## Supplementary file

### Appendix 1 Search strategy

Example Medline search strategy (Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions (R1946 to May 12, 2021. Filter: Cochrane highly sensitive RCT filter))

| Search number | Search term                                                                 | Results |
|---------------|-----------------------------------------------------------------------------|---------|
| 1             | Vaping/                                                                     | 1728    |
| 2             | Electronic Nicotine Delivery Systems/ or E-cigarette vapor/                  | 4469    |
| 3             | "Nebulizers and Vaporizers"/ and (nicotine or tobacco).mp.                  | 170     |
| 4             | e-cig$.mp.                                                                  | 5672    |
| 5             | Ecig$.mp.                                                                   | 136     |
| 6             | (Vape or vaping or vaper or vapors).mp.                                     | 3065    |
| 7             | (Vapori#e$ adj3 (cigarette$ or nicotine)).mp.                               | 105     |
| 8             | (electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.| 6400    |
| 9             | (e-sigaret$ or "e-sigaret$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarette$ électronique$" or sigaret$ electronique$ or sigaret$ electronik$ or sigaret$ electronika$ or sigaret$ electronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp. | 92      |
| 10            | (mods adj5 (tobacco or nicotine)).mp.                                       | 3       |
| 11            | Juul$.mp.                                                                   | 221     |
| 12            | (e-juice$ or e-liquid$).mp.                                                 | 701     |
| 13            | (cig-a-like$ or cigalike$ or ciga-like$).mp.                                | 61      |
| 14            | (e-hookah$ or electronic hookah$ or "hookah pens").mp.                     | 28      |
| 15            | (ENNDS or electronic non-nicotine delivery).mp.                            | 7       |
| 16            | ((NMND$ and nicotin$) or non-medicinal nicotine delivery system$).mp.       | 0       |
| 17            | or/1-16                                                                    | 8362    |
| 18            | (Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp. | 285     |
| 19            | ("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.| 169     |
| 20            | (Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.              | 27      |
| 21            | ((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.            | 6       |
| 22            | (IQOS or iFuse or Ploom).mp.                                                | 153     |
| 23            | (electrically-heated smoking system and (nicotin$ or tobacco$)).mp.        | 1       |
| 24            | (Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřáť tabák" or "opvarmet tobak" or "uppvärmde tobak" or "kuumututud tubakas" or "pinainit na tabako" or "läämmitetty tupakka" or "shan taba mai tsanani" or "hitâô töbåk" or "apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "incălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabacho caliente" or "tsitlmiş tütün" or "ugwayi ovuthayo" or "thuóc là nồng").mp. | 23      |
| 25            | or/18-24                                                                   | 476     |
| 26            | 17 or 25                                                                   | 8567    |
| 27            | ((randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ab. or drug therapy.fs.) not exp animals/ not humans.sh. | 605775  |
| 28            | 26 and 27                                                                  | 379     |
## Appendix 2 List of articles excluded at full text stage

### Original search

| Reference | Reason for exclusion |
|-----------|----------------------|
| 1. Adriaens K, Van Gucht D, Declerck P, et al. | Control (Participants were allowed to continue smoking) |
| 2. Baldassarri SR, Bernstein SL, Chupp GL, et al. | Intervention (NRT given in combo with EC) |
| 3. Chaumont M, Bernard A, Pochet S, et al. | Study design (crossover and short duration treatment) |
| 4. Harhay MO, Troxel AB, Brophy C, et al. | Intervention (Secondary analysis of Halpern trial but only analysing effects of monetary intervention) |
| 5. Kumral TL, Salturk Z, Yildirim G, et al. | Outcomes |
| 6. Lee SM, Tenney R, Wallace A, et al. | Study design (conference abstract) |
| 7. Li J, Hajek P, Pesola F, et al. | Study design |
| 8. Martin F, Talikka M, Ivanov NV, et al. | Intervention (too short treatment length) |
9. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure. *Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):391-403. doi: 10.3109/1354750x.2015.1094134 [published Online First: 2015/11/12]

Control

10. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 3. Biomarkers of biological effect. *Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):404-10. doi: 10.3109/1354750x.2015.1094135 [published Online First: 2015/11/04]

