Choosing the Appropriate Modeling Method for a Given Problem: Causal Modeling, Health Economic Modeling, Constrained Optimization, or Simulation?

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Purpose of Workshop

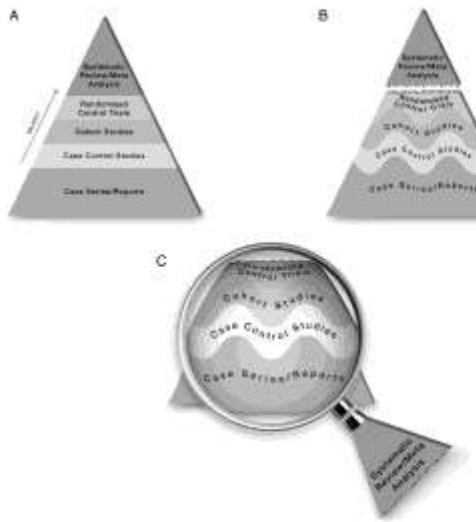
There are a variety of available approaches available to researchers for approaching different types of health economic evaluation problems. Most training sessions at ISPOR focus on the specifics of a particular approach. Rather than focus on the details of any particular approach, this workshop will focus on the higher order issue of choosing the correct approach in the first place.

Methods

- Causal Modeling
- Health Economic Modeling
- Optimization Models
- Simulation Models

Causal Modeling and Real World Evidence

The proposed new evidence-based medicine pyramid.



M Hassan Murad et al. Evid Based Med 2016;21:125-127

EBM

Aspects of Bias Addressed by Randomization

- Balances comparison groups on both observed and *unobserved* characteristics
- Greatly simplifies analysis

- But inclusion/exclusion criteria and intensive follow-up in trials introduce issues of generalizability of findings
- Small trials can be highly variable in their findings

Regulatory Imperatives Driving the Interest in Real World Evidence

- Under the *Prescription Drug User Fee Act* (PDUFA) VI FDA has mandated that:
  1. By the end of FY 2018, FDA must conduct a public workshop focused on RWE;
  2. By the end of FY 2019, FDA must fund pilot and methodology specifically targeted toward RWE and regulatory decision-making; and
  3. By end of FY 2021, FDA must publish draft guidance for RWE applications.
- The 21st Century Cures Act mandates (section 3022) that FDA propose a framework and enact a program to evaluate RWE to support approval of new indications and to satisfy post-approval requirements.

It's An Observational Study; What Could Possibly Go Wrong?

A High Profile Case Where RCTs and Differed

- The Nurses Health Study (observational) had found a protective cardiovascular risk from HRT.
  - Stampfer MJ et al. Postmenopausal Estrogen Therapy and Cardiovascular Disease: Ten-Year Follow-up from the Nurses' Health Study. N. Engl. J. Med 325, 756-762 (1991).
- The Women's Health Initiative (RCT) found just the opposite
  - Rossouw JE et al. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial. JAMA 288, 321-333 (2002)

Why Not Use RCTs for All of our Questions?

- Observational data has some important advantages
  - Timeliness
  - Less restrictive eligibility criteria
  - Longer follow-up
  - Larger sample size
  - Lower cost

The Women’s Health Initiative Revisited

- Hernan MA et al. Observational Studies Analyzed Like Randomized Experiments: An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease. Epidemiology 19, 766-779 (2008)
- Goodman SN, Schneeweiss S. and Baiocchi M. Using Design Thinking to Differentiate Useful From Misleading Evidence in Observational Research. JAMA 317, 705-707 (2017).

When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials?

Jessica M. Franklin[1] and Sebastian Schneeweiss[1]

Regulators consider randomized controlled trials (RCTs) as the gold standard for evaluating the safety and effectiveness of medications, but their costs, duration, and limited generalizability have caused some to look for alternatives. Real world evidence based on data collected outside of RCTs, such as registries and longitudinal healthcare databases, can sometimes substitute for RCTs, but concerns about validity have limited their impact. Greater reliance on such real world data (RWD) in regulatory decision making requires understanding why some studies fail while others succeed in producing results similar to RCTs. Key questions when considering whether RWD analyses can substitute for RCTs for regulatory decision making are WHEN one can study drug effects without randomization and HOW to implement a valid RWD analysis if one has decided to pursue that option. The WHEN is primarily driven by externalities not controlled by investigators, whereas the HOW is focused on avoiding known mistakes in RWD analyses.

