Analysis and Modelling of the Thrombolysis Process for Acute Ischemic Stroke Patients at Urban and Rural Hospitals

by

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Abstract

Background: Thrombolysis is the process of treating acute ischemic stroke (AIS) patients with tissue plasminogen activator (tPA), where effectiveness critically relies on rapid treatment. Fast treatment with tPA has been reported in many urban hospitals, but rural hospitals struggle to reduce treatment times. The study objectives are as follows: 1) to analyze healthcare professionals' views on various treatment topics in Nova Scotia; 2) to map and compare the thrombolysis treatment process in urban and rural settings in Nova Scotia; 3) to provide a detailed conceptual framework of the thrombolysis process focusing on intra-hospital activities; and 4) to assess the potential impact of process improvements that can result in faster door-to-needle time (DNT) when applied to urban and rural settings.

Methods: Structured interviews were conducted with healthcare professionals involved in stroke treatment across three Nova Scotian hospitals (1 urban and 2 rural). Interview data were used to develop a detailed process map for each site, which provided the foundation to then create a conceptual framework. The interview results and conceptual framework were used to develop an ARENA discrete-event simulation (DES) model to replicate treatment processes at both urban and rural hospitals.

Results: There were 23 health care professionals interviewed at 3 sites. The analysis of the interview data showed a total of 11 urban-rural treatment differences. Additionally, 11 patient-related and 29 system treatment delays were found. Five scenarios were tested with the DES model, using median DNT as the primary outcome measure. The scenario results include the following maximum DNT reductions: patients arriving via Emergency Medical Services (EMS) remaining on the EMS stretcher to imaging (9.2%, 95% CI 7.9 – 10.5), administration of tPA in the imaging area (12.6%, 95% CI 12.4 – 12.8), pre-registering patients arriving via EMS (1.7%, 95% CI 0.3 – 3.1), reducing both the treatment decision time and tPA preparation time by 35% (11.0%, 95% CI 10.0 – 12.0), and combining all scenarios (26.7, 95% CI 24.5 – 28.9%).

Conclusions: The majority of treatment delays encountered are system delays. There is a general consensus that there is an urban-rural treatment gap, and physicians in rural settings are more hesitant to treat with tPA. The detailed conceptual framework further clarifies intra-hospital logistics of the thrombolysis process. Significant DNT improvements are achievable in urban and rural settings through implementing process changes and reducing activity durations.

List of Abbreviations Used

- AIS: Acute Ischemic Stroke
- CI: Confidence Interval
- CIHR: Canadian Institutes of Health Research
- COREQ: Consolidated Criteria for Reporting Qualitative Research
- CT: Computed Tomography
- CTA: Computed Tomography Angiography
- CTAS: Canadian Triage Acuity Scale
- DES: Discrete-Event Simulation
- DNT: Door-to-Needle Time
- DTCT: Door-to-CT
- DTN: Door-to-Needle
- ED: Emergency Department
- EMS: Emergency Medical Services
- EVT: Endovascular Thrombectomy
- INR: International Normalized Ratio
- IQR: Interquartile Range
- IV: Intravenous
- NG: Nasogastric
- OR: Operations Research
- PV: Private Vehicle
- REB: Research Ethics Board
- tPA: Tissue Plasminogen Activator

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Chapter 1: Introduction

Stroke is a devastating disease, but is treatable with tissue plasminogen activator (tPA) (1) and endovascular thrombectomy (EVT) (2–6). In 2019, stroke ranked fourth for cause of death in Canada (7), and is the leading cause of severe disability (8). When having a stroke, a person loses approximately 1.9 million neurons and 14 billion synapses every minute (9). Additionally, each hour without treatment equates to losing the amount of neurons that would normally take 3.6 years to be lost (9). These statistics have led to the commonly referenced motto “time is brain”. This thesis will be focused on acute ischemic stroke (AIS) patients treated with tPA, which is called thrombolysis treatment, a proven treatment since 1995 (1). An ischemic stroke is caused by a lack of blood flow to an area of the brain due to the presence of a blockage or clot in an artery in the brain (10). tPA is a clot-busting medication, which works by dissolving the blood clot, thus returning blood flow to the brain (11). Patients can benefit from tPA up to 4.5 hours from time of symptom onset (12), but it is critical to treat AIS patients rapidly as the effectiveness of tPA is highly time dependent (13), and it has been shown that there are better patient outcomes when treated more rapidly (12,14).

