The Value of Bayesian Approaches in the Regulatory Setting: Lessons from the Past and Perspectives for the Future

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Disclaimer

This talk reflects my views and represent my own best judgement. These comments do not bind or obligate FDA

Outline

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I. Past Experience
Bayesian clinical trials for the regulation of medical devices

I.1. Initial Idea - 1998
Why Bayesian methods to regulate medical devices?

- Mechanism of action is often physical, not pharmacokinetic; localized effects rather than systemic
- Medical device companies conduct pre-clinical animal studies and bench testing
- There is often information available on trials overseas
- Available prior information on similar devices (previous generations)
- If you modify a device slightly, the behavior may be very similar (but you still need to notify the FDA)
- In contrast, if you modify a drug formulation slightly, the safety and efficacy may not be well understood
- Availability of historical controls for borrowing strength

Why 1998?

- Computational feasibility (simulations, MCMC)
- Philosophical debate shift: subjectivity/objectivity
- Least burdensome provision in the regs (1997)
- Expected payoff: smaller (shorter) trials

HIMA/FDA Workshop – November 1998
"Bayesian Methods in Medical Devices Clinical Trials"

- Health Industry Manufacturers Association (today's AdvaMed)
- Presentations by Don Berry, Bill Strawderman, Mike Escobar (academia)
- Case Studies: Medtronic, Becton-Dickinson, Cyberonics, Guidant (industry)
- Discussions by G. Campbell, T. Irony, G. Pennello, (government)
- Over 200 in attendance

First Bayesian Approvals

TransScan T-2000 Multi-frequency Impedance Breast Scanner

- Adjunct to mammography for women with BIRADS 3 or 4
- Approved April 16, 1999
- Strength borrowed from two other studies
- Bayesian multinomial logistic hierarchical model
- “Model predicts a substantial reduction in total number of false-negative biopsies, while increasing the net number of cancers detected.”

  www.fda.gov/cdrh/pdf/p970033b.pdf

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INTERFIX Intervertebral Body Fusion Device

(for Degenerative Disk Disease)

- Bayesian interim analysis
- Non-informative prior
- Predictive distribution to stop the trial early
- Exchangeability assumption
- 1st Bayesian Label

  www.fda.gov/cdrh/pdf/p970015b.pdf

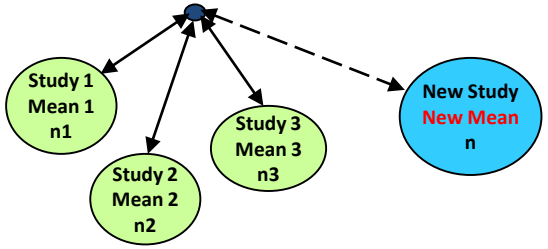
I. 2. The use of prior information

- It can increase the efficiency of clinical trials
- It can reduce the size and duration of trial: same decision reached faster
- Sources:
  - ✓ clinical trials conducted overseas
  - ✓ sponsor's own previous studies
  - ✓ legally available data on same or similar products
  - ✓ data registries
  - ✓ pilot (feasibility) studies
  - ✓ prior information on control groups
  - ✓ adult prior information extrapolated for pediatric population

Possibilities

- Controls borrowing from Historical Controls
- New Device borrowing from Similar Devices
- Multi-center trials: borrowing strength across different centers (a major issue in medical device trials due to variation among centers - physicians)

Bayesian Hierarchical Models



Borrowing ↑ as Variability among studies ↓

New study sample size ↑ as Borrowing ↓

Patients are not exchangeable across studies

Studies are exchangeable

Regulatory Perspective

- Agreement to be reached in advance between sponsor and FDA (exchangeability; suitability of the prior)
- Desire to control type I error (significance level $\alpha = 5\%$)
- No subjective prior (expert opinion)
- Caution with advisory panel meetings: could disagree
- Clinical reviewers need to agree with exchangeability assumption

Priors might be too informative: Remedies

- discount the prior distribution in some way
- increase the stringency of the success criterion
- increase the sample size of the pivotal trial
- Bayesian hierarchical models

Regulatory Perspective

- Problematic to control type I error rates at traditional α values: 5% or 2.5%
  - ✓ Tradition needs to be relaxed (increase α); otherwise all prior information is discounted ➔ no gains
- Arbitrarily redefine new levels of α :
  - ✓ Discount prior
  - ✓ Power priors with arbitrary discount parameters
  - ✓ Arbitrary effective sample size (try elicitation from clinicians)
  - ✓ Hierarchical models with arbitrary hyper parameters
- Priors may have more patients than current trial: arbitrarily discount prior distribution (50% ?)

Regulatory Perspective

- Problematic to use hierarchical models with only one prior study (can't estimate the variability among studies)
- Clinicians: often unsure about exchangeability assumption
- Subjectivity
  - ✓ How to choose the prior? Whose prior?
  - ✓ Selection bias: unfavorable prior information may have been omitted or selected (control group)
  - ✓ Will future regulators or advisory panel members agree with current regulators?
- Legal: prior information may not be legally available

