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AMERICAN THORACIC SOCIETY DOCUMENTS

Recommendations for the Appropriate Structure, Communication, and Investigation of Tobacco Harm Reduction Claims

An Official American Thoracic Society Policy Statement

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Rationale: The tobacco harm reduction literature is replete with vague language, far-reaching claims, and unwarranted certainty. The American Thoracic Society has increasingly recognized the need for a framework for reliably making such claims. Evidence-based standards improving the scientific value and transparency of harm reduction claims are expected to improve their trustworthiness, clarity, and consistency.

Methods: Experts from relevant American Thoracic Society committees identified key topic areas for discussion. Literature search strategy included English language articles across Medline, Google Scholar, and the Cochrane Collaborative databases, with expanded search terms including tobacco, addiction, smoking, cigarettes, nicotine, and harm reduction. Workgroup members synthesized their evidentiary summaries into a list of candidate topics suitable for inclusion in the final report. Breakout groups developed detailed content maps of each topic area, including points to be considered for suggested recommendations. Successive draft recommendations were modified using an iterative consensus process until unanimous approval was achieved. Patient representatives ensured the document's relevance to the lay public.

Results: Fifteen recommendations were identified, organized into four framework elements dealing with: estimating harm reduction among individuals, making claims on the basis of population impact, appropriately careful use of language, and ethical considerations in harm reduction.

Discussion: This statement clarifies important principles guiding valid direct and inferential harm reduction claims. Ideals for effective communication with the lay public and attention to unique ethical concerns are also delineated. The authors call for formal systems of grading harm reduction evidence and regulatory assurances of longitudinal surveillance systems to document the impact of harm reduction policies.

Keywords: addiction; prevention; smoking; e-cigarettes; tobacco dependence

Contents

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I prefer an attitude of humility corresponding to the weakness of our intellectual understanding of nature and of our own being.
—Albert Einstein in a 1949 letter

Overview

During the production of the Official American Thoracic Society (ATS) Research Statement on research needs in tobacco dependence, the scientific literature on tobacco harm reduction was found to be replete with vague language, far-reaching claims, and unwarranted certainty as to outcome (1). In light of the well-documented, intentionally deceptive past practices of the tobacco industry, it is important that the scientific and clinical community improve the reliability, reproducibility, and transparency of tobacco harm reduction claims by establishing clear and precise guidelines for use in communications with the lay and professional public. Such a shared framework is integral to the future development of evidence-based policies, comparative assessment of varied approaches to harm reduction, and development of generally accepted research methods useful to future investigators.

The recommendations set forth in this statement are not intended to suggest a position on the relative merits of harm reduction *per se*, nor are these observations intended to settle the current debate over the most appropriate approach to harm reduction. This statement does not review or endorse any individual approach to achieving harm reduction goals. Rather, this statement is intended to provide a framework for establishing "standards of practice" related to tobacco harm reduction claims. Clearly, complete remediation of tobacco smoke exposure remains the primary objective and should never be compromised as a matter of expediency. However, for circumstances in which achieving this goal is not yet possible, consensus on evidence-based standards for improving the reliability and transparency of harm reduction claims would be expected to improve the claim's trustworthiness for patients, provide clarity for clinicians, offer consistency of approach for researchers, and set a future direction for regulators.

To this end, this report seeks to summarize evidentiary insights within four identified criteria for valid harm reduction claims. The report makes fifteen key recommendations, including those outlined here.

I. Claims of Harm Reduction Must Be Accompanied by Explicit Estimates of the Anticipated Impact on Individuals

- Inference based on emerging or incomplete evidence is an acceptable technique for estimating the anticipated impact of harm reduction strategies on individuals, particularly in instances where the impact on human illness is expected to be delayed. Inferential methods should be explicitly described when making harm reduction claims.
- Inferential claims relying on surrogate markers of disease, or on markers of exposure to risk-associated constituents, should explicitly state the nature of, and degree of certainty in, the relationship between markers and the specific harms reduced.
- When using number of cigarettes consumed as a surrogate measure of exposure, explicit care should be taken to account for anticipated compensatory adjustments in smoking topography (i.e., physical characteristics of smoking behavior, such as puff count, puff volume, average flow, puff duration, and interpuff interval).
- When based on animal or cell culture models, comprehensive narrative statements of relevance of the chosen models to actual human experience should accompany the claim.
- Given our understanding of the protean biopsychosocial consequences of nicotine dependence, the potential for causing or sustaining addiction should be accurately represented in risk trade-off calculations.

II. Claims of Harm Reduction Must Be Accompanied by Explicit Estimates of the Anticipated Population-based Impact

- Population-based harm reduction claims should be accompanied by a statement of known or suspected risk trade-offs incurred. Risk trade-off estimations should include the impact on the entire community, not just the smoke-exposed subset. Calculations should account for potential tobacco use promotion and incorporate relevant *nonhealth* outcomes in their formulation.
- It should not be assumed that harm reduction claims are generalizable to all population subgroups. Claims should specifically state the age cohort to which they apply and the anticipated impact on adolescents and specify applicability to pregnancy and lactation.

III. Harm Reduction Claims Must Be Carefully Constructed to Explicitly Avoid Overstatement or Misrepresentation

- Harm reduction claims should be presented in lay language, state the perspective(s) from which they are derived, and include an explicit range of possible outcomes expected from implementation.
- Harm reduction claimants should exercise caution in language choices, explicitly minimizing the potential for exaggeration of effect size, misattribution of protective effect, or other potential misunderstandings on release to the public.

- Product-oriented population harm reduction claims should account for all known (including unintended) uses or modifications of the product in modeling impact, particularly when estimating impact on tobacco-naive users.

IV. The Investigation and/or Regulation of Potential Harm Reduction Strategies Must Pay Careful Attention to the Ethical Considerations Unique to This Concern

- Given the established evidence of safety and efficacy of harm reduction methods for people unprepared to make a quit attempt, marginal harm reduction calculations must use best available options as the comparator, rather than the no-intervention condition. In all cases, harm reduction claims should be accompanied by clear statements of their methodologic decisions in these respects.
- The hazards inherent to prospective population-based evaluations of tobacco harm reduction strategies may qualify as "greater than minimal risk." Care should be taken to assess research risks in comparison to current standards of care for reducing harm among people unprepared to quit, rather than in comparison to the no-intervention condition.
- Harm reduction researchers must protect the autonomy of subjects by discussing the unique nature of risk inherent to harm reduction protocols. Promoting an understanding sufficient for subjects to legitimately assume risk protects subjects from unforeseen or tragic consequences of participation through fair methods that promote just outcomes.
- Harm reduction policies should state the perspective(s) from which they are derived, guard against inequitable allocation of resources, provide assurance of longitudinal surveillance, and inform the public of important developments in understanding.
- Harm reduction claims should be accompanied by a narrative statement of the potential for unintended/involuntary impact on non–index users.

