Review of: "IQOS® Cross-Sectional and Cohort US Study Documentation"

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Potential competing interests: No potential competing interests to declare.

This is a manuscript documenting IQOS cross-sectional and longitudinal cohort post-market adult consumer studies as part of US FDA's MRTPA authorization. While the manuscript is quite well-written, I have several remarks that I believe would further improve the readability of the manuscript:

1. Introduction section, Page 2, "…most viable risk…": The word viable here seems to be a misnomer. On the contrary, complete cessation is often not feasible/viable for a significant group of smokers. Please revise.
2. Introduction section, Page 3, "Therefore, approaches to THR involve underage prevention, …., and the availability of RR product that do not burn tobacco": This statement is inaccurate. Both "underage prevention" & "cessation support" are not part of THR strategies as those activities seeks to prevent/eliminate tobacco use, while THR is defined as "minimizing harms and decreasing total mortality and morbidity, without completely eliminating tobacco and nicotine use" (Author's reference #3). Please revise.
3. Study Design subsection, page 4, para 4: Author mentioned that there are Appendices 1, 2, and 3 for the questionnaires, but I am not able to locate it. Please ensure that they are uploaded correctly. Additionally minor typo that should be revised by author in the following part of the sentence "…for the for the…".
4. Figure 1: I would recommend that the author edit the layout of the legend so that it is located to the right of the figure (instead of at the bottom). It would be less awkward to read and save some space.
5. Study population subsection, page 7, para 1: The four inclusion criteria for the current established IQOS group may be a bit too restrictive; hence authors may run into difficulty during the recruitment process. While authors mentioned that they will implement several recruitment models if those models were not successful in fulfilling the recruitment target, authors may want to redefine the current established IQOS group definition.
6. Study population subsection, page 7, para 5, "These sample sizes…. with over 90% power,…": Instead of stating "… over 90%...", please clarify the exact percentage so it is more specific.
7. Study population subsection, page 7, para 5, "Informed by discontinuation…of IQOS cohorts from other countries,…": These statement is incorrect since Authors' references all refer to electronic cigarettes cohorts, not IQOS cohort. Please revise.
8. Study Outcome Measures subsection, Page 9: Below module 3 (titled "Initiation, switching to IQOS, transition to/back to cigarette smoking, and quitting behaviors") there is a module titled "Quitting Behaviors". Is this a separate module? If so, it should be numbered as module 4. Additionally, why are there two "quitting behavior" modules? It seems that there should not be "…and quitting behaviors" in the title of Module 3. Please revise.

9. Result section, page 16, para 2: Authors stated that the IQOS CP PACS have been fielded for two months. Please specify these month and year.
10. Discussion section, page 16, para 3, “There exist a plethora….perceptions in European markets”: This statement is incorrect as Authors include two Japanese studies (Reference #16 and #19. Please revise.
11. Discussion section, page 16, para 3, “…, this is one of the first FDA reviewed and approved protocols…,”: Could Author add a reference for this statement?
12. Discussion section, page 17, para 1, “…intended to measure perception of risk of IQOS products…”: This sentence is confusing, I thought the health risk (along with cardiovascular/respiratory outcomes) modules are independent of risk perception module. How does these two modules linked? Please clarify.
13. Discussion section, page 17, para 2, “Based on rigorous analysis….prior studies,…”: Reference #38 should not be included here? Authors did not use GEE/regression for sampling approach.
14. The manuscript is quite abbreviation heavy, and their use are often inaccurate, hence reader may not easily follow it. I would recommend Authors to apply the following revision to the whole text:

    - Remove abbreviation that was only used sparingly (e.g. Abstract, “MRTPA”; Study Procedure subsection, Page 8, para 3, “GEP”).
    - Remove term that have been abbreviated earlier (e.g. Objective subsection, Page 3, para 4, “modified risk tobacco product” should be deleted since Authors have used MRTP in the last para of Intro section; Informed consent procedures, Page 15, para 3, “informed consent statement” should be deleted since Authors have used ICS in the Study Inclusion and Exclusion Criteria subsection).
    - Introduce abbreviation earlier when the term was first mentioned (e.g. Study Design subsection, Page 4, para 2, “PMUSA” should be introduced earlier in Introduction section, Page 3, para 3).
    - Introduce what the abbreviation stands for (e.g. Study Design subsection, Page 4, para 3, “ALCS”)
    - Ethical conduct of studies subsesction, page 15, para 12: Both (CASRO, 2016) and (ESOMAR, 2016) should not been introduced at the middle of the clause, but at the end of the clause.

15. The manuscript should reduce its use of unnecessary adjective/adverb as it may makes the manuscript sounds more subjective. This includes:

    - Confidentiality subsection, page 15, para 4: please delete “….highly…”
    - Discussion section, page 16, para 3: please delete “…may be definitively…”