Control

11. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 1. Study design and methodology. *Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):382-90. doi: 10.3109/1354750x.2015.1094133 [published Online First: 2015/11/04]

Control

12. Picavet P, Haziza C, Lama N, et al. Reduced exposure to harmful and potentially harmful constituents after 90 days of use of tobacco heating system 2.2 in Japan: A comparison with continued combustible cigarette use or smoking abstinence. *Toxicology Letters* 2016;259:S141. doi: 10.1016/j.toxlet.2016.07.597

Study design (conference abstract)

13. Pravettoni G, Masiero M, Lucchiari C, et al. The role of electronic cigarettes in smoking cessation among heavy smokers undergoing a lung cancer screening program: Preliminary results of a randomized controlled study. *Psycho-Oncology* 2016;25:72. doi: 10.1002/pon.4082

Study design (conference abstract)

Update search

| Reference | Reason for exclusion |
|-----------|----------------------|
| 1. Watson, N. L., et al. (2021). "The association between frequency of e-cigarette use and long-term smoking cessation outcomes among treatment-seeking smokers receiving a behavioral intervention." *Drug and alcohol dependence* 218 (no pagination). | Study design (Patient not randomised to e-cigarettes observational data only for this) |
| 2. McRobbie, H. J., et al. (2020). "Nicotine replacement treatment, e-cigarettes and an online behavioural intervention to reduce relapse in recent ex-smokers: a multinational four-arm RCT." *Health Technology Assessment (Winchester, England)* 24(68): 1-82. | Intervention (Patient choice of NRT or e-cigarettes) |
Appendix 3 Model parameters and inconsistency assessment

We specified the following parameters: 250,000 ‘burn-in’ iterations to be discarded, 500,000 iterations for analysis, and three separate chains. Diagnostic tests were run to check model convergence. Thinning of the chains was specified to reduce the risk of autocorrelation. Default priors as specified by the ‘gemtc’ package were used. For this analysis, we selected NRT as the reference treatment because it was a common control treatment in the RCTs identified, which is a common standard of care in international clinical guidelines for treatment of tobacco dependence.1

A key assumption of NMA is that of evidence consistency that is, that estimates of treatment effects from direct and indirect evidence agree. We have compared the main model (consistency model) against an inconsistency model that assumes unrelated mean (relative) effects using a function of the ‘gemtc’ package.2,3 We also compared the direct head-to-head meta-analysis results versus the NMA outputs to further check for potential inconsistency. Meta-analyses for the direct comparisons were run using the metagen function in the ‘meta’ package for the R programming language.4,5

Appendix 4 PRIMSA diagram

Records identified through database searching (n=1880)
(Ovid Medline: n=344; Elsevier Embase: n=827; Cochrane Trials: n=709)

Records after duplicates removed:
(n=1396)

Records screened:
(n=1396)

Records excluded:
(n=1364)

Full-text articles assessed for eligibility
(n=32)

Full-text articles excluded with reasons for exclusion:
(n=13)

Studies included in quantitative synthesis
(n=15)
2 RCTs reported in 4 publications for heat-not-burn products
9 RCTs reported in 15 publications for ENDS

Studies included in quantitative synthesis
(n=16)
2 RCTs reported in 4 publications for heat-not-burn products
10 RCTs reported in 16 publications for ENDS

Updated searches May 2021
(n=3190)
(Ovid Medline n= 379; Ovid Embase n=1903; Cochrane Trials n=908)
Included 1 RCT for ENDS
## Appendix 5 RCT characteristics