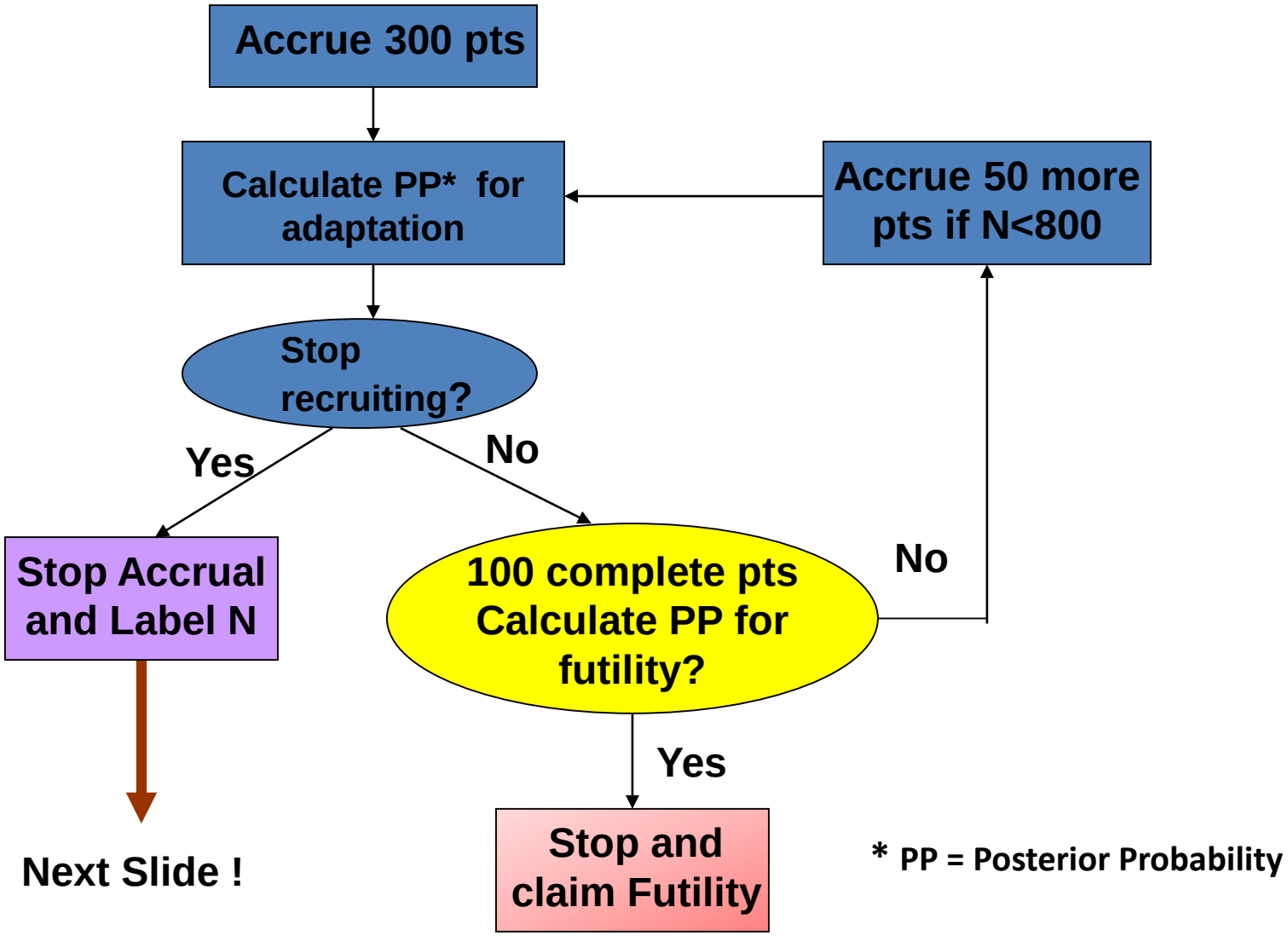
I. 3. Bayesian Adaptive Designs

- Inherent to the Bayesian approach (Likelihood Principle)
- Can reduce the size (length) of a trial ➔ faster decision
- Can increase the size (length) of a trial. If it happens, **it is needed**
- Interim analyses for decisions on stopping or continuing **recruiting** based on predictive distributions ➔ sample size decided and optimized during the trial ➔ *"Goldilocks" trials*
- Modeling: results at early follow-up times predict results at the final follow-up. Model refined at interim looks when all follow-up results from patients recruited early are available.
- Adaptive randomization
  - ✓ Probability of assignment to a treatment depends on data obtained thus far
  - ✓ May be ethically appealing: if allocate more patients to the best treatments

Example: Bayesian adaptive design

- Treatment vs. Control: Success or Failure at 24 months
- Follow-up times: 3, 6, 12 and 24 months
- Interim looks
  - For sample size adaptation
  - For effectiveness
  - For futility
- Constant or varying accrual rate
- *Model: earlier visits are used to predict 24-month results of patients that have not yet reached the 24-month follow-up*
- Assumes exchangeability among patients recruited early and later in the trial

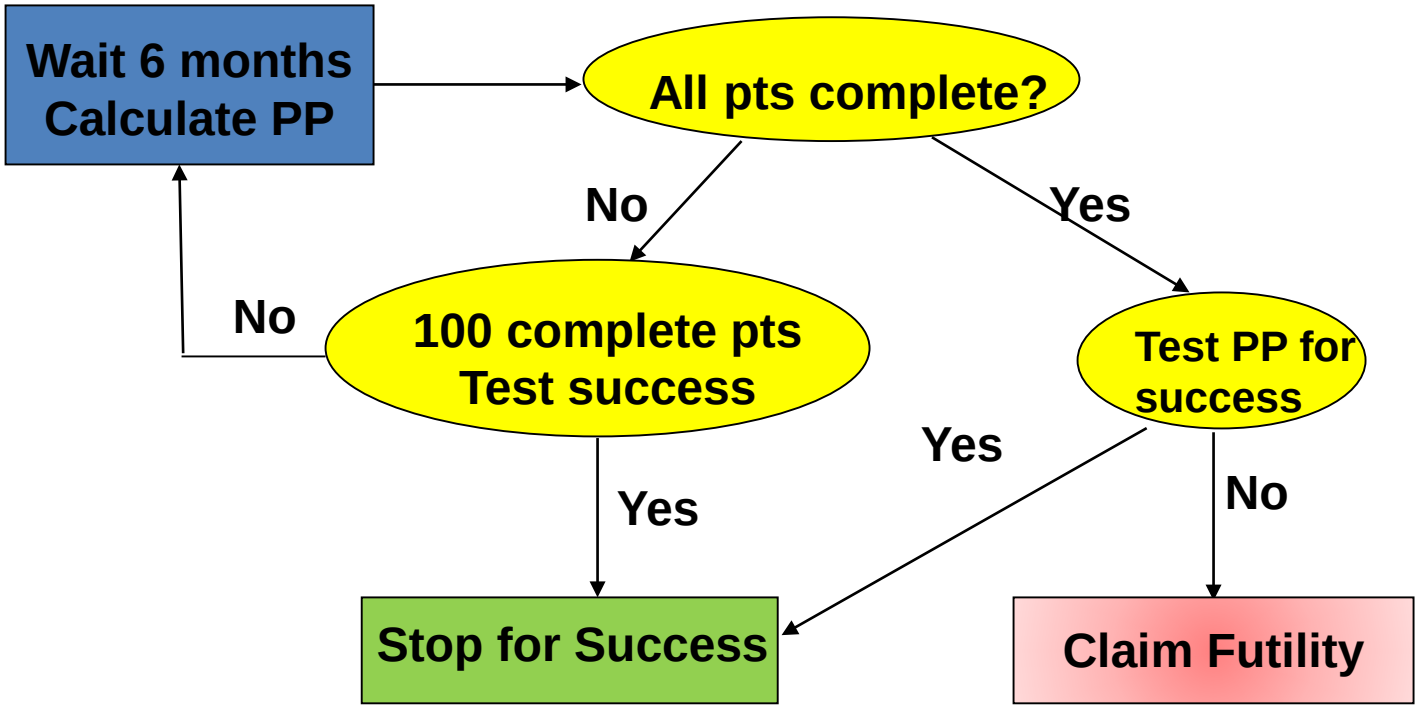
Interim Looks for Sample Size Adaptation



Interim looks for Effectiveness

N is now fixed

Four interim looks at 6, 12 and 18 months



Regulatory Perspective

- Increase the probability of trial success (insurance)
- Achieve optimal sample size
- Advantageous when there is no prior information
- Crucial when using prior information (hierarchical model): amount of strength to be borrowed is uncertain ➔ avoid failure for lack of power
- Very advantageous when Bayesian modeling is used to predict an endpoint from earlier follow up visits – savings in sample size

Regulatory Perspective

- Stopping early occurs when surprises arise:
  - Treatment is better (success) or worse (futility) than predicted
  - Sample variability is smaller than predicted
  - Bayesian model makes good predictions (correlation among follow up times is high)
- **Simulations** were used to assess operating characteristics of the trial design - control type I error rates and power (no mathematical formulas for Bayesian adaptive designs)

I. 4. Simulations

Simulate the trial thousands of times making assumptions about the true value of the endpoints and look at the average performance:

How often does it get the right answer?

