The Food and Drug Administration Guidance on Patient Reported Outcomes and the Regulation of Modified Risk Tobacco Products

Donald L. Patrick, PhD, MSPH
University of Washington

Presented at Virtual CROM Symposium 2020 on Consumer Reported Outcome Measures in Tobacco and Nicotine Research
10 December 2020
16:00-19:00

Disclaimer and Disclosure

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Donald Patrick receives Honoria from Philip Morris International

Goals of Presentation

- To outline key aspects of the scientific and regulatory context of the FDA PRO Guidance
- To highlight how the patient voice has been integrated into regulatory decision-making
- To provide suggestions for how the Guidance applies to regulation of MRTPs in Consumer Reported Outcome Measures (CROMs)

FDA Mission

- protect the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.
- responsible for the safety and security of most of our nation's food supply, all cosmetics, dietary supplements and products that give off radiation.
- responsible for regulating tobacco products

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Approved by the FDA Reorganization Coordinator & Principal Delegation Control Officer
29 March 2018

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Legend:
---- Direct report to DHHS General Counsel
. . . . .Indirect reporting relationship to the Office of Chief Scientist

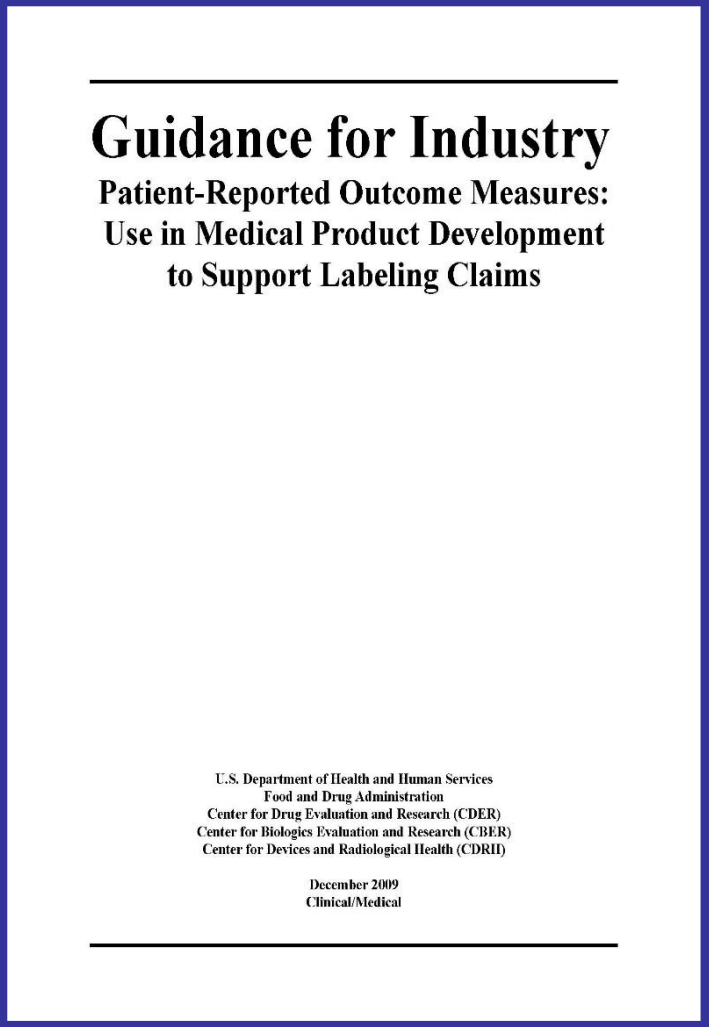
Outcome Assessment at the FDA is

- Measurement of the effects of an intervention (benefit or harm to a patient) = comparison between test and control group
- "*The purpose of conducting clinical investigations of a drug [is to distinguish the effect of a drug [sic] from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.*" 21CFR 314.126

Treatment Benefit and Harms

- Treatment benefit, for example comparing different MRTPs with combustible cigarettes, may be *measured* as
  - Comparative efficacy (e.g., an improvement or delay in the development of symptoms or decrements in function compared to placebo or an active comparator)
  - Comparative safety (e.g., a reduction or delay in treatment-related toxicity or other safety-related concern compared to placebo or an active comparator)

2009: Final FDA PRO Guidance



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

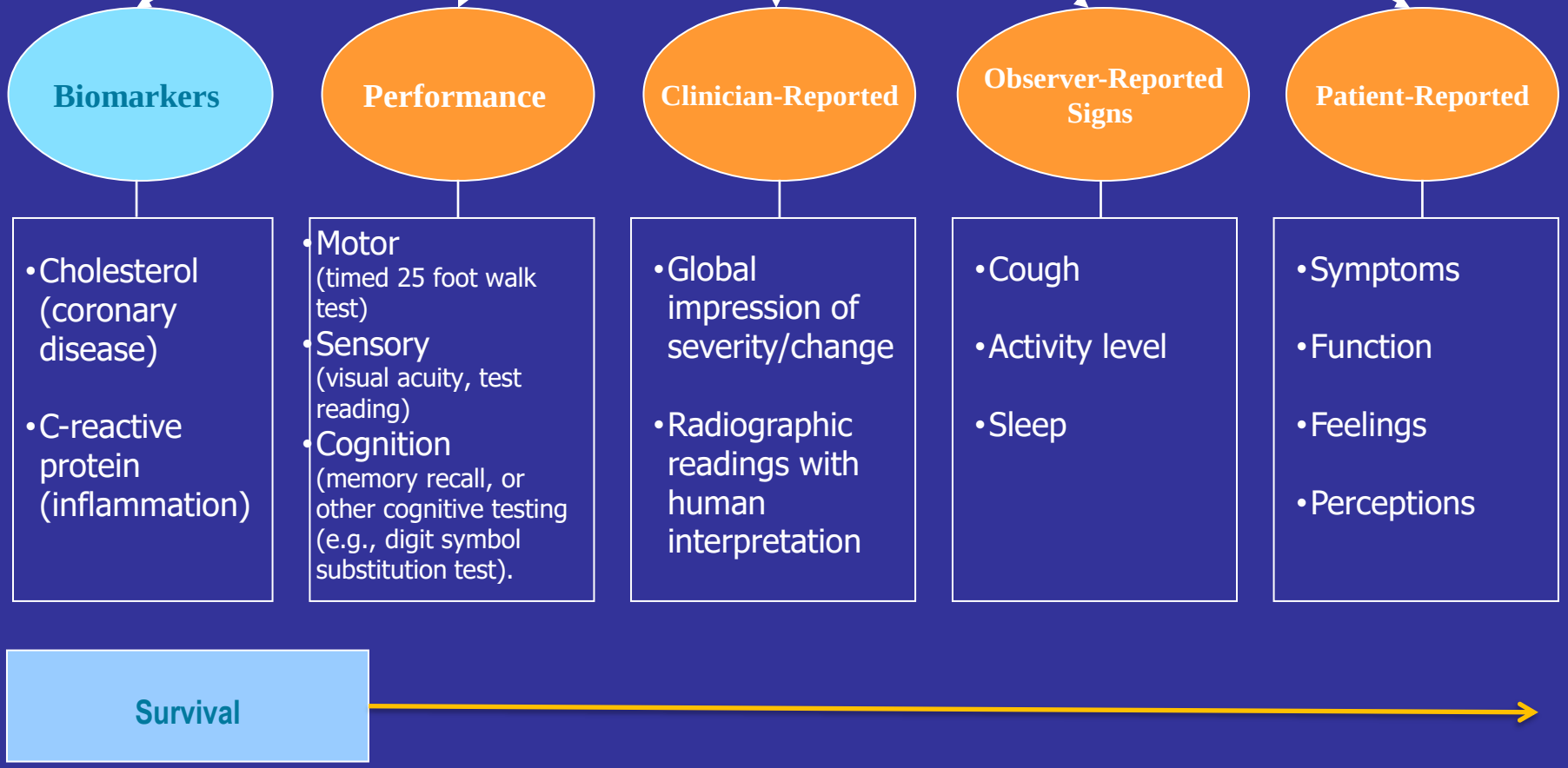
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

