

PhenX: Agent measures for tobacco regulatory research

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ABSTRACT

The current paper describes the PhenX (Phenotypes and eXposures) Toolkit Tobacco Regulatory Research Agent specialty area and the Agent Working Group's (WG's) 6-month consensus process to identify high-priority, scientifically supported measures for cross-study comparison and analysis. Eleven measures were selected for inclusion in the Toolkit. Eight of these are interviewer-administered or self-administered protocols: history of switching to lower tar and nicotine cigarettes, passive exposures to tobacco products, tobacco brand and variety (covering cigars, cigarettes and smokeless tobacco separately), tobacco product adulteration (vent-blocking or filter-blocking) and tobacco warning label exposure and recall. The remaining three protocols are either laboratory-based or visual inspection-based: measurement of nicotine content in smoked or smokeless tobacco products and the physical properties of these two classes of products. Supplemental protocols include a biomarker of exposure and smoking topography. The WG identified the lack of standard measurement protocols to assess subjective ratings of tobacco product flavours and their appeal to consumers as a major gap. As the characteristics of tobacco products that influence perception and use are tobacco regulatory research priorities, the reliable assessment of flavours remains an area requiring further development.

INTRODUCTION

In 2002, the National Tobacco Monitoring, Research and Evaluation Workshop reviewed the state of the science in tobacco surveillance using a conceptual framework adapted from the classical infectious disease model's Host, Agent, Vector and Environment (HAVE) paradigm.^{1 2} This adaptation posits tobacco product users or potential users as the Host, tobacco products as the Agent, tobacco manufacturers and retailers as the Vector and tobacco control efforts and the family, peer, community and other systemic factors as the Environment. The workshop recommended improvements to tobacco product (Agent) monitoring,² including the need to develop new surveillance systems for quantifying the ingredients and emissions of tobacco and tobacco smoke and to improve methods of assessing the uptake and metabolism of these constituents by tobacco users. The constituents of mainstream smoke recommended for surveillance included specific polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs), total and free-base nicotine, volatile organic compounds, aromatic amines and metals. The cigarette design attributes recommended for monitoring included tobacco blend,

additives and filter ventilation. The 2002 workshop also recommended research to help define machine-smoking protocols for monitoring emissions reflective of human smoking behaviour, marketplace product sampling and population monitoring of smoking topography, emissions of toxic constituents, biomarkers of exposure and, eventually, risk of tobacco-related diseases. In addition, the workshop acknowledged that, at the time, the tobacco industry was the major source of data on tobacco and tobacco smoke and strongly recommended that independently funded research should be the main source of such data in the future.

However, much has changed in the tobacco products landscape in the ensuing decade, and a re-examination of the proposal for improved systematic surveillance is required. Throughout the 2000s, the marketing and sale of smokeless tobacco products grew, as did the prevalence of their use. The electronic cigarette (e-cigarette) was commercially introduced in the mid-2000s, and the nicotine delivery capability of these devices has improved with successive generations. In 2009, the Family Smoking Prevention and Tobacco Control Act provided authority to regulate cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco to the US Food and Drug Administration (FDA); in 2016, the FDA extended its authorities to cover all tobacco products, including but not limited to cigars, e-cigarettes and hookah.^{3 4} The changes in the tobacco product landscape, combined with the need to continue to add to the evidence base to inform state, local and federal regulation, prompted the National Institutes of Health (NIH), in partnership with the FDA, to convene working groups (WGs) of experts to review available measures for tobacco regulatory research (TRR) and recommend standard measures for use for comparison across studies. In collaboration with the PhenX initiative (consensus measures for Phenotypes and eXposures; <https://www.phenx.org/>), the WGs prioritised standard measures through an established consensus process and disseminated the measurement protocols through the PhenX Toolkit (<https://www.phenxtoolkit.org/>).⁵ The PhenX TRR initiative, directed by a TRR Panel (TRRP) of senior scientists and federal agency representatives, adopted the 2002 workshop's 'HAVE' organising framework and convened WGs of experts in each of the HAVE domains to recommend prioritised collections of measures as research standards.^{1 2} These measures are recommended for inclusion in TRR studies to facilitate cross-study collaboration and replication of findings.⁶ This paper presents the deliberations and outcomes of the Agent WG.



