INTRODUCTION:
Draft guidance issued by the US FDA on modified risk tobacco product (MRTP) applications includes the FDA’s expectation that clinical studies are conducted that investigate the impact of the use of MRTPs on levels of biomarkers of exposure (BoE) and biomarkers of biological effect (BoBE).
For an exposure modification order, the draft guidance includes seeking information that includes:
• “Consumers actually use the product in a way that exposes them to the specified reduced level of the substance or substances.”
• “The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measureable and substantial reduction in morbidity or mortality is reasonably likely in subsequent studies.” (1)

STUDY ONE: Reduced toxicant prototype (RTP) cigarettes with substantially reduced levels of machine-measured tobacco smoke toxicants, compared to conventional products, were evaluated in a 6-week single-blinded randomised controlled study with occasional clinical confinement (Trial registration: ISRCTN7215735). All smoking subjects smoked a conventional cigarette for 2-weeks, and baseline urinary biomarker of exposure (BoE) measures were determined for Day 14. Control groups continued to smoke the conventional cigarette while test groups switched to one of three RTP designs. Clinical confinement and additional assessments were performed for all smoking groups after 2 and 4-weeks.

On average, smokers who switched to RTPs with reduced machine yields of specific toxicants had reduced levels of corresponding BoEs though there were large variations across individuals and BoEs were always lower in non-smokers. (2)

To fully understand the impact of the switch to the RTP on toxicant exposure, smoking subjects were permitted to smoke ad libitum throughout. Daily cigarette consumption varied throughout the study without obvious trend, with the exception of the last day of the study (Day 42 - Figure 1) where all groups showed a tendency to increase in cigarettes per day (CPD) which was significant for two groups (one control and one test). It was concluded that this increase was probably due to the imminent end in supplied (free) cigarettes. As the statistical analysis plan aimed to compare BoE levels at end of study with baseline measures, this potential artefact can influence the study conclusions.

Potential implications: Studies that employ natural and ad libitum smoking to ensure realistic conclusions may need measures, such as designs that run longer than needed for clinical assessment, in order to avoid study-induced behavioural changes influencing the findings.

STUDY TWO: Reduced toxicant prototype (RTP) cigarettes were evaluated in a controlled 6-month single blinded study with occasional clinical confinement (Trial registration: ISRCTN81286286) (Figure 2). Study cigarettes were supplied free of charge and subjects were allowed to smoke ad libitum throughout the study. Daily cigarette consumption during ambulatory periods was self-reported using a smartphone-like ePRO device (Electronic patient reported outcomes). Analysis of biomarker and other study endpoints is ongoing.

Following a switch on Day 14 to either the RTP or control cigarette there was an observed increase in self-reported daily cigarette consumption (Figure 3). It was also observed that subjects smoked fewer cigarettes during clinical confinement periods than ambulatory periods. Daily cigarette consumption was observed for a further 2-months after completion of the main 6-month study. During this period most subjects returned to their screening and baseline consumption levels. To understand the reasons for the change in daily cigarette consumption the screening and baseline levels, a questionnaire was administered on day 108/109 (Figure 4).

CONCLUSIONS:
Each of the study examples above illustrate some of the potential challenges in assessing toxicant exposure in groups of tobacco users. Non-residential or occasional clinical confinement studies are likely to provide more realistic data, but, in particular, the provision of free product can impact on subject behaviour and hence exposure assessments.

REFERENCES:
(1) US FDA, Modified risk tobacco product applications – draft guidance for industry, March 2012.
(2) Shepperd et al, Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes. Regulatory Toxicology and Pharmacology. March 2013 (in press).
(3) Cunningham et al, A longitudinal study to track changes in smoking behaviour of smokers of 10mg ISO tar cigarettes in Germany – third time point, SRNT, POS1-43, Houston, Texas, March 2012.

Conflict of interest Statement:
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