Rapid Analysis in the Sentinel System to Inform Regulatory Decision-Making

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Disclaimer

- The presenters have no conflict of interest to disclose

- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

Addressing Emerging Safety Issues

When potential safety issues emerge, the FDA

- Evaluates all available evidence
- May request additional information
- **May engage in scientific efforts to gather additional information**
- Engages in comprehensive discussions within the Agency (e.g. input from regulatory/scientific advisory bodies)
- May request external advice (e.g. Advisory Committee meetings)

Some situations may call for rapid action

- Serious risk identified / potential changes to benefit-risk balance
- Identification of population(s) at higher risk for targeted risk minimization/mitigation
- Management of public health emergencies

FDA Tools

- Public Communications
  - Drug Safety Communications (DSCs)
    - New or updated information on potential or actual changes to products benefit / risk profile
    - Includes *emerging DSCs*
  - Safety Labeling Changes / FDA approved prescribing information
- Addition/modification/removal REMS
- Initiation/release of post-marketing requirements
- Change in approved indications or dosages
- Marketing withdrawal

When Decisions Can't Wait? A Look at Urgency Part 1

Is there an immediate danger of irreversible harm?

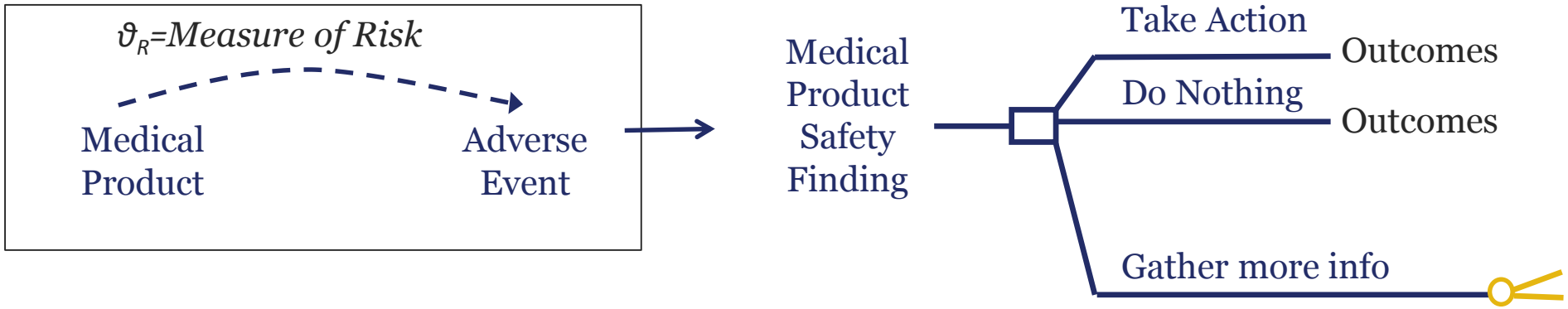

To Your Health

Pregnant women took generic Viagra in a clinical drug trial. Eleven babies died.

- FDA response: conducted rapid assessment in Sentinel to evaluate nature and extent of exposure among pregnant women in real-world settings in the U.S.

https://www.sentinelinitiative.org/drugs/assessments/phosphodiesterase-type-5-pde5-inhibitor-utilization-among-women

Regulatory Decision-Making: How to Manage and Message Uncertainty



FDA Sentinel utilization study: Dispensing of in-utero PDE5 inhibitor occurred in 96 of 3.3M pregnancies resulting in live birth. By trimester, the exposure prevalence was 2.61, 0.62, and 0.62 per 100,000 live-birth pregnancies.