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Table 1 Initial Agent scope

Brand and variety	Product emissions
Consumption measurements	Product characterisation
Abuse liability	Product physical assessments/product design features
Product adulteration	Topography
Product adulteration	Toxicology
Product appeal	Warning label awareness and exposure

METHODS

Developing the scope of the Agent Collection

The TRRP established the initial scope of the WGs, tasking the Agent WG with identifying measures of tobacco product characteristics (ie, nicotine content, tobacco blend, device/product features, delivery system and additives/flavours), tobacco product toxicity and biomarkers of exposure. The TRRP suggested 12 elements (table 1) for the Agent WG members' consideration for inclusion in the PhenX Toolkit.

Complementary measures already in the PhenX Toolkit

From the more than 366 measures already in the Toolkit at the time the Agent WG was assembled, the WG identified 16 existing

Table 2 Complementary Agent measures already in the PhenX Toolkit

Element	PhenX measure (PhenX id)	Domain/collection name
Brand and variety	Tobacco (Non-Cigarette)–Product Use (081400)	Oral health (Domain)
	Point of Sale Environment for Alcohol and Tobacco (550800)	SAA (Collection)
Consumption measurements	Cigarette Price–Quantity of Cigarettes Purchased (550100)	SAA (Collection)
	Tobacco 30 Day Quantity and Frequency (Adolescent [030803] and Adult [030804])	Alcohol, tobacco and other substances (Domain)
	Cigarette Nicotine Dependence (031000)	
	Tobacco–Age of Initiation of First Cigarette Use (Adolescent [030701] and Adult [030703])	
	Tobacco–Age of Offset of Cigarette Use (Adolescent [030903] and Adult [030902])	
Abuse liability	Smoking Status (Adolescent [030603] and Adult [030604])	
	Acute Subjective Response to Substances–Current–Specific–Tobacco (520104)	SAA (Collection)
Product appeal	Point of Sale Environment for Alcohol and Tobacco (550800)	SAA (Collection)
Product constituents	Motives–ATOS–Specific–Tobacco (520504)	SAA (Collection)
Product emissions	Current Environmental Tobacco Smoke Exposure (060700)	Environmental exposures (Domain)
	Passive Smoke Exposure (070301)	Cancer (Domain)
Topography measures	Substance Abuse and Dependence–Past Year–Tobacco (510403)	SAA (Collection)
Toxicology	Air Contaminants in the Home Environment (061101)	Environmental exposure (Domain)
	Urine Assay for Tobacco Smoke Exposure (091701)	Respiratory (Domain)

Note: Product Adulteration, Characterisation, Physical Assessments/Design Features and Warning Label Awareness and Exposure have no relevant measures in the Toolkit.

SAA, Substance Abuse and Addiction.

PhenX measures that were complementary to the Agent scope (table 2).

Expertise of the Agent WG

Agent WG members were selected based on their experience with the development, evaluation and use of Agent measures in studies investigating tobacco product–user interactions, tobacco chemical constituent analysis and product design features, biomarkers of human exposure to tobacco carcinogens, tobacco packaging and product regulation and smoking topography. The WG consisted of two co-chairs, five content experts and two TRRP liaisons with backgrounds in behavioural science, chemistry, engineering, toxicology and psychology. Agent specialty area experts from the FDA and NIH also participated in the WG's deliberations and meetings. In addition, WG members consulted with numerous specialty area experts regarding the availability and selection of specific protocols. Each WG member was assigned to review two to three scope elements to identify possible measures for inclusion in the Toolkit.

WG deliberations

The Agent WG avoided duplication of measures through consultation with other TRR WGs convened at the same time. These measures included the following: (1) Compliance with Cigarette Packaging and Labeling Policies (Environment WG); (2) Pregnancy Status–Mother and Baby Health (Host: Biobehavioral WG); (3) Pregnancy Status and Tobacco Use (Host: Biobehavioral WG); (4) Amount, Type and Frequency of Recent Cigarette Use (Host: Biobehavioral WG) and (5) House Rules about Smoking (Host: Social/Cognitive WG).