Although elimination of risk should remain the goal of public health authorities, this statement highlights the special requirements for ethically pursuing the reduction of harm within the complex social/biological context of tobacco dependence. This framework represents a means of assuring the public that threats to the validity of harm reduction claims have been minimized and of maximizing the public's confidence in such claims. Furthermore, we call for several implementation steps to be used, including the development of a formal system of harm reduction evidence grading, a longitudinal surveillance system to document the impact of a harm reduction interventions, and a careful reexamination of the ethical constraints on harm reduction research when effective harm elimination interventions exist.

Introduction

It has been well established that tobacco products, particularly combustible cigarettes, causally increase risk for numerous diseases and other adverse consequences in a dose-dependent manner and that abstaining or reducing exposure consequently reduces this risk (2). Some benefits accrue immediately, and others continue to accumulate over a lifetime (3, 4). Accordingly, the concept of a safer cigarette has, for many years, seemed straightforward: build a reduced-risk device through the practical application of dose–response concepts (5). Unfortunately, such past efforts proved unsuccessful and, ultimately, misleading (6). After the 1964 Surgeon General's report causally linking smoking to lung cancer, and in response to declining rates of smoking in the United States, tobacco companies began applying adjectives such as "light," "mild," or "low," with the implication of reduced risk, taking advantage of popular assumptions about cigarette constituent dose–response. Those assumptions did not hold up to subsequent scientific inquiry.

The 1981 report of the Surgeon General addressed the "changing cigarette" and concluded that federal policy should continue to call for smoking cessation, given the discordance between machine-measured yields and the potential for harm (7). The report pointed out that reduced-yield cigarettes *might* reduce harm, *if* users did not change their smoking patterns. However, compensatory behaviors did occur in response, and lower-yield cigarettes did not lead to decreased risk (2, 8). In fact, over recent decades, the risk of lung cancer associated with smoking has increased despite a contemporaneous trend of declining measured tar yield. Nonetheless, popular misconceptions persisted, changing the pattern of tobacco product use and providing an illusory pathway for those who wished to continue smoking while "avoiding" harm (9).

During the 1980s, the notion that nicotine caused a compulsive behavioral disorder in a manner similar to other drugs of abuse was gaining acceptance, culminating in the 1988 Surgeon General's statement that cigarette smoking is the behavioral manifestation of addiction (10). Consequently, the proposition emerged that health professionals should mitigate the harms of tobacco smoke exposure among those patients so severely dependent as to be unable to completely cease smoking. Nicotine replacement therapies were developed, offering the possibility of using medicinal nicotine therapies for harm reduction objectives when "cessation" was otherwise impossible (11).

Subsequent observational studies of Swedish cohorts using moist snuff (snus) suggested that increasing use of snus was associated with favorable trends in incidence of lung cancer and other tobacco-related illnesses. The conversation regarding useful strategies for harm reduction had thus extended to include the relative public health value of alternatives to *smoked* tobacco, including chew and pipe tobacco (12, 13). Once again, implied and direct harm reduction claims blossomed within popular media. Alongside this growing interest in tobacco products as harm reduction devices, the Institute of Medicine issued a landmark, comprehensive set of recommendations for formally assessing and regulating the harm reduction potential of products introduced into the market (Figure 1) (14).

Analogies to Other Disciplines

The reduction of harm is a central precept of medical care, routine in the management of chronic conditions like asthma, diabetes, or hypertension. The concept of "harm reduction" has also evolved in the public health arena, with a range of public health policies targeted at individuals, families, or communities and designed to mitigate the negative physical or social consequences of a variety of human endeavors (15). Educational harm reduction strategies focus on decreasing dangerous exposures by increasing awareness and modifying social norms. For example, focused attention on the impact of driving drunk has helped

BOX 1
Regulatory Principles

Regulatory Principle 1. Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.

Regulatory Principle 2. All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various tobacco smoke constituents should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

Regulatory Principle 3. Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models as well as appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency.

Regulatory Principle 4. Manufacturers should be permitted to market tobacco-related products with exposure-reduction or risk-reduction claims only after prior agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, as compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that measurable reduction in morbidity and/or mortality (in subsequent clinical or epidemiological studies) would be anticipated, as judged by independent scientific experts.

Regulatory Principle 5. The labeling, advertising, and promotion of all tobacco-related products with exposure-reduction or risk-reduction claims must be carefully regulated under a "not false or misleading" standard with the burden of proof on the manufacturer, not the government. The agency should have the authority and resources to conduct its own surveys of consumer perceptions relating to these claims.

Regulatory Principle 6. The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct post-marketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.

Regulatory Principle 7. In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to increase the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects or other adverse health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information.

Regulatory Principle 8. All added ingredients in tobacco products, including those already on the market, should be reported to the agency and subject to a comprehensive toxicological review.

Regulatory Principle 9. The regulatory agency should be empowered to set performance standards (e.g., maximum levels of contaminants; definitions of terms such as "low tar") for all tobacco products, whether conventional or modified, or for classes of products.

Regulatory Principle 10. The regulatory agency should have enforcement powers commensurate with its mission, including power to issue subpoenas.

Regulatory Principle 11. Exposure reduction and risk reduction claims for drugs that are supported by appropriate scientific and clinical evidence should be allowed by the FDA.

Figure 1. Institute of Medicine recommendations for regulatory principles guiding the use of "Reduced Harm" designation (reprinted from Reference 14). FDA = U.S. Food and Drug Administration; PREP = Potential Reduced-Exposure Products.

normalize safe ride techniques such as designated drivers. Safer sex education aimed at teen students has reduced transmission of infectious disease, decreased teen pregnancy rates, and promoted safer sexual decision making among those engaged in sexual activity (16, 17). Alternatively, harm reduction strategies have also focused on minimizing the *sequelae* of exposures, without directly impacting behaviors. Examples include free or low-cost HIV testing, integrating primary care services within substance abuse treatment programs, and lung cancer screening programs.

Perhaps most familiar are the strategies that attempt to "manage" the variables that confer harm in circumstances where the behavior itself may not be directly modifiable. Public policies such as needle exchange programs (18, 19) and safe injection locations (20), wet shelters to manage safe alcohol consumption among the homeless (21), and free condom distribution in community health centers (22) adopt a nonbinary understanding of risk and acknowledge that continued adverse behavior need not confer continued harm. Theoretically, promoting the use of nicotine delivery systems or alternative tobacco products as a means of managing addiction while reducing the exposure to cigarette smoke, divorced from any expectation of reduction in tobacco use behaviors, *could* be considered an analogous example of this type of risk management approach to harm reduction *if* the erroneous assumptions that undermined past attempts are not repeated. The urgent need for a fresh approach to the tobacco epidemic remains intact.

