MDM Policy & Practice
1–14

DOI: 10.1177/2381468318774804
journals.sagepub.com/home/mdm

Health Technology Optimization Analysis: Conceptual Approach and Illustrative Application

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Abstract

We present a conceptual approach to determine the optimal solution to delivering a health technology, consistent with the objective of maximizing patient outcomes subject to resources available to a publicly funded health system. The article addresses two key policy questions: 1) adding system values through appropriate planning of health services delivery and 2) considering the tradeoff between patient outcomes and costs to the health system through appropriate use of health technologies for conditions with time-dependent treatment outcomes. We develop a health technology optimization framework that considers geographical variation and searches for the best delivery method through a pairwise comparison of all possible strategies, factoring in controlled variables including disease epidemiology, time or distance to hospitals, available medical services, treatment eligibility, treatment efficacy, and costs. Taking variations of these factors into account would help support a more efficient allocation of health resources. Drawing identified strategies together then creates a map of optimal strategies. We apply the proposed method to a policy-relevant health technology assessment of endovascular therapy (EVT) for treating acute ischemic stroke. The best strategy for providing EVT relies on the geographical location of stroke onset and the decision maker's preference for either patient outcomes or economic efficiency. The proposed method produced an optimization map showing the optimal strategy for EVT delivery, which maximizes patient outcomes while minimizing health system costs. In the illustrative case study, there were no tradeoffs between health outcomes and costs, meaning that the delivery strategies that were clinically optimal for patients were also the most cost-effective. In conclusion, the health technology optimization approach is a useful tool for informing implementation decisions and coordinating the delivery of complex health services such as EVT.

Keywords

cost-effectiveness analysis, endovascular therapy, health system optimization, health system planning, health technology assessment, stroke

Date received: September 14, 2017; accepted: April 6, 2018

Comparative cost-effectiveness analysis (CEA) is widely used to inform decision making on priority setting in health care.[1–4] However, CEA provides limited information on how to appropriately use health technologies for conditions with time-dependent treatment outcomes (e.g., acute ischemic stroke),[5–9] particularly information on how to promote patient outcomes while minimizing the burden on scarce health system resources. There is room for outcome and cost improvement through appropriate use of such health technologies, which would

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consider geographical location, population density, disease epidemiology, and distribution of available medical services. Taking variations of these factors into account in system planning would help support a more efficient allocation of health resources, especially in jurisdictions with a degree of population dispersion.

In many jurisdictions, there are health technology assessment (HTA) programs that support decision making on the adoption and use of health technology.[10–12] An HTA report incorporates comprehensive judgement about the use of a particular health technology in terms of its relevance to policy recommendations, social demographics, ethics, efficacy, and safety considerations, and provides details on the cost components considered, how to value future costs and effectiveness, and how the costs and effectiveness are aggregated for different populations.[13,14] Appropriately delivering health services affects patient outcomes and, subsequently, costs to the health system, and thus such factors should be taken into consideration at the level of health system planning; however, these implications of system planning and appropriate use of health services are uncommonly mentioned in both HTA reports and CEA studies.

To move beyond the standard approach used in HTA reports and CEA studies, we present a conceptual approach to explore health technology optimization (HTO), which determines the optimal solution to delivering a health technology, consistent with the objective of maximizing patient outcomes subject to the resources available to the health system. This HTO approach is only relevant to situations where a new health technology or treatment is proven to result in better patient outcomes when delivered in an optimal health care scenario. The proposed HTO approach builds on the methodology used in HTAs as an extension of existing CEA studies. The HTO approach addresses two categories of health policy concerns: 1) adding system values through appropriate planning of health services delivery and 2) considering the tradeoff between patient outcomes and costs to the health system. We present this approach with an application to a policy-relevant HTA of endovascular therapy (EVT) for treating acute ischemic stroke (AIS). The illustrative case study focuses on how an HTO solution for the delivery of a health technology such as EVT improves patient outcomes and economic efficiency, and on what the tradeoff is between patient outcomes and system costs. The proposed HTO approach is applicable to other disease conditions for which the treatment outcomes are affected by the geographical location and distribution of available medical services.

Our analysis was motivated by policy requirement for the implementation of EVT in the province of Alberta, Canada. While Alberta is in a good position to provide EVT, benefiting from the initiative of a successful international randomized controlled trial,[15] appropriate use of the treatment is an outstanding issue to be addressed. Currently in Alberta, EVT is provided in two comprehensive stroke centers (CSCs) in the cities of Edmonton and Calgary, and there are 15 additional primary stroke centers (PSCs) scattered across the province. In the current transportation model, patients eligible for EVT will be transported to a PSC for medical examination and initial treatment if they are close to the PSC, and those within a certain distance (e.g., a radius of 200 km) from a CSC will be directly transported to the CSC. However, the decision on whether to bypass the PSC is unclear in areas that are a certain distance from both CSCs and PSCs. Our analysis offers a health economic rationale for policy in these ambiguous areas.

Lessons from EVT for AIS provide insight into the impact of local geography and population dispersion on care delivery planning. Delays in treatment for patients who start with a diagnosis of a proximal large-vessel occlusion and receive intravenous alteplase at a local hospital before interhospital transfer to access EVT have worse outcomes compared with those who are directly transferred to an endovascular-capable hospital.[15–18] However, if the stroke onset location is relatively closer to a local hospital (PSC) than an endovascular-capable hospital (CSC), patients may benefit from going to the PSC for faster intravenous alteplase access and diagnostic determination of endovascular eligibility. Therefore, the decision to bypass or go to the PSC depends on the travel time (distances) to the local hospital and the endovascular-capable hospital, the likelihood of EVT eligibility, and the time-dependent treatment effect.

Institute of Health Economics, Edmonton, Alberta, Canada (CY, YZ); University of Calgary, Calgary, Alberta, Canada (MDH, NK); Cardiovascular Health & Stroke SCN, Alberta Health Services, Alberta, Canada (BM); University of Alberta, Edmonton, Alberta, Canada (TJ, AWC); Alberta Health Services, Edmonton, Alberta, Canada (SA, AWC). The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research was done at the Institute of Health Economics, and results from the research were presented at the 8th Annual Canadian Stroke Congress, September 9–11, 2017, Calgary, Alberta, Canada, and will be presented at the Health Technology Assessment international (HTAi) 2018 annual meeting, June 1–5, 2018, Vancouver, British Columbia, Canada. Financial support for this research was provided entirely by a financial contribution from Alberta Health through the Alberta Health Technologies Decision Process, the Alberta model for health technology assessment and policy analysis. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the study.