### Appendix table 1 Eligibility criteria regarding smoking history from included RCTs

| Study ID   | N (cigarettes smoked per day) | Length of time smoking | Intention to quit smoking                                                                 | Prior use of smoking cessation aids                                                                 |
|------------|--------------------------------|------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| ASCEND⁹    | ≥10                            | At least 1 year        | Those who wanted to stop smoking                                                          | Excluding those using cessation drugs                                                                  |
| ECLAT⁷     | ≥10                            | At least 5 years       | Those not currently attempting to quit smoking or wishing to do so in the next 30 days    | Use of smokeless tobacco or NRT (no time frame given)                                                |
| TEC⁸       | –                              | –                      | –                                                                                         | No strong preference to use or not to use NRT or e-cigarettes, and were currently not using either type of product |
| Halpern 2018⁸ | –                              | –                      | –                                                                                         | –                                                                                                     |
| Lee 2019¹⁰ | ≥10                            | At least 3 years       | Those who were motivated to stop smoking entirely or to reduce their cigarette consumption | Excluded those who had attempted to stop smoking in the past 12 months by using other NRTs             |
| BETOFREE¹¹ | ≥10                            | At least 10 years      | Those with a high motivation to stop smoking                                              | Excluded any use of NRTs or e-cigarettes                                                              |
| Holliday 2019¹² | ≥10                            | –                      | Intention to quit was not an inclusion criterion for this study                           | Included those not currently using an e-cigarette, or not having used one for more than 2 days in the last 30 days |
| Hatsukami 2019¹³ | ≥5                              | At least 1 year        | Excluded if planning to quit smoking in the next 3 months                                 | Excluded those currently using NRT or cessation medication                                             |
| Lee 2018¹⁴ | >2                             | –                      | –                                                                                         | Excluded those who were currently using smoking cessation pharmacotherapy or currently used e-cigarettes daily. |
| Eiseberg 2020¹⁵ | ≥10                            | –                      | Moderate or strong desire and intention to attempt to quit                               | Excluded individuals who had used a smoking cessation therapy in the past 30 days, an e-cigarette in the past 60-days, or had ever used an e-cigarette for 7 days consecutively or more. |
Appendix table 2 Sociodemographic characteristics of participants

| Characteristic              | ASCE ND16 | ECL AT7 | TE C8 | Halp ern 20189 | Lee 201910 | BETOF REE11 | Holliday 201912 | Lee 201814 | Hatsuk ami 201913 | Eiseberg 202015 |
|----------------------------|-----------|---------|-------|----------------|-------------|-------------|----------------|-------------|---------------------|-----------------|
| Age in years               | Median    | -       | 41    | 44             | -           | -           | -              | -           | 47                  | (-)             |
|                           | (IQR)     | (33-52) | (34.4-54) | -              | -           | -           | -              | -           |                     |                 |
| Mean (SD)                  | 42.4      | 44      | 42.3  | 62.8           | 44.3        | 53.5        | -              | 52          |                     |                 |
|                           | (12.7)    | (12.5)  | (8.3 )| (4.58)         | (10.7)      | (-)         | -              | (13)        |                     |                 |
| Gender (male)              | 38%       | 63%     | 52%   | 49%            | 100%        | 63%         | 90%            | 50.8%       | 53%                 |                 |
| Ethnicity                  | 33% Māori | -       | -     | -              | -           | 6.3% Asian or Asian British | 6% Latino | 37.9% black, 8.7% other non-white | 1-6% black * |
| Education (second level or lower) | 49%       | 31%     | 30%   | 61%            | -           | -           | 41.7%          | 37-39%*     |                     |                 |
| Employed                   | -         | 70%     | 100%  | 100%           | -           | 75%         | 90%            | -           |                     |                 |
| Entitled to free prescriptions | -        | 40.7%   | -     | -              | -           | -           | -              | -           |                     |                 |
| Married                    | -         | -       | -     | 90%            | -           | -           | -              | -           |                     |                 |

*Only reported by treatment arm
- range across arms reported
IQR: Interquartile range
SD: Standard deviation