For the purpose of this statement, when considering claims of harm reduction as they relate to tobacco smoke exposure and the potential to impact the public health, we refer exclusively to the 2001 definition developed by the Institute of Medicine: "A product is harm-reducing if it lowers total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants" (14).

Recognition of Need for Rapidly Available Harm Estimates

The recent introduction of novel tobacco products, such as the electronic (e)-cigarette, has reignited debate over the proper placement of harm reduction within the

overall tobacco public health strategy. Concern over unsubstantiated harm reduction claims and the potential threat to public health that they represent has been the subject of debate for a decade (23). Previous frameworks for establishing an evidence-based approach to validating harm reduction claims have included core components such as establishing standard methods for determining relative risk across products, clarification of the relationships between toxicants and health outcomes, and monitoring the potential population-based impact of these claims on tobacco initiation or delays in cessation. The need for evidentiary certainty, however, is necessarily counterbalanced by the need for rapid implementation, given the magnitude of the threat posed by continued tobacco smoke exposure. Some authors have even called for *post hoc* monitoring as an ethically acceptable method of evidence generation, due in large part to tobacco's unique position as a worldwide risk agent and the urgency to prevent its otherwise inevitable casualties (24, 25).

As more potential harm reduction products are developed, how should we then balance the need for rapid availability with the need for a reasonable assurance the harm reduction claims are accurate? How should we make focused harm reduction claims explicitly precise without sacrificing clarity for the user (26, 27)? The scientific community has a responsibility to counter impulsive, nonscientific conclusions that are often based on the enormity of the problem, the political positions of the agents, or the commercial potential of the products. As a social institution, science has an obligation to look beyond itself and help with global problems (28). It is our responsibility to ensure information is consistent with established scientific norms, maintaining the integrity of the data, the trustworthiness of conclusions, and the transparency of aims (29, 30). By its very nature, research on tobacco harm reduction has been too often limited by inadequate size, scope, or duration to yield useful guidance (31).

Language as an Obstacle to Progress

Responding to the accumulating data on the risks of cigarette smoking, the tobacco industry began earnestly introducing filters to their product lines in 1950. Filtered cigarettes quickly became the predominant product sold in the United States (32). Beginning in the 1970s, the tobacco industry implicitly and falsely made harm reduction claims in its marketing of cigarettes with reduced yield of tar and nicotine, forming the basis for litigation against the tobacco industry brought by the U.S. Department of Justice under the Racketeer Influenced and Corrupt Organizations Act (33).

Clearly, neither the public health nor the scientific basis for harm reduction policies and product regulation would be expected to benefit from continued use of poorly defined terms such as "light" or "low tar." In the absence of standardized language, the commercial value of implicit branding should be expected to remain enormous (34–36), particularly in those jurisdictions where regulatory and public scrutiny of tobacco products may be much less vigorous (37). Even in instances when these traditional imprecise terms are restricted from use, the implications of their meaning can carry over into branded messaging and package design (38). Vague harm reduction language allows for consumer misdirection, particularly when commercial implications are large (39, 40).

Harm reduction strategies are primarily based on principles of toxicology and human biology but are also distinctively a function of risk perception and communication science. If the goal of harm reduction is to enhance the capacity of adults to make an informed decision concerning the use of tobacco, an appropriate balance must be struck between avoiding irrelevance through excessive precision on one hand and allowing for vagueness and innuendo through imprecision on the other. Attention to language is essential to developing a uniform database of reproducible results from which to draw reliable conclusions. Unproven or premature reduced-risk claims, or reduced-exposure claims that are mistakenly interpreted as reduced-risk claims, are a significant threat to the notion of informed consent and autonomous control over risk management.

This experience has led to general wariness of harm reduction claims within the tobacco control community. Continued use of vague or misleading terms when making future harm reduction claims would be expected to continue to undermine trustworthiness, particularly when collaboration with the tobacco industry was involved in claim generation (41, 42).

Rather than adopt a policy position on any particular approach to achieving harm reduction goals, the ATS Tobacco Action Committee sought to establish evidence-based "standards of practice" in making tobacco harm reduction claims, expected to improve both claim trustworthiness and consistency of approach necessary for regulatory direction.

Methods

To ensure balanced advice and input from a variety of perspectives, an expert panel was convened in February 2016 that included members drawn from several leadership committees of the American Thoracic Society (ATS). In addition to members of the ATS Tobacco Action Committee, the expert panel included representation from the Documents Development Committee, Health Policy Committee, Ethics and Conflict of Interest Committee, and the Pediatrics Assembly. To ensure relevance of project design to the broadest set of stakeholders, external support was obtained from two patient representatives identified through the ATS Patient Advocacy Roundtable and from the Centers for Disease Control Office on Smoking and Health.

Work proceeded in three phases. In the conceptualization phase, the project chair moderated open-ended discussion among work group members, aimed at identifying the major themes that would go on to form the framework for recommendations. Key topic areas along with possible points of discussion were identified. Individuals within the workgroup were identified who could review the literature in each topic area, prepare slide presentations that would familiarize workgroup members with available evidence, and set the stage for more in-depth discussion. A full workgroup meeting was convened using internet-based conferencing tools, during which each of the topic areas was discussed in turn. Transcripts of the discussion were used to generate broad outlines of content areas to be explored further.

Members searched several databases, including Medline, Google Scholar, and the Cochrane Collaborative, to identify primary sources and reviews. Searches were limited to articles published between 1950 and 2017

and available in English. Expanded search terms were used to identify the evidence, including MeSH headings: Tobacco (D014026), Smoking (D012907), Tobacco Products (D062789), Electronic Nicotine Delivery Systems (D066300), Nicotine (D009538), and Harm Reduction (D040261), in addition to keywords unique to each thematic area. Workgroup members synthesized their evidentiary summaries into a list of candidate topics suitable for inclusion in the final report.

Breakout group conference calls were scheduled 1 week after the initial meeting, with each call focused on a single topic area and moderated by the project chair. The breakout groups were charged with developing detailed, annotated content maps of their topic areas, including points to be considered for suggested recommendations. Workgroup members were encouraged to self-select to breakout sessions that most closely aligned with their expertise. All workgroup members and external contributors participated in at least one of the topic area calls.

In the document development phase, the workgroup held a full-day, in-person meeting during which evidence-based content maps developed during the conceptualization phase were refined into a structured outline that would roughly correspond to the final format of the statement. At this stage, the workgroup was asked to finalize the set of recommendations that would be included in the statement. Writing assignments were generated for each of the workgroup members, who were then charged with submitting a 250- to 500-word summary of their assigned recommendation(s). These executive summaries were edited for length and style and then combined to form the document first draft.

