Estimating the potential effect of modified risk tobacco product use (MRTP) on population mortality: A dynamic population modeler (DPM)

Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

April 17, 2014

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ENVIRON

Model development in the regulatory context

Life cycle of a model

- *Conceptual approach*
- *Development*
- *Validation*
- *Maintenance*

Life cycle of a model – CONCEPTUAL APPROACH

- *Population model*
- *Potential exposure to two products*
- *Approach and results must be easy to communicate to non-statisticians*
- *Relevant to regulatory assessment (FDA requirements for MRTP applications)*
  - *Net effect on population mortality due to beneficial or harmful changes in tobacco use behavior*
  - *Tipping points for beneficial vs. harmful transitions*

Life cycle of a model – DEVELOPMENT

Time variable and transitions

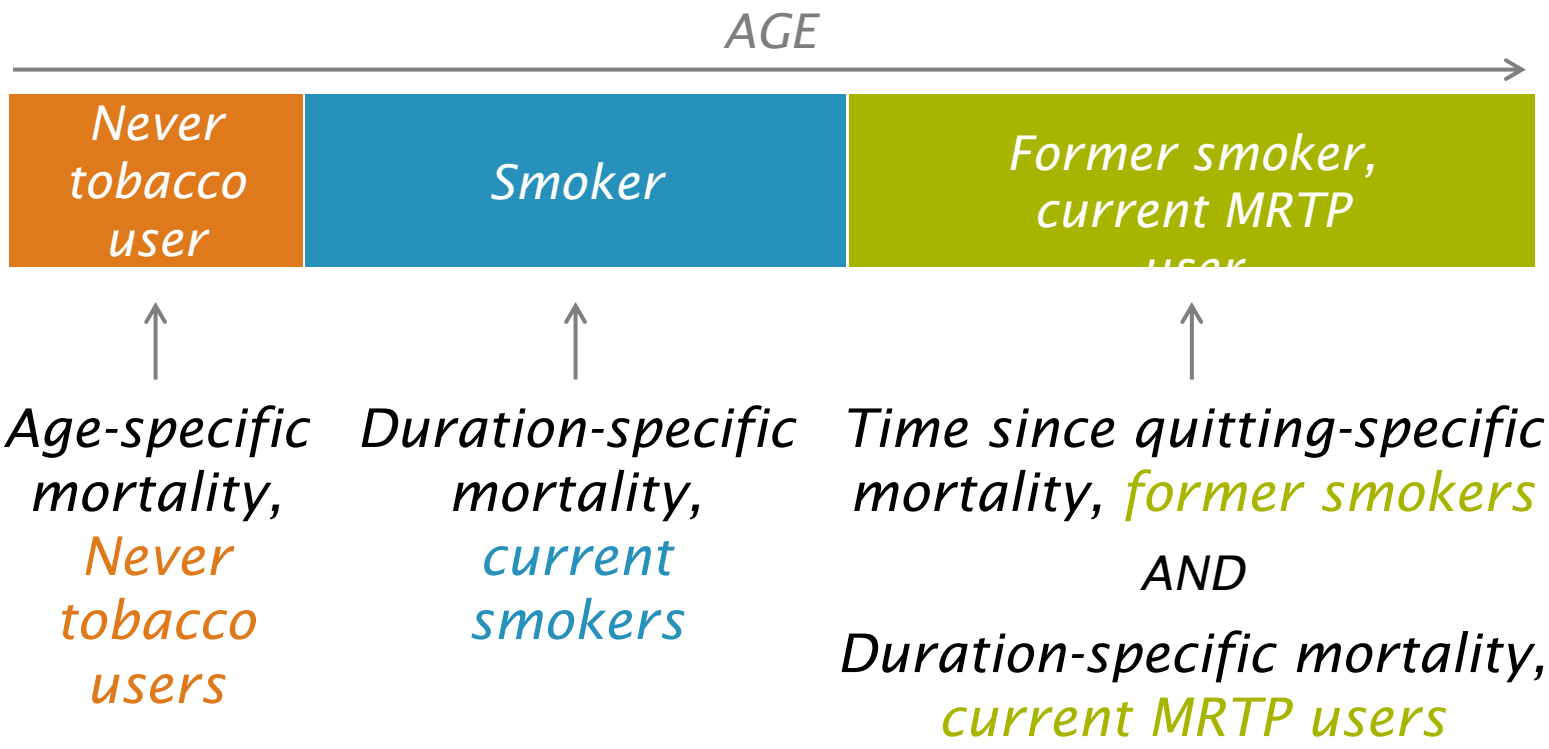
- *DPM follows hypothetical population over time*
  - *Time variable=Age (categorical)*
  - *User specified start/end age and category width*
- *Keeps track of transitions (exposure history)*
  - *Transition = Change from one exposure state to another, e.g., switching from smoking to MRTP*
  - *All commonly observed exposure histories are accommodated; restriction to a subset possible*
  - *User specified transition probabilities*