- No regulatory action warranted at this time given reassuring level of exposure among pregnant women in the U.S.

https://www.sentinelinitiative.org/drugs/assessments/phosphodiesterase-type-5-pde5-inhibitor-utilization-among-women

When Decisions Can't Wait? A Look at Urgency Part 2

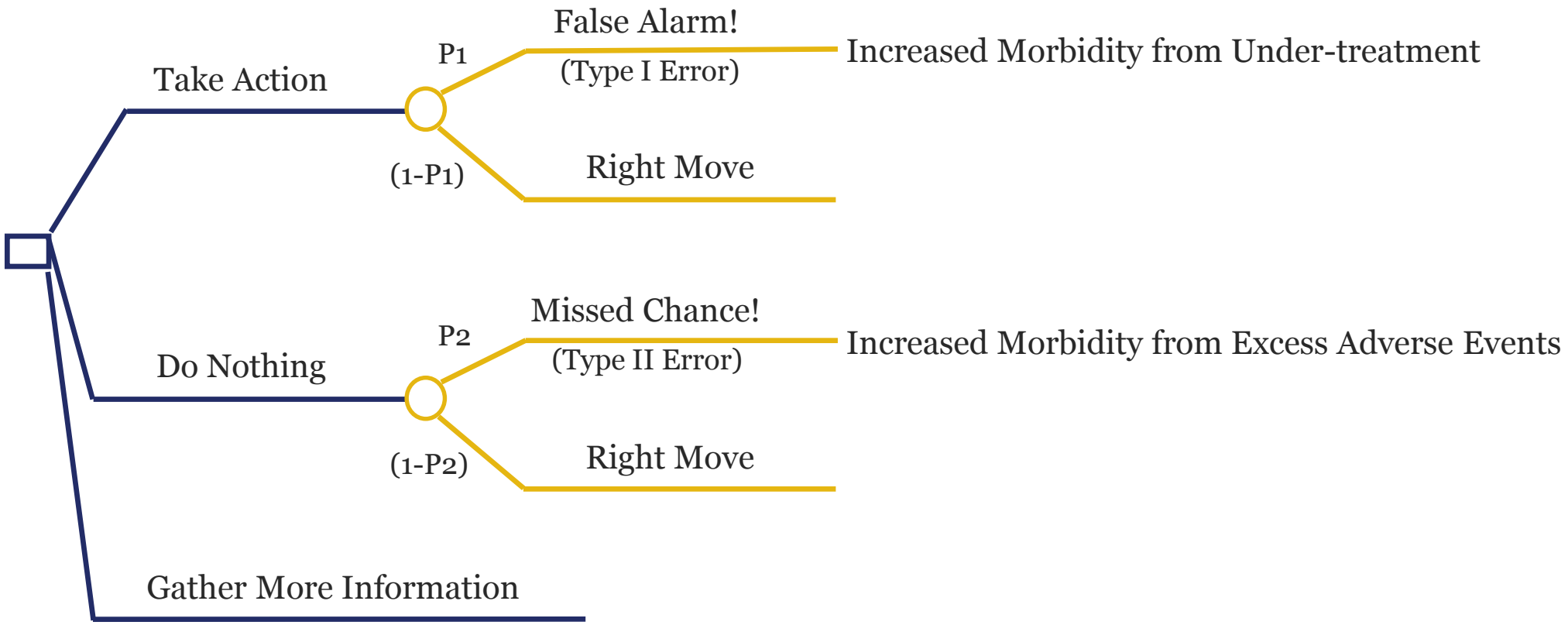
Is there a less immediate danger but a substantial public health burden?

More Blood Pressure Medication Voluntary Recalls due to Cancer Concerns

- FDA response: evaluated dispensings of medications in the U.S. potentially contaminated with N-nitrosamine impurities
  - N-nitrosamine compounds are potent genotoxic agents in several animal species; several are classified as probable human carcinogens by IARC*
  - Examples of N-nitrosamine compounds include N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA). NDEA is considered to be potentially more carcinogenic than NDMA