In the prepublication phase, successive drafts were circulated to workgroup members for review and modification, using an iterative consensus process until unanimous approval was achieved. During this phase, patient representatives were asked to help the workgroup ensure the document's relevance to the lay public and to compose a statement of relevance from the patient perspective. Suggested questions to be considered included: What are the types of harm reduction terms most frequently encountered by patients in lay literature? What terms seem misleading, or are to be avoided? Which kinds of measures of individual or population health would be most acceptable to the lay consumer? What regulatory standards (e.g., degree of certainty, long-term monitoring, etc.) would give patients confidence in a harm reduction claim? How should complex and or competing harm reduction claims be communicated to patients in the setting of a clinical visit?

The resulting final draft policy statement was subject to review by the ATS Documents Editor, the ATS Board of Directors, and anonymous peer reviewers, per ATS policy.

Recommendations

Four standards for ensuring the validity of any harm reduction claim were identified, along with several important considerations relevant to each (Table 1). Criteria I through III apply to the specific construction of the claim itself, and criterion IV applies to the development and implementation of the claim. To be considered valid, harm reduction claims must meet all four criteria, specifically:

I. Claims of harm reduction must be accompanied by explicit estimates of the anticipated impact on individuals.
II. Claims of harm reduction must be accompanied by explicit estimates of the anticipated population-based impact.
III. Harm reduction claims must be carefully constructed to explicitly avoid overstatement or misrepresentation.
IV. The investigation and/or regulation of potential harm reduction strategies must pay careful attention to the ethical considerations unique to this concern.

For example, a claim of the form *X is healthier than Y* would not be considered valid, because it fails to explicitly state the anticipated health effect on individuals and populations, and the use of vague terms like "healthier" does not go far enough in explicitly avoiding overstatement. Specific recommendations guiding application of each of the framework criteria include the following.

Estimating the Potential Harm Reduction Impact on Individuals

Inference is an acceptable technique for estimating the anticipated impact of harm reduction strategies on individuals, particularly in instances where the impact of the strategy on human illness is expected to be delayed. In all cases, inferential methods used should be explicitly described when making harm reduction claims.

In contrast to a factual claim (e.g., formaldehyde concentration measured in smoke from product A is lower than that measured from product B), inferential claims are evaluative in nature, using a factual premise to support a conclusion (e.g., product A is safer than product B). Inferential claims may be explicit, typically containing indicator words such as "thus" or "therefore," or may be implicit, where the critical link between the premise and the conclusion is alleged or assumed. An appropriately structured inferential claim should explicitly state the predetermined choices made among the alternative inferential options that might have been used to estimate human risk from data that are not fully adequate or are not drawn directly from human experience. For example, a harm reduction claim might assume normal renal function and average toxicant dose exposures; specification of the impact of these assumptions on risk modeling, and the variability associated with the alternative conditions, should be explicit (43).

Inferential harm reduction claims relying on surrogate biological markers of disease, or on markers of exposure to risk-associated constituents, should explicitly state which measures were used to estimate harm, the relationship of the marker to the specific harms reduced, and the degree to which certainty in this relationship has been established at the time the harm reduction claim is made.

A search of the available literature reveals a wide variety of methods that have been used to develop the data foundation for inferential tobacco harm reduction claims. Inferential claims have been made using both direct (e.g., toxicant concentrations, nicotine concentrations, pharmacokinetic metrics) and indirect (e.g., gene expression, airflow obstruction, cytokine production) surrogate measures of effect. This flexibility is in part driven by the biology of the harm being evaluated and in part by the limitations of available technology. Flexibility is good, in that it allows for a robust investigation of the target biology, but can undermine confidence in the claim if the scientific rationale for methods chosen and assumptions made in risk assessment are not immediately clear. Given that these

Table 1. Framework for Valid Harm Reduction Claims

Framework Criteria	Important Considerations
Claims of harm reduction must be accompanied by explicit estimates of the anticipated impact on individuals	• When is inference acceptable? When is direct observation necessary? • Most appropriate way of dealing with inherent uncertainty? • Direct vs. indirect measures of impact? Influence of compensation? • How to deal with competing effects? (i.e., reduced harm A = increased harm B) • Hierarchy of evidence for "reduced harm" designation?
Claims of harm reduction must be accompanied by explicit estimates of the anticipated population-based impact	• What is the relationship of estimated individual effects to anticipated population effects? (Ecologic fallacy?) • Assessing short- vs. long-term harms? Surveillance? • Direct vs. indirect measures of population effect? Requirements for complex modeling? • How to deal with social/cultural/environmental harms? • Managing risk trade-offs—within group vs. between group • Non–index user harms? Fetal/childhood/pregnancy/lactation • Unintended uses/exposures • Hierarchy of epidemiologic evidence of "reduced harm"?
Harm reduction claims must be carefully constructed to explicitly avoid overstatement or misrepresentation	• Why is precision important? Lessons from prior deceptive practices • Variety of definitions currently in use • Preferred terms/definitions?
The investigation and/or regulation of potential harm reduction strategies must pay careful attention to the ethical considerations unique to this concern	• Balancing need for action against need for reassurance • Implications for research methods? • Monitoring unanticipated effects (both positive and negative) • Is compulsion (dependence) itself a "harm"? • Mechanism for informing public of important developments?

default decisions can have substantial effects on the results of risk assessments, it should never remain a question as to whether the best available scientific information and defaults have been used to examine the problem (44).

When using number of cigarettes consumed as a surrogate measure of exposure, explicit care should be taken to account for anticipated compensatory adjustments in smoking topography during smoking "reduction."

The extent to which smoking topography (i.e., puff frequency, puff volume, hold duration, etc.) changes when lower-yield products are used is important for accurately assessing the risk associated with the product. Even in harm reduction strategies aimed at reducing exposure to cigarette smoke by means of reducing the number of cigarettes consumed, it is possible for users to alter topography enough to minimize the anticipated risk reduction. For example, consuming 10 cigarettes isn't by necessity less dangerous than consuming 20 when the qualitative characteristics of the smoking behavior compensate for the quantitative change in number of cigarettes consumed. There is evidence that the potential for compensation varies significantly by product (45, 46). Findings support the notion that smokers compensate for nicotine, but factors including cigarette draw resistance, sensory effects of nicotine, and conditioned stimuli may also be relevant. In all cases where harm reduction claims are based on observable changes in cigarette consumption, measures of compensation should be integrated into harm calculations.

Comprehensive narrative statements regarding the relevance of laboratory models of harm to actual human experience should accompany harm reduction claims when based on animal or cell culture models.