Methods

EVT and Transportation Methods/Strategies for Acute Ischemic Stroke

We illustrate the HTO approach with an example of EVT for patients with AIS in Alberta. The standard treatment for AIS is intravenous alteplase (a type of recombinant tissue plasminogen activator).[5,19,20] Recent randomized controlled trials have proven the efficacy and safety of EVT in AIS,[15,21–24] and the cost-effectiveness of EVT (either with or without alteplase depending on clinical factors) compared with alteplase alone has been demonstrated in various studies.[25–29] Due to constraints in facilities and expertise, the EVT procedure can only be performed in CSCs, which are typically located in tertiary hospitals in metropolitan areas, while alteplase treatment is an intravenous drug and is more widely available in PSCs, in local hospitals.

This system setting and time-sensitive nature of the disease treatment produce two types of patient transportation methods. Under the first method, known as *mothership*, the emergency medical services (EMS) transport the patient directly to a CSC, where treatment with alteplase and/or EVT may be administered. Under the second method, known as *drip-and-ship*, patients are transported to a local PSC, where medical assessment is made and alteplase is administered. Patients who are additionally eligible for EVT are then transported to a CSC, and those who are ineligible for EVT stay at the PSC.[7,30]

The choice of a mothership or drip-and-ship approach is influenced by transport time, as both treatments (alteplase and EVT) are extremely time-sensitive, as well as by diagnostic accuracy, as clinical diagnoses of stroke type are imperfect. Brain imaging is required to definitively determine eligibility for treatment and, in the system setting, this is currently only available at a hospital facility. Finally, EVT is a more effective treatment than alteplase for the subset of patients eligible for EVT, but alteplase is more widely applicable to a greater proportion of ischemic stroke victims.

The major potential advantage of the mothership method is speedy access to EVT for eligible patients, a treatment that is associated with better patient outcomes (e.g., a lower modified Rankin Scale [mRS] score). Within a given geographical radius, the mothership method is less costly for this cohort due to lower transportation costs and better long-term patient outcomes with the associated reduced potential of health resource consumption in the long run, comparing untreated patients with worse patient outcomes.[31] However, due to the potential for false-positive decisions in the field assessment, transporting patients who are actually not eligible for EVT to a CSC results in unnecessary transportation costs and delays in treatment (as otherwise these patients could have received treatment at the closest PSC). Under the drip-and-ship method, while some eligible patients experience delays in receiving EVT, patients in general get faster access to alteplase administration. The advantages of the drip-and-ship method thus include the potential of better patient outcomes (as they receive alteplase treatment faster), as well as lower transportation costs.

Overall, the problem of stroke transport and treatment is an ideal case study for HTO. An appropriate selection of a method/strategy would improve both patient outcomes and system value. There are six mutually exclusive strategies by mode of transportation in our system settings, as shown in Table 1.

Definition of Geographical Areas

An essential attribute of the analysis is to assess the impact of time from stroke onset to treatment on both clinical and economic outcomes. Given that patients may unexpectedly suffer a stroke anywhere, it is important to classify patients so that the transportation distance or time from onset scene to the closest PSC or CSC can be well defined. The basic geographical unit adopted in the analysis is the census dissemination area (DA) defined by Statistics Canada, which is the fourth-level (lowest) census geographical unit of Canada. Each DA has a representative point (i.e., coordinate point) that was determined using a population-weighted method. This analysis assumed that the transportation time from a representative point to a PSC/CSC represented the time for all patients within that DA. We cluster DAs in the province into five regions according to their distance to a PSC/CSC:

- *Green Regions:* consist of DAs that have a driving distance of less than 30 kilometers to a PSC
- *Metro Regions:* consist of metropolitan areas surrounding Edmonton and Calgary
- *North Region:* consists of northern areas that are closest to one of three PSCs in northern Alberta
- *West Region:* consists of western areas that are located west of two PSCs in western Alberta
- *Other Region:* consists of DAs not included in those described above

Table 1 Transportation Strategies: Definitions and Time/Distance

Number	Strategy	Definition	Time/Distance
Mothership method			
1	Mothership by ground	Patients are transported by EMS ambulance directly from onset scene to the CSC	EMS driving time from a DA representative point to the closest CSC
2	Mothership by flight	Patients are transported by EMS ambulance to the closest airport or local hospital with a helicopter-landing zone, and then transported by flight to the CSC	Driving time from a DA representative point to the closest hospital where a helicopter can land (or closest airport, if a fixed-wing aircraft is used), plus flight time and distance to the closest CSC
Drip-and-ship method			
Drip-and-ship by ground		EMS ambulance is used to transport patients from onset scene to the PSC and then the CSC (if necessary), with a focus on minimizing time in one of two ways:	
3	Minimum time to alteplase	Patients are transported to the closest PSC so that the time before receiving alteplase is minimized	Driving time from a DA representative point to the closest PSC, plus driving time from the PSC to CSC
4	Minimum time to EVT	The PSC is selected in a way that minimizes the total transportation time from onset scene to the PSC plus the transportation time from the PSC to the CSC	Driving time from a DA representative point to a PSC that minimizes the total transportation time from onset scene to the PSC plus the transportation time from the PSC to CSC, plus driving time from the PSC to CSC
Drip-and-ship by flight		EMS ambulance is used to transport patients from onset scene to the PSC. After assessment and treatment with alteplase (if applicable), patients eligible for EVT will be transported by flight to the CSC, with a focus on minimizing time in one of two ways:	
5	Minimum time to alteplase	Patients are transported to the closest PSC so that the time before receiving alteplase is minimized	Driving time from a dissemination area representative point to the closest PSC, plus flight time and distance from the PSC to CSC
6	Minimum time to EVT	The PSC is selected in a way that minimizes the total transportation time from onset scene to the PSC plus the transportation time from the PSC to the CSC	Driving time from a dissemination area representative point to a PSC that minimizes total transportation time from onset scene to the PSC plus from the PSC to CSC, plus flight time and distance from the PSC to CSC

CSC, comprehensive stroke center; DA, dissemination area; EMS, emergency medical services; EVT, endovascular therapy; PSC, primary stroke center.