As it is critical to treat AIS patients fast, the Canadian Best Practice Guideline states the median time to treatment should be 30 minutes for the door-to-needle time (DNT), which is the time from hospital arrival to start of treatment (15). DNT is a critical measure of hospital efficiency linked to patient outcomes. It can be challenging to achieve the median 30-minute DNT target due to treatment delays, both patient and system related (16). Patient-related delays are due to factors directly affecting the patient, such as hypertension, while system factors are caused by inefficiencies in the treatment process itself. Fast treatment with tPA has been reported in many urban hospitals, but rural hospitals can struggle to reduce treatment times (17,18). Therefore, there is a need to understand the barriers to fast treatment in rural hospitals to ensure equitable care. It was anticipated that the urban-rural disparity of AIS treatment would be pronounced in Nova Scotia due to resource differences and population distribution. The east coast province has small populations dispersed over wide rural areas, with 43% of the province’s population residing in rural communities (19).

To overcome delay factors, there has been extensive research done determining processes and strategies that result in shorter DNT (20,21). It has been shown that implementing multiple strategies can lead a hospital to reduce their median DNT to 20 minutes (18). It can be challenging to test these strategies, as they can be time consuming to trial and implement and could disturb established care pathways. This leads to the clear benefit of using discrete-event simulation (DES) to provide a safe and efficient way to model processes and determine the impact of process changes. DES allows complex healthcare systems with stochastic elements, such as stroke pathways, to be replicated to provide insights and recommendations for improvements. DES has been shown to be effective to model pre-hospital (22,23), intra-hospital (24–27), and both pre and intra-hospital aspects of acute stroke pathways (28–35). Several studies have included overviews of the key pre-hospital or intra-hospital thrombolysis activities (22,29,30,33–36), but there was a lack of detail regarding intra-hospital activities and sequences. Additionally, process differences based on pathway type or out of hour resource differences are not well-defined in the literature. It is important to fill the noted gaps to identify the barriers to fast treatment in rural hospitals, and to provide clarity of intra-hospital logistics, which can both lead to solutions to reduced DNT.

This thesis includes two studies that were conducted addressing AIS treatment in urban and rural settings. Study 1 (37) is a qualitative study involving the participation of three Nova Scotian hospitals, 1 urban site and 2 rural sites. The objectives for Study 1 (37) were: 1) to analyze healthcare professionals' views on various thrombolysis treatment topics in Nova Scotia; and 2) to map and compare the thrombolysis treatment process for AIS patients in urban and rural settings in Nova Scotia. Study 2 is a quantitative study that used the data collected from Study 1 (37) as a foundation, and has the following more generalized objectives: 1) to provide a detailed conceptual framework of the thrombolysis process, focusing on intra-hospital activities; and 2) to assess the potential impact of process improvements that can result in faster DNT when applied to urban and rural settings using a DES model. Chapter 2 and Chapter 3 include the manuscripts for Study 1 (37) and Study 2, respectively. Each study manuscript includes an introduction, detailed methodology, results, discussion that notes study limitations, as well as key findings. Chapter 4 includes a discussion which relates the individual studies, the generalizability of the works, overall study limitations, and opportunities for future research. Finally, Chapter 5 highlights the key conclusions drawn from the two studies and states the overall contributions from the works.

Chapter 2: Study 1 - Analysis of Thrombolysis Process for Acute Ischemic Stroke in Urban and Rural Hospitals in Nova Scotia Canada (37)

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2.1 Abstract

Background: Stroke is a devastating disease, but it is treatable with alteplase or tissue plasminogen activator (tPA). The effectiveness of tPA is highly time-dependent, meaning rapid treatment is critical. Fast treatment with tPA has been reported in many urban hospitals, but hospitals in rural locations struggle to reduce treatment times. This qualitative study examines current thrombolysis processes in one urban and two rural hospitals in Nova Scotia, Canada, by mapping and comparing the treatment process in these settings for acute ischemic stroke (AIS) patients, and by analyzing the healthcare professionals views on various treatment topics.