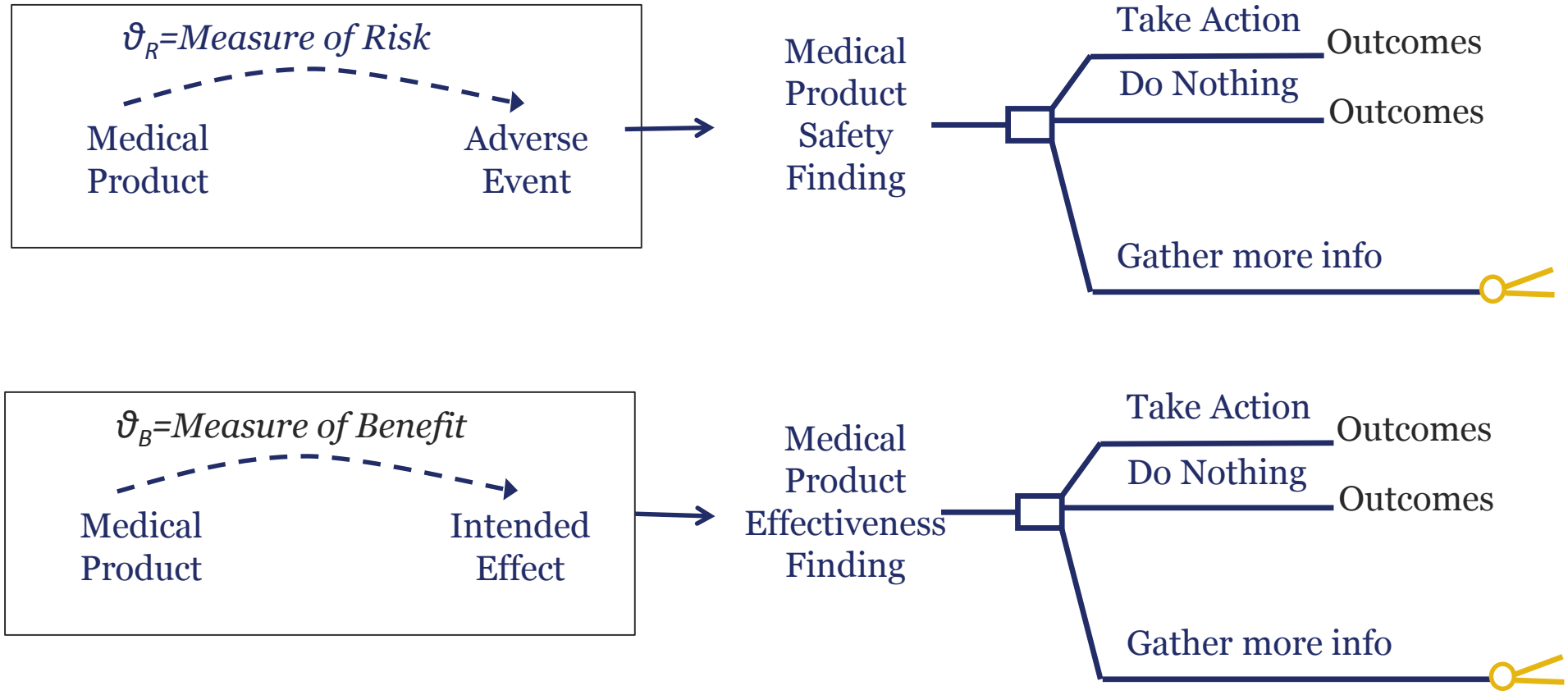
IARC = International Agency for Research on Cancer
https://www.sentinelinitiative.org/assessments/drugs/use-valsartan-angiotensin-ii-receptor-blockers-arb-and-angiotensin-converting

Competing Risks: What is the Public Health Cost of Reducing Uncertainty (Waiting for Better/More Data)?



BUT…the outcomes depend on unknown θ_R (…and θ_B) and availability of alternative treatments

Regulatory Decision-Making: How to Manage and Message Uncertainty



When Decisions Can't Wait? A Look at Urgency Part 2

Is there a less immediate danger but a substantial public health burden?

FDA Sentinel drug utilization study findings:

- Valsartan users: exposure to probably*-contaminated products: 8% (2014), 34% (2016), 25% (2018)
- NDEA-contaminated products accounted for all probably*-contaminated products (2014)
- NDMA-contaminated products accounted for 70% of probably*-contaminated products (2016-2018)

*Exposure identified via NDC but batch /lot information is unavailable.

