E-cigarette manufacturers' compliance with clinical trial reporting expectations: a case series of registered trials by Juul Labs, Inc.

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Abstract

Background

Electronic cigarettes are a frequently debated topic in public health. It is essential that clinical trials examining e-cigarettes are fully and accurately reported, especially given long-standing concerns about tobacco industry research. We assess the reporting of clinical trials sponsored by Juul Labs Inc., the largest e-cigarette company in the US against accepted reporting standards.

Methods

We searched ClinicalTrials.gov for all trials sponsored by Juul Labs Inc. and determined those with registry data consistent with coverage by the FDA Amendments Act 2007 (FDAAA). For trials with a primary completion date more than one year earlier, we searched ClinicalTrials.gov, the academic literature, and a Juul-funded research database (JLI Science) for results. For located results we compared reported outcomes to registered outcomes in line with CONSORT reporting guidelines.

Results

We located five registered trials sponsored by Juul Labs Inc. that appeared covered by the FDAAA 2007 in the public data. All five trials did not have results available on ClinicalTrials.gov. We found one publication and four poster presentations reporting results for four of the five covered trials outside of ClinicalTrials.gov. Of 61 specified outcomes, just 28 were CONSORT compliant. Specific outcome reporting issues are detailed.

Discussion

Our findings raise substantial concerns regarding these trials. Clinicians, public health professionals, and the public cannot make informed choices about the benefits or hazards of e-cigarettes if the results of clinical trials are not completely and transparently reported. Clarification and potential enforcement of reporting laws may be required.

What this paper adds

- Reporting biases can lead to distortions of evidence. Without complete and timely reporting of clinical trials, stakeholders are left without the best possible evidence to inform their decision-making. Clinical trial registries provide a key tool for investigating accountability in preventing biases.
- Despite considerable attention paid to e-cigarette research, and longstanding concerns about industry funded tobacco research, we could locate no prior work specifically investigating reporting biases among registered e-cigarette industry sponsored research.
- Our results show that Juul Labs Inc., the largest e-cigarette manufacturer in the US, has not completely reported their sponsored clinical research, including a failure to report any results to ClinicalTrials.gov. This piece provides an examination of how outcome reporting biases manifest in the published accounts of trials when compared to pre-registered outcomes.

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Background

Electronic nicotine delivery systems (ENDS, or e-cigarettes) are controversial. Some see them as an important weapon in the struggle against smoking.[1] Others question their real world effectiveness as quitting aids, their short and long-term safety, and their role in promoting nicotine addiction.[2,3] Over 40 countries have banned the sale of e-cigarettes, with others restricting marketing.[4] In early 2020 the US Government banned most flavoured e-cigarette cartridges amid concerns about uptake in non-smoking teenagers.[5] Given these ongoing questions, it is essential that e-cigarette research is made fully available in a timely manner to inform medical and public health decision-making.

The importance of complete reporting of clinical trial results is recognized by international bodies.[6,7] In the US, the FDA Amendments Act (FDAAA) 2007 and its 2017 Final Rule requires the sponsors of certain trials to report results within one year of primary completion directly to the ClinicalTrials.gov registry.[8,9] However, it is not sufficient simply to report: reporting trials *accurately* is promoted by guidelines such as CONSORT, which aims to improve the reporting of clinical trials through "complete, clear, and transparent information on its methodology and findings" and is endorsed by over 500 academic journals.[10] Protocols and trial registrations should be published prospectively to avoid undisclosed "outcome-switching" and selective non-reporting which can exaggerate benefits and obfuscate harms of interventions.[11–13]