Clinical Trial Endpoints and Examples

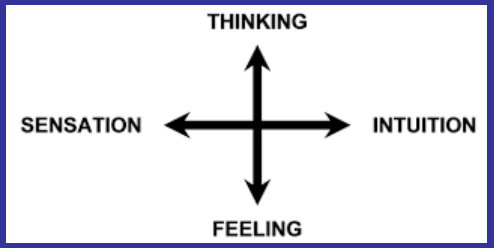
Orange ovals are Clinical Outcome Assessments
Blue Ovals are Survival and Biomarkers

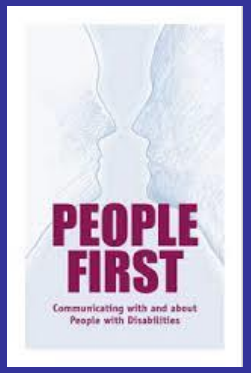


Why COAs?

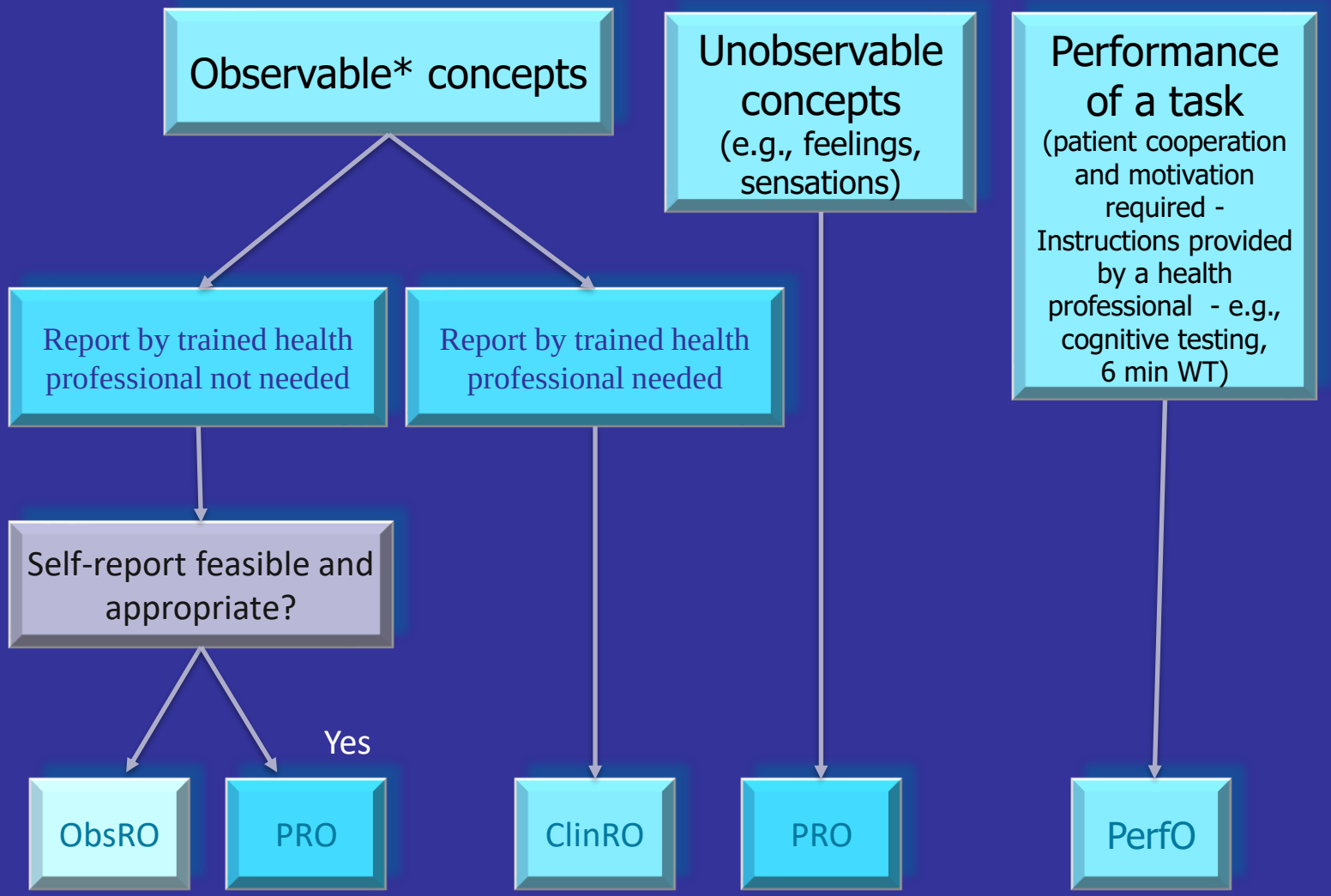
- Competition and cost require evidence of value to all stakeholders.
- Payers interested in technology assessment and evidence-based treatments.
- Regulators like US Food and Drug Administration and European Medicines Agency require for approval.
- Consumer and patient voices rising in importance with patient-centeredness.

In the best interest of people and patients





Choosing Clinical Outcome Assessments



Guidance puts emphasis on good measurement science from theory, social sciences, epidemiology, and outcomes research

- Assessment of measurement properties followed the American Psychological Association *Standards for Psychological and Educational Assessment*
- Reliability and validity assessment
- Interpretation of results
- Psychometric approaches including classical test theory item response theory and Rasch analysis

