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

William Crown, PhD[1],*, Nasuh Buyukkaramikli, PhD[2], Praveen Thokala, PhD[3], Alec Morton, PhD[4], Mustafa Y. Sir, PhD[5], Deborah A. Marshall, PhD[6], Jon Tosh, PhD[7], William V. Padula, PhD, MS[8], Maarten J. Ijzerman, PhD[9], Peter K. Wong, PhD, MS, MBA, RPh[10], Kalyan S. Pasupathy, PhD[11],*

1 Optum Labs, Boston, MA, USA; 2 Scientific Researcher, institute of Medical Technology assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands; 3 Research Fellow, University of Sheffield, Sheffield, UK; 4 Professor of Management Science, Department of Management Science, Strathclyde Business School, University of Strathclyde, Glasgow, Scotland, UK; 5 Assistant Professor, Health Care Policy & Research, Faculty - Information and Decision Engineering, Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Rochester, MN, USA; 6 Canada Research Chair, Health Services & Systems Research; Arthur J.E. Child Chair in Rheumatology Research; Director, HTA, Alberta Bone & Joint Health Institute; Associate Professor, Department Community Health Sciences, Faculty of Sciences, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada; 7 Senior Health Economist, DRG Abacus, Manchester, UK; 8 Assistant Professor, Department of Health Policy & Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; 9 Professor of Clinical Epidemiology & Health Technology Assessment (HTA); Head, Department of Health Technology & Services Research, University of Twente, Enschede, The Netherlands; 10 Vice President and Chief Performance Improvement Officer, Illinois Divisions and HSHS Medical Group, Hospital Sisters Health System (HSHS), Belleville, IL. USA; 11 Associate Professor - Healthcare Policy & Research, Scientific Director – Clinical Engineering Learning Labs, Lead – Information and Decision Engineering, Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Rochester, MN, USA.

*Corresponding authors – Kalyan S. Pasupathy (Pasupathy.Kalyan@mayo.edu) and William Crown (William.Crown@optum.com)

Abstract

Providing health services with the greatest possible value to patients and society given the constraints imposed by patient characteristics, health care system characteristics, budgets, etc. relies heavily on the design of structures and processes. Such problems are complex and require a rigorous and systematic approach to identify the best solution. Constrained optimization is a set of methods designed to identify efficiently and systematically, the best solution (the optimal solution) to a problem characterized by a number of potential solutions in the presence of identified constraints. This report identifies: 1) key concepts and the main steps in building an optimization model; 2) the types of problems where optimal solutions can be determined in real world health applications and 3) the appropriate optimization methods for these problems. We first present a simple graphical model based upon the treatment of "regular" and "severe" patients, which maximizes the overall health benefit subject to time and budget

30 constraints. We then relate it back to how optimization is relevant in health services research for
31 addressing present day challenges. We also explain how these mathematical optimization methods relate
32 to simulation methods, to standard health economic analysis techniques, and to the emergent fields of
33 analytics and machine learning.

34 **Keywords:** Decision making, care delivery, policy, modeling

1. Introduction

In common vernacular, the term "optimal" is often used loosely in health care applications to refer to any demonstrated superiority among a set of alternatives in specific settings. Seldom is this term based on evidence that demonstrates such solutions are, indeed, *optimal* – in a mathematical sense. By "optimal" solution we mean the *best possible solution* for a given problem given the complexity of the system inputs, outputs/outcomes, and constraints (budget limits, staffing capacity, etc.). Failing to identify an "optimal" solution represents a missed opportunity to improve clinical outcomes for patients and economic efficiency in the delivery of care.

Identifying optimal health system and patient care interventions is within the purview of mathematical optimization models. There is a growing recognition of the applicability of constrained optimization methods from operations research to health care problems. In a review of the literature [1], note more than 200 constrained optimization and simulation studies in health care. For example, constrained optimization methods have been applied in problems of capacity management and location selection for both healthcare services and medical supplies [2-5].

Constrained optimization is an interdisciplinary subject, cutting across the boundaries of mathematics, computer science, economics and engineering. Analytical foundations for the techniques to solve the constrained optimization problems involving continuous, differentiable functions and equality constraints were already laid in the 18th century [6]. However, with advances in computing technology, constrained optimization methods designed to handle a broader range of problems trace their origin to the development of the simplex algorithm--the most commonly used algorithm to solve linear constrained optimization problems--in 1947 [7-11]. Since that time, a variety of constrained optimization methods have been developed in the field of operations research and applied across a wide range of industries. This creates significant opportunities for the optimization of health care delivery systems and for providing value by transferring knowledge from fields outside the health care sector.

In addition to capacity management, facility location, and efficient delivery of supplies, patient scheduling, provider resource scheduling, and logistics are other substantial areas of research in the application of constrained optimization methods to healthcare [12-16]. Constrained optimization methods may also be very useful in guiding clinical decision-making in actual clinical practice where physicians and patients face constraints such as proximity to treatment centers, health insurance benefit designs, and the limited availability of health resources.

Constrained optimization methods can also be used by health care systems to identify the optimal allocation of resources across interventions subject to various types of constraints [17-23]. These methods have also been applied to disease diagnosis [24, 25], the development of optimal treatment algorithms [26, 27], and the optimal design of clinical trials [28]. Health technology assessment using tools from constrained optimization methods is also gaining popularity in health economics and outcomes research [29].

Recently, the ISPOR Emerging Good Practices Task Force on Dynamic Simulation Modeling Applications in Health Care Delivery Research published two reports in *Value in Health* [30, 31] and one in Pharmacoeconomics [32] on the application of dynamic simulation modeling (DSM) to evaluate problems in health care systems. While simulation can provide a mechanism to evaluate various scenarios, by design, they do not provide optimal solutions. The overall objective of the ISPOR Emerging Good Practices Task Force on Constrained Optimization Methods is to develop guidance for health services researchers, knowledge users and decision makers in the use of operations research methods to optimize healthcare delivery and value in the presence of constraints. Specifically, this task force will (1) introduce constrained optimization methods for conducting research on health care systems and individual-level outcomes (both clinical and economic); (2) describe problems for which constrained optimization

82   methods are appropriate; and (3) identify good practices for designing, populating, analyzing, testing and
83   reporting results from constrained optimization models.