For the toxicology element, the Agent WG proposed a protocol for a urine assay for 1-hydroxypyrene (1-HOP) in smokers and non-smokers.⁷ Similarly, the Host: Biobehavioral WG recognised the need for biomarkers measuring individuals' levels of toxicants and recommended the following three measures: Cotinine in Serum, 4-(Methylnitrosamino)–1-(3-pyridyl)–1-butanol (NNAL) in Urine and Expired Air Carbon Monoxide. Members from both WGs discussed the rationale for each proposed biomarker and agreed that they are distinct measures. 1-HOP informs the level of PAH exposure in smokers and non-smokers and provides critical information on the relationship between tobacco exposure and human cancer. Cotinine in Serum measures the primary metabolite of nicotine to estimate exposure to secondhand smoke. NNAL in Urine measures exposure to TSNA carcinogens. Finally, Expired Air Carbon Monoxide provides a measure of exposure to vapor-phase toxicants and is a non-invasive way to determine smoking status.

The WG held extended discussions on which Agent measures to include in the Toolkit. Priority was given to measures that had demonstrated utility, could be easily incorporated into research studies and were considered acceptable for the foreseeable future. While several constructs were considered desirable for the Toolkit, such as measures for e-cigarettes, they did not have existing standard measurement protocols and were not selected for inclusion. As a result, the WG did not recommend measurement protocols for the following types of subjective rating scales: perceived taste, smell, chemesthetic and/or flavour intensity of sampled flavouring agents or tobacco products; the degree of 'liking/disliking' of sampled flavouring agents or tobacco products; the degree of 'wanting' of flavours or tobacco products as an indication of their consumer appeal based on visual, olfactory or other perceptual/cognitive cues and tobacco product appeal. The WG recommended standard laboratory protocols to describe the physical properties of tobacco products, levels of tobacco exposure, nicotine content and

smoking topography variables. Interviewer-administered protocols were recommended to evaluate respondents' histories of vent or filter blocking, switching to lower tar and nicotine cigarettes, exposure to tobacco products and preferred type and brand.

Measures for community outreach

As a result of the WG's deliberations, 10 measures were shared with the research community for review and comment: (1) History of Switching to Lower Tar and Nicotine Cigarettes (interviewer administered), (2) Nicotine Content (laboratory), (3) Passive Exposures to Tobacco Products (interviewer assisted), (4) Physical Properties of Tobacco Products (two protocols: physical examination and laboratory), (5) Puffing Profile Measurement (laboratory), (6) Tobacco Brand and Variety (interviewer administered and self-reported), (7) Tobacco Product Adulteration–Vent or Filter Blocking (interviewer administered), (8) Tobacco Warning Label Exposure and Recall (self-reported or interviewer administered), (9) House Rules and Tobacco Use (interviewer administered) and (10) Urine Assay for Tobacco Carcinogen Exposure: 1-HOP (bioassay).

The WGs obtained feedback from subject matter experts and potential PhenX TRR Toolkit users by e-mailing professional society listservs, registered PhenX Toolkit users, TRR investigators funded through the FDA–NIH partnership and experts who participated in other PhenX WGs or Panels as part of a community outreach process. Potential respondents were given 2 weeks to review and comment on each measure's value and applicability to their future research interests. The WG received helpful feedback and used the comments to choose the final measures and protocols. Nine people responded to the outreach email with general comments about some or all of the proposed measures. Six of those individuals indicated whether the measures were useful or not, with all measures having support from four to six respondents.

Between July 2014 and December 2014, Agent WG members completed their review and recommendations of measures and protocols for the Toolkit. Requests to the research community for recommendations of valid subjective rating scales for tobacco product flavours and tobacco product appeal did not yield results, and no suggested measurements were provided. Although the FDA is interested in the characteristics of tobacco products that influence people's perceptions, researchers are still struggling to find methods to assess flavour reliably.

RESULTS

The Agent WG identified eight measures for inclusion in the PhenX Toolkit. One of the eight recommended measures, House Rules About Tobacco Use, seemed more appropriate in the Host: Social/Cognitive collection and, thus, it resides there (for more details, see the Host: Social/Cognitive WG paper presented elsewhere in this issue).⁸ The remaining seven recommended measures included two quantifying tobacco product characteristics: (1) visual and laboratory-based inspections of the physical properties of cigarettes, filtered cigars and smokeless tobacco and (2) laboratory-based assessments of the quantities of nicotine in the tobacco filler of smoked tobacco, smokeless tobacco and e-liquids. Also chosen for inclusion in the Toolkit were (3) reported measures of product adulteration, (4) brand and variety, (5) history of switching and quitting, (6) exposure to emissions and (7) warning label awareness and exposure. From the beginning, WG members were aware that the scope of the Agent specialty area lends itself to time-consuming measurements of physical properties. Thus, although two of the selected measures (Nicotine Content and Physical Properties of Tobacco Products) were identified as high burden (ie, requiring

longer completion times and specialised equipment and training), they were nonetheless deemed appropriate for inclusion.