Appendix table 3 Smoking characteristics of the RCT participants

| Characteristic              | ASCE ND16 | ECL AT7 | TE C8 | Halp ern 20189 | Lee 201910 | BETOF REE11 | Holliday 201912 | Lee 201814 | Hatsuk ami 201913 | Eiseberg 202015 |
|----------------------------|-----------|---------|-------|----------------|-------------|-------------|----------------|-------------|---------------------|-----------------|
| Age started smoking (years) | Mean (SD) | 15.5    | 16.8  | -              | -           | 17.4        | 15.7           | -           | -                   | -               |
|                           | (4.5)     | (3.9)   | -     | -              | -           | (3.7)       | (3.0)          | -           |                     |                 |
| Median (IQR)              | -         | 16      | -     | -              | -           | -           | -              | -           | -                   |                 |
|                           | (14)      | (18)    | -     | -              | -           | -           | -              | -           |                     |                 |
| Number of years smoking continuously | -         | -       | -     | -              | -           | -           | -              | -           | -                   |                 |
| Characteristic                                      | ASCE ND16 | ECLAT7 | TE C8 | Halpern 20189 | Lee 201910 | BETOF REE11 | Hollday 201912 | Lee 201814 | Hatsu kami 201913 | Eiseberg 202015 |
|---------------------------------------------------|-----------|--------|-------|---------------|------------|-------------|----------------|------------|-------------------|-----------------|
| Mean (SD)                                         | 24.7*     | -      | -     | 18 (10–29)    | -          | 32 (-)      | -              | -          | -                 | (14)            |
| Median (IQR)                                      | -         | -      | -     | 22 (8.8)      | -          | -           | -              | -          | -                 | -               |

**Number of cigarettes smoked per day**

| Mean (SD)                                         | 17.9 (6.3) | -      | -     | 20* (-)       | 19.4 (7.8) | 17.4 (6.6) | 13 (-)        | 21 (11)    | -                 | -               |
| Median (IQR)                                      | 20 (15–25) | 15 (10) | 10 (5–15) | - (-)       | -          | -           | 15 (-)        | -          | -                 | -               |

| Lives with other smokers                         | 54%        | -      | -     | -             | -          | -           | -              | -          | -                 | -               |
| At least one quit attempt (%)                    | 55%        | 51%    | 40%   | 90% (-)       | -          | -           | 89% (-)        | 93%*       | 89% ever tried*    | -               |
| Mean self-efficacy to quit                       | 3.7 of 5-point scale | -      | -     | 6 out of 10 confidence about quitting | -          | -           | -              | -          | -                 | -               |

| Mean FTND score (SD)                             | 5.5 (2.0)  | 5.8 (2.2) | 4.6 (2.4) | 4.1 (2.2) | 4.3 (1.9) | 5.0 (2.1) | 3.1 (medi an) | 6 (2)      | -                 | -               |
| FTND score >5 (%)                                | 55%        | -      | -     | -             | -          | -           | 36% (-)        | 43%        | -                 | -               |
| Mean GN-SBQ score (SD)                           | 20 (8.3)   | 20.0 (7.2) | -    | -             | -          | -           | -              | 20 (8)     | -                 | -               |
| E-cigarette use                                  | -         | -      | 34%   | -             | -          | -           | -              | -          | -                 | -               |
| Past NRT use                                     | -         | -      | 74%   | -             | -          | -           | -              | -          | -                 | -               |

*Calculated
**Only reported by treatment arm -range across arms reported

IQR: Interquartile range
FTND: Fagerström Test for Nicotine Dependence
GN-SBQ: Glover-Nilsson Smoking Behavioral Questionnaire
SD: Standard deviation
### Appendix 6 RCT cessation results