84   The ISPOR Emerging Good Practices Task Force on Constrained Optimization Methods will produce two
85   reports. In this first report, we introduce readers to constrained optimization methods. We present
86   definitions of important concepts and terminology, and provide examples of health care decisions where
87   constrained optimization methods are already being applied. We also describe the relationship of
88   constrained optimization methods to health economic modeling and simulation methods. The second
89   report will present a series of case studies illustrating the application of these methods including model
90   building, validation, and use.

2.   Definition of Constrained Optimization

93   Constrained optimization is a set of methods designed to efficiently and systematically find the best
94   solution to a problem characterized by a number of potential solutions in the presence of identified
95   constraints. It entails maximizing or minimizing an objective function that represents a quantifiable
96   measure of interest to the decision maker, subject to constraints that restrict the decision maker's freedom
97   of action. Maximizing/minimizing the objective function is carried out by systematically selecting input
98   values for the decision from an allowed set and computing the objective function, in an iterative manner,
99   until the decision yields the best value for the objective function, a.k.a optimum. The decision that gives
100 the optimum is called the "optimal solution". In some optimization problems, two or more different
101 decisions may yield the same optimum. Note that, *programming* and *optimization* are often used as
102 interchangeable terms in the literature, e.g., linear programming and linear optimization. Historically,
103 programming referred to the mathematical description of a plan/schedule, and optimization referred to
104 the process used to achieve the optimal solution described in the program.

106 The components of a constrained optimization problem are its objective function(s), its decision
107 variable(s) and its constraint(s). The **objective function** is a function of the decision variables that
108 represents the quantitative measure that the decision maker aims to minimize/maximize. **Decision
109 variables** are mathematical representation of the constituents of the system for which decisions are being
110 taken to improve the value of the objective function. The **constraints** are the restrictions on decision
111 variables, often pertaining to resources. These restrictions are defined by equalities/inequalities involving
112 functions of decision variables. They determine the allowable/feasible values for the decision variables. In
113 addition, **parameters** are constant values used in objective function and constraints, like the multipliers
114 for the decision variables or bounds in constraints. Each parameter represents an aspect of the decision-
115 making context: for example, a multiplier may refer to the cost of a treatment.

3.   A Simple Illustration of a Constrained Optimization Problem

118 Imagine you are the manager of a health care center, and your aim is to benefit as many patients as
119 possible. Let us say, for the sake of simplicity, you have two types of patients-- regular and severe patients,
120 and the demand for the health service is unlimited for both of these types. Regular patients can achieve
121 two units of health benefits and severe ones can achieve three units. Each patient, irrespective of severity,
122 takes 15 minutes for consultation; only one patient can be seen at any given point in time. You have one
123 hour of total time at your disposal. Regular patients require $25 of medications, and severe patients
124 require $50 of medications. You have a total budget of $150. What is the greatest health benefit this
125 center can achieve given these inputs and constraints?

126 At the outset, this problem seems straightforward. One might decide on four regular patients to use up all
127 the time that is available. This will achieve eight units of health benefit while leaving $50 as excess budget.
128 An alternate approach might be to see as many severe patients as possible since treating each severe
129 patient generates more per capita health benefits. Three patients (totaling $150) would generate 9 health

130 units leaving 15 minutes extra time unused. There are other combinations of regular and severe patients
131 that would generate different levels of health benefits and use resources differently.

132 This is graphically represented in Figure 1, with regular patients on the x-axis and the severe patients on
133 the y-axis. Line CF is the time constraint limiting total time to one hour. Line BG is the budget constraint
134 limiting to $150. Any point to the south-west of these constraints (lines) respectively, will ensure that time
135 and budget do not exceed the respective limits. The combination of these together with non-negativity of
136 the decision variables, gives the feasible region.

137 The lines AB-BD-DF-FA form the boundary of the feasibility space, shown shaded in the figure. In
138 problems that are three or more dimensional, these lines would be hyperplanes. To obtain the optimal
139 solution, the dashed line is established, the slope depends on the relative health units of the two decision
140 variables (i.e., the number of regular and severe patients seen). This dashed line moves from the origin in
141 the north-east direction as shown by the arrow. The optimal solution is two regular patients and two
142 severe patients. This approach uses the entire one-hour time as well as the $150 budget. Since regular and
143 severe patients achieve two- and three-unit health benefits, respectively, we are able to achieve 10 units of
144 health benefit and still meet the time and budget constraints.

145 No other combination of patients is capable of achieving more benefits while still meeting the time and
146 budget constraints. Note that not all resource constraints have to be completely used to attain the optimal
147 solution. This hypothetical example is a small-scale problem with only two decision variables; the number
148 of regular and severe patients seen. Hence, they can be represented graphically with one variable on each
149 axis.

150 With the difficulty in representing larger problems graphically, we turn to mathematical approaches, such
151 as the simplex algorithm to find the solutions. The simplex algorithm is a structured approach of
152 navigating the boundary (represented as lines in two dimensions and hyperplanes in three or more
153 dimensions) of the feasibility space to arrive at the optimal solution. Table 1 summarizes the main
154 components of the example and notes several other dimensions of complexity (linear vs nonlinear,
155 deterministic vs stochastic, static vs dynamic, discrete/integer vs continuous) that can be incorporated
156 into constrained optimization models.

