OPTIMAL TRANSPORT SCENARIO FOR ACCESS TO EVT WITH CONSIDERATION OF PATIENT OUTCOMES AND COST

by

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Table of Contents

List of Tables

List of Figures

Abstract

There are two treatments for ischemic stroke: medical treatment (tPA) and endovascular therapy (EVT). EVT can only be used to treat ischemic strokes caused by a large vessel occlusion (LVO). EVT is only offered at hospitals with sufficient resources.

A previously published model predicts the outcome of patient's who screen positive for an LVO based on how they were transported, Drip and Ship (tPA only facility first, then EVT facility) or Mothership (direct to EVT facility). Both patient outcome and transport cost functions were developed for these strategies. The addition of rotary wing transportation was conditionally applied to inter-facility transfer scenarios where it provided a time advantage.

In most regions, both outcome and cost can be optimized to indicate whether Drip and Ship or Mothership is preferred. Regions exist where outcome and cost are divergent however, the difference between Mothership and Drip and Ship in these regions is marginal.

Glossary

Abbreviation	Full Text
API	Application Programming Interface
CSC	Comprehensive Stroke Centre
C-STAT	Stroke Triage Assessment Tool
CT	Computed Tomography
CTA	Computed Tomography Angiography
DALY	Disability Adjusted Life Years
DESTINE	Decision Support Tool in Endovascular Transport
DIDO	Door In Door Out
DnS	Drip and Ship
DTN	Door to Needle
DTP	Door to Puncture
EHS	Emergency Health Services
EMS	Emergency Medical Services
EVT	Endovascular Therapy
FMC	First Medical Contact
ICH	Intracerebral Hemorrhage
LAMS	Los Angeles Motor Scale
LVO	Large Vessel Occlusion
MSP	Medical Service Plan
mRS	Modified Rankin Scale
MS	Mothership
nLVO	Non-Large Vessel Occlusion
NTDO	Needle To Door Out
PSC	Primary Stroke Centre
QALY	Quality Adjusted Life Years
RACE	Rapid Arterial Occlusion Evaluation
SM	Stroke Mimic
tPA	Tissue Plasminogen Activator

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Chapter 1: Introduction

Stroke is the second leading cause of death and first leading cause of disability worldwide.[1] There are two types of stroke – hemorrhagic and ischemic. A hemorrhagic stroke is caused by a bleed in the brain, and an ischemic stroke is caused by a blockage in the brain. Ischemic strokes are most prevalent. The American Heart Association reported that ischemic strokes made up 87% of all strokes suffered in 2020.[2]

Ischemic stroke is a time dependant disease. The stroke community commonly encapsulates this with the phrase *Time is Brain*. Time is Brain is a concept which was first introduced by Gomez et al in 1993[3] and was later quantified in 2006 by Saver[4] who demonstrated that approximately 1.9 million neurons are lost every minute an ischemic stroke goes untreated. This normalized the idea that stroke is a highly time dependent disease for which minutes matter. Therefore, treatment needs to occur quickly and efficiently. There are currently two treatments for ischemic stroke.

Prior to 2015, ischemic strokes could only be treated using a thrombolytic drug, Intravenous recombinant tissue Plasminogen Activator (IV-rtPA) which is commonly referred to as "tPA" but is also known as alteplase. Physicians administer tPA aiming to dissolve the clot causing the stroke and return blood flow to the affected area of the brain. In medical terms this is called reperfusion.

tPA was first accepted as treatment for an ischemic stroke around 1995 after a series of trials were published proving its safety and efficacy.[5–7] It is widely accepted that for a patient to benefit from tPA it must be administered within 4.5 hours of the onset of their stroke.[8] However, administering tPA within this time frame does not guarantee reperfusion as only approximately 30% of patients treated with tPA see improvement in their symptoms.[7] The effectiveness of tPA is time dependant and was quantified with a decay curve in 2014.[9]

Ischemic strokes can be further classified by the location of the stroke causing clot. Large Vessel Occlusions (LVO) are defined as blockages of the internal carotid artery, proximal, posterior, middle, and anterior cerebral arteries.[10] A blockage in any other vessel in the brain is known as a non-Large Vessel Occlusion (nLVO). In 2015, a series of five clinical trials proved the safety and efficacy of a new treatment for ischemic stroke now known as Endovascular Therapy (EVT).[11–15] These trials proved EVT is an effective treatment for LVO ischemic strokes, and also indicated far better patient outcomes when compared to treatment with tPA alone. EVT is an endovascular surgery, during which a physician attempts to restore blood flow to the affected areas of the brain by removing the clot using a specialized retrieval device. In a successful procedure, reperfusion is achieved.

Initial trials[11–15] indicated that EVT is an effective treatment for up to 6 hours after the onset of an LVO ischemic stroke. Two subsequent trials[16,17] proved that EVT can be effective in treating an LVO ischemic stroke for up to 24 hours after onset in some patients. However, between 6 and 24 hours the proportion of patients eligible for EVT rapidly decreases[16,17] and timely access to treatment remains paramount. How long a patient stands to benefit from EVT after the onset of an LVO ischemic stroke varies on a case by case basis and is typically dependant on how much brain can be saved by performing the treatment. The time dependency of EVT was quantified with a decay curve in 2016 for EVT.[18]

Patients suffering an ischemic stroke can be eligible for both EVT and tPA treatment. If a patient is eligible for both treatments, tPA is usually administered first to get a head start on restoring blood flow and a subsequent EVT procedure is performed to remove the rest of the clot and completely restore blood flow. Due to the nature of stroke as a disease, the effectiveness of both tPA and EVT are time dependent.[9,18] The probability of reperfusion vs time curves looks slightly different for tPA and EVT but in general the probability of an excellent outcome exponentially decays as time from stroke onset increases. As a result of this both treatments have time windows in which they have been proven effective. tPA is an effective treatment for up to 4.5 hours after the onset of an ischemic stroke.[8] EVT was originally thought to be effective for 6 hours after onset but recent DEFUSE-3 and DAWN trials have proven that it can be effective for as long as 24 hours after onset (depending on an individual patient's diagnostic scans).[16,17]

EVT procedures require expensive resources and expert medical professionals which results in there being very few medical centres capable of delivering EVT. The following health centre descriptions have broader meanings in the stroke community but for simplicity in this thesis, the terms will be used as follows: Centres that are EVT enabled are commonly referred to in the stroke community as Comprehensive Stroke Centres – CSCs. Medical centres capable of administering tPA but unable to perform EVT are referred to as Primary Stroke Centres – PSCs.

It has been established that a system providing fast access to treatment is critical to stroke patient outcomes, but a system is only as effective as its gatekeeper. An ischemic stroke can only be confirmed using CT (computed tomography) scan; a CTA (computed tomography angiography) scan confirms a large vessel occlusion. CT and CTA scans are only offered in a hospital setting, apart from CT enabled ambulances which are extremely costly and therefore rare. By virtue of this, the gatekeeper to the ischemic stroke system is pre-hospital diagnostic stroke tools. Pre-hospital screening scales are a quick clinical assessment developed for use by paramedics in the field to assess a patient's likelihood of having a stroke. There are now pre-hospital stroke scales that are being used by paramedics to detect the possible presence of an ischemic stroke caused by an LVO. If any of these new field screening tools are positive, it indicates a high likelihood the patient is said to have a suspected LVO ischemic stroke.

Following the identification of a suspected LVO ischemic stroke in the field, the best course of action for transportation is uncertain for any patient whose stroke onset occurs outside the direct catchment area of a CSC. This uncertainty stems from the time dependency of the disease – is it best to transport the patient to the nearest PSC for tPA and confirmation of the LVO ischemic stroke diagnosis then transfer to a CSC for EVT, or is it best to bypass the nearest stroke facility and transport directly to an EVT enabled facility? The former is referred to as *Drip and Ship*, and the latter *Mothership*. In the Drip and Ship method, the patient typically receives tPA earlier, but the start of the EVT procedure is delayed. In the Mothership method, the start of tPA is often delayed, but the EVT procedure begins earlier. Additionally, in the Drip and Ship method, only those patients with a confirmed LVO will be transported to the EVT-enabled facility.

In the short period since the acceptance of EVT into common medical practice, a rich area of research has developed surrounding which transportation method is best, Drip and Ship or Mothership. This thesis assumes transportation is completed using ground transportation, i.e., Ambulance. However, air transportation can reduce a patient's overall time to treatment and is commonly used for the inter-facility transfers occurring as a part of the Drip and Ship method. Air transportation is costly and healthcare resources are limited and therefore, worthy of investigation. This thesis aims to investigate in which scenarios Drip and Ship, or Mothership are preferred with consideration of patient outcomes and transport costs including both air and ground transportation options.

Chapter 2: Literature Review

A review of the existing literature surrounding the transportation dilemma for suspected LVO ischemic stroke patients, the inclusion of inter-facility transfer via air, and transport cost modelling was conducted and is presented in the following sections.

2.1 The Cutting Edge of Suspected LVO Patient Transport Decision Modelling

The goal of optimizing transport decisions for ischemic stroke patients is to maximize the patient's chance of functional independence in their life post-stroke. Numerous elements play a part in an ischemic stroke patient's outcome, which can be broken down into two groups: patient specific and system specific elements. Patient specific elements are attributes that a patient possesses such as age, sex, pre-existing conditions, contraindications to treatment and collateral circulation. System specific elements are characteristics of the stroke system of care such as efficiency, time to treatments, distances to stroke treatment facilities, and pre-hospital stroke and LVO screening tools. This lengthy list of outcome-influencing elements supports the idea that transport decisions for ischemic stroke patients are multifactorial and therefore complex. As is the case when modelling most systems, assumptions must be made pertaining to which factors that influence the model should be the focus. Models considering various combinations of outcome-influencing factors have been published in the literature and are described below.

The elements involved in modeling and planning stroke systems of care were summarized by Lima et al.[19] . This piece highlights the technologies and methods on the cutting edge of modern stroke care. With this, the authors comment on the importance of developing regional systems of care for acute stroke care delivery and the complex relationships that exist between patient outcomes and pre-hospital scales, transport decisions and triage algorithms. Ultimately this article explains the factors which affect the outcomes for LVO ischemic stroke patients and highlights the ongoing research efforts to improve them.

A decision tree approach to model the transport decision for suspected stroke patients was presented by Venema et al.[20] . Their model includes both patient and system specific characteristics such as a patient's age and sex, likelihood of a confirmed LVO diagnosis, hospital locations and time to treatment efficiencies. This study uses quality adjusted life years (QALYs) as an outcome metric to estimate the impact a decision has on the patients quality and quantity of life after treatment. The base case of this model indicated that for a 68 year old man whose likelihood of a confirmed LVO diagnosis is 34% direct transport to a CSC is preferred when the CSC is located 45 minutes away from the patient.

A model using similar patient specific input parameters was developed by Schlemm et al.[21] , and it compared 10 scenarios with various circumstances considered in each. This model produces an output the indicates what score on the RACE pre-hospital scale should represent the cut-off point for direct transport to a CSC. This approach allows the pre-hospital scale to act as the dynamic threshold for the decision while accounting for the fact that not all regions should have the same threshold for making the decision to transport directly to the CSC facility. Disability adjusted life years (DALYs) are used as the outcome metric used in this study, which are similar to the

QALYs used in the Venema et al.[20] study. Ten different triage scenarios were evaluated, some realistic and some abstract. In many of the real world and abstract scenarios the strategy produced by the model was expected to result in a population-wide gain of 8 to 18 DALYs.

Early access to treatment is dependant on the pre-hospital identification of suspected ischemic strokes but what happens in a system where no formal pre-hospital LVO screening has been adopted? Xu et al.[22] considered two scenarios, the first assuming the system has no formal LVO screening in place and the second a recognized pre-hospital LVO screening tool in place. The results produced in this model indicate Drip and Ship as the preferred method in a system with efficient PSC treatment times but no formal LVO screening in place. When PSC treatment times were slowed, Mothership was preferred regardless of if a formal LVO screening tool was employed.

Simulation provides different insights into the complexities of the transport decision paradigm for ischemic stroke patients. Bogle et al.[23] developed a discrete event simulation model to assess the pre-hospital portion of the stroke system of care in two American counties. This model assumes that if an LVO could be confirmed in the field the optimal transport decision would always be the Mothership method. This model provides insight into where and when over triage (defined as patients who are transported directly to a CSC but end up ineligible for EVT) is prevalent versus under triage (defined as patients who are not transported directly to a CSC but are eligible for EVT). This model was used to identify how different transport protocol and triage practices affect the volume of patients transported according to the Mothership method.

Numerous output metrics have been used to access the impact of transport decisions for suspected LVO ischemic stroke patients. Schlemm et al.[24] developed two benefit-harm ratios to quantify the impact of a decision made. The first ratio is associated with the Drip and Ship method and is calculated by weighing the increase in a patient's onset to EVT time and decrease in their onset to tPA time. The second ratio is associated with the Mothership method and is calculated by weighing the decrease in a patient's onset to EVT time and increase in their onset to tPA time. This model is also unique in its consideration of more than one PSC location. This consideration models private healthcare system better than a public system like Canada has but is still a novel aspect of this model. This model indicates an optimal decision for a randomly generated geographic scenario. The primary findings reported for this model indicate that in approximately one third of the scenarios tested the "benefit" of a reduction in a patient's onset to EVT time exceeded the "harm" of an increase in a patient's onset to tPA time, meaning the Mothership method was preferred in these scenarios.

Some of this research takes place in a generalized solution space, but others have attempted to apply research methods to specific regions. To do this Google application programming interfaces (API) are useful as they allow communication with other software developed by Google, such as google maps. Tajaddini et al. [25] applied Google API to their research attempt to optimize CSC catchment areas in a region of Australia. The primary goal of this was to develop a simplistic Google model to optimize the catchment areas of CSCs in the region. A secondary and more complex version of the model included road conditions, traffic, and forecasted demand.

This publication proved the effectiveness of Google API as a useful tool in designing the optimal catchment areas for CSCs.

2.2 The Evolution of the DESTINE Model

Research surrounding transport decisions for suspected LVO ischemic stroke began shortly after EVT was introduced as the best practice for treating these patients. An early contribution to this body of work was published by Milne et al.[26] outlining the DESTINE (Decision Support Tool in Endovascular transport) project. This project consists of the development of a model to predict the probability of an excellent outcome for a suspected LVO patient based upon how they were transported to treatment, according to the Mothership or Drip and Ship method. This model determines a patient's probability of an excellent outcome based on their relative location to the PSC and CSC facility upon the onset of their stroke and several other input variables such as treatment efficiency at each facility. This model was meant to serve as a preliminary model and starting point for future work.

Building on both the Milne et al.[26] publication as well as a second iteration of the preliminary model[27], Holodinksy et al.[28] aimed apply a conditional probability model to existing clinical trial data and test its ability to identify when Mothership and Drip and Ship protocols are preferred. This version of the model recognizes some of the shortcomings of pre-hospital stroke scales by accounting for those patients who were suspected to have an LVO by a pre-hospital scale but were later confirmed with a different diagnosis such as non-LVO, ICH, or stroke mimics. Inputs considered in this model are onset location (EMS pickup location), door-to-treatment times at PSCs and CSCs, travel times between centres, and the possibility of patients incorrectly suspected of having LVO. Fifteen scenarios were analyzed in this project. Scenarios vary by travel time between PSC and CSC (10, 30, 60, 90, 120 minute scenarios evaluated) as well as by treatment times at both the PSC and CSC (optimal performance at both the PSC and CSC, slow performing system at PSC, slow performing system at CSC scenarios evaluated). In this analysis an excellent outcome was defined as a 90 day mRS score of 0-1. The resulting conclusion made was that a conditional probability model could be successful if implemented as a triage algorithm for LVO ischemic stroke patient transport decision making.

Developing an algorithm that can make good patient transport decisions is only half the battle – the other half is the implementation and usability of the interfaces and methods applied along with the algorithm. Holodinsky et al.[29] published a paper in 2019 discussing the testing process they used to evaluate the usability of the interface associated with the model discussed in the previous paragraph.[28] They enrolled several participants in their study from varying backgrounds (physicians, healthcare administrators, paramedics and nurses) asking each of them to use the interface, provide feedback on its usability and interpret its output. This paper establishes a valid method for testing the interpretation of model output. This is a necessary step in an iterative design process to end up with a final product useful to those who will end up using it.

2.3 Access to Endovascular Therapy

Unlike administering tPA, EVT is not a simple procedure for hospital facilities to offer as it requires specialized personal and equipment. For this reason, EVT is a centralized procedure in most jurisdictions which makes access more complex for patients whose onset occurs outside the catchment area of a CSC. Since this procedure has only recently been accepted into common practice, very few jurisdictions have mastered delivering equal access to EVT for all eligible patients.[30]

There are many reasons for limited access to EVT but a consistently cited issue is a bottleneck at the PSC for patients transported according to the Drip and Ship method. Minimizing the bottle neck has potential to be the single greatest modifier of outcome for LVO patients transported according to the Drip and Ship method.[31] This can be accomplished with in hospital system efficiency improvement, and/or the consideration of the Mothership method for some patients whose stroke occurs outside the catchment area of a CSC.

It is known that treating an ischemic stroke with EVT has proven to produce better patient outcomes than treating with just tPA alone.[11–15] From this it is reasonable to infer that better access to EVT will result in better patient outcomes. Better patient outcomes are synonymous with more functional independence and a better quality of life post-stroke which consequently results in a reduction in the financial burden associated with the long term care and rehabilitation of patients recovering from an ischemic stoke.

2.4 Cost Analysis of LVO Ischemic Stroke and Patient Transport Decisions

While addressing resource issues that exist in stroke systems of care in Canada, Whelan et al.[32] highlight the initial costs involved with delivering stroke care as overwhelming but go on to mention the major cost savings associated with the prevention of disability. The cost savings associated with the prevention of disability are harder to conceptualize since they are often made up of many "smaller" costs, but these are important to consider when attempting to understand the overall cost of delivering a stroke system of care.

Several publications have presented the cost savings associated with the functional independence EVT can help LVO patients achieve. Achit et al.[33] compared LVO patient data for those treated with both EVT and tPA with those who were treated with tPA alone. Only patients who achieved functional independence were included in this study which was quantified as those patients who achieved a 90-day mRS score between 0 and 2. The results of this study showed that patients treated with both EVT and tPA had an increased rate of functional independence of 10.9% for an increased cost of $2,116.00 USD ($3,740.00 CAD). This proved the use of EVT and tPA to be cost effective in comparison to tPA alone.

A few publications investigate the cost effectiveness of EVT using QALYs. Heggie et al.[34] assessed the cost effectiveness of EVT using two timelines, 90 days and a lifetime. To do so Heggie et al. performed a meta-analysis of seven EVT clinical trials. This analysis found that over a 90 day time horizon the EVT procedure cost 5207 GBP ($9,204.00 CAD) per 0.025 QALY gain, which was considered cost ineffective. However, over a lifetime this analysis found that the EVT procedure costs £3,466.00 GBP ($6,127.00 CAD) per QALY gained, which was considered cost effective. This study cited its primary finding to be that the benefit of EVT procedure outweighs the cost incurred by its implementation. Another publication[35] aimed to study the cost effectiveness of EVT in a similar manner but focused on patients treated with EVT between 6 and 24 hours of their stroke onset. Pizzo et al.[35] assessed the cost effectiveness for this cohort of patients on a 20 year time horizon using a Markov model and QALYs. This study found the cost of EVT was $1,564.00 USD ($1,952.00 CAD) when the procedure was performed 12 hours after onset, $5,253.00 USD ($6,643.00 CAD) when it was performed 16 hours after onset, and $3,712.00 USD ($4,633.00 CAD) when performed 24 hours after onset. These results demonstrated that EVT is cost effective up to 24 hours after onset.

The SWIFT-PRIME[13] investigation team, who published one of five clinical trials to prove the efficacy of EVT, used the data they collected during their trial to assess the cost effectiveness of treating an LVO ischemic stroke with tPA and EVT versus tPA alone. This analysis was performed by Shireman et al. [36] considers total hospitalization costs of patients treated in the SWIFT-PRIME[13] trial. This investigation found the initial hospitalization costs of patients treated with both EVT and tPA to be $17,183.00 USD ($21,444.00 CAD) higher than tPA treatment alone which was driven by the obvious difference in procedure cost. At 90 days patients treated with both EVT and tPA were still found to be higher than patients treated with tPA only, but over a lifetime the cost savings associated with being treated with EVT and tPA were projected to be $23,203.00 USD ($28,957.00 CAD) when compared to lifetime projections for patients treated with tPA only. This indicates cost effectiveness of treating LVO patients with both tPA and EVT versus tPA alone.

As discussed above, several publications have proved the cost effectiveness of the EVT procedure by proving that better outcomes reduce the cost associated with post-stroke disability. Yan et al[37] investigated the overall cost associated with stroke care in 2018. This publication is the first introduction of health technology optimization procedures applied to EVT transportation decisions. The method is stated to optimize the decision making process by maximizing patient outcomes and minimizing costs to the system. This analysis produced a map illustrating the optimal transportation strategy for any stoke onset location with consideration of both transportation and hospitalization costs associated with stroke. This analysis contributed to the field by proving that the delivery of EVT optimized to maximize patient outcomes is also optimally cost effective.

2.5 Gaps in the Literature

Following this review of the literature on patient transport decision models for suspected LVO ischemic stroke patients, a lack of research surrounding the benefits of inter-facility transfer via rotary wing is apparent. Rotary wing is commonly the chosen mode of transportation for the inter-facility transfer that occurs as a part of the Drip and Ship method. Air transportation obviously reduces the travel time between facilities which therefore means the time the patient spends outside a hospital facility is minimized.

There is also a lack of information surrounding the cost implication of transportation decisions. The use of air transport is costly, and though decisions should always be made according to what is best for the patient, it is important to understand the financial impact this has on the healthcare system.

This thesis aims to fill these gaps by creating a model that accesses both patient outcomes with the inclusion of the advantages and complexities involved with inter-facility air transport as well as the costs associated. This thesis will also aim to provide insight into the relationship between patient transport decisions and the cost of transport associated with the most likely transportation mode given several scenarios.

Chapter 3: Methodology

Building on the conditional probability model by Holodinsky et al. [28] that was described in the literature review section, the model is expanded to include air transport between the PSC and CSC and a quantification of transport cost. Specifically, the model considers two things:

1. A suspected LVO ischemic stroke patient's probability of an excellent outcome given the method used to transport them to treatment – Mothership or Drip and Ship,
2. The expected cost of the transportation method used to accomplish the chosen method.

This model is probability based and determines the effect a transport decision has on both an ischemic stroke patient's outcome and the cost of their transport to treatment. This evidence based approach is intended to help inform transport protocols for suspected LVO ischemic stroke patients.

The formulations presented in the subsections of this chapter compute both patient outcome and transportation cost functions for a suspected LVO ischemic stroke patient. These formulations determine the probability of an excellent patient outcome and the cost of transportation, using the Mothership and Drip and Ship method. The probability of an excellent outcome and expected transportation cost are then compared to determine in which scenarios each method is preferred.

3.1 Time to Treatments

For a stroke patient, time to treatment is defined as the window of time between the onset of the stroke and the beginning of treatment. Time to treatment is paramount for ischemic stroke patients. A patient's *onset to needle* time is defined as the time between stroke onset and the start of tPA treatment as tPA is administered via intravenous. A patient's *onset to puncture* time is defined as the time between stroke onset and with the time of groin puncture, which is the start of the EVT procedure. Several events occur between a patient's stroke onset and treatment, all of which take time. A patient's overall time to treatment is composed as the sum of several interim events. Times to treatment differ for patients transported using a Mothership method vs a Drip and Ship method, these distinctions are described in the following subsections.

3.1.1 Scene of Stroke Time Variables

There are various time intervals that are part of the overall onset to treatment time that are critical to the model being presented. The time intervals associated with the scene of stroke that precede the transport of the patient are used in the time to treatment formulation of both the Mothership and Drip and Ship methods. These variables are described below:

First medical contact (FMC) is the time when the 911 call is made after the patient's condition has been noticed. The time between the onset of the suspected stroke and the 911 call is denoted below as $t_{\text{onset to FMC}}$. After the 911 call has been placed, there is a delay prior to the ambulance arrival, which is denoted below as $t_{\text{FMC to ambulance}}$. The time the paramedic crew spends at the scene of the suspected stroke before departing for treatment is denoted below as $t_{\text{on scene}}$. These time variables are denoted below:

$t_{onset\ to\ FMC} = Time\ between\ stroke\ onset\ and\ First\ Medical\ Contact\ (FMC)$

$t_{FMC\ to\ ambulance} = Time\ between\ FMC\ and\ ambulance\ arrival$

$t_{on\ scene} = Time\ spent\ at\ scene\ of\ stroke\ before\ departure\ for\ hospital$

Once the paramedic crew has identified that the patient is indeed suspected of suffering an LVO ischemic stroke and assuming the scene of the suspected stroke is outside the direct catchment area of a CSC, the patient is transported using either the Mothership and Drip and Ship transport method must be made.

3.1.2 Mothership Time to Treatments

If the transport decision to follow the Mothership method is made, the patient is transported directly to the closest CSC for both tPA and EVT. Variables specific to the Mothership method are denoted below using the following subscript.

$\mathrm{MS} = \text{subscript associated with the Mothership method}$

The time it takes to travel between the scene of the stroke and the CSC by ground ambulance is denoted below as $\mathrm{t_{scene\ to\ CSC|G}}$. It is assumed that any transport direct from the scene of the stroke will occur via ground ambulance because landing an air ambulance at the scene of a stroke is uncommon.

$t_{scene\ to\ CSC|G} = Travel\ time\ from\ scene\ of\ stroke\ to\ CSC\ using\ Ground\ Transportation$

A patient transported according to the Mothership method receives the entirety of their stroke treatment at the CSC. This means that any time variables related to inter-facility transfer do not apply in this case. Keeping in mind that their initial travel from the scene of the stroke to the CSC and initial treatment was extended because the scene of their stroke occurred outside the direct catchment area of the CSC.

Upon arrival at the CSC and the confirmation of an ischemic stroke diagnosis the patient will first be treated with tPA. The beginning of the tPA treatment is marked by the administration of the tPA bolus. The time between a patient's arrival to either a PSC or CSC and the beginning of tPA treatment is referred to as a patient's Door to Needle (DTN) time. A patient transported according to the Mothership method receives tPA at the CSC and their corresponding DTN time is denoted below as $\mathrm{t_{DTN\ @\ CSC}}$.

$t_{DTN\ @\ CSC} = Time\ between\ arrival\ at\ CSC\ and\ tPA\ beginning\ given\ a\ Mothership\ protocol$

The beginning of EVT treatment is marked by the groin puncture that occurs to insert the catheter used to retrieve the clot. The time between a patient's arrival at the CSC and the beginning of EVT treatment is referred to as a patient's Door to Puncture (DTP) time. The DTP time for a patient transported according to the Mothership method is denoted below as $t_{DTP|MS}$.