PRO Instrument Development and Application: An Iterative Process

i. Identify Concepts

- Identify claims
- Identify relationships among all endpoints
- Identify concepts relevant to patients
- Determine intended population
- Develop expected relationships among items & concepts/domains

ii. Create Instrument

- Generate items
- Choose administration method, recall period & response scales
- Draft instructions
- Format instrument
- Draft procedures for scoring & administration
- Pilot test draft instrument
- Refine instrument & procedures

iii. Assess Measurement Properties

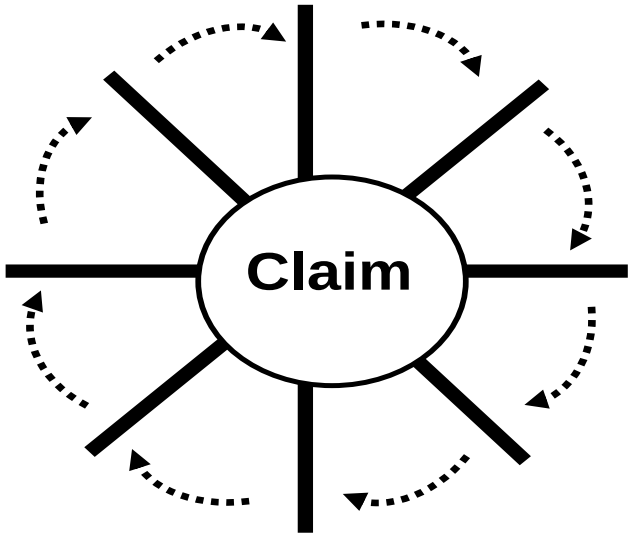
- Assess score reliability, validity, & ability to detect change
- Evaluate administrative & respondent burden
- Add, delete, or revise items
- Confirm conceptual framework
- Finalize instrument formats, scoring, procedures & training materials

iv. Collect, Analyze, & Interpret Data

- Prepare protocol & statistical analysis plan
- Identify responder definition
- Evaluate cumulative distribution curve
- Present interpretation of treatment benefit

v. Modify Instrument

- Change concepts measured, populations studied, research application, response options, recall period, or method of administration
- Translate & culturally adapt to other languages



So what was new about the Guidance from previous outcomes research?

- Concentration on content validity within context of use
  - --validity not a property of the instrument; it has to be evaluated within target population

    and

    actual application (context of use)
  - --"*it depends*" becomes operationalized
- Separation of ability to detect change from interpretation of change
  - --*responsiveness* NOT a characteristic of the instrument but of instrument in context of use

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

Understanding the Disease or Condition 1

A. Natural history of the disease or condition
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

B. Patient subpopulations
- By severity
- By onset
- By comorbidities
- By phenotype

C. Health care environment
- Treatment alternatives
- Clinical care standards
- Health care system perspective

D. Patient/caregiver perspectives
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

Conceptualizing Treatment Benefit 2

A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
- Survives
- Feels (e.g., symptoms)
- Functions

B. Define context of use (COU) for clinical trial:
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C. Select clinical outcome assessment (COA) type:
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

Selecting/Developing the Outcome Measure 3

A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

B. Begin COA development
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification as exploratory endpoint

C. Complete COA development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

Starting with the End in Mind: What is a Claim to the FDA?

- Statement or implication of *treatment benefit*
- Requires substantial evidence by regulation in two well-controlled clinical trials
- PROs may relate to safety or efficacy claims depending on context
- Secondary endpoint does not mean secondary importance
- Claims both in labeling (indications, clinical studies) and in promotion (pamphlets, media, literature)

Swedish Match North America, Inc. (SMNA) MRTPA

- June 2014: MRTPA submission for 10 smokeless snus tobacco products

  The 'ask': adjustment, removal of warnings (package & ads):

- To keep the "WARNING: Smokeless tobacco is addictive."
- To revise the "WARNING: This product is not a safe alternative to cigarettes."
- To eliminate the "WARNING: This product can cause mouth cancer."
- To eliminate the "WARNING: This product can cause gum disease and tooth loss."

- "WARNING: Smokeless tobacco is addictive."
- "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."
- Warning deleted
- Warning deleted

SMNA MRTPA: CTP Denial

FDA REVIEW CONCLUSIONS – DECEMBER 2016

- Regarding the risks relative to cigarettes, FDA recommended that Swedish Match consider a revised claim that was more precisely tailored to the supporting science, e.g.:
  - an adequately tested explicit claim;
  - placed outside the health warning; and
  - communicates information on the differences in specific health risks between the eight General Snus products and cigarettes.

- FDA also recommended that if Swedish Match chose to conduct a new consumer perception study, it should address the deficiencies of its initial study, including:
  - Ensuring the study stimuli test the proposed modified risk information verbatim; and
  - If the proposed claim appears in the warning, then the study should examine the impact of that context on consumer perception and understanding.

SMNA MRTPA Amendment

- September 2018: submission of an amendment for 8 products
  1. Revised claim (outside Warnings)

> "Using General Snus instead of cigarettes puts you at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

+ 2 test claims

- Focus of February 2019 TPSAC meeting
  2. New consumer perception study [Perceptions and Behavioral Intentions (PBI) Study], addressing the revised claim and the methodological concerns previously identified by FDA

SMNA MRTPA Amendment: Response

- CTP:
- [Study] results provide supportive evidence for Swedish Match's revised claim

Consumer Research in 2014 Submission	PBI Study
Used study items with flaws that limited interpretability	Used improved measures to assess most outcomes

Understanding	The claim improved U.S. consumers' understanding of the products' health risks relative to cigarettes, smokeless tobacco, and dual use of the products with cigarettes.
Intentions	The claim increased intentions to buy *General Snus* among adult tobacco consumers who could benefit their health by completely switching, with no statistically significant increase among non-users of tobacco.

- TPSAC: Positive vote
- October 22, 2019, FDA grants first-ever modified risk orders to eight smokeless tobacco products

Product labeling: Swedish snus claim

FDA Decision to Authorize Marketing of Proposed MRTP:

FDA must consider

- the relative health risks to individuals of tobacco product
- the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to tobacco product that is the subject of the application;
- the increased or decreased likelihood that persons who do not use tobacco products will start using tobacco product that is the subject of the application;
- the risks and benefits to persons from the use of the tobacco product as compared to the use of products for smoking cessation approved as medical products to treat nicotine dependence; and
- comments, data, and information submitted by interested persons.

To authorize marketing of proposed MRTP:

FDA must consider

- Description of the proposed tobacco product and any proposed advertising and labeling
- Conditions for using the tobacco product
- Formulation of the tobacco product
- Sample product labels and labeling
- All documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions.
- Data and information about how consumers actually use the tobacco product

Building a CROM Scientific Program for MRTP Applications with PRO Assessments in two main categories:

- A focus on content validity of assessments
  - What is the most important content for consumers of MRTP and for regulators?
  - Good principles of qualitative research in concept elicitation and cognitive interviewing
- Attention to measurement characteristics of the instrument in context
  - Conceptual framework for the items\subscales and method to obtain them
  - Responses in "severity" or "frequency" of experience
  - Recall period from diary to 3 month recall
  - Reliability and validity
  - Ability to detect change and interpretation of that change
  - Cross-cultural validity

Tobacco Products: Principles for Designing and Conducting Tobacco Product Perception and Intention Studies

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments regarding this draft guidance may be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Electronic comments may be submitted to https://www.regulations.gov. Alternatively, submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD, 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9 a.m. – 4 p.m. EDT.