157

158 **Figure 1. Graphical Representation of Solving a Simple Integer Programming Problem**

159

160   The mathematical formulation of the model is as follows:

161

162   Max $f_R x_R + f_L x_L$ (objective function)
163   subject to $c_R x_R + c_L x_L \leq B$ (budget constraint)
164                    $t_R x_R + t_L x_L \leq T$ (time constraint)
165                    $x_R, x_L \geq 0$ and integer   (decision variables)

166

167   Where:
168   c_R, c_L = cost of regular and severe patients, respectively
169   B = total budget available
170   t_R, t_L = time to see regular and severe patients, respectively
171   T = total time available
172   f_R, f_L = health benefits of regular and severe patients, respectively
173   x_R, x_L = number of regular and severe patients, respectively

174

175   In the current version of the problem, the parameters are:
176   $f_R = 2$ health benefit units, $f_L = 3$ health benefit units
177   $c_R = \$25$, $c_L = \$50$, $B = \$150$
178   $t_R = 0.25$ hours, $t_L = 0.25$ hours, $T = 1$ hour

179

180   So the model is as follows:

181

182   Max $2 x_R + 3 x_L$ (objective function)
183   subject to $25 x_R + 50 x_L \leq 150$ (budget constraint)
184                    $0.25 x_R + 0.25 x_L \leq 1$ (time constraint)
185                    $x_R, x_L \geq 0$ and integer

186

187   As described above, Figure 1 illustrates the graphical solution to this model. However, problems with
188   higher dimensionality must use mathematical algorithms to identify the optimal solution. The problem
189   described above falls into the category of *linear optimization*, because although the constraints and the
190   objective function are linear from an algebraic standpoint, the decision variables must be in the form of
191   integers. As it will be discussed further in section 5, there are other optimization modelling frameworks,
192   such as combinatorial, nonlinear, stochastic and dynamic optimization.

193   As the algorithms for *integer optimization* problems can take much longer to solve computationally than
194   those for linear optimization problems, one alternative is to set the integer optimization problem up and
195   solve it as a linear one. If fractional values are obtained, the nearest feasible integers can be used as the
196   final solution. This should be done with caution, however. First, rounding the solution to the nearest
197   integers can result in an infeasible solution or, and second, even if the rounded solution is feasible, it may
198   not be the optimal solution to the original integer optimization problem. *Nonlinear optimization* is
199   suitable when the constraints or the objective function are non-linear. In problems, where there is
200   uncertainty, such as the estimated health benefit of each patient might receive in the above example,
201   *stochastic optimization techniques* can be used.

202   *Dynamic optimization (known commonly as dynamic programming)* formulation might be useful when
203   the optimization problem is not static, that the problem context and parameters change in time and there
204   is an interdependency among the decisions at different time periods (for instance, when decisions made at
205   a given time interval, say number of patients to be seen now, affects the decisions for other time periods,

206 such as the number of patients to be seen tomorrow). Table 1 summarizes the model components in the
207 hypothetical problem, relates it to health services with examples and identifies the specific terminology.

208 **Table 1. Model Summary and Extensions**

209

210 **4.   Problems That Can Be Tackled with Constrained Optimization Approaches**
211

212 In this section, we list several areas within health care where constrained optimization methods have been
213 used in health services. The selected examples do not represent a comprehensive picture of this field, but
214 provide the reader a sense of what is possible. In Table 2, we compare problems using the terminology of
215 the previous section, with respect to decision makers, decisions, objectives, and constraints.

216 **Table 2. Examples of Health Care Decisions for which Constrained Optimization is**
217 **Applicable**

218 **5.   Steps in a Constrained Optimization Process**
219

220 An overview of the main steps involved in a constrained optimization process [33] is described here and
221 presented in Table 3. Some of the steps are common to other types of modeling methods. It is important to
222 emphasize that the process of optimization is iterative, rather than comprising a strictly sequential set of
223 steps.

224 **a) Problem structuring**
225

226 This involves specifying the objective, i.e. goal, and identifying the decision variables, parameters and the
227 constraints involved. These can be specified using words, ideally in non-technical language so that the
228 optimization problem is easily understood. This step needs to be performed in collaboration with all the
229 relevant stakeholders, including decision makers, to ensure all aspects of the optimization problem are
230 captured. As with any modeling technique, it is also crucial to surface key modeling assumptions and
231 appraise them for plausibility and materiality.

232 **b) Mathematical formulation**
233

234 After the optimization problem is specified in words, it needs to be converted into mathematical notation.
235 The standard mathematical notation for any optimization problem involves specifying the objective
236 function and constraint(s) using decision variables and parameters. This also involves specifying whether
237 the goal is to maximize or minimize the objective function. The standard notation for any optimization
238 problem, assuming the goal is to maximize the objective, is as shown below:

239 Maximize $z = f(x_1, x_2, \ldots x_n, p_1, p_2, \ldots p_k)$
240 subject to
241 $c_j(x_1, x_2, \ldots x_n, p_1, p_2, \ldots p_k) \leq C_j$
242 for $j = 1, 2, \ldots m$
243 where, $x_1, x_2, \ldots x_n$ are the decision variables, $f(x_1, x_2, \ldots x_n)$ is the objective function; and $c_j(x_1, x_2, \ldots x_n, p_1,$
244 $p_2, \ldots p_k) \leq C_j$ represent the constraints. Note that the constraints can include both inequality and equality
245 constraints and that the objective function and the constraints also include parameters $p_1, p_2, \ldots p_k$, which
246 are not varied in the optimization problem. Specification of the optimization problem in this mathematical
247 notation allows clear identification of the type (and number) of decision variables, parameters and the
248 constraints. Describing the model in mathematical form will be useful to support model development.