$t_{DTP|MS} = Time\ between\ arrival\ at\ CSC\ and\ EVT\ beginning\ given\ a\ Mothership\ protocol$

Even though the DTP time of a patient transported according to the Mothership method corresponds to the same facility as that of a patient transported according to the Drip and Ship method, they are differentiated with subscripts because they tend to differ for logistical reasons. When following the Mothership method, the patient is being transported directly from the scene of the stroke to the CSC. This means that EVT eligibility is unknown at the time of arrival and needs to be confirmed with CT and CTA scans, therefore increasing their door to puncture time relative to that of a patient transported according to the Drip and Ship method.

The overall time to tPA and EVT treatment for the Mothership method were previously defined by Holodinksy et al[28] and used in this thesis. Eq. 1 and Eq. 2 define the onset to needle and onset to puncture times, respectively for a patient transported using the Mothership method.

$$t_{onset\ to\ needle|MS} = t_{onset\ to\ FMC} + t_{response} + t_{on\ to\ scene} + t_{scene\ to\ CSC} + t_{DTN\ @\ CSC} \qquad Eq.\ 1$$

$$t_{onset\ to\ puncture|MS} = t_{onset\ to\ FMC} + t_{response} + t_{on\ scene} + t_{scene\ to\ CSC} + t_{DTP|MS} \qquad Eq.\ 2$$

A visual aid included below as Figure 1 is a timeline which illustrates the relationships between the time variables defined above. The size of the intervals within the timeline are not to scale. The right side of Figure 1 (highlighted in yellow) correspond to the time variables defined above in Section 3.1.1. The left side (highlighted in blue) correspond to time variables defined previously in this section which are specific to a patient transported according to the Mothership method. Additionally, the “Transport Protocol Decision” is noted to indicate the approximate point in the timeline where the decision to transport the patient according to the Mothership method is made.

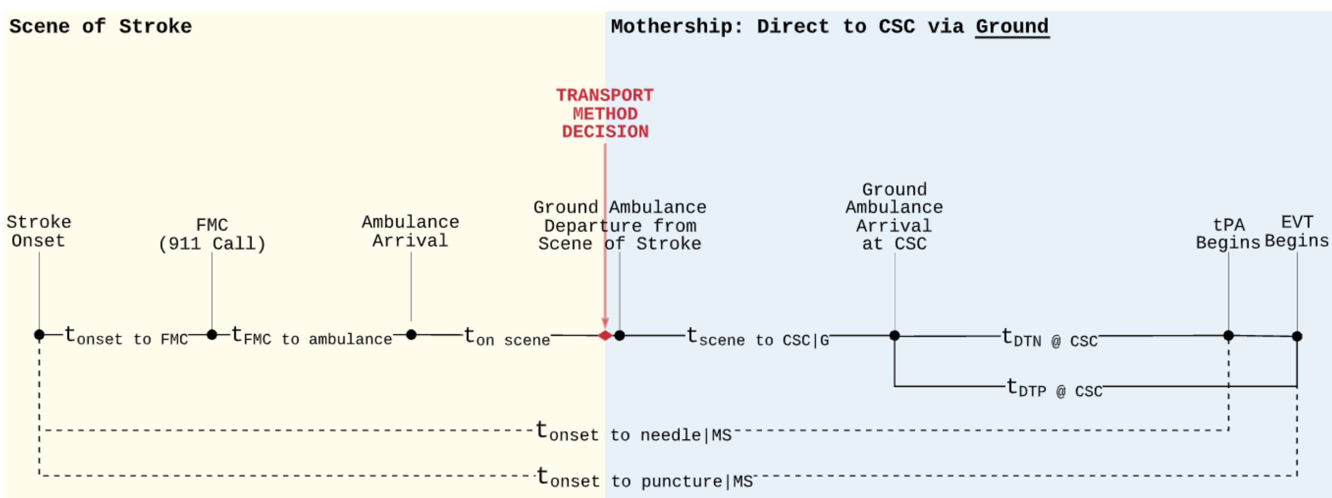

Figure 1: Mothership Method Timeline

3.1.3 Drip and Ship Time to Treatments

If the transport decision is to follow the Drip and Ship method, the patient is transported to the PSC for tPA. Variables specific to the Drip and Ship method are denoted below using the following subscripts.

DnS = subscript associated with the Drip and Ship method

G = subscript associated with ground transportation

A = subscript associated with air transportation

The time it takes to travel between the scene of the stroke and the PSC is denoted below as $\mathrm{t}_{\mathrm{scene\ to\ PSC|G}}$.

$$t_{scene\ to\ PSC|G} = Travel\ time\ from\ scene\ of\ stroke\ to\ PSC\ using\ Ground\ Transportation$$

Upon arrival at the PSC and the confirmation of an ischemic stroke diagnosis the patient will be treated with tPA. The DTN time of a patient transported according to the Drip and Ship method is denoted below as $\mathrm{t}_{\mathrm{DTN\ @PSC}}$.

$$t_{DTN\ @\ PSC} = Time\ between\ arrival\ at\ PSC\ and\ tPA\ beginning\ given\ a\ Drip\ and\ Ship\ protocol$$

If a patient was transported according to the Drip and Ship method after the administration of tPA and the determination of their EVT eligibility has been confirmed they are transferred to the CSC for EVT. The time between the start of their tPA treatment and their departure from the PSC is referred to as a patient's Needle to Door Out (NTDO) time. This is denoted below as t_{NTDO}. Similarly, the time between a patient's arrival to and departure from the PSC is referred to as their Door-In-Door-Out (DIDO) time, which is the sum of their DTN time and their NTDO time. This is denoted below as t_{DIDO}.

$$t_{NTDO} = Needle\ to\ Door\ Out\ time\ between\ tPA\ and\ PSC\ departure$$

$$t_{DIDO} = Door\ In\ Door\ Out\ time\ between\ arrival\ and\ departure\ at\ the\ PSC$$

The transfer time for a patient transported according to the Drip and Ship method is the total time it takes to prep the patient for the transfer plus the travel time between facilities. Transfer time is denoted below as $t_{transfer}$.

$$t_{transfer} = Time\ to\ prep\ for\ transfer\ plus\ travel\ time\ between\ PSC\ and\ CSC$$

The inter-facility transfer in the Drip and Ship method can occur via either ground or air transportation. If the transfer occurs via ground ambulance the transfer time is simply the time it takes to travel via ground ambulance between the PSC and CSC. This is denoted below as $t_{PSC\ to\ CSC|G}$. If the transfer occurs via air ambulance there are significant lead times that must be considered. The time required to perform necessary pre-flight checks after the initiation call and before the aircraft can take off is referred to as the alarm to wheels up time, denoted below as $t_{alarm\ to\ wheels\ up}$. The travel time for the aircraft to get from its base to the PSC is denoted below as $t_{airbase\ to\ PSC}$. The time the air ambulance crew spends on the ground at the PSC before departing in route to the CSC is referred to as the on-ground time, denoted below as $t_{on\ ground\ @\ PSC}$. Once the aircraft arrives at the PSC the patient can be loaded and transported to the CSC, this travel time is denoted below as $t_{PSC\ to\ CSC|A}$.

$t_{PSC\ to\ CSC|G} = Travel\ time\ between\ PSC\ and\ CSC\ facilities\ using\ ground\ transportation$

$t_{alarm\ to\ wheels\ up} = \ Lead\ time\ between\ call\ initiation\ and\ departure\ for\ rotary\ wing\ vehicle$

$t_{airbase\ to\ PSC} = Rotary\ wing\ travel\ time\ between\ airbase\ and\ PSC$

$t_{on\ ground\ @\ PSC} = Time\ spent\ on\ the\ ground\ after\ landing\ on\ the\ PSC\ before\ departure$

$t_{PSC\ to\ CSC|A} = Travel\ time\ between\ PSC\ and\ CSC\ facilities\ using\ air\ transportation$

Following the arrival and preparation of a patient transferred from the PSC to the CSC the patient moves directly to begin EVT. The time between arrival at the CSC and the puncture that begins the EVT procedure is the patient's DTP time. The DTP time for a patient transported according to the Drip and Ship method is denoted below as $t_{DTP|DnS}$. A patient transported according to the Drip and Ship can deteriorate during their inter-facility transfer. This is most likely to happen when a transfer takes longer than 60 minutes. In the event of a long transfer to ensure the patient is still eligible for EVT, they are often re-imaged upon their arrival at the CSC which adds to their DTP time.

$t_{DTP|DnS} = Time\ between\ arrival\ at\ CSC\ and\ EVT\ beginning\ given\ a\ Drip\ and\ Ship\ protocol$

When following the Drip and Ship method, the CSC is notified as soon as the patient's eligibility for EVT is confirmed at the PSC. This gives the EVT team more time to prepare for the procedure and therefore shortens the Door to Puncture time relative to that of a patient transported according to the Mothership method. This is why, the subscript for DTP times differentiates between the Mothership and Drip and Ship patient.

The overall time to tPA and EVT treatment for the Drip and Ship method were defined previously by Holodinsky et al[28] and used in this thesis. The onset to puncture formulation was modified for the inclusion of inter-facility air transportation and the consideration of re-imaging in the case of a long transfer. Eq. 3 and Eq. 4 below, define the onset to needle and onset to puncture times, respectively for a patient transported using the Drip and Ship method.

$$\boldsymbol{t_{onset\ to\ needle|DnS} = t_{onset\ to\ FMC} + t_{response} + t_{on\ scene} + t_{scene\ to\ PSC} + t_{DTN\ @\ PSC}} \qquad Eq.\ 3$$

$$\boldsymbol{t_{onset\ to\ puncture|DnS} = t_{onset\ to\ FMC} + t_{response} + t_{on\ scene} + t_{scene\ to\ PSC} + t_{DTN\ @\ PSC} + t_{transfer} + t_{DTP|DnS}} \qquad Eq.\ 4$$

The transfer time for a patient depends on which mode of transportation is used for the interfacility transfer. When air is used the transfer time is defined using a max function. The max function accounts for the simultaneous relationship between preparing a patient for transfer and initiating an air transfer by comparing the times involved with both. The outcome of the max function plus $t_{PSC\ to\ CSC|A}$ is the total transfer time for a patient transferred between facilities via air, this is shown below in Eq. 4.1 . It is assumed that the air ambulance is landing at a helipad at both the PSC and CSC within this definition of air transfer time. If ground is used the transfer time is defined as the sum of t_{NTDO} plus $t_{PSC\ to\ CSC|G}$, this is shown below in Eq. 4.2. The max function is omitted from the ground transfer function because the ground ambulance to arrive is already on scene.

$$\boldsymbol{t_{transfer|A} = max\,(t_{NTDO}, t_{alarm\ to\ wheels\ up} + t_{airbase\ to\ PSC} + t_{on\ ground\ @\ PSC}) + t_{PSC\ to\ CSC|A}} \qquad \textit{Eq. 4.1}$$

$$\boldsymbol{t_{transfer|G} = t_{NTDO} + t_{PSC\ to\ CSC|G}} \qquad \textit{Eq. 4.2}$$

Figure 2 and Figure 3 illustrate the relationship between the time variables defined previously for a patient transported according to the Drip and Ship method whose inter-facility transfer took place via ground and air, respectively. The size of the intervals within these timelines are not to scale. The right side of these Figures (highlighted in yellow) correspond to time variables defined above in Section 3.1.1. The left side (highlighted in green) correspond to time variables defined previously in this section for ground (Figure 2) and air (Figure 3) inter-facility transfers. The "Transport Protocol Decision" is noted on these timelines to indicate the approximate point in the timeline where the decision to transport the patient according to the Drip and Ship method is made. The "Air Advantage Decision" is also noted on these timelines to indicate the approximate point in the timeline where the decision to carry out the inter-facility transfer via ground (Figure 2) or air (Figure 3) is made. Finally, the "Re-image Decision" is noted on these timelines to indicate the approximate point where the decision to re-image at the CSC is made.

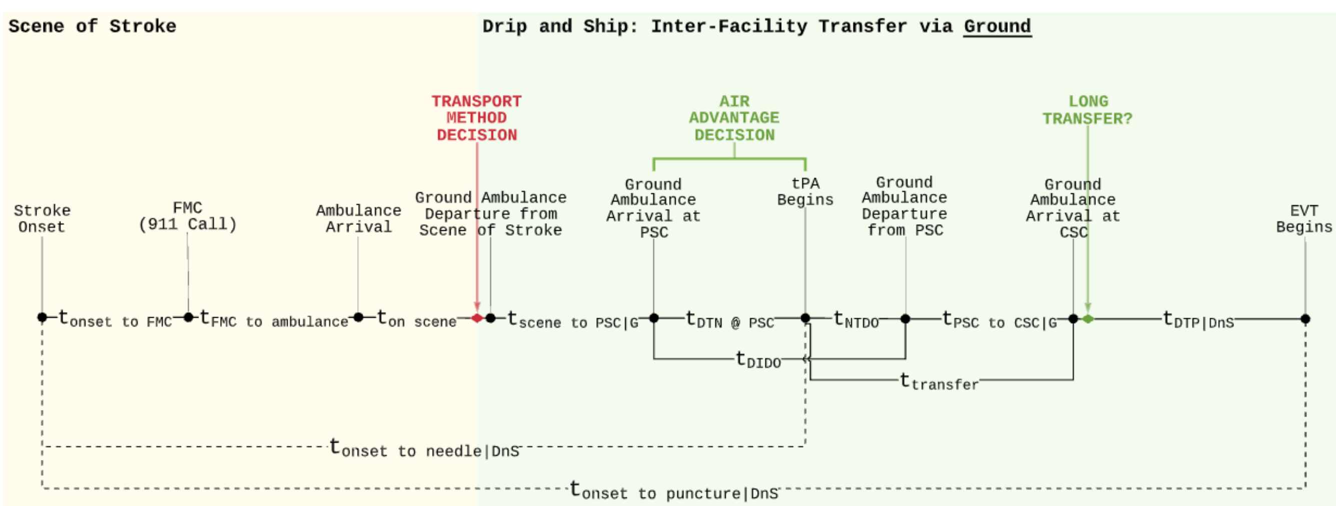

Figure 2: Drip and Ship Method Timeline with Inter-facility transfer via Ground

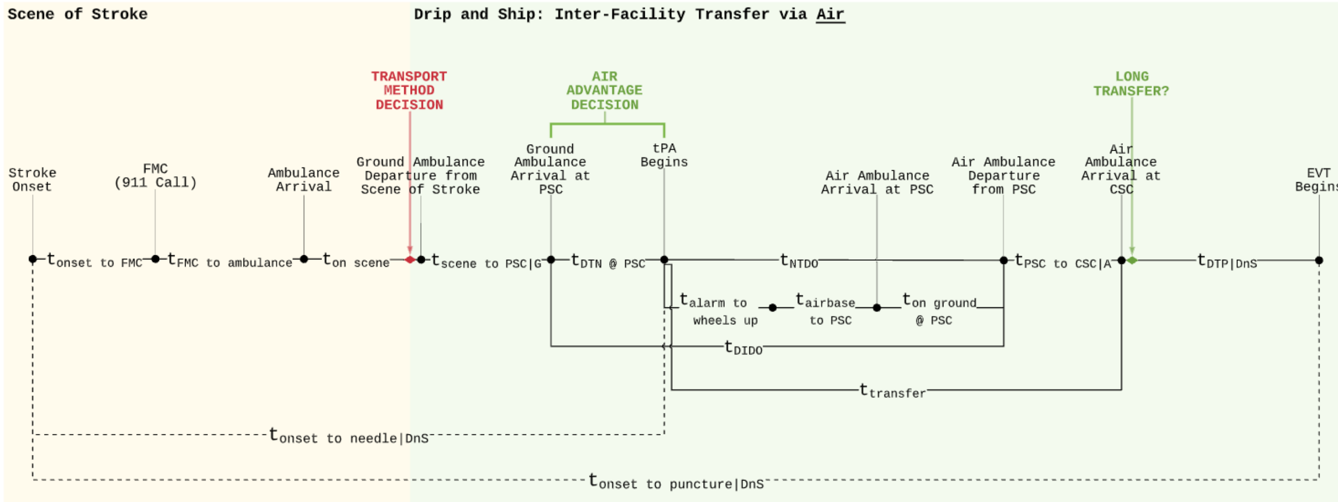

Figure 3: Drip and Ship Method Timeline with Inter-facility transfer via Air

3.2 Final Diagnosis for Suspected LVO Patients

An LVO ischemic stroke can only be confirmed using CT and CTA scans, which are only available in a hospital setting. If paramedics in the field observe stroke symptoms, they use a quick clinical assessment called a "pre-hospital screening tool" to quantify the likelihood that the observed symptoms are being caused by an LVO. If the patient screens positive for a probable LVO ischemic stroke the patient's interim field diagnosis is referred to as a *suspected LVO ischemic stroke*.

Three common pre-hospital screening tools are considered in this model. The Los Angeles Motor Scale (LAMS) was developed in 2003[38] and proven effective for LVO identification in 2018[39]. LAMS assesses three clinical indicators of stroke: facial strength, arm strength and grip strength. A score of four or more on the LAMS indicates a suspected LVO. The Rapid Arterial oCclusion Evaluation Scale (RACE) was developed in 2014[40]. RACE assesses five clinical indicators of stroke: facial palsy, arm motor function, leg motor function, gaze, and aphasia/agnosia. A RACE score of five or more indicates a suspected LVO. Lastly, the Stroke Triage Assessment Tool (C-STAT) was developed in 2015[41]. C-STAT assesses three clinal symptoms of stroke: conjugate gaze, arm weakness, and the presence of an abnormal level of consciousness commands. A C-STAT score of 2 or more indicates a suspected LVO.

Four primary final diagnosis exist for a patient who screens positive on one of these scales for an LVO in the field.[28]

1. LVO Ischemic Stroke
2. nLVO Occlusion Ischemic Stroke
3. Intracerebral Hemorrhage (ICH)
4. Stroke Mimic (SM)

A nLVO is an ischemic stroke where the clot is not located in a large vessel of the brain. An ICH is a hemorrhagic stroke, caused by a bleed in the brain. A SM is an ailment that presents symptoms of a stroke but results in a different final diagnosis (for example a seizure).

The following variables have been assigned to represent the final diagnosis proportions for patients who screen positive for an LVO in the field. The values assigned to these variables are dependant on which pre-hospital stroke scale is in use. These values are derived from standardized measures like the positive predictive value, sensitivity, and specificity. The sum of all four proportions must always sum to equal one.

$$\alpha = \Pr\{\text{LVO}|\text{Positive Screen}\}$$

$$\beta = \Pr\{\text{nLVO}|\text{Positive Screen}\}$$

$$\chi = \Pr\{\text{ICH}|\text{Positive Screen}\}$$

$$\gamma = \Pr\{\text{SM}|\text{Positive Screen}\}$$

$$1 = \alpha + \beta + \chi + \gamma$$

3.3 Proportion of LVO Patients Treated with Endovascular Therapy

Not all patients suffering from an LVO ischemic stroke are treated with EVT. An LVO patient may be deemed ineligible for EVT treatment because of some condition(s) they possess. Conditions of such are called *contraindications*. Contraindications exclude a patient from being eligible for treatment because of an increased risk posed to the patient if the treatment were given. There are several contraindications to EVT such as: poor collateral circulation, a presumed inability to access the clot or tortuous vessels in the opinion of the neuro-interventional team, a lack of brain to save (large core) in the opinion of the neuro-interventional team, contraindication to the contrast agents used for imaging, contraindication to the alloys the retrieval device is made of, previously diagnosed terminal illness, etc.[42-43]

To account for patients with contraindications to EVT, a probability was formulated in the model.[44] Y is defined as the probability of a patient receiving EVT given they are suffering an LVO ischemic stroke. This is equivalent to the proportion of all LVO patients receiving EVT.

$$\mathrm{Y} = \Pr\{\mathrm{EVT}|\mathrm{LVO}\} = \text{Probability of EVT treatment given an LVO diagnosis}$$

The total proportion of patients eligible for EVT are those who screen positive in the field and have a confirmed LVO and who possess no contraindications to the EVT procedure. This proportion is modeled by the product of α and Y. In the Drip and Ship transport method, only these patients $(\alpha * \mathrm{Y})$ will be transferred to the CSC for EVT.

Like EVT, contraindications to tPA treatment do exist. This model does not include a similar variable to model the proportion of patients who possess contraindications to tPA. From a mathematic perspective, including a variable to account for a proportion of patients with contraindications to tPA and assigning the same value at both the PSC and CSC would result in the same results as a model without considerations of tPA contraindications.

3.4 Consideration of the 4.5 Hour Time to Treatment Constraint on tPA

Contraindicators also exist for tPA treatment as they do for EVT. The contraindications of tPA treatment were not considered as a part of this model. This model assumes that every patient with a confirmed diagnosis of an ischemic stroke, nLVO and LVO patients, will receive tPA treatment. If a constant proportion of ischemic stroke patients are assumed to be treated with tPA regardless of the method used to transport them to treatment would result in the same results as the model being presented without this. Ideally, to consider contraindicators of tPA and the proportion of patients treated with tPA one would assign a different value for a patient transported according to a Mothership method vs a Drip and Ship method however, this is out of the scope of this model.

The only restriction placed on tPA treatment in this model relates to a patient's onset to needle time. Current guidelines restrict treatment with tPA to 4.5 hours (270 minutes) from onset [8], meaning that if a patient's stroke symptoms began more than 4.5 hours prior to the potential start of their tPA treatment in either a PSC or CSC facility they are no longer eligible for tPA treatment. Whether or not a patient was within the 4.5 hour period since the onset of their stroke was calculated within the model using the following equations. Eq. 5 calculates the maximum time that can be used to transport the patient to the facility to remain within the 4.5-hour window for a patient transported according to the Mothership method who receives tPA at the CSC. Eq. 6 calculates the same for a patient transported according to the Drip and Ship method. If either of these equations are negative the patient would not be eligible for tPA upon arrival at the facility.

$$t_{MS\ max\ drive\ to\ tPA\ @\ CSC} = 270 - t_{Onset\ to\ FMC} - t_{Response} - t_{On\ scene} - t_{DTN\ @\ CSC} \qquad Eq.\ 5$$

$$t_{DnS\ max\ drive\ to\ tPA\ @\ PSC} = 270 - t_{Onset\ to\ FMC} - t_{Response} - t_{On\ scene} - t_{DTN\ @\ PSC} \qquad Eq.\ 6$$

3.5 Probabilities of Ground and Air Inter-facility Transfers

For an ischemic stroke patient, time saved is extremely valuable as it equates to millions of neurons saved. Air transportation can provide significant time savings in some scenarios. The inclusion of air transportation is a critical element of this model as it is commonly used in real-life implementations of the Drip and Ship method.

Rotary wing aircraft often can land at a facility if the facility has a helipad. Fixed wing aircraft are much more restricted in where they can land as they typically require a runway. For these reasons, the model assumes a lead time, speed, and landing capability of a rotary wing air ambulance only.

To develop a probability of an air transfer occurring between facilities a few things were considered: the distance between the facilities, airworthy weather, and air resource availability.

3.5.1 Formulation of Probability of Air or Ground Transfer

The overall probability of an inter-facility transfer occurring via air transportation is the product of the probability of air transportation being considered, probability of air worthy weather and the probability of air resource availability.

The probability of considering air for an inter-facility transfer is derived from the idea of a time advantage. Air transportation will only be used if it can provide a time advantage to a patient by getting them to EVT treatment quicker than a ground ambulance can. The mathematical formulation for this time advantage is defined below as Eq. 7.

$$\Delta T = Time\ Advantage\ air\ transportation\ provides\ to\ an\ inter\text{-}facility\ transfer$$

$$\Delta T = t_{PSC\ to\ CSC|G} - (t_{alarm\ to\ wheels\ up} + t_{airbase\ to\ PSC} + t_{on\ ground\ @\ PSC} + t_{PSC\ to\ CSC|A}) \qquad Eq.\ 7$$

The time advantage formulation is used to model the probability of air being considered for an inter-facility transfer is a piecewise linear function. To model the consideration of air for an inter-facility transfer it was assumed that the time advantage offered by air must meet a certain threshold for air transportation to be considered. This threshold is denoted in the model as ΔT_1, where if the time advantage offered in a scenario is less than or equal to this threshold, air transportation is not considered. Likewise, a threshold was created to model the point where ground transportation is no longer considered for the transfer and air is the only option. This threshold is denoted in the model as ΔT_2, where if the time advantage offered in a scenario is greater than or equal to the threshold air is considered with a probability of 100 %. Between these two thresholds a linear interpolation function was formulated to find the probability of considering air given the time advantage air can offer in the scenario.

$$\Delta T_1 = Air\ time\ advantage\ threshold\ to\ begin\ considering\ inter\text{-}facility\ transfer\ via\ air$$

$$\Delta T_2 = Air\ time\ advantage\ threshold\ that\ justifies\ only\ considering\ inter\text{-}facility\ trasnfer\ via\ air$$

The time advantage provided by air transportation is not the only factor considered when deciding which mode of transportation to use for the inter-facility transfer. Weather and availability of air resources also play a big part in the decision between air and ground transportation. The probability of airworthy weather and air resource availability (such as the aircraft, pilot, or other crew members) are also considered in modelling the probability of an inter-facility transfer occurring via air. These probabilities are both constant within the model.

The probability of air transfer is formulated below as Eq. 8. The piecewise linear function that models the probability of air transportation consideration described above is formulated below as Eq. 8.1.

$$\Pr\{Air\ Transfer\} = \Pr\{Air\ Consideration|\Delta T\} * \Pr\{Airworthy\ Weather\} * \Pr\{Air\ Resource\ Availability\} \quad \textit{Eq. 8}$$

$$\Pr\{Air\ Consideration|\Delta T\} = \begin{cases} 0 , & if\ \Delta T \leq \Delta T_1 \\ \dfrac{\Delta T - \Delta T_1}{\Delta T_2 - \Delta T_1}, & if\ \Delta T_1 < \Delta T < \Delta T_2 \\ 1 , & if\ \Delta T \geq \Delta T_2 \end{cases} \quad \textit{Eq. 8.1}$$

The probability of ground transfer is therefore:

$$\Pr\{Ground\ Transfer\} = 1 - \Pr\{Air\ Transfer\} \quad \textit{Eq. 9}$$

The underlying assumption made in this formulation is that if a patient cannot be transferred via air ambulance, they will be transported via ground ambulance. In practice, this may not be the case due to time to treatment eligibility guidelines and how fast the patient's stroke is progressing. The decision between modes of transportation is only being made in a Drip and Ship method meaning the patient has already been administered tPA and is being transferred for EVT. Originally to be eligible for EVT a patient's onset had to have occurred less than 6 hours before the beginning of their EVT treatment however, more recent studies have shown that some patients can benefit from EVT for up to 24 hours[16,45] after onset of their stroke. Benefitting from

EVT for longer periods is a very patient specific trait that can only be identified with CT and CTA scans. For these reasons, the assumption that every patient is transferred via ground if air is unavailable is valid.

