However, the THC content observed may be sufficient to pro-
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derlabeling is less concerning as CBD appears to neither have
steptoensurelabelaccuracyoftheseconsumerproducts.Un-
tinued need for federal and state regulatory agencies to tak

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 re-
sponse. 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 Admin-
istration4 (eg, actual CBD content was negligible or less
than 1% of the labeled content), suggesting that there is a con-
tinued 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 doses4,5;
however, the THC content observed may be sufficient to pro-
duce intoxication or impairment, especially among children.6
Although the exclusive procurement of products online is a
study limitation given the frequently changing online mar-
tetspace, these products represent the most readily available to US
consumers. Additional monitoring should be conducted to de-
termine changes in this marketplace over time and to compare
internet products with those sold in dispensaries. These find-
ings highlight the need for manufacturing and testing stand-
ards, and oversight of medicinal cannabis products.

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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 accu-
rately reflect the trial protocol and whether registration im-
proves 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 com-
mittee for the region of Helsinki and Uusimaa, Finland. Reg-
istry 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 amend-
ments), registry record, and publication.

Using descriptive statistics and multivariable logistic re-
gression adjusting for characteristics in Table 1, we determined
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% CI 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 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, 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

<table>
<thead>
<tr>
<th>Discrepancy*</th>
<th>No. of Trials With Discrepancies for ≥1 Primary Outcome/ Total Trials (%)</th>
<th>Registry vs Protocol</th>
<th>Published Article vs Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed protocol-defined primary outcome</td>
<td>13/67 (19)†</td>
<td>5/55 (9)‡</td>
<td></td>
</tr>
<tr>
<td>Reported as nonprimary</td>
<td>2/67 (3)§</td>
<td>5/55 (9)‡</td>
<td></td>
</tr>
<tr>
<td>Omitted</td>
<td>12/67 (18)§</td>
<td>1/55 (2)‡</td>
<td></td>
</tr>
<tr>
<td>New primary outcome</td>
<td>3/63 (5)†</td>
<td>7/56 (13)†</td>
<td></td>
</tr>
<tr>
<td>Changed from nonprimary to primary</td>
<td>3/63 (5)†</td>
<td>6/56 (11)†</td>
<td></td>
</tr>
<tr>
<td>Not listed in protocol</td>
<td>1/63 (2)‡</td>
<td>1/56 (2)‡</td>
<td></td>
</tr>
<tr>
<td>Any discrepancy in primary outcome</td>
<td>16/69 (23)‡</td>
<td>9/58 (16)‡</td>
<td></td>
</tr>
</tbody>
</table>

* Categories are not mutually exclusive; a trial could have more than 1 type of discrepancy for different primary outcomes.
† Denominator represents registered trials that defined at least 1 primary outcome in the protocol.
‡ Denominator represents registered trials that defined at least 1 primary outcome in the registry.
§ Denominator represents registered trials that defined at least 1 primary outcome in the protocol or registry.

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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Concept and design: Chan, Hemminki.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chan, Hemminki.

Critical revision of the manuscript for important intellectual content: All authors.

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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...