

A randomised, controlled study to evaluate the effects of switching from cigarette smoking to using a Tobacco Heating Product, on health effect indicators in healthy subjects

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Introduction

Clinical studies carried out over 7 days have shown that toxicant exposure is lower in tobacco heating products (THPs) compared to conventional cigarettes¹. Pre-clinical assessment studies have further demonstrated reduced chemical emissions from THPs, and biological effects following THP exposure, compared to cigarette smoke². However, it is unclear if these reductions are sustained and if they translate to reductions in smoking-related health risks.

Objective

To test the hypothesis that reduction in exposure to toxicants will result in changes in biomarkers of exposure (BoE) and biomarkers of biological effect (BoBE), when smokers switch to using THPs compared with smokers who continue to smoke. Furthermore, that these changes are directionally similar to changes seen in smokers who cease smoking, over 12-months in an ambulatory setting.

Methods

This novel study, conducted in the UK (ISRCTN81075760), has been approved by a local Research Ethics Committee and run in accordance with ICH-GCP. Subjects will be of either gender (aged 23–55 years). Regular smokers will be randomly allocated to either continue to smoke their own brand cigarettes or switch to smoking a THP for 360 days. A separate smoking cessation group will be made up of regular smokers who intend to quit and will be provided with assistance with quitting (NRT/varenicline/counselling). The last group will be participants who have never smoked. Subjects will attend a total of 13 non-residential clinic visits plus a Screening Visit and a Follow-up Visit over a period of 12 months. BoE, BoBE and questionnaire assessments will be evaluated in this study. Safety evaluations will include adverse events, vital signs, clinical laboratory evaluations, physical examinations, electrocardiogram, and lung function tests.