- Calculate error rates for Bayesian trial designs
- Increase trial predictability and help sponsors prepare and budget for different scenarios and surprises
- Readily understood by clinicians who can observe what will happen under various scenarios
- Provide ability to "look into the future" to avoid "anticipated regret": if the trial were to fail, what would we do differently in retrospect?

"When you do the real trial, it is not the first time you are doing it, it is 1,000,001th!"

Regulatory Perspective

- Simulations are conducted at the design stage
- Devise a comprehensive number of scenarios to generate data (need clinicians input)
- Make assumptions to generate data
- Could assess and control error rates (type I and type II) under "all plausible scenarios and assumptions"
- It may be more difficult for the FDA to review
- It may take more effort to reach agreement with the FDA at the design stage
- Sponsor's documentation including the simulation code is useful to facilitate the review

Simulations are essential to strategize trial design

- Independently of whether the design is Bayesian or not
- Choose design type:
  - ✓ Adaptive or not?
  - ✓ Bayesian or frequentist?
  - ✓ Will prediction be used?
  - ✓ Sophisticated adaptation or just sample size re-estimation?
- Calculate probabilities of success under different scenarios
- Calculate expected trial duration and expected trial cost
- Optimize clinical trial design features

Design features to be optimized

- Stopping rules for success and futility
- Number and timing of interim analyses
- Prior probabilities; hierarchical model parameters; discount factors
- Predictive model
- Minimum sample size (*should also consider safety*)
- Maximum sample size
- Randomization ratio
- Accrual rate (not too fast and not too slow)
- Dose/treatment selection
- Number of centers
- Use of covariates (subgroup analysis)

I.5. Predictive Probabilities

- Probability of future events given observed data
- Probability of results for a future patient in the trial
- Probability of results for missing patients
- Help to decide when to stop a trial
- Help to decide whether to stop or to continue recruiting
- Help physicians and patients make decisions about the use of a treatment (if used in labeling)
- Predict a clinical outcome from a valid surrogate (modeling)
- Adjust trial results for missing data

II. Decision Analysis

Foundations of the Bayesian Approach
Approval of medical products

Learn from evidence about benefits and harms of medical products in the presence of uncertainty to make better decisions

Expected Utility of Decision d_i

$$E[U(d_i)] = \sum_{j=1}^{n} U(d_i, \theta_j) p(\theta_j | x)$$

Optimal Decision: $d_{opt} = arg\ max_{d_i} E[U(d_i)]$

Whose Utility?

- Regulators? FDA Reviewers?
- Society?
- Patients?
- Physicians and caregivers?
- Payers?

II.1. Benefit-Risk determinations for medical products

General Idea

Medical product submitted for approval

Does the benefit outweigh the risk?

Possible decisions

- Approve
- Don’t approve
- Request more information (value of information?)

Points for consideration and discussion

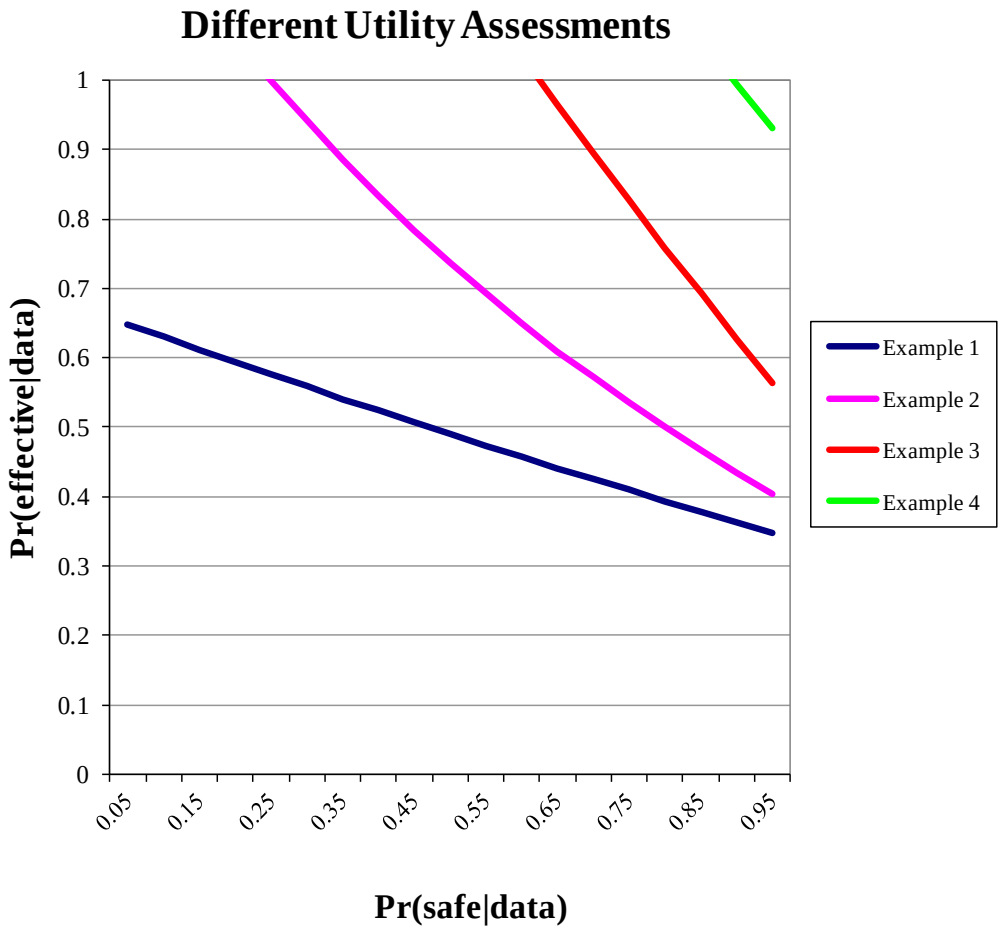
Utility assessment: Benefit-Risk tradeoff

- How to assess utilities to the benefits and risks?
- Who should assess utilities (reviewers, physicians, patients, public)?
- Should a tradeoff between safety and effectiveness be pre-specified?
- How should we assess the value (or cost) of obtaining additional safety and effectiveness information?
- How should we assess the optimal amount of information (time) that warrants action?