Additional copies are available online at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/default.htm. You may send an e-mail request to SmallBiz.Tobacco@fda.hhs.gov to receive an electronic copy of this guidance. You may send a request for hard copies to U.S. Food and Drug Administration, Center for Tobacco Products, Attn: Office of Small Business Assistance, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993-2000.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products

October 2020

Overall approach

- Match study design to aims of studies including clinical and tobacco product perception and intention studies

  --does not include actual product use research
- Use best practices and qualified personnel specific to design and methods, i.e. qualitative and quantitative research

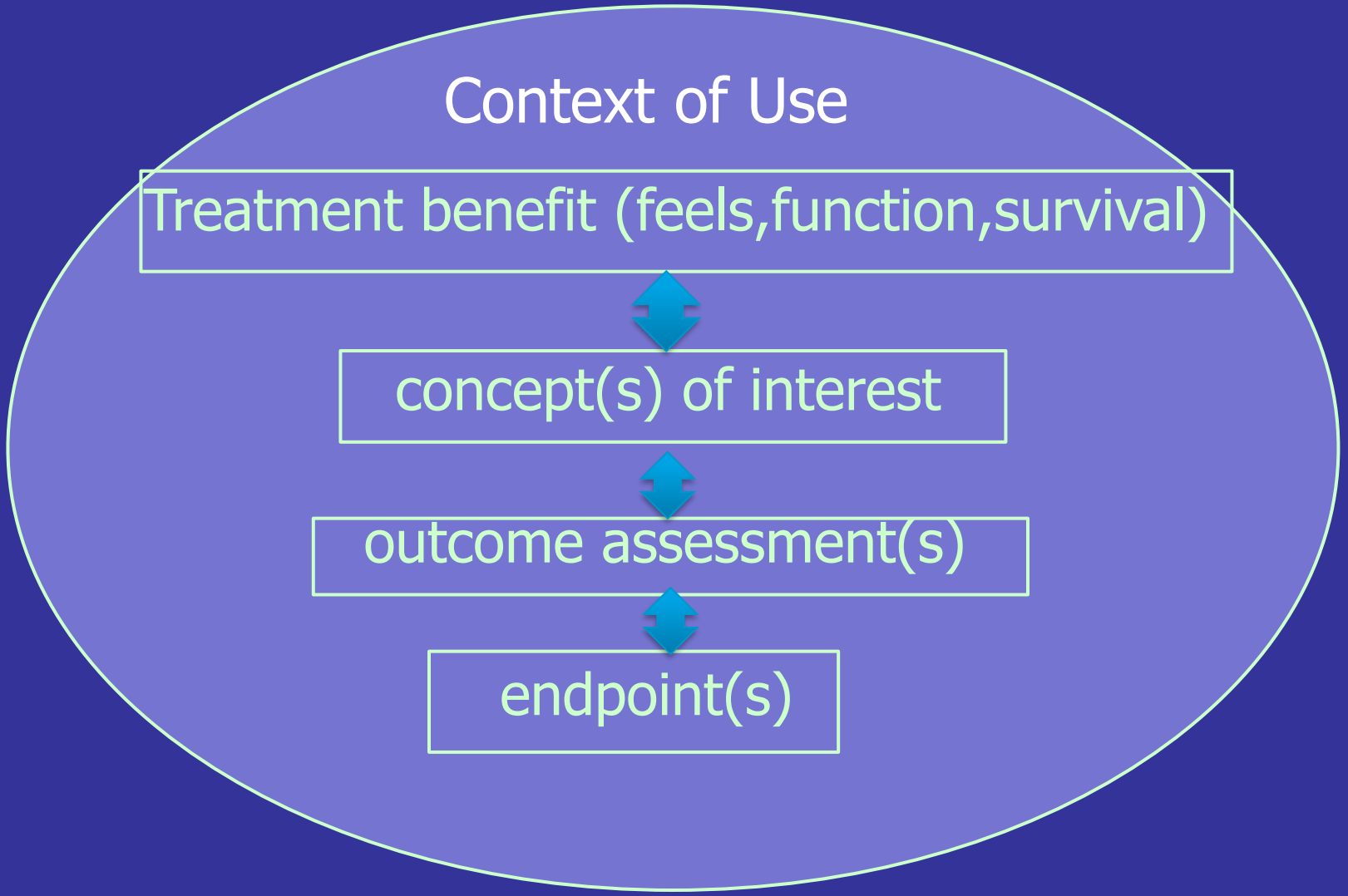
  --for example, best practices in peer-reviewed literature

  --scientific evidence for best practices
- Develop study aims and approaches

  --matching approach to the aims

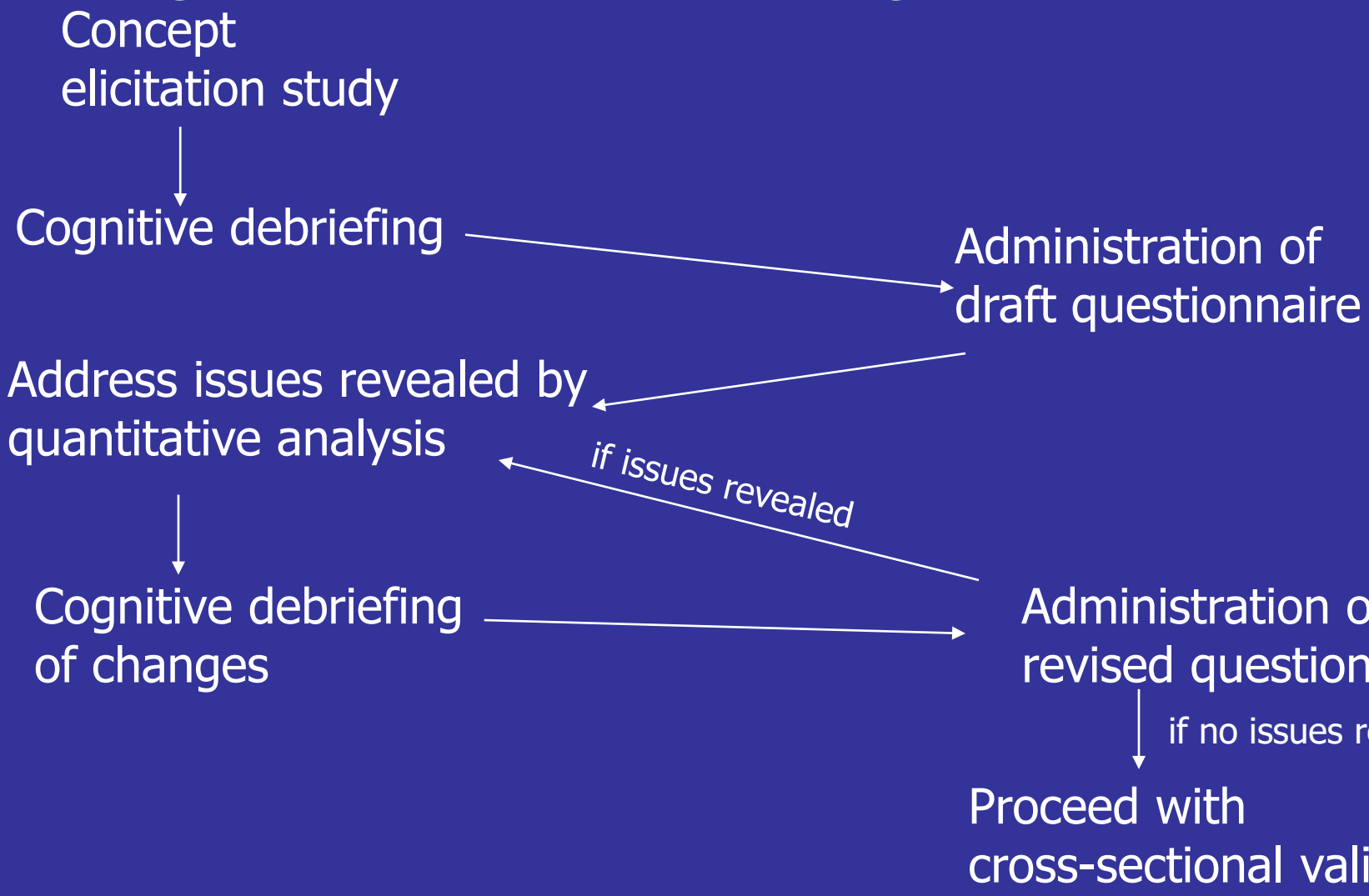
  --right combination and timing of qualitative and quantitative
- Power studies to find no differences