**Appendix table 4 RCT results with smoking cessation at 24 or 26 weeks**

| Study ID | Treatment  | N = cessation events | N = arm total | Quit rate | Verified | Comparison | RR   | LCI     | UCI     | p-value |
|----------|------------|----------------------|---------------|-----------|----------|------------|------|---------|---------|---------|
| ASCEND⁶  | ENDS       | 21                   | 289           | 7%        | Yes      | ENDS vs NRT | 1.26 | 0.68    | 2.34    | 0.46    |
| ASCEND⁶  | NRT        | 17                   | 295           | 6%        | Yes      | ENDS vs ENNDS | 1.77 | 0.54    | 5.77    | 0.44    |
| ASCEND⁶  | ENNDS      | 3                    | 73            | 4%        | Yes      | ENDS vs ENNDS | 1.77 | 0.54    | 5.77    | 0.44    |
| ECLAT⁷   | ENDS       | 22                   | 200           | 11%       | Yes      | –           | 1    | –       | –       | –       |
| ECLAT⁷   | ENNDS      | 5                    | 100           | 5%        | Yes      | ENDS vs ENNDS | 2.20 | 0.86    | 5.64    | 0.10    |
| TEC⁸     | ENDS       | 155                  | 438           | 35%       | No*      | –           | 1    | –       | –       | –       |
| TEC⁸     | NRT        | 112                  | 446           | 25%       | No*      | ENDS vs NRT  | 1.40 | 1.14    | 1.72    | –       |
| Halpern 2018⁹ | ENDS     | 12                   | 1,199         | 1%        | Yes      | ENDS vs no additional treatment | 8.14 | 1.06    | 62.46   | 0.04**  |
| Halpern 2018⁹ | No additional treatment | 1              | 813          | 0%        | Yes      | ENDS vs no additional treatment | 8.14 | 1.06    | 62.46   | 0.04**  |
| Lee 2019¹⁰ | ENDS     | 16                   | 75            | 21%       | Yes      | –           | 1    | –       | –       | –       |
| Lee 2019¹⁰ | NRT       | 21                   | 75            | 28%       | Yes      | ENDS vs NRT  | 0.76 | 0.43    | 1.34    | 0.34    |
| BETOFREE¹¹ | ENDS     | 13                   | 70            | 19%       | Yes      | –           | 1    | –       | –       | –       |
| BETOFREE¹¹ | ENNDS     | 11                   | 70            | 16%       | Yes      | ENDS vs ENNDS | 1.18 | 0.57    | 2.46    | 0.65    |
| BETOFREE¹¹ | No additional treatment | 7              | 70            | 10%       | Yes      | ENDS vs no additional treatment | 1.86 | 0.79    | 4.38    | 0.16    |
| Holliday 2019¹² | ENDS     | 6                    | 40            | 15%       | Yes      | –           | -    | -       | -       | -       |
| Holliday 2019¹² | No additional treatment | 2              | 40            | 5%        | Yes      | ENDS vs no additional treatment | 3.00 | 0.64    | 13.98   | 0.16    |
| Eiseberg 2020¹⁵ | ENDS     | 5                    | 128           | 4%        | Yes      | –           | -    | -       | -       | -       |
| Eiseberg 2020¹⁵ | ENNDS     | 3                    | 127           | 2%        | Yes      | ENDS vs ENNDS | 1.65 | 0.40    | 6.77    | 0.48    |
| Eiseberg 2020¹⁵ | No additional treatment | 1              | 121           | 1%        | Yes      | ENDS vs no additional treatment | 4.73 | 0.56    | 39.88   | 0.15    |

*Not verified at this timepoint

**This study intended to use the Holm method to determine significance, however, we report the unadjusted difference here as this is what is extracted for all studies. Using the Holm method, this comparison was not considered significantly different.

RR: Relative risk; LCI: Lower confidence interval; UCI: Upper confidence interval
Appendix table 5 RCT results with smoking cessation at 52 weeks

| Study ID | Treatment | N=cessation events | N=arm total | Verified | Comparison       | RR  | LCI  | UCI  | p-value |
|----------|-----------|--------------------|-------------|----------|------------------|-----|------|------|---------|
| ECLAT 7  | ENDS      | 22                 | 200         | Yes      | ENDS vs ENNDS    | 2.7 | 0.7  | 7.7  | 0.06    |
|          | ENNDS     | 4                  | 100         | Yes      | ENDS vs ENNDS    | 2.5 | 0.5  | 6    | <0.001  |
| TEC^8    | ENDS      | 79                 | 439         | Yes      | ENDS vs NRT      | 1.8 | 1.3  | 3.0  | <0.001  |
| TEC^8    | NRT       | 44                 | 447         | Yes      | ENDS vs NRT      | 1.8 | 1.3  | 8    | <0.001  |
| Halpern 2018^9 ENDS | 4 | 1,199 | Yes | ENDS vs no additional treatment | 6.1 | 1.0 | 113 | 0.22 |
| Halpern 2018^9 No additional treatment | 0 | 813 | Yes | ENDS vs no additional treatment | 6.1 | 1.0 | 113 | 0.22 |

RR: Relative risk  
LCI: Lower confidence interval  
UCI: Upper confidence interval