Franklin J. and Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clinical Pharmacology and Therapeutics 2017.

Guide Posts That Can Improve Reliability of Database Study Results

1. Active Comparator, same treatment modality
2. New Users
3. High-dimensional proxy adjustment
4. Control for Medication Adherence
5. Avoiding design flaws:
   - reverse causation
   - adjustment for causal intermediaries
   - immortal time bias
   - depletion of susceptibles

Current (limited) literature Suggests Observational Studies Yield Results Similar to RCTs

- Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review). The Cochrane Library 2014, Issue 4.
  - Cochrane Collaborative review of 14 prior reviews comparing RCTs to observational studies. Collectively, these reviews included data on 1583 meta analyses spanning 228 medical conditions.
  - 11 of 14 studies (79%) found no difference in ratios of odds ratios (ROR)
  - One review suggested larger ROR for observational studies
  - Two reviews suggested smaller ROR for observational studies
  - **"Our results showed that, on average, there is little difference between the results obtained for RCTs and observational studies."**
- Earlier Studies
  - Benson K, Hartz AJ. A Comparison of Observation Studies and Randomized, Controlled Trials. N Engl J Med 2000; 342: 1878-86
  - Concato J, Shah N, Horwitz RI. Randomized, Controlled Trials, Observation Studies and the Hierarchy of Research Designs. N Engl J Med 2000; 342: 1887-92

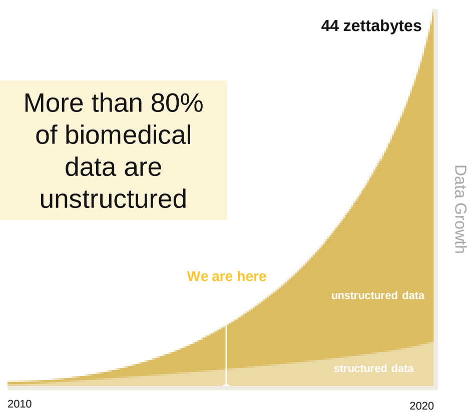
Skillsets Vary Widely By Method

- Pragmatic Trials
- Epidemiology—more clinical oriented
  - Propensity Score Matching
  - Inverse Probability Weights
- Econometrics—more policy oriented
  - Instrumental Variables
  - Differences-in-Differences
- Health care domain knowledge
  - Clinical
  - Economics
  - Claims and EMR data

Health Care Big Data Will Change Skillset Further

- Genomics
- Curated Medical Literature
- Health Care Claims
- Medical and Mobile Device Feeds
- Electronic Medical Records

More than 80% of biomedical data are unstructured



Health Economic Modeling

Outline

- Aim of the models used in HTA
- Modelling techniques employed in HTA
  - Types of modeling approaches
  - Assumptions involved
- Data/input requirements
- Good practice guidelines
- Outputs from model analyses
- Resources/skill sets needed

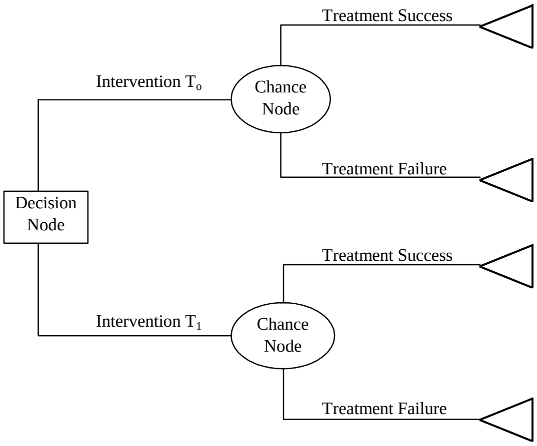
Health Economic modelling

- Randomized controlled trials (RCTs) only have a short follow-up so cannot generalize cost-effectiveness results
  - Also, doing RCTs is quite expensive
- Network meta analyses (NMA) only provide information about relative effectiveness, need to understand if the benefits are worth the costs
- Aim: Need to estimate the benefits (e.g. QALYs) and costs of different interventions over the life time, hence the need for 'health economic modelling'