Qualitative descriptions of the demonstrated strength of linkage between human physiology and the chosen surrogate model should be explicit when basing inferential harm reduction claims on the results of such studies. In instances where the correlation is unknown or in doubt, this should be explicitly stated. Also, the relevance of exposure conditions, including route of administration, dose or concentration, timing, duration, etc., to normative human exposure conditions should be explicitly stated (44).

When making a harm reduction claim, the range of possible outcomes expected from implementation should be explicitly stated.

A narrative description of the known or suspected mediators and moderators of the harm reduction effect and a description of how the effect of implementation is expected to be distributed within the population should accompany all explicit claims of harm reduction. In addition, the temporality of the effect should be described explicitly and the limits of certainty defined. When should the user expect this claim to take effect? How long will the effect last? Is there need for longitudinal monitoring (Figure 2) (44)?

New nicotine dependence is not just the antecedent to illness but a manifestation of altered brain biology. Regardless of the impact harm reduction strategies have outside of the central nervous system, the potential for causing or sustaining addiction should be accurately represented in risk trade-off calculations.

Nicotine causes dependence through its action on nicotinic cholinergic receptors in the mesolimbic centers of the brain (47, 48). Nicotine addiction manifests as a compulsive disorder, with withdrawal causing significant depressed mood, insomnia, frustration, anxiety, and agitation to a degree comparable to that caused by opiates, amphetamines, and cocaine (49). Relapse often follows prolonged periods of abstinence (50). Adolescent brains are

BOX 2-3
Agency Guidance on Risk Characterization: Attention to Uncertainty

A 1992 guidance memorandum reinforces principles enunciated in the 1983 Red Book and in EPA's 1986 risk-assessment guidelines and was a forerunner of later guidance documents.

> Highly reliable data are available for many aspects of an assessment. However, scientific uncertainty is a fact of life for the risk assessment process as a whole. . . . Scientists call for fully characterizing risk not to question the validity of the assessment, but to fully inform others about critical information in the assessment. . . . Even though risk characterization details limitations in an assessment, a balanced discussion of reliable conclusions and related uncertainties enhances, rather than detracts, from the overall credibility of each assessment [Reprinted in NRC 1994, Appendix B, pp. 352-353].

The *Risk Characterization Handbook* (EPA 2000b) instructs risk assessors to, among other things, "carry forward the key information from hazard identification, dose-response, and exposure assessment, using a combination of qualitative information, quantitative information, and information about uncertainties" (p. 24) and "describe the uncertainties inherent in the risk assessment and the default positions used to address these uncertainties or gaps in the assessment" (p. 21).

After highlighting the emphasis on "transparency" in EPA's 1995 risk-characterization policy (EPA 1995), the *Staff Paper* (EPA 2004a) notes that "one of the major comments on EPA risk assessment practices is that they do not characterize uncertainty and variability transparently enough" (p. 33). The statement of task for EPA (2004a) confirms that "this is an issue EPA is attempting to address" (p. 33). (See Box 2-4 for related peer-review commentary on one assessment.)

Figure 2. National Research Council's statement on the need for attention to scientific uncertainty in risk characterization (reprinted from Reference 44). EPA = Environmental Protection Agency.

especially vulnerable to the negative consequences of nicotine exposure, given the high degree of plasticity during this period. Early exposure potentially alters the normal course of brain growth and development, affecting learning, reasoning, mental health, attention, impulse control, and personality (2, 51–53). Nicotine has a powerful gateway effect on the brain, making susceptibility to the addictive effects of other psychoactive drugs more likely and recovery from other addictions more difficult and conferring a long-term propensity to relapse (54, 55). Given the complexity of nicotine's effect on human psychosocial development, and the potential lifelong consequences of early exposure, the inherent primary harm of the compulsive disorder produced by nicotine should in no case be undervalued in individual harm reduction estimates or trivialized in the discussions surrounding population-based approaches to reducing the impact of the epidemic.

Harm Reduction Claims Based on Population Impact Estimates

Surrogate measures of population impact should form the basis of inferential harm reduction claims only when the measures have a well-established link to actual harm reduction outcomes. In all cases, the nature of the assumed link, and the degree of certainty in this relationship, should be explicitly stated when making such claims.

Intermediate markers of population risk behaviors, such as knowledge/attitudes regarding harms, intention to quit, cigarette sales data, and even prevalence of smoking, may be poor indicators of population-based harm. The relationship between such surrogate measures and actual health behaviors is chaotic and weak, particularly when indirect measures such as sales data are used. Given that smoking is known to be unhealthy, it is easy to assume that reduced prevalence of smoking is definitionally less unhealthy. However, relationships between behavioral exposures and outcome that are true in individuals may not be proportionally true within populations, often requiring complex, multilevel modeling to reflect the true anticipated population effects (56, 57). As such, use of surrogate markers of population harm reduction should be avoided unless there is accompanying epidemiologic evidence of direct association in a representative population. As an example, consider that the association between elevated cholesterol levels and ischemic heart disease was not considered proof that reductions in cholesterol would save lives until that hypothesis was supported by evidence generated in a representative population cohort (58, 59). Similar intellectual rigor should apply to the impact of presumed tobacco harm reduction strategies on population health. Known mediators and moderators should be disclosed.

Population-based harm reduction claims should be accompanied by a statement of known and/or suspected risk trade-offs incurred by the population. Risk trade-off estimations should include the impact on the entire community where appropriate, not just the smoke-exposed subset.

Public health is by its nature a communal good, with burdens and benefits that often fall unevenly on different subgroups. This potential for trade-offs raises a particular set of challenges when making harm reduction claims relevant to tobacco. Although in financial systems the greatest rewards are often associated with the greatest risks, the risks of poorly designed tobacco policy are both personal and profound, making the calculus for considering such trade-offs much less clear. The two most frequently cited adverse concerns remain the unintentional maintenance of tobacco use by persons who would otherwise quit and the initiation of tobacco use among persons who would otherwise never use tobacco. Judgments regarding between-group risk tradeoffs—as when the health of one group benefits while that of another is harmed—should include input from the affected groups within the decision-making algorithm. Within-group risk trade-offs are also foreseeable; how do we correctly value avoidance of a known risk if the trade-off involves increasing another? Are disability-adjusted life-years saved an appropriate metric for considering the trade-off? Finally, in a setting of limited resources, investment in one harm reduction strategy may delay or otherwise undermine the development of other, potentially more effective, approaches. Is there an economic metric appropriate for the trade-off calculation? Given that the inherent risk trade-offs are complicated, and that agreed-on metrics for judging acceptability are lacking, the evidentiary standard in support of such claims needs to be high until precedent guidance is available for the U.S. Food and Drug Administration and other regulatory agencies as they try to correctly set this balance (60). This high evidentiary standard should be no higher than those applied to other conditions but also should not be lower.