Life cycle of a model – DEVELOPMENT

Mortality

- *DPM estimates all-cause mortality expected under the modeled exposure histories*
  - *Base case: Cigarettes only*
    - *Embedded Poisson model*
    - *Poisson model input: User specified deaths and person-years by age, years of smoking and years since quitting*
  - *Counterfactual: Cigarettes and MRTP*
    - *For cigarettes: Embedded Poisson model*
    - *For MRTP use: Rates for current (former) smokers reduced by user specified excess relative risk (ERR) for MRTP use vs. smoking*

Example: Mortality rate calculation for smokers who switched to MRTP*



**All mortality rates are age-specific, based on Poisson model, current (former) smoker rates reduced by ERR to obtain current (former) MRTP rates*

Life cycle of a model – DEVELOPMENT

Model type and output

- *DPM is implemented in WinBUGS using Monte Carlo techniques*
- **All model input is specified by the DPM user**
- *Standard age-specific output*
  - *Number of survivors*
  - *Number of person-years*
  - *Probability of surviving to the last age category*
  - *Age-specific difference between counterfactual and base case scenarios*
  - *Estimated variability (for number of survivors and difference between survivors)*

Life cycle of a model – VALIDATION

Sorting process: *Verified using Excel*

Predictive ability: *DPM approximates real population life tables if appropriate input is specified*

- *Base case*
  - *2006 US life table for men*
  - *1980 cigarette smoking initiation and cessation rates*
- *Counterfactual scenario*
  - *2006 Swedish life table for men*
  - *Initiation and cessation of cigarettes and snus based on exposure patterns in Sweden*
- *Age-specific estimates of survivors are within ±0.5% of population values*

Life cycle of a model – MAINTENANCE

- *Internet-based platform for the DPM has been developed and is maintained by ENVIRON*

Model development in the regulatory context

Information available to stakeholders

- *Conceptual approach, strengths, limitations*
- *Source, quality, uncertainty of input*

Information available to stakeholders – APPROACH, STRENGTHS, LIMITATIONS

- *Original DPM*
  - *Published; Bachand & Sulsky, 2013, Regul Toxicol Pharmacol, 67, 246-251*
  - *Detailed documentation available to FDA*
- *Expanded versions of DPM*
  - *Manuscripts in preparation*
  - *Detailed documentation available to FDA*

Information available to stakeholders – SOURCE, QUALITY, UNCERTAINTY OF INPUT

DPM use

- *ALL INPUT INTO THE DPM IS USER-SPECIFIED*
- *Therefore, the user determines source, quality and uncertainty of the input*
- *DPM allows user to account for uncertainty in model input and output*

DPM validation

- *Detailed documentation of data sources for model validation available to FDA*

Model development in the regulatory context

Model evaluation

- Access by stakeholders
- Peer review
- Transparency
- Flexibility to incorporate new scientific findings (easy to expand)

Model evaluation – ACCESS BY STAKEHOLDERS

- *User-friendly, internet-based platform automates DPM's functions*
- *Allows FDA/CTP access to and use of the DPM*