249 **c) Model development**
250

251 The next step after mathematical formulation is model development. Model development involves solving
252 the mathematical problem described in the previous step, and often performed iteratively.   The model
253 should estimate the objective function and the left hand side (LHS) values of the constraints, using the
254 decision variables and parameters as inputs. The complexity of the model can vary widely. Similar to
255 other types of modeling, the complexity of the model will depend on the outputs required, the level of
256 detail included in the model, whether it is linear or non-linear, stochastic or deterministic, static or
257 dynamic.

d) Perform model validation

260 As with any modeling, it is important to ensure that the model developed represents reality with an
261 acceptable degree of fidelity [33]. The requirements of model validation for optimization are more
262 stringent than for, for example, simulation models, due to the need for the model to be valid for all
263 possible combinations of the decision variables. Thus, appropriate caution needs to be taken to ensure
264 that the model assumptions are valid and that the model produces sensible results for the different
265 scenarios. At the very least, the validation should involve checking of the face validity (i.e. experts evaluate
266 model structure, data sources, assumptions, and results), and verification or internal validity (i.e. checking
267 accuracy of coding).

e) Select optimization method

269 This step involves choosing the appropriate optimization method, which is dependent on the type of
270 optimization problem that is addressed. Optimization problems can be broadly classified, depending
271 upon the nature of the objective functions and the constraints-for example, into linear vs non-linear,
272 deterministic vs stochastic, continuous vs discrete, or single vs multi-objective optimization. For instance,
273 if the objective function and constraints consist of linear functions only, the corresponding problem is a
274 linear optimization problem. Similarly, in deterministic optimization, the parameters used in the
275 optimization problem are fixed while in stochastic optimization, uncertainty is incorporated. Optimization
276 problems can be continuous (i.e. decision variables are allowed to have fractional values) or discrete (for
277 example a hospital ward may be either open or closed; the number of CT scanners which a hospital buys
278 must be a whole number).

279 Most optimization problems have a single objective function, however when optimization problems have
280 multiple conflicting objective functions, they are referred to as multi-objective optimization problems. The
281 optimization method chosen needs to be in line with the type of optimization problem under
282 consideration. Once the optimization problem type is clear (e.g. discrete or nonlinear), a number of texts
283 may be consulted for details on solution methods appropriate for that problem type [33-36].

284 Broadly speaking, optimization methods can be categorized into *exact approaches* and *heuristic*
285 *approaches*. Exact approaches iteratively converge to an optimal solution. Examples of these include
286 simplex methods for linear programming and the Newton method or interior point method for non-linear
287 programming [34, 37]. Heuristic approaches provide approximate solutions to optimization problems
288 when an exact approach is unavailable or is computationally expensive. Examples of these techniques
289 include relaxation approaches, evolutionary algorithms (such as genetic algorithms), simulated annealing,
290 swarm optimization, ant colony optimization, and tabu-search. Besides these two approaches (i.e. exact or
291 heuristic), other methods are also available to tackle large-scale problems as well (e.g. decomposition of
292 the large problems to smaller sub-problems).

293 There are software programs that help with optimization; interested readers are referred to the website of
294 INFORMS (www.informs.org) for a list of optimization software. The users need to specify, and more
295 importantly understand, the parameters used as an input for these optimization algorithms (e.g., the
296 termination criteria such as the level of convergence required or the number of iterations).

297   **f) Perform optimization/sensitivity analysis**

298 Optimization involves systematically searching the feasible region for values of decision variables and
299 evaluating the objective function, consecutively, to find a combination of decision variables that achieve
300 the maximum or minimum value of the objective function, using specific algorithms. Once the
301 optimization algorithm has finished running, in some cases, the identified solution can be checked to
302 verify that it satisfies the "optimality conditions" (i.e. Karush-Kuhn-Tucker conditions) [38], which are the
303 mathematical conditions that define the optimality. Once the optimality is confirmed, the results need to
304 be interpreted.

305 First, the results should be checked to see if there is actually a feasible solution to the optimization
306 problem, i.e. whether there is a solution that satisfies all the constraints. If not, then the optimization
307 problem needs to be adjusted, (e.g., relaxing some constraints or adding other decision variables) in order
308 to broaden the feasible solution space. If a feasible optimal solution has been found, the results need to be
309 understood – this involves interpretation of the results to check whether the optimal solution, i.e., values
310 of decision variables, constraints and objective function makes sense.

311 It is also good practice to repeat the optimization with different sets of starting decision variables to
312 ensure the optimal solution is the global optimum rather than local optimum. Sometimes, there may be
313 multiple optimal solutions for the same problem (i.e. multiple combinations of decision variables that
314 provide the same optimal value of objective function). For multi-objective optimization problems (i.e.
315 problems with two or more conflicting objectives), Pareto optimal solutions are constructed from which
316 optimal solution can be identified based on the subjective preferences of the decision maker [39, 40].

317 It is good practice to run the optimization problem using different values of parameters, in order to verify
318 the robustness of the optimization results. Sensitivity analysis is an important part of building confidence
319 in an optimization model, addressing the structural and parametric uncertainties in the model by
320 analyzing how the decision variables and optimum value react to changes in the parameters in the
321 constraints and objective function, which ensures that the optimization model and its solution are good
322 representations of the problem at hand.

323 Sometimes a solution may be the mathematically optimal solution to the specified mathematical problem,
324 but may not be practically implementable. For example, the "optimal" set of nurse rosters may be
325 unacceptable to staff as it involves breaking up existing teams, deploying staff with family responsibilities
326 on night shifts, or reducing overtime pay to level where the employment is no longer attractive. Analysts
327 should resist the temptation to spring their optimal solution on unsuspecting stakeholders, expecting
328 grateful acceptance: rather, those affected by the model should be kept in the loop through the modeling
329 process. The optimal solution may come as a surprise: it is important to allow space in the modeling
330 process to explore fully and openly concerns about whether the "optimal" solution is indeed the one the
331 organization should implement.