Appendix 7 RCT missing and lost to follow-up data

Appendix table 6 Missing data and lost to follow-up in RCTs

| Study ID  | How was missing data handled? | Number lost to follow-up/discontinued at 6 months | Number lost to follow-up/discontinued at 12 months |
|-----------|-------------------------------|--------------------------------------------------|--------------------------------------------------|
| ASCEND    | Assumed participants with missing smoking status were smoking | 22% in ENDS, 27% in NRT and 22% in ENNDS arm | |
| ECLAT     | Assumed that all those individuals who were lost to follow-up are classified as failures | - | 35% in ENDS group A, 37% in ENDS group B and 45% in nicotine e-cigs group |
| Halpern 2019 | Persons with incomplete follow-up data classified as smokers | This trial does not clearly report loss to follow-up although it is clear there was a very large dropout rate. The study authors defined an engaged cohort as those who had logged on to the trial website at least once. ENDS were only available through logging onto the website so those who were not 'engaged' in the e-cigarette group received no treatment. In the usual care group 15.9% were engaged and 21.1% of the e-cigarette group were engaged | - |
| Study ID     | How was missing data handled?                                                                                                                                                                                                                                                                                                                                 | Number lost to follow-up/discontinued at 6 months                              | Number lost to follow-up/discontinued at 12 months |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|
| Lee 2019    | Method for imputing missing data not reported                                                                                                                                                                                                                                                                                                               | 5.3% in the ENDS group and 18.6% in the NRT group                               | -                                                |
| TEC         | To assess the effect of missing data on the primary outcome, the authors conducted four prespecified sensitivity analyses, which excluded participants who did not attend at least one behavioral-support session, excluded participants who used the non-assigned product for at least 5 consecutive days, excluded participants who did not complete the 52-week follow-up, and imputed missing information with the use of multiple imputation by chained equations. Missing data were imputed for 136 participants in each group, and 50 data sets were imputed | 19.8% in the ENDS group and 24.6% in the NRT group                             | 18.9% in the ENDS group and 23.5% in the NRT group |
| BETOFREE    | Method for imputing missing data not reported                                                                                                                                                                                                                                                                                                               | 25.7% in the ENDS group, 27.1% in the NRT group and 25.7% in the no additional treatment group | -                                                |
| Holliday 2019 | Participants with missing smoking outcome data (e.g. those not attending for review) were considered as continuing smokers or to have resumed smoking                                                                                                                                                                                                                 | 27.5% in both groups                                                             | -                                                |
| Hatsukami 2019 | Unclear how missing data handled for adverse events                                                                                                                                                                                                                                                                                                         | At eight weeks there was 23.7% dropout rate in the ENDS arm and 30.3% in the NRT arm | -                                                |
| Lee 2018    | Unclear how missing data handled for adverse events                                                                                                                                                                                                                                                                                                         | 20% at eight weeks in NRT and 10% for ENDS                                      | -                                                |
| Eisenberg 2020 | Two methods, primary analysis participants missing data assumed to have returned to smoking at baseline level, sensitivity analysis multiple imputation                                                                                                                                                                                                            | 12% in ENDS group, 14.1 in ENNDS group, 29.8% in no additional treatment        | -                                                |
Appendix 8 Sensitivity analyses for NMA at 24—26 weeks

Appendix figure 1 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 1- excluding light smokers

Appendix figure 2 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 2-excluding unverified data

Appendix figure 3 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 3-excluding low dose nicotine e-cigarette
Appendix 9 Adverse events

Appendix table 7 documented adverse events

| Study ID   | Vital signs | Psychiatric | Cardiovascular | Pulmonary | Rebound and withdrawal and addiction potential | Serious adverse events |
|------------|-------------|-------------|----------------|-----------|------------------------------------------------|------------------------|
| ASCEND     | N           | N           | N              | N         | Y                                              | Y                      |
| ECLAT      | Y           | Y           | N              | Y         | Y                                              | Y                      |
| TEC        | N           | Y           | Y              | Y         | Y                                              | Y                      |
| Halpern    | N           | N           | N              | N         | N                                              | N                      |
| Lee        | N           | N           | N              | Y         | Y                                              | Y                      |
| BETOFREE   | Y           | Y           | Y              | Y         | Y                                              | N                      |
| Holliday   | N           | N           | N              | N         | Y                                              | Y                      |
| Lee        | N           | N           | Y              | Y         | N                                              | Y                      |
| Hatsukami  | Y           | N           | N              | Y         | N                                              | N                      |
| Eisenberg  | N           | Y           | Y              | Y         | N                                              | Y                      |