Overall Approach



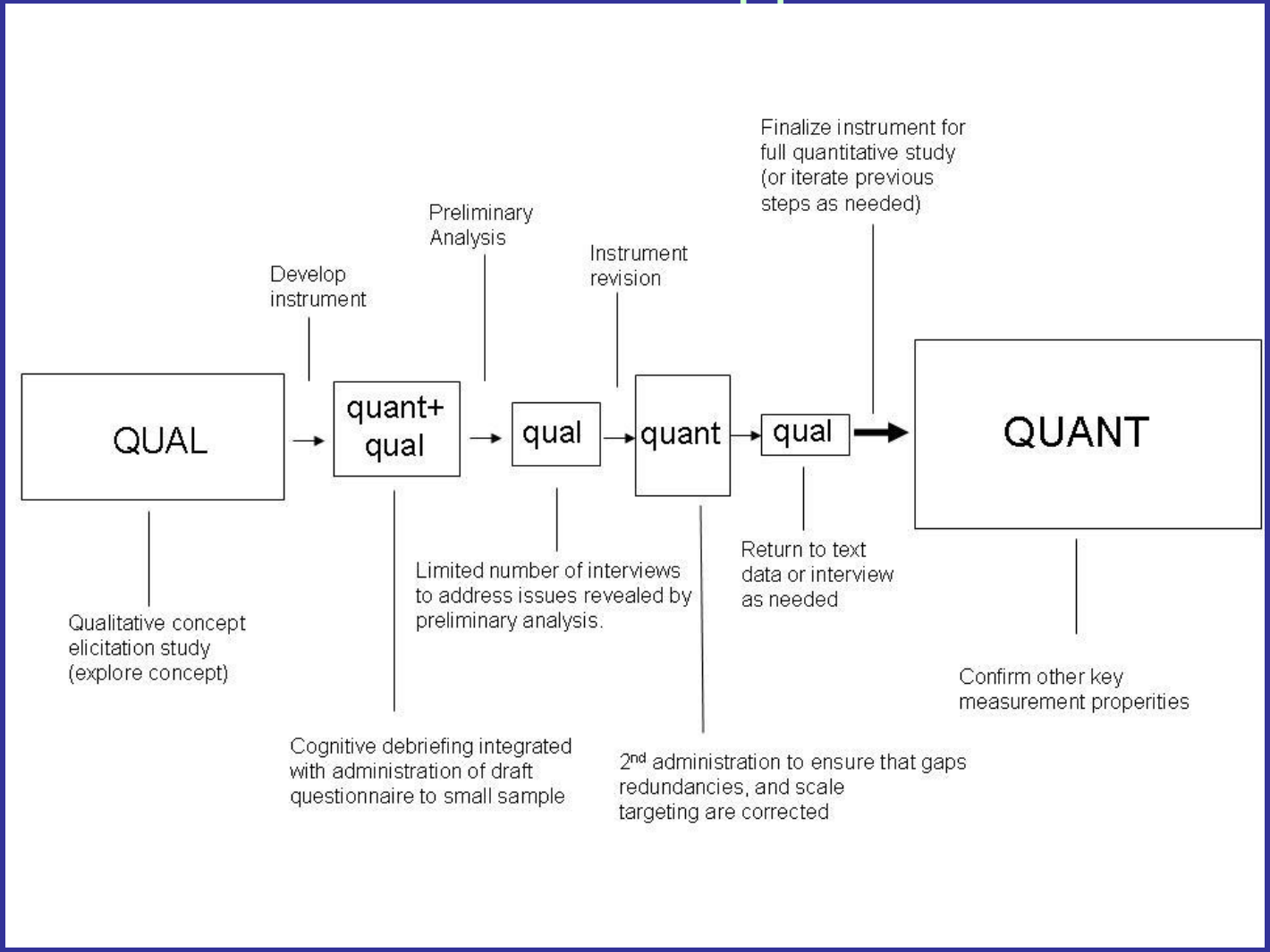
Mixed Methods to Document Content Validity

Qualitative----------Quantitative



Mixed Methods in Qualitative and Quantitative Research:

An Iterative Approach



Benefits of Mixed Methods

- Errors in rating scale content can be detected before full psychometric evaluation
  - Detect ambiguous, poorly worded, or off-concept items
  - Detect gaps in measurement or duplicative items
  - Detect incomplete range in the context of use
- Expensive psychometric studies, even if well-planned and hypothesis-based, may not detect important content problems
- When content problems are detected too late, instrument revision may no longer be an option
  - Clinical trial results are compromised
  - Patients, caregivers and clinicians do not have the information they need to make optimal treatment decisions

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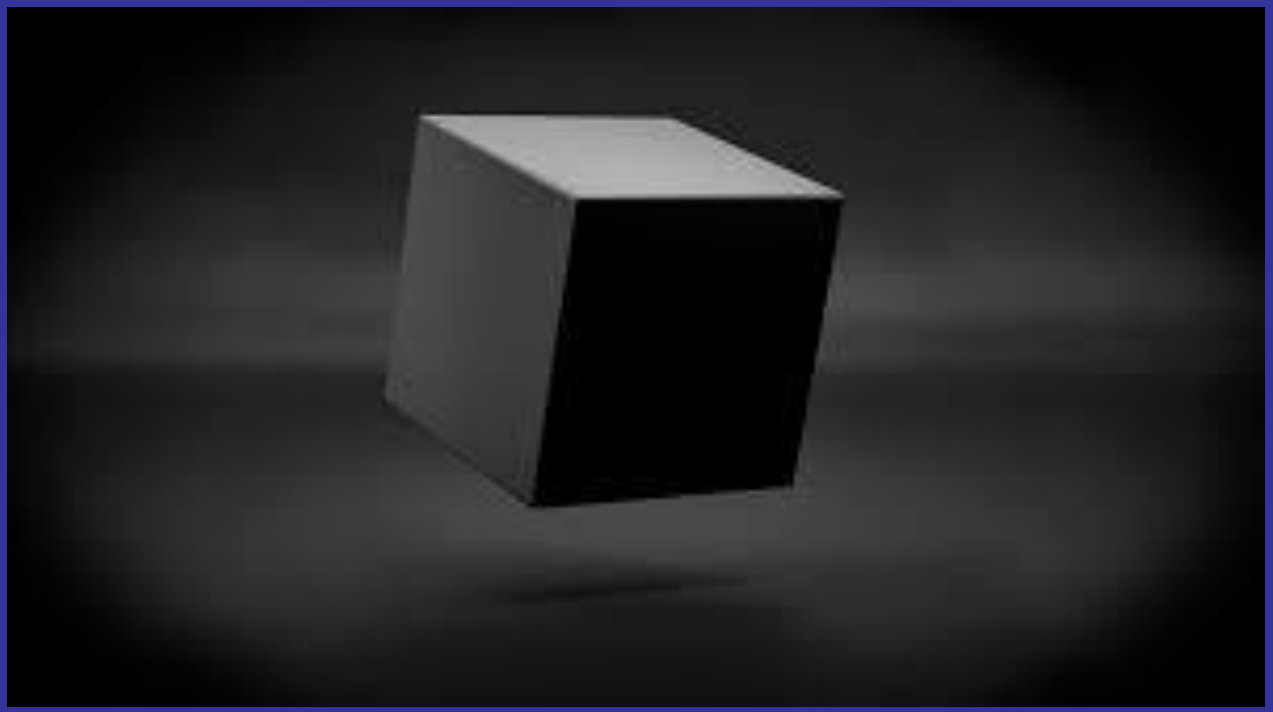
Understanding Smoking and Behavioral Intention