History of switching to lower tar and nicotine cigarettes (PhenX id=730101)

The interviewer-administered National Health Interview Survey (NHIS) protocol consists of three questions for respondents 18 years or older to determine the number of times a smoker has gone a day without smoking and whether a respondent has ever switched to cigarettes perceived as less harmful.⁹ This protocol assesses a user's attempts to quit smoking and/or switch to cigarettes with perceived reduced toxicity. The protocol is available in English and Spanish.

Nicotine content (PhenX id=730301)

Nicotine in tobacco exists predominantly in two pH-dependent forms. Protonated nicotine is the predominant form in tobacco, but tobacco additives can increase the pH and convert a fraction of the nicotine into the non-protonated free-base form, which is more bioavailable and readily absorbed and may increase its addictiveness. The WG selected a laboratory-based protocol to quantify nicotine in smoked or smokeless tobacco products using solvent extraction coupled with gas chromatography and selected ion monitoring mass spectrometry. In this protocol, a gas chromatography/mass spectrometry system quantifies the amount of nicotine and then analyses the pH and the amount of nicotine in smokeless tobacco, tobacco filler and e-cigarette liquid contents or refill solutions (e-liquids). This protocol is an established standard operating procedure used by the Tobacco Laboratory Management System, Tobacco and Volatiles Branch, Division of Laboratory Sciences (DLS), National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC).¹⁰ Useful reference materials include the University of Kentucky's Research Cigarettes (<https://ctrp.uky.edu>) and the smokeless reference tobacco types available from North Carolina State University (<https://www.tobacco.ncsu.edu/strp.html>).

The protocol provides step-by-step instructions for solution and analytical standard preparation, laboratory methods, blank and sample preparation, system setup, the creation of calibration curves, analyses and calculations, quality assessment and the estimation of measurement uncertainty. The protocol is available in English. It should be noted that this protocol was judged to take more than 15 min to implement because of the major equipment and specialised training required.

Passive exposures to tobacco products (PhenX id=730401)

This protocol includes items from the National Adult Tobacco Survey (NATS)⁶ and the Population Assessment of Tobacco and Health (PATH) Survey.¹¹ Collectively, the questions assess a respondent's exposure to smoke in different environments, including work, home and social settings. This protocol estimates the physicochemical environmental exposures to tobacco products encountered by respondents and the population as a whole, including users and non-users of tobacco. For the purposes of this protocol, 'smoking' and/or 'smoke tobacco' and/or 'used tobacco' include smoking tobacco products that are burned (eg, combustible cigarettes, little cigars, cigarillos, hookah/water pipes) but NOT vaping and e-cigarettes. In the Secondhand Smoke Exposure Section of the protocol (questions 17 and 19), vaping and e-cigarette use are addressed by specifying e-cigarettes as a separate category of tobacco product.

The NATS yields data that are representative and comparable at both the national and state levels. The PATH Study is a nationally

representative, in-person, longitudinal cohort study of non-users and users of tobacco products and those at risk for tobacco use across the US Respondents 12 years old and up provide information about their tobacco use, attitudes and health and specific biospecimens (ie, buccal cell, urine and blood) are collected from adults in one or more data collection waves. PATH Study data will contribute to an evidence base for assessing and monitoring the FDA's current and future regulatory activities in meeting its mandate under the Tobacco Control Act, including product standards, new and potential modified risk products, health warnings and health education campaigns.

The interviewer-administered protocol can be administered to youths (12–17 years) and adults (18+ years) and is available in English and Spanish. To fully capture the extent of passive exposure, the Agent WG recommends that investigators also administer questions from the Passive Smoke Exposure (PhenX id=0 70 301) measure included in the PhenX Toolkit.