Appendix table 8 Pulmonary adverse events documented

| Symptom                | Study      | E-cigarette NRT N ENNDS No additional treatment Total N events |
|------------------------|------------|---------------------------------------------------------------|-------------------------------------------------|
| Shortness of breath    | TEC^8      | 66 64 - - 130                                                  |
|                        | ECLAT^7    | 12 - 5 - 17                                                   |
|                        | Lee 2019^10| - - - -                                                       |
|                        | BETOFREE^11| 92 103 106 - 301                                              |
|                        | Eisenberg 2020^15 | 53 - 61 43 157                      |
| Cough                  | TEC^8      | 97 111 - - 208                                                |
|                        | ECLAT^7    | 26 - 11 - 37                                                  |
|                        | Lee 2019^10| 3 3 - - 6                                                     |
|                        | BETOFREE^11| 54 50 36 - 140                                                |
| Reference | Authors | Year | PubMed ID | Journal | Volume | Issue | Pages |
|-----------|---------|------|-----------|---------|--------|-------|--------|
| 1. | Nilan K, McNeill A, Murray RL, McKeever TM, Raw M. | 2018 | 31091166 | Addiction (Abingdon, England) | 113 | 8 | 1499-1506 |
| 2. | Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. | 2018 | 28599502 | Network meta-analysis for decision making. New Jersey, USA: John Wiley & Sons Ltd. | 2018 | | |
| 3. | van Valkenhoef G, Kuiper J. | 2018 | 30032296 | Network meta-analysis using Bayesian methods: Package 'gemtc'. Version 0.8-4. | 2020 | | |
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| 8. | Hajek P, Phillips-Waller A, Pruzlj D, et al. | 2018 | 30549844 | A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. | 2019a;380(7):629-637 | | |
| 9. | Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. | 2018 | 30567598 | A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. N Engl J Med. | 2018;378(24):2302-2310 | | |
| 10. | Lee SH, Ahn SH, Cheong YS. | 2018 | 30241746 | Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: A randomized controlled study. Journal of the American Board of Family Medicine : JABFM. | 2019;32(4):567-574 | | |
| 11. | Masiero M, Lucchiari C, Mazzocco K, et al. | 2018 | 30472786 | E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: Preliminary results by randomized controlled trial. Nicotine Tob Res. | 2019;21(1):119-126 | | |
| 12. | Holliday R, Preshaw PM, Ryan V, et al. | 2018 | 30538082 | A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis. Pilot Feasibility Stud. | 2019;5:74 | | |
| 13. | Hatsukami D, Meier E, Lindgren BR, et al. | 2018 | 30427966 | A randomized clinical trial examining the effects of instructions for electronic cigarette use on smoking-related behaviors, and biomarkers of exposure. Nicotine Tob Res. | 2019 | | |
| 14. | Lee SM, Tenney R, Wallace AW, Arjomandi M. | 2018 | 30532119 | E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ. | 2018;6:e5609 | | |
| 15. | Eisenberg MJ, Hébert-Losier A, Windle SB, et al. | 2018 | 30077151 | Effect of e-Cigarettes Plus Counseling vs Counseling Alone on Smoking Cessation: A Randomized Clinical Trial. JAMA. | 2020;324(18):1844-1854 | | |
| 16. | Bullen C, Howe C, Laugesen M, et al. | 2018 | 30472786 | Electronic cigarettes for smoking cessation: A randomised controlled trial. Lancet (London, England). | 2013;382(9905):1629-1637 | | |
PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