In an August 2019 commentary, Tan and colleagues raised concerns about industry sponsored vaping research.[14] They focus on JLI Science, a Juul Labs, Inc. (Juul Labs) research centre, that supports e-cigarette studies. Juul Labs is a major e-cigarette company holding 27% of the US market share in 2017.[15] Tan and co-authors noted a lack of transparency around JLI Science's funding mechanisms, research processes, and potential conflicts of interest. When auditing the JLI Science website the authors could not locate details on governance, funding, study selection, and reporting of Juul Labs-supported research that would allow proper assessments of influence. These findings raise concerns that research arising from this centre may be used to "positively portray the tobacco industry and lobby against regulatory actions" as has occurred in the past. Examining these transparency concerns has only grown in importance given the June 2020 Premarket Tobacco Product Application submission to the US Food and Drug Administration (FDA) by Juul Labs that relies on their "comprehensive research program...examining the public health impact of the JUUL System."[16]

We therefore set out to examine whether results of e-cigarette clinical trials sponsored by Juul Labs were reported by international standards on trial reporting timelines and the CONSORT trial reporting guidelines. [6–8,10]

Methods

Inclusion Criteria

We searched ClinicalTrials.gov for all interventional clinical trials in which Juul Labs was the primary sponsor. We assessed whether each trial had data fields consistent with coverage under the FDAAA 2007, based on established inclusion logic derived from official documentation.[8,17–20] The "FDA-regulated Device Product" field, added to

ClincialTrials.gov when the Final Rule came into effect, denotes coverage by device regulations and is used to aid determinations of whether FDAAA reporting requirements apply to a given trial.[19,20] As with all information on ClinicalTrials.gov, this field is attested to as accurate by the sponsor and reviewed in quality control by ClinicalTrials.gov staff before being made publicly available.[8,21] While official determination of coverage under FDAAA would not solely be based on registered data elements, the use of ClinicalTrials.gov data for public audit of potential FDAAA coverage is expressly encouraged in the Final Rule preamble ("Public users of ClinicalTrials.gov, other than responsible parties, should be able to understand whether a registered trial is an applicable clinical trial") and has informed prior analyses.[17,22,23]

Aligned to both the FDAAA 2007 and accepted ethical standards, we expected results to be available within one year from primary completion both on ClinicalTrials.gov and via any other dissemination routes.[6,24]

Results Searches

To assess each trial's reporting status two authors (NJD, HMD) searched 1) ClinicalTrials.gov 2) the academic literature via PubMed and Google Scholar and 3) the JLI Science "Research Library" database (https://jliscience.com/research-library). For searches outside ClinicalTrials.gov the trial ID, principal investigator (PI), and keywords derived from the trial title and design were used as search terms. Publications of results were matched to registrations using either the presence of a trial ID or a comparison of the study aims, authors/affiliations, design, sample size, and outcomes. Each assessor independently compared reported results with the currently specified outcomes on ClinicalTrials.gov, based on CONSORT items 6 (i.e., disclose changes to trial outcomes), 17 (i.e., report all outcomes)

and 18 (i.e., identify non-specified analyses performed).[10] Changes from the prespecified outcomes to current outcomes on the registry, obtained via the ClinicalTrials.gov archive site, are noted.

Each outcome was classed as: “fully reported; “reported with issues” where there was a substantial undeclared deviation from how an outcome was specified; “properly declared” if unreported or changed, but with disclosure; “unreported” if it was not located; or “unclear” if it could not be assessed. Findings from searches and outcome assessments were discussed in committee and discrepancies resolved by consensus. We narratively report our assessments including any issues with outcome reporting and justifications for certain assessments. We provide summary statistics on our search results and outcome assessments. All assessment data are shared openly in supplementary materials and on FigShare [link upon acceptance].

Results

Study Population

On 1 August 2020, searching ClinicalTrials.gov for “Juul Labs, Inc”, the standardised sponsor name for the company on ClinicalTrials.gov, returned 11 registrations. We excluded one trial (NCT04452175) because Juul Labs was a collaborator, not the primary sponsor. Five further trials were excluded as their registrations were inconsistent with potential FDAAA coverage (NCT04143256, NCT04123041, NCT04107779, NCT04088175 & NCT03700112). None of these excluded trials had results available on ClinicalTrials.gov, and only NCT03700112 was completed for over a year as of 1 August 2020 and could have been included. Table 1 includes the title and primary completion dates (PCD) for all excluded trials with additional information is available in the appendix.