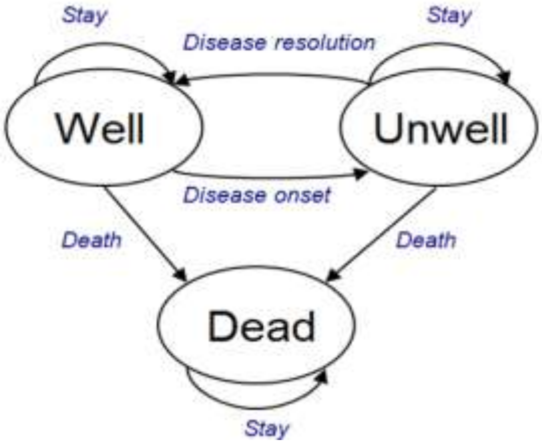
Types of Models

- The first type of decision-analytic model is the "**decision tree**" model.
  - used to determine optimal strategies when a decision-maker encounters several decision alternatives under conditions of uncertainty
- Other popular types of models in HTA are "**Markov**" or **semi-Markov** models (state stransition models)
  - These models use a finite number of discrete health states to model the disease and estimate the flow of people through these states over time
- **Partitioned-survival models** are becoming more prominent in disease states that use time-to-event data, particularly oncology.
- Another type of model is a **discrete event simulation model**
  - patient-level simulation commonly using Monte Carlo analysis to model specific events experienced by individual patients.
- For an overview of model taxonomies, please see Brennan et al. (2006)

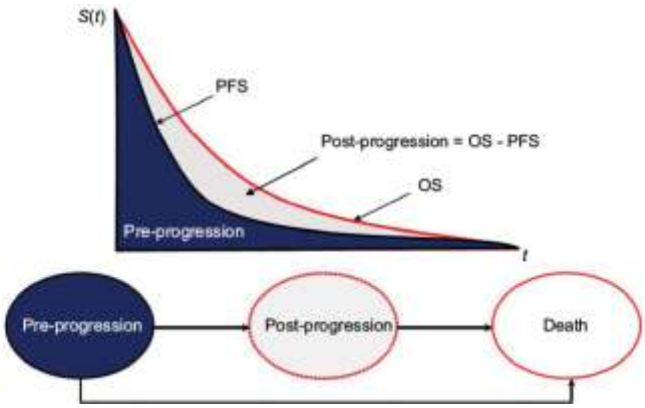
Decision Tree Models



Markov models



Partitioned survival models



https://www.dovepress.com/evaluating-the-cost-effectiveness-of-afatinib-after-platinum-based-the-peer-reviewed-fulltext-article-CEOR

Typical assumptions involved

- Cohort models (i.e. decision trees, Markov and partitioned survival models) estimate population averages, so assume each patient is the same
- Decision trees
  - Patients can be classified into clear groups with specific outcomes
  - Patients move to these groups in short time horizon
- Markov models
  - Memoryless assumption (i.e. all the patients in a given state are the same irrespective of how they got there)
  - Transition probabilities are constant over time (i.e. the risk of moving to a different state is same irrespective of how long patients are in a state)
- Partitioned survival models
  - Survival (OS or PFS) can be estimated (typically) using a parametric distribution (e.g. Exponential, Gamma, Weibull, etc)

Inputs for health economic models

Types	Sources	Uses
Effectiveness	'Published papers'	Parameter values
Costs	Routine data	Model structure
Resource use / activity	Reference sources	Sensitivity analysis
Health states	Local / clinical / expert opinion	Validation / consistency / calibration
Utility values	Sponsor submissions	
Indirect comparators		
Longer term outcomes		
'Other' interventions		
Natural history		
Epidemiology		

HTA Modelling Guidelines

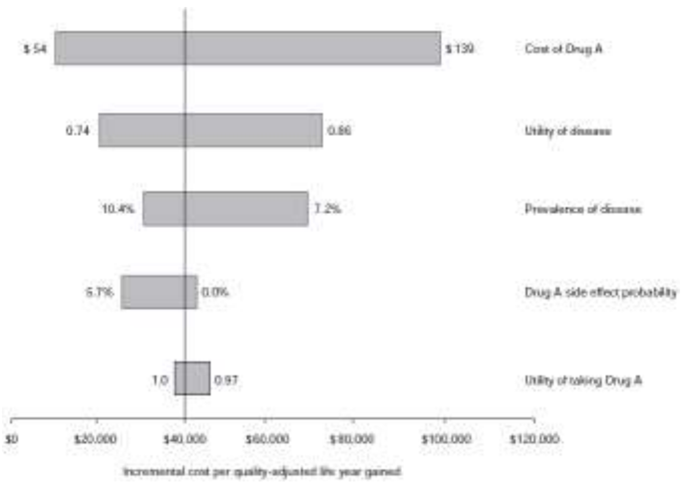
- ISPOR-SMDM Modelling Good Research Practices Task force https://www.ispor.org/workpaper/Modeling-Good-Research-Practices-Overview.asp
- Also, HTA organisations (e.g. NICE, ICER, etc) specify the methods guide for performing cost-effectiveness analyses, which include their preferences such as
  - Cost-effectiveness metric (Cost Per QALY)
  - Discount Rates (for costs and benefits)
  - Utility Measures (e.g. EQ-5D)
  - Time Horizon
  - Perspective (e.g. payer or societal)
  - Preferred sources/methods for identifying inputs
  - Reporting