Definition of Optimal Strategy

Whether or not a strategy is optimal depends on the priority of the decision maker. The analysis assesses two potential types of decision approaches, in which the decision maker prioritizes either producing the best patient outcomes or providing the most economically efficient health services. Accordingly, "optimal strategy" can be defined in one of two ways:

- *Best in clinical outcomes:* A strategy is considered to be optimal if patients under the strategy have the highest likelihood of achieving good outcomes than under other strategies.
- *Best in system value:* A strategy is considered to be optimal if it is associated with the highest incremental net monetary benefit (iNMB) among the six strategies, at a given willingness-to-pay threshold.

The first approach defines optimal strategy based on patient outcomes only, while the second approach considers both cost and health benefit measured using quality-adjusted life years (QALYs). The iNMB is an equivalent expression of an incremental cost-effectiveness ratio (ICER) that measures the comparative cost-effectiveness, with the highest iNMB indicating the most favorable option.[32–34] We applied a threshold of $50,000 per QALY in the baseline analysis and \$100,000 and \$200,000 per QALY in the sensitivity analysis.[35]

We judge the strategies by establishing metrics that align the six strategies with the optimal criteria defined above. More specifically, we compare the six mutually exclusive strategies in pairs and identify the pair that meets the optimal criteria within each DA. The optimal solution is the set of identified strategies.

Analytic Model

Given that time is important in that early treatment improves outcomes,[9,24,30] we developed an individual patient-level analytic matrix that captured the impact of geographical location and distribution of available medical services. The matrix was applied to calculate the expected patient outcomes and associated costs for patients within each DA. It is uncertain if a patient is eligible for EVT plus alteplase, EVT alone, or alteplase alone until brain and neurovascular imaging is completed. We therefore developed a two-stage model to assess the eligibility and cost under the mothership method compared with the drip-and-ship method. For the first stage, a decision tree model (Figure A.1 in the appendix) was developed under the mothership method versus the drip-and-ship method with a time horizon from onset to 90 days poststroke, including EMS transportation, emergency department visit, and acute hospitalization. Under the mothership method, patients were first assessed in the field, with those eligible for EVT transported directly to a CSC. Note that, due to the potential for false-positive assessment in the field, some patients who were not eligible for EVT were shipped to the CSC, resulting in unnecessary transportation costs and delays in treatment. Under the drip-and-ship method, patients were transported to a PSC for assessment and alteplase treatment (if applicable). Based on results of the assessment at the PSC, patients who are eligible for EVT were shipped to a CSC, and those who were not stayed at the PSC. Note that the potential for errors during the assessment at the PSC could result in EVT-eligible patients with false-negative results not being transferred to the CSC, and those who are ineligible for EVT with false-positive results being incorrectly transferred to the CSC; the potential for such errors was taken into account in the model. The outcomes from the first-stage decision tree model were the costs per patient and the likelihood of a patient receiving EVT plus alteplase, EVT alone, or alteplase alone.

For the second stage, the long-term costs were assessed using a Markov model (Figure A.2 in the appendix). The outcomes of the Markov model were the long-term costs of functionally independent (i.e., a mRS score between 0 and 2) and disabled (i.e., a mRS score between 3 and 5) patients at 90 days poststroke. The logic behind the Markov model is that health care costs for stroke patients in the long run rely on patients' health status at discharge. In other words, patients with functional independence (mRS 0–2) or death (mRS 6) at discharge were associated with less resource use than surviving disabled patients (mRS 3–5).[27,29,31]

The outcomes generated from the two-stage model in combination with time-dependent clinical efficacy, travel time/distance, and death rates on stroke were applied to assess the optimal strategy for each DA. The analysis adopted a payer's perspective and considered direct medical service costs, including costs of transportation, diagnostic imaging, physician services, hospitalization, outpatient visits, rehabilitation, and long-term care. Costs were discounted at an annual rate of 5%.

Model Inputs

Transportation time is a function of distance and transport modality and plays an important role in estimating clinical and economic outcomes, because treatment effect is time-dependent and transportation costs are charged on the basis of mileage (for fixed-wing aircraft) or mission time (for helicopters). Transportation time or distance was considered in the analysis for each strategy, as defined in Table 1.

Clinical and epidemiological inputs included the incidence of acute ischemic stroke and hemorrhagic stroke, the probability of patients being eligible for EVT and/or alteplase, and the probability of good outcomes (mRS 0–2) for patients receiving EVT and/or alteplase. The likelihood of good outcomes depends on the time from onset to initial treatment. Holodinsky and others[7] and Milne and others[36] developed a statistical model estimating the probability of good outcomes for acute ischemic stroke patients who received EVT treatment under the mothership and drip-and-ship methods, using data from the ESCAPE trial.[15] Saver and others[5] examined the effect of time to treatment on patient outcomes using a real-world sample of 58,000 alteplase-treated patients; this study indicated a 4% decrease in good outcomes for every 15-minute delay in treatment. The probability of good outcomes for patients with alteplase alone was assumed to be 0.293 at median time from stroke onset to start of intravenous alteplase of 125 minutes, based on the ESCAPE trial.[15]

Our literature search did not find any published literature indicating the accuracy of preliminary assessment at

Table 2 Clinical Inputs

Variable	Input	Values Used in Sensitivity Analysis	Source
Probability of being eligible for EVT + alteplase within EVT patients	0.75[a]	95% CI: 0.73–0.78	Badhiwala et al.[21]
Sensitivity of field test	0.81[b]	0.90	Nazliel et al.[39]
Specificity of field test	0.89[b]	0.6	Nazliel et al.[39]
Probability of good outcomes, alteplase alone	0.293[c]	95% CI: 0.22–0.37	ESCAPE[15]
Sensitivity of identifying EVT patients at the PSC	0.9	1[d]	Expert opinion
Probability of being eligible for EVT after reassessment at a CSC	0.5	0.7[d]	Expert opinion
Door-to-needle time at the PSC (minutes)	30	60	Fonarow et al.[41] and Kamal et al.[42]
EQ-5D score, mRS of 0–2	0.71	95% CI: 0.68–0.74	Dorman et al.[40]
EQ-5D score, mRS of 3–5	0.31	95% CI: 0.29–0.34	Dorman et al.[40]

CI, confidence interval; CSC, comprehensive stroke center; EQ-5D, EuroQol-5 dimension; EVT, endovascular therapy; mRS, modified Rankin Scale; PSC, primary stroke center.