Physical properties of tobacco products

These measures are a set of standard physical tests for cigarettes and filtered cigars to capture the following design descriptors: length, circumference, tobacco weight, filter type and filter ventilation. The selected protocols evaluate and compare both existing product modifications and new products and brands, which can help investigators to better understand the effects of design features on product chemistry.

Cigarettes and filtered cigars (PhenX id=730501)

The 1999 Massachusetts Benchmark Study¹² protocol included physical methods and tests to evaluate the length, circumference, filter ventilation, tobacco weight, filter composition and filter overwrap length of cigarettes and filtered cigars. This information is collected directly through visual inspections. This validated protocol is more accurate than self-report protocols, and it addresses many physical attributes of cigarettes and cigars with well-established instructions.

The available protocols provide different approaches for analysing various physical characteristics of cigarettes and cigars, and the Agent WG recommended specific approaches for the following reasons:

- ▶ For cigarette length, although the method described by Brown and Williamson requires a specially designed wooden measuring device, one advantage is that it measures both the cigarette length and the filter length.¹³ In lieu of a special measuring device, the use of digital callipers or other laboratory-grade measurement devices is acceptable.
- ▶ For tobacco weight, the procedure described by Philip Morris is highly detailed and does not require special equipment.¹³
- ▶ For filter type, the procedure used by Philip Morris was chosen because it provides specific instructions on how to proceed if visual examination is not conclusive.¹³
- ▶ Cigarette circumference is of interest because of its use in marketing to women and its implied relevance to reduced health risks.^{14–16}
- ▶ Filter ventilation significantly affects nicotine delivery and, consequently, puff volume, intensity and frequency; smoke strength perception and health perceptions.

The protocol is available in English, and staff must be trained in using the specialised equipment cited in the protocol. In addition to the wooden measuring device described above, a Cerulean CD2 Express or Borgwaldt S10 device is used to measure the circumference.

Smokeless tobacco (PhenX id=730502)

The selected laboratory measurement protocol⁶ provides instructions for measuring the total moisture content within smokeless tobacco products (ie, dry snuff, moist [wet] snuff, moist [wet] snuff portion packs, plug, twist, loose leaf, dry snuff portions packs, snus, snus portion packs and pellet or compressed). The Toolkit provides instructions for sample preparation, total moisture determination, quality assurance and Good Laboratory Practice and sampling guidelines.^{17 18}

The protocol is available in English. Laboratory personnel must be trained in Good Laboratory Practice guidelines to ensure proper quality assurance and quality control procedures, and specialised equipment is required.

Tobacco brand and variety

Cigars (PhenX id=730701)

The selected protocol was adapted from the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) because it is a large survey (each survey wave includes approximately 240 000 respondents) of the US non-institutionalised adult civilian population.¹⁹ The TUS-CPS has been consistently conducted since 1992. The three interviewer-administered questions determine the cigar brand and type smoked by respondents most often in the past 30 days.

The interviewer-administered protocol is available in both English and Spanish and can be given to youths (12–17 years) and adults (18+ years). These questions can also be administered in a computerised or non-computerised format (ie, a paper-and-pencil instrument). Computer software is necessary to develop computer-assisted instruments, and the interviewer will require a laptop computer or handheld computer.

Cigarettes (PhenX id=730702)

The recommended protocol was adapted from the 2014 National Survey on Drug Use and Health (NSDUH) because this survey is the primary combined source of information on the use of drugs, alcohol and tobacco in the civilian, non-institutionalised population of the USA. The study was initiated in 1971 and is currently conducted on an annual basis. NSDUH is administered to individuals aged 12 years and older.¹¹ Six computer-administered questions determine the type of cigarette brand (eg, filter vs non-filter, hard pack, menthol) used most often by the respondent in the past 30 days. Although NSDUH asks about Marlboro in item 5, the Agent WG recommended that other brands also be asked about.

While the source instrument was administered by computer, the WG suggests that these questions could also be administered in a non-computerised format. The self-administered protocol can be used in youths (12–17 years) and adults (18+ years) and is available in both English and Spanish.

Smokeless tobacco (PhenX id=730703)

Eleven questions to discern the smokeless tobacco brands or varieties used and purchased by respondents within a 12-month period were selected from the PATH Study.¹¹ The interviewer-administered protocol requires the interviewer to show images of the various product categories to prompt the respondent. The protocol can be used in adults (18+ years) and is available in both English and Spanish.