332   **g) Report results**
333

334 The final optimal solution, and if applicable, the results of the sensitivity analyses should be reported. This
335 will include the results of the optimum 'objective function' achieved and the set of 'decision variables' at
336 which the optimal solution is found. Both the numerical values (i.e. the mathematical solution) and the
337 physical interpretation, i.e., the non-technical text describing the meaning of numerical values, should be
338 presented. The optimal solution identified can be contextualized in terms of how much 'better' it is
339 compared to the current state. For example, the results can be presented as improvement in benefits such
340 as QALYs or reduction in costs.
341

342 It is often necessary to report the optimization method used and the results of the 'performance' of the
343 optimization algorithm, e.g., number of iterations to the solution, computational time, convergence level,
344 etc. This is important as it helps users understand whether a particular algorithm can be used "online" in a
345 responsive fashion, or only when there is significant time available, e.g. in a planning context. Dashboards
346 can be useful to visualize these benefits and communicate the insights gained from the optimal solution
347 and sensitivity analyses.
348

349 **h) Decision making**
350

351 The final optimal solution and its implications for policy/service reconfiguration should be presented to all
352 the relevant stakeholders. This typically involves a plan for amending the 'decision variables', (e.g., shift
353 patterns, screening frequency--see Table 2 for examples of decision variables--to those identified in the
354 optimal solution). Before an optimal solution can be implemented, it will require getting the 'buy-in' from
355 the decision makers and all the stakeholders, e.g., frontline staff such as nurses, hospital managers, etc., to
356 ensure that the numerical 'optimal' solution found can be operationalized in a 'real' clinical setting. It is
357 important to have the involvement of decision makers throughout the whole optimization process to
358 ensure that it does not become a purely numerical exercise, but rather something that is implemented in
359 real life. After the decision is made, data should still be collected to assess the efficiency and demonstrate
360 the benefits of the implementation of the optimal solution.
361

362 If decision makers are not directly involved in model development they may choose not to implement the
363 "optimal" solution as it comes from the model. This is because the model may fail to capture key aspects
364 of the problem (for example, the model may maximize aggregate health benefits but the decision maker
365 may have a specific concern for health benefits for some disadvantaged subgroup). This does not
366 (necessarily) mean that the optimization modeling has not been useful – enabling a decision maker to see
367 how much health benefit must be sacrificed to satisfy her equity objective may prove to be beneficial
368 towards the overall objective. After the decision is made the story does not come to an end: data should
369 continue to be collected to demonstrate the benefits of whatever solution is implemented, as well as
370 guiding future decision making.
371

372 Table 3 presents the two different stages in optimization i.e. the modeling stage and optimization stage,
373 highlighting that model development is necessary before optimization can be performed. The goal of
374 constrained optimization is to identify an optimal solution that maximizes or minimizes a particular
375 objective subject to existing constraints.

376 **Table 3. Steps in an Optimization Process**

377

378 **6.   Relationship of Constrained Optimization to Related Fields**
379

380 The use of constrained optimization can be classified into two categories. The first category is the use of
381 constrained optimization as a decision-making tool. The simple illustration in section 3 and all the
382 examples in section 4 are considered to fall under this category. The second category is the use of
383 constrained optimization as an auxiliary analysis tool. In this category, optimization is an embedded tool
384 and the results of which are often not the end results of a decision problem, but rather they are used as
385 inputs for other analysis/modeling methods (e.g. optimization used in the multiple criteria decision
386 making; in calibrating the inputs for health economic or dynamic simulation models; in machine learning
387 and other statistical analysis methods like solving regression models or propensity score matching).

388 As a decision-making tool, optimization is complementary to other modeling methods such as health
389 economic modeling, simulation modeling and descriptive, predictive (e.g. machine learning) and

390 prescriptive analytics. Most modeling methods typically only evaluate a few different scenarios and
391 determine a good scenario *within* the available options. In contrast, the aim of optimization methods is to
392 efficiently identify the *best* solution overall, given the constraints. In the absence of using optimization
393 methods, a brute force approach, in which all possible options are sequentially evaluated and the best
394 solution is identified among them, might be possible for some problems. However, for most problems, it is
395 too complex and too time consuming to identify and evaluate all possible options. Optimization methods
396 and heuristic approaches might use efficient algorithms to identify the optimal solution quickly, which
397 would otherwise be very difficult and time consuming.

398 Also, model development using these other methods might be necessary before optimization, especially in
399 situations where the objective function or constraints cannot be represented in a simple functional form.
400 Thus, all models currently used in health care such as health economic models, dynamic simulation
401 models and predictive analytics (including machine learning) can be used in conjunction with
402 optimization methods.

a) Constrained Optimization Methods Compared with Traditional Health Economic Modeling in Health Technology Assessments

406 Constrained optimization methods differ substantially from health economic modeling methods
407 traditionally used in health technology assessment processes [41]. The main difference between the two
408 approaches is that traditional health economic modeling approaches, such as Markov models, are built to
409 estimate the costs and effects of different diagnostic and treatment options. If decision makers are basing
410 their judgements on modeling results, they may not formally consider the constraints and resource
411 implications in the system. Constrained optimization methods provide a structured approach to optimize
412 the decision problem and to present the best alternatives given an optimization criterion, such as
413 constrained budget or availability of resources.

414 These differences have major implications. There is an opportunity to learn from optimization methods to
415 improve Health Technology Assessment (HTA) processes [42-46]. Optimization is a valuable means of
416 capturing the dynamics and complexity of the health system to inform decision making for several
417 reasons. Constrained optimization methods can:

i. Explicitly take budget constraints into account - Informed decision making about resource
   allocation requires an external estimate of the decision-maker's willingness to pay for a unit of
   health outcome – the threshold. Decision making based on traditional health economic models
   then relies on the principle that by repeatedly applying the threshold to individual HTA decisions,
   optimization of the allocation of health resources will be achieved.

   However, the focus of health economics (HE) is usually about relative efficiency without explicit
   consideration of budget because many jurisdictions do not explicitly implement a constrained
   budget nor do they employ mechanisms to evaluate retrospectively cost-effectiveness of medical
   technologies currently in use.

ii. Address multiple resource constraints in the health system, such as resource capacity: Constrained
    optimization methods also allow consideration of the effect of other constraints in the health
    system, such as capacity or short-term inefficiencies. Capacity constraints are usually neglected in
    health economic models. In HE models, the outcomes are central to decision makers while the
    process to arrive at these outcomes is most of the time ignored.