Methods: Structured interviews were conducted with healthcare professionals involved in stroke treatment across the three sites. The interviews focused on the various activities in the thrombolysis treatment at each site. Additionally, participants were asked about the following 10 topics: comfort treating acute ischemic stroke patients; perceptions about tPA; appropriate tPA treatment window; stroke patient priority; tPA availability; patient consent; urban-rural treatment differences; efficiency of their treatment process; treatment delays; and suggested process improvements. Results were analyzed using the Framework Method, as well as through the development of process maps.

Results: 23 healthcare professionals were interviewed at 2 rural hospitals and 1 urban hospital. Acute ischemic stroke patients are triaged as the highest or urgent priority at each included site. Physicians are more hesitant to treat with tPA in rural settings. A total of 11 urban-rural treatment differences were noted by the rural sites. Additionally, 11 patient-related and 29 system treatment delays were described. A process map was developed for each site, representing the arrival by ambulance and by private vehicle pathways.

Conclusions: Guidelines and clear protocols are critical in reducing treatment times and ensuring consistent access to treatment. The majority of treatment delays encountered are system delays, which can be appropriately planned for to reduce delays within the care pathway. There is a general consensus that there is an urban-rural treatment gap for acute ischemic stroke patients in Nova Scotia, and that continuing education is key in rural hospitals to improve Emergency Department (ED) physician comfort with treating patients with tPA.

Keywords: acute ischemic stroke, tissue plasminogen activator (tPA), thrombolysis, door-to-needle time, emergency department, delay factors, stroke pathways, urban-rural treatment gap

2.2 Introduction

In 2019, stroke ranked fourth for cause of death in Canada (7) and is the leading cause of severe disability (8). When having a stroke, a person loses approximately 1.9 million neurons, and 14 billion synapses every minute (9). Additionally, each hour without treatment results in a person losing the amount of neurons that would normally take 3.6 years to be lost (9), leading to the popularly referenced motto "time is brain". Treatment with alteplase or tissue plasminogen activator (tPA) for Acute Ischemic Stroke (AIS) has been a proven treatment since the mid 1990's (1). Patients can benefit from being treated with tPA up to 4.5 hours from time of symptom onset (12). Although, it was shown that patients have better outcomes when treated more rapidly with tPA (12,14), as the effectiveness of tPA is highly time dependent (13). For maximal benefit, patients should be treated with tPA as quickly as possible (12,14). Therefore, current Canadian guidelines indicate that patients should be treated with tPA within 30 minutes from their arrival at the hospital (15). This is referenced as a door-to-needle (DTN) time, meaning the length of time it takes from the moment they arrive at the hospital to the start of tPA treatment.

Delays in tPA treatment have been found to be associated with patient factors as well as system factors (16). To overcome these delay factors, there has been extensive research done on the processes and strategies that result in shorter DTN times (20,21). It has been shown that using multiple strategies can reduce a hospital's median DTN time to 20 minutes (18). The top strategies include: receiving pre-notification by Emergency Medical Services (EMS) and having a single call activation of the stroke team; moving the patients directly to the computed tomography (CT) scanner on the EMS stretcher; having a rapid registration process; and administering tPA in the scanner area (20). Acute stroke management practices in rural areas have been labeled as sub-optimal, resulting in a gap in quality of treatment in urban and rural areas (38). A recent study that reduced DTN times across an entire population showed that urban and community hospitals with access to neurologists at all times were able to reduce their median DTN times to 35 and 34 minutes from 65 and 73 minutes respectively, but rural hospitals were only able to reduce their DTN times to a median of 54 minutes from 84 minutes (17). There is a need to better understand the barriers to fast treatment in rural hospitals to ensure equitable care.

It was anticipated that the disparity between rural and urban treatment of AIS is pronounced in Nova Scotia, a Canadian province located on the east coast of the country, due to resource differences and population distribution. Stroke treatment in Nova Scotia is challenging as small populations are dispersed over wide rural areas. According to the 2016 Canadian Census, 43% of the province's population resides in rural communities (19). It was shown that there is a higher risk of incident stroke in rural areas (39), estimated to be 23% higher in large rural areas and 30% higher in small rural towns, when being compared with urban areas (39). Therefore, there is a critical need to ensure that rural populations in Nova Scotia receive equitable access to efficient treatment. This study aims to shed some light on the differences in the thrombolysis process between urban and rural hospitals in Nova Scotia. The objectives for the study are the following: 1) to analyze the healthcare professionals views on various treatment topics; and 2) to map and compare the thrombolysis treatment process for acute stroke patients in urban and rural settings in Nova Scotia.