Table 1 - Details of Excluded Trials

NCT ID	Official Title	Primary Completion Date
NCT04143256	An Open-Label, Multi-Center Study to Evaluate Selected Constituents in the Exhaled Breath Samples From the Use of JUUL Nicotine Salt Pod System Product (5% and 3% Virginia Tobacco, Mint, Mango, Menthol) Users and Conventional Cigarettes (Non-Menthol and Menthol Flavors)	12 December 2019
NCT04123041	A Randomized, Open-Label, Cross-Over Study to Characterize the Nicotine Uptake and Subjective Effects With Use of JUUL Electronic Nicotine Delivery Systems With Multiple Flavors and Nicotine Concentrations, Usual Brand of Combustible Cigarettes, a Comparator E-Cigarette and Nicotine Gum in Adult Smokers	18 December 2019
NCT04107779	A Randomized, Open Label, Parallel Group Study in Adult Smokers to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure After Switching Either Exclusively or Partly to Using JUUL Electronic Nicotine Delivery Systems With Two Different Nicotine Concentrations	17 February 2020
NCT04088175	A Randomized, Open-Label, Cross-Over Study to Characterize Puffing Topography With Use of JUUL Electronic Nicotine Delivery Systems (ENDS) in Adult, Closed-System ENDS Consumers	23 January 2020
NCT03700112	An Open Label, Randomized Crossover Study Comparing Nicotine Pharmacokinetics of Seven Electronic Cigarette Products and One Traditional Cigarette Across Two Delivery (10 Puff and Ad-libitum) Conditions, in Healthy Adult Smokers.	24 February 2019
NCT04452175	Cigarette Consumption After switchinG to High or Low Nicotine strENght E-cigaretteS In Smokers With Schizophrenia (GENESIS)	March 2022

Five trials were registered consistent with the Final Rule's "Applicable Clinical Trial" (ACT) criteria.[17,20] All are interventional and affirm they are on an "FDA-regulated Device Product".[18] It was not immediately apparent why Juul Labs inconsistently identified similar trials as being on FDA-regulated products. The meaning of this field is not ambiguous in ClinicalTrials.gov materials [19,20] and since data on ClinicalTrials.gov, especially those relating to FDAAA coverage, are attested to as accurate on submission, we maintained our original inclusion/exclusion criteria in line with the public data. Results were expected for all five trials as the PCD was more than one year ago as of 1 August 2020. Table 2 includes the key dates for each included trial.

Table 2 - Included Trials and Key Dates

Trial ID	Registration First Submitted	Last Updated Posted Date	Study Start Date	Primary Completion Date	Study Completion Date	FDAAA 2007 Results Due Date

NCT03463837	7 March 2018	3 January 2019	4 March 2018	27 July 2018	13 August 2018	27 July 2019
NCT03605641	16 July 2018	5 December 2018	17 September 2018	2 December 2018	2 December 2018	2 December 2019
NCT03593239	1 June 2019	9 January 2019	29 June 2018	26 July 2018	26 July 2018	26 July 2019
NCT03596034	6 June 2018	2 October 2018	9 August 2018	26 September 2018	26 September 2018	26 September 2019
NCT03719391	17 October 2018	3 January 2019	19 October 2018	21 November 2018	28 November 2018	21 November 2019

Results Searches:

Searches were conducted in August 2020. None of the five trials had results reported to ClinicalTrials.gov. We located conference posters containing results for four of the five trials on the JLI Sciences website and one publication in the literature reporting more in depth results from one of the posters. Three of the posters were available under a year from the provided primary completion date. Details of available results and outcome discrepancies are narratively described below. Additional trial details are available in the supplemental appendix.

Trial Details:

NCT03463837

This study examined "biomarkers of exposure" across various tobacco products including four Juul products. There were no meaningful changes to outcomes after first registration, however this trial was retrospectively registered by three days (Table 2) while the follow-up for the primary outcomes was just five days.