Tobacco product adulteration—vent or filter blocking (PhenX id=730801)

This interviewer-administered protocol consists of eight fixed-response questions and one open-ended question asking adult

(18 years or older) respondents whether they currently or have ever filter-blocked or vent-blocked cigarettes and their perceptions of the effects of doing so.²⁰ The questionnaire has been used to collect data from a substantial sample of smokers in the USA. The protocol is available in English.

Tobacco warning label exposure and recall (PhenX id=730901)

Respondents are asked two questions from the PATH Study¹¹ to assess their exposure to health warnings and their ability to recall message content. These questions facilitate measuring the effectiveness of health warnings on tobacco packages. Responses have been associated with perceptions of risk that may promote smoking cessation and reduce uptake among young people.

The health warning measures used in the PATH Study are very similar to those used in other countries, such as the International Tobacco Control (ITC) Survey. The 2015 ITC 4-Country Survey is an international cohort study of tobacco use whose overall objective is to measure the psychosocial and behavioural impact of key national-level policies. This survey is being used in more than 20 countries.²¹

Although the PATH Study is an interviewer-administered survey, the Agent WG suggests that these questions could also be self-administered. The protocol can be administered to adults (18+ years) and youths (12–17 years of age) and is available in both English and Spanish.

House rules about tobacco use (PhenX id=711101)

Two questions from the PATH Study¹¹ ask respondents to assess whether smoking combusted and non-combusted tobacco products is permitted in the home. Parents' rules about smoking in the home reflect their actions to regulate smoking and their children's exposure to smoking.

Although taken from the Wave 1 Adult PATH Study instrument, these two questions are also included in the Wave 1 Youth instrument and may, therefore, be asked of both adult and adolescent populations (12 years and up). These measures reside in the Host: Social/Cognitive collection.

Supplemental measures

The PhenX Toolkit includes additional information for Toolkit users, including measures considered by the WG but not selected for inclusion in the Specialty Collection, under a section titled 'Supplemental Information (SI)'. For the Agent Specialty Collection, the Urine Assay for Tobacco Carcinogen Exposure: 1-HOP (available at https://www.phenxtoolkit.org/toolkit_content/supplemental_info/trsp_agent/measures/Urinary_Biomarker.doc) and the Puffing Profile (available at https://www.phenxtoolkit.org/toolkit_content/supplemental_info/trsp_agent/measures/Puffing_Profile.doc) were chosen by the WG for inclusion in the SI. The WG expressed that while the measurement of 1-HOP is a 'tried and true' method for assessing exposure to PAHs, it is non-specific to tobacco. WG members agreed that the Host: Biobehavioral WG's NNAL in Urine measure was a more specific biomarker. Regarding the Puffing Profile measure, its burden and complexity, requirement of analytical skills and inability to accurately collect data on novel electronic products made it a good candidate for the SI.

Table 3 lists seven different measures with a total of 10 protocols that meet the measurement needs of different tobacco products (eg, cigarettes, cigars, smokeless tobacco, e-cigarettes). A brief description is provided for each measurement protocol. Additional references to published articles and manuals of procedures for the protocols are provided under 'General References' for each measure in the PhenX Toolkit.

Table 3 The ten Agent measures recommended and approved for inclusion in the PhenX Toolkit

Measure name (PhenX id)	Description of measurement protocol
History of Switching to Lower Tar and Nicotine Cigarettes (730101)	Interviewer-administered protocol determining the number of times a smoker has gone a day without smoking and whether a respondent has ever switched to cigarettes perceived as less harmful.
Nicotine Content (730301)	Laboratory-based protocol quantifying nicotine in smoked or smokeless tobacco products.
Passive Exposures to Tobacco Products (730401)	Interviewer-administered protocol to assess a respondent's exposure to smoke in different environments.
Physical Properties of Tobacco Products (730501 & 730502)	Cigarettes and Filtered Cigars (730501): Visual inspection protocol determining the length, circumference, filter ventilation, tobacco weight, filter composition and filter overwrap length of cigarettes and filtered cigars. Smokeless Tobacco (730502): Laboratory protocol assessing the total moisture content within various smokeless tobacco products.
Tobacco Brand and Variety* (730701, 730702 & 730703)	Cigars (730701): Interviewer-administered protocol determining the cigar brand and type smoked by respondents. Cigarettes (730702): Self-administered protocol determining the type of cigarette brand used most often by the respondent in the past 30 days. Smokeless Tobacco (730703): Self-administered protocol determining the smokeless tobacco brands or varieties used and purchased by respondents within a 12-month period.
Tobacco Product Adulteration—Vent or Filter Blocking (730801)	Interviewer-administered protocol determining whether respondents currently or have ever filter-blocked or vent-blocked cigarettes and their perceptions of the effects of doing so.
Tobacco Warning Label Exposure and Recall (730901)	Self-administered protocol assessing exposure to health warnings and ability to recall message content.