Idea
Utility Assessments and Thresholds for Approval

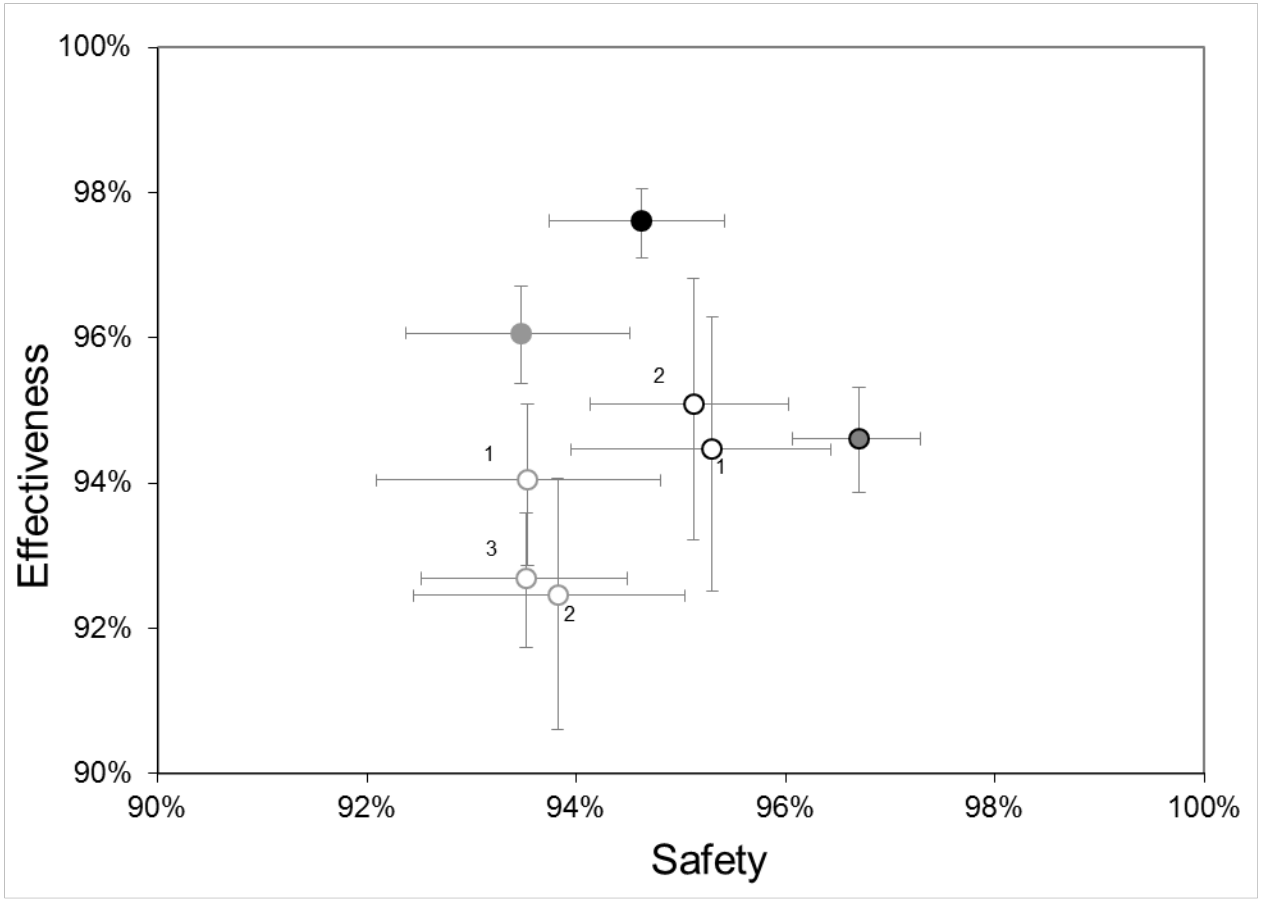
Device treatments

1. Life threatening disease: no alternative is available
2. Life threatening disease: alternative is available
3. Other devices exist but nothing works well (osteoarthritis)
4. Several good alternatives exist (stricter)



Real example: carotid stents

Analysis of Safety and Effectiveness of previously approved carotid stents to retrospectively determine the approval threshold



Factors for Benefit Risk Determination
guidance and article (1)

- Benefits: type, magnitude, probability, duration
- Risks: severities, types, probabilities, duration, risk of false positives and false negatives for diagnostic devices

Additional Factors: Context

- ***Uncertainty***
- Severity and chronicity of the disease
- ***Patient tolerance for risk and perspective on benefit***
- Availability of alternative treatments
- Risk mitigation
- Post-market information
- Novel technology for unmet medical need

II. 2 Uncertainty

- Design, conduct, quality of clinical studies
- Potential biases
- Missing data, data quality
- Quality of analyses; sensitivity analyses
- Subgroup analyses
- Generalization of results – subgroups; small sample size?
- What is the probability that a patient in the intended population will receive the benefits or incur the risks?
- Significance level (?)

Assess the strength of statistical evidence in light of other factors. Would accept more uncertainty if the potential benefit is substantial for an unmet need, if the safety profile is better than existent, if patients would accept more uncertainty,.