We located two results outside of ClinicalTrials.gov: a poster presented at the 25th Annual Meeting of the Society for Research on Nicotine and Tobacco on 23 February 2019 and

available on the JLI website; [25] and an article published online in the journal *Nicotine & Tobacco Research* on 5 November 2019.[26] As of writing, *Nicotine & Tobacco Research* has not endorsed the CONSORT guidelines.[27] The paper includes all the outcomes reported in the poster in addition to adverse events and a declaration that the three pharmacokinetic outcomes would be reported in a future publication. Across both publications: the primary outcome was fully reported; six (32%) of the 19 secondary outcomes were fully reported; five (26%) were reported with issues; three (16%) were not reported but properly declared; and one (5%) was unclear, leaving four (21%) entirely unreported.

Of the five outcomes reported with issues, four were measures of nicotine equivalents in the urine (nicotine, cotinine, trans-3'-hydroxycotinine, and Glucuronides) that were specified separately but reported as a grouped measure; the other was measuring "future intent to use" which specified no specific scale in the registry then reports the brief Wisconsin Inventory of Smoking Dependence Motives (WISDM). WISDM includes some aspects that could be indicative of "intent to use" in combination with non-prespecified measures of dependence.[28]

The three secondary outcomes related to nicotine equivalents measured in the blood are noted in the paper's methods but could not be located anywhere in the results or appendices. Product malfunctions were grouped with adverse events. While no malfunctions were listed, there was no statement to confirm that none occurred despite being listed as a discrete outcome. In the absence of such a statement, we could not properly assess this outcome.

NCT03605641

This was an open label study to examine emissions across three different environments for a Juul device, a competitor device (Vuse solo), and conventional cigarettes. Carbon monoxide (CO) was removed from two outcomes on 18 September 2018, the day after the provided start date. No results were found on ClinicalTrials.gov.

Searches revealed no results in the academic literature. The JLI Science website contains a poster presented at the 6th Annual Global Forum on Nicotine on 14 June 2019.[29] Of the 12 prespecified primary outcomes on ClinicalTrials.gov eight (67%) are fully reported, two (17%) have issues with their reporting based on the components specified in the outcome, and two (17%) are not reported.

In the poster, outcomes describing "room air samples" were not consistently and clearly reported for both use conditions despite identical specification in the registry entry. Select carbonyls in exhaled breath (acetaldehyde and acrolein) were not reported. Propylene glycol in exhaled breath is mentioned in the results text as "elevated" with reference to "Figure 2", but does not appear in "Figure 2" and is therefore considered unreported. Exhaled CO is reported in the poster but room air CO is not; both were removed as outcomes on ClinicalTrials.gov. Lastly, measurements on particle size are missing for one of the group/setting pairs with no explanation.

NCT03593239

This study intended to examine the nicotine pharmacokinetics of various Juul 1.7% and 5% nicotine salt products across four primary and two secondary outcomes. No outcome definitions meaningfully changed from first registration. Searches revealed no results in the academic literature or the JLI Science research database.

NCT03596034

This study assessed "puff topography" (PT) in adult smokers using the "Juul 5% Electronic Nicotine Delivery Systems" product. No outcome definitions meaningfully changed from first registration.

Searches revealed no results in the academic literature. The JLI Science website contains a poster with results presented at the 6th Annual Global Forum on Nicotine on 14 June 2019.[30] All five (100%) primary outcomes are reported, however only two of the seven (29%) secondary outcomes are reported. The "self-reported product use" secondary outcome was conservatively determined to be fully reported despite slight differences in how consumption was measured compared to the prespecified outcome. The five unreported secondary outcomes were subjective measures, specifically: cigarette dependence, smoking urges, effect of nicotine, affect (via Positive and Negative Affect Scale), and nicotine withdrawal.

NCT03719391

This study examined the nicotine pharmacokinetics of various Juul 5% nicotine salt products, Vuse Solo e-cigarettes, Nicorette 4mg nicotine gum, and standard combustible cigarettes. The primary outcomes were vaguely specified pharmacokinetic measurements of nicotine uptake in the plasma referencing a statistical analysis plan (SAP) that could not be located. No outcome definitions meaningfully changed from first registration.