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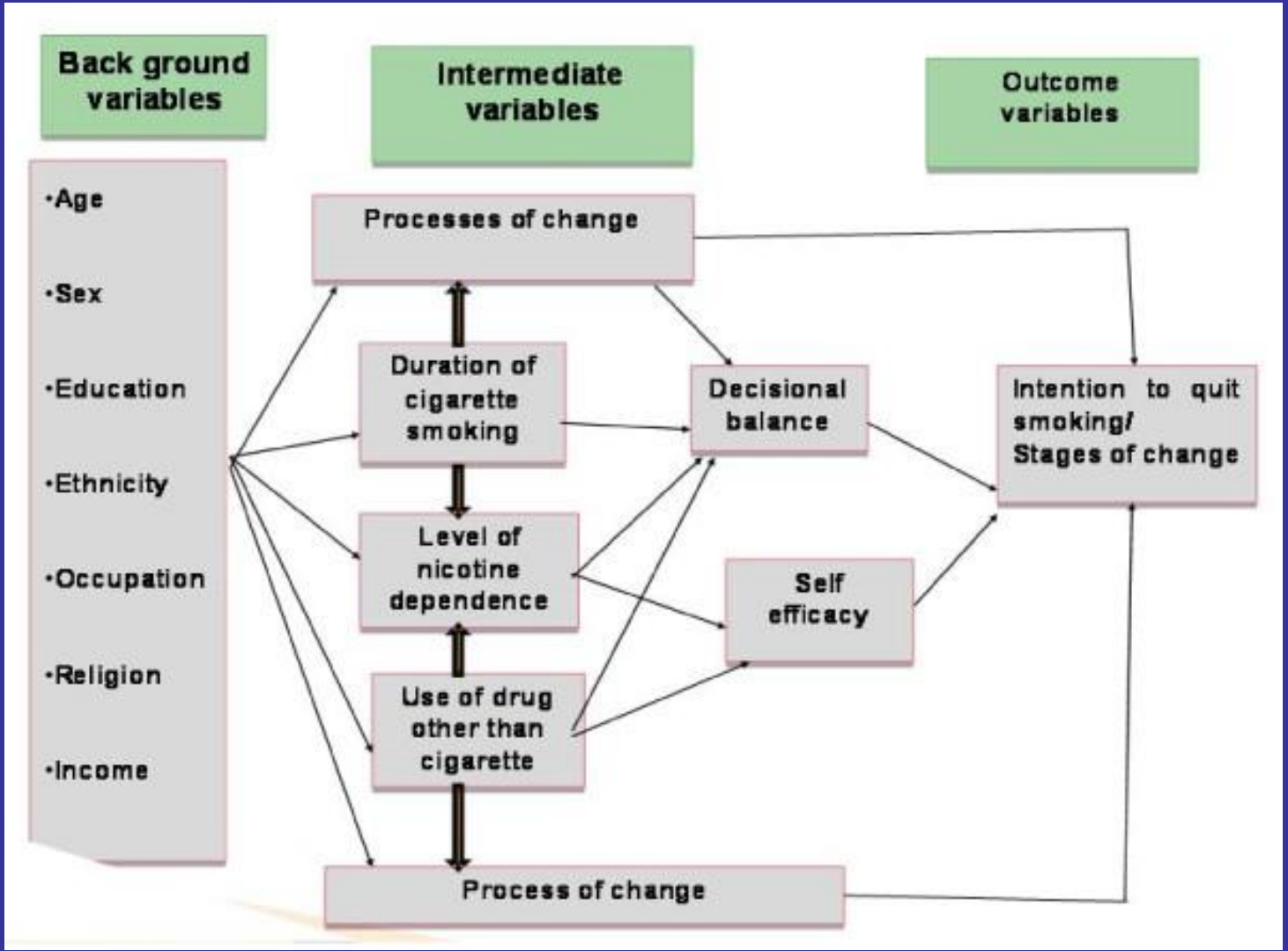