3.6 Definition of an Excellent Outcome

The outcome functions described in Section 3.7 estimate the probability of an excellent outcome for a patient who screens positive for an LVO in the field. This function is used in the model to determine which transportation method produces the highest probability of an excellent patient outcome. The quantify a patient's outcome the 90-day Modified Rankin Scale (mRS) is used.

The mRS is a common metric used to evaluate stroke patient outcomes. The evaluation of this metric done 90 days post stroke is referred to as a patient's 90 day mRS and is widely accepted as an accurate measure for how affected the patient was by their stroke[46]. The 90-day mRS score is evaluated using a series of questions and results in a score between zero (no symptoms) and six (death). A score of zero indicates the patient has no symptoms of their stroke 90 days after it occurred. A score of one indicates the patient has no disability but has some symptoms. A score of zero or one is considered an excellent outcome for an ischemic stroke patient.[47] In the following model formulation the notation mRS 0-1 refers to an excellent outcome. All clinical trials for both tPA and EVT used 90-day mRS as their primary endpoint. Typically, outcomes have been dichotomized in these trials to good and bad, where a 90-day mRS of 0 or 1 is considered a good or excellent outcome. The formulations described below for modeling good outcomes are derived from the pooled analysis of the clinical trials for both treatments.[9,48]

3.7 Probability of Excellent Outcome for a Suspected LVO Patient

The following probability function formulations are modifications of those presented by Holodinsky et al[28] and modified for use in this model.

The probability of an excellent outcome for a patient who screens positive in the field for an LVO is equal to the sum product of the four possible final diagnosis' and their respective probabilities of an excellent outcome. Each term in the equation corresponds to one of four final diagnoses for a patient who screened positive in the field for an LVO. Each term multiplies the proportion of patients with each final diagnosis by the probability of achieving a 90-day mRS score of 0 or 1 given the final diagnosis, as presented in the clinical trials. Definitions of the four possible final diagnoses of a patient who screens positive in the field for an LVO can be found above in Section 3.2. The definition of an excellent outcome according to the mRS can also be found above in Section 3.6.

The high-level formulation for a patient's probability of an excellent outcome can be found below in Eq. 10.

$$\begin{aligned}\mathbf{Pr}\{\boldsymbol{mRS}\ \mathbf{0-1}|\boldsymbol{positive\ LVO\ screen}\} \\ = \boldsymbol{\alpha}(\mathbf{Pr}\{\boldsymbol{mRS}\ \mathbf{0-1}|\mathbf{LVO}\}) + \boldsymbol{\beta}(\mathbf{Pr}\{\boldsymbol{mRS}\ \mathbf{0-1}|\boldsymbol{nLVO}\} \\ + \boldsymbol{\chi}(\mathbf{Pr}\{\boldsymbol{mRS}\ \mathbf{0-1}|\boldsymbol{ICH}\}) + \boldsymbol{\Upsilon}(\mathbf{Pr}\{\boldsymbol{mRS}\ \mathbf{0-1}|\boldsymbol{SM}\})\end{aligned} \qquad \textit{Eq. 10}$$

The probability of an excellent outcome for ICH and SM patients are not time dependant and are therefore constants. The probability of an excellent outcome for both classes of ischemic stroke patients, nLVO and LVO, are time dependant. Pooled clinical trial data was used to develop a time dependant function to predict the probability of an excellent outcome given an nLVO and separate time dependant functions to predict the probability of an excellent outcome given an LVO[28]. The subsequent paragraphs describe how the constants and functions are used to develop this model.

An LVO patient can be treated with both tPA and EVT unless the patient possesses contraindications to one or both treatments. The overall probability of an excellent outcome for an LVO patient is defined by the probabilities of an excellent outcome for both procedures. The probability of possessing a contraindication to EVT is explained, defined, and assigned to the Y variable in Section 3.3 of this report.

As previously explained in Section 0, no contraindications of tPA were considered in this model. The only restriction placed on tPA treatment in this model is the treatment time window for tPA being 4.5 hours (270 minutes) [8]. This means that if a patient's stroke symptoms began more than 4.5 hours prior to their confirmed ischemic stroke diagnosis in either a PSC or CSC facility they are no longer eligible for tPA treatment. This is reflected in the model for both nLVO and LVO patients since both can be treated with tPA.

The expected probability of an excellent outcome for an LVO patient is formulated below as Eq. 10.1 and has two variations contingent on a patient's onset to needle time. The first variation reflects a scenario where the patient's onset to needle time is less than or equal to 4.5 hours, meaning they are eligible for tPA treatment and the model assumes they will receive it. The first variation is formulated below as Eq. 10.1A. The second variation reflects a scenario where the patient's onset to needle time surpasses the 4.5 hour threshold for tPA eligibility, meaning the only course of treatment for their stroke is EVT. The second variation is formulated below as Eq. 10.1B. Within the two variations three probability components exist and are subsequently described.

Eq. 10.1A models the expected probability of an excellent outcome for a patient who has been diagnosed with an LVO and treated with tPA, it consists of three terms. The first is the probability of an excellent outcome given that the patient has been treated with tPA. The second term is multiplied by the compliment probability of an excellent outcome given tPA treatment and then subsequently broken down into two parts, those who have contraindications to EVT and those who do not. For the proportion of patients who do not have contraindications to EVT their probability of an excellent outcome also includes the probability of an excellent outcome given that they have been treated with EVT. The proportion of patients who do possess contraindications to EVT their probability of an excellent outcome also includes the probability of an excellent outcome from an LVO patient given that they receive no treatment.

Eq. 10.1B models the probability of an excellent outcome for an LVO patient who does not receive tPA treatment and therefore whose only treatment option is EVT, it consists of the sum of two terms. The first refers to the proportion of these patients who do not have contraindications to EVT their probability of an excellent outcome also includes the probability of an excellent outcome given that they have been treated with EVT. The second refers to the proportion of patients who do possess contraindications to EVT their probability of an excellent outcome also includes the probability of an excellent outcome from an LVO patient given that they receive no treatment at all.

$$\mathbf{Pr\{\boldsymbol{mRS}\ 0-1|\boldsymbol{LVO}\}} = \begin{cases} \Pr\{mRS\ 0-1|LVO\}_A, & t_{onset\ to\ needle} \leq 4.5\ hours \\ \Pr\{mRS\ 0-1|LVO\}_B, & t_{onset\ to\ needle} > 4.5\ hours \end{cases} \qquad \textit{Eq. 10.1}$$

$$\mathbf{Pr\{\boldsymbol{mRS}\ 0-1|\boldsymbol{LVO}\}_A} = \Pr\{mRS\ 0-1 \,|\, LVO\ \&\ tPA\} + \left[\left(1-\Pr\{mRS\ 0-1 \,|\, LVO\ \&\ tPA\}\right) \cdot \left[Y\left(\Pr\{mRS\ 0-1 \,|\, LVO\ \&\ EVT\}\right) + (1-Y)\left(\Pr\{mRS\ 0-1 \,|\, LVO \& no\ treatment\}\right)\right]\right] \qquad \textit{Eq. 10.1A}$$

$$\mathbf{Pr\{\boldsymbol{mRS}\ 0-1|\boldsymbol{LVO}\}_B} = \left[Y\left(\Pr\{mRS\ 0-1 \,|\, LVO\ \&\ EVT\}\right) + (1-Y)\left(\Pr\{mRS\ 0-1 \,|\, LVO \& no\ treatment\}\right)\right] \qquad \textit{Eq. 10.1B}$$

Further definition of the probability terms shown above in Eq. 10.1A and Eq. 10.1B are formulated below in Eq. 10.1.1-Eq. 10.1.3. The probabilities of an excellent outcome for an LVO patient given they were treated with tPA or EVT are found in Eq. 10.1.1 and Eq. 10.1.2, respectively. These formulations were developed and published by Holodinsky et al[28]. The probability of an excellent outcome for an LVO patient given they received no treatment can be found in Eq. 10.1.3 and was developed by Holodinsky et al[28] using ESCAPE[49] trial data.

$$\Pr\{mRS\ 0-1 \,|\, LVO\ \&\ tPA\} = 0.2359 + 0.0000002(t_{onset\ to\ needle})^2 - 0.0004(t_{onset\ to\ needle}) \qquad \textit{Eq. 10.1.1}$$

$$\Pr\{mRS\ 0-1 \,|\, LVO\ \&\ EVT\} = 0.394 + 0.00000004\left(t_{onset\ to\ puncture}\right)^2 - 0.0002(t_{onset\ to\ puncture}) \qquad \textit{Eq. 10.1.2}$$

$$\Pr\{mRS\ 0-1 \,|\, LVO \& no\ treatment\} = 0.07 \qquad \textit{Eq. 10.1.3}$$

An nLVO patient is only eligible for tPA treatment. The probability of an excellent outcome for an nLVO patient was developed by Holodinsky et al[28] and is shown below in Eq. 10.2. Like the probability of an excellent outcome defined for an LVO patient, this formulation has two variations contingent on a patient's onset to needle time. The first variation reflects a scenario where the patient's onset to needle time is less than or equal to 4.5 hours, meaning they are eligible for tPA treatment and the model assumes they will receive it. The first variation is formulated below as Eq. 10.2A. The second variation reflects a scenario where the patient's onset to needle time surpasses the 4.5-hour threshold for tPA eligibility, meaning there is no treatment available for the patient. The second variation is formulated below as Eq. 10.2B.

The probability of an excellent outcome given a nLVO given no treatment was used in the original formulation of these functions[28] but the constant value of 0.4622 assigned to it originates from a pooled-analysis[9] performed using data from several trials of the effects of tPA on ischemic stroke patients.

$$\mathbf{Pr\{mRS\ 0-1|nLVO\}} = \begin{cases} \Pr\{mRS\ 0-1|nLVO\}_A\,, & t_{onset\ to\ needle} \le 4.5\ hours \\ \Pr\{mRS\ 0-1|nLVO\}_B\,, & t_{onset\ to\ needle} > 4.5\ hours \end{cases} \qquad \textit{Eq. 10.2}$$

$$\mathbf{Pr\{mRS\ 0-1|nLVO\}_A} = 0.6343 - 0.00000005(t_{onset\ to\ needle})^2 - 0.0005(t_{onset\ to\ needle}) \qquad \textit{Eq. 10.2A}$$

$$\mathbf{Pr\{mRS\ 0-1|nLVO\}_B} = \Pr\{mRS\ 0-1\,|nLVO\&no\ treatment\} \qquad \textit{Eq. 10.2B}$$

$$\Pr\{mRS\ 0-1\,\big|\, nLVO\&no\ treatment\} = 0.4266 \qquad \textit{Eq. 10.2.1}$$

The probability of an excellent outcome for an intracerebral hemorrhage patient is not time dependant and is therefore a constant value. This is shown below in Eq. 10.3. This constant was used in the original formulation[28] of these functions but originates from several trials of intracerebral hemorrhage treatment[50–54].

$$\mathbf{Pr\{mRS\ 0-1|ICH\}} = 0.24 \qquad \textit{Eq. 10.3}$$

The probability of an excellent outcome for a stroke mimic patient is also not time dependant. The constant probability representing this is shown below in Eq. 10.4. This constant was used in the original formulation[28] of these functions but originates from several trials of stroke mimics[55–59].

$$\mathbf{Pr\{mRS\ 0-1|SM\}} = 0.90 \qquad \textit{Eq. 10.4}$$

3.8 Expected Transportation Cost

Transportation cost functions were developed with the assumption that the overall cost of transportation is composed of both a fixed cost element as well as a cost element that varies with the distance traveled. Fixed transportation costs include expenses independent from the distance the ambulance travels such as: vehicle insurance, depreciation of vehicle value, salary of ambulance dispatchers, and other overhead costs associated with delivering ambulance services. Variable transportation costs include expenses dependant on the distance traveled by the vehicle such as: fuel, paramedic salary, vehicle maintenance and other distance dependant costs associated with delivering ambulance services. Paramedic salary was included in the variable costs to assign the cost of paramedic time that is dedicated to the stroke cases, which could otherwise be spent on other diseases.

3.8.1 Cost Function Variable Definitions

The following variables were defined for use in the Transportation Cost functions developed as a part of this model:

TC = Transportation Cost (\$)

$\mathrm{TC}\{\mathrm{D}_{\mathrm{X\ to\ Y}}\}$ = Transportation Cost of travelling the distance between X and Y (\$)

G = subscript associated with ground transportation

A = subscript associated with air transportation

F_G = Fixed cost of ground transporation assumed by model (\$)

F'_G = Fixed cost of ground transporation inter-facility transfer assumed by model (\$)

V_{G} = Variable cost of ground transporation asummed by model (\$/km)

F_A = Fixed cost of air transporation asummed by model (\$)

V_A = Variable cost of air transporation asummed by model (\$/km)

$\mathrm{D}_{\mathrm{scene\ to\ CSC}}$ = Distance between the scene of the stroke and the CSC (km)

$\mathrm{D}_{\mathrm{scene\ to\ PSC}}$ = Distance between the sceneof the stroke and the PSC (km)

$\mathrm{D}_{\mathrm{PSC\ to\ CSC}}$ = Distance between the PSC and the CSC (km)

$\mathrm{D}_{\mathrm{airbase\ to\ PSC}}$ = Distance between the airbase and the PSC (km)

The addition of air transportation and cost functions required distances, not just times. To calculate these distances constant speeds were assumed for each mode of transportation. Distances were calculated using the times defined in Section 3.1 and assumed speeds defined in Section 4.6.

Distances traveled were assumed to be equal for both air and ground ambulances within the model. In the real world, the distance traveled by a ground ambulance is approximately 1.4 times the straight-line distance traveled by an air ambulance[60] and this should be considered if using these formulations on a real-world map.

3.8.2 Return to Base Penalty for Ground Transportation

The cost of an ambulance is not the only consideration in deciding on how to transfer a patient between two facilities. The displacement of an ambulance over a long distance disrupts a community's ambulance coverage and can result in paramedics working long over-time hours having to transport patients long distances via ground. To account for an ambulance needing to return to its base location once a patient has been delivered to their final location and to align the model more closely with how decisions are made, the cost of ground transportation from the scene of the stroke to a patient's final facility destination was doubled for both Mothership and Drip and Ship methods.

Returning to base was only accounted for in ground transportation scenarios since community ambulance coverage is not an issue for air ambulances. Air ambulances are employed within an ambulance response system to be travel long distances and therefore accounting for their time back to base does not enhance the model.

3.8.3 Cost Function Formulations

In a Mothership method, the patient is transported directly from the scene of the stroke to the CSC for tPA and EVT treatments. This means the transportation cost function for a Mothership method is simple. As shown in Eq. 11, the transportation cost for a Mothership method is made up of the fixed cost of ground transportation plus the variable cost times the distance traveled. It is assumed that air transportation cannot be used in the Mothership method since it is unlikely that an air ambulance could land at the scene of the stroke[61].

$$\boldsymbol{TC_{MS}} = \boldsymbol{F_G} + \left(\mathbf{2} * \left(\boldsymbol{D_{scene\ to\ CSC|G}} * \boldsymbol{V_G}\right)\right) \qquad \textit{Eq. 11}$$

In a Drip and Ship method, the patient is first transported to the PSC for tPA which allows for the opportunity to rule out an LVO diagnosis and/or EVT eligibility. Only patients with confirmation of an LVO diagnosis and EVT eligibility are transferred from the PSC to the CSC. This brings an opportunity for transportation cost savings which was modelled by formulating an expected cost for a patient transported using a Drip and Ship method. The first term in Eq. 12 accounts for the cost of transportation between the scene of the stroke and the PSC in a Drip and Ship method, this term of the equation is further defined in Eq. 12.1. Again, it is very unlikely that a helicopter could land at the scene of the stroke for transport to the PSC and therefore it was assumed that transport from the scene of the stroke to the PSC could only occur via ground transportation[61]. The subsequent terms of Eq. 12 model the inter-facility transfer including the probabilities that it is medically necessary and the probabilities of it occurring via air or ground.

The probability a patient who is suspected to have an LVO in the field has a confirmed LVO diagnosis, this is represented by the alpha (α) variable which was defined above in Section 3.2. The proportion of confirmed LVO patients who are eligible for EVT treatment is represented by the Y variable which was defined above in Section 3.3. The alpha and Y variables are multiplied together to represent the proportion of LVO patients that are eligible for EVT and who therefore will require an inter-facility transfer in a Drip and Ship method. Patients who require an inter-facility transfer in a Drip and Ship method can be transported using either a ground or air ambulance. The probability of the transfer occurring via both methods is calculated for the given scenario (described in Section 3.5) and multiplied by the cost of that transportation method. Eq. 12.2 and Eq. 12.3 further define the transportation cost of ground and air transportation, respectively. Eq. 12.3 includes the distance travelled by the air ambulance between the airbase and PSC plus the distance between the PSC and CSC. The distance between the base and the PSC was considered negligible for a ground ambulance as communities have constant ground ambulance coverage.

Eq. 12.2 includes a prime version of the fixed ground transportation cost, F'_G. This was used to model the fixed cost of ground transportation used for inter-facility transfer. The knowledge of a potential inter-facility transfer becomes available as soon as the decision to transport the patient using a Drip and Ship method is made. It is understood that there is a significant chance a suspected LVO patient will have a confirmed LVO diagnosis and will be eligible for EVT. This means the patient will require further transport to a CSC. It was assumed that forewarning of a potential inter-facility transfer allows for logistical decisions to be made in advance about how the transfer will occur. Therefore, F'_G represents the fixed cost associated with an inter-facility transfer via ground transportation which is assumed to be less than F_G, the fixed cost associated with scene to facility ground transportation.

$$\boldsymbol{TC_{DnS} = TC\{D_{scene\ to\ PSC|G}\} + \alpha * Y * \left(\left[\mathbf{Pr}\{Ground\ Transfer\} * TC\{D_{PSC\ to\ CSC|G}\}\right] + \left[\mathbf{Pr}\{Air\ Transfer\} * TC\{D_{PSC\ to\ CSC|A}\}\right]\right)} \quad \textit{Eq. 12}$$

$$\boldsymbol{TC\{D_{scene\ to\ PSC|G}\}} = F_G + \left(2 * \left(V_G * D_{scene\ to\ PSC|G}\right)\right) \quad \textit{Eq. 12.1}$$

$$\boldsymbol{TC\{D_{PSC\ to\ CSC|G}\}} = F'_G + \left(2 * \left(V_G * D_{PSC\ to\ CSC|G}\right)\right) \quad \textit{Eq. 12.2}$$

$$\boldsymbol{TC\{D_{PSC\ to\ CSC|A}\}} = F_A + \left(V_A * \left(D_{airbase\ to\ PSC} + D_{PSC\ to\ CSC|A}\right)\right) \quad \textit{Eq. 12.3}$$

3.9 Output Analysis and Visualization

There is no uncertainty in the decision to transport patients whose stroke onset occurs within the catchment area of a CSC, as a patient would be transported directly to the CSC for treatment. Therefore, it is only necessary to employ the model in the investigation of transportation decisions for areas outside the catchment area of the CSC. To demonstrate the results of this investigation in a manner than can be applied stroke systems universally generic temporospatial diagrams were implemented. The subsections below will introduce and explain the implementation of these diagrams and how they will be used to display the results of the model.

3.9.1 Introduction to the Temporospatial Diagram

The temporospatial diagram consists of several concentric circles and two markers to represent the PSC and CSC facilities. In Figure 4 the yellow circle in represents the location of the PSC and the blue diamond represents the location of the CSC. The distance between the concentric circles shown in Figure 4 represents five minutes of driving time. Since the designed experiments will only evaluate scenarios where the patient's onset occurs outside the catchment area of the CSC, the concentric circles are truncated in Figure 4 halfway between the PSC and CSC.

The temporospatial diagram will be colour coded to depict the results of the model. The colour coding will indicate which transportation method is associated with the highest probability of an excellent patient outcome and which method is least expensive.

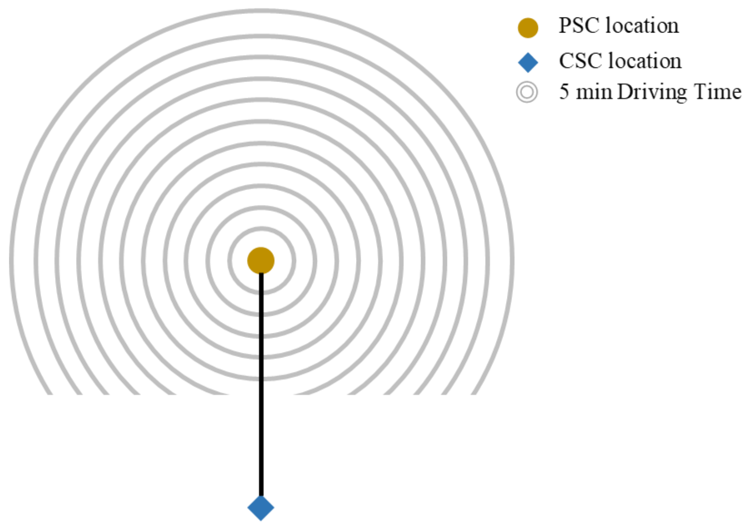

Figure 4: Temporospatial Diagram for Model Output

3.9.2 Scene Location Relative to the PSC and CSC

A point on the diagram is called a pixel. Each pixel within the bounds of the concentric circles represents a potential scene for the onset of a stroke. The relative position of each potential scene to the PSC and CSC facilities is calculated using the equation of a circle.

The formulation of the model requires the primary units of the relative position of the scene be units of time. The resolution of the diagram represents the conversion factor between diagram pixels to time, this is shown in Eq. 13. In the model, resolution is assigned value which indicates the number of pixels equate to one unit of time.

Below are definitions of the coordinate points used in the equation of a circle calculations below.

PSC_X = X coordinate location of the PSC (pixels)

PSC_Y = Y coordinate location of the PSC (pixels)

CSC_X = X coordinate location of the CSC (pixels)

CSC_Y = Y coordinate location of the CSC (pixels)

$Scene_X$ = X coordinate location of a scene (pixels)

$Scene_Y$ = Y coordinate location of a scene (pixels)

The rearranged version of the equation of a circle used to calculate the driving times from the scene to the PSC and the scene to the CSC are shown below in Eq. 14 and Eq. 15. The coordinates of the PSC are the center of the solution space. The CSC shares the x-coordinate of the PSC as depicted by Eq. 16. The y-coordinate of the CSC is located below the PSC as depicted below in Eq. 17. The distance between the PSC and CSC is varied in experiment scenarios which is described in Section 5.1. These equations are used to calculate the relative position of every pixel on the diagram. A visualization of these calculations for an example scene is found below in Figure 5.

$$Resolution = \frac{pixels}{distance} \quad \text{Eq. 13}$$

$$D_{scene\ to\ PSC} = \frac{\sqrt{(Scene_X - PSC_X)^2 + (Scene_Y - PSC_Y)^2}}{Resolution} \quad \text{Eq. 14}$$

$$t_{scene\ to\ PSC|G} = \frac{D_{scene\ to\ PSC}}{Speed|G} \quad \text{Eq. 14.1}$$

$$D_{scene\ to\ CSC} = \frac{\sqrt{(Scene_X - CSC_X)^2 + (Scene_Y - CSC_Y\ )^2}}{Resolution} \quad \text{Eq. 15}$$

$$t_{scene\ to\ CSC|G} = \frac{D_{scene\ to\ CSC}}{Speed|G} \quad \text{Eq. 15.1}$$

$$CSC_X = PSC_X \quad \text{Eq. 16}$$

$$CSC_Y = PSC_Y - (t_{PSC\ to\ CSC} * Resolution) \quad \text{Eq. 17}$$

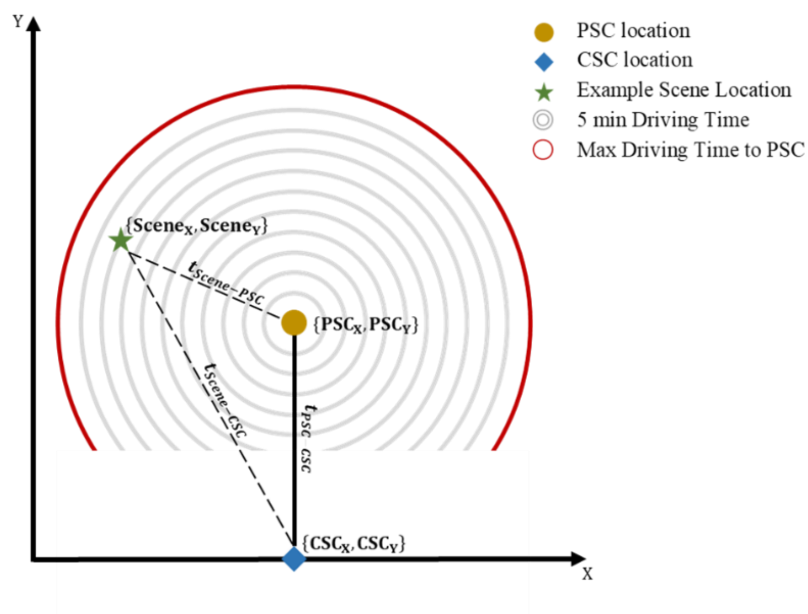

Figure 5: Temporospatial Diagram to Illustrate Calculations for an Example Scene

3.9.3 Model Implementation using MATLAB

Each potential scene's relative position to the PSC and CSC is calculated using the methods detailed in Section 3.9.2. The time between the scene and the CSC (Eq. 15.1) is plugged into the model formulation to calculate the probability of an excellent outcome (Eq. 10) if a patient picked up at the scene were transported according to the Mothership method. Likewise, the calculated time between that scene and the PSC (Eq. 14.1) is plugged into the model formulation to calculate the probability of an excellent outcome (Eq. 10) if a patient picked up at that scene were transported according to the Drip and Ship method. These two probabilities of an excellent outcome are compared and the method which yields the highest probability of an excellent outcome is noted.

The relative position of each scene is also used in the transportation cost formulation. This distance between the scene and the CSC (Eq. 14) is plugged into the model formulation to calculate the expected cost of transporting a patient from the scene according to the Mothership method (Eq. 11). Similarly, the distance between the scene and the PSC (Eq. 15) is plugged into the model formulation to calculate the expected cost of transporting a patient from the scene according to the Drip and Ship method (Eq. 12). These two costs are compared and the least expensive method of transportation from the scene is noted.