II. 3. Patient Input

Patient tolerance for risk and perspective on benefit

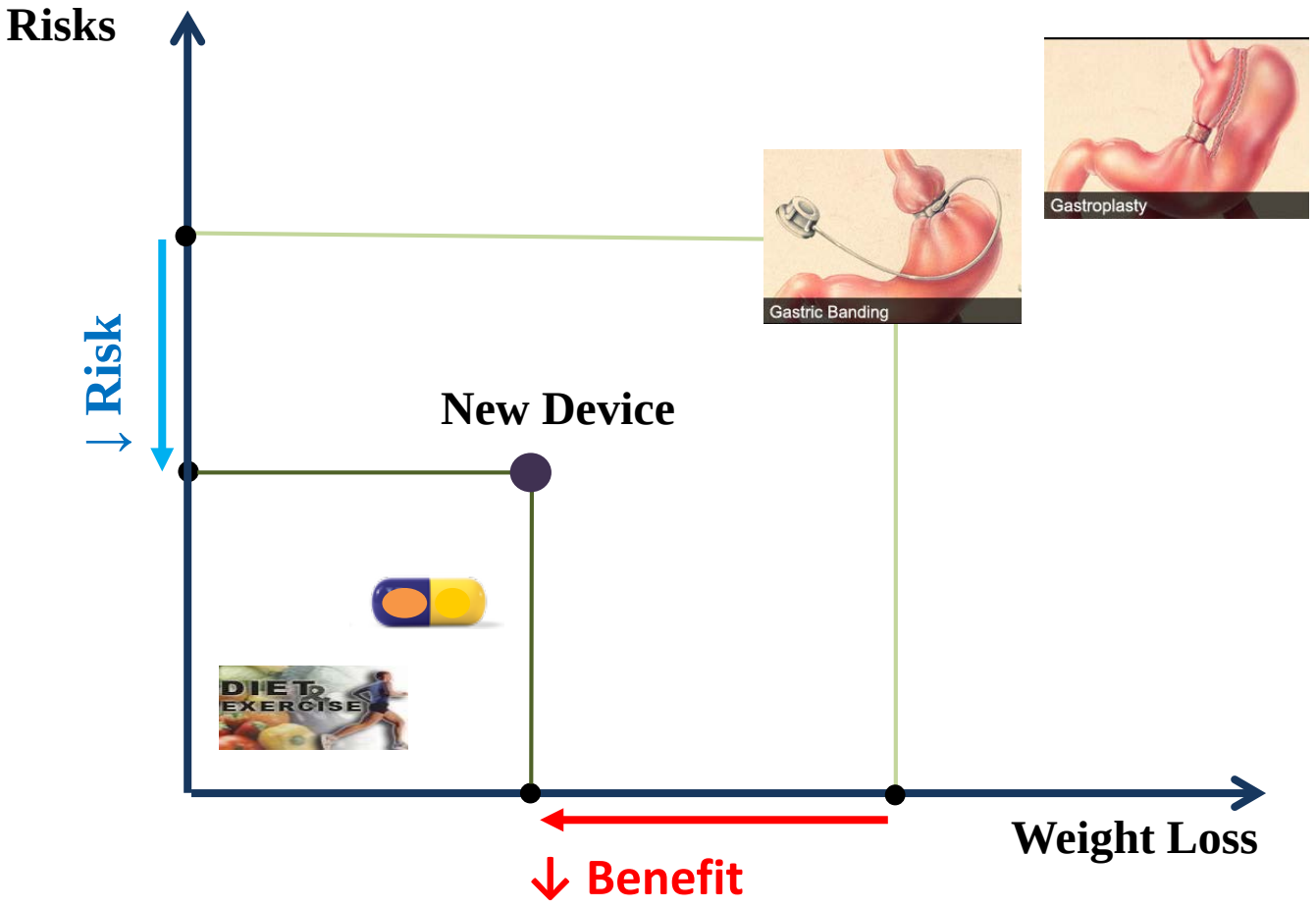
*"Risk tolerance will **vary** among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. … FDA would consider **evidence** relating to patients' perspective of what constitutes a meaningful benefit."* ***(guidance (1))***

The CDRH - CBER Benefit-Risk guidance document for medical devices did not say how to submit Patient Preference Information to the Center

Proof of Concept: Obesity Study

- Explore how to elicit and incorporate patient preferences into regulatory decision making
- Device treatments for obesity involve difficult benefit-risk tradeoffs
- Broad array of devices in the pipeline with diverse benefit-risk profiles
- Assess feasibility of eliciting patient preferences
- Assess the use of quantitative patients preferences
- Patient input had been anecdotal during public hearings
- Explore the use of results in regulatory decision making process

Which is a favorable Benefit-Risk tradeoff?



Obesity Study

- Sample: ~650 subjects with BMI ≥ 30; willing to lose weight
- Administered via the Internet

Discrete-Choice Experiment (DCE)

- Respondents evaluate choices between pairs of hypothetical weight-loss device-treatments
- Each treatment is defined by its attributes and levels (including surgical procedure)
- Only devices; subjects assumed insurance covers all costs
- The pattern of choices reveals the patients' preferences
- Ex: Patients would tolerate 2 more months of mild AEs to lose 25 more pounds

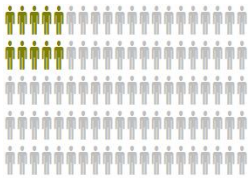
Attributes and Levels: Obesity Study

Attribute	Levels
Type of Operation	Endoscopic Laparoscopic Open Surgery
Diet restrictions	Eat ¼ cup at a time Wait 4 hours between eating Can't eat hard-to-digest foods
Average weight-loss	5% of body weight 10% of body weight 20% of body weight 30% of body weight
How long weight-loss lasts	6 months 1 year 5 years
Comorbidity improvement	None Reduce risk (or current dosage) by half Eliminate risk (or current dosage)