Model evaluation – PEER REVIEW

- *Published manuscript in peer reviewed journal*
- *Pre-publication reviews*
- *Presented at several national epidemiology meetings*
- *Presented at FDA CTP "listening session"*
- *Presented at FDA sponsored panel session at the Joint Statistical Meetings in August 2013 (Dynamic Modeling in Tobacco Control Policy)*
- *Presented at FDA CTP public workshop on statistical models in December 2013*
- *Additional documentation available to FDA*

Model evaluation – TRANSPARENCY

- *All input into the DPM is user-specified*
- *User-friendly internet-based platform enables FDA/CTP access to and use of the DPM*
- *Examples can be recreated*
- *New examples can be tested*

Model evaluation – FLEXIBILITY

- *Several versions of the DPM address different aspects of tobacco harm reduction*

	Original DPM	Version 2	Version 3	Version 4
Product added to the market (e.g. MRTP)	√	√	√	
Product removed from the market (e.g. menthol cigs)				√
All-cause mortality	√			√
Cause-specific mortality		√		
*Morbidity**			√	

**Approximated by applying quality of life adjustments to person-years estimated by DPM*

Model evaluation – FLEXIBILITY

- *Additional expansions in progress*

- *DPM allows output of different metrics (survivors, person-years, probability of surviving to last age category)*
- *DPM can easily accommodate new scientific findings, such as may be expected from post-market studies of MRTP users*

Model development in the regulatory context

Extrapolation

- *Caution when extrapolating beyond conditions for which the model was constructed*

Extrapolation – DPM LIMITATIONS

- *DPM*
  - *Employs simplifying assumptions*
- *Input selected by the user*
  - *Limited by the available data*
  - *Precision and validity of outcome estimates depend on certainty and validity of model input*

Model development in the regulatory context

DPM strengths

- *DPM satisfies requirements for model development in the regulatory context*
- *To our knowledge, the DPM is the first and, so far, the only model to directly address specific requirements of the FSPTCA for MRTP applications*

Contact Information

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- *Major support: RAI Services Company (Winston-Salem, NC)*
- *Additional support: Swedish Match (Stockholm, Sweden)*

The dynamic population modeler described here was developed independently of the sponsors.

Thank you

Supplemental Material

DPM validation: 2006 US life table versus model-based estimates

(starting with 1,000,000 13-year old male never tobacco users)

Age category	Survivors based on US life table	Survivors based on base case (US)
38-42	957,654	958,800
43-47	940,866	940,900
48-52	915,745	915,800
53-57	880,470	880,800
58-62	832,268	832,100
63-67	764,922	764,500
68-72	674,217	671,800

DPM validation: 2006 Swedish life table versus model-based estimates

(starting with 1,000,000 13 year old male never tobacco users)

Age category	Survivors based on Swedish life table	Survivors based on exposure scenario (Sweden)
38-42	980,999	980,674
43-47	972,889	971,210
48-52	959,782	957,976
53-57	936,838	935,577
58-62	902,590	900,804
63-67	846,884	844,862
68-72	764,275	759,182

Example - Harmful transition: Base case non-tobacco users initiate MRTP

Smoking initiation: **US, males, 2008**[a]
Smoking cessation: **US, males, 2005-2008**[a]
MRTP initiation: **Among base case non-tobacco users: 5% initiate MRTP in the counterfactual (first 3 age categories only)**
MRTP cessation: **None**