Population-based harm reduction claims, accompanied by a statement of risk trade-offs, should also incorporate known and/or suspected non–health-related variables in their disclosure.

Few smokers perceive social approval of their smoking, and most report that tobacco companies cannot be trusted to tell

the truth. Denormalization of tobacco use has been independently associated with intentions to quit smoking and probability of abstinence at follow-up (61). The relationship between social stigma and smoking, particularly for adolescent, minority, or otherwise disenfranchised groups, raises questions about what impact the regulatory concept of "more acceptable than smoking" will have on tobacco use prevalence over time. Popular assumptions are that more people will be attracted to the more acceptable option. However, we have not adequately considered how tobacco-related stigma overlaps with other social identity stigmas, with evidence that some groups are in fact attracted to the less-acceptable options, potentially exacerbating health inequities (1). Use of mathematical models to predict future public health scenarios should explicitly state which assumptions were used in calculations, the confidence intervals of values used, the strength of available evidence used as the basis for the model, and the results of sensitivity analyses surrounding all assumptions that influenced the conclusions (62). Methods count—it is clear that inadequately concealed or nonblinded trials exaggerate intervention effect estimates. For this reason, it is incumbent on the authors of harm reduction claims to disclose potential effects of methodological bias on the claimed benefit, including reporting sensitivity analyses restricted to data generated in trials at low risk of bias (63). In all cases, harm reduction claims should be accompanied by conflict of interest disclosures.

It should not be assumed that harm reduction claims are generalizable to all age groups. Harm reduction claims should specifically state the age cohort to which they most ideally apply.

Potential harms of tobacco smoke exposure can vary substantially by population subgroup. Child and adolescent brains have increased susceptibility to the development of nicotine addiction (64). A product that may reduce harms for adults who are tobacco users, but paradoxically increase risk of future tobacco use among children, may be seen as a net overall increase in population harm, given the relative societal implications of unintentionally promoting tobacco use. Because adolescent development is characterized by risk-taking behaviors and experimentation, the issue is not merely whether a harm reduction claim accurately represents the potential value to incumbent smokers but whether the "harmful but safer" message will inadvertently lead to substantial harms in a younger cohort while benefitting an older cohort, because of differential effects of communication (65).

It should not be assumed that harm reduction claims are generalizable to pregnant women or to the developing fetus. Harm reduction claims should specifically state their applicability to pregnancy and lactation.

Undeniably, the safest method of tobacco harm reduction during pregnancy is to stop smoking. Smoking during pregnancy may cause considerable harm to the fetus, which may have lifelong consequences. Smoke exposure during pregnancy has been related to increased risk of preterm birth, small for gestational age births, sudden infant death (66), and structural airway changes in newborn babies (67). Reduced lung function at birth is related to reduced lung function 10 years later (68) and at 16 years of age with associated allergic comorbidities (69). Even the grandchildren of smoking grandmothers experience increased asthma prevalence during childhood (70, 71). Compared with continued tobacco use, epidemiologic evaluation of potential harm reduction strategies among pregnant smoking women have suggested similar increases in preterm births (72), small for gestational age births (73), and early neonatal mortality and stillbirths (74). Given that the underlying mechanisms for these findings have yet to be worked out, and at least a portion of the reproductive harms appear to be caused by nicotine (75, 76), conclusions regarding impact on reproductive health should be considered independently from similar strategies aimed at the general population. Consideration of population-based harm reduction strategies should include consideration of impact on reproductive health.

Careful Use of Language in Harm Reduction Claims

Harm reduction claims should be presented in lay language.

As scientific content becomes increasingly available online, journal editors frequently require summaries that are written specifically for the lay public. Nowhere is this requirement more likely to have an immediate impact than on work that includes inferential harm reduction claims. Making research findings, including limitations, understandable to the public can help raise awareness and speed adoption but can raise unreasonable expectations of improved health if poorly executed. The challenge inherent to meeting this important goal is to balance the need for simplification with avoiding distortion (77). Use everyday language and familiar examples. Address the question "what does this mean to me?" Anchor risk reduction estimates to other familiar, tangible examples of everyday life.

Harm reduction claims should exercise caution in language choices, explicitly minimizing the potential for exaggeration of effect size, misattribution of protective effect, or other potential misunderstandings once released to the public.

Inferential harm reduction claims should be based on data rather than theoretical or "common sense" rationales. Objective data are critical to avoiding a repeat of baseless harm reduction claims made about numerous products in the past (78, 79). Resulting false perceptions of reduced harm (80) have made it difficult to alter public behavior once suggestions of paradoxically increased harms came to light (2). Scientific claims are particularly prone to exaggeration (81, 82), often accompanied by press releases that can readily reach the public, and may result in false perceptions or misunderstanding (83, 84). The importance of avoiding overreaching conclusions cannot be overstated.

Product-oriented population harm reduction claims should account for all known, albeit perhaps unintended, uses or modifications of the product in the modeling or impact calculations, particularly when estimating impact on tobacco-naive users.

The observed uses of products intended to reduce the harm of tobacco smoke exposure often diverge from the expected. Accessorization, disassembly, or combination with other products may not be intended by the manufacturer, but use patterns that have significant prevalence may have significant public health impact and influence on harm reduction estimates (85, 86). Even misapplication of intended uses, such as flavorant customization, vape cloud competitions, direct ingestion, or excessive voltage adjustment of electronic nicotine delivery devices, may directly or inadvertently increase harms to tobacco-naive

users (87). Particularly because flavored products appear to be targeted to adolescents and young adults, harm reduction claims should account for uses that may have nothing to do with the reduction or cessation of tobacco use.

Given the evidence establishing the efficacy and safety of pharmacologic harm reduction methods for people unready or unwilling to make a quit attempt, marginal harm reduction calculations should use the best available harm reduction approach as the comparator rather than the no-intervention condition. In all cases, harm reduction claims should be accompanied by clear statements of the methodologic decisions made in this respect.