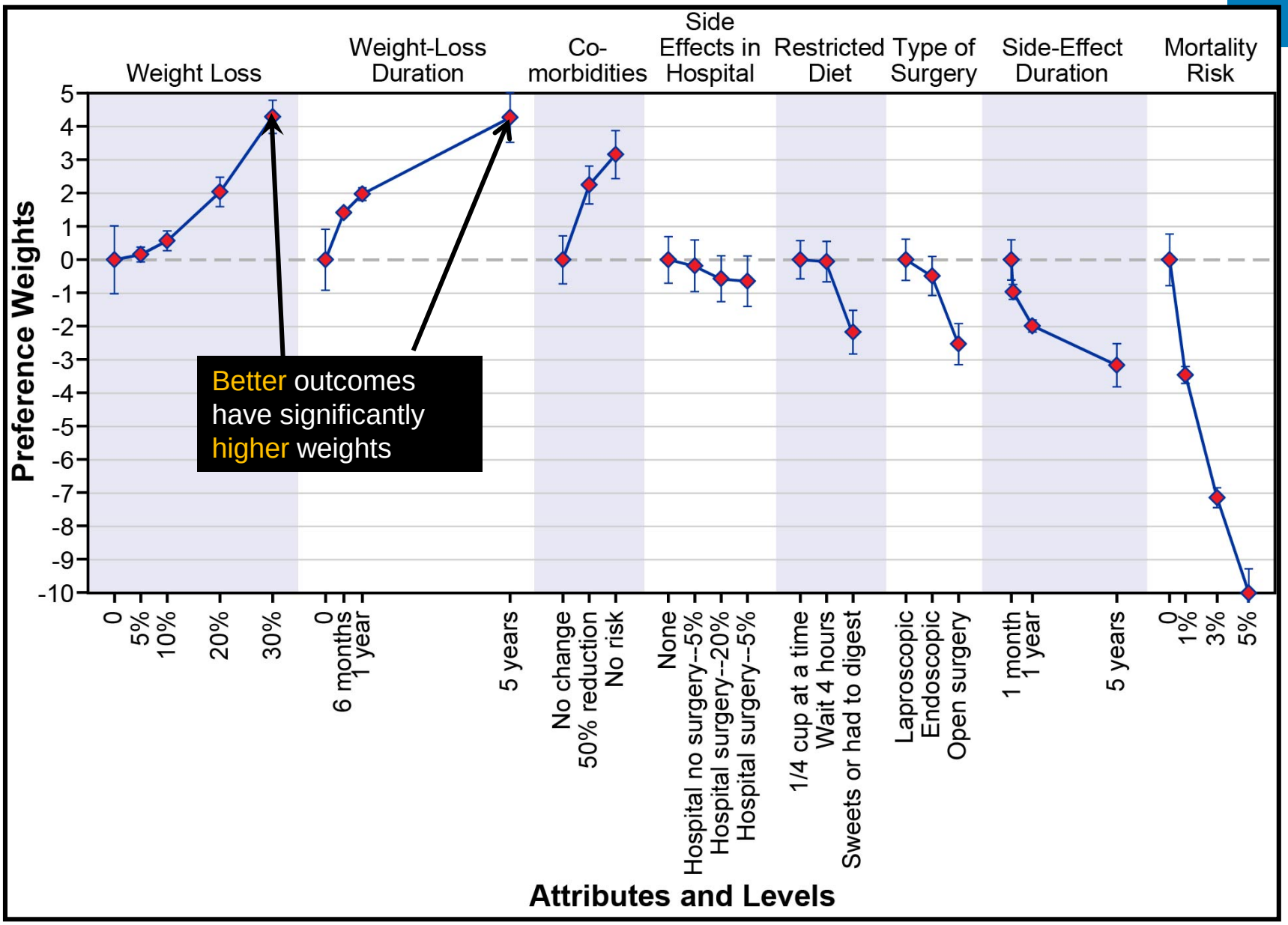
Attributes and Levels: Obesity Study

Attribute	Levels
How long side effect lasts	None 1 month 1 year 5 years
Chance of serious Side Effects requiring hospitalization	None 5% chance hospitalization, **no** surgery 20% chance hospitalization., **no** surgery 5% hospitalization **for** surgery
Chance of dying from getting weight-loss device	None 1% 3% 5% 10%

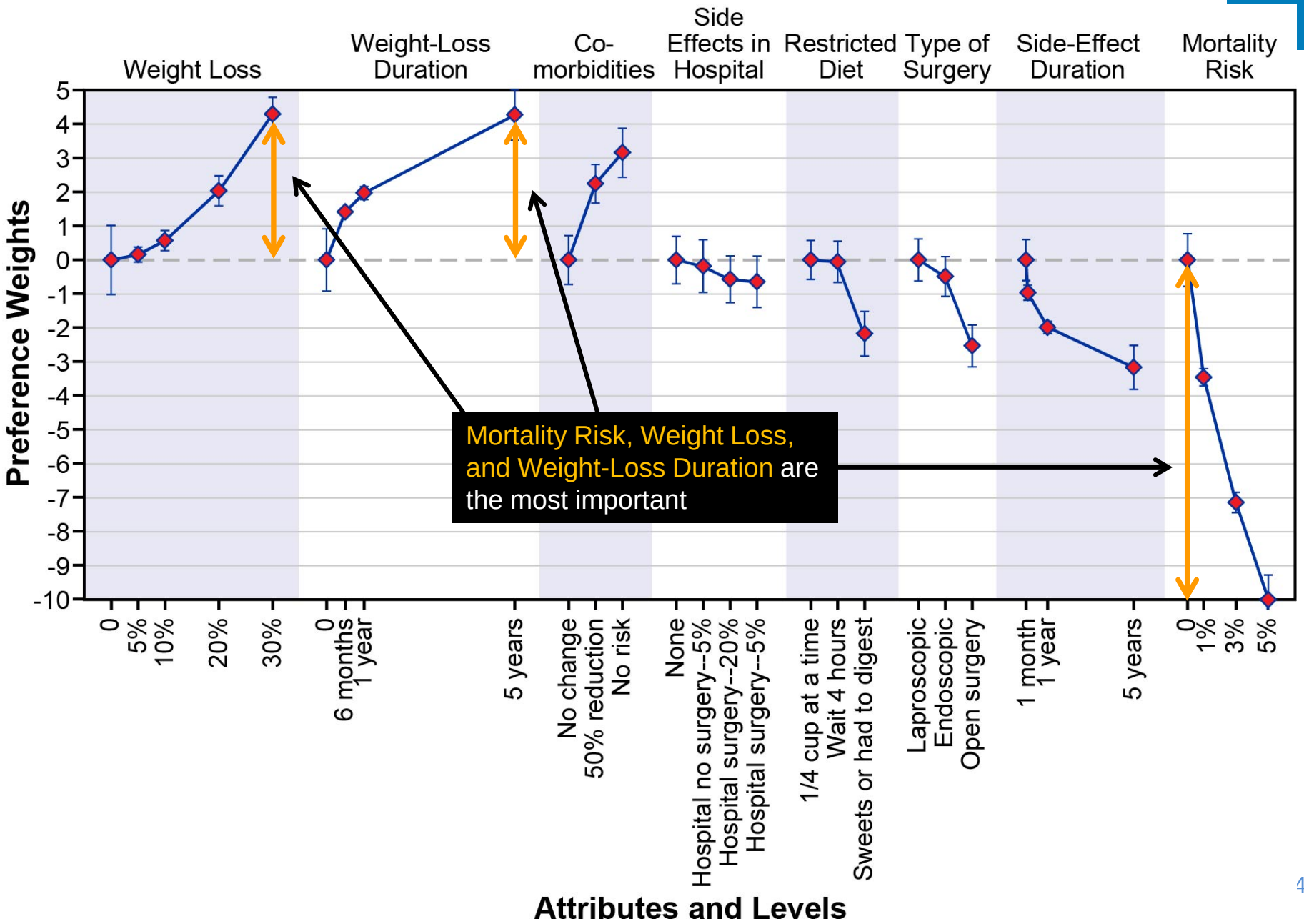
Choice Question Example

Feature	Device A	Device B
Type of operation	Endoscopic surgery	
Recommended diet restriction	Wait 4 hours between meals	
On average, how much weight is lost	30 lbs.	60 lbs.
On average, how long the weight loss lasts	Weight loss lasts 5 years	Weight loss lasts 1 year
Average reduction in dose of prescription drugs for diabetes at the lower weight	Eliminates the need for prescription drug	
On average, how long side effects last (Remember that side effects will limit your ability to do daily activities several times a month.)	Last 1 month	Last 1 year
Chance of a side effect requiring hospitalization	None	
Chance of dying from getting the weight loss device	 **10%** **(10 out of 100)**	 **1%** **(1 out of 100)**
Which weight-loss device do you think is better for people like you?	 Device A	 Device B

Results: Preference Weights



Results: Preference Weights



Decision Aid Tool

- Calculates the minimum benefit patients would require for a treatment with a given mortality risk and other attributes
- Calculates the maximum risk patients would accept for a treatment with given weight-loss benefit and other attributes
- Results reported for various levels, from risk averse to risk tolerant
- Calculates the proportion of patients who would choose to get the device instead of status quo
- The estimated values inform clinicians in the determination of the "***minimum clinically significant benefit***" that will be used in the clinical trial design and analysis

Decision Aid Tool: MAR

Device outcomes and features	Enter device characteristics	
Total Body Weight loss (TBWL%)	14.3%	Type
Side effect duration (months)	60	Type
Chance of side effects requiring hospitalization	5%, surgery	List
Recommended diet restrictions	Can't eat sweets	List
Expected duration of weight loss (months)	60	Type
Comorbidities: Reduce treatment dose / chance	No change	List
Type of operation	Laparoscopic surgery	List
[illegible]	[illegible]	Type

Select group of interest: Middle 50% of sample (List)