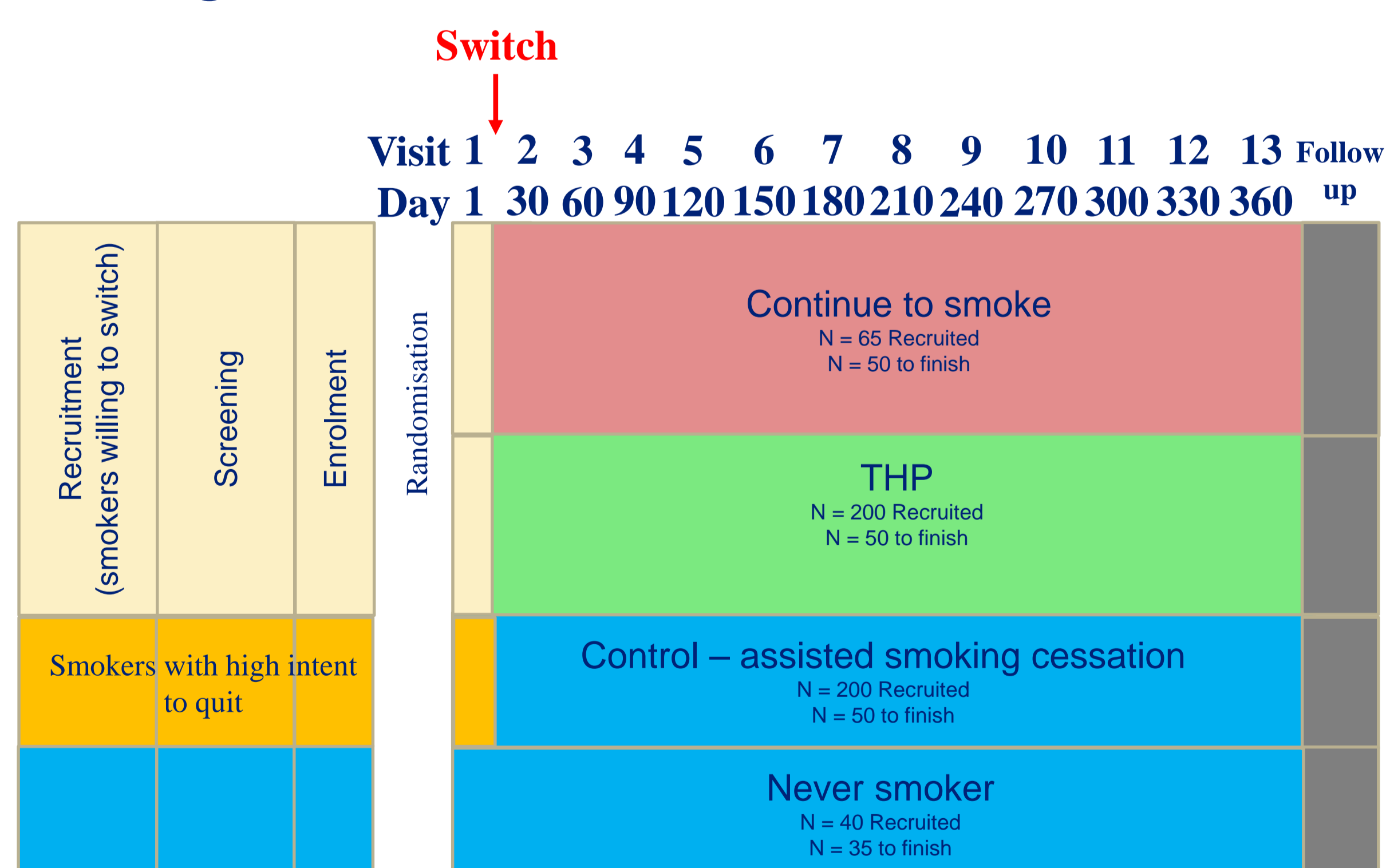


Figure 1. Study Design

Subject Compliance

Study subjects are expected to remain compliant to the study arm they are assigned to. To monitor compliance of smoking cessation and switch to THP, biomarkers of compliance will be included and monitored at study visits.

Compliance Monitoring (Analysis Schedule 2)

- Blood cyanoethyl-valine haemoglobin adducts (CeVal)
- Urinary N-nitroso-anatabine (NAT)
- Urinary N-nitroso-anabasine (NAB)
- Electronic Diaries (all study visits)

Study Endpoints

Analysis Schedule	Timepoint (Day)
1	All Days
2	1, 30, 60, 90, 180, 270, 360
3	1, 90, 180, 270, 360

Biomarkers of Exposure (BoE) <small># denotes Primary Objective Biomarker</small>	Analysis Schedule
Exhaled Carbon Monoxide	1
Urinary total nicotine equivalents, NNAL [#] , NNN, NAT, NAB	2
Urinary 3-HPMA, HMPMA, SPMA, MHBMA, CEMA, 1-OHP, HEMA	2
Urinary 4-aminobiphenyl, 2-aminonaphthalene, ortho-toluidine	2
Blood cyanoethyl-valine haemoglobin adducts (CeVal)	2

Biomarkers of Biological Effect (BoBE) <small># denotes Primary Objective Biomarker</small>	Analysis Schedule
Oxidative stress	
Urinary 8-epi-PGF2 α Type III [#] , 4-hydroxy-nonenal	2
Plasma Homocysteine, 3-nitrotyrosine	3
Inflammation	
White blood cell count	2
Plasma sICAM-1, MCP-1, hsCRP, E-Selectin	3
Coagulation	
Urinary 11-dehydrothromboxane B2	2
Plasma PAI-1, tPA, Fibrinogen	3
Vascular tone	
Plasma Endothelin-1	3
Exhaled Nitric Oxide	2
Finger Plethysmography (Peripheral Arterial Tone)	3
Blood Lipids	
HDL/LDL cholesterol, triglycerides	2
Arterial Stiffness	
Augmentation Index [#]	2
Carotid-femoral pulse wave velocity	2
Lung Function	
FEV ₁ , FVC, FEF ₂₅₋₇₅	2
Other	
Plasma Glucose	3
Body weight, waist circumference, fat analysis	3
6-minute walk test	2
Urinary creatinine	2
Exploratory Endpoints	
Plasma tetrahydrobiopterin (BH4)	
Nasal epithelial cell and PBMC transcriptomics	To be determined
Serum NMR lipoprotein analysis	
Serum metabolomics	

Conclusions

Recently Public Health England have indicated further research is required into THPs³. Data from this study will advance scientific understanding of the changes in both BoE and BoBE following a switch from cigarette smoking to a tobacco heating product, and smoking cessation.

References

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3. McNeill A, Brose LS, Calder R, Bauld L & Robson D (2018). Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. Retrieved from <https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review>

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