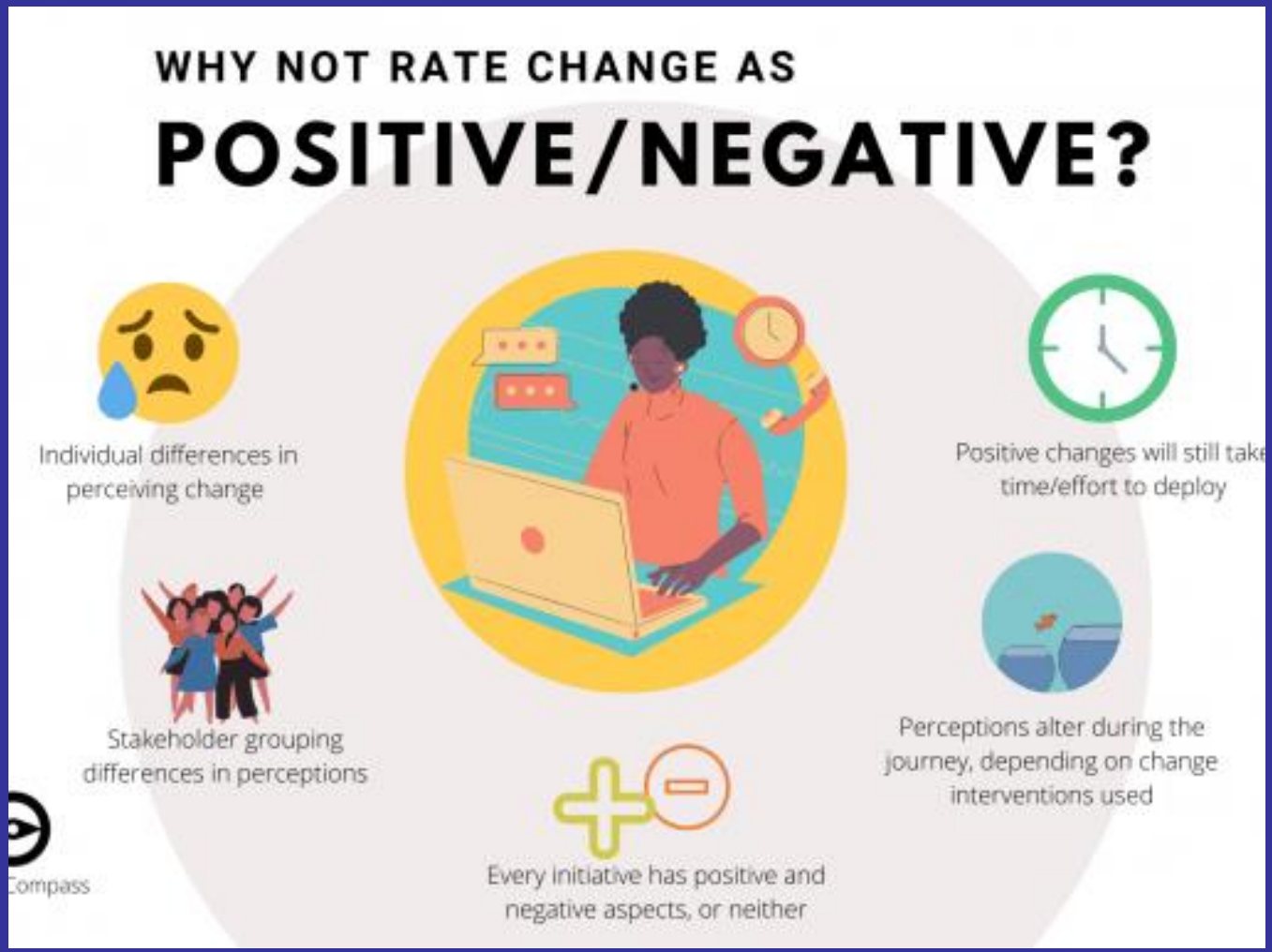
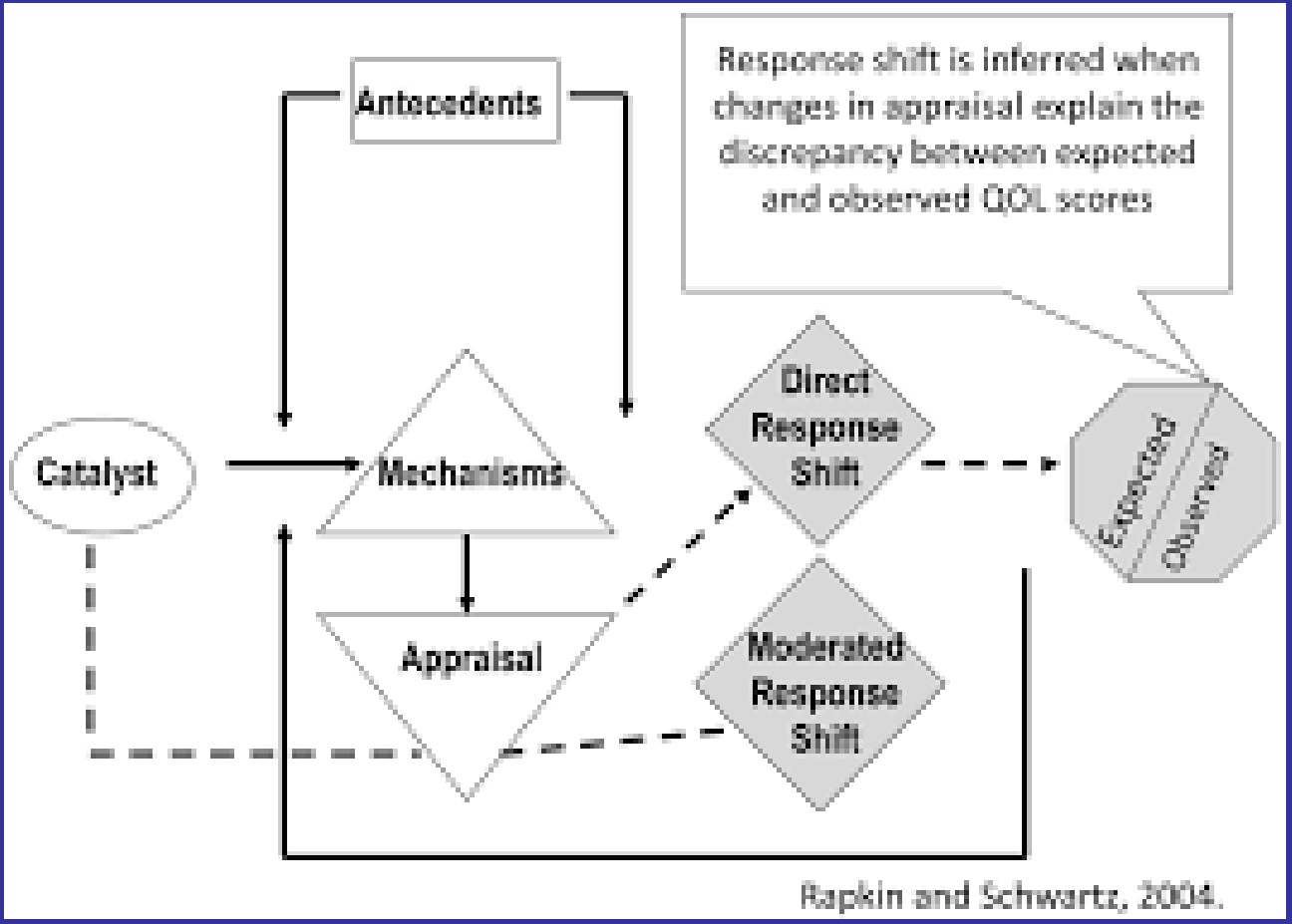