Age: **13-72, 5-year intervals**

Hypothetical population size **= 1,000,000**

DYNAMIC POPULATION MODEL

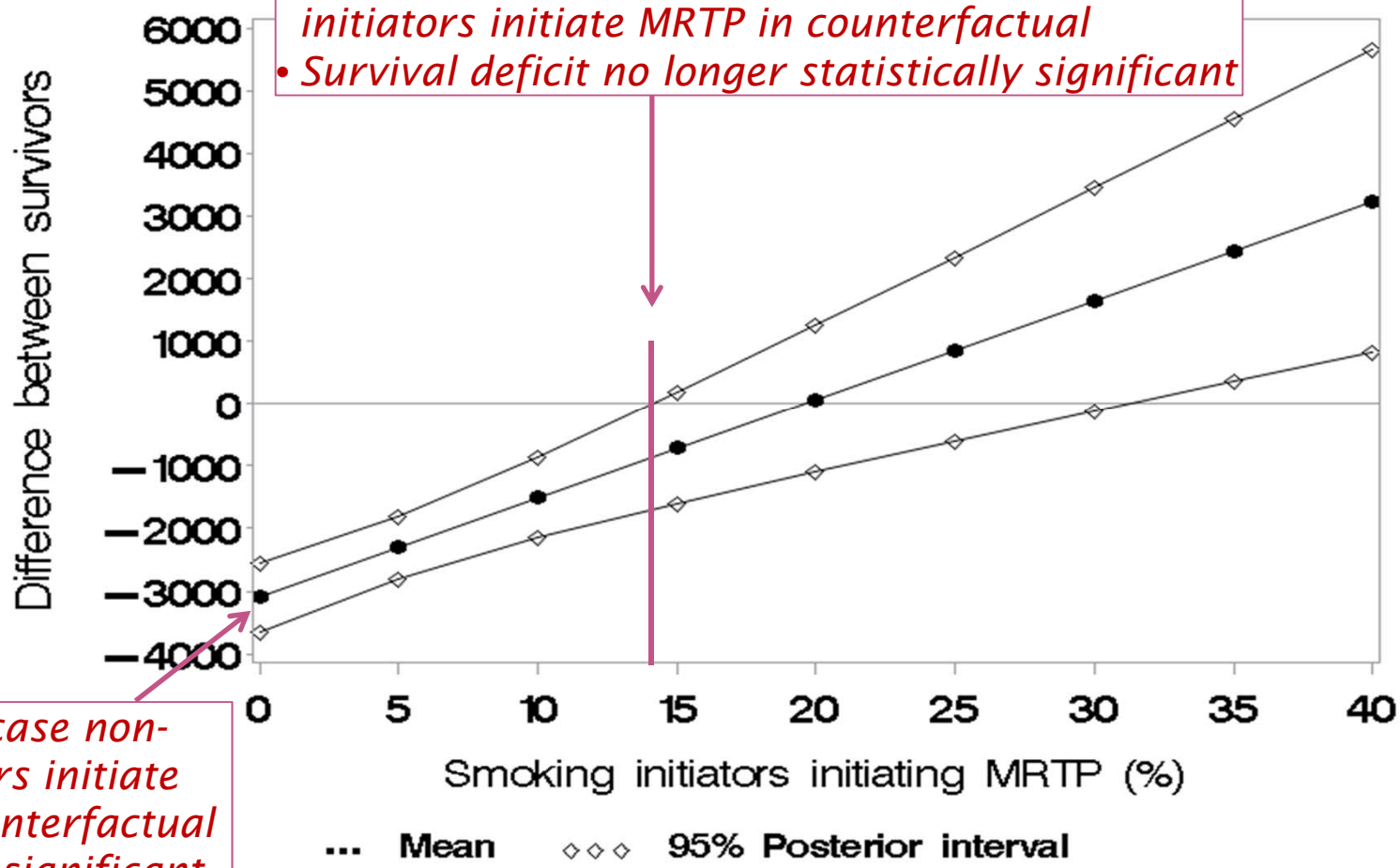
Person-years, deaths by age, years of smoking, quitting (base case): **Based on men in Kaiser Permanente (KP) study**[a]

*ERR=***0.11**[b]

[a] *Including estimated variability*
[b] *Levy et al., 2004*

Example cont. - Adding a beneficial transition: Base case smoking initiators initiate MRTP