The foundation for the ethical investigation, implementation, and regulation of harm reduction strategies rests in the strong fiduciary commitment to public health and human rights. Ethically sound consideration of potential harm reduction strategies requires an honest evaluation of the evidence supporting efficacy, assurance that the public understands the relative risks and benefits, and a plan to closely monitor the long-term health and behavioral effects, including unintended consequences. In these pursuits, appropriate choice of comparator is of utmost importance to fulfilling the fiduciary role. Even the simplest analysis of benefit requires comparison of the expected baseline effect to the observed effect under harm reduction conditions (ΔE). For circumstances in which no known remedy is available, it is acceptable to estimate ΔE using the status quo ante (i.e., no intervention) as comparator. However, in circumstances where a proven, accepted remedy for the status quo ante *does* exist, it is no longer ethically acceptable to estimate ΔE using the baseline condition as comparator unless informed consent is assured (88). Rather, the marginal effectiveness compared with standard interventions should be used ($m\Delta E$). An analysis that declares the superiority of a new intervention using a comparator that is no longer in practice, or is no longer considered to be standard of care, is not appropriate for assessing $m\Delta E$ (89). In light of the well-developed evidence in favor of a standard for using pharmacologic methods of treating the compulsive disorder of dependence *even among people unready or unwilling to make a quit attempt*, $m\Delta E$ can no longer ethically be estimated against the inactive comparator because of the strong possibility of introducing comparator bias (90, 91). All harm reduction claims should make their methodology clear in these respects.

Ethical Considerations When Claiming Harm Reduction

Hazards of prospective population-based evaluations of tobacco harm reduction strategies may qualify as "greater than minimal risk." Care should be taken to assess research risks in comparison to current standards of care for reducing harm among people unready or unwilling to quit, rather than in comparison to the no-intervention condition.

There are inherent uncertainties to all new potential harm reduction strategies. Evaluation methods are aimed at reasonably reducing these uncertainties. Although patients, physicians, and even researchers may *believe* a particular harm reduction approach has value, our fiduciary responsibility is executed through judicious investigation using methods that maximize potential benefit while minimizing potential risks. Because safe and effective harm reduction methods exist, new proposed harm reduction methods may represent greater than minimal risk if they are evaluated *against* the established standard, rather than *in addition to* that standard (92). In population-based studies, justifying such a deviation from the standard of practice on the basis of cost or other systematic barriers may be unethical, particularly if the population includes vulnerable members of the community (e.g., adolescents, the mentally ill, polysubstance abusers) or unfairly favors the privileged (e.g., those with greater-than-average pharmaceutical insurance coverage and access to health care). Both the Maryland Court of Appeals and U.S. Office of Human Research Protections determinations in the Johns Hopkins study of lead paint harm reduction rejected the position that risk research is less ethically problematic when performed on people who are already disadvantaged by ongoing exposure. In light of both the affective dysregulation characteristic of nicotine addiction and the obvious life-or-death consequences of uncontrolled tobacco dependence, it remains an open question as to whether current smokers inherently qualify as a vulnerable population (93, 94). However, designs that allow only for abatement of harmful exposures when harm-eliminating interventions exist may warrant reevaluation in light of the instructive lessons the lead paint harm reduction study offers (95).

Harm reduction researchers must protect the autonomy of research subjects by discussing the unique nature of the risks of such research with those subjects and by promoting their individual understanding.

Autonomy is respected in human subject research when participants have the capacity to understand the risks they are assuming, are given the information necessary to achieve that understanding, have their understanding verified by a researcher qualified to make such an assessment, and consent voluntarily to assume the risks of the research. The nature and severity of the risks of the research need not be known in their entirety to be acceptable to the subject. However, the fact that certain risks are unknown must be included in the informed consent discussion if the participant's assumption of risk is to be considered valid.

Unlike current standards of care for cessation and harm reduction, the long-term risks of harm reduction methods are not yet fully known—a fact that must be disclosed during the consent process in a manner that meets the needs of the particular research subject. Human subjects may be vulnerable to coercion if a condition exists that has compromised their judgment regarding how the research applies to their individual circumstances. Given the nature of ongoing marketing efforts, it remains a particular responsibility of harm reduction investigators to avoid overemphasizing unproven benefits or minimizing unknown risks.

Harm reduction researchers should protect research subjects from unforeseen or tragic consequences of their research through fair methods that promote just outcomes.

Fairness is ensured when a uniform process is consistently applied. Ideally, that process promotes justice, or the equitable distribution of benefits and harms within a group of people who have assumed the same set of risks. Fairness is a process, justice is the result. Justice in research demands that harms are minimized as much as possible across a group of research subjects, regardless of the degree to which they

voluntarily assumed the risk of harm. To fairly mitigate harm, consistent methods for detecting, reporting, and responding to new harms identified during investigation are imperative. These methods should be expressly discussed during the informed consent process. In the interest of fairness, it is important for investigators and regulatory agencies to note the potential biases that may arise from new intellectual or commercial conflicts of interest.

Adopted harm reduction strategies should guard against inequitable allocation of resources.

Harm reduction strategies should be aimed at mitigating not only the harms accrued to the individuals engaging in the target activity but also the harms accrued to others who may be affected. The unintended social costs of implementation should remain of concern. Poorly implemented approaches may disproportionately accrue harms or benefits to subsets of the population in an unfair manner. In that regard, harm reduction strategies should be tailored to the specific needs of vulnerable populations. Those most likely to be targeted and affected by unsubstantiated harm reduction claims, including low-income populations who suffer disproportionate tobacco-related health burdens, should be part of the discussion designing reduction policies that serve them. Involving a wide range of stakeholders in the development and implementation of evidence-based harm reduction strategies will encourage culturally and ethically acceptable implementation.

Harm reduction claims should specifically state the perspective(s) from which they are derived.

When evaluating the validity of a specific harm reduction claim and the data on which the claim was built, it is easy to forget that, in its broadest sense, the topic of "harms of tobacco smoke" and their potential for modification is protean and likely to mean very different things to independent evaluators approaching the topic from different perspectives. Individual patients may be affected by harm reduction claims in ways that are not easily reflected in scientific analysis. Externalities such as preexisting conditions, family history, or the social acceptability of the proposed harm reduction strategy are likely to be considered differently in individual utility estimates (96). It is possible that clinicians will face competing concerns that are difficult to balance when implementing harm reduction strategies. For example, how does the potential for reducing future cancer risk compete with the potential to impact the effectiveness of concurrent medications today, or with the economic impact of uncovered costs of long-term interventions? Finally, regulators may evaluate harm reduction claims from a population-based perspective, within which variation in individual results may be superseded by concerns for the community's well-being or the legal/political environment within which harm reduction policies are enacted (97).

Harm reduction claims should be accompanied by a narrative statement of the potential for unintended impact on non–index users.

Although it is true that nonusers can be exposed to tobacco smoke through second- and third-hand mechanisms as well as through accidental ingestion, the only appropriate reference condition for evaluating the potential impact of harm reduction claims on the nonuser portion of the population is the "absent" condition. Secondhand exposure refers to inhalation by a nonuser in proximity to the user, and thirdhand exposures related to toxicant exposure from surface deposits, either through dermal absorption or off-gassing/inhalation (98). Accidental ingestion occurs when a product is ingested or absorbed unintentionally, such as when a toddler child ingests it or spills it on his/her skin in the course of exploring the world. Products that have the potential to appeal to a young child and/or may be easy to access increase risk of accidental ingestion. Reduced risk products that have substantial appeal to the nonuser may also serve as a gateway to the higher-risk products, thus increasing their use (99). Because harm reduction claims are typically aimed at people who may also be influenced by the risk sustained by others in their community (e.g., children, coworkers, etc.), all such claims should provide an accurate accounting of the known impact on non–index user risk profiles (100).