2.3 Methods

A qualitative study was conducted in order to better understand the treatment process in rural and urban hospitals. There were two rural sites chosen and one urban site to be able to compare the differences between urban and rural hospitals. The consolidated criteria for reporting qualitative research (COREQ) was consulted to report key aspects of the study in the following domains: the research team, study design, and analysis and findings (40). The qualitative study was completed by conducting interviews with key healthcare professionals who are involved in AIS treatment at each site. TB conducted the interviews and data analysis, and was a Master of Applied Science in Industrial Engineering student at the time of the study.

2.3.1 Site Context

These sites were selected to provide a fair representation, with a limited sample size, of the different hospitals in Nova Scotia providing thrombolysis treatment, based on the presence and absence of neurologists in-hospital, and varying CT technologist availability. Site 1 is the urban site and the province's only comprehensive stroke centre. Site 1 is a large teaching hospital with approximately 800 beds, and is a level 1 trauma centre. Some important distinctions regarding this site are that it is located in an urban setting, neurologists are always available during the treatment process, CT technologists are always available within the hospital; and it is the only hospital in Nova Scotia to provide endovascular treatment (EVT) to AIS patients. Site 2 is a rural hospital with approximately 200 beds located in a small town. A distinction from the urban site (Site 1) is that ED physicians are primarily responsible for thrombolysis, and they do not have neurologists on site. They do however similarly have a CT technologist always available within the hospital. Site 3 is another rural hospital with roughly 100 beds, located in a small town, with ED physicians primarily responsible for thrombolysis. This site does not have access to CT technologists out of hours within the hospital. Out of hours, the on-call CT technologist has to travel into the hospital when required. The 3 sites defined regular hours as 8am to 4pm or 5pm, Mondays to Fridays. Out of hours are considered all times outside of regular hours, meaning evenings and weekends. Human resource differences and the resulting treatment process changes, between regular and out of hours, are further defined for each site in the treatment process results section. The described site distinctions and the local target and current median DTN times for each site are shown in Table 1. It can be seen that Site 2 currently has the lowest median DTN time, while Site 3 has the highest.

Table 1: Site Distinctions with Local Target and Current Median Door-to-Needle Times. DTN: Door-to-Needle, CT: Computed Tomography, ED: Emergency Department.

Site	**Site Distinctions**	**Local Target Median DTN Time (min)**	**Current Median DTN Time (min)** (41) June 2019 to May 2020
Site 1 (Urban)	• Province's only comprehensive stroke centre • Large urban teaching hospital • Level 1 trauma center • Approx. 800 beds • Neurologists and stroke neurologists • 24/7 CT technologists within hospital	30	50
Site 2 (Rural)	• Rural hospital • Approx. 200 beds • ED physicians • 24/7 CT technologists within hospital	30	40
Site 3 (Rural)	• Rural hospital • Approx. 100 beds • ED physicians • CT technologists within hospital during regular hours, and some evenings/weekend shifts	60	77.5

All of these sites have a stroke coordinator, who oversees the site's stroke care. Study participants were recruited for interviews from each site through the stroke coordinator. The participants include all of those involved in the treatment of acute ischemic stroke patients. In the urban setting, the target roles recruited included: ED nurse, ED physician, CT technologist, paramedic, neurologist, neurology resident, stroke neurologist, stroke nurse, and stroke coordinator. In the rural setting, the target roles that were recruited included: ED nurse, ED physician, CT technologist, paramedic, radiologist, and stroke coordinator.

2.3.2 Ethics and Consent

This study was carried out in accordance with the recommendations of the Nova Scotia Health Research Ethics Board (REB). The study protocol, with the REB file number 1025975, was approved by the Board. Written informed consent was obtained for each participant involved in the study prior to the participant being interviewed. There was no compensation provided to any participants.

2.3.3 Data Collection

Data was collected from September to October 2020, using structured interviews with various professionals that are involved in the AIS treatment process. The interview participants were selected by the site's stroke coordinator using a purposive sampling method. Upon selection, TB approached participants by email to complete the consent process and schedule their interview. Each interview included only TB and an individual participant, with no non-participants present. Participants completed a single interview, and were informed of the study objectives at the beginning of the interview.