    For health policy makers and health care planners, such capacity considerations are critical and
    cannot be neglected. Likewise, some technologies are known for short-term inefficiencies, e.g.,
    large equipment such as PET-MR imaging, are usually not taken into consideration. It takes a

437   certain amount of time before a new device operates efficiently, and such short-term inefficiencies
438   do influence implementation [47].

439 iii.   Account for system behavior and decisions over time: Traditional health economic models are
440   often limited to informing a decision of a single technology at a single point in time. Health
441   economic models with a clinical perspective, such as a whole disease model [48, 49], or a
442   treatment sequencing model, may allow the full clinical pathway to be framed as a constrained
443   optimization problem that accounts for both intended and unintended consequences of health
444   system interventions over time with feedback mechanisms in the system.

445

446   Each combination of decisions within the pathway can be a potential solution, constrained by the
447   feasibility of each decision, e.g., the licensed indication for various treatments within a clinical
448   pathway. These whole disease and treatment sequencing models can evaluate alternative guidance
449   configurations and report the performance in terms of an objective function (cost per QALY, net
450   monetary benefit) [50, 51].

451 iv.   Inform decision makers about implementability of solutions that are recommended: Health
452   economic models are not typically constrained – it is assumed that resources are available as
453   required and are thus affordable, similarly the evidence used in the models come from controlled
454   clinical settings, which are idealized settings compared to real clinical setting. An advantage of
455   constrained optimization is the ability to obtain optimal solutions to decision problems and have
456   sensitivity analyses performed. Such analyses inform decision makers about alternate realistic
457   solutions that are feasible and close to the optimal solution.

458 Thus, in some sense, classic health economics models are 'hypothetical' to illustrate the potential value as
459 measured by a specific outcome with respect to cost, whereas optimization is focused on what can be
460 achieved in an operational context. This suggests constrained optimization methods have great value for
461 informing decisions about the ability to implement a clinical intervention, program, or policy as they
462 actually consider these constraints in the modeling approach.

463

464   **b) Constrained Optimization Methods Compared with Dynamic Simulation Models**

465

466 Dynamic simulation modeling methods (DSMs), such as system dynamics, discrete event simulation and
467 agent based modeling are used to design and develop mathematical representations, i.e., formal models, of
468 the operation of processes and systems. They are used to experiment with and test interventions and
469 scenarios and their consequences over time in order to advance the understanding of the system or
470 process, communicate findings, and inform management and policy design [30-32, 52-54]. These
471 methods have been broadly used in health applications [55-57].

472 Unlike constrained optimization methods, DSMs do not produce a specific solution. Rather they allow for
473 the evaluation of a range of possible or feasible scenarios or intervention options that may or may not
474 improve the system's performance. Constrained optimization methods, in general, seek to provide the
475 answer to which of those options is the "best". Hence, the types of problems and questions that can be
476 addressed with DSMs [30-32] are different from those that are addressed with optimization methods.
477 However, both types of methods can be complementary to each other in helping us to better understand
478 systems.

479 Traditionally, constrained optimization methods have served two distinct purposes in DSM development.
480 1) model calibration – fitting suitable model variables to past time series is discussed elsewhere [30-32];
481 2) evaluating a policy's performance/effect relative to a criterion or set of criteria. However, the
482 complexity of DSMs compared to simple analytic models may render exact constrained optimization
483 approaches cumbersome, inappropriate and potentially infeasible due to the large search space e.g., using
484 methods of optimal control.

485 Due to this complexity, alternatives to exact approaches such as heuristic search strategies are available.
486 Historically, these types of methods have been used in system dynamics and other DSMs. Due to their
487 heuristic nature, there is no certainty of finding the "best" or optimal parameter set rather "good enough"
488 solutions. Hence, the ranges assigned need careful consideration in order to get "good" solutions, i.e.,
489 prior knowledge of sensible ranges both from knowledge about the system and knowledge gained from
490 model building.

491 Optimization is used as part of system dynamics to gain insight about policy design and strategy design,
492 particularly when the traditional analysis of feedback mechanisms becomes risky due to the large numbers
493 of loops in a model [58]. Similar procedures to evaluate policies and strategies can be can be utilized in
494 discrete event simulation (DES) and agent based modeling (ABM), e.g., simulated annealing algorithms
495 and genetic algorithms.

c) Constrained Optimization Methods as Part of Analytics

497 Constrained optimization methods fall within the area of analytics as defined by the Institute for
498 Operations Research and the Management Sciences (INFORMS, https://www.informs.org/Sites/Getting-
499 Started-With-Analytics). Analytics can be classified into: descriptive, predictive and prescriptive analytics
500 (Figure 2), and discussed below. Constrained optimization methods are a special form of prescriptive
501 analytics.

502   i.   Descriptive analytics concern the use of historical data to describe a phenomenon of interest—
503   with a particular focus on visual displays of patterns in the data. Descriptive analytics is
504   differentiated from descriptive analysis which uses statistical methods to test hypotheses about
505   relationships among variables in the data. Health services research typically uses theory and
506   concepts to identify hypotheses, and historical data are used to test these hypotheses using
507   statistical methods. Examples may include natural history of aging, disease progression,
508   evaluation of clinical interventions, policy interventions, and many others. Traditional health
509   services for the most part falls within the area of descriptive analytics.
510   ii.   Predictive analytics and machine learning focus on forecasting the future states of disease or
511   states of systems. With the increased volume and dimensions of health care data, especially
512   medical claims and electronic medical record data, and the ability to link to other information
513   such as feeds from personal devices and socio demographic data, big data methods such as
514   machine learning are garnering increased attention [59].
515   Machine learning methods, such as predictive modeling and clustering, have an important
516   intersection with constrained optimization methods. Machine learning methods are valuable
517   for addressing problems involving classification, as well as data dimension reduction issues.
518   And maybe most importantly, optimization often needs forecasts and estimates as inputs,
519   which can be obtained from the results of machine learning algorithms. A discussion of
520   machine learning methods is beyond the scope of this paper.