Actions:

- Coordinated voluntary recall
- Communications – DSCs, updates, press announcements
- Continuing assessments, e.g.; retesting of all valsartan products; multinational study to assess impact of Nitrosamine contamination and ARBs recall

https://www.sentinelinitiative.org/assessments/drugs/use-valsartan-angiotensin-ii-receptor-blockers-arb-and-angiotensin-converting
https://www.sentinelinitiative.org/methods-surveillance-tools/methods/quantitative-assessment-impact-nitrosamine-contamination
https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

A Look at Types of Uncertainty

- Design / Model Uncertainty – Did I pick the right **design** to represent my study question and make appropriate adjustments to produce an unbiased effect estimate?
- Parametric Uncertainty – Did I choose the right study **parameters** to best represent my design concepts (e.g. new user design)?
- Measurement Uncertainty - If the secondary-use electronic health data I have is an approximation of the clinical experience, did I appropriately choose **electronic codes** to reflect that experience?
- Stochastic Uncertainty – Since I can't measure everyone, did I **power** my study so as to obtain an appropriately representative sample of the population?

These uncertainties are present in any study, but measurement uncertainty is amplified when you're racing against time to develop evidence…

https://pubmed.ncbi.nlm.nih.gov/22020903/

When Decisions Can't Wait? Part 3: Urgency Re-defined

Sentinel's multi-site datasets are built on a series of rigorous quality checks that must "pass" for data to be declared production-ready

- Not all datasets pass and evaluation of these datasets takes time.

Data are generally "settled" and longitudinally complete to be considered eligible for regulatory decision-making. This also means the data are lagged.

Are there times when the cost of waiting for data to settle is too much?

- Sentinel has used Rapid Data with Influenza Vaccine Safety while working against the clock.
- Monitored 8 million doses over 10 week period. Goal was early detection of adverse events expected at 1 event/20,000 doses.
- Large claims databases were more lagged but provided the required power for detection. In this analysis, size was a more critical factor than data lag timing.

https://pubmed.ncbi.nlm.nih.gov/26572776/

Risks with “Rapid” Data: Strength of Measurement Error?

- Data are not “settled” and typically have varying right censor dates depending on source data update cycles
  - Incomplete picture of clinical experience
    - More pronounced with claims data which typically arrives in multiple streams with different lag points
    - Unadjudicated claims or open claims are subject to revision
    - EHR data is not immune: Post-discharge updates v. within-hospitalization updates
    - “Daily” feeds can capture intermediate variables (e.g., differential diagnosis subject to change)
  - Exposures may be assessed more completely than Outcomes (which may be later arriving)
    - Bias will depend on study design (e.g., active new user cohort v self-controlled) and whether or not delays are non-differential
    - There are some analytic solutions for partially-elapsed data capture but they do not apply to all designs
  - Trend analyses may be misleading without appropriate data lockpoints

When Decisions Can't Wait? Part 3: Urgency Re-defined

Is there an immediate danger of irreversible harm AND data are still accruing such that there is a greater risk of getting it wrong?

- Unknown pathophysiology and impact of COVID-19

- Examples of current COVID-19 related work
  - Near real time drug utilization to help inform potential shortages in critical drugs
    - Exploring capabilities of inpatient data capture for various data systems
    - Sentinel data as part of a mosaic approach evaluating data at different ends of supply chain
  - Natural History of disease with a focus on coagulopathy
    - Focus on inpatient data, monitoring ~60,000 COVID hospitalizations weekly

https://www.sentinelinitiative.org/assessments/fda-sentinel-systems-coronavirus-covid-19-activities

Data will never be Perfect, How can we assure they meet Minimum Standards (i.e., are Fit for Purpose)?

- Set and adhere to minimum data standards for any study question
- Use the best available data to suit the question and consider secondary v. primary data collection. Understand what data curation / quality control has been implemented.
- Understand measurement error: what is being measured, on whom, and with what delay?
  - Incomplete capture is more likely in secondary use data in an emergency setting
  - Selection bias is more likely in an emergency setting. Who is getting treated?
  - Missingness due to right censoring matters. Consider data lockpoints carefully.
- Resist the urge to answer every question with the same data source. Longitudinal research questions require longitudinal data sources.

Managing and Messaging Uncertainty in Rapid Decisions

When there is a need for urgency in decision-making, we should always strive to move swiftly but deliberately to maximize public health outcomes under the best available information.

But in a world of imperfect, late-breaking information, we should emphasize **transparency** in data choices, study design choices, and be clear about uncertainty and limitations.