If I perceive a change, is it positive, negative, or neither?



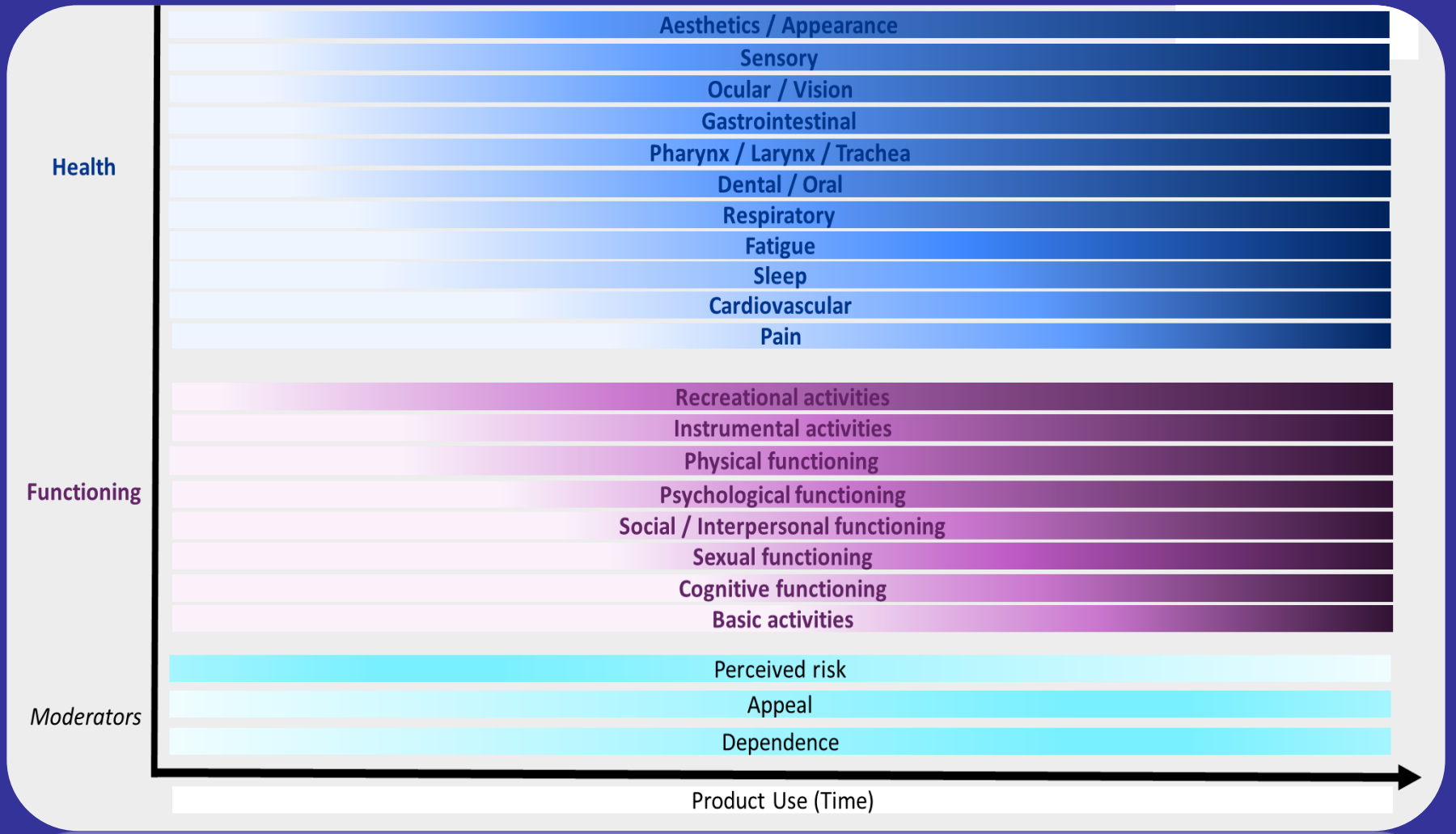
Change in appraisal of smoking perceptions

"*I am used to it...I haven't noticed a change*", may change observed score…called response shift



The HOW of good measurement: Focus on *what* matters to people

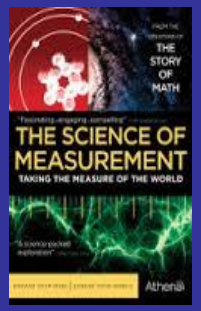
Multiple Concepts and Domains Arise in MRTP Research

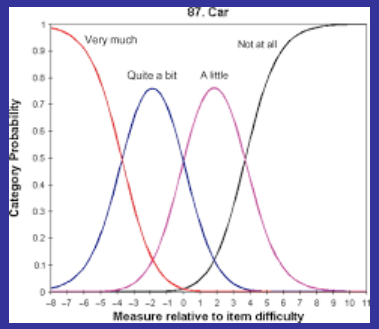


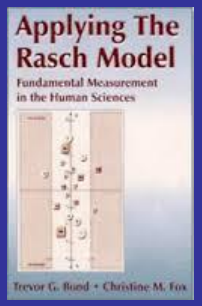
How do we deal with this complexity?

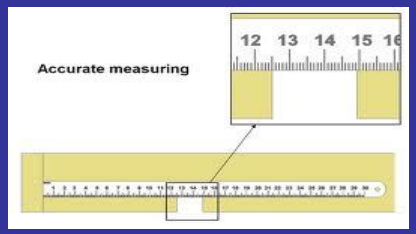
- Focusing on what matters to whom and when
- More attention to importance of content to consumers and experts
- Use of concept mapping, card sorts, mixed methods, and new methods

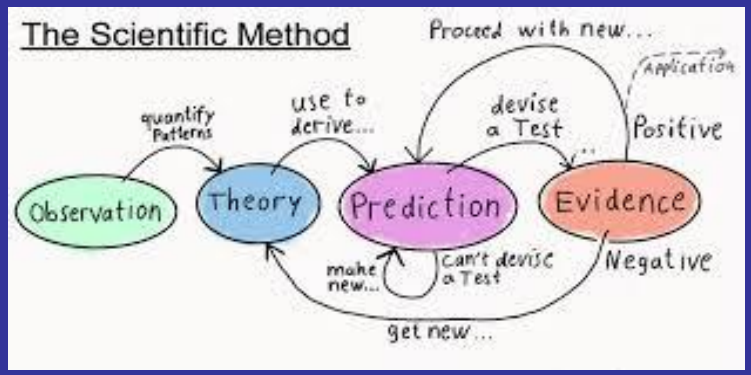
Practicing good measurement science











ISPOR's 11 PRO/COA Good Practices Task Force Reports* - 1

1. Translation and Linguistic Validation of PRO Instruments (2005†; 2009)
2. Measurement Equivalence Between Electronic and Paper-Based PRO Measures (2009)
3. Content Validity in Existing PRO Instruments and Their Modification (2009)
4. Content Validity in Newly Developed PRO Instruments Part 1 – Eliciting Concepts for a New PRO Instrument (2011)
5. Content Validity in Newly-Developed PRO Instruments Part 2 – Assessing Respondent Understanding (2011)
6. ePRO Systems Validation (2013)
7. Assessment of PROs in Children and Adolescents (2013)

**Based on FDA's PRO Guidance for Industry, 2009*

† Landmark methodology report: Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation

ISPOR's 11 PRO/COA Good Practices Task Force Reports - 2

8. Mixed Modes to Collect PRO Data in Clinical Trials (2014)
9. Clinical Outcome Assessments: A Conceptual Foundation (2015)
10. Clinician-Reported Outcomes (ClinROs) Good Measurement Practices (2017)
11. PRO and Observer Reported Outcomes (ObsRO) Assessment in Rare Disease Clinical Trials (2017)

Under development

- Measurement Comparability of PROMs (*in development; 2021; will update #2 & #8 reports*)
- Performance-based Outcomes Assessments – Part 1: Introduction (*in development; 2021*)
- Performance-based Outcomes Assessments – Part 2: Emerging Good Practices (*upcoming*)

Summary of Advances with the PRO Guidance

- Encourages Well-Documented Qualitative studies to ensure content
  - Concept elicitation
  - Cognitive debriefing
- Strong emphasis on the patient perspective (for patient-reported outcome (PRO) instruments)
- Measurement evidence encouraged from different psychometric theories and methods, no specific method emphasized

BUT challenges may include…

- ambiguous meaning from discordant data
- challenges in targeting measures to populations
- difficulties balancing comprehensiveness and parsimony
- Dealing with results that may be method dependent