We located no results searching the academic literature but found a matching poster on the JLI Science website from the 2020 Annual Meeting of the Society for Research on Nicotine

& Tobacco on 14 March 2020.[31] The primary outcome was reported however just two (20%) of the 10 secondary outcomes were fully reported without issue. One (10%) additional secondary outcome was partially reported and seven (70%) were unreported without any disclosure.

Various measures were reported that fit the broad "pharmacokinetic parameters" primary outcome. While we could not access the SAP we conservatively counted it as fully reported given there were pharmacokinetic details. For one of the secondary outcomes, the complete modified Product Evaluation Scale (mPES) was specified but only a single sub-scale ("Satisfaction") was reported. Missing outcomes included measures of blood pressure, heart rate, product usage, and two additional subjective scales (Nicotine Withdrawal Questionnaire and Product Direct Effect Questionnaire).

Summary of Results

All trials assessed did not report results on ClinicalTrials.gov. Only one of five trials had any results reported in the academic literature, but with notable inconsistencies. Four trials were reported in conference posters shared on the JLI Science website: these provide only brief methods and none completely reported all prespecified outcomes with no disclosure regarding altered outcomes or additional results available elsewhere.

Overall just 28 of 61 (46%) prespecified outcomes across all five trials were reported or properly declared, and 8 (13%) additional outcomes were reported but with issues; by outcome type 15 of 23 (65%) primary outcomes and 13 of 38 (26%) secondary outcomes were accounted for in any results reports. Problematic outcomes were either examining specific levels of molecules arising from tobacco use in various contexts (e.g., urine, breath,

room air, plasma) or subjective measures. Among the eight outcomes reported with issues, six measured specific molecules and two were subjective scales and among the 24 missing outcomes, 11 were examining molecule concentrations and nine were subjective measures. Summary results for outcome assessments are presented in Table 3. Detailed annotations for all outcome assessments are provided in supplementary material.

Table 3 - Reporting of Juul Sponsored Clinical Trials

Measure	NCT03463837	NCT03605641	NCT03593239	NCT03596034	NCT03719391	Total (%)
Results reported on ClinicalTrials.gov	No	No	No	No	No	0
Results reported outside of ClinicalTrials.gov	Yes (Poster & Paper)	Yes (Poster)	No	Yes (Poster)	Yes (Poster)	4 (80%)
Number of prespecified primary outcomes required to report	1	12	4	5	1	23
Number of primary outcomes fully reported	1 (100%)	8 (67%)	0	5 (100%)	1 (100%)	15 (65%)
Number of primary outcomes partially reported	0	2 (17%)	0	0	0	2 (9%)
Number of prespecified secondary outcomes required to report	19	0	2	7	10	38
Number of secondary outcomes fully reported	6 (32%)	0	0	2 (29%)	2 (20%)	10 (26%)
Number of secondary outcomes reported with issues	5 (26%)	0	0	0	1 (10%)	6 (16%)
Number of outcomes unreported or switched but declared	3 (16%)	0	0	0	0	3 (8%)
Unable to assess	1 (5%)	0	0	0	0	1 (3%)

Discussion

Non-reporting and selective outcome reporting are well documented sources of bias in clinical research.[11,17,32] Prior work assessing registrations consistent with FDAAA coverage found 74% of industry-sponsored trials and 63% of non-industry-sponsored trials had reported results at any time after becoming due.[17] Another prior investigation by our team on selective outcome reporting at top medical journals found that among 67 trial manuscripts with 915 specified outcomes, 524 (57.2%) were reported correctly and an additional 5 were reported but switched between primary and secondary designations.[33] Other studies have consistently shown more complete reporting of results to ClincialTrials.gov compared to journal articles.[34–37]