*Selected for inclusion in the Core Tier 2 collection.⁵

DISCUSSION

The goal of the Agent WG was to identify widely used and accepted assessments of measures of tobacco product characteristics (ie, nicotine content, tobacco blend, device/product features, delivery system and additives/flavours), tobacco product toxicity and biomarkers of exposure. Because many important elements either existed in the Toolkit already (eg, tobacco use, nicotine dependence, outcome expectancies) or were being addressed by other tobacco WGs (eg, economic demand, motivation to quit), the Agent WG focused its attention specifically on the characteristics of the product per se and questionnaire measures that described the product (rather than the user).

A particular challenge for the Agent WG was that most measures of the product itself require specialised equipment and advanced training, far beyond what is typically associated with other measures in the PhenX Toolkit. For example, measuring filter ventilation requires equipment that is sold by only a few companies (ie, makers of tobacco manufacturing equipment) and costs thousands of dollars. Similarly, measuring smoke emissions requires smoking machines and additional chromatography/mass spectroscopy equipment that can easily require an investment of more than a million dollars. These resource issues were recognised as barriers by the 2002 National Tobacco Monitoring, Research and Evaluation Workshop,² and they continue to affect the field. Thus, the WG prioritised those measures that could reasonably be performed by investigators themselves (eg, weight, length,

diameter, overwrap) or in collaboration with existing independent laboratories with the required capabilities (eg, ventilation, nicotine content).

Agent WG members eliminated the measures of smoking topography recommended by the 2009 WG² from the Toolkit. Measuring topography requires special equipment and detailed knowledge of how to process and interpret the data.²² As a result, this measure was felt to be too high burden for inclusion in the Toolkit. Indeed, although topography is a useful process measure to understand cross-product differences in usage patterns, other measures (eg, biomarkers of exposure) would be superior in assessing differences in exposure to harmful and potentially harmful constituents. Furthermore, the collection of appropriate biospecimens could be integrated into ongoing studies in anticipation of later analysis (biobanking) of the markers identified by the Host: Biobehavioral WG.²³

The WG selected four questionnaire measures to capture domains of product use. This choice proved challenging given that the usual consumption measures were already covered in the Toolkit. Recording the precise brand a consumer uses is important, and the preferred way of collecting this information is to use existing measures that capture the brand of cigarettes, cigars and smokeless tobacco. As of August 2017, no standardised approaches were available for collecting brand information for hookah or e-cigarettes. Given the dynamics and breadth of the market, this lack was perceived as a weakness and identified as an area for additional research and development. To further probe brand history, two items were included to measure whether a consumer had ever switched to another brand to reduce perceived harm.

Product adulteration was a challenging topic in general because it is an understudied area. The best example that could be identified in the tobacco domain was the behavioural blocking of filter-vents on cigarettes determined to be lower-tar based on machine measurements.²⁴ A series of questions was included to assess the awareness of filter vents, whether the respondent had ever intentionally blocked them and the perceived effects of doing so on health. Product adulteration is a particular concern for regulatory science; indeed, drug regulators often address the potential for adulteration when considering formulations with abuse potential (eg, opiates for pain relief). More research is required to identify potential avenues of adulteration in the tobacco context and, where appropriate, questionnaire approaches to measurement.

Flavours are a particular concern in tobacco products because they (with the exception of menthol) are banned in cigarettes in the USA, parts of Canada and the European Union and are implicated in the abuse potential of e-cigarettes, cigars and hookah.^{25–27} However, the WG elected not to include measures of flavour in the Toolkit at this time because there are few validated measures of flavour perception specific to tobacco.²⁸ Ongoing research studies (<https://prevention.nih.gov/tobacco-regulatory-science-program/research-portfolio>) are examining flavour issues in tobacco use, and in the future, better measures of flavour preference and perception may become available.