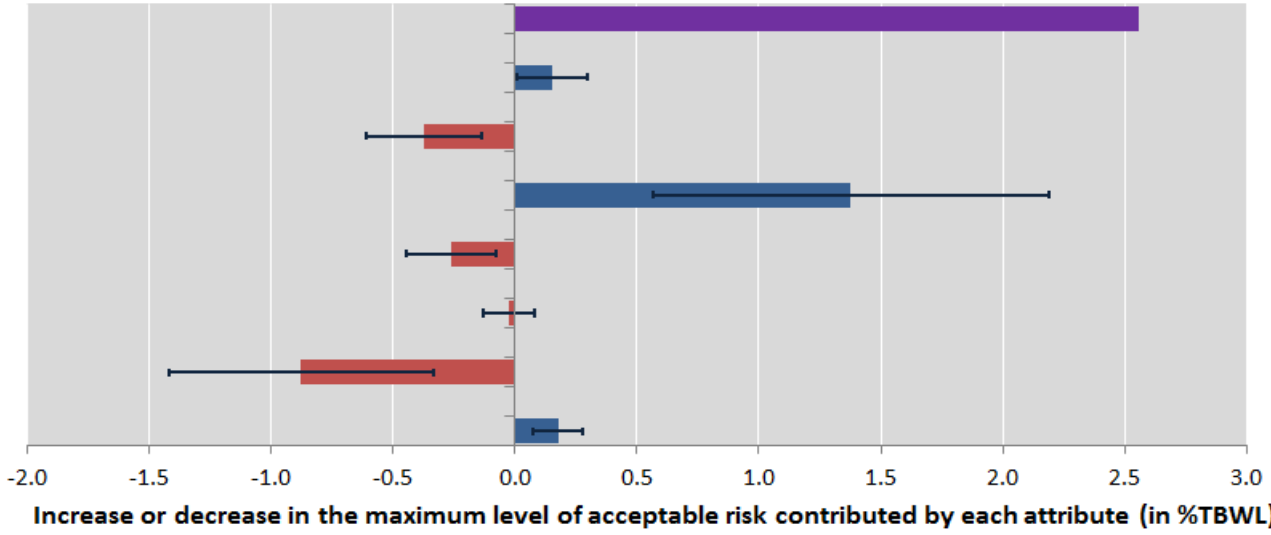
Enter base weight for the sample: 244 (lbs.) (Type in)

Select type of calculation:
- Minimum acceptable weight-loss benefit
- Maximum acceptable mortality risk
- Percent judged better than no device

Maximum Acceptable Risk for Selected Group: 0.08% (95% CI 0.03 to 0.21)

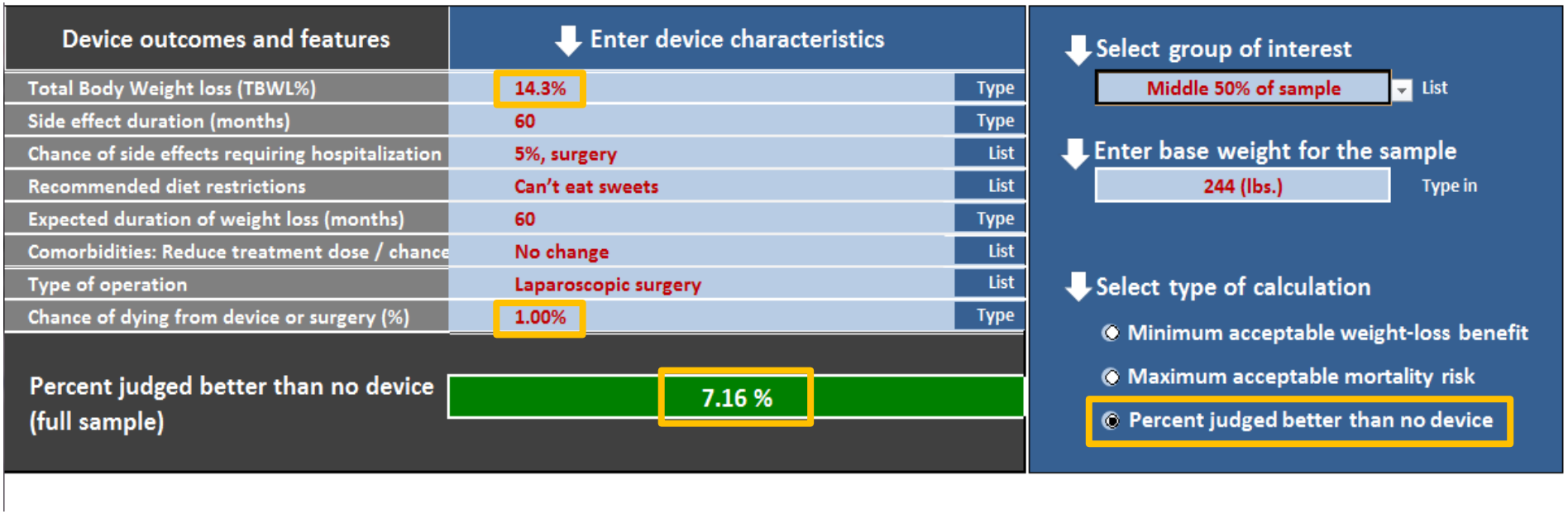
MAR

Relative contributions of device attributes



Decision Aid Tool

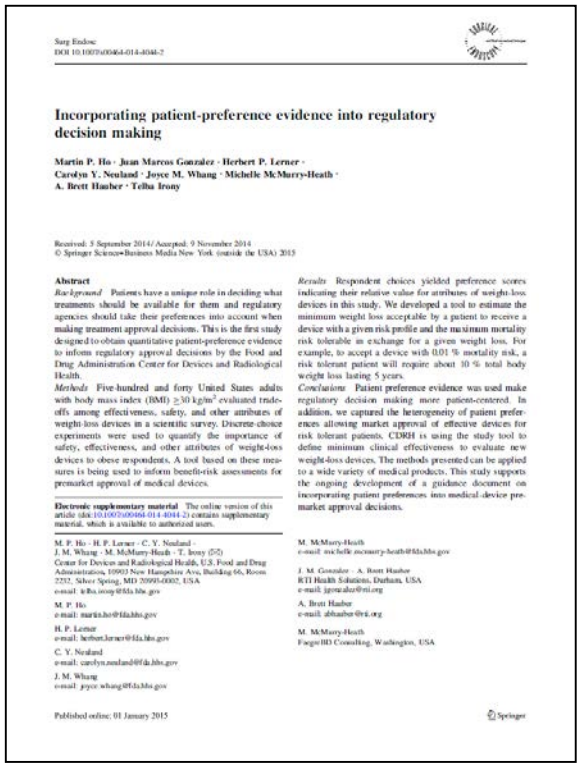
Proportion of Patients who prefer receiving the device over their status quo