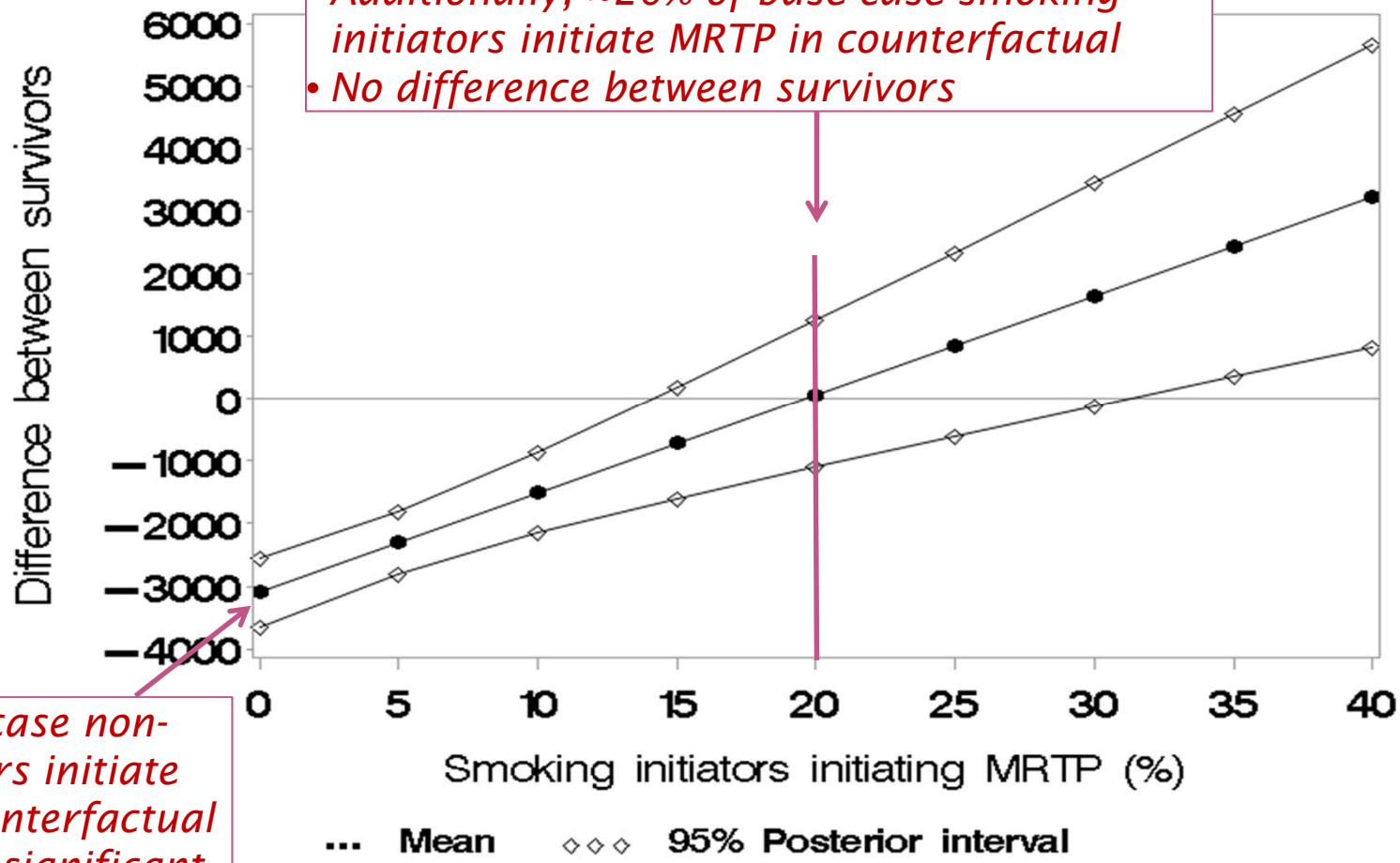
- *Additionally, ≈14% of base case smoking initiators initiate MRTP in counterfactual*
- *Survival deficit no longer statistically significant*



- *5% of base case non-tobacco users initiate MRTP in counterfactual*
- *Statistically significant survival deficit*

Example cont. - Adding a beneficial transition: Base case smoking initiators initiate MRTP