We are aware of the longstanding research literature on financial conflicts of interest and concerns around the poor quality and selective publication of tobacco-industry research.[38–40] Recent reviews have concluded that conflicts of interest are an important factor in interpreting the findings of e-cigarette research.[41,42] Many journals have policies to not publish research sponsored by the tobacco industry due to their notable history of past research distortion and misconduct.[43–45] Given this history, tobacco-industry funded e-cigarette research may be of questionable scientific value. Still, the fact remains that these trials occurred and may be used as evidence in regulatory proceedings. It is important that the trials are reported fully and transparently in line with best practices so that they can be critically interpreted, assessed for potential bias, and properly considered in full by the broader medical and public health community, as with all trials research.

Results disseminated through JLI Science, in the form of conference posters with space limitations, cannot be counted on to convey complete results which may complicate or bias their inclusion in future evidence synthesis. ClinicalTrials.gov provides a robust

dissemination route, independent of journals and without space restrictions, in which this research can be freely shared. While this route lacks peer review and some methodological detail it also provides clear summary statistics, with minimal potential for narrative spin, in a standard discoverable format.

Reasons for non-reporting can vary substantially.[46] Juul Labs has sponsored relatively few registered trials: prior work has shown reporting under FDAAA requirements increases with more sponsored trials on ClinicalTrials.gov; it is possible that more experienced sponsors have deeper knowledge of their obligations, ethical or legal, and can implement more robust reporting practices and expectations at scale.[17] It should be noted, however, that Juul Labs is part owned by Altria, formerly Philip Morris, a major tobacco company with an established research programme.[14] We cannot speculate on what the unreported results from these clinical trials may be or why they occurred; prior research shows that trials with less favourable results overall are less likely to reported;[47] and that even within reported trials, non-significant outcomes are less likely to be reported.[48] These are the very issues that FDAAA 2007 set out to address.[9]

Strengths and Limitations

In reporting detailed examinations of each trial's outcomes, we aimed to provide both insight into our evaluations and concrete examples of how outcome reporting bias occurs in the literature. Many studies have summarised the issue of outcome reporting bias and established it as an issue, and we hope this case series offers useful detail and examples of how this can occur in practice.[11,33]

This work has limitations. As with all studies reliant on bibliographic searches some results may exist but were not located. However, per ICMJE and CONSORT best practice, trial IDs should be clearly present in the abstracts and text of clinical trial publications.[10,49] If our trial ID and keyword searches could not locate relevant publications across multiple databases, low discoverability would represent a breach of best practice.

Data accuracy and availability is another potential limitation. Study documents with more detail on outcomes may exist. We could not locate any public source of trial protocols or SAPs for Juul Labs sponsored research. If changes to outcomes occurred, they should be reflected on ClincialTrials.gov and in any publications. Inaccurate or out-of-date data on the registry may lead to misclassification based on our inclusion/exclusion criteria and outcome evaluations. The availability of posters for four of the five trials further confirms that the trials did occur and full results could be made available. We believe sponsors have a clear ethical and, in the case of trials covered under FDAAA, legal responsibility to ensure their trial registrations are kept up to date and therefore should be held accountable to the public information they attest to accurately providing to the registry.[50] While officially determining FDAAA coverage may require complex regulatory consideration, we believe that, consistent with the Final Rule, public accountability based on registered data on ClinicalTrials.gov has an important role to play in improving the quantity and quality of trial reporting.

We also note that for the five trials considered, registration data was “Verified” meaning the information was reviewed after registration and attested to as accurate. At minimum, it appears that incorrect registry data has been consistently provided for some of Juul’s registered trials. The confusion caused by similar Juul-sponsored trials having different

"FDA-regulated device" status suggests that either the regulatory background of these trials varies in ways a public user cannot easily ascertain or that Juul have not properly ensured accurate information is being registered on ClinicalTrials.gov.