Two interview guides were developed for the study and can be found in Supplementary Materials. Pilot testing of the interview guides was completed with another student to determine comprehension of the questions, and interview duration. There was one standard interview guide for all healthcare professionals containing 33 questions, and one guide tailored to stroke coordinators containing 25 questions. Section 1 of the standard interview guide focuses on topics 1 to 10 listed in Table 2 to provide contextual details of the thrombolysis treatment at each site, while section 2 of the guide aimed to develop a detailed process map for the treatment process at each site from the perspective of different professionals. The questions for section 1 were developed based on the causes of delays that were identified in the literature (16) and the behavioral barriers to tPA treatment by emergency physicians (42–44). The questions for section 2 of the structured interview were developed for the purpose of understanding details of the specific steps in the treatment process from the perspective of the various healthcare professionals that were being interviewed. The basis of the questions for section 2 were based on previous studies that aimed to improve the tPA treatment process (20).

Table 2: 11 Interview Topics. AIS: Acute Ischemic Stroke, tPA: Tissue Plasminogen Activator.

Topic
1. Comfort treating AIS patients
2. Perceptions about tPA
3. Appropriate tPA treatment window
4. AIS patient priority
5. tPA availability
6. Patient consent
7. Urban-rural treatment differences
8. Efficiency of their treatment process
9. Treatment delays at their site (patient-related and system)
10. Suggested process improvements at their site
11. Other topics

The stroke coordinator guide had many overlapping questions with the standard guide, although it did not include 3 of the topics from section 1: comfort treating AIS patients, perceptions about tPA, and patient consent as the stroke coordinators are not directly involved with AIS treatment. The interview guide prepared for stroke coordinators had additional questions in section 1 on the following topics: human resource limitations, key metrics in data analysis, following treatment protocols, as well as the opportunity to add any general background information regarding treatment at their hospital.

Interviews were designed to take approximately 45 minutes to complete and were conducted using Microsoft Teams (version 1.3.00.24758, Microsoft Corporation, Redmond, WA, USA), a video-conferencing platform, or via direct phone call. Audio recording was used to collect data for all interviews.

2.3.4 Qualitative Analysis

The qualitative analysis of the interviews used the Framework Method, as well as process mapping for each included site. The Framework Method is a 7-step qualitative analysis technique used in health research that helps to reduce data into an organized matrix format that aids response comparison (45). The Framework Method provides high-level structured steps to the qualitative analysis process that can be applied to any topic, and allowed for study goals to be accomplished using a deductive approach. The 7 steps involved in the Framework Method are the following: 1) transcription of interviews: 2) familiarization with the interview content; 3) developing interview codes; 4) developing a working analytical framework by producing analysis categories: 5) applying the analytical framework: 6) charting data into the framework matrix: and 7) interpreting the data (45). Each interview was manually transcribed verbatim and was reviewed for familiarization of content. There was a single code associated with each question from the interview guide that directly related to the 10 pre-established topics that are listed in Table 2 and treatment process activities. Topic 11 noted in Table 2 encompasses other topics noted outside of the 10 pre-established topics from section 1. Due to the simplicity of the developed codes, it was not required for further categories to be established. The transcript content was coded accordingly, summarized data and meaningful quotes were entered into the framework matrices produced in Microsoft Excel, and the findings were interpreted. Member checking was done during the interview process to improve accuracy and validity of the results. Specifically, this was done by asking follow-up questions during the interviews or repeating back a participants' response to ensure clarity. For section 2 of the interview guide, email correspondence to some of the participants was conducted to obtain further details about their process.

To summarize, two matrices were produced for each of the three sites. No software was used to support analysis. The first matrix developed for each site included the 11 topics listed in Table 2. The second matrix consisted of process details extracted from interviews for each site for the purpose of developing process maps. Treatment process activities were ordered sequentially in the matrix using the thorough responses from each participant. The second matrix helped to clarify the sequence of activities at each site, as well as highlight site variation in the order of treatment process activities. The second matrix allowed for the sorting of the collected data and to highlight differences of the two pathways of focus: patients arriving by Emergency Medical Services (EMS) with pre-notification (for both regular and out of hours), as well as patients arriving by private vehicle (for both regular and out of hours). It was important to include the private vehicle pathway in addition to the EMS pathway as the beginning of the treatment processes differ. These two pathways were detailed graphically in a developed process map integrating both pathways for each site. Although EMS personnel were not included in the study, the pre-hospital pathway was felt to be effectively captured by interviewing healthcare professionals who closely interact with this portion of the care pathway. The pre-hospital pathway is critical to incorporate into site process maps as there are parallel activities that take place in-hospital during this period to prepare for the incoming AIS patient based on the information received from EMS personnel. Each process map produced in Microsoft Excel is considered a cross-functional workflow diagram, also referred to as a swim-lane diagram, as the diagram clearly sectioned the process activities into categories of people/departments who are responsible for sections of the process using grouping of activities and colour coding to illustrate the care pathways (46).