The Drip and Ship method also involves an inter-facility transfer which involved the time between the PSC and CSC but since this is a fixed distance that only varies between experiments this portion of the calculation is the same regardless of the scene location.

The described approach is known as complete enumeration. For all scenes, the results are calculated as described above, compared, and the best option is selected. From this, the results illustrate where the cost and outcome functions agree and disagree on the best transportation method.

The model was implemented using the R2020a version of MATLAB accessed using an academic licence. The results of the model are displayed using a temporospatial diagram which was created in MATLAB using the 2D plot and imshow functions.

The code described below began with code written for the previous publication.[28] This code was altered to include air transportation, consideration of contraindications to EVT and several other elements included in this analysis. The transportation cost function and code are novel.

Portions of the code which are relevant to the analysis the model performs have been included in Appendix A. The code is structured using sub routines each dedicated to a phase of the formulation. There are five total sub routines, each of which are outlined with a dashed line in the code diagram shown below in Figure 6.

The main module and first subroutine begin by initializing necessary variables then immediately calls the second subroutine called User Prompt which asks the user a series of questions using the "Inputdlg" and "Menu" functions. These questions assign values to run parameter variables such as the position of the PSC and CSC. For ease of use when running multiple experiments, the MATLAB implementation was coded to ask the user a series of questions regarding the number of experiments to be run, if the user would like to save the output temporospatial diagram to a designated file location, and if the default constants are to be assumed or not. This front-end interface makes for an easily manipulated model which reduces the risk of human error related bugs when trying to change a run parameter to run a different variation of the model.

Next, Pixel Colour Generation, the third subroutine is called, and the analysis begins. This starts by initializing a for loop to increment through all the pixels in the output temporospatial diagram. If the pixel is uncoloured and within the PSC catchment region, then the relative location of the pixel to the PSC and CSC is calculated. With this and still within the for loop, the fourth and fifth two sub routines are called. The fourth subroutine calculates the probabilities of an excellent outcome for a patient whose stroke onset occurs at the scene the current pixel using Eq. 10. For brevity in Figure 6, the probabilities have been abbreviated as they are shown below:

- $\mathrm{Pr_{MS}} = \mathrm{Pr}\{mRS\ 0 - 1|positive\ LVO\ screen\}_{MS}$
- $\mathrm{Pr_{DnS}} = \mathrm{Pr}\{mRS\ 0 - 1|positive\ LVO\ screen\}_{DnS}$

The fifth subroutine calculates the transportation costs associated with transporting the patient from the scene according to a Mothership and Drip and Ship methods using Eq. 11 and Eq. 12. Once these four data points have been calculated they are then passed to an if/else series to determine which colour they will be assigned. Once the colour assignment for the pixel is determined, the RGB colour code for the pixel is stored in an array and the for loop iterates to the next pixel. The Pixel Colour Generation subroutine runs until all the pixels within the PSC catchment region have been assigned a colour at which point the subroutine ends and returns to the main module to create and return the temporospatial diagram.

The output temporospatial diagram is created using the array storing the pixel colour assignments, and the built in MATLAB functions “Imshow” and “Plot”. The Imshow function is first used to lay the pixels in the correct location on the temporospatial diagram. Next the concentric circles, PSC, and CSC markers are placed on the temporospatial diagram using the Plot function. If the experiment result requires 4.5-hour threshold arcs, these are also placed on the temporospatial diagram using the Plot function. Once this is complete the temporospatial diagram is returned.

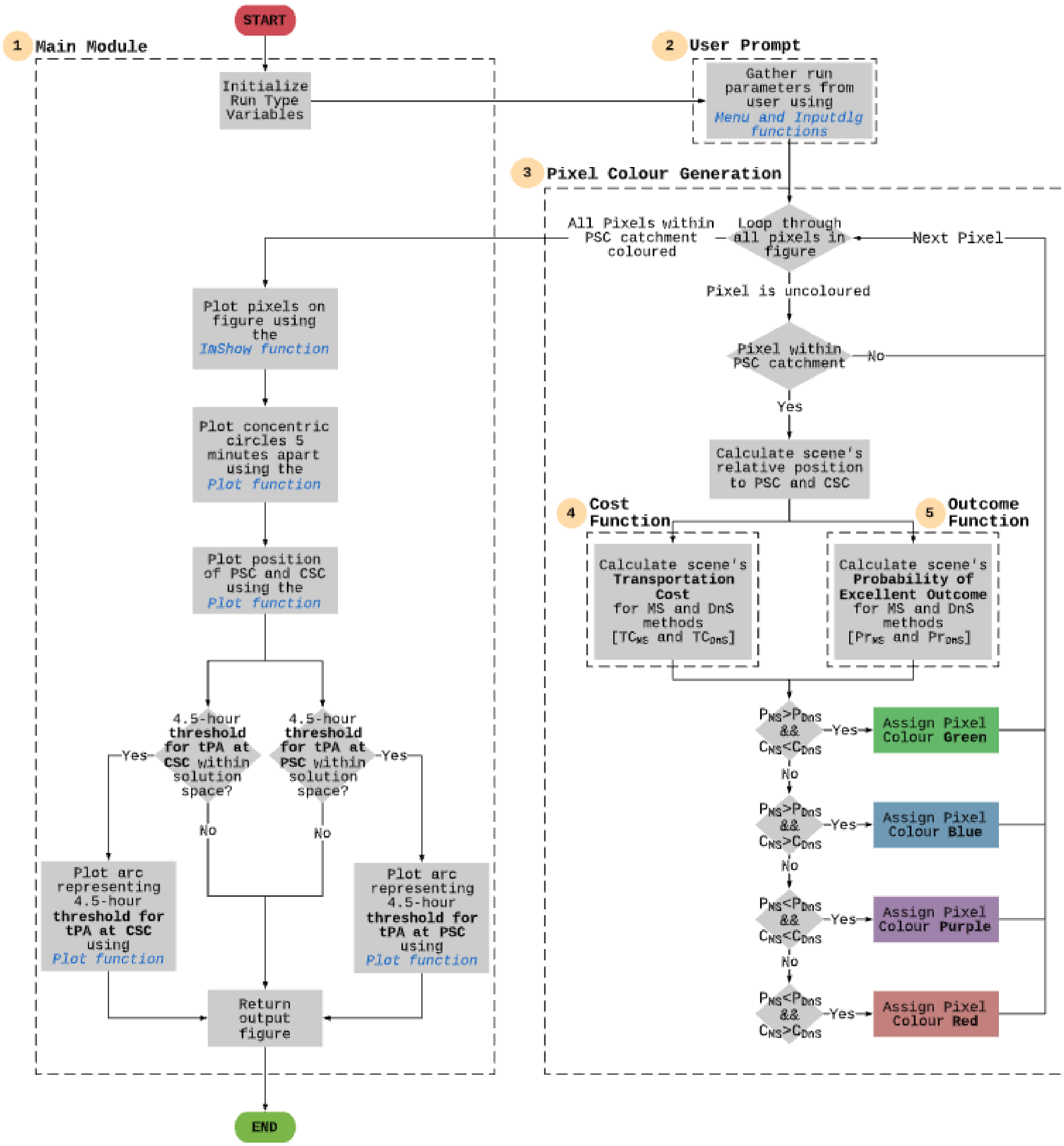

Figure 6: MATLAB Code Diagram

Chapter 4: Data

Several variables within the model assume a constant value. The following subsections outline the investigating done to assign practical values to these variables.

4.1 Final Diagnosis for Suspected LVO Patients

The true positive field identification rate of an LVO and proportion of patients having another final diagnosis varies depending on which screening tool is used. Table 1 shows the proportion of patients corresponding to each four of the final diagnoses for screening tools LAMS, RACE, and C-STAT [28].

Table 1: Final Diagnosis Suspected LVO Patient Proportions[28]

		LVO Positive Score		
Final Diagnosis	Variable	LAMS ≥ 4	RACE ≥ 5	C-STAT ≥ 2
Large Vessel Occlusion	α	0.4538	0.5294	0.4000
Non-Large Vessel Occlusion	β	0.1092	0.1176	0.1826
Intracerebral Hemorrhage	χ	0.3445	0.3137	0.2957
Stroke Mimic	γ	0.0924	0.0392	0.1217
		1.000	1.000	1.000

4.2 Health System Constants

There are several constants that related to patient response and the health system. A few constant time variables used in the patient outcome formulations were kept the same as they were in the previous publication[28] to allow for comparison of results, these include onset to first medical contact, ambulance response and on-scene times.

Nova Scotia's LifeFlight has a goal of 15 minutes for the lead time between the call to initiate an air transfer and the aircraft being "wheels up" for their rotary wing aircraft.[61] A transfer is considered long if it exceeds 60 minutes. The definition of air and ground transfer times are different and are defined above in Eq. 4.2 and Eq. 4.1. These times and their constant values are shown below in Table 2.

Table 2: Time Constants

Time Constant	Minutes
$t_{\text{onset to FMC}}$	30
t_{response}	15
$t_{\text{on scene}}$	15

$t_{alarm\ to\ wheels\ up}$	15
$t_{on\ ground\ @\ PSC}$	20
$t_{long\ transfer}$	60

4.3 Airworthy Weather and Air Resource Availability

A 2005 study done in Nova Scotia analyzed EHS Life Flight's aborted air ambulance mission data from July 1997 and June 2001.[62] This paper published reasons for aborted missions and the corresponding percentage of total flights aborted for each stated reason. There areonly two reasons for aborted air missions relevant to ischemic stroke patients described in this study. The first being missions aborted due to weather unsuited for flying. This study states that 9.6 percent of missions are aborted due to weather unsuitable for flying, the compliment of this being 90.4 percent was used as the probability of airworthy weather. The second reason for aborted air missions is a lack of air resource (aircraft and crew) availability at the time of the request. This study states that 3.5 percent of missions are aborted due to a lack of air resource availability, the compliment of this being 96.5 percent was used as the probability of air resource availability.

These probabilities are consistent across all experiments and varied only in the sensitivity analysis. A summary of these probabilities can be found below in Table 3.

Table 3: Air Probability Constants

Air Probability Constant	Value
Pr{Airworthy Weather}	90.4 %
Pr{Air Resource Availability}	96.5 %

4.4 Probability of Considering Inter-facility Transfer via Air

Two thresholds must be assumed for the formulation of air consideration presented in section 3.5.1. A negligible time advantage was modeled as 10 minutes and a large time advantage was modeled as 40 minutes. These thresholds feed into the modeled likelihood that air transportation is considered for the inter-facility transfer given the Drip and Ship method.

Time advantage given by utilizing air for the inter-facility transfer given the driving time between the PSC and CSC facilities is described above in Section 3.5.1 as Eq. 7. The probability of considering an inter-facility transfer via air is also defined above in Section 3.5.1 as Eq. 8.1. Figure 7 illustrates this probability (y-axis) given a range of time advantages (x-axis).

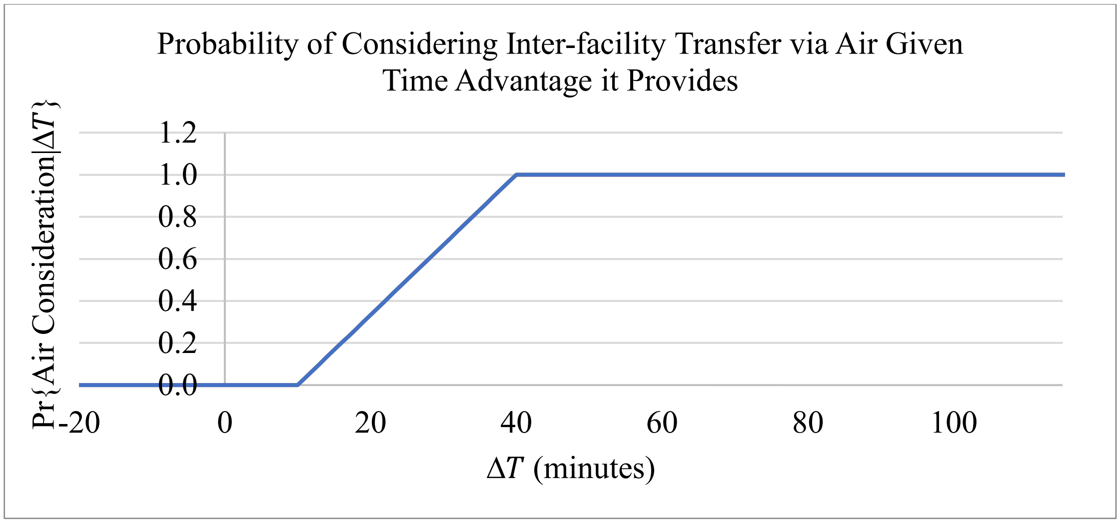

Figure 7: Probability of Considering Inter-facility Transfer via Air

4.5 Cost of Ambulance Services

The cost of ground ambulance services is mostly subsidized in Canada for patients using the service within their home province. Because of this, researching the true of cost of ambulance services proved difficult and it was decided that the closest value to the true cost would be the price listed for a non-citizen of the province. A few provinces offer cost information of this kind, Table 4 summarizes the information found.

Table 4: Cost of Ambulance Services for non-Residents of Various Provinces

	Ground Rates		Rotary Wing Air Rates	
	Flat	Variable	Flat	Variable
Nova Scotia EHS non-Canadian	$1,099.35[63]	-	-	-
Nova Scotia EHS out of province	$732.95[63]	-	-	-
Nova Scotia EHS	-	$1.06[64] per litre of fuel	-	-
British Columbia EHS patients without medical service plan	$848.00[65]	-	-	$4,394.00[65] per hour
STARS Calgary	-	-	-	$3,600.00[66] per hour
Ambulance New Brunswick "un-entitled" resident	$650.00[67]	-	-	-
Ambulance New Brunswick out of province resident	-	-	$6,500.00[67]	-

The format of the researched transport costs in Table 4 did not match the formulation of transport costs in the model. Therefore, the transport costs in Table 4 are used to inform an educated assignment of the cost variables in the model. The model assumes a constant fixed ground cost, F_G, of $500.00 and a variable ground cost, V_G, of $5.00 per km which is applied in every instance of ground travel except an inter-facility ground transfer. An inter-facility ground transfer is identified as a possibility as soon as the paramedics suspect an LVO ischemic stroke in the field.

It is assumed that this gives the logistics team routing the ambulances more advanced noticed that an ambulance may be required for the transfer and therefore most likely results in a lesser fixed cost associated with ground transport. The fixed ground cost assumed for a ground inter-facility transfer, F'_G, is \$400.00. The model also assumes a fixed air cost of \$2,500.00 and a variable air cost of \$12.00 per km.

Transportation costs are consistent across all experiments and varied only in the sensitivity analysis. These costs are summarized below in Table 5.

Table 5: Cost Constants

Cost Constant	Value
F_G	\$ 500.00
F'_G	\$ 400.00
F_A	\$ 2,500.00
V_G	5 \$/km
V_A	12 \$/km

4.6 Ambulance Speed Assumptions

In urban areas ground ambulances average speed is around 67 km/hr, in rural areas this increases to approximately 100 km/hr.[68] The model assumes a constant value of 80 km/hr for ground transportation which is approximately the average of urban and rural speeds.

Nova Scotia's air ambulance service, EHS LifeFlight, employs two Sikorsky S-76C+ helicopters to provide their services to the province.[69] The specification document for the Sikorsky S-76 fleet indicates a maximum cruising speed of 287 km/h and an average cruising speed of 254 km/hr.[70] The model assumes the average constant speed of 254 km/hr for air ambulance transportation.

Ambulance speeds are consistent across all experiments. The constant speeds are summarized below in Table 6.

Table 6: Speed Constants

Speed Constant	Value
Ground Ambulance Speed	80 km/hr
Helicopter Ambulance Speed	254 km/hr

Chapter 5: Experiment Design

Several experiments were designed to model various real-world scenarios. The variables kept consistent across all experiments were defined and assigned values in Chapter 4. Several values for three key different input variables are used for experiments. The key input variables chosen are the driving time between the PSC and CSC, time to treatment efficiency, and LVO patient EVT eligibility. The combination of scenarios created using these three key input variables creates sixteen experiments. The definition of these input variables and the scenarios created for each are defined in the subsequent sections of this chapter.

5.1 Driving Time Between the PSC and CSC Facilities

The first varied input in the experiments is the time between the PSC and CSC. Four scenarios were defined for experiments on this model. These scenarios were defined assuming ground transportation and are converted to air transportation times when necessary. The first scenario models one hour of driving time between the facilities and subsequent scenarios represent an additional hour of driving time, up to four hours. Table 7 shows the four different scenarios for time between the PSC and CSC facilities used in experiments.

Table 7: Driving Time Between the PSC and CSC Scenarios

Time (min)	Scenario 1	Scenario 2	Scenario 3	Scenario 4
$t_{PSC-CSC\|G}$	60	120	180	240

The scenarios defined in Table 7 differ from the five defined in the previous publication[28] but it was decided that the representation of longer distances between facilities was important for modelling the use of air transportation. Another contributing factor in the decision to use longer times between facilities was the reality of long ground transfer times in the maritime provinces.

Air ambulance systems typically centralize resources in a location nearest the CSC. For this reason, it was assumed that the time between the airbase and PSC were equal to the distance between the PSC and CSC.

The probability of an inter-facility transfer occurring via air depends on the time between the PSC and CSC, the probability of airworthy weather and the probability of resource availability as shown above in Eq. 8. Therefore, Table 8 shows the probability of the inter-facility transfer occurring via air or ground for a patient transferred according to the Drip and Ship method given each Hospital Location Scenario.

Table 8: Probability of Air Transfer for each Hospital Location Scenario

$t_{PSC-CSC\|G}$	60 min	120 min	180 min	240 min
$\Pr\{Air\ Trasnfer\}$	0 %	0%	62.79 %	87.15 %
$\Pr\{Ground\ Trasnfer\}$	100 %	100%	37.21 %	12.85 %

5.2 Time to Treatment Efficiency Scenarios

The second varied input is the times to treatment efficiency. Two efficiency scenarios were defined for experiments on this model. These definitions are consistent with those used in the previous publication[28] in order to produce comparable results.

Two efficiency scenarios were defined by varying these times. The first hospital scenario models a system where an inefficiency in time to treatment at the PSC facility exists but the CSC performing optimally, this is referred to as the inefficient scenario. The second efficiency scenario models a system where both the PSC and CSC perform optimally, this is referred to as the efficient scenario. Table 9 shows the time values associated with each efficiency scenario. The bolded values in this table indicate the differences between the two scenarios.

Table 9: Time to Treatment Efficiency Scenario Definitions

Time	Inefficient Scenario	Efficient Scenario
$t_{DTN\ @\ PSC}$	**60 min**	**30 min**
t_{DIDO}	Door to Needle + **60 min**	Door to Needle + **20 min**
$t_{DTN\ @\ CSC}$	30 min	30 min
$t_{DTP\vert MS}$	60 min	60 min
$t_{DTP\vert DnS}$	Long Transfer: 45 min Otherwise: 30 min	Long Transfer: 45 min Otherwise: 30 min

5.3 EVT Eligibility Scenarios

The final varied input in the experiments is the proportion of LVO patients who are eligible for EVT, i.e. do not possess contraindications to the procedure, which is referred to as the EVT Eligibility Scenario. Since contraindications to EVT therapy are common, only a proportion of LVO patients are treated with EVT. This is discussed in detail in Section 3.3 where the *Y* variable was defined to represent the proportion of EVT patients treated with EVT.

A retrospective study[71] of LVO ischemic stroke patients at an academic medical center was completed between 2010 and 2014. The study aimed to arrive at a proportion of LVO patients who are eligible for EVT treatment outside of a clinical trial setting. The retrospective data was compared to the inclusion criteria of the five original EVT clinical trials[11–15] and the proportion of patients who would have been eligible for EVT according to each set of inclusion criteria was noted. This method concluded that there is a great deal of variability in the proportion of LVO patients treated with EVT is between 62% and 100% of LVO patients would have been treated with EVT according to these criteria. These results prove that the proportion of LVO patients treated with EVT is very dependent on the set of radiological inclusion criteria being used in daily practice.

Interventional neuroradiologists involved with the development of this model indicated that between 50 and 70% of LVO patients are treated with EVT according to their experience.[72] It is not likely that in a physician's everyday practice 100% of LVO patients would be treated with EVT. Taking this into consideration, two EVT eligibility proportions were chosen to use in experiments for this model. The first scenario assumes a more stringent set of EVT inclusion criteria. The second scenario assumes a less stringent set of EVT inclusion criteria. Table 10 shows the proportions associated with each EVT Eligibility Scenario.

Table 10: EVT Eligibility Scenario Definitions

Proportion of LVO patients eligible for EVT	EVT Scenario 1	EVT Scenario 2
Y	50%	70%

Chapter 6: Results

Transport method decisions between Mothership and Drip and Ship for a suspected LVO patient with consideration of patient outcome and transportation costs are presented in this chapter. The Drip and Ship method accounts for the probability of the inter-facility transfer to occur via ground or air transportation modes. Scenarios are presented to illustrate the impact of hospital treatment time efficiencies, distances between PSC and CSC facilities, and the proportion of LVO patients treated with EVT. In each experiment the maximum distance from the PSC was assumed equal to the distance between the PSC and CSC which explains the increasing radius from left to right in the results presented in the following subsections.

The LAMS pre-hospital screening tool is assumed for all the results shown unless otherwise stated. Similar tables for the RACE and C-STAT pre-hospital screening tools can be found in Appendix B and Appendix C, respectively.

The thick yellow line shown in some of the figures indicates the 4.5-hour tPA threshold for transporting a patient via the Mothership method. A patient whose stroke onset occurs above this yellow line is ineligible for tPA if transported according to a Mothership method because their travel time from the scene of their stroke to the CSC causes their onset to needle time to exceed the 4.5-hour threshold for tPA. This threshold is further explained above in Section 3.4, Eq. 5.

Similarly, a thick white line shown in some of the figures below indicates the 4.5-hour tPA threshold for transporting a patient according to the Drip and Ship method. A patient whose stroke onset occurs outside of this white line is ineligible for tPA if transported according to a Drip and Ship method because their travel time from the scene of their stroke to the PSC causes their onset to needle time to exceed the 4.5-hour threshold for tPA. This threshold is further explained above in Section 3.4, Eq. 6. If a suspected LVO patient's scene of stroke onset is outside of the 4.5-hour threshold for tPA at both facilities, they can only be treated with EVT.

The maps illustrating the experiment results are coded using four colours to indicate which method achieves the best clinical outcome, which method is least expensive and if they coincide.

- The red colour illustrates areas on the maps where the Drip and Ship method results in a higher probability of an excellent patient outcome and is least expensive.
- The purple colour illustrates where the Drip and Ship method results in a higher probability of an excellent patient outcome, but the Mothership method is least expensive
- The blue colour illustrates where Mothership method results in a higher probability of an excellent patient outcome, but the Drip and Ship method is least expensive.
- Areas coded with purple and blue are referred to as divergent results as the two functions produce contradicting results for which method is better.
- Finally, the green colour illustrates where the Mothership results in a higher probability of an excellent patient outcome and is least expensive.

Table 11 summarizes the meaning of the colour coding. Colour blind accessible results and a corresponding legend can be found in Appendix D – Appendix G.

Table 11: Colour Code Legend

Colour	Highest Probability of an Excellent Outcome	Least Expensive Transport Cost
	Drip and Ship	Drip and Ship
	Drip and Ship	Mothership
	Mothership	Drip and Ship
	Mothership	Mothership

6.1 Baseline Results

Sixteen baseline experiments were run on the model to model several real-world scenarios. The results of these experiments are shown below. PSC efficiency scenarios, two EVT eligibility scenarios, and four driving time between the PSC and CSC scenarios were combined to create these experiments.

Figure 8 and Figure 9 illustrates the results for experiments run with inefficient and efficient treatment times at the PSC, respectively. The base case results are shown in the first row of Figure 8. The base case was run with inefficient treatment times at the PSC and 50% EVT eligibility for LVO patients. Each of the four scenarios for driving time between the PSC and CSC are shown under the base case conditions.

Figure 8: Results for LAMS Experiments Run with **Inefficient Hospital Scenario**

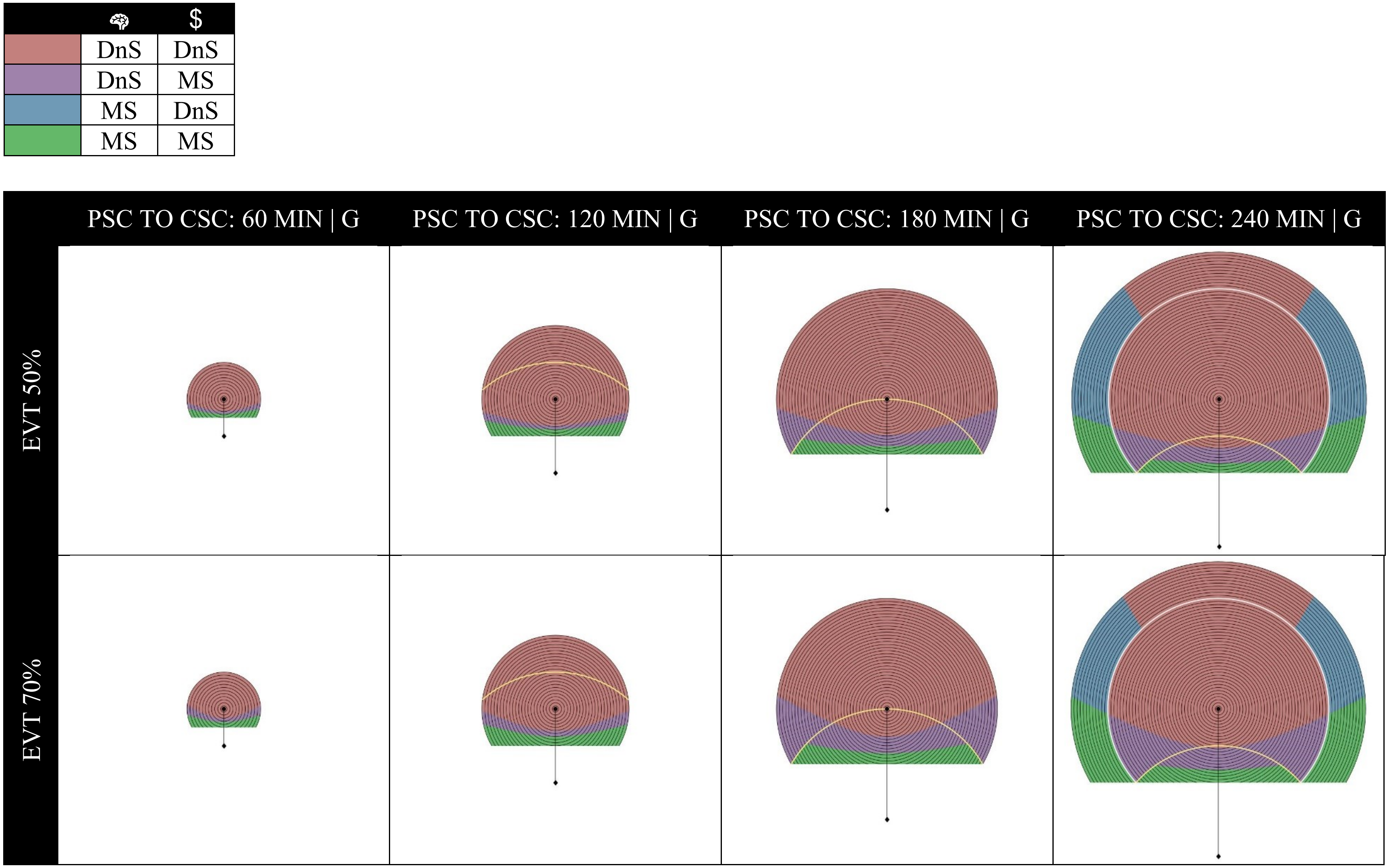

Figure 9: Results for LAMS Experiments Run with **Efficient Hospital Scenario**

6.1.1 Base Case: Inefficient PSC and 50% EVT Eligibility

The experiments run which assume an inefficient PSC and 50% EVT eligibility for LVO patients are considered the base case of these results. Four driving times between the PSC and CSC were run under the base case criteria and are shown in the first row of Figure 8.