Regulatory Impacts of the Obesity Study

- The study, published in 2015 (***see Surgical Endoscopy (2)***), quantifies patients' values to help define minimum clinically meaningful benefit
- Method adaptable for other medical products
- DCE: Only one of existing preference elicitation methods
- Maestro System, a vagus nerve stimulator indicated for weight-loss, was approved on January 14, 2015: estimated 10% patients accepting the device was instrumental to its approval
- Motivated development of a project by MDIC & CDRH: catalog of methods for eliciting patient preference ***(see report (3))***
- Helped develop the Patient Preference Info guidance document (2016) by CDRH & CBER ***(see guidance (4))***

Patient Preference Initiative



Surg Endosc
DOI 10.1007/s00464-014-4044-2

Incorporating patient-preference evidence into regulatory decision making

Martin P. Ho · Juan Marcos Gonzalez · Herbert P. Lerner · Carolyn Y. Neuland · Joyce M. Whang · Michelle McMurry-Heath · A. Brett Hauber · Telba Irony

Received: 5 September 2014 / Accepted: 9 November 2014

Abstract
Background Patients have a unique role in deciding what treatments should be available for them and regulatory agencies should take their preferences into account when making treatment approval decisions. This is the first study designed to obtain quantitative patient-preference evidence to inform regulatory approval decisions by the Food and Drug Administration Center for Devices and Radiological Health.
Methods Five-hundred and forty United States adults with body mass index (BMI) ≥30 kg/m² evaluated trade-offs among effectiveness, safety, and other attributes of weight-loss devices in a scientific survey. Discrete-choice experiments were used to quantify the importance of safety, effectiveness, and other attributes of weight-loss devices to obese respondents. A tool based on these measures is being used to inform benefit-risk assessments for premarket approval of medical devices.
Results Respondent choices yielded preference scores indicating their relative value for attributes of weight-loss devices in this study. We developed a tool to estimate the minimum weight loss acceptable by a patient to receive a device with a given risk profile and the maximum mortality risk tolerable in exchange for a given weight loss. For example, to accept a device with 0.01 % mortality risk, a risk tolerant patient will require about 10 % total body weight loss lasting 5 years.
Conclusions Patient preference evidence was used make regulatory decision making more patient-centered. In addition, we captured the heterogeneity of patient preferences allowing market approval of effective devices for risk tolerant patients. CDRH is using the study tool to define minimum clinical effectiveness to evaluate new weight-loss devices. The methods presented can be applied to a wide variety of medical products. This study supports the ongoing development of a guidance document on incorporating patient preferences into medical-device premarket approval decisions.

Electronic supplementary material The online version of this article (doi:10.1007/s00464-014-4044-2) contains supplementary material, which is available to authorized users.

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Published online: 01 January 2015
Springer

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Document issued on August 24, 2016.
This document will be in effect as of October 23, 2016.

The draft of this document was issued on May 18, 2015.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov).

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

See references (2), (3), (4)

III. Lessons Learned

III. Lessons Learned

- Strict control of type I error at a traditional α is problematic
  - If fixed at the same α level, all prior distribution is discounted
  - Discount factors
    - ✓Direct discount
    - ✓Power priors
    - ✓Hyper-parameters of hierarchical models
    - ✓Effective sample size
  - Discount factors are arbitrary, too abstract and difficult for clinicians to provide input. Originate endless discussions

- If control is required, α should be determined based on the amount of uncertainty tolerated (by patients, clinicians or reviewers) through a decision analysis method: **see *(5) Patient Centered Clinical Trials (Drug Discovery Today)***

III. Lessons Learned

- Strategy: use the full Bayesian approach with a success threshold for the posterior probability ***See Ebola Trial in Clinical Trials (6)***
- Threshold could be determined via full decision analysis
- Hierarchical model hyperparameters; arbitrary and difficult to assess due to scarcity of clinical input (clinicians don't get it)
- Hierarchical models are problematic when used with only 2 studies (variability between 2 studies cannot be estimated)
- Prior information may be available but not legally available

III. Lessons Learned

- Adaptive Bayesian design is a must when prior distributions are used ➔ avoid near misses
- Simulations: extremely helpful at the design stage to strategize and optimize trial designs
- The use of predictive distributions in labels is very useful but require the statisticians involvement

IV. Perspectives for the Future

Promising areas for use of prior information

- Pediatric trials: extrapolation from adult population;
  (***See 2015 pediatric draft guidance (7))***
- Safety (ex. Hepatitis B Vaccine Heplisav) ***(see review memo (8))***
- Expansion of indication
- Rare diseases or Small populations
- Unmet medical need for life threatening or irreversible debilitating diseases
- Expedited Access Program (EAP) (CDRH and CBER):
  (See EAP guidance (9)) If control of type I error is required, the significance level needs to be higher

Value of Bayes to regulate medical products

- Account for the totality of evidence by using prior distributions
- Introduce flexibility into the design of clinical trials – adaptive designs and likelihood principle
- Use decision analysis to make “hard” regulatory decisions
- Define thresholds for approval (or amount of evidence, or uncertainty tolerated, or significance level) by taking into account additional factors reflecting context

Value of Bayes to regulate medical products

- The strength of evidence may be scientifically determined in light of other factors:
  - ✓ Medical need (unmet?)
  - ✓ Severity and chronicity of the disease
  - ✓ Does the treatment precludes future treatments (e.g. gene therapy)
  - ✓ Patient value for benefit and tolerance for risk and

- More uncertainty could be accepted if:
  - ✓ The benefit is substantial for an unmet medical need
  - ✓ The safety profile is better than existent
  - ✓ Patients and physicians will accept it

Value of Bayes to regulate medical products

- Patient Input
  - ✓ Patient preference information is an important complement to clinical and statistical evidence and can enhance regulatory decision making
  - ✓ Evidence on patient preference can be scientifically obtained
  - ✓ Patient preference information can provide insights to reviewers who may have very limited experience with rare disease patients

Statisticians cannot not miss this boat!

References

(1) Benefit-Risk

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FDA U.S. FOOD & DRUG ADMINISTRATION

Extra slides: Choice Model

For any pair of Device Profiles A and B with *k* attributes the expected probability of choosing device A ($C=A$) is given by

$$\text{Prob}(C = A) = \frac{1}{1 + \exp(\sum_k \beta_A - \sum_k \beta_B)}$$

Here the mean odds ratio for any 2 treatment profiles is

$$\exp(\sum \beta_A - \sum \beta_B)$$

Choice Model

The statistical model uses observed choice patterns to quantify preferences

Assumed the logit-choice probability function [a]

$$\text{Prob}\left[C^i_{j1}, \ldots, C^i_{jT}\right] = \prod_{t=1}^{T}\left[\frac{\exp\left[U^i_{jt}\right]}{\sum_{j=1}^{J}\exp\left[U^i_{jt}\right]}\right]$$

The model controls for differences across respondents' preferences (heterogeneity)

Many choice practitioners employ the model as accepted good practice

[a] The use of a logit form for the choice probability function was based on McFadden's seminal work on the analysis of choice behavior (1974).