev. Health* **2021**, *4*, 115–131. [CrossRef]
73. Weaver, C.M.; Fukagawa, N.K.; Liska, D.A.; Mattes, R.D.; Matuszek, G.; Nieves, J.W.; Shapses, S.A.; Snetselaar, L.G. Perspective: US Documentation and Regulation of Human Nutrition Randomized Controlled Trials. *Adv. Nutr.* **2021**, *12*, 21–45. [CrossRef] [PubMed]
74. Hébert, J.R.; Frongillo, E.A.; Adams, S.A.; Turner-McGrievy, G.M.; Hurley, T.G.; Miller, D.R.; Ockene, I.S. Perspective: Randomized Controlled Trials Are Not a Panacea for Diet-Related Research. *Adv. Nutr.* **2016**, *7*, 423–432. [CrossRef] [PubMed]
75. Ioannidis, J.P. Implausible results in human nutrition research. *BMJ* **2013**, *347*, f6698. [CrossRef]
76. Schoenfeld, J.D.; Ioannidis, J.P. Is everything we eat associated with cancer? A systematic cookbook review. *Am. J. Clin. Nutr.* **2013**, *97*, 127–134. [CrossRef]
77. Feehan, A.K.; Garcia-Diaz, J. Investigator Responsibilities in Clinical Research. *Ochsner J.* **2020**, *20*, 44. [CrossRef] [PubMed]
78. European Commission; European Medicines Agency; Head of Medicines Agencies. *ILL European Commission of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC (OJXXXXXX)*; European Commission: Luxembourg, 2019.
79. Maruani, A.; Boutron, I.; Baron, G.; Ravaud, P. Impact of sending email reminders of the legal requirement for posting results on ClinicalTrials.gov: Cohort embedded pragmatic randomized controlled trial. *BMJ* **2014**, *349*, g5579. [CrossRef]
80. Tetteh, O.; Nuamah, P.; Keyes, A. Addressing the quality of submissions to ClinicalTrials.gov for registration and results posting: The use of a checklist. *Clin. Trials* **2020**, *17*, 717–722. [CrossRef]
81. Eichler, H.-G.; Sweeney, F. The evolution of clinical trials: Can we address the challenges of the future? *Clin. Trials* **2018**, *15*, 27–32. [CrossRef]
82. Vazquez, E.; Gouraud, H.; Naudet, F.; Gross, C.P.; Krumholz, H.M.; Ross, J.S.; Wallach, J.D. Characteristics of available studies and dissemination of research using major clinical data sharing platforms. *Clin. Trials* **2021**, *18*, 657–666. [CrossRef]
83. Siebert, M.; Gaba, J.; Renault, A.; Laviolle, B.; Locher, C.; Moher, D.; Naudet, F. Data-sharing and re-analysis for main studies assessed by the European Medicines Agency—A cross-sectional study on European Public Assessment Reports. *BMC Med.* **2022**, *20*, 177. [CrossRef]