Early access to tPA offered by the Drip and Ship method is beneficial if the time lost during a stopover at the PSC does not result in significant delays to accessing EVT. Inefficiencies at the PSC result in large regions where the Drip and Ship stopover is more detrimental than beneficial to a patient's outcome. The results of experiments run with reduced efficiency at the PSC are shown in Figure 8.

The experiment run with base case criteria and 60 minutes between the PSC and CSC illustrates three coloured regions. The bottom of the temporospatial diagram is coloured green which illustrates that both the patient outcome and transportation cost functions indicate Mothership as the optimal method of transportation for patients whose stroke onsets occur in this region. Just above this green region the colour code shifts from green to blue which indicates a shift in which transport method is expected to be least expensive. In this blue region, Mothership is still associated with the highest probability of an excellent outcome, but Drip and Ship is now expected to be the least expensive method of transport. This blue region of divergence appears between the PSC and CSC markers, which requires the ambulance to transport the patient further away from the CSC when transporting the patient according to the Drip and Ship method from the scene. This means patients who require transfer for EVT ultimately end up travelling further when transported according to the Drip and Ship method, which explains why Mothership is expected to be least expensive. The top of the temporospatial diagram is coloured red which indicates that both the patient outcome and transportation cost functions indicate Drip and Ship as the optimal method of transportation in this region.

As the distance between the PSC and CSC facilities increases a stopover for tPA at the PSC becomes a more appealing option regardless of inefficient PSC treatment times. This is the case for two reasons, the first being the travel time between the PSC and CSC is now longer than the delay caused by inefficient treatment times at the PSC. The second reason for this is an increased probability that an inter-facility transfer will take place via air, which allows time lost to inefficiencies at the PSC to be made up in the air. This is evident in the results shown as Drip and ship becomes more prevalent and only a slight region of blue divergence is shown.

The results are similar in the base case when the distance between the PSC and CSC is increased to 180 and 240 minutes. In these experiments the divergence shown between the PSC and CSC is coded purple to indicate that Drip and Ship produces the highest probability of an excellent outcome, but Mothership is expected to be least expensive. This is due to an increase in the probability of an inter-facility transfer occurring via air as the distance between the two facilities has increased. The second region of divergence shown in these results of this experiment are coded blue to indicate that Mothership produces the highest probability of an excellent outcome, but Drip and Ship is expected to be least expensive. This region appears outside of the 4.5-hour threshold for receiving tPA at the PSC and CSC. This means the PSC cannot offer the patient any form of treatment for their stroke which therefore means EVT is the only form of treatment for a patient whose stroke onset occurs in this region. The PSC can offer access to air transportation between facilities but in this scenario the PSC is assumed to be running inefficiently which hinders the time savings offered by air transportation in most cases

6.1.2 Inefficient PSC and 70% EVT Eligibility

In general, increasing the percentage of LVO patients treated with EVT affects both patient outcomes and expected transportation cost. In most cases receiving EVT increases an LVO patient's probability of an excellent outcome. This causes the model to favour Mothership in more regions as the onset to puncture time becomes relevant for a larger proportion of patients. From a transport cost perspective increasing the proportion of LVO patients who receive EVT increases the proportion of patients who require an inter-facility transfer as part of the Drip and Ship method. This increases the expected cost of the Drip and Ship method in all experiments but especially in those with a high probability of inter-facility via air, which results in more areas that show the Mothership option as being cheaper.

In experiments run with inefficient PSC treatment times the increase to 70% EVT eligibility presents itself in different ways amongst the four scenarios for time between the PSC and CSC. In the 60-minute scenario, the red region notably shrinks and shifts to blue. This is indicative of the inverse affect that an increase in EVT eligibility has on patient outcome and transportation cost. The red region shrinks and shifts to blue which indicates that the method associated with the highest probability of an excellent outcome has changed from Drip and Ship to Mothership. The green region in this experiment grows slightly with a shift from blue to green indicating that the Mothership is now expected to be least expensive.

An increase in the proportion of LVO patients treated with EVT causes a shift in region of divergence shown in the experiment run with 120 minutes between the PSC and CSC. The region of divergence shifts from blue to purple relative to the base case. This means an increase in the size of the region where Mothership produces the highest probability of an excellent outcome.

The impact on the experiments run with 180 and 240 minutes between the PSC and CSC facilities is again similar. In these experiments the purple region of divergence shown between the PSC and CSC grows as a result of the increase in the expected cost associated with Drip and Ship, and a larger region where mothership will result in better patient outcomes.

6.1.3 Efficient PSC and 50% EVT Eligibility

The results for experiments run with improved efficiency at the PSC are shown in Figure 9.

Relative to the base case a more efficient PSC means more patients should stopover for tPA at the PSC as time added to a patient's onset to puncture time are worth the benefits of receiving tPA early. This is reflected in the results of experiments run for the Efficient Hospital Scenario as large regions where the Drip and Ship method produces better results. In general, this presents itself in the results as significantly less blue coded divergent regions where Mothership is associated with the highest probability of an excellent outcome, but Drip and Ship is expected to be least expensive. Since PSC efficiency has no impact on expected transport cost, the differences noted between the base case and this scenario are exclusively a product of a change in the patient outcome function.

Better efficiency at the PSC increases the region inside the 4.5-hour threshold for tPA at the PSC. Which makes a stopover at the PSC for tPA more beneficial to patients whose stroke occurs near the outer bounds of the modelled region. This causes the blue divergence to completely disappear in the experiment run with 180 minutes between the PSC and CSC, and significantly shrinks the blue region in the 240-minute experiment.

6.1.4 Efficient PSC and 70% EVT Eligibility

The results for experiments run with an efficient PSC and 70% EVT eligibility differ only slightly from the results of experiments run with experiments run with an efficient PSC and 50% EVT eligibility. However, relative to the base case the results differ significantly. Improved efficiency at the PSC leads to more regions where Drip and Ship produces the highest probability of an excellent outcome. However, an increased proportion of LVO patients receiving EVT leads to an increase in the expected cost of transportation for the Drip and Ship method especially in experiments where the probability of an inter-facility transfer occurring via air is high. The combination of these two things causes more regions of purple coded divergence which is evident in the results from these experiments shown in thew second row of Figure 9.

6.2 Advanced Results

The results presented previously indicate which method of transport is more likely to produce an excellent patient outcome and which method of transport is expected to be least expensive. However, these results are missing a way to quantify the magnitude of difference between Mothership and Drip and Ship for both outcome and transport cost. Since the results of the model vary so much based on the location of the potential scene of the stroke, an average difference would not be an effective measure to quantify the difference between Mothership and Drip and Ship. Instead, six points have been selected on four experiments to provide insight into the magnitude of difference between the Mothership and Drip and Ship methods. The experiments run with 240 minutes of ground driving time between the PSC and CSC were chosen to display advanced results because all four colours are illustrated. The location of the points is the same across all four experiments shown and their placement is shown below in Figure 10. The six calculated probabilities of an excellent outcome and expected transport costs associated with the Mothership and Drip and Ship methods are shown below for the four experiments in Table 12, Table 13, Table 14, and Table 15.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

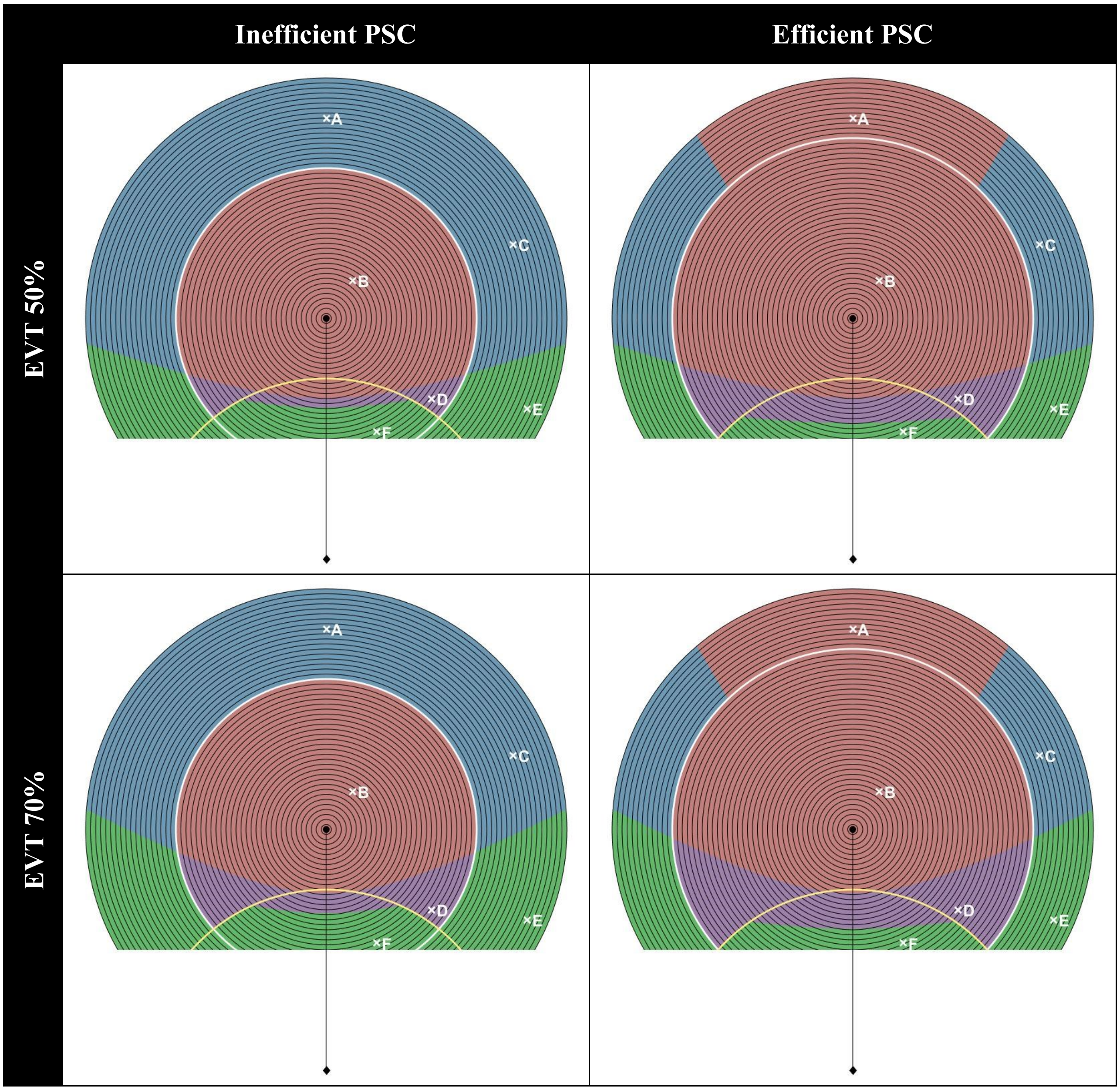

Figure 10: Point Locations for Advanced Results of Experiments Run with 240 minutes Ground Driving Time between the PSC and CSC

Table 12: Base Case: Point Values for Advanced Results for **Inefficient PSC and 50% EVT Eligibility**

		A	B	C	D	E	F
Colour		**Blue**	**Red**	**Blue**	**Purple**	**Green**	**Green**
Pr{mRS 0-1	"+" LVO screen}$_{DnS}$	28.65%	**36.83%**	28.65%	**35.04%**	28.58%	35.21%
Pr{mRS 0-1	"+" LVO screen}$_{MS}$	**28.67%**	29.26%	**28.94%**	29.60%	**29.37%**	**36.22%**
TC_{DnS}		**$4,444.30**	**$2,391.50**	**$4,446.70**	$3,537.70	$4,701.80	$3,425.20
TC_{MS}		$6,566.70	$4,422.80	$5,566.10	**$3,251.70**	**$4,033.30**	**$2,519.80**

Table 13: Point Values for Advanced Results for **Inefficient PSC and 70% EVT Eligibility**

		A	B	C	D	E	F
Colour		Blue	Red	Blue	Purple	Green	Green
Pr{mRS 0-1	"+" LVO screen}$_{DnS}$	30.19%	**38.30%**	30.18%	**36.45%**	30.09%	36.63%
Pr{mRS 0-1	"+" LVO screen}$_{MS}$	**30.21%**	31.04%	**30.59%**	31.52%	**31.19%**	**37.91%**
TC_{DnS}		**$4,875.30**	**$2,822.60**	**$4,877.70**	$3,968.70	$5,132.90	$3,856.20
TC_{MS}		$6,566.70	$4,422.80	$5,566.10	**$3,251.70**	**$4,033.30**	**$2,519.80**

Table 14: Point Values for Advanced Results for **Efficient PSC and 50% EVT Eligibility**

		A	B	C	D	E	F
Colour		Red	Red	Blue	Purple	Green	Green
Pr{mRS 0-1	"+" LVO screen}$_{DnS}$	**28.77%**	**37.50%**	28.77%	**35.67%**	28.71%	35.85%
Pr{mRS 0-1	"+" LVO screen}$_{MS}$	28.67%	29.26%	**28.94%**	29.60%	**29.37%**	**36.22%**
TC_{DnS}		**$4,444.30**	**$2,391.50**	**$4,446.70**	$3,537.70	$4,701.80	$3,425.20
TC_{MS}		$6,566.70	$4,422.80	$5,566.10	**$3,251.70**	**$4,033.30**	**$2,519.80**

Table 15: Point Values for Advanced Results for **Efficient PSC and 70% EVT Eligibility**

		A	B	C	D	E	F
Colour		Red	Red	Blue	Purple	Green	Green
Pr{mRS 0-1	"+" LVO screen}$_{DnS}$	**30.36%**	**38.99%**	30.36%	**37.11%**	30.26%	37.29%
Pr{mRS 0-1	"+" LVO screen}$_{MS}$	30.21%	31.04%	**30.59%**	31.52%	**31.19%**	**37.91%**
TC_{DnS}		**$4,875.30**	**$2,822.60**	**$4,877.70**	$3,968.70	$5,132.90	$3,856.20
TC_{MS}		$6,566.70	$4,422.80	$5,566.10	**$3,251.70**	**$4,033.30**	**$2,519.80**

The first row of Tables 12–15 indicates the colour coding of the region where the point is located. In the second and third rows of Tables 12–15 the bolded text indicates the method which produces the highest probability of an excellent outcome and the yellow colour in some cells indicates that the difference between the probabilities is greater than 4%. In the fourth and fifth rows of Tables 12–15 the bolded text indicates the method expected to be least expensive and the yellow colour in some cells indicates a cost difference of $1000.00.

The only point selected that changes colour coding with an experiment variable is Point A. The colour coding changes from Blue to Red when the efficiency at the PSC is improved. This change indicates that the highest probability of an excellent outcome shifts from Mothership to

Drip and Ship, which is illustrated by the bolded probability in the second and third rows of Tables 12–15. The difference between the probabilities of an excellent outcome for Mothership and Drip and Ship are consistently marginal across all four experiments but the increased efficiency at the PSC is enough for Drip and Ship to overcome Mothership.

These advanced results provide more context than the baseline results and a few things become evident. Drip and Ship is expected to be least expensive at Point B and Mothership is expected to be over $1000.00 more expensive in experiments run with 50% EVT eligibility for LVO patients. However, when the EVT eligibility for LVO patients is increased to 70% the gap between the expected cost for Mothership and Drip and Ship closes and the difference shifts to becomes less than $1000.00 but Drip and Ship is still expected to be least expensive. This is due to more patients requiring an inter-facility transfer and since there are 240 minutes between the PSC and CSC the probability of the inter-facility transfer happening via air is high. Point B is also the only point with an outcome difference greater than 4% and transport cost difference greater than $1000.00, which remains consistent across all four experiments. This can be attributed to the relative location of point B to the PSC.

The increase from 50% to 70% EVT eligibility is shown to impact Points E and F in a similar manner. Mothership is expected to be least expensive at these points but in experiments run with 50% EVT eligibility the difference between Mothership and Drip and Ship is not expected to be greater than $1000.00. This changes when the EVT eligibility is increased to 70%. In this case the increase from 50% to 70% EVT eligibility widens the gap as Drip and Ship is expected to become more expensive.

Points B and D are the only two which indicate an excellent outcome probability greater than 4%. This is consistent across all four experiments and can be attributed to location of these two points. Both Point B and D are located inside the 4.5-hour threshold for tPA at the PSC, but outside the 4.5-hour threshold for tPA at the CSC. This means that transporting a patient whose stroke onset occurs at these points using the Mothership method eliminates the patient’s eligibility for tPA.

6.3 Summary of Results

The experiments presented illustrate the results of the model with three varied input parameters including treatment efficiency at the PSC, proportion of confirmed LVO patients treated with EVT and driving distance between the PSC and CSC. The resulting temporospatial diagrams show how different combinations of these input variables impact transport method decisions. In most cases, the method which produces the highest probability of an excellent outcome aligns with the least expensive transport method but when this is not the case these results provide insights into why.

The advanced results provide insights into the magnitudes of the differences between Mothership and Drip and Ship from both the patient outcome and transport cost perspectives. Point B is closest to the PSC and both functions converge to a Drip and Ship decision. This is the only point where the excellent outcome probabilities have a difference greater than 4% and the transport costs have a difference greater than $1000.00. All five other points illustrated indicate that the difference between the excellent outcome probabilities or the transport cost is marginal.

Chapter 7: Sensitivity Analysis

The model's sensitivity to a few variables is required to analyze any uncertainty in the model's input variables. The three following input variables which are held constant in model were tested as a part of this sensitivity analysis:

- Probabilities of airworthy weather and air resource availability
  - $\Pr\{Airworthy\ Weather\}$
  - $\Pr\{Air\ Resource\ Availability\}$
- Fixed and variable costs of air transportation
  - F_A
  - V_A

These variables were chosen because they have the greatest amount of uncertainty and are likely to change from region to region if this model were implemented in a real-world scenario.

7.1 Probability of Airworthy Weather and Air Resource Availability

The probabilities of airworthy weather and air resource availability appear together within the model, never independently. The product of these two probabilities is multiplied by the probability of air consideration to equal the overall probability of an inter-facility transfer via air. The probability of air consideration is varied with the distance between the PSC and CSC, but the probabilities of airworthy weather and air resource availability are constant at 90.34% and 96.47%, respectively. These values were assumed based on a publication[62] written on Nova Scotia's aborted air ambulance missions in 2005 and the air ambulance program in Nova Scotia has changed significantly since then. For this reason, these values add uncertainty to the model.

Two scenarios are presented to test the model's sensitivity to the probabilities of airworthy weather and air resource availability. The values assumed in these scenarios are shown below in Table 16 and Table 17.

Table 16: Sensitivity Analysis Air Probabilities Scenario 1

Variable	Probability
$\Pr\{Airworthy\ Weather\}$	80%
$\Pr\{Air\ Resource\ Availability\}$	90%

Table 17: Sensitivity Analysis Air Probabilities Scenario 2

Variable	Probability
$\Pr\{Airworthy\ Weather\}$	50%
$\Pr\{Air\ Resource\ Availability\}$	50%

Four experiments run were run with 240 minutes of driving time between the PSC and CSC to illustrate the model's sensitivity to the air probabilities being analyzed. The results for air probability scenarios 1 and 2 are shown below in Figure 11 and Figure 12.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

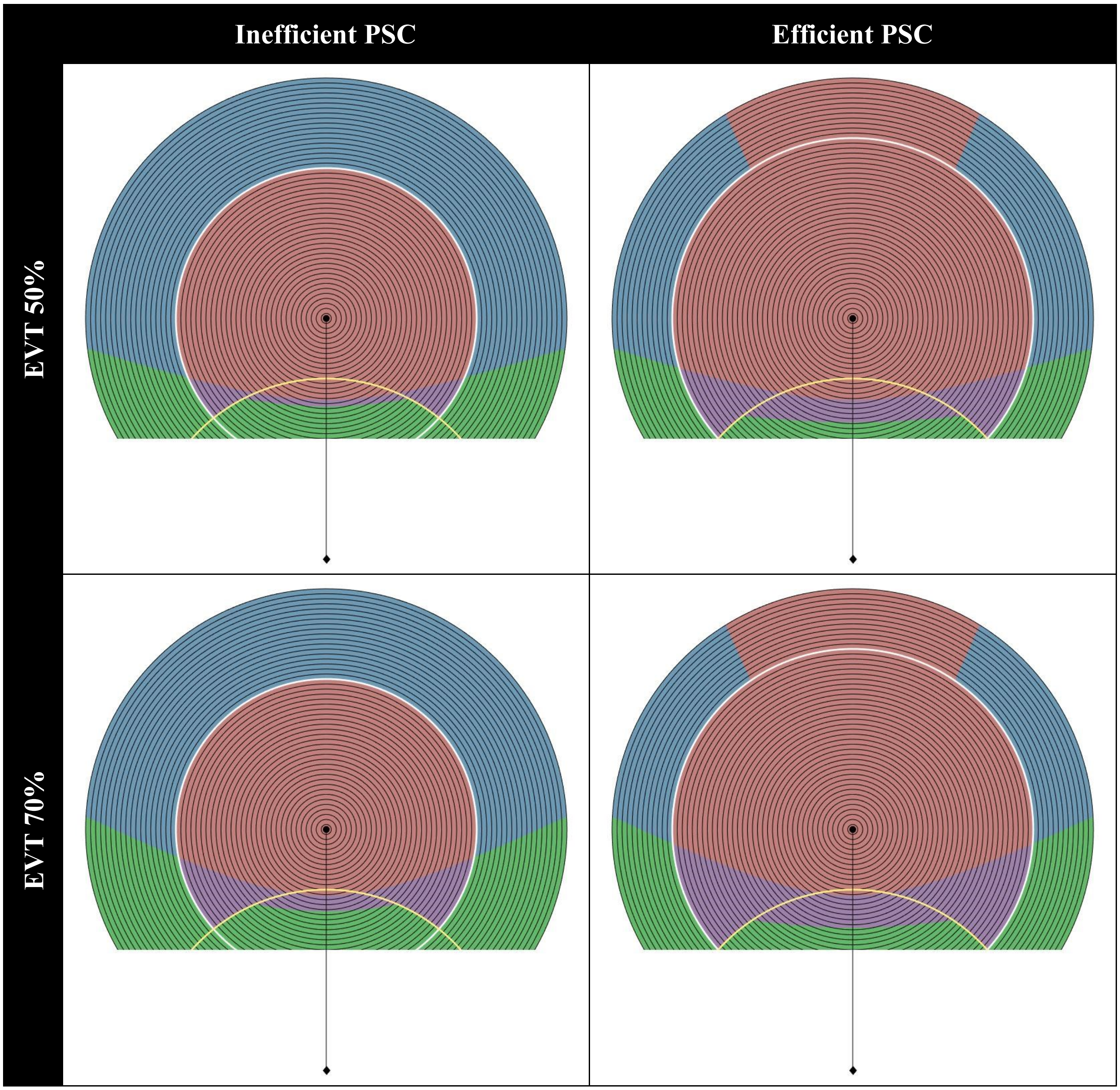

Figure 11: Sensitivity Analysis Results of Experiments Run with 240 minutes Ground Driving Time between the PSC and CSC with **Air Probability Scenario 1**

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

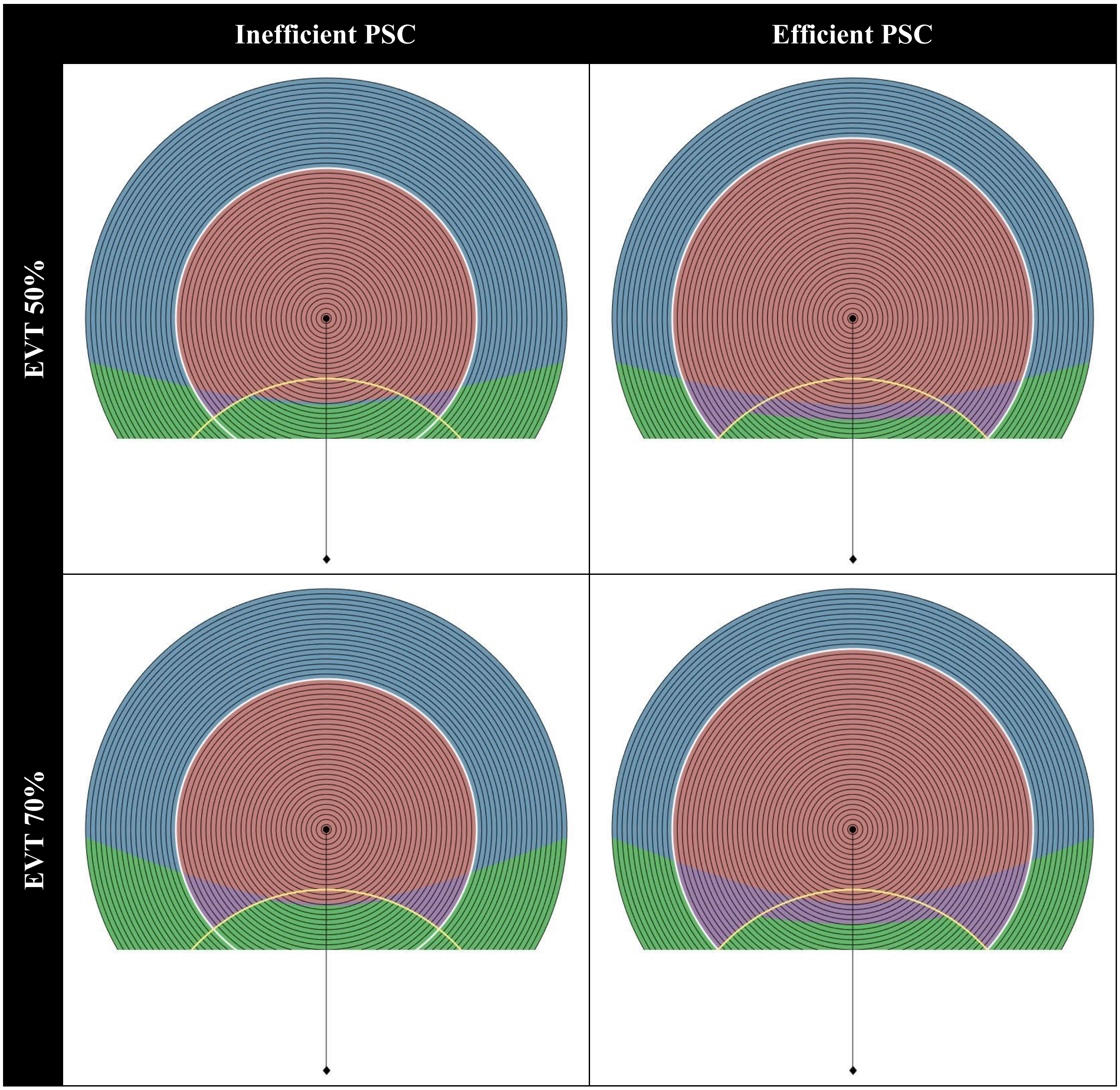

Figure 12: Sensitivity Analysis Results of Experiments Run with 240 minutes Ground Driving Time between the PSC and CSC with **Air Probability Scenario 2**

The results of this sensitivity analysis on the air probabilities indicate that the model is not very sensitive to a change in these values. The results of the experiments run with the first air probability scenario shown in Figure 11 do not indicate a significant difference from the baseline results. A slight decrease in the width of the red region in the results of experiments run for an efficient PSC appears to be the only change. The decrease in the probabilities of airworthy weather and air resource availability reduce the likelihood of an inter-facility transfer occurring via air. This has caused a shift in which method the produces a higher probability of an excellent outcome in the regions that cause the shrinkage of the red region. For patients in this region, Drip and Ship only produces a higher probability of an excellent outcome when the probability of an inter-facility transfer occurring via air is higher. When the likelihood of an inter-facility transfer via air is further decreased in the second air probability scenario the red region in experiments run for an efficient PSC completely disappears.