Warning label exposure was included in the scope of the Agent WG because warnings are required to appear on product packaging and advertisements. Thus, such labels are an integral part of the product, and label awareness and recall may reflect the extent to which the user interacts with and attends to the product. Measures of label exposure will also become increasingly important as the 'deeming' regulation expands the types of tobacco products carrying warning labels.

The Agent WG engaged in a 6-month consensus process to identify high-priority, scientifically supported measures around tobacco products. The lack of standard measurement protocols

to assess subjective ratings of tobacco product flavours and their appeal to consumers was identified as a major gap. As TRR investigations seek to understand the characteristics of tobacco products that influence people's perception and use, the reliable assessment of flavours will require further development. Additionally, better measurements of product use for tobacco products other than cigarettes and smokeless tobacco should be developed, especially units of consumption and use patterns for hookah and e-cigarettes. Furthermore, lower-cost approaches to the measurement of toxicants in tobacco products and biomarkers in tobacco product users, such as higher-throughput methods with lower sample requirements, proxy measures^{29–30} or the formation of cooperative groups to share testing costs by pooling samples from multiple smaller studies, are urgently needed. We also recommend increased emphasis on the further development of analytic chemistry methodologies to increase understanding of the toxicological, biochemical and metabolic properties of newer tobacco products. The continued evolution of the measurement of biomarkers of harmful exposure resulting from the use of older and more recent tobacco products may also reduce cost barriers to researchers.

Although the WG supported the inclusion of seven tobacco product-specific measurements (mainly interviewer-administered or laboratory-based measures) in the PhenX Toolkit, we emphasise the need for ongoing studies of the properties (reliability and validity) of these measures as they are applied to newer, non-combustible tobacco products in both young and adult users.

What this paper adds

- ▶ Tobacco product characteristics (ie, nicotine content, tobacco blend, device/product features, delivery system and additives/flavours), tobacco product toxicity and biomarkers of exposure are well known to influence the initiation and maintenance of the use of tobacco products and, thus, are highly relevant to regulatory considerations.
- ▶ The continuous proliferation of novel tobacco products as advertised and marketed across a variety of platforms introduces challenges to scientists seeking to support evidence-based regulatory decision-making because suitable measures may not be readily available or widely known.
- ▶ The Agent Working Group made consensus recommendations to investigators in the field concerning the best methods to assess history of switching to lower tar and nicotine cigarettes, passive exposures to products, tobacco brand and variety (covering cigars, cigarettes and smokeless tobacco separately), tobacco product adulteration (vent-blocking or filter-blocking), tobacco warning label exposure and recall, measurement of nicotine content in smoked or smokeless tobacco products and the physical properties of these two classes of products.
- ▶ As tobacco regulatory science evolves, it will be critical for investigators to consistently use valid and comprehensive measures of multiple sources of tobacco product qualities and their influence on use.

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Contributors GES, TPH and KLW led the conceptualisation of the manuscript and the coordination of the writing team. RJO and GES drafted the scientific content of the manuscript, and TPH, DSN and RG drafted the Methods and Results sections of the manuscript. CHW, GES, TPH and KLW reviewed the draft and provided substantive revisions. The Co-Chairs and Members of the PhenX TRR Agent WG identified and proposed preliminary measures and voted on final measures included in the PhenX TRR Agent Specialty Collection. TRRP members NLB and Dana M van Bommel, FDA Center for Tobacco Products (CTP), ensured that the WG process maintained fidelity with overall project goals. Federal Agency Liaisons Tricia Johnson, FDA CTP, and KMW ensured project consistency with agency goals and priorities. NIH Project Coordinator KLW proposed the PhenX TRR initiative and contributed to its execution and completion. The PhenX team coordinated and facilitated the WG process, including project oversight and leadership (TPH), supervisory management (DSN) and project management (RG). PhenX NIH Program Official Erin M Ramos, National Human Genome Research Institute (NHGRI), provided project guidance and funding coordination. Carol M Hamilton, RTI International, is the PhenX Principal Investigator and provided project guidance and supervision.

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