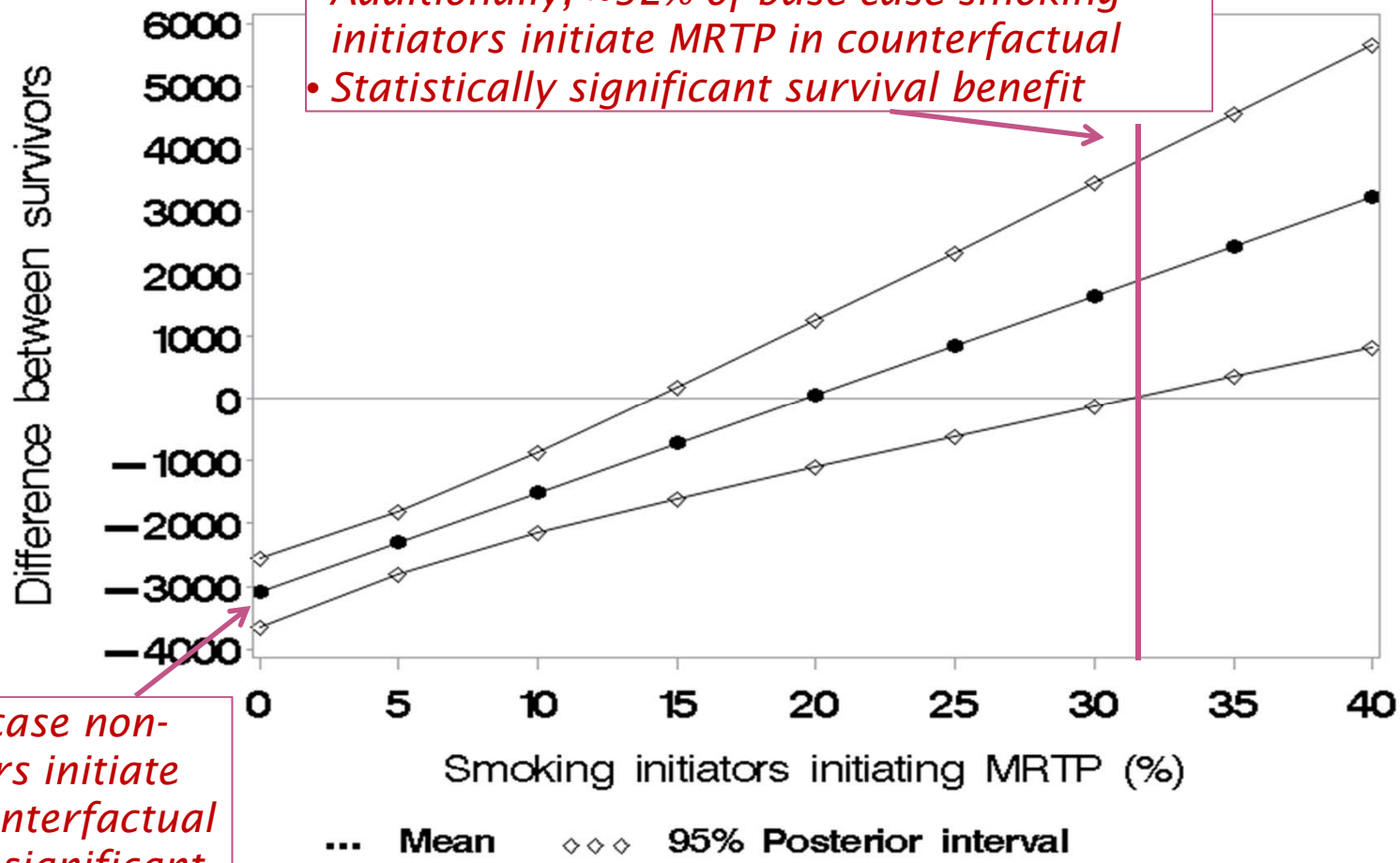
- *Additionally, ≈20% of base case smoking initiators initiate MRTP in counterfactual*
- *No difference between survivors*



- *5% of base case non-tobacco users initiate MRTP in counterfactual*
- *Statistically significant survival deficit*

Example cont. - Adding a beneficial transition: Base case smoking initiators initiate MRTP

- *Additionally, ≈32% of base case smoking initiators initiate MRTP in counterfactual*
- *Statistically significant survival benefit*



- *5% of base case non-tobacco users initiate MRTP in counterfactual*
- *Statistically significant survival deficit*