2.4 Results

There were 23 healthcare professionals recruited for the study. There were 8 participants from Site 1, and the roles included were: stroke coordinator, stroke neurologist, recent neurology resident graduate, current neurology resident, stroke nurse, ED nurse, and CT technologist. Site 2 included 9 participants, and Site 3 included 6 participants, each with the following roles involved in the interviews: stroke coordinator, ED physician, ED nurse, and CT technologist.

2.4.1 Section 1 Interview Topic Results

The results from the topics 1-6, and 8 listed in Table 2, are summarized for each site in Table 3. It is important to note that patient priority is defined using the Canadian Triage and Acuity Scale (CTAS), which is 5 level acuity scale. Patients receiving a CTAS level of 1 are deemed to be the most urgent patients, while a CTAS 5 indicates the least urgency. The following lists some of the key topics with summarized descriptions of the results from these topics.

Table 3: Topics 1-6, and 8 Summarized Results. AIS: Acute Ischemic Stroke, tPA: Tissue Plasminogen Activator, CTAS: Canadian Triage Acuity Scale.

Topic	Site 1 (Urban)	Site 2 (Rural)	Site 3 (Rural)
1. Comfort treating AIS patients (Low, Moderate, High)	High	High	Moderate
2. Perceptions about tPA (Hesitant, Neutral, Accepting)	Accepting	Neutral-Accepting	Hesitant-Accepting
3. Appropriate tPA treatment window (from onset of symptoms)	Ideally within 3 hours, up to 4.5 hours	Ideally within 3 hours, up to 4.5 hours	Ideally within 3 hours or earlier, up to 4.5 hours
4. AIS patient priority	CTAS 1, top priority	CTAS 2, urgent priority	CTAS 2, urgent priority
5. tPA availability	No issue	No issue	No issue
6. Patient consent	Given by patient or family member, but generally inferred consent.	Given by patient or family member. Discussion on tPA risk factors.	Given by patient or family member. Discussion on tPA risk factors, checklist completed.
8. Efficiency of their treatment process	Efficient, but not optimal. Inefficiencies remain between imaging and administration stage.	Efficient and streamlined. Some inefficiency remains in treatment decision stage.	Efficient. Inefficiencies remain between imaging and administration stage.

2.4.1.1 Comfort Treating AIS Patients and Perceptions About tPA

The healthcare professionals were generally comfortable treating AIS patients, noting how comfort can be fostered with higher treatment frequency, and that the time sensitive nature of the treatment is an obstacle. A recent graduate from the neurology residency program stated *"over the years, we get quite a bit of comfort with treating patients with tPA and seeing stroke patients."* (Site 1 Participant 2). A Site 3 ED physician noted that the infrequency of providing thrombolytic treatment results in *"not a good comfort"* (Site 3 Participant 2) with the treatment, noting some ED physicians at Site 3 will not provide thrombolysis treatment and will instead draw on expertise of local internists, while their colleague added the pressure that is felt to provide this care pathway with a lack of individual comfort. An Emergency Department (ED) physician from Site 2 noted that the largest challenges are *"the time pressure and the uncertainty of diagnosis"* (Site 2 Participant 9) that accompanies AIS patients, which was echoed by another ED physician at the site. A Site 3 ED physician added that there are many stroke mimics that could mislead a patient's diagnosis, which leads to the feeling of uncertainty. The necessity to administer tPA rapidly was acknowledged by all healthcare professionals, one ED nurse stating *"the faster the better"* (Site 1 Participant 6), while another noted *"time is of the essence"* (Site 2 Participant 6).

In regard to the medication itself, some reservations were noted regarding the evidence and subsequent risks. A neurology resident at Site 1 saw tPA as a *"powerful medication"* adