

Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online

Cannabinoid	Average Observed Concentration Across Tests, mg/mL	
	Mean (SD)	Median (Range)
Cannabidiol ^a	30.96 (80.86)	9.45 (0.10-655.27)
Cannabidiolic acid	1.35 (6.74)	0 (0-55.73)
Cannabigerol	0.08 (0.55)	0 (0-4.67)
Cannabinol	0	0
Δ-9-Tetrahydrocannabinol	0.45 (1.18)	0 (0-6.43)
Δ-9-Tetrahydrocannabinolic acid	0	0

^a The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

14.01%-31.35%), cannabidiolic acid (up to 55.73 mg/mL) in 13 of the 84 samples tested (15.48% [95% CI, 9.28%-24.70%]), and cannabigerol (up to 4.67 mg/mL) in 2 of the 84 samples tested (2.38% [95% CI, 0.65%-8.27%]).

Discussion | Among CBD products purchased online, a wide range of CBD concentrations was found, consistent with the lack of an accepted dose. Of tested products, 26% contained less CBD than labeled, which could negate any potential clinical response. The overlabeling of CBD products in this study is similar in magnitude to levels that triggered warning letters to 14 businesses in 2015-2016 from the US Food and Drug Administration³ (eg, actual CBD content was negligible or less than 1% of the labeled content), suggesting that there is a continued need for federal and state regulatory agencies to take steps to ensure label accuracy of these consumer products. Underlabeling is less concerning as CBD appears to neither have abuse liability nor serious adverse consequences at high doses^{4,5}; however, the THC content observed may be sufficient to produce intoxication or impairment, especially among children.⁶ Although the exclusive procurement of products online is a study limitation given the frequently changing online marketplace, these products represent the most readily available to US consumers. Additional monitoring should be conducted to determine changes in this marketplace over time and to compare internet products with those sold in dispensaries. These findings highlight the need for manufacturing and testing standards, and oversight of medicinal cannabis products.

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- Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473.
- Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid dose and label accuracy in edible medical cannabis products. *JAMA*. 2015;313(24):2491-2493.
- US Food and Drug Administration. 2016 Warning letters and test results for cannabidiol-related products. <https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm>. Accessed August 15, 2017.
- Babalonis S, Haney M, Malcolm RJ, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend*. 2017;172:9-13.
- Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a *Cannabis sativa* constituent. *Curr Drug Saf*. 2011;6(4):237-249.
- Crippa JA, Crippa AC, Hallak JE, Martín-Santos R, Zuardi AW. Δ9-THC intoxication by cannabidiol-enriched cannabis extract in two children with refractory epilepsy. *Front Pharmacol*. 2016;7:359.

Association of Trial Registration With Reporting of Primary Outcomes in Protocols and Publications

A major aim of trial registration is to help identify and deter the selective reporting of outcomes based on the results.^{1,2} However, it is unclear whether registered outcomes accurately reflect the trial protocol and whether registration improves the reporting of primary outcomes in publications. We evaluated adherence to trial registration and its association with subsequent publication and reporting of primary outcomes.

Methods | We conducted a cohort study of all initiated clinical trial protocols approved in 2007 by the research ethics committee for the region of Helsinki and Uusimaa, Finland. Registry records and articles published up to February 2017 were identified using keywords to search trial registries, PubMed, EMBASE, Cochrane Central, Finnish databases (Medic, ARTO, TUHAT), and Google. Trial characteristics and outcomes were extracted in duplicate from each protocol (including amendments), registry record, and publication.

Using descriptive statistics and multivariable logistic regression adjusting for characteristics in **Table 1**, we determined

Table 1. Study Characteristics Associated With Prospective Registration, Publication, and Publication Without Discrepant Primary Outcomes

Trial Characteristic	Clinical Trials, No. (N = 113)	Registered		Published ^a		Published Without Discrepant Primary Outcomes ^b	
		No. (%) ^c	AOR (95% CI) ^d	No. (%) ^c	AOR (95% CI) ^d	No. (%) ^c	AOR (95% CI) ^d
Prospectively registered							
Yes	69			47 (68)	4.53 (1.12-18.34)	44 (64)	5.79 (1.42-23.65)
No	44			17 (39)	1 [Reference]	11 (25)	1 [Reference]
Intervention type							
Drug or biologic	75	64 (85)	30.99 (7.70-124.66)	45 (60)	0.30 (0.07-1.29)	42 (56)	0.46 (0.11-2.01)
Other	38	5 (13)	1 [Reference]	19 (50)	1 [Reference]	13 (34)	1 [Reference]
Planned sample size ^e							
≥200	62	48 (77)	4.41 (1.18-16.45)	45 (73)	2.75 (1.09-6.92)	40 (65)	2.69 (1.06-6.83)
<200	51	21 (41)	1 [Reference]	19 (37)	1 [Reference]	15 (29)	1 [Reference]
No. of sites							
Multicenter	88	62 (70)	1.82 (0.46-7.22)	56 (64)	1.80 (0.58-5.58)	48 (55)	1.09 (0.33-3.57)
Single center	25	7 (28)	1 [Reference]	8 (32)	1 [Reference]	7 (28)	1 [Reference]
Sponsor							
Industry	53	46 (87)	1.97 (0.50-7.81)	36 (68)	1.23 (0.42-3.61)	33 (62)	1.35 (0.47-3.89)
Non-industry	60	23 (38)	1 [Reference]	28 (47)	1 [Reference]	22 (37)	1 [Reference]
Design							
Controlled	99	61 (62)	0.95 (0.16-5.79)	56 (57)	1.09 (0.30-3.88)	49 (49)	1.39 (0.39-4.98)
Uncontrolled	14	8 (57)	1 [Reference]	8 (57)	1 [Reference]	6 (43)	1 [Reference]

Abbreviation: AOR, adjusted odds ratio.

^a Publication year ranged from 2008 to 2016; median time from ethics approval to publication was 5 y (interquartile range, 3.5-6).

^b Published article compared with protocol.

^c Row percentage.

^d Multivariable logistic regression adjusting for listed trial characteristics.

^e Median sample size was 200 (interquartile range, 70-732).

the prevalence of and variables associated with prospective registration (within 1 month after the trial start date to allow for incomplete start dates and processing delays in the registry); the proportion of trials with at least 1 discrepant primary outcome in the protocol compared with (1) the registry and (2) the publication; and the association between prospective registration and subsequent publication without discrepant primary outcomes compared with the protocol. A 2-sided *P* value of less than .05 was used for statistical significance, and odds ratios (ORs) with 95% CIs were calculated using Stata/SE (StataCorp), version 12.1.

Discrepancies were defined as (1) a new primary outcome being reported that was not specified as primary in the protocol; or (2) a protocol-defined primary outcome being omitted or downgraded (reported as secondary or unspecified) in the registry or publication. For comparison with registries, we used the primary outcomes defined in the most recent protocol or amendment dated before the initial registration date. For comparison with publications, we used the most recent protocol version regardless of amendment date.

Results | Among 113 trials, 69 (61%) were prospectively registered and 64 (57%) were published. Trials involving drug or biologic interventions and larger sample sizes were more likely to be registered (Table 1).

A primary outcome was not defined in 23 protocols (20%). Discrepancies were found in at least 1 primary outcome defined in the registry for 16 of 69 prospectively registered trials (23%) when compared with the protocol, whereas

9 of 58 published trials (16%) with defined primary outcomes had discrepancies between the publication and the protocol (Table 2). Discrepancies between the protocol and publication were more common in unregistered trials (6 of 11 trials [55%]) than registered trials (3 of 47 [6%]) (*P* < .001). Only 1 published article acknowledged the changes to primary outcomes.

Prospective registration was significantly associated with subsequent publication (68% of registered trials vs 39% of unregistered trials; adjusted OR, 4.53 [95% CI, 1.12-18.34]) (Table 1). Registered trials were also significantly more likely than unregistered trials to be subsequently published with the same primary outcomes as defined in the protocol (64% of registered trials vs 25% of unregistered trials; adjusted OR, 5.79 [95% CI, 1.42-23.65]).