Policy Implications

ClinicalTrials.gov provides sponsors with information on registered trials that are likely to be covered in the backend PRS system.[19] However proactive public information on coverage of specific trials under FDAAA has not occurred. Furthermore, to our knowledge, no fines or warning letters for non-reporting under FDAAA have ever been issued by the FDA to any sponsor.[17,51] This lack of transparency is unfortunate and can lead to ambiguity about which trials are covered, lessening the impact of FDAAA reporting requirements.

There is regulatory consistency around the fact that tobacco products, like ENDS, are considered drug/device products in certain circumstances (e.g., smoking cessation claims).[52–54] Furthermore, the FDAAA Final Rule is clear that the intent to market a drug or device has no bearing on requirements to report the trial results of unapproved and uncleared treatments beholden to the law.[24] The FDAAA Final Rule discusses the similar dual-regulatory pathway of dietary supplements noting that "a substance characterized by a responsible party as a dietary supplement could be considered a 'drug' subject to section 505 of the FDC Act under the applicable drug clinical trial definition if the trial is studying a use that meets the drug definition under the FDC Act."[8] Similarly, another Final Rule (21 CFR Parts 201, 801, and 1100) notes that coverage as a drug/device vs. a tobacco product would depend on aspects of the trial itself that can only be determined after evaluation of the "methods and measures" to determine "the purposes for which a product is being investigated."[55] The complexity of these various laws, regulatory pathways, and legal

precedents complicate the issue of FDAAA coverage for ENDS products and obstructs public transparency and accountability.

This ambiguity is apparent when examining our sample. The uptake of nicotine in the body is an important component of nicotine addiction.[56] Three of the five trials in our sample examine nicotine biomarkers or pharmacokinetics. Trials excluded from our analysis share similar outcomes. It is unclear whether these outcomes aid in making claims about the "delivery of a pharmacologically active dose of nicotine" which are generally exempted from drug/device regulations, investigate "modified risk tobacco product" designations that allow claims relative to other tobacco products outside of drug/device regulations, or fall under unapproved or uncleared drug/device rules due to their clinical subject matter and outcomes. Additional Juul sponsored trials directly address smoking cessation with relevant outcomes like product use, dependency, urge to smoke, and aspects of withdrawal raising similar coverage questions. Juul's inconsistent designations may be the result of similar confusion about how to classify these trials.

Clarity here may require a more active approach to FDAAA enforcement. Despite criticisms, the FDA has not engaged in direct approaches to enforcing the registration and reporting requirements of the FDAAA.[17,57] Previous comments from President Joe Biden have shown support for active enforcement of results reporting requirements which may signal receptiveness of the current administration to these issues.[58]

Failing general efforts to make FDAAA coverage more definitive to the public, the FDA may consider specifically clarifying the reporting responsibilities of tobacco-industry sponsors under the law. If registered industry-sponsored clinical research into tobacco products

supports various tobacco-specific regulatory pathways, instituting reporting requirements as a condition of these applications could bypass complicated FDAAA 2007 considerations entirely. The public and the scientific community have a clear interest in ensuring the results of research on tobacco products is made fully available and current dissemination routes appear lacking. In any case, setting aside legal obligations, we note that there is also a strong ethical expectation that all clinical trial results should be reported completely in a timely manner and this investigation also shows notable deficiencies in outcome reporting.[6,7]

Conclusion

We describe issues with reporting of Juul Labs Inc. sponsored clinical trials. No trials reported on ClinicalTrials.gov nor fully accounted for all registered outcomes via other dissemination routes. The FDA should act to further clarify whether trials of ENDS products are covered under the FDAAA and encourage compliance as appropriate. Even in the event that these trials are mis-identified as covered under FDAAA, we hope that Juul will consider setting a higher standard of transparency and work to voluntarily submit all full results to ClinicalTrials.gov consistent with their registered outcomes.

Competing Interest Statement

The authors declare no direct conflicts on interest related to this work. BG has received research funding from the Laura and John Arnold Foundation, The Good Thinking Society, Wellcome Trust, the NHS National Institute for Health Research, the NHS National Institute for Health Research School of Primary Care Research, the Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science and is a co-founder of the AllTrials Campaign. NJD and HMD

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