A reduction in the likelihood of an inter-facility transfer occurring via air results in a reduction in the expected cost of the Drip and Ship method. Another notable difference between the baseline and the results shown for the second air probability scenario is a decrease in the purple region of divergence. This occurs as a result of growth of the red region and is caused by the decrease in the expected cost of an inter-facility transfer.

7.2 Cost of Air Transport

The cost of operating an air ambulance service is commonly not information which is available to the public. This is because air ambulance services are often private organizations who hold government contracts. What is available to the public are cost estimates based on the patient's citizenship in the province the air transport began. This information was used to estimate the cost $1200.00 as the fixed cost and $12.00 per km as the cost of air ambulance services for the model. However, as with any estimation these values add uncertainty to the model.

Two scenarios are presented to test the model's sensitivity to the cost of air transport. The values assumed for these scenarios are shown below in Table 18 and Table 19.

Table 18: Sensitivity Analysis Air Transport Cost Scenario 1

Variable	Cost
F_A	$5,000.00
V_A	$15.00

Table 19: Sensitivity Analysis Air Transport Cost Scenario 2

Variable	Cost
F_A	$8,000.00
V_A	$20.00

Four experiments run were run with 240 minutes of driving time between the PSC and CSC to illustrate the model's sensitivity to the air probabilities being analyzed. The model output for these experiments run with air transport cost scenarios 1 and 2 are shown below in Figure 13 and Figure 14.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

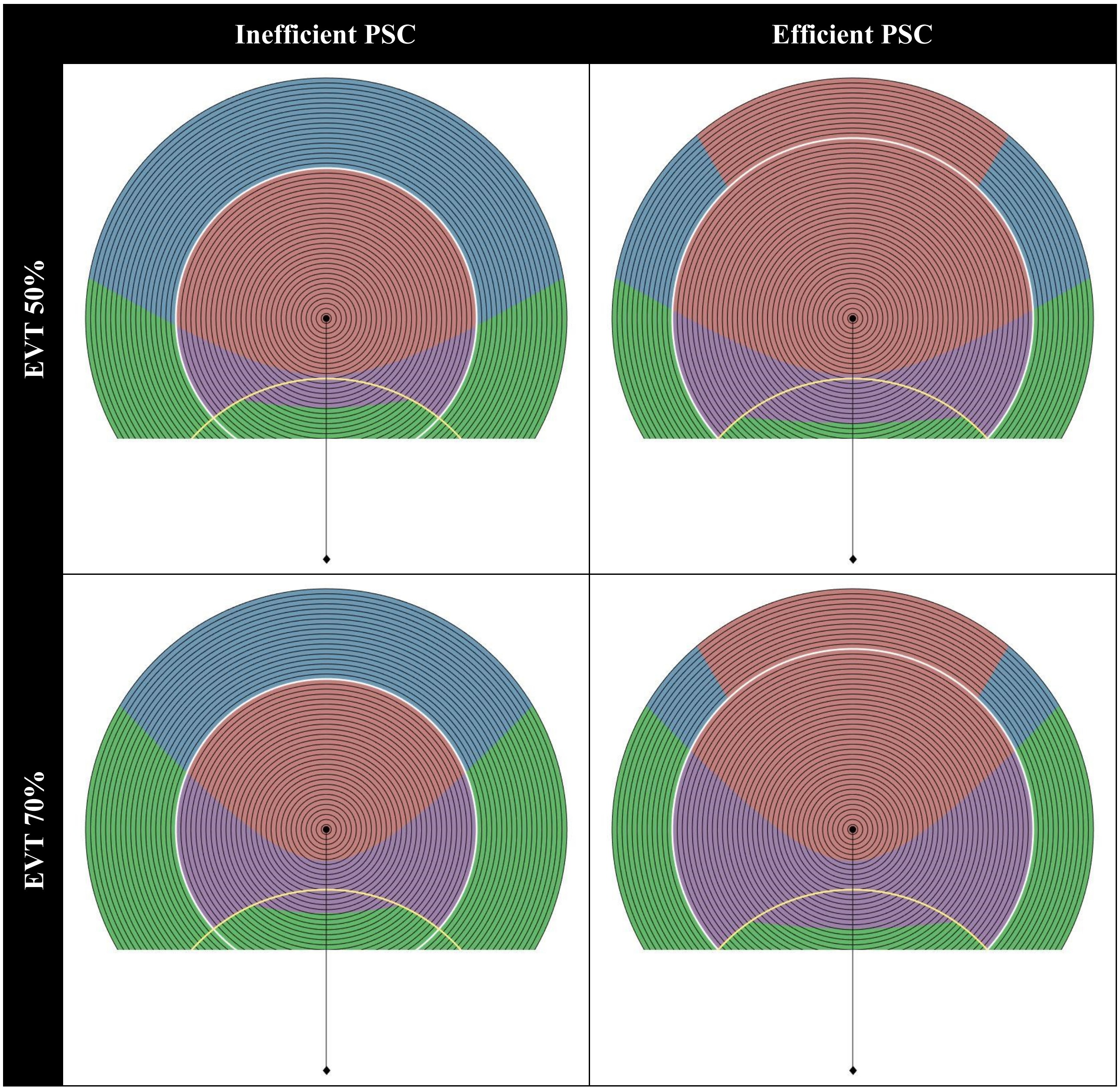

Figure 13: Sensitivity Analysis Results of Experiments Run with 240 minutes Ground Driving Time between the PSC and CSC with **Air Transport Cost Scenario 1**

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

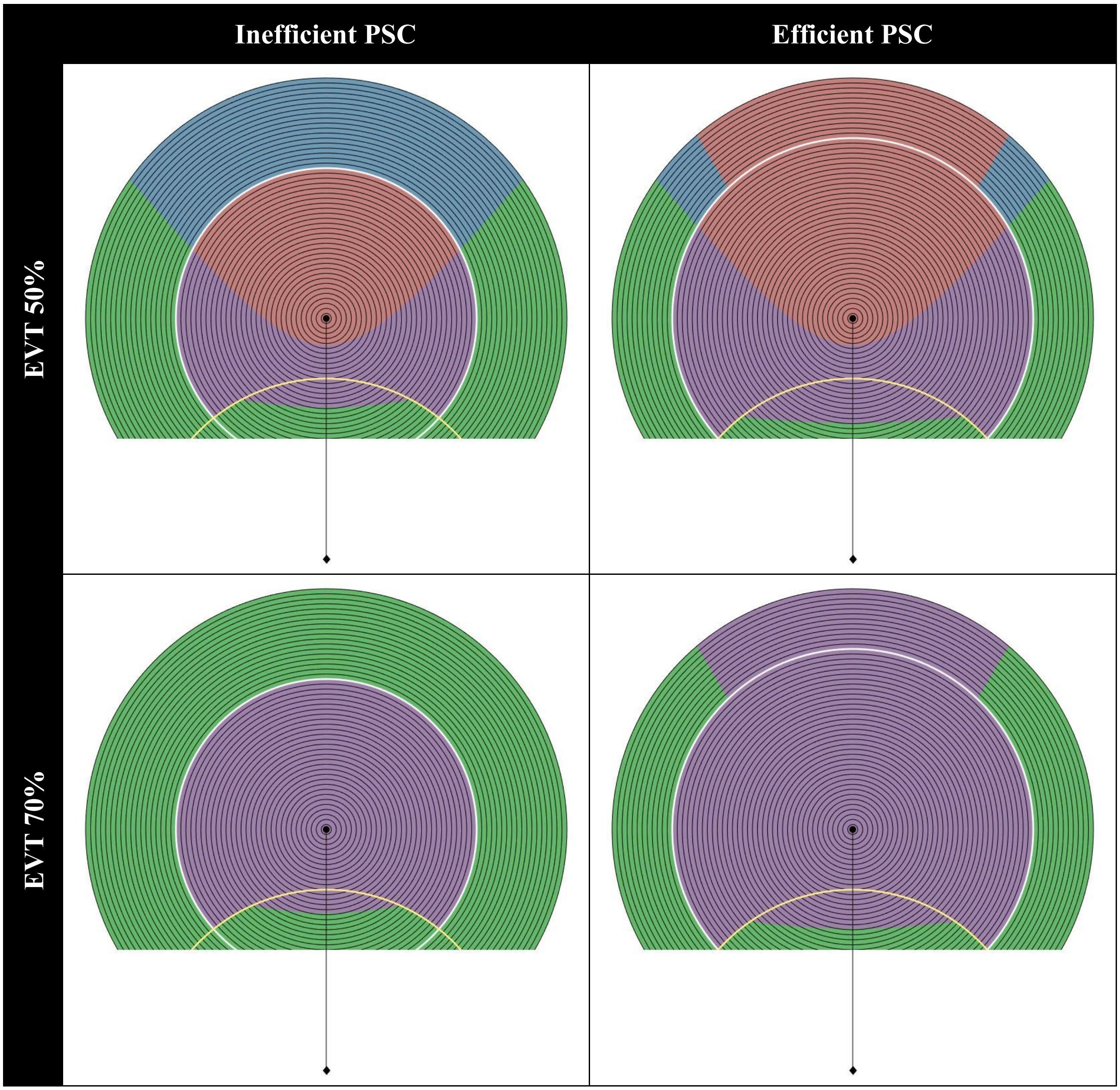

Figure 14: Sensitivity Analysis Results of Experiments Run with 240 minutes Ground Driving Time between the PSC and CSC with **Air Transport Cost Scenario 2**

The result of an increase in the cost of air transport are more drastic than that of the air probabilities. The model is moderately sensitive to the cost of air transport as can be seen from the results shown in Figure 13 and Figure 14.

The results shown in Figure 13 are similar to the baseline but there is notable change in the regions of divergence. The blue regions of divergence shrink, and the purple regions of divergence significantly grow with an increase in the cost of air transport. The disparity between the cost of air and ground transport is increased significantly with the increase in the cost of air transport which leads larger regions where Mothership is the least expensive transport method.

The results shown in the first row of Figure 14 show results with even less blue divergence and larger regions of purple divergence. The increase in the cost of air transport in this scenario results in significantly less area where Drip and Ship is cost effective. However, when the EVT eligibility is increased from 50% to 70% the results of this air transport cost scenario indicate that Drip and Ship is never cost effective.

Chapter 8: Discussion

8.1 Informing Protocol for Transporting Suspected LVO Ischemic Stroke Patients

The purpose of this research is to inform transportation protocol for LVO ischemic stroke patients. This research does so by analyzing the results of experiments designed to provide insight into when Mothership and Drip and Ship methods are better for patients whose stroke onset occurs outside the catchment area of a CSC. Insight into the costs associated with these methods is a novel contribution to the research surrounding ischemic stroke transportation decisions. Understanding the monetary impact of these decisions is important as healthcare has a finite budget and allocating it efficiently is a critical objective of an effective healthcare system.
Transportation Decisions for Regions Located Between the PSC and CSC

The temporospatial diagrams terminate at the halfway point between the PSC and CSC as Mothership is clearly the optimal decision for patients within the catchment area of a CSC facility. Despite this, the results of the presented experiments unanimously indicate a region between the PSC and CSC where Mothership is better from the perspective of both a patient outcome and transportation costs. The size and shape of this region vary with experiment inputs but never disappear completely meaning the threshold for where Mothership should be considered optimal is always beyond the halfway point between the PSC and CSC facilities. This should be reflected in the transportation protocol for patients with a suspected LVO and whose stoke onset occurs in between the PSC and CSC. The input which affects the size and shape of the green unanimous Mothership region appears to be the efficiency of the PSC facility. This should be taken into consideration when implementing transportation protocol for a suspected LVO ischemic stroke patient.

Areas between the PSC and CSC consistently indicate regions of divergence. This is primarily due to the need to backtrack when the Drip and Ship method is indicated for a higher probability of an excellent outcome for the patient. When developing protocol for slightly more complex cases such as a patient whose contraindications to tPA can be identified at the scene of the stroke this divergence may indicate regions where choosing Mothership would generate transportation cost savings. However, the research surrounding assuming the Mothership method for patient's with known contraindications to tPA is limited and seems to provide and somewhat inconsistent.[76,77] One study[76] suggests that Mothership transportation for patients with known contraindications to tPA does result in shorter onset to puncture times. However, this study[76] found no significant improvement in the 90-mRS score for patients with contraindications to tPA who were transported according to the Mothership method.

8.1.1 Transport Decisions for Patients Outside the 4.5 Hour Window for tPA at the PSC

Patients who are outside the 4.5-hour time window for tPA at the PSC still stand to benefit from the Drip and Ship protocol in certain instances. The prevalence of these instances is highly dependent upon the time to treatment efficiencies at the PSC. Poor efficiency at the PSC also impedes air transportation ability to reduce an LVO patients time spent in-transit to EVT. For this reason, time to treatment efficiencies should be considered when developing protocol for patients outside the 4.5-hour time window for tPA at the PSC.

This conclusion could also be extrapolated slightly to inform protocol for patients with lengthy onset to FMC times, such as patients who wake up with stroke symptoms. In these cases, efficiency at the PSC may put the patient outside the 4.5 hour time window and the time savings air transportation offers in this instance should be assessed when developing transport protocol for these patients. EVT has been proven effective for these patients[78] but there is limited research surrounding transport protocol for patients with contraindications to tPA does suggest that Mothership reduces onset to puncture time.[76] However, this research does not investigate the time savings associated with air transportation when analyzing patients who were transported according to the Drip and Ship method.

8.1.2 Extrapolating the Results for Patients with a Prolonged Onset to FMC time

The model assumes 20 minutes between stroke onset and FMC. This time varies significantly from patient to patient and is difficult to model accurately for all stroke patients. However, due to the generalized nature of the temporospatial diagrams the probability of an excellent outcome can be extrapolated for a patient whose onset to FMC time differs from the 20 minutes assumed within the model. This can be done using the concentric circles as a guide as increasing the time between the scene and facility would result in the same change in outcome as a prolonged onset to FMC time.

8.1.3 The Consequence of Making Cost-Ineffective Transport Decisions

Ultimately, the transportation method decision should be made according to what is best for the patient. The results of this model indicate that in most regions making a patient outcome oriented decision coincides with making a transportation cost effective decision. However, the results do indicate regions where transportation cost and patient outcome functions diverge. In these regions additional analysis is needed. For example, better patient outcomes result in less need for stroke rehabilitation and/or less dependence long term care facilities. This lesser expense in post stroke care likely offsets the added cost being incurred to transport a patient to treatment.

8.2 Benefits of Inter-facility Transfer via Air

Air transportation is a costly resource but is worthwhile if it can positively impact a patient's probability of an excellent outcome. In inclusion of inter-facility transfers via air is novel in this field of research and is shown to increase the area where Drip and Ship produces the highest probability of an excellent outcome relative to the results produced by Holodinsky et al.[28] This is due to the time savings realized in the Drip and Ship method when an inter-facility transfer takes place via air.

The results of these experiments show that in most cases the transportation method associated with the highest probability of an excellent outcome for the patient is also the method associated with the least transportation expense. Most of the results shown do not indicate divergent conclusions from the outcome and transportation cost functions. This is the case even when the inter-facility transfer associated with the Drip and Ship method has a high probability of occurring via air transportation. This indicates that the opportunity to confirm a patients EVT eligibility provides cost savings of a large enough magnitude to make Drip and Ship with inter-facility transfer via air a more cost effective method of transportation relative to Mothership via ground in many regions.

8.3 Limitations and Future Studies

A few limitations exist within this model. The first being the exclusion of fixed wing air transportation. It is understood that rotary wing transportation is more commonly used for inter-facility transfers via air but is not the exclusive choice. Fixed wing transportation comes with different logistic challenges than rotary wing but can also offer air transportation in different circumstances than rotary wing.

The inclusion of fixed wing transportation for inter-facility transfers would add value to this model. Fixed wing transportation involves a faster speed when in the air but also is less flexible than rotary wing transportation in where it can take off and land. Unlike a rotary wing aircraft, a fixed wing aircraft requires a runway for take-off and landing. This means that the aircraft cannot land at a hospital facility and instead lands at the closest runway where the patient is then picked up and transported to the hospital facility via ground ambulance. These logistical complexities must be considered to properly model fixed wing as an option for inter-facility.

The second limitation of this model is an underlying assumption made for patients who are outside the 4.5-hour time window for tPA at the PSC. It was assumed that if these patients are transported according to the Drip and Ship method that they are subject to the same timeline as a patient who is receiving tPA. This is likely not the case, a patient who is known to be ineligible for tPA upon arrival at the PSC can be transferred for EVT immediately after their LVO diagnosis and EVT eligibility is confirmed. In reality this is probably a shortened timeline relative to a patient who arrives at the PSC for tPA and is subsequently transferred for EVT.

Rotary wing air transfers provide quicker access to EVT when patients are first transported to a PSC facility following the Drip and Ship protocol. These time savings can be an asset to all patients, even those who are unable to receive tPA as treatment for their ischemic stroke. Future studies should consider the logistical differences between a patient who receives tPA and is subsequently transferred to the CSC via air for EVT versus a patient who bypasses tPA treatment but is still transferred to the CSC via air for EVT. It is possible that the logistical differences in these scenarios amount to a significant difference in time spent at the PSC, which should be considered in future iterations of the model.

Currently the model assumes the initiation of air transportation takes place around the time tPA is administered. However, if air transportation is initiated sooner the time savings air transportation can offer to a scenario may significantly increase. If air transportation were to be initiated before the LVO ischemic stroke diagnosis is confirmed the time advantage for a patient requires an inter-facility transfer is almost guaranteed to be significant. This would likely provide better outcomes for LVO patients transported according to the Drip and Ship method. Future iterations of the model should include this analysis. In order to properly make this addition to the model a cost must be assumed for instances when air transportation is initiated and but later rescinded when the patients diagnosis is confirmed. Testing this within the current model would take a few minor revisions to the time advantage and transport costs associated with air transportation.

A variation of this model could help inform protocol for patients with known contraindications to tPA. When the paramedic team has identified that a patient has known contraindications to tPA at the scene of the stroke the transportation protocol should reflect this. This model could be modified and run on experiments the reflect scenarios where patients have known contraindications to tPA. This would yield results indicating where the inter-facility transfer via air is beneficial for these patients and when it is not.

This research establishes that choosing a transport method to maximize a suspected LVO patient's probability of an excellent outcome usually also minimizes the transport cost. However, patient outcomes also have a cost benefit to the healthcare system, as improved outcomes in stroke have been associated with shorter length of stay in both acute and rehabilitation and have also resulted in fewer patients requiring long-term care.[73–75] These cost savings may be greater than the increased cost of transport. However, the potential balance in transportation cost to downstream hospital costs was not evaluated in this study.

One previous study sought to investigate which transport method yielded the best outcome for LVO ischemic stroke patients and how this compared to the most cost-effective method. This study included downstream hospital costs along with the cost of transport. This study applied an algorithm to a specific real-world scenario and uses QALYs and a Markov analytic model to assess transport decisions. No trade-offs between patient outcome and cost effectiveness were found, meaning the transport method which yielded the best patient outcome was also found to be least expensive.[37] The results of this thesis only compare patient outcomes to transport costs but still yield similar results. This model identified small regions where a trade-off between patient outcome and transport cost exists but also found that when a trade-off exists the difference between a Mothership and Drip and Ship decision is marginal.

Future studies should include downstream hospital costs and the cost benefit of improved patient outcomes. The cost savings associated with downstream hospital costs and improved patient outcomes may compensate for a more expensive transport method in regions where a trade-off has been identified.

Chapter 9: Conclusion

The addition of inter-facility transfers via rotary wing transportation is a novel contribution to the field of transport decisions for suspected ischemic stroke patients. Without air transportation Drip and Ship means a shorter onset to needle time but an extended onset to puncture time relative to the Mothership method. The addition of air transportation provides a time advantage which reduces the difference in onset to puncture time between Mothership and Drip and Ship. This results in higher probabilities of an excellent outcome for the Drip and Ship method and therefore more regions optimized with the Drip and Ship method. In particular, more regions between the PSC and CSC are optimized with Drip and Ship when inter-facility transfer via air is considered.

The analysis of transport cost is also a novel contribution to this field of work. The inclusion of air transport is costly, and insight into the relationship between transport cost and patient outcomes is valuable when designing strategies to transport suspected ischemic stroke patients to treatment. The Drip and Ship method includes inter-facility transport via air, which is more costly than inter-facility transfer via ground. However, Drip and Ship also offers the opportunity to confirm the patient's EVT eligibility before the transfer takes place. Prior to this work, it was not understood if the ability to confirm EVT eligibility was enough to offset to the cost of transporting a patient via air. This work has confirmed that in most cases the patient's probability of an excellent outcome can be maximized with the same transport decision which minimizes the expected transport cost. This indicates that the ability to confirm a patient's EVT eligibility does indeed offset the cost of an inter-facility transfer via air in most regions.

It was known that increasing the efficiency at the PSC results in more regions being optimized with the Drip and Ship method. This model included EVT eligibility to analyze the impact this has on transport decisions. An increase in the proportion of LVO patients eligible for EVT results in more regions where Mothership optimizes a patient's probability of an excellent outcome but increases the expected transport cost of the Drip and Ship method. This means that an increase in the proportion of LVO patients eligible for EVT results in an increase in the size of divergent regions.

In conclusion, in most cases a decision to maximize the patient's probability of an excellent outcome also minimizes the expected transport cost. Several variables impact the transport decision, and the size of regions where divergent results are observed. However, divergent regions only illustrate a significant difference between Mothership and Drip and Ship in one objective. This means transport decisions can be made to maximize the patient's probability of an excellent outcome as the marginal cost difference in divergent regions is likely to be recovered as there are downstream hospital cost savings associated with better patient outcomes.