Discussion | Clinical trials were often unregistered, unpublished, and discrepant in the reporting of primary outcomes across information sources. Limitations include the unclear generalizability beyond the Finnish jurisdiction and the limited sample size.

Although discrepancies are commonly found between registries and publications,³ which may reflect selective outcome reporting, the rationale is less clear for different primary outcomes appearing between the registry and protocol prior to results being known. Potential reasons for such discrepancies include clerical oversight or intentional suppression from disclosure. The original protocol and amendments should be made publicly available so that

Table 2. Proportion of Trials With Discrepancies in Primary Outcomes When Comparing Protocols With Prospective Registry Records and Published Articles

Discrepancy ^a	No. of Trials With Discrepancies for ≥1 Primary Outcome/ Total Trials (%)	
	Registry vs Protocol	Published Article vs Protocol
Changed protocol-defined primary outcome	13/67 (19) ^b	5/55 (9) ^e
Reported as nonprimary	2/67 (3) ^b	5/55 (9) ^e
Omitted	12/67 (18) ^b	1/55 (2) ^e
New primary outcome	3/63 (5) ^c	7/56 (13) ^f
Changed from nonprimary to primary	3/63 (5) ^c	6/56 (11) ^f
Not listed in protocol	1/63 (2) ^c	1/56 (2) ^f
Any discrepancy in primary outcome	16/69 (23) ^d	9/58 (16) ^g

^a Categories are not mutually exclusive; a trial could have more than 1 type of discrepancy for different primary outcomes.

^b Denominator represents registered trials that defined at least 1 primary outcome in the protocol.

^c Denominator represents registered trials that defined at least 1 primary outcome in the registry.

^d Denominator represents registered trials that defined at least 1 primary outcome in either the protocol or registry.

^e Denominator represents published trials that defined at least 1 primary outcome in the protocol.

^f Denominator represents published trials that defined at least 1 primary outcome in the published article.

^g Denominator represents published trials that defined at least 1 primary outcome in either the protocol or published article. Five trials had only discrepancies that were favorable to the main intervention, 3 had only unfavorable discrepancies, and 1 had a neutral combination of both favorable and unfavorable discrepancies.

editors, peer reviewers, and readers can identify any unacknowledged changes to protocol-defined outcomes in the registry or publication.^{4,5} The protocol should provide a complete description of the primary outcomes and other key elements of the study plans.⁶ Amendments should be transparently reported.

Prospective registration was associated with publication and publication without discrepancies in the primary outcomes. Journal editors, regulators, research ethics committees, funders, and sponsors should implement policies mandating prospective registration for all clinical trials. Only with accessible, complete information can interventions be adequately evaluated for patient care.

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- Dwan K, Gamble C, Williamson PR, Kirkham JJ; Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias—an updated review. *PLoS One*. 2013;8(7):e66844.
- Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*. 2004;291(20):2457-2465.
- Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. *BMC Med*. 2015;13:282.
- Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov—the final rule. *N Engl J Med*. 2016;375(20):1998-2004.
- Chan A-W, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet*. 2014;383(9913):257-266.
- Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207.

COMMENT & RESPONSE

Alendronate and Hip Fracture in Patients Using Glucocorticoids

To the Editor Dr Axelsson and colleagues¹ evaluated the association between alendronate use and risk of hip fracture among older adults taking prednisolone. Although the availability of a large population-based cohort is a major strength, their study design comparing prevalent alendronate users with nonusers raises several concerns.

First, treated patients were required to have at least 3 months of alendronate use and evidence of current use at the start of follow-up for outcomes. Therefore, alendronate users who experienced safety events early in the treatment course and discontinued treatment because of the adverse event would not have been eligible for inclusion in this study. This could have resulted in underestimation of safety events due to depletion of susceptible patients from the treatment group.^{2,3}

Second, the outcome assessment was not anchored to treatment start but to enrollment in the Senior Alert program