[a] A meta-analysis of 8 randomized controlled trials indicated that 988 of 1,313 EVT patients received alteplase. We estimated the mean and 95% CI using the data.

[b] The sensitivity and specificity used in the baseline analysis were those reported by Nazliel et al. at LAMS cutoff of 4 and higher. We conducted a sensitivity analysis with the parameter values of 0.9 and 0.6 at LAMS cutoff of 3.

[c] The value 0.293 was the probability at median time from stroke onset to start of intravenous alteplase of 125 minutes. The 95% CI calculated using data from the ESCAPE trial.

[d] We assumed an improved technology at the PSC with all EVT eligible patients transported to a CSC and 70% of them remaining eligible after reassessment.

a PSC under the drip-and-ship method. Based on expert opinion, we assumed that 90% of patients who were potentially eligible for EVT would be identified as such at a PSC and transported to a CSC; among the patients transported to a CSC, it was assumed that only 50% remain eligible for EVT after reassessment and reimaging at the CSC. We further conducted a sensitivity analysis to test the impact of a PSC having a higher level of technology and specialists than this baseline, and therefore being able to provide more accurate preliminary assessments.

Patients receiving EVT were identified from program leaders at the CSCs in Alberta, who indicated that there were 191 patients who received the procedure in the province in 2016. Note that clinical experts expect that the number of current EVT procedures may underestimate the number of patients eligible for EVT. A study by Rai and others reported an incidence rate of 10 to 20 EVT cases per 100,000 person-years in the United States[37]; this converts to 400 to 800 cases for Alberta's population of 4 million. A similar result was published in an Australian study that reported an incidence rate of 11 to 22 EVT cases per 100,000 person-years.[38] Based on the literature in combination with expert opinion, we assumed that the number of EVT procedures could increase to 500 per year; a sensitivity analysis was therefore conducted to test the impact of increasing the number of EVT procedures to 500.

Other clinical inputs (Table 2) include the probability of being eligible for EVT plus alteplase within EVT patients (0.75) based on Badhiwala and others,[21] and the sensitivity and specificity of field test (0.81 and 0.89) by Nazliel and others.[39] The transition of natural history after 90 days poststroke were obtained from Xie and others.[29] The study reported that the transition probabilities between functional independence, disability, and death varied from 0.0034 to 0.0372, dependent on the transition direction and months poststroke. The quality of life for stroke patients was from the study by Dorman and others,[40] which reported the EuroQol-5 dimension (EQ-5D) scores by severity of functional independence and disability. Costs included EMS ground and flight transportation, diagnostic imaging, physician services, hospitalization, rehabilitation, and long-term care. All resources utilized in the management of stroke were measured during five phases of preadmission, hospitalization to 3 months, 4 to 6 months, 7 to 9 months, and 10 to 12 months poststroke. We used the resource intensive weight to estimate costs. In order to estimate the lifetime cost after stroke, the Markov model requires separate cost inputs for patients who are functionally independent (mRS 0–2) and for patients who are disabled (mRS 3–5) at 90 days poststroke. However, medical costs estimated from the administrative health databases were for overall stroke patients and there was no information for us to

Table 3 Cost Inputs

Description	Cost ($)	Standard Deviation	Distribution	Source
EMS transportation				
Ground ambulance (per trip), metro	539.79		None	AHS
Ground ambulance (per trip), rural	1251.84		None	AHS
STARS (per hour)	9174.00		None	STARS
STARS, if 24% funding from AHS (per hour)	2202.00		None	STARS
Fixed-wing flight (per mile)	16.00		None	AHS
Pre-admission				
Emergency department visit[a]	870.82	347.76	Gamma	NACRS
CT/CTA	342.72	128.00	Gamma	NACRS
Physician	525.05	397.92	Gamma	Physician claim
Telehealth	70.45	53.97	Gamma	Physician claim
Hospitalization to 90 days poststroke, per patient				
EVT procedure[b]	18000.00	3826.53	Gamma	AHS
Hospitalization	26232.79	33777.35	Gamma	DAD
Outpatient	712.87	1201.16	Gamma	NACRS
CT/CTA	147.26	358.27	Gamma	NACRS
Physician	2712.01	2976.36	Gamma	Physician claim
Rehabilitation	11209.84	21105.15	Gamma	DAD, NACRS
Long-term care	2857.94	4555.61	Gamma	ACCIS
91 to 180 days, per patient				
Hospitalization	4668.77	17984.33	Gamma	DAD
Outpatient	543.59	1295.19	Gamma	NACRS
CT/CTA	93.92	378.47	Gamma	NACRS
Physician	809.57	1500.62	Gamma	Physician claim
Rehabilitation	4950.49	17390.54	Gamma	DAD, NACRS
Long-term care	3142.76	5674.70	Gamma	ACCIS
181 to 270 days, per patient				
Hospitalization	2232.70	11608.41	Gamma	DAD
Outpatient	288.71	700.57	Gamma	NACRS
CT/CTA	50.17	234.87	Gamma	NACRS
Physician	595.60	1415.17	Gamma	Physician claim
Rehabilitation	2097.73	11946.62	Gamma	DAD, NACRS
Long-term care	3078.93	5774.60	Gamma	ACCIS
271 to 365 days, per patient				
Hospitalization	2134.17	11417.76	Gamma	DAD
Outpatient	273.28	622.35	Gamma	NACRS
CT/CTA	71.85	296.41	Gamma	NACRS
Physician	511.60	1101.71	Gamma	Physician claim
Rehabilitation	983.02	9022.96	Gamma	DAD, NACRS
Long-term care	3156.79	6104.72	Gamma	ACCIS

ACCIS, Alberta Continuing Care Information System; AHS, Alberta Health Services; CT, computed tomography; CTA, CT angiography; DAD, Discharge Abstract Database; EMS, emergency medical services; EVT, endovascular therapy; NACRS, National Ambulatory Care Reporting System; STARS, Shock Trauma Air Rescue Society.

[a] Cost of CT/CTA was excluded from the cost of the emergency department visit.

[b] The cost of EVT included the physician fee. In our model, we used $15,000 to which the physician fee subtracted from the cost equaled.

estimate the cost for stroke patients in each subgroup. The analysis therefore applied information from a costing study to break down the overall cost into patient subgroups.[31] Based on the study, the cost was 65% and 145% of the overall cost for patients with functional independent and disabled status, respectively. Table 3 presents the cost inputs and their sources. All costs were converted to 2016 Canadian dollars using the Alberta Consumer Price Index.

The analysis used Google Maps Distance Matrix API to estimate the driving time from a DA representative point to the destination hospital(s). Times calculated with this technology were discounted by 10% to represent the driving time of an EMS ground ambulance. A sensitivity analysis was performed by using the discount rate of 0% and 20%, respectively. According to data from the Shock Trauma Air Rescue Service (STARS), the analysis considered the average time for patient packaging (i.e., preparing for removal from onset scene) to be 30 minutes, and the average time for loading/unloading a patient to/from an EMS ground ambulance to be 10 minutes. The STARS network database also provided data on the time to tertiary care, including the time for an ambulance to get to a patient, the patient packaging time, and the out of hospital time (i.e., the time for a ground or air ambulance from a location [stroke onset site or a hospital] to a hospital). We used these data to estimate the total time from PSCs/local hospitals to CSCs via ground or air ambulance.

We conducted a scenario analysis to assess the extent to which the optimal strategy improved patient outcomes and cost. The decision on using the mothership versus drip-and-ship method is obvious in some regions. For example, mothership is the selected transportation model in areas close to a CSC, while in areas far from a CSC, patients are transported using drip-and-ship. However, in areas within a certain distance to a CSC, the decision is unclear. In these regions, we therefore conducted a scenario analysis to compare the outcomes and costs under optimal strategy versus a scenario that assumed all patients were transported through the mothership method.

Uncertainty surrounding the two-stage model inputs was handled using 5,000 Monte Carlo simulations with mean outcomes being applied to assess the optimal strategy for each DA. Some assumptions on model inputs may have an impact on the economic outcomes; we therefore conducted a deterministic sensitivity analysis to test how variation in these variables affects our results. More specifically, we conducted a sensitivity analysis on the variables of expanding the EVT treatment from 191 to 500 eligible patients, assuming all patients eligible for EVT were transported to a CSC and 70% of patients transported to a CSC remained eligible for EVT after reassessment at the CSC, assuming longer door-to-needle time at the PSC from 30 minutes to 60, and varying the willingness-to-pay threshold from $50,000 to $100,000 and $200,000 per QALY, the EVT procedure cost within the range of $10,000 to $20,000, the sensitivity and specificity of field test to 90% and 60%, respectively, the probability of being eligible for EVT plus alteplase within EVT patients from 73% to 78%, and the discount rate of ambulance travel time from 0% to 20%.

Results

There are two EVT-capable CSCs in the cities of Edmonton and Calgary and an additional 15 PSCs across the province of Alberta (Figure 1). Eligible patients would be transported either directly to a CSC or first to a PSC for medical examination and initial treatment and then to a CSC (if necessary) for EVT therapy. Figure 1 shows the geographical areas and optimal transportation models. The strategies that generated maximum good outcomes are presented in Figure 1A. Note that drip-and-ship by ground generated lower good outcomes than drip-and-ship by flight, and therefore was not an optimal strategy for any of the DAs. Figure 1B shows the strategies that maximized system value, that is, those associated with the highest iNMB. As shown in the two figures, the drip-and-ship method was optimal only in DAs far from the CSCs and in some areas close to a PSC. Figure 1C shows the affected areas by changing from optimal clinical outcomes (Figure 1A) to optimal economic efficiency (Figure 1B).

Table 4 shows the population by optimal strategy and region. In the Green and Other Regions, 49% and 37% of the population, respectively, was under mothership by flight when considering optimal clinical outcomes; these switched to mothership by ground or drip-and-ship when considering optimal system value. In the Metro Regions, 1% were under mothership by flight when considering optimal clinical outcomes; these switched to mothership by ground when considering optimal system value. When investigating the strategies within one region, it was observed that the mothership method was the optimal strategy in the Metro Regions; in the Green and Other Regions, the optimal strategy was the combination of the mothership and drip-and-ship methods.

As shown in Table 5, when considering optimal clinical outcomes, the overall cost (standard deviation [SD]) per patient was $291,769 ($11,576), the likelihood (SD) of good outcomes was 41.82% (0.013), and the QALY (SD) was 3.255 (0.039); when considering optimal system value, the overall cost (SD) per patient decreased by $4,045 ($8,998), as did the likelihood of good outcomes and QALY (by 0.15% [0.005] and 0.004 [0.012], respectively). The incremental cost per QALY gained was over one million dollars if the decision making prioritizes optimal clinical outcomes compared with optimal system value.

Optimal strategies identified in the analysis confirmed the current practice of transporting stroke patients in metropolitan regions and areas far from a CSC. Currently in Alberta, mothership is the most commonly used transportation model in regions close to metropolitan Edmonton and Calgary, while in areas far from a CSC (i.e., North and West Regions), patients are shipped using drip-and-ship. In areas within a certain distance to

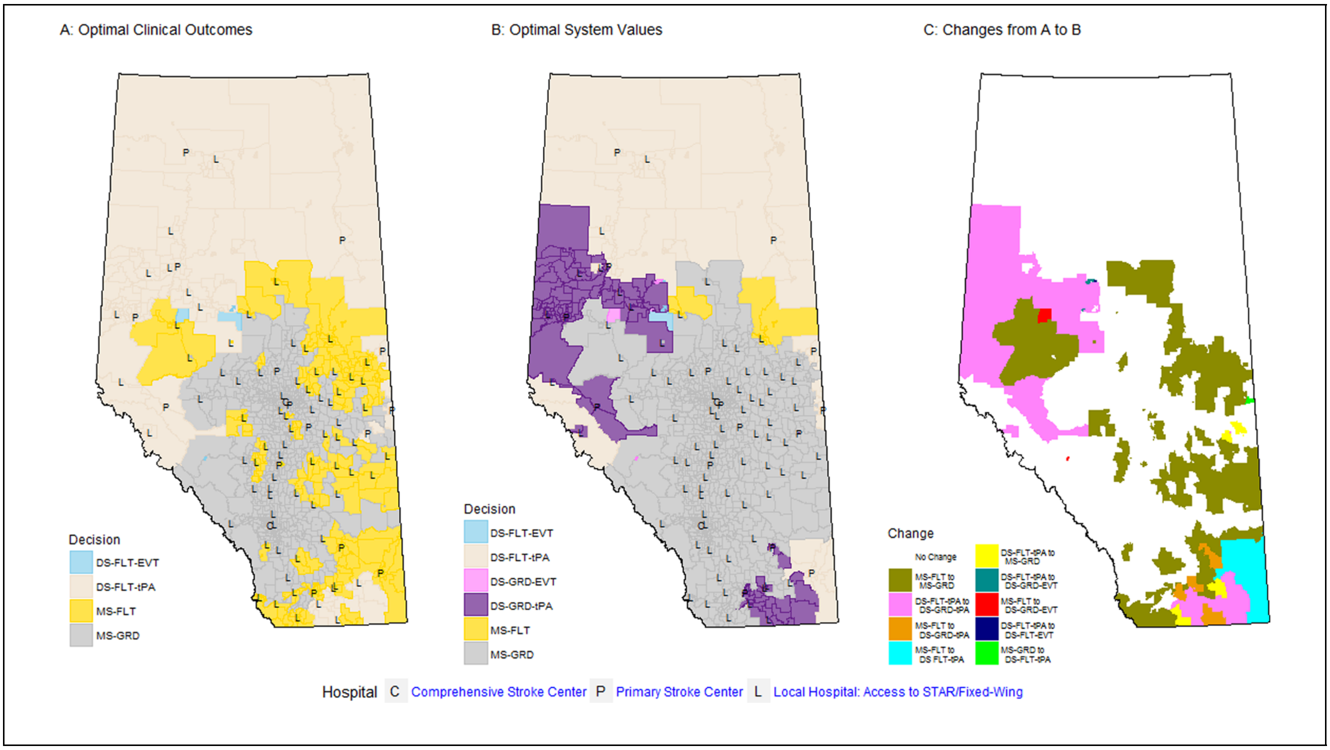

Figure 1 Distribution of optimal strategies
DS-FLT-EVT, drip-and-ship by flight with minimum time to EVT; DS-FLT-tPA, drip and ship by flight with minimum time to thrombolysis with alteplase; DS-GRD-EVT, drip-and-ship by ground with minimum time to EVT; DS-GRD-tPA, drip and ship by ground with minimum time to thrombolysis with alteplase; MS-FLT, mothership by flight; MS-GRD, mothership by ground.

Table 4 Population Under Each Strategy

Region[a]	MS GRD	MS FLT	DS GRDtPA	DS GRDEVT	DS FLTtPA	DS FLTEVT	Overall
Optimal good outcomes							
Green	85,338 (14%)	302,184 (49%)			231,569 (37%)		619,091
Metro	2,804,589 (99%)	23,088 (1%)					2,827,677
North					52,739 (96%)	1,976 (4%)	54,715
West					28,604 (99.5%)	141 (0.5%)	28,745
Other	417,635 (59%)	261,714 (37%)			28,767 (4%)		708,116
Overall	3,307,562 (78%)	586,986 (14%)			341,679 (8%)	2,117 (0%)	4,238,344
Optimal system value							
Green	211,174 (34%)		204,835 (33%)		203,082 (33%)		619,091
Metro	2,827,677 (100%)						2,827,677
North			24,982 (46%)	2,386 (4%)	26,067 (48%)	1,280 (2%)	54,715
West			28,604 (99%)	141 (1%)			28,745
Other	650,002 (92%)	16,846 (2%)	34,236 (5%)		7,032 (1%)		708,116
Overall	3,688,853 (87%)	16,846 (0%)	292,657 (7%)	2,527 (0%)	236,181 (6%)	1,280 (0%)	4,238,344

DS FLT-tPA (EVT), drip-and-ship by flight with minimum time to alteplase (EVT); DS GRD-tPA (EVT), drip-and-ship by ground with minimum time to alteplase (EVT); EVT, endovascular therapy; MS FLT, mothership by flight; MS GRD, mothership by ground.
[a] Refers to method section for region definitions. Green Regions stand for areas having a driving distance of less than 30 kilometers to a PSC; Metro Regions for metropolitan areas surrounding Edmonton and Calgary; North Region for northern Alberta areas; West Region for western Alberta areas; and Other Region for areas not included in those described above.

Table 5 Cost ($) and Outcomes by Decision Preference and Scenario

Strategy	Cost (SD)	Good Outcome (SD)	QALY (SD)	ICER per QALY
Affected population by switching optimal strategies: 755,857 (18%) out of 4.2 million in the province				
Optimal system value	$287,725 (4,141)	41.67% (0.016)	3.251 (0.044)	
Optimal clinical outcome	$291,769 (11,576)	41.82% (0.013)	3.255 (0.039)	
Difference between optimal clinical outcome and system value	$4,045 (8,998)	0.15% (0.005)	0.004 (0.012)	$1,011,167
Scenario analysis I: Affected population by replacing optimal outcomes with MS GRD: 260,336 (20%) out of 1.3 million in Green and Other Regions				
MS GRD	$294,490 (1,904)	39.10% (0.015)	3.182 (0.042)	
Optimal clinical outcome	$296,383 (4,813)	41.38% (0.006)	3.237 (0.016)	
Difference between optimal clinical outcome and MS GRD	$1,894 (5,216)	2.28% (0.015)	0.055 (0.043)	$34,432
Scenario analysis II: Affected population by replacing optimal system value with MS GRD: 449,185 (34%) out of 1.3 million in Green and Other Regions				
MS GRD	$293,350 (1,983)	40.01% (0.016)	3.206 (0.043)	
Optimal system value	$291,315 (1,206)	41.13% (0.010)	3.230 (0.028)	
Difference between optimal system value and MS GRD	–$2,035 (1,271)	1.12% (0.014)	0.023 (0.037)	Dominate

ICER, incremental cost-effectiveness ratio; MS GRD, mothership by ground; QALY, quality life-adjusted year; SD, standard deviation.

a CSC (i.e., the Green and Other Regions), the decision is unclear. In order to assess how the optimal strategies (combined mothership and drip-and-ship) improve outcomes and cost in these regions, we compared the optimal strategies with a hypothetical scenario that patients under the drip-and-ship were instead transported through mothership by ground. Mothership by ground was chosen as a comparator as it represented the transportation model used in the majority of areas (78% and 87%; Table 4).

As shown in Table 5, the probability of good outcomes increased by 2.28% and 1.12% and the QALY by 0.055 and 0.023, under optimal clinical outcomes and optimal system value compared with mothership by ground, respectively. The strategies that generated optimal good outcomes were associated with $1,894 ($1,983) more in cost (SD), while the strategies that maximized system value saved $2,035 ($1,271) in cost (SD). Compared with mothership by ground, the optimal strategies can be deemed to be a favorable option, given low ICER of $34,432 for optimal clinical outcomes and improved QALY at less cost for optimal system value.

Table A.1 in the appendix shows the incremental cost, QALY, and cost-effectiveness ratios under a number of one-way sensitivity analyses.

The baseline analysis was conducted using the EVT program information of 191 EVT procedures conducted annually in Alberta. However, literature and expert opinion suggest that there are more patients eligible for EVT.[37,38] In order to assess the impact of variation in the number of EVT patients, we conducted a sensitivity analysis that considered a scenario with 500 eligible patients in the province, all of whom accessed and received EVT treatment. The scenario of 500 patients was associated with an increase in QALY at less cost, compared with 191 EVT patients. There were limited data available on the accuracy of medical assessments at PSCs for EVT eligibility at PSCs. A sensitivity analysis was conducted by assuming increased accuracy of the assessment from baseline values to all patients eligible for EVT were transported to a CSC and 70% of transported patients remained eligible for EVT after reassessment at the CSC. Results indicated that the mothership method was replaced with the drip-and-ship method in some areas under better assessments at PSCs. Sensitivity analyses were conducted by varying the door-to-needle time at the PSC from 30 minutes in the baseline analysis to 60 minutes. When the door-to-needle time increased to 60 minutes, drip-and-ship was replaced with mothership in some areas close to PSCs, under both optimal clinical outcomes and system value. Further sensitivity analyses were conducted by varying the procedure cost from $15,000 in the baseline analysis to $10,000 or $20,000, the willingness-to-pay threshold from $50,000 to $100,000 and $200,000 per QALY, the sensitivity and specificity of field test to 90% and 60%, respectively, the probability of being eligible for EVT plus alteplase within EVT patients from 73% to 78%, and the time reduction rate of ambulance travel from 0% to 20%.

As shown in Table A.1 in the appendix, the determined optimal strategies were less sensitive to changes in these variables. We assessed the impact of these variables in three comparative scenarios. When comparing the strategy of optimal clinical outcomes with optimal system value and the strategy of optimal system value with mothership by ground, the sensitivity analysis revealed consistent outcomes with the baseline analysis, with the ICERs ranging from $ 0.64 to $2.52 million and the optimal system value dominated mothership by ground in that it produced more QALYs at less cost. When comparing optimal clinical outcomes with mothership by ground, consistent outcomes were also achieved in general, with the ICERs ranging from $16,463 to $55,213 per QALY, while the ICER was $34,432 per QALY in the baseline analysis. One exception was the accuracy of diagnostic examination at the PSC, to which the cost-effectiveness result was sensitive. When increasing the accuracy, the ICER of optimal clinical outcomes over mothership by ground went up to approximately $103,000 per QALY. While it was observed that increasing the accuracy improved clinical outcomes, QALY, and costs in both strategies, the improvement was seen at a faster pace with mothership by ground. This made the cost increment larger ($4,222 v $1,894 in the sensitivity analysis v baseline analysis) and QALY improvement smaller (0.041 v 0.055) for optimal clinical outcomes versus mothership by ground, which drives up the ICER. A possible explanation is that all patients eligible for EVT would be transported first to a PSC under drip-and-ship, as did a small portion of patients under mothership (due to errors in the field test). Given that the sensitivity analysis assumed a 100% true positive rate of diagnostic examination at the PSC, all eligible patients would eventually be transported to a CSC for EVT treatment, regardless of the transportation models. In this circumstance of sensitivity analysis, drip-and-ship underperformed compared to mothership, as the former delayed EVT treatment for all eligible patients, resulting in a decline in the cost-effectiveness of optimal clinical outcomes that combined both mothership and drip-and-ship.

Discussion

Even when a health technology has been proven to be cost-effective and is adopted by a health system, appropriate planning of treatment delivery is critical to realization of both the economic and patient-centered benefits. In this illustrative case study on acute ischemic stroke treatment, there are six delivery strategies for acute ischemic stroke patients to receive EVT, and we identified a combination of strategies that maximized both patient outcomes and system value. We assessed benefits of the optimal strategies in regions where the decision on whether to transport a patient first to a closer PSC is not obvious, and demonstrated that transportation models that combined mothership and drip-and-ship offered improved clinical outcomes, quality of life, and value for money for patients eligible for EVT. We also compared two decision preferences, of prioritizing clinical outcomes versus system value. In the majority of areas both preferences were equivalent, and in approximately 18% of the population who were affected by the approach switch (Table 5), the model maximizing system value was more cost-effective than the former.

The basic logic behind the optimization framework (HTO approach) is to search for the best strategy for each geographical location. The search process is a pairwise comparison of all possible strategies, factoring in controlled variables including disease epidemiology, time or distance to hospitals, available medical services, treatment eligibility, treatment efficacy, and costs. Drawing identified strategies together then creates a mapping of optimal strategies. An important concept of this article is the need to identify the potential effects of delivery strategies for resource allocation by examining patient outcomes and costs at the level of small geographical areas. The set of strategies associated with highest clinical outcomes or incremental net monetary benefit for each area represents the optimal models for system planning of health services.

The HTO approach is particularly important for decision making in geographical areas where choosing a correct transportation model is difficult. Clinical and economic outcomes may in fact be very different in reality, depending on geographical location and/or type of delivery model. For example, in our illustrative case study, mothership might be a preferable option for patients in metro areas close to a CSC, since this model saves both time to treatment and associated costs; in contrast, for patients far from a CSC or very close to a PSC, drip-and-ship might outperform mothership due to its advantage in faster initial alteplase treatment and medical assessment. While it may not seem difficult to make the correct decision on delivery method for patients in these areas, for patients located between a CSC and a PSC, an HTO approach could be a powerful tool to assess the tradeoff between the possible methods. Our analysis in these areas seems in favor of the HTO approach, as shown in Table 5.

In the EVT case study, with the aim to determine optimal delivery strategies, we considered the fact that travel time (distance) from the stroke onset scene to the hospital had an impact on transportation costs and good patient outcomes. Therefore, in our model, costs and patient outcomes were the function of the geographical location of stroke onset. The mothership method was determined to be the best strategy in metro areas surrounding CSCs. In areas close to PSCs, the best strategy was a mix of the mothership and drip-and-ship methods. In other areas not close to either CSCs or PSCs, the best strategy was also a mix of mothership and drip-and-ship. Mothership by ground and drip-and-ship by flight minimizing time to thrombolysis with alteplase were the two best strategies overall and applicable to the largest geographic areas. Mothership by ground was the best in areas of intermediate distance from CSCs, but drip-and-ship by flight minimizing time to thrombolysis with alteplase was preferable in areas very remote from CSCs but of near or intermediate distance to PSCs (Figure 1A and B).

Designing an optimal strategy must also take the priority of the decision maker into account. The HTO analysis considered two decision options where the priority was either to achieve the best clinical outcomes or achieve the best incremental net monetary benefit (i.e., system value). Note that each option comprised a combination of the mothership and drip-and-ship methods. In the first decision option, a delivery strategy was defined as optimal if it generated the highest clinical outcomes; in the second decision option, a delivery strategy was defined as optimal if it was associated with the highest system value. Results indicated that both options are equivalent in the large majority of regions throughout the province. In some areas, when adopting system value, the method of transporting patients by flight switched to ground ambulance. For these areas, the tradeoff between clinical optimization and system value optimization favors the second option, given the enormous cost for the first option to produce an additional QALY (see Figure 1C and Table 5).

A sensitivity analysis revealed that the determined decision options were more efficient in terms of generating better patient outcomes at lower cost, when expanding EVT treatment to all eligible patients. One possible interpretation of the finding is that, the better the access to EVT, the higher the economic and patient outcomes are. Sensitivity analyses were also conducted to test the impact of model assumptions on determined optimal strategies. Results suggested that the determined strategies were quite stable in variations of the variables under investigation. The accuracy of medical assessments at PSCs is an exception. Under the assumption of perfectly identifying patients eligible for EVT at the PSC and when comparing the strategy of optimal clinical outcomes with mothership by ground, while an improvement in clinical outcomes, quality of life, and costs was observed under both strategies, the analysis showed a large increase in ICER from $1,894 at baseline to approximately $103,000 per QALY. This implies that the cost-effectiveness was sensitive to the change in the accuracy. However, when comparing the strategy of optimal system value with mothership by ground, the outcomes were consistent with the baseline analysis, in which the optimal system value was a dominant strategy over mothership by ground.

It is, of course, true that the present health system structure influences the HTO approach and analysis. This case study was conducted in the province of Alberta, Canada, where we benefit from a single health system for the whole province with coordinated prehospital and hospital care, a structured stroke system of 17 hospitals around the province, and a vertically integrated strategic clinical network, into which this new treatment is placed. That same structure is not present in many jurisdictions around the world. Future extension of the HTO approach might focus on other structures.

Alberta has been working on improving its network of transportation models for stroke patients, and our analysis provides economic insight into the planning of care delivery. Currently, the province has initiated an evaluation of the EVT transportation pathway that considers not only the economic arguments but also formalizing a network for eligibility assessment; collaboration among prehospital, acute inpatient, and postdischarge care; and a reduction in time to treatment.

In conclusion, the HTO approach is a useful tool for informing implementation decisions and coordinating the delivery of complex health services such as EVT. The best strategy for providing EVT relies on the geographical location of stroke onset and the decision maker's preference for either patient outcomes or economic efficiency. The HTO approach produced an optimization map showing the optimal strategy for EVT delivery. While the decision priorities of optimal clinical outcomes versus optimal system value were equivalent in the large majority of the province, prioritizing clinical outcomes was associated with an enormous cost for additional QALY in approximately 18% of the population affected by the priority shift, suggesting that the latter was more favorable in terms of added value for money. A noticeable improvement in cost and effectiveness was demonstrated in areas where the choice of correct transportation model was uncertain.

Acknowledgments

This work was supported by Alberta Health, Alberta Health Services, Emergency Link Centre and Operations, the Shock Trauma Air Rescue Society, and the University of Calgary. We would like to thank the two anonymous referees, Christopher McCabe, and Philip Jacobs for comments on previous draft; Bing Guo, Susan Armijo-Olivo, and Arianna Waye for collecting information on clinical inputs; and Stefanie Kletke, Lisa Tjosvold, and Tennile Tavares for research assistance.

Supplemental Material

The online supplementary appendix for this article is available on the *Medical Decision Making Policy & Practice* website at http://journals.sagepub.com/home/mpp.

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