521   However, the interested reader will find a detailed introduction elsewhere [60, 61]. Machine
522   learning has the ability to "mine" data sets and discover trends or patterns. These are often
523   valuable to establish thresholds or parameter values in optimization models, where it is
524   otherwise difficult to determine the values. Constrained optimization can also leverage the
525   ability of machine learning to reduce high dimensionality of data, say with thousands or
526   millions of variables to key variables.

527   iii.   Prescriptive analytics uses the understanding of systems, both the historical and future based
528   on historical (descriptive) and predictive analytics respectively to determine future course of
529   action/decisions. Traditional (without optimization) clinical trials and interventions fall under
530   the category of prescriptive analytics ("Change what will happen" in figure). Constrained
531   optimization is a specialized form of prescriptive analytics, since it helps with determining the
532   *optimal* decision or course of action in the presence of constraints
533   (https://www.informs.org/Sites/Getting-Started-With-Analytics/Analytics-Success-Stories).
534

535 **Figure 2. Descriptive, Predictive, and Prescriptive Analytics.**

536

537 **7.   Summary and Conclusions**

538

539 This is the first report of the ISPOR Constrained Optimization Methods Emerging Good Practices Task
540 Force. It introduces readers to the application of constrained optimization methods to health care systems
541 and patient outcomes research problems. Such methods provide a means of identifying the best policy
542 choice or clinical intervention given a specific goal and given a specified set of constraints. Constrained
543 optimization methods are already widely used in health care in areas such as choosing the optimal location
544 for new facilities, making the most efficient use of operating room capacity, etc.

545 However, they have been less widely used for decision making about clinical interventions for patients.
546 Constrained optimization methods are highly complementary to traditional health economic modeling
547 methods and dynamic simulation modeling—providing a systematic and efficient method for selecting the
548 best policy or clinical alternative in the face of large numbers of decision variables, constraints, and
549 potential solutions. As health care data continues to rapidly evolve in terms of volume, velocity, and
550 complexity, we expect that machine learning techniques will also be increasingly used for the development
551 of models that can subsequently be optimized.

552 In this report, we introduce readers to the vocabulary of constrained optimization models and outline a
553 broad set of models available to analysts for a range of health care problems.   We illustrate the
554 formulation of a linear program to maximize the health benefit generated in treating a mix of "regular"
555 and "severe" patients subject to time and budget constraints and solve the problem graphically. Although
556 simple, this example illustrates many of the key features of constrained optimization problems that would
557 commonly be encountered in health care.

558 In the second task force report, we describe several case studies that illustrate the formulation, estimation,
559 evaluation, and use of constrained optimization models. The purpose is to illustrate actual applications of
560 constrained optimization problems in health care that are more complex than the simple example
561 described in the current paper and make recommendations on emerging good practices for the use of
562 optimization methods in health care research.

563

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683 **Optimization TFR Acknowledgements**