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Appendix A – Relevant MATLAB Code

```
function [ pixel, pixel_overlay, alpha, TimeConstant, parameters, t_270, a, ScreeningTool, PA, Plot_Title,
Stockholm, PGround, ...
    PAir,AirGrndProbability,HospDistDef_L,HS] = ...
    Two_PixelColorGeneration( Res, pixel_row, pixel_column, io, jo, P_min, P_max, MultiRun,RunNum,PicSave,
MultiRunNumEnd,GradientRun)

%This function fills in the RGB triplets into each pixel based on the
%probability of the best transportation model and its relationship to the
%probability scale (P_min -- P_max)

[parameters, TimeConstant, t_270, ScreeningTool,SpeedConversion, DtoE, AirGrndProbability, TransportationCost,
PA, Plot_Title, Stockholm ,...
    PGround, PAir, XL_Output,TagOn,HospDistDef_L,HS]=Three_Pacman_Prompt(MultiRun, RunNum, MultiRunNumEnd);

t_PSC_CSC_MS=TimeConstant.Ground_PSC_CSC;

a=TimeConstant.PSC_Max*Res;

pixel = ones(pixel_row, pixel_column, 3);
pixel_overlay = ones(pixel_row, pixel_column, 3);
alpha = zeros(pixel_row, pixel_column);

CircRad=TimeConstant.PSC_Max*Res;
CircleRatio=(pi*CircRad^2)/pixel_row^2;

for i=1:pixel_row
    for j=1:pixel_column

        %Locate all the pixels that are within the circle of interest and
        %above the halfway point between PSC and CSC
        %(i-io)^2+(j-jo)^2=(TimeConstant.PSC_Max)^2
        %i=1/2*(512*factor+a) is the horizontal coordinate of the halfway
        %point between PSC and CSC
        RndNum=rand();
        if ((i-io)^2+(j-jo)^2)<=(TimeConstant.PSC_Max*Res)^2 && i<=1/2*(pixel_row + t_PSC_CSC_MS * Res)
            if PicSave==1 || RndNum<=OutputPercent
                %Calculate the distance from pixel position(i,j) to the location
                %of PSC (io,jo) and CSC (io+a,jo)

                %Equation of a circle below
                %r1=time to PSC, r2= time to CSC
                r1=sqrt((j-jo)^2+(i-io)^2)/Res;
                r2=sqrt((j-jo)^2+(i-(io+t_PSC_CSC_MS * Res))^2)/Res;

                %Call for the probability function, input the distance calculated
                %above and compare the probability of good outcome for
                %the MS approach and the DnS approach
                [C_DnS, C_MS, C_DnS_G, C_DnS_A, C_DnS_1] = Four_Cost_Functions(r1,r2,TimeConstant,
TransportationCost, AirGrndProbability, SpeedConversion, DtoE, parameters, PA, Stockholm);

                [P_DnS, P_MS, OTN_DnS, OTP_G, OTP_A, OTN_MS, OTP_MS] =
Five_Probability_Functions(r1,r2,TimeConstant,parameters, PA, Stockholm, AirGrndProbability);
                %P_DnS_G, P_DnS_A]


                if P_MS>P_DnS && C_MS<C_DnS
                    colour='Green';
                    pixel(i,j,:) = 1/255 * [100 184 105];

                    % Colour blind friendly (comment above and uncomment below to use) --- Dark Blue
                    % pixel(i,j,:) = 1/255 * [15 32 128];


                elseif P_MS>P_DnS && C_MS>C_DnS
                    colour='Blue';
                    pixel(i,j,:) = 1/255 * [111 154 182];

                    % Colour blind friendly (comment above and uncomment below to use) --- Orange
                    % pixel(i,j,:) = 1/255 * [245 121 58];

                elseif P_MS<P_DnS && C_MS<C_DnS
                    colour='Purple';

                    pixel(i,j,:) = 1/255 * [159 130 171];

                    % Colour blind friendly (comment above and uncomment below to use) --- Light Blue
                    % pixel(i,j,:) = 1/255 * [133 192 249];
```

```
                elseif P_MS<P_DnS  && C_MS>C_DnS
                    colour='Red';
                    pixel(i,j,:) = 1/255 * [195 128 125];

                    % Colour blind friendly (comment above and uncomment below to use) --- Magenta/Purple
                    % pixel(i,j,:) = 1/255 * [169 90 161];
                end
            end
        end
    end
end
```

TRANSPORT COST FUNCTION

```
function [C_DnS, C_MS, C_DnS_G, C_DnS_A, C_DnS_1] = Four_Cost_Functions(A,B,TimeConstant, TransportationCost,
AirGrndProbability, SpeedConversion, DdToEuc, parameters,PA,Stockholm)
    Alpha = parameters(1);

    GroundReturnFactor_DnS1=2;  %This is to account for the ground ambulance having to come back to its base
    GroundReturnFactor_DnS2=2;  %Dns Leg 2 PSC to CSC
    GroundReturnFactor_MS=2;    %MS PAt to CSC

    Y=Stockholm(2);

    C_MS=TransportationCost.FixedGround + GroundReturnFactor_MS*(TransportationCost.VariableGround *
((TimeConstant.Response+B)*(SpeedConversion.Ground/60)));

    C_DnS = (TransportationCost.FixedGround + GroundReturnFactor_DnS1*(TransportationCost.VariableGround *
((TimeConstant.Response+A)*(SpeedConversion.Ground/60))))...
          + Alpha*Y*((1-(PA * AirGrndProbability.Weather * AirGrndProbability.Available))...
          * (TransportationCost.FixedGround_Prime + (GroundReturnFactor_DnS2*TransportationCost.VariableGround
* (TimeConstant.Ground_PSC_CSC*(SpeedConversion.Ground/60))))...
          +((PA * AirGrndProbability.Weather * AirGrndProbability.Available)...
          *(TransportationCost.FixedAir + (TransportationCost.VariableAir * DdToEuc *
((TimeConstant.Air_Base_PSC+TimeConstant.Air_PSC_CSC)*(SpeedConversion.Ground/60))))));

   %BELOW IS ONLY FOR THE EXCEL OUTPUT
   %For output to excel and analysis only
   C_DnS_1= ((TransportationCost.FixedGround + (GroundReturnFactor_DnS1*TransportationCost.VariableGround *
((TimeConstant.Response+A)*(SpeedConversion.Ground/60)))));
   %Cost of going by ground for both legs without prob of going by ground considered
   C_DnS_G =  Alpha*Y*((TransportationCost.FixedGround_Prime +
(GroundReturnFactor_DnS2*TransportationCost.VariableGround *
(TimeConstant.Ground_PSC_CSC*(SpeedConversion.Ground/60)))));

   %Cost of going by air for second leg and ground the first without prob of air considered
   C_DnS_A = Alpha*Y*((TransportationCost.FixedAir + (TransportationCost.VariableAir * DdToEuc *
(((TimeConstant.Air_Base_PSC+TimeConstant.Air_PSC_CSC))*(SpeedConversion.Ground/60)))));
     %
end
```

PROBABILITIY OF AN EXCELLENT OUTCOME FUNCTION

```
function [P_DnS, P_MS, t_onset_needle_DnS,t_onset_puncture_DnS_G, t_onset_puncture_DnS_A, t_onset_needle_MS,
t_onset_puncture_MS] = Five_Probability_Functions(A,B,TimeConstant,parameters,PA,Stockholm,AirGrndProbability)

%Both A and B are ground times, A is used in both DnS scenarios then Time
%constant is used for the time to PSC (ground or air), B is only used for
%mothership, which means it needs to be a grounf time


    P_mRS01_HS=0.24; P_mRS01_SM=0.90;

    alpha=parameters(1);
    beta=parameters(2);
    chi=parameters(3);
    gamma=parameters(4);

    X=@(t_otn) ((t_otn>270)*0) + ((t_otn<=270)*Stockholm(1));
    Y=Stockholm(2);
    Z=@(t_otn) ((t_otn>270)*0) + ((t_otn<=270)*Stockholm(3));

    P_AirTransfer= PA * AirGrndProbability.Weather * AirGrndProbability.Available;
    P_GroundTransfer= 1-P_AirTransfer;
```

```
    %%
    %LVO DRIP AND SHIP
    %X=time from PSC, Z=time from CSC
    t_onset_needle_DnS=TimeConstant.FMC + TimeConstant.Response + TimeConstant.OnScene + A +
TimeConstant.DTN_PSC;

    ReImageMins=15;

    DTP_DnS_Ground= TimeConstant.DTP_DS;
    if TimeConstant.NTDO + TimeConstant.Ground_PSC_CSC > TimeConstant.LongTransfer_thresh &&
X(t_onset_needle_DnS)< 1 && Y<1 && Z(t_onset_needle_DnS)<1
        DTP_DnS_Ground= TimeConstant.DTP_DS + ReImageMins;
    end
    t_onset_puncture_DnS_G=TimeConstant.FMC + TimeConstant.Response + TimeConstant.OnScene + A +
TimeConstant.DTN_PSC...
        + TimeConstant.NTDO + TimeConstant.Ground_PSC_CSC + DTP_DnS_Ground;

    DTP_DnS_Air= TimeConstant.DTP_DS;
    if TimeConstant.NTDO + TimeConstant.Air_PSC_CSC > TimeConstant.LongTransfer_thresh &&
X(t_onset_needle_DnS)< 1 && Y<1 && Z(t_onset_needle_DnS)<1
        DTP_DnS_Air= TimeConstant.DTP_DS + ReImageMins;
    end
        t_onset_puncture_DnS_A= TimeConstant.FMC + TimeConstant.Response + TimeConstant.OnScene + A +
TimeConstant.DTN_PSC...
    + max([TimeConstant.NTDO, TimeConstant.Air_Lead + TimeConstant.Air_Base_PSC + TimeConstant.Air_OnGround]) +
TimeConstant.Air_PSC_CSC + DTP_DnS_Air;

    P_mRS01_LVO_tPA_DnS=(0.2359+2e-7.*t_onset_needle_DnS.^2-0.0004*t_onset_needle_DnS);

    P_mRs01_LVO_noTreatment=0.07; %ESCAPE Trial, Jessalyn Stockholm Model


    %LVO DnS GROUND
    %The minimum probability of P_mRS01_CSC is 0.129 after 1505 minutes
    P_mRS01_EVT_DnS_G=(0.3394+4e-8.*t_onset_puncture_DnS_G.^2-0.0002.*t_onset_puncture_DnS_G);

    %LVO DnS AIR
    %The minimum probability of P_mRS01_CSC is 0.129 after 1505 minutes
    P_mRS01_EVT_DnS_A=(0.3394+4e-8.*t_onset_puncture_DnS_A.^2-0.0002.*t_onset_puncture_DnS_A);

    P_mRS01_EVT_DnS_Overall= (P_AirTransfer*P_mRS01_EVT_DnS_A) + (P_GroundTransfer*P_mRS01_EVT_DnS_G);

    P_mRS01_LVO_DnS_OverAll= X(t_onset_needle_DnS) * (P_mRS01_LVO_tPA_DnS + ((1-P_mRS01_LVO_tPA_DnS) * ((Y *
P_mRS01_EVT_DnS_Overall) + ...
        ((1-Y) * P_mRs01_LVO_noTreatment)))) + (1-X(t_onset_needle_DnS)) * ((Y * P_mRS01_EVT_DnS_Overall) +
((1-Y) * P_mRs01_LVO_noTreatment));

    %Following two are for excel output and analysis only, just the prob of
    % outcome without the prob of air and ground factored
        P_EVT_G= X(t_onset_needle_DnS) * (P_mRS01_LVO_tPA_DnS + ((1-P_mRS01_LVO_tPA_DnS) * ((Y *
P_mRS01_EVT_DnS_G) + ...
            ((1-Y) * P_mRs01_LVO_noTreatment)))) + (1-X(t_onset_needle_DnS)) * ((Y * P_mRS01_EVT_DnS_G) + ((1-
Y) * P_mRs01_LVO_noTreatment));

        P_EVT_A= X(t_onset_needle_DnS) * (P_mRS01_LVO_tPA_DnS + ((1-P_mRS01_LVO_tPA_DnS) * ((Y *
P_mRS01_EVT_DnS_A) + ...
            ((1-Y) * P_mRs01_LVO_noTreatment)))) + (1-X(t_onset_needle_DnS)) * ((Y * P_mRS01_EVT_DnS_A) + ((1-
Y) * P_mRs01_LVO_noTreatment));

    %%
    %LVO MOTHERSHIP
    %Mothership probability functions
    %X=time from PSC, Z=time from CSC
    t_onset_needle_MS= TimeConstant.FMC + TimeConstant.Response + TimeConstant.OnScene + B +
TimeConstant.DTN_CSC;
    t_onset_puncture_MS= TimeConstant.FMC + TimeConstant.Response + TimeConstant.OnScene + B +
TimeConstant.DTP_MS;

    % The minimum probability is 0.0968 after 270 minutes
    P_mRS01_LVO_tPA_MS=0.2359+2e-7.*t_onset_needle_MS.^2-0.0004*t_onset_needle_MS;

    %The minimum probability of P_mRS01_CSC is 0.129 after 1505 minutes
    P_mRS01_EVT_MS=0.3394+4e-8.*t_onset_puncture_MS.^2-0.0002.*t_onset_puncture_MS;

    P_mRS01_LVO_MS= X(t_onset_needle_MS) * (P_mRS01_LVO_tPA_MS + ((1-P_mRS01_LVO_tPA_MS) * ((Y *
P_mRS01_EVT_MS) + ((1-Y) * P_mRs01_LVO_noTreatment))))...
        + (1-X(t_onset_needle_MS)) * ((Y * P_mRS01_EVT_MS) + ((1-Y) * P_mRs01_LVO_noTreatment));

    %%
    %nLVO
    P_mRs01_nLVO_noTreatment= 0.4622;
```

```
    %nLVO DRIP AND SHIP
    %the minimum probability of P_mRS01_nLVO is 0.4622 after 270 minutes
    P_mRS01_nLVO_tPA_Dns=(0.6343-5e-8.*(t_onset_needle_DnS).^2-0.0005*t_onset_needle_DnS);
    P_mRS01_nLVO_DnS= (Z(t_onset_needle_DnS)* P_mRS01_nLVO_tPA_Dns) + ((1-
Z(t_onset_needle_DnS))*P_mRs01_nLVO_noTreatment);

    %nLVO MOTHERSHIP
    %the minimum probability of P_mRS01_nLVO is 0.4622 after 270 minutes
    P_mRS01_nLVO_tPA_MS=(0.6343-5e-8.*(t_onset_needle_MS).^2-0.0005.*t_onset_needle_MS);
    P_mRS01_nLVO_MS= (Z(t_onset_needle_MS)* P_mRS01_nLVO_tPA_MS) + ((1-
Z(t_onset_needle_MS))*P_mRs01_nLVO_noTreatment);

    %%
    %FINAL COMBINED PROBBILITIES

    P_DnS=alpha.*P_mRS01_LVO_DnS_OverAll + beta.*P_mRS01_nLVO_DnS +...
        chi.*P_mRS01_HS + gamma.*P_mRS01_SM;

    P_MS=alpha.*P_mRS01_LVO_MS+ beta.*P_mRS01_nLVO_MS+...
        chi.*P_mRS01_HS + gamma.*P_mRS01_SM;

end
```

Appendix B – Results Assuming a RACE Pre-hospital Scale

	🧠	$
(red)	DnS	DnS
(purple)	DnS	MS
(blue)	MS	DnS
(green)	MS	MS

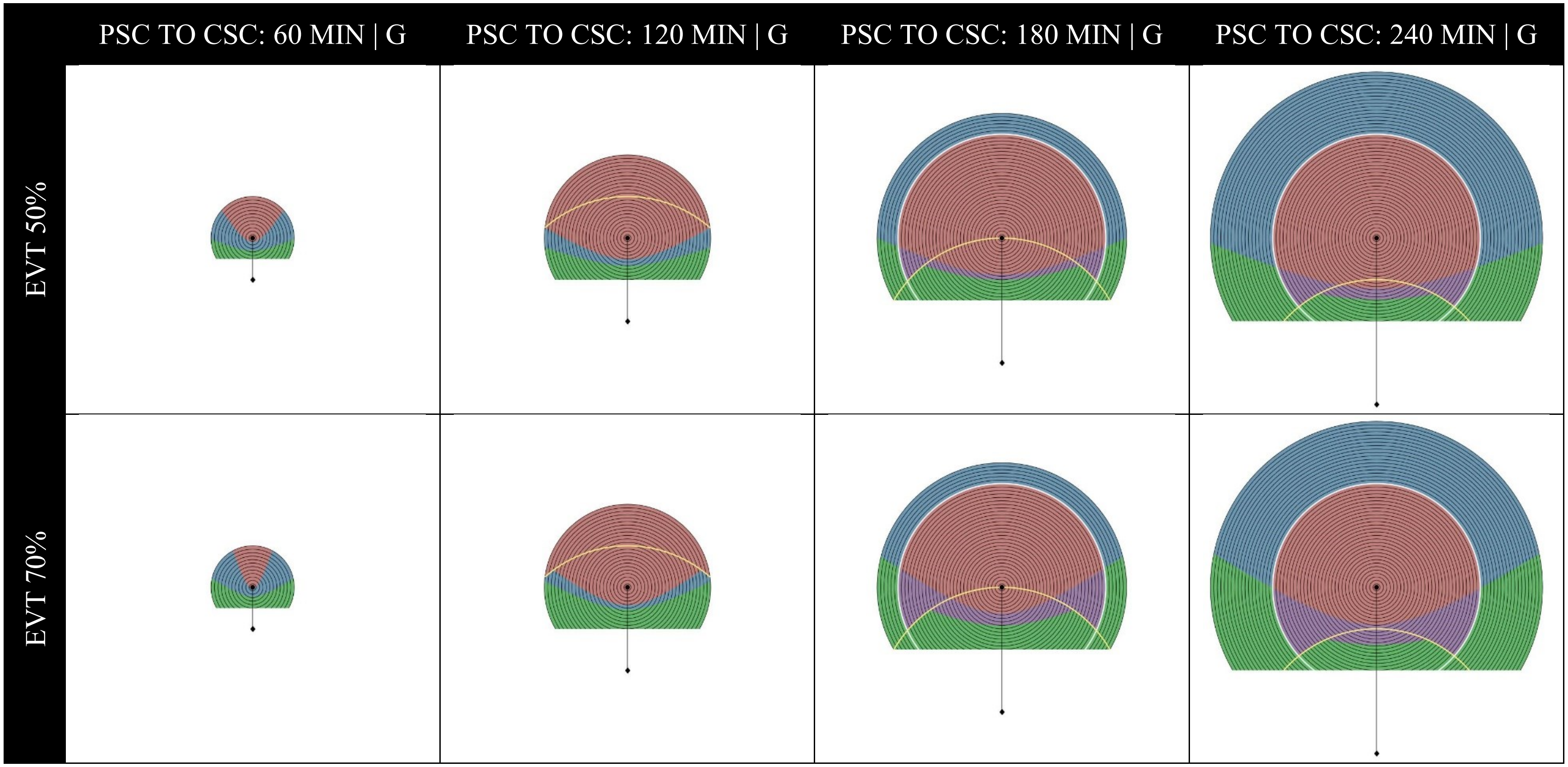

Figure 15: Results for RACE Experiments Run with **Inefficient Hospital Scenario**

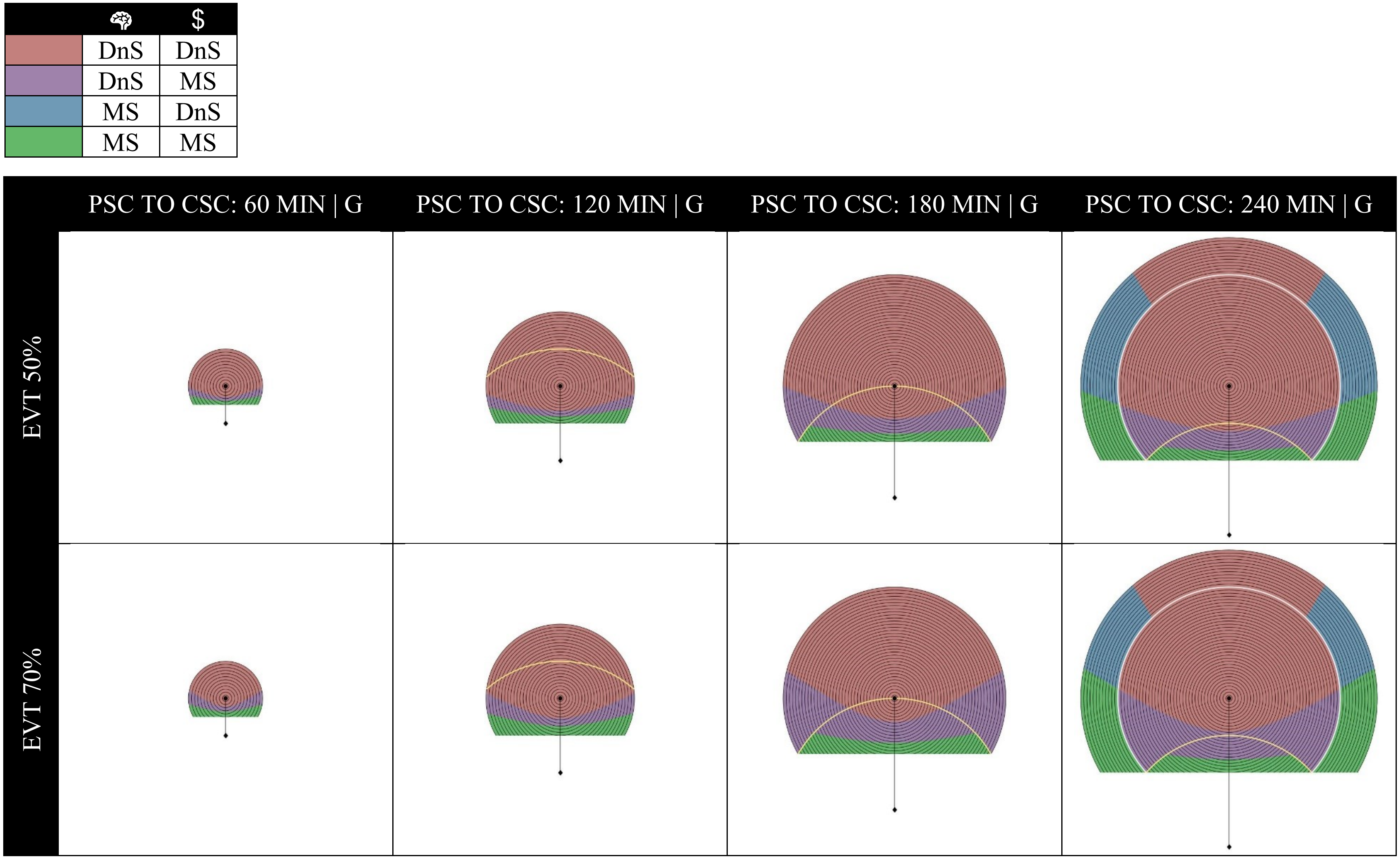

Figure 16: Results for RACE Experiments Run with **Efficient Hospital Scenario**

Appendix C – Results Assuming a C-STAT Pre-hospital Scale

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

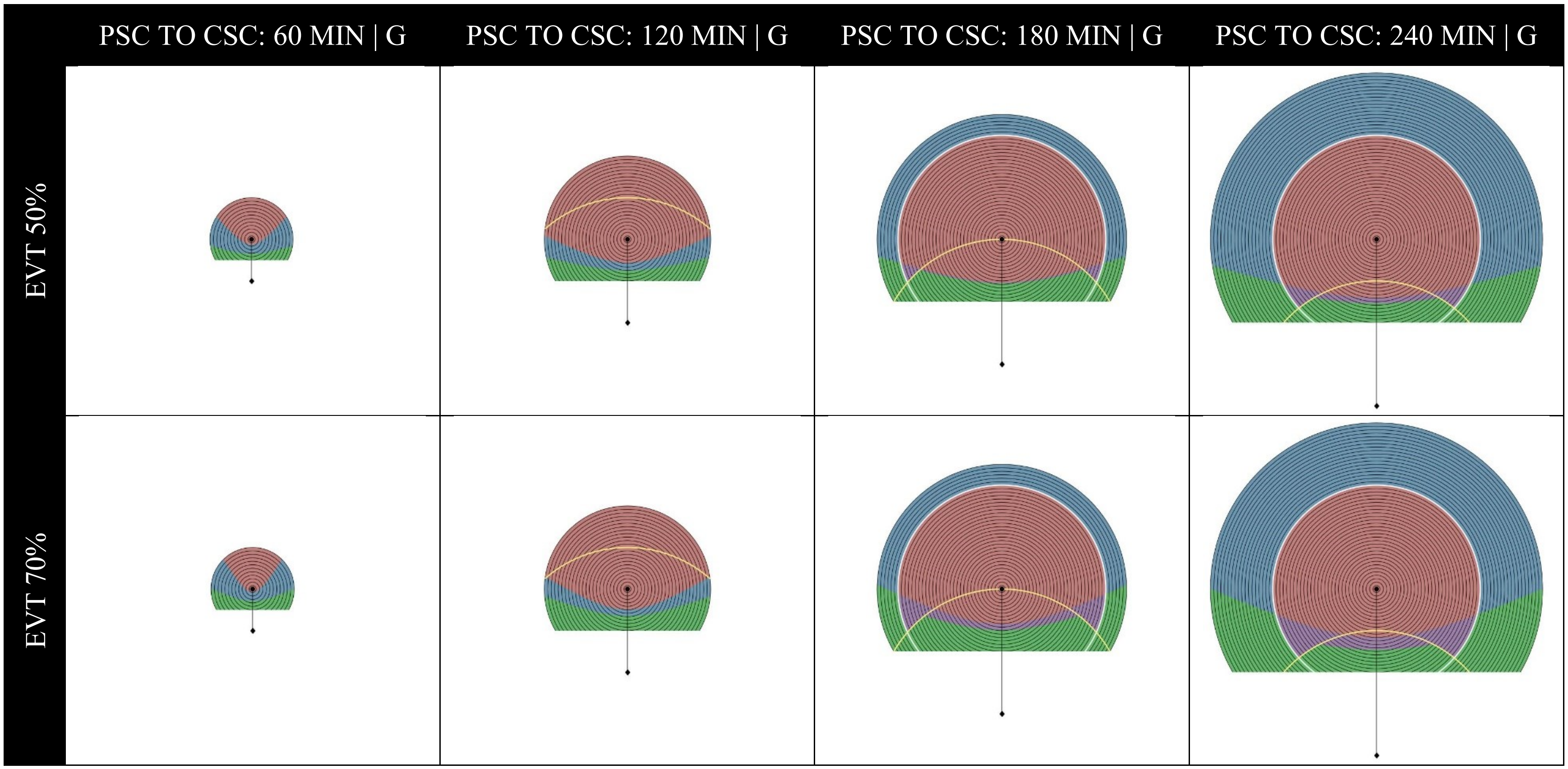

Figure 17: Results for C-STAT Experiments Run with **Inefficient Hospital Scenario**

	🧠	$
(red)	DnS	DnS
(purple)	DnS	MS
(blue)	MS	DnS
(green)	MS	MS

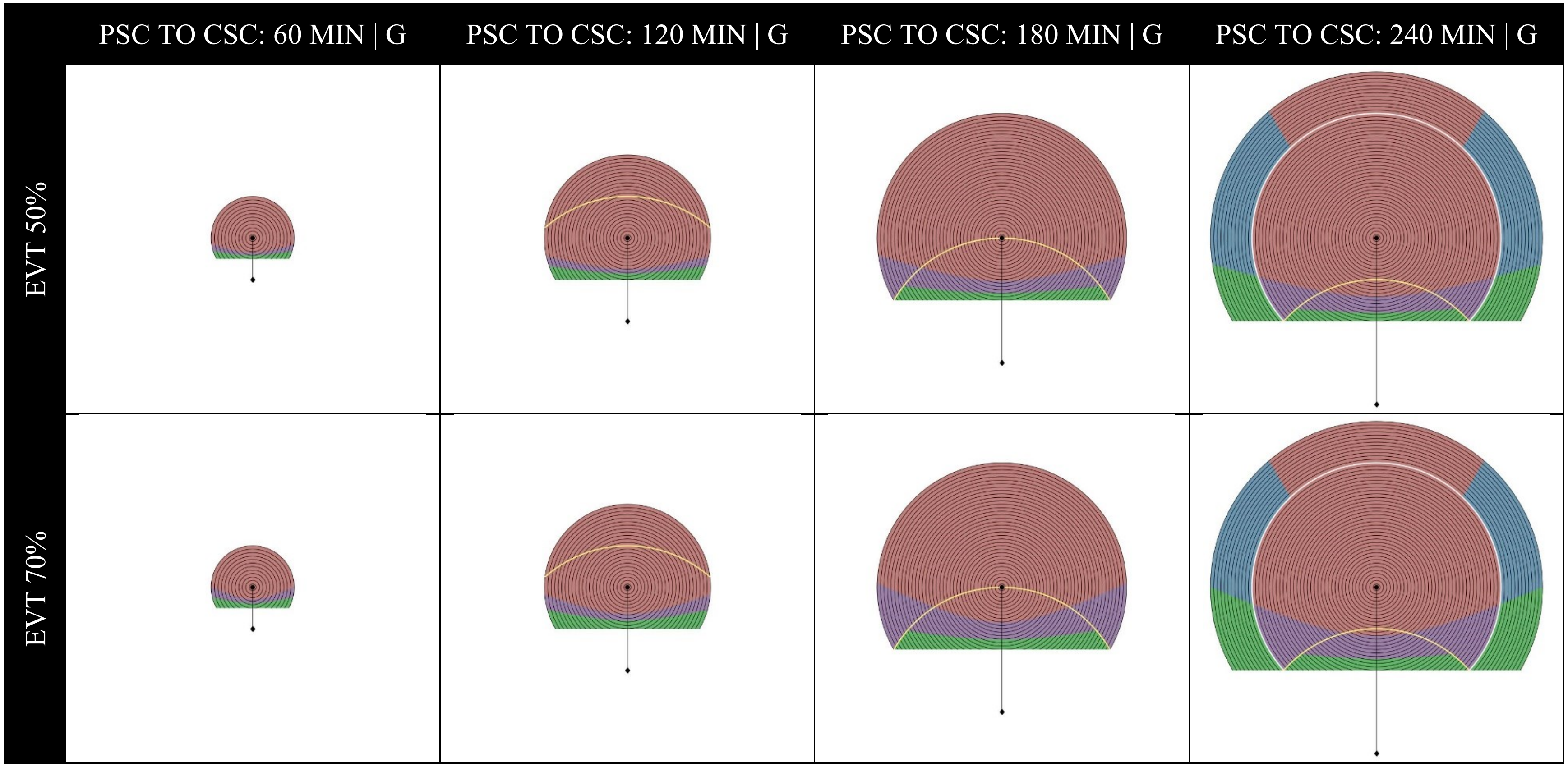

Figure 18: Results for C-STAT Experiments Run with **Efficient Hospital Scenario**

Appendix D – Colour Blind Accessible Legend

Below Table 20 includes a legend for the colour blind accessible results figures.