| Section/Topic | Item # | Checklist Item | Reported on Page # |
|---------------|--------|----------------|--------------------|
| TITLE         | Title  | Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis). | 2 |
| ABSTRACT      | Structured summary | Provide a structured summary including, as applicable: **Background:** main objectives. **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name. | 2 |
| INTRODUCTION  | Rationale | Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted. | 3 |
|               | Objectives | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| METHODS       | Protocol and registration | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. | 3 |
|               | Eligibility criteria | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification). | 4 |
|               | Information sources | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3 |
|               | Search | Present full electronic search strategy for at least one |  |
| Study selection          | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3 |
|-------------------------|----|-----------------------------------------------------------------------------------------------------------------|---|
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3 |
| Data items              | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3 |
| Geometry of the network | S1 | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. | 4 |
| Risk of bias within individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 3 |
| Summary measures        | 13 | State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses. | 4 |
| Planned methods of analysis | 14 | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:  
  - Handling of multi-arm trials;  
  - Selection of variance structure;  
  - Selection of prior distributions in Bayesian analyses; and  
  - Assessment of model fit. | 4 and suppl appendix |
| Assessment of Inconsistency | S2 | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found. | 4 and suppl appendix |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6/7 |
| Additional analyses     | 16 | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:  
  - Sensitivity or subgroup analyses;  
  - Meta-regression analyses;  
  - Alternative formulations of the treatment network; and  
  - Use of alternative prior distributions for Bayesian analyses (if applicable). | 8 |
### RESULTS†

| Section                                      | Page |
|----------------------------------------------|------|
| **Study selection**                         | 17   |
| Give numbers of studies screened, assessed   |      |
| for eligibility, and included in the review, |      |
| with reasons for exclusions at each stage,   |      |
| ideally with a flow diagram.                | 5    |
| **Presentation of network structure**        | S3   |
| Provide a network graph of the included      |      |
| studies to enable visualization of the        |      |
| geometry of the treatment network.           | 8    |
| **Summary of network geometry**              | S4   |
| Provide a brief overview of characteristics   |      |
| of the treatment network. This may include    |      |
| commentary on the abundance of trials and    |      |
| randomized patients for the different        |      |
| interventions and pairwise comparisons in     |      |
| the network, gaps of evidence in the         |      |
| treatment network, and potential biases      |      |
| reflected by the network structure.          | 7    |
| **Study characteristics**                    | 18   |
| For each study, present characteristics for   |      |
| which data were extracted (e.g., study size,  |      |
| PICOS, follow-up period) and provide the     |      |
| citations.                                   | SUPPL appendix |
| **Risk of bias within studies**              | 19   |
| Present data on risk of bias of each study   |      |
| and, if available, any outcome level        |      |
| assessment.                                  | Suppl appendix |
| **Results of individual studies**            | 20   |
| For all outcomes considered (benefits or      |      |
| harms), present, for each study: 1) simple   |      |
| summary data for each intervention group,    |      |
| and 2) effect estimates and confidence       |      |
| intervals. Modified approaches may be noted  |      |
| to deal with information from larger         |      |
| networks.                                    | 8    |
| **Synthesis of results**                     | 21   |
| Present results of each meta-analysis done,  |      |
| including confidence/credible intervals.     |      |
| In larger networks, authors may focus on     |      |
| comparisons versus a particular comparator   |      |
| (e.g., placebo or standard care), with full  |      |
| findings presented in an appendix. League    |      |
| tables and forest plots may be considered to |      |
| summarize pairwise comparisons. If additional |      |
| summary measures were explored (such as      |      |
| treatment rankings), these should also be    |      |
| presented.                                   | 8    |
| **Exploration for inconsistency**            | S5   |
| Describe results from investigations of       |      |
| inconsistency. This may include such        |      |
| information as measures of model fit to      |      |
| compare consistency and inconsistency models, |      |
| P values from statistical tests, or summary  |      |
| of inconsistency estimates from different    |      |
| parts of the treatment network.              | 9    |
| **Risk of bias across studies**              | 22   |
| Present results of any assessment of risk of |      |
| bias across studies for the evidence base    |      |
| being studied.                               | 6    |
| **Results of additional analyses**           | 23   |
| Give results of additional analyses, if done  |      |
| (e.g., sensitivity or subgroup analyses,     |      |
| meta-regression analyses, alternative network |      |
| geometries studied, alternative choice of     |      |
| prior distributions for Bayesian analyses,    |      |
| and so forth).                               |      |
| **DISCUSSION**                               |      |
| Summarize the main findings, including the    |      |
| strength of evidence for each main outcome;  |      |
| consider their relevance to key groups (e.g.,|      |
| healthcare providers, users, and policy-     |      |
| makers).                                     | 9-12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).* |
| --- | --- | --- |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |
| **FUNDING** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. |

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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