Discussion

Tobacco dependence represents a vexing paradox. Several decades of massive investment in tobacco control policies and the development of effective therapeutic strategies have resulted in a remarkable overall reduction in tobacco use prevalence. Yet, we continue to be frustrated by persistent and unacceptably high rates of tobacco use, especially among children, the poor, and the disenfranchised (2). Long-established traditions, based on a theoretical framework that artificially divorces free will from the biological functions of the brain, have been implicated as limits to our creativity in solving this problem (101, 102). The obdurate nature of tobacco dependence has understandably resulted in low implicit estimations of the probability of altering its course, and these low expectations naturally lead to disengagement and learned "hopelessness" among clinicians (103, 104). From this perspective, desperation may appear to warrant advocating for unproven approaches to reducing harm in the hope of saving lives that would otherwise be lost (105). It is precisely when the stakes are so high that fidelity to scientific principles is most crucial to the public health (106).

Harm reduction strategies should never represent a capitulation to the easier, cheaper, or more expedient options. Elimination of risk is, and should remain, the goal of public health authorities. This statement is not intended to endorse "harm reduction" as a compromise position but rather to highlight the special requirements for ethically pursuing the reduction of harm within the complex social/biological context of tobacco dependence. In all cases, improving the dissemination of interventions that are already known to be safe and effective remains the primary harm reduction tactic.

This statement clarifies several important notions intrinsic to the thoughtful application of harm reduction principles. First, reductions in tobacco toxicant exposure are too often conflated with reductions in the harms of tobacco use. We understand this to be a false equivalence on many levels. Individually, we understand the relationship between risk and exposure to be nonlinear. On a population level, we understand risk to be unequally distributed between subgroups. Imagine a theoretical circumstance in which reductions in tobacco use are concentrated within the subset of a population less susceptible to the

outcome of interest, rendered so by the distribution of important genetic, social, or environmental moderators of disease. We also understand the impact that behavioral compensation has on exposure, regardless of measured toxicant levels. Facile assumptions proved to be ecologic fallacies in the past and should not be repeated.

Second, the statement highlights the complexity of weighing risk trade-offs in such a chaotic system. Given that benefits of a particular approach to harm reduction are likely to accrue unequally within a population, it remains imperative that those of us wishing to make harm reduction claims be judicious in estimating the magnitude of that difference—across age groups, between sexes, and over time. Because evidence-based approaches to helping people remediate their tobacco use risks already exist, including in circumstances characterized by reluctance to discontinue the smoking behavior, the marginal effectiveness of newly introduced interventions should only be assessed against the effectiveness of established approaches, not against the no-intervention condition. Choosing the comparator most relevant to each population subgroup is necessary to manage the significant potential for comparator bias within an analysis and the potential for misleading estimations of risk during the conduct of research. In all cases, authors should favor careful fidelity to the scientific method, to avoid both *false claims of harm reduction* and *rejection of valid harm reduction.* It bears repeating that for tobacco-naive youth, the only ethically acceptable comparators are the tobacco-less condition.

Finally, this statement challenges the premise that the development or maintenance of dependence can be separated from a discussion of the harms to be reduced. We know that dependence behaviors stem from addiction—a pathologic disruption of normal brain biology. We also know that this disruption is associated with unhealthy or maladaptive sequelae that extend well beyond whether smoking continues. Policy makers cannot responsibly assess the impact of harm reduction claims if dependence, and *all* its consequent ill effects, are trivialized or ignored.

It is hard to imagine an area of regulatory science more prone to confirmation and availability biases. Recommendations guiding the appropriate structure, communication, and investigation of tobacco harm reduction claims offer regulators and scientists a series of methodologic remedies to this problem and represent a means of assuring the public that these threats to validity have been checked to the extent possible. To maximize the public's confidence in harm reduction claims, several additional steps should be taken. For example, the scientific community should develop a formal system of evidence grading, specific to the context of harm reduction work, that incorporates measures of study design, consistency of results, directness of the evidence, and precision of measures into a summary grade, useful for communicating confidence in the claim (107, 108). Regulators must provide assurance that longitudinal surveillance systems are in place to document the impact of a harm reduction intervention, inform the public of developments that might alter their confidence in the claim, and serve as an early warning system for unintended consequences (109).

The known influence of cognitive biases also affects our ethical responsibilities in study design. The moral construct of informed consent is the basis for the participant's assumption of risk. This requirement elevates the researcher's responsibility for clarity and transparency, particularly when an unreasonable or premature expectation of benefit might be anticipated among participants. Fairness mandates that the risk of harm reduction interventions be assessed as "greater than minimal" if the risk profile of the intervention is unclear, because, in this context, "risk" refers to the impact of study participation and is not assessed in comparison to the risk of ongoing tobacco use.

Patient Perspective

It sometimes feels like people who smoke cigarettes are the modern-day lepers. Marginalized, stigmatized, and constantly reminded that smoking kills, people affected by nicotine dependence can spend their adult years caught between the metaphorical rock and hard place. Each day presents another opportunity to quit, yet each thought of quitting is accompanied by an impulse to leave it alone until after the next cigarette. Days, months, years go by waiting for the next health complication. Some of us face lung cancer, some respiratory infections, and some progressive disability and breathlessness. All of us face the dreadful possibility that our actions will eventually hurt someone we love. These are the hidden costs of tobacco use.

It stands to reason that people who smoke would naturally be attracted to products that claim to reduce the harms of smoking while allowing for continued tobacco use. It also stands to reason that people in such a position would be vulnerable to the effects of misinformation, exaggeration, and outright hucksterism when products making harm reduction claims are introduced to the market. This ATS policy statement refines the conversation considerably, bringing us closer to a reliable set of "rules" for engendering confidence and sorting fact from fiction.

We expect clinicians to use their best judgment while helping us minimize our risks. Thus, we expect data informing their judgment to be reliable and clear. By articulating the ethical responsibilities of scientists and government regulators when making harm reduction claims, the ATS statement helps guide the future standards by which we assess and communicate real-world risk to the community. The additional effort inherent to these recommendations is a price worth paying if it helps us avoid the mistakes of the past and reduce the impact of tobacco on our children and grandchildren. ■

This official policy statement was prepared by an *ad hoc* subcommittee of the ATS Tobacco Action Committee.

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