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699 **Figure 1. Graphical Representation of Solving a Simple Integer Programming Problem**
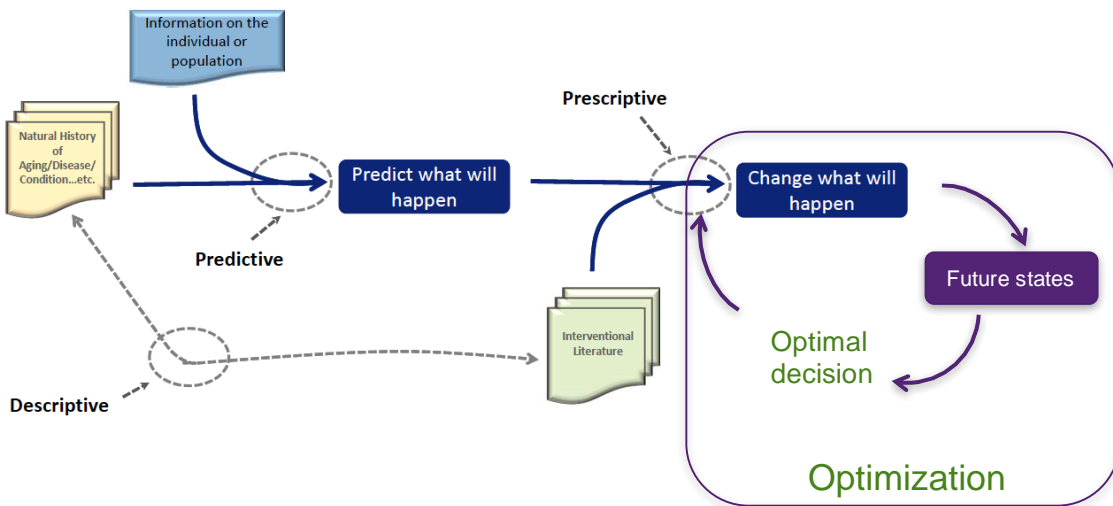
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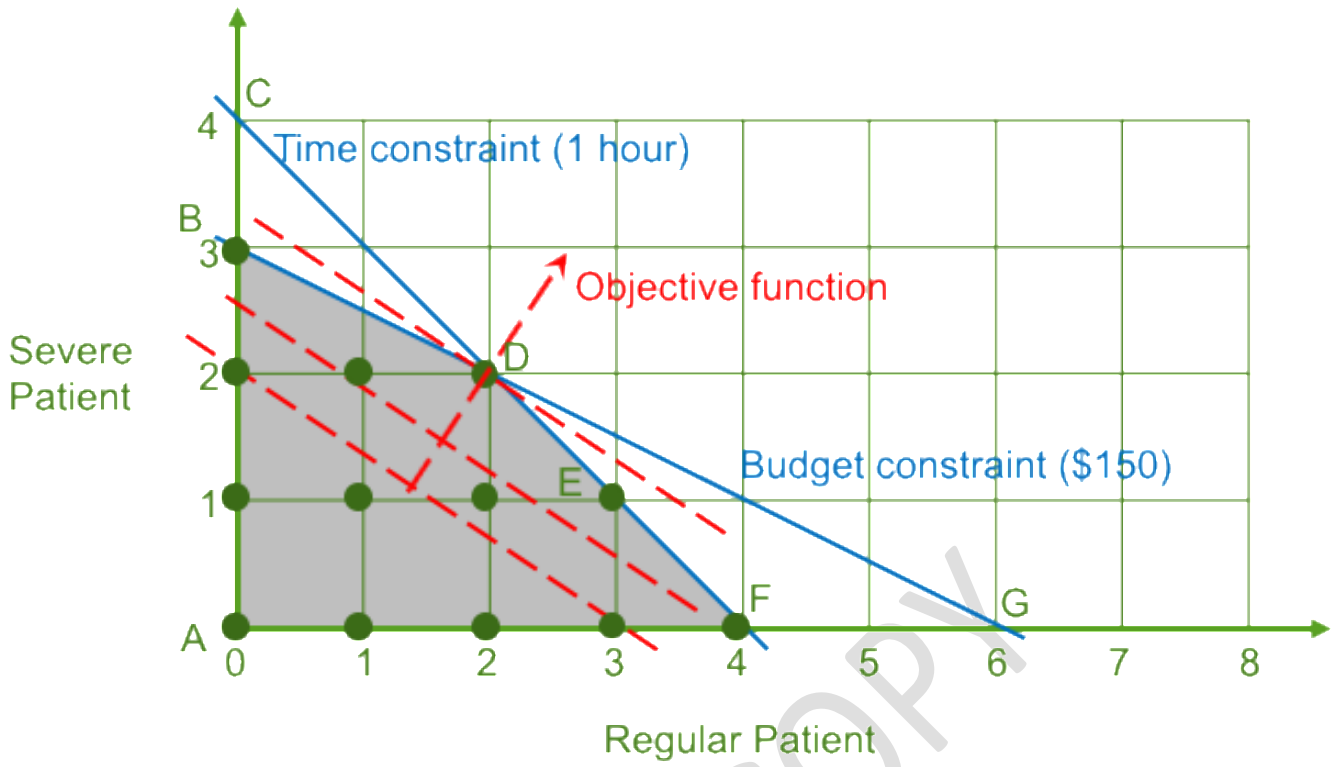
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703 **Figure 2. Descriptive, Predictive, and Prescriptive Analytics.**

Wilson, ISPOR 2014

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709 **Table 1. Model Summary and Extensions**

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	Hypothetical problem	**Real-life Health Services**	**Terminology**
Aim	Maximize health/health care benefits	Maximize health/health care benefits	Objective function
Options available	Regular or severe patients	Service lines, case mix, service mix, etc.	Decision variables
Constraints	Total cost $\leq$ \$15 Total time $\leq$ 1 hour	Budget constraint Time constraint Resource constraint (e.g. staff, beds, etc.)	Constraints
Evidence base	Cost of each patient, health benefits of each patient and the time taken for consultation	Costs, health benefits, and other relevant data associated with each intervention to be selected	Model (to determine the objective function and constraints)
Complexity	*Static* The problem does not have a time component; decision made in one time period does not affect decisions made in another *Deterministic* All the information is assumed to be certain (e.g Cost of each patients, health benefits of each patient and the time taken for consultation) *Linear* (i.e. each additional patient costs the same and achieves same health benefits) *Integer/discrete* The decision variables (number of patients) can only take discrete and integer values	*Dynamic* The optimization problem and parameters may change in different time points, and the decision made at any point in time can affect decisions at later time points (e.g. there can be a capacity constraint defined on 2 months, whereas the planning cycle is 1 month) *Stochastic* Know that the information is uncertain (i.e. uncertainty in the costs and benefits of the interventions) *Non-linear* (objective function or constraints may have a non-linear relationship with the model parameters, e.g. total costs and QALYs typically have a non-linear relationship with the model parameters) *Continuous* The decision variables can take fractional values (e.g. number of hours)	Optimization method

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740 **Table 2. Examples of Health Care Decisions for which Constrained Optimization is**
741 **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	Maximize population health	Overall health budget, other legal constraints for equity
Resource allocation for infectious disease management	Public health agencies, health protection agencies	Optimal vaccination coverage level	Minimize disease outbreaks and total costs	Availability of medicines, disease dynamics of the epidemic
Allocation of donated organs	Organ banks, transplant service centers	Matching of organs and recipients	Maximize matching of 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
Outpatient scheduling	Clinical department managers	Detailed schedules	Minimize over- and under-utilization of health care staff	Availability of appointment slots
Hospital facility location	Strategic health planners	Set of physical sites for hospitals	Ensure equitable access to hospitals	Maximum acceptable travel time to reach a hospital

742

743 **Table 3. Steps in an Optimization Process**

Stage	Step	Description
Modeling	Problem structuring	Specify the objective and constraints, identify decision variables and parameters, and list and appraise model assumptions
	Mathematical formulation	Present the objective function and constraints in mathematical notation using decision variables and

		parameters
	Model development	Develop the model; representing the objective function and constraints in mathematical notation using decision variables and parameters
	Model validation	Ensure the model is appropriate for evaluating all possible scenarios (i.e. different combinations of decision variables and parameters)
Optimization	Select optimization method	Choose an appropriate optimization method and algorithm based on the characteristics of the problem
	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
	Report results	Report the results of optimal solution and sensitivity analyses
	Decision making	Interpret the optimal solution and use it for decision making

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