Results: Types of analyses

$$\frac{(\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{control}})}{(\text{QALYs}_{\text{intervention}} - \text{QALYs}_{\text{control}})} = \textbf{ICER}$$

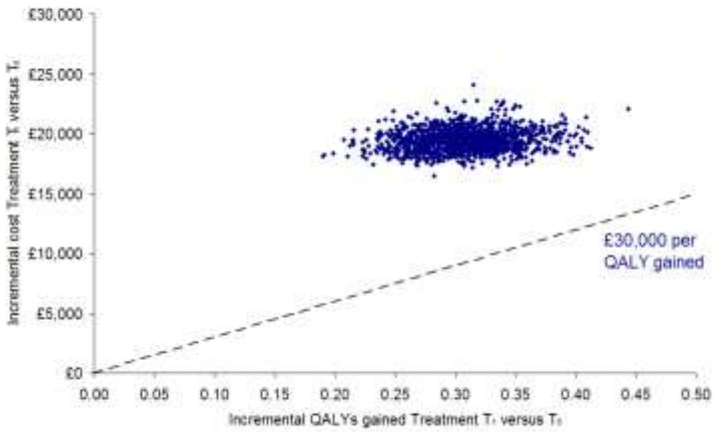
- Deterministic results
  - true values of the model parameters are known with certainty
- Deterministic Sensitivity analysis
  - Varying one or several model parameters to examine the impact upon the cost-effectiveness results
- Stochastic/Probabilistic analysis
  - parameter values lie on a distribution with unique characteristics

Deterministic sensitivity analysis (One-way sensitivity analysis)

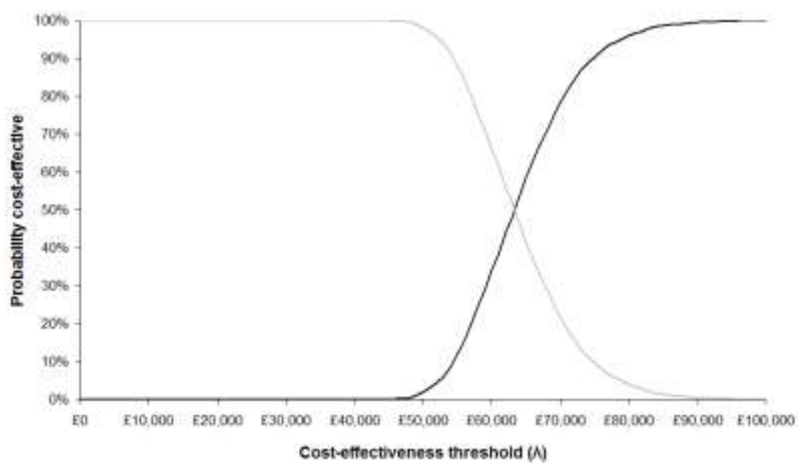


https://thehealthscience.com/topics/tornado-diagram

Probabilistic sensitivity analysis: Cost-effectiveness plane & Scatterplots



Probabilistic sensitivity analysis: Cost-effectiveness acceptability curves



Resources/Skillsets

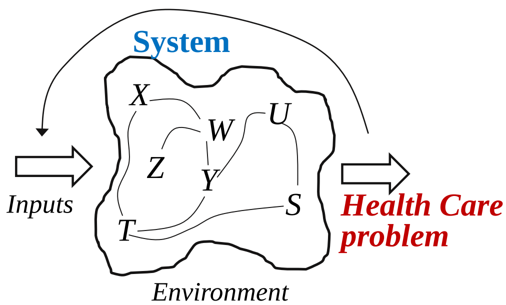
- Popular software are **Excel** and **TreeAge** (proprietary)
- Many **free software packages** (e.g., R)
- Most modellers in Health Economic Evaluation use the cohort models and program in **Excel** is used for many modeling purposes. Easy to understand and implement.
- However, there remain some limitations which can be addressed using simulation modelling techniques

Simulation Modelling

Complexity and Interactions = Dynamic System

Healthcare delivery *processes…*

Include *feedback, non-linear* and *spatial* relationships between entities that change *behaviors* and make *outcomes* difficult to anticipate



Why a Systems Perspective and Simulation Modelling for Planning Health Care Delivery?

- Health Care is a **Complex System:** multiple stakeholders and interactions, non-linearities, uncertainty, etc.
- **Interactions:** Simulation models support the design and re-design of systems by enabling a better understanding of the complexity and behaviour of the system that is modelled. This translates into quality and healthcare improvement.
- Models are means to synthesize data when direct experimentation is not possible or feasible.
- Mechanism to logically and systematically examine a policy problem.
- Evaluate intended and unintended consequences of an intervention using alternative "what if…?" scenarios BEFORE implementing.
- Identify need for additional data – what are the gaps?

SIMULATE Checklist

SIMULATE	Does your problem require:
System	Modeling multiple events, relationships and stakeholders representing healthcare delivery processes?
Interactions	Including non-linear or spatial relationships between stakeholders that influence beh anticipate?
Multilevel	Modeling a h Operational p
Understanding	Modeling a c cannot be so
Loops	Modeling fee and the cons
Agents	Modeling mu and change t
Time	Time-depend either betwee change?
Emergent	Considering the intended and unintended consequences of health system interventions to address policy resistance and achieve target outcomes?

- The more of these characteristics, the more likely dynamic simulation modeling is to apply
- Does not (yet) discriminate between the different simulation modeling approaches (ABM, DES and SD)

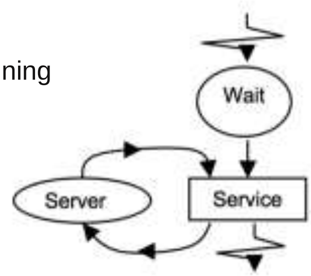
System Dynamics Simulation Model

– E.g. utilization of a system of hospital(s) (departments)

- Core elements:
  - – Feedback:
    - Feedback processes infer that effect is not proportional to the cause i.e. nonlinearity
  - – Accumulations (stocks):
    - Accumulation or aggregation of something (e.g.,people, beds)
  - – Rates (flows):
    - Flows feed in and out of stocks and have the same units of stocks per time unit (e.g., people per hour, beds per year, and oxygen per minute)
  - – Time Delays:
    - People accumulate in stocks if the rate of flow out is less than in to the stock

Discrete Event Simulation

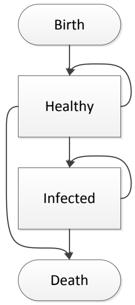
– E.g. surgical planning



- Core elements:
  - Process: *representing the system that is being studied*
  - Entities: *flowing through the process and have work done on them*
  - Resources: *used in the workflow to process entities*
  - Events: *cause changes in the state of the entity and/or system*

Agent Based Simulation Model

- E.g. infectious disease modelling



- Core elements:
  - **Entities:** *transition between states based on events and interactions*
  - **Interactions:** *dynamic behavior of the entities and their environment*
  - **Network:** *set of (dynamic) rules to determine the interactions*
  - **Space:** *entities' behavior is influenced by their spatial location*

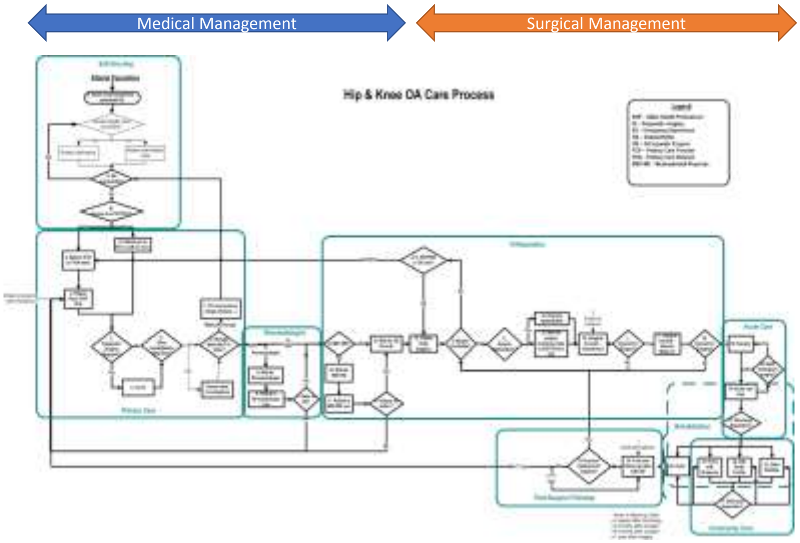
Example: System Dynamics Model of Osteoarthritis (OA)

To create a decision-support tool for strategic service planning of care for hip & knee osteoarthritis patients

- Tool to enable policy makers, service planners and administrators, and clinicians to evaluate care quality and system performance
- Balancing the tradeoffs between accessibility, effectiveness and efficiency across the continuum of care from OA onset, through medical and surgical management
- Inform choices about health system interventions considering intended and unintended consequences

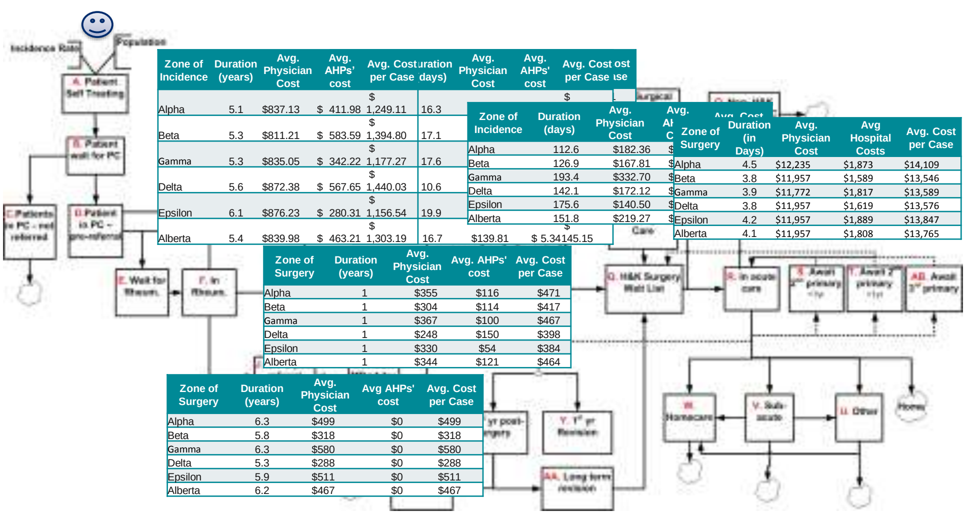
Goal: Sustainable plan for OA care

Example: System Dynamics OA Model Process Diagram



- Vanderby SA, Carter MW, Noseworthy T, Marshall DA. *Modeling the complete continuum of care using system dynamics: the case of osteoarthritis in Alberta. J Simulation 2015; 9(2): 156-169*

Sample OA Patient Pathway From Primary Care to Orthopedic Surgeon



Zone of Incidence	Duration (years)	Avg. Physician Cost	Avg. AHPs' cost	Avg. Cost per Case
Alpha	5.1	$837.13	$ 411.98	$ 1,249.11
Beta	5.3	$811.21	$ 583.59	$ 1,394.80
Gamma	5.3	$835.05	$ 342.22	$ 1,177.27
Delta	5.6	$872.38	$ 567.65	$ 1,440.03
Epsilon	6.1	$876.23	$ 280.31	$ 1,156.54
Alberta	5.4	$839.98	$ 463.21	$ 1,303.19

Duration (days)	Avg. Physician Cost	Avg. AHPs' cost	Avg. Cost per Case
16.3			$
17.1			
17.6			
10.6			
19.9			
16.7	$139.81	$ 5.34	$ 145.15

Zone of Incidence	Duration (days)	Avg. Physician Cost	Avg. AHPs' Cost
Alpha	112.6	$182.36	$
Beta	126.9	$167.81	$
Gamma	193.4	$332.70	$
Delta	142.1	$172.12	$
Epsilon	175.6	$140.50	$
Alberta	151.8	$219.27	$

Zone of Surgery	Duration (in Days)	Avg. Physician Cost	Avg Hospital Costs	Avg. Cost per Case
Alpha	4.5	$12,235	$1,873	$14,109
Beta	3.8	$11,957	$1,589	$13,546
Gamma	3.9	$11,772	$1,817	$13,589
Delta	3.8	$11,957	$1,619	$13,576
Epsilon	4.2	$11,957	$1,889	$13,847
Alberta	4.1	$11,957	$1,808	$13,765

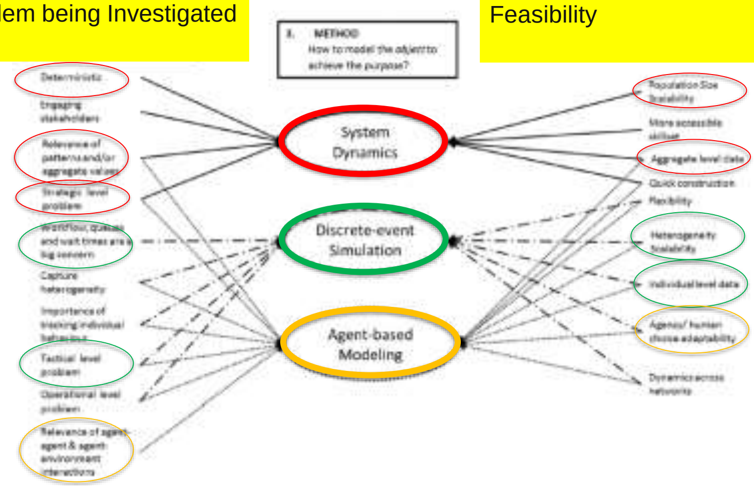
Zone of Surgery	Duration (years)	Avg. Physician Cost	Avg. AHPs' cost	Avg. Cost per Case
Alpha	1	$355	$116	$471
Beta	1	$304	$114	$417
Gamma	1	$367	$100	$467
Delta	1	$248	$150	$398
Epsilon	1	$330	$54	$384
Alberta	1	$344	$121	$464

Zone of Surgery	Duration (years)	Avg. Physician Cost	Avg AHPs' cost	Avg. Cost per Case
Alpha	6.3	$499	$0	$499
Beta	5.8	$318	$0	$318
Gamma	6.3	$580	$0	$580
Delta	5.3	$288	$0	$288
Epsilon	5.9	$511	$0	$511
Alberta	6.2	$467	$0	$467

Criteria for Selecting Dynamic Simulation Model

Purpose of the Model
Problem being Investigated

Scope of the Model (boundary)
Feasibility



Examples of Problems Addressed with Simulation Modelling Methods

System Level	Types of Problems	Potential Approaches	Intervention Example
Strategic level	Policy	System Dynamics Agent Based Modeling	Informing regional policy regarding implementation of a centralized intake system for referral to an appropriate provider for assessment and specialist consultation for patients with musculoskeletal pain.
Tactical level	Management	Agent Based Modeling Discrete Event Simulation	Wait time management for referral for a specific service e.g., consultation with orthopaedic surgeon or rheumatologist
Operational level	Logistics	Agent Based Modeling Discrete Event Simulation	Scheduling surgical dates for joint replacement in the operating room Evaluating the change in hospital services due to a delay of total joint replacement in cases of severe osteoarthritis.

Constrained Optimization

Optimization Task Force Report 1 – Introduction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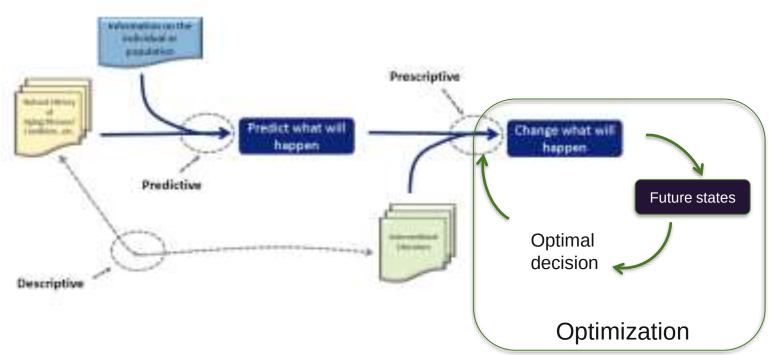
Constrained Optimization Methods in Health Services Research—An Introduction: Report 1 of the ISPOR Optimization Methods Emerging Good Practices Task Force

William Crown, PhD, Nasuh Buyukkaramikli, PhD, Praveen Thokala, PhD, Alec Morton, PhD, Mustafa Y. Sir, PhD, Deborah A. Marshall, PhD, Jon Tosh, PhD, William V. Padula, PhD, MS, Maarten J. Ijzerman, PhD, Peter K. Wong, PhD, MS, MBA, RPh, Kalyan S. Pasupathy, PhD

What is Optimization?

- **Optimization** is a key tool in the ***analytics armamentarium.***
  - "**Optimization:** Narrowing your choices to the very best when there are virtually innumerable feasible options and comparing them is difficult" INFORMS, The Science of Better http://www.scienceofbetter.org/what/index.htm
  - "In a mathematical programming or **optimization** problem, one seeks to minimize or maximize a real function of real or integer variables, subject to constraints on the variables." The Mathematical Programming Society http://www.mathprog.org/mps_whatis.htm
- **Take home**: Optimization is an ***applied, practical*** subject, but a ***highly technical*** one that uses cutting edge math and computation

Optimization Link to Analytics



Wilson, ISPOR 2014

Mathematical Formulation of Constrained Optimization Models

Maximize $z=f(x_1, x_2, \ldots. x_n, p_1, p_2, \ldots. p_k)$
subject to
$c_j(x_1, x_2, \ldots. x_n, p_1, p_2, \ldots. p_k) \leq C_j$
for $j=1,2,..m$
where, $x_1, x_2, \ldots. x_n$ are the decision variables,
$f(x_1, x_2, \ldots. x_n, p_1, p_2, \ldots. p_k)$ is the objective function; and
$c_j(x_1, x_2, \ldots. x_n, p_1, p_2, \ldots. p_k) \leq C_j$ represent the constraints.

Constraints can include both inequality and equality constraints and the objective function and the constraints also include non-decision variables $p_1, p_2, \ldots. p_k$, which are not varied in the optimization problem.

Variety of Optimization Models

- Function/relationship: Linear vs. Nonlinear
- Time: Static vs. dynamic
- Variable type: Continuous vs. Integer
- Probability: Deterministic vs. stochastic

Steps in Building an Optimization Model

Stage	Step	Description
Modeling	Problem structuring	Specify the objective and constraints, identify decision variables and non-decision variables, and list and appraise model assumptions
	Mathematical formulation	Present the objective function and constraints in mathematical notation using decision variables and constant parameters
	Model development	Develop the model to estimate the objective function and constraints using decision variables and non-decision variables
	Model validation	Ensure the model is appropriate for evaluating all possible scenarios (i.e. different combinations of decision variables and non-decision variables)
Optimization	Select optimization method	Choose an appropriate optimization method and algorithm based on the characteristics of the model
	Perform optimization/sensitivity analysis	Use the optimization algorithm to search for the optimal solution and examine performance of optimal solution for reasonable values of parameters and decision variables
	Report results	Report the results of optimal solution
	Decision making	Interpret the optimal solution and use it for decision making

Examples of Health Care Decisions for Which Constrained Optimization is Applicable

Type of health care problem	Typical decision makers	Typical decisions	Typical objectives	Typical constraints
Resource allocation within and across disease programs	Health authorities, insurance funds	List of interventions to be funded	Increase population health	Overall health budget
Resource allocation for infectious disease management	Public health agencies, health protection agencies	Optimal vaccination coverage level	Ensure disease outbreaks can be rapidly and cost effectively contained,	Availability of medicines, disease dynamics of the epidemic
Allocation of donated organs	Organ banks, transplant service centers	Matching of organs and recipients	Matching organ donors with potential recipients	Every organ can be received by at most one person
Radiation treatment planning	Radiation therapy providers	Positioning and intensity of radiation beams	Minimizing the radiation on healthy anatomy	Tumor coverage and Restriction on total average dosage
Disease management Models	Leads for a given disease management plan	Best interventions to be funded, best timing for the initiation of a medication, best screening policies	Identify the best plan using a whole disease model, maximizing QALYs	Budget for a given disease or capacity constraints for healthcare providers
Workforce planning/ Staffing / Shift template optimization	Hospital managers, all medical departments (e.g., ED, nursing)	Number of staff at different hours of the day, shift times	Increase efficiency and maximize utilization of healthcare staff	Availability of staff, human factors, state laws (e.g., nurse-to-patient ratios), budget
Inpatient scheduling	Operation room/ ICU planners	Detailed schedules	Minimize waiting time	Availability of beds, staff

Interactive Polling

53

Additional Discussion