Table 20: Colour Blind Accessible Colour Coding Legend

Colour Blind Accessible Colour	Highest Probability of an Excellent Outcome	Least Expensive Transport Cost
	Drip and Ship	Drip and Ship
	Drip and Ship	Mothership
	Mothership	Drip and Ship
	Mothership	Mothership

Appendix E – Colour Blind Accessible Results Assuming a LAMS Pre-hospital Scale

Figure 19 is a colour blind accessible version of the results shown in Section 6.1, Figure 8.

	🧠	$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

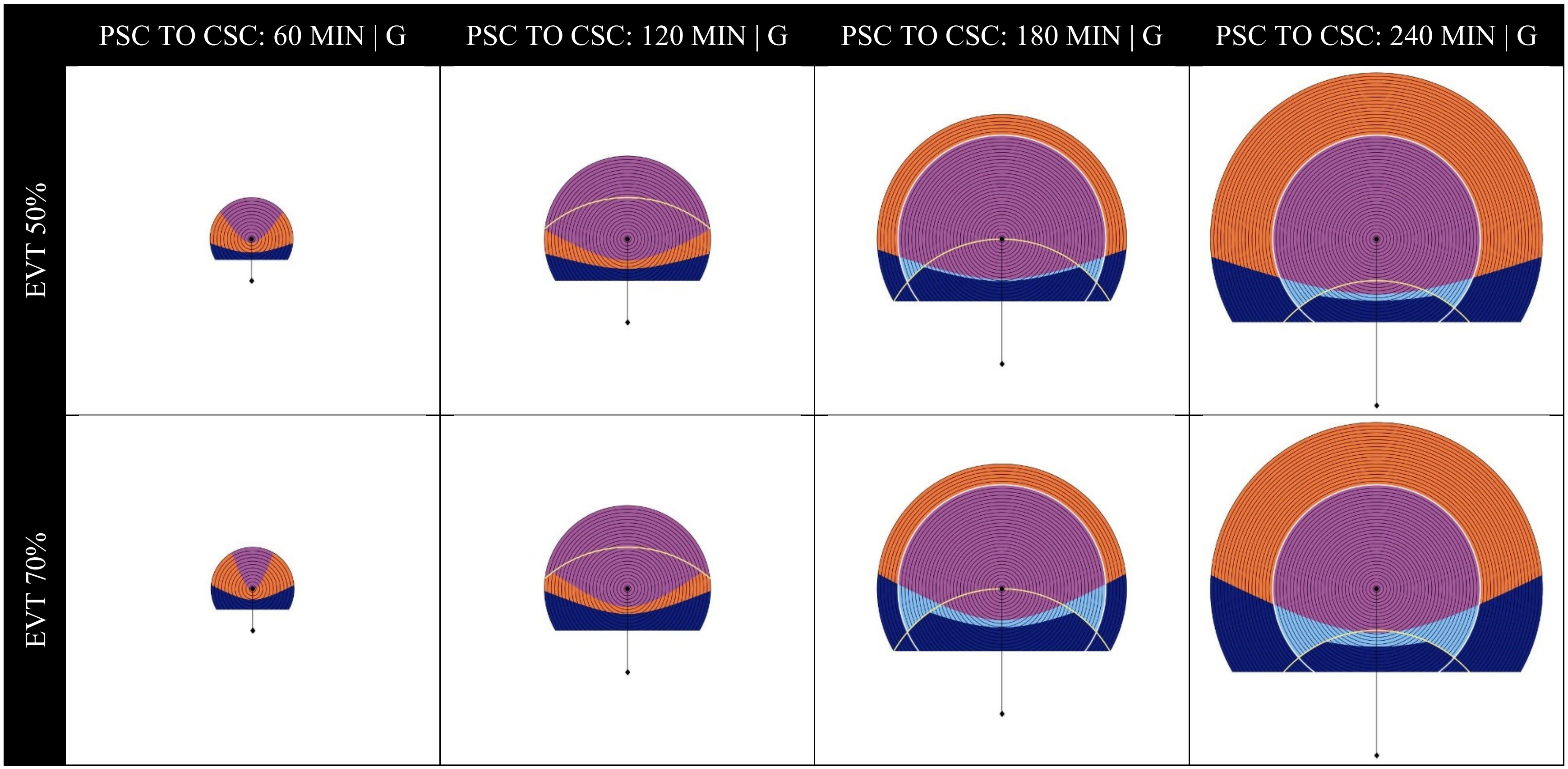

Figure 19: Colour Blind Accessible Results for LAMS Experiments Run with **Inefficient Hospital Scenario**

Figure 20 is a colour blind accessible version of the results shown in Section 6.1, Figure 9.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

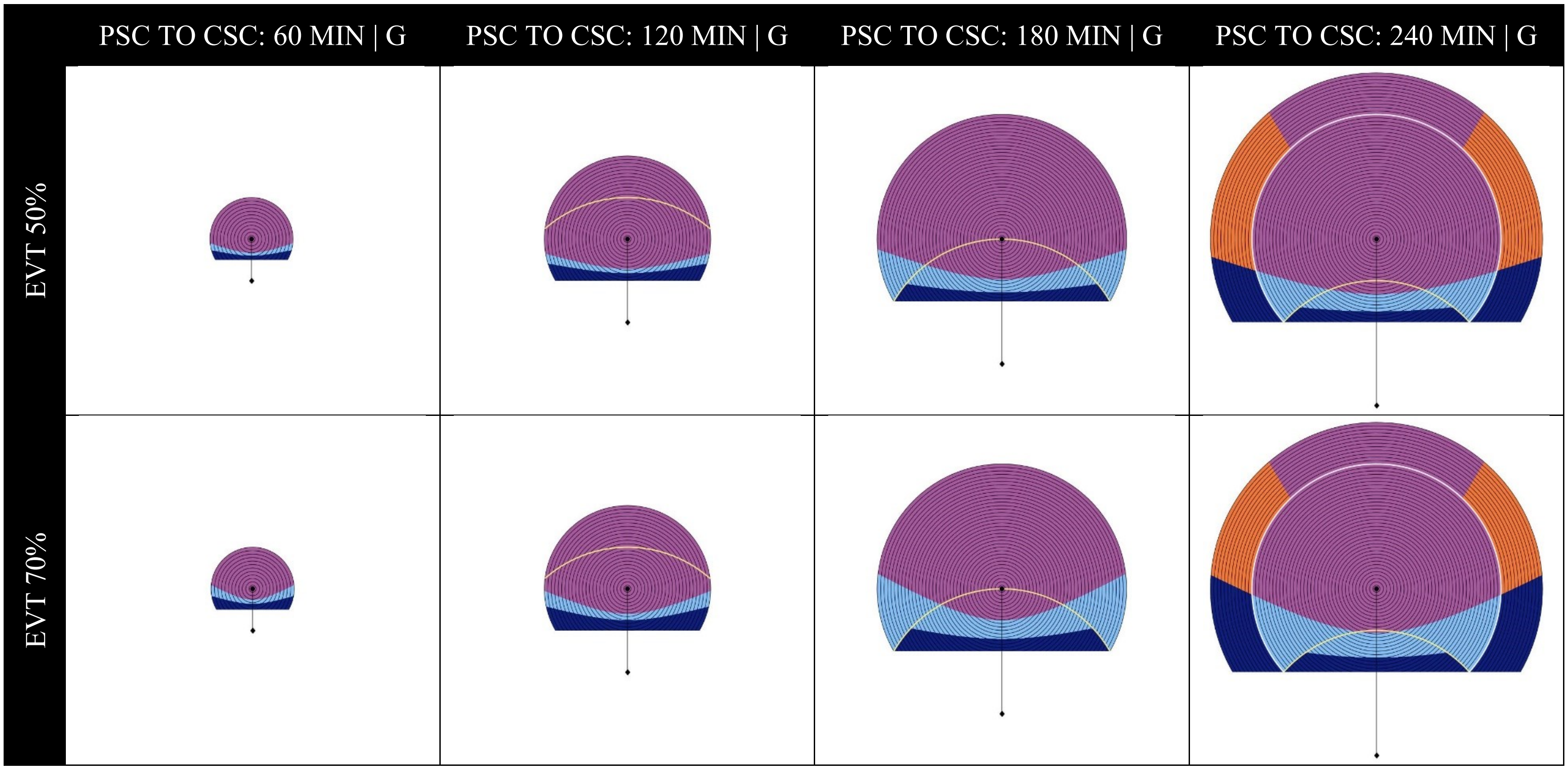

Figure 20: Colour Blind Accessible Results for LAMS Experiments Run with **Efficient Hospital Scenario**

Appendix F – Colour Blind Accessible Results Assuming a RACE Pre-hospital Scale

Figure 21 is a colour blind accessible version of the results shown in Appendix B, Figure 15.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

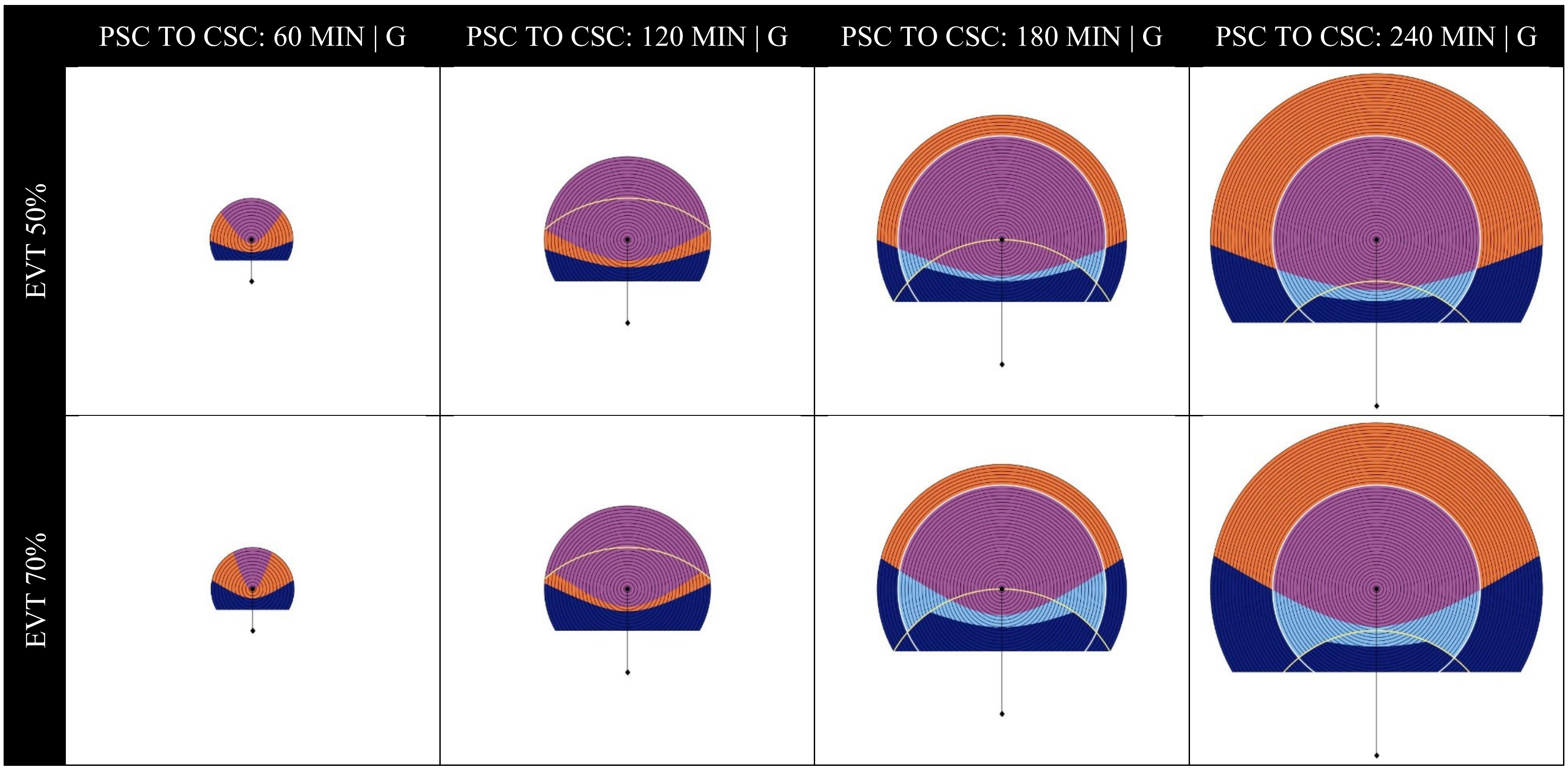

Figure 21: Colour Blind Accessible Results for RACE Experiments Run with **Inefficient Hospital Scenario**

Figure 22 is a colour blind accessible version of the results shown in Appendix B, Figure 16.

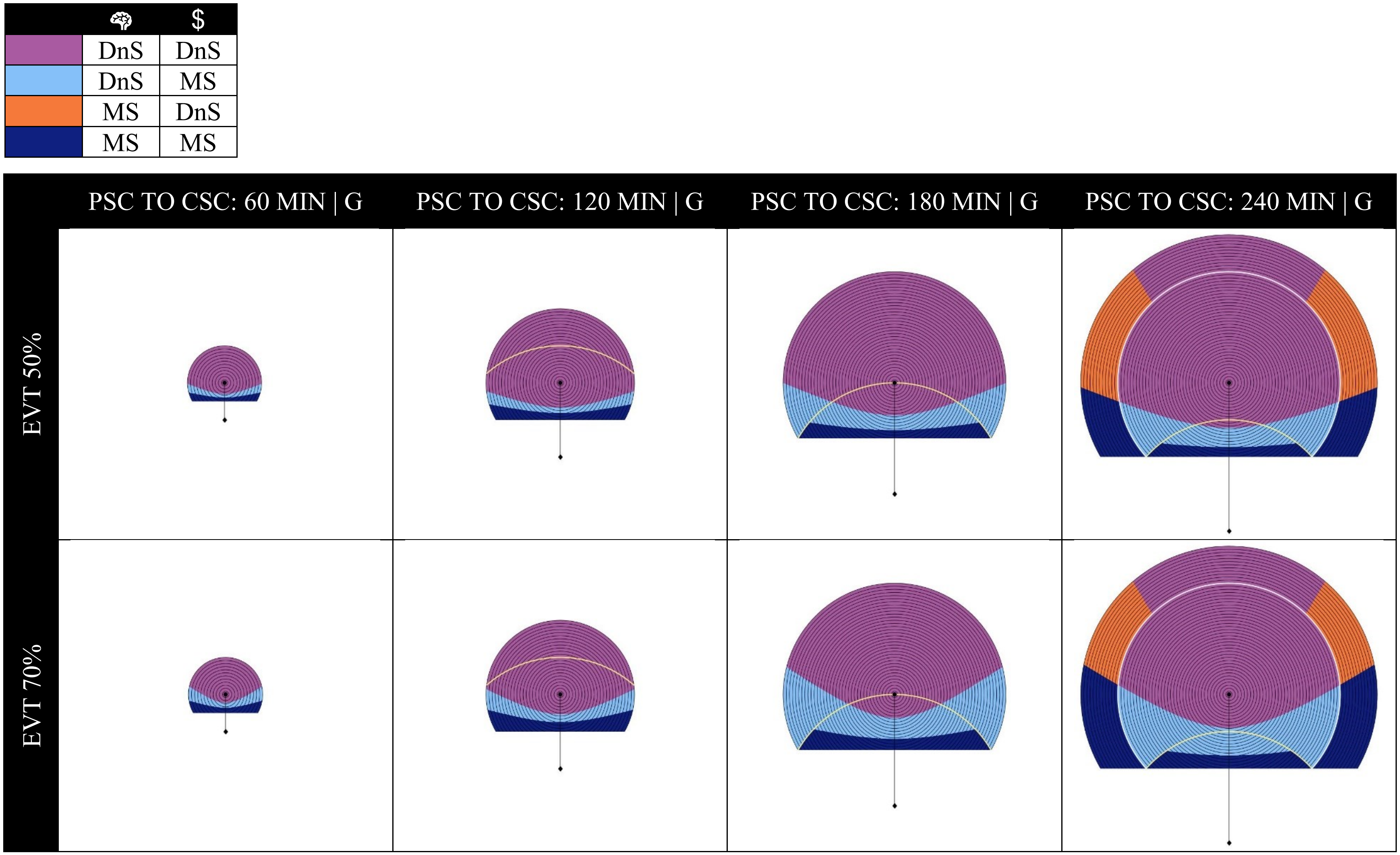

Figure 22: Colour Blind Accessible Results for RACE Experiments Run with **Efficient Hospital Scenario**

Appendix G – Colour Blind Accessible Results Assuming a C-STAT Pre-hospital Scale

Figure 23 is a colour blind accessible version of the results shown in Appendix C, Figure 17.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

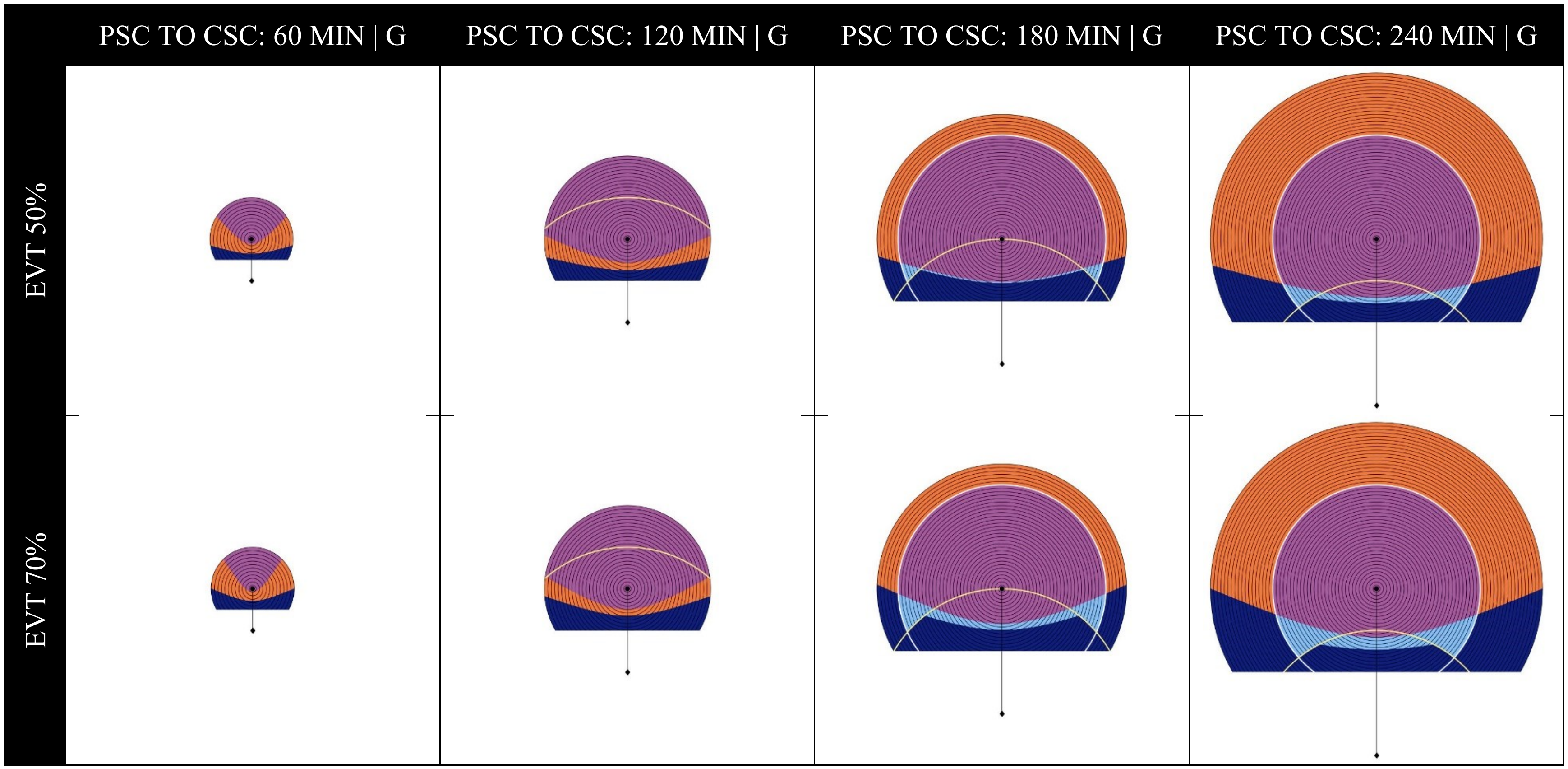

Figure 23: Colour Blind Accessible Results for C-STAT Experiments Run with **Inefficient Hospital Scenario**

Figure 24 is a colour blind accessible version of the results shown in Appendix C, Figure 18.

		$
	DnS	DnS
	DnS	MS
	MS	DnS
	MS	MS

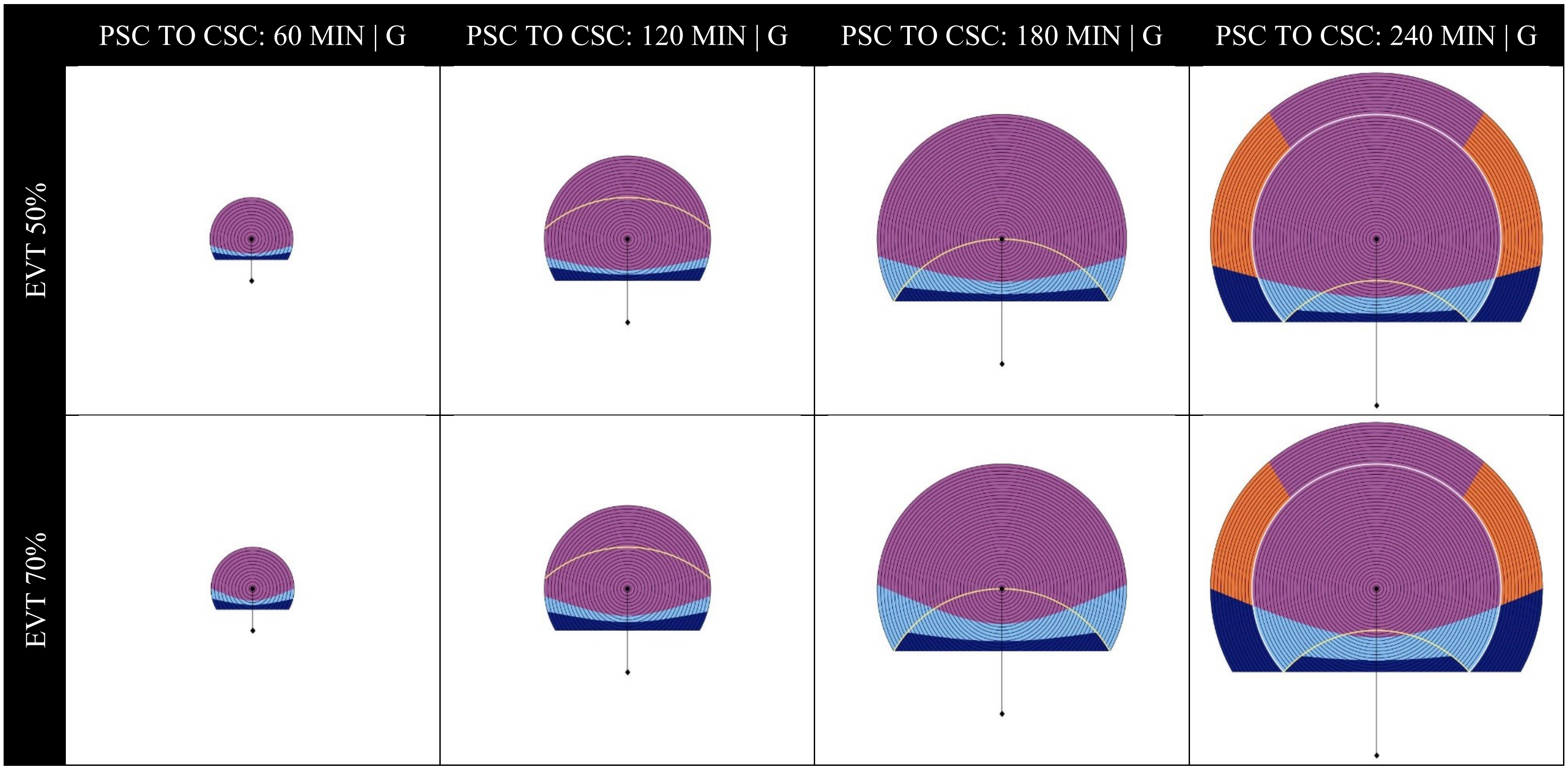

Figure 24: Colour Blind Accessible Results for C-STAT Experiments Run with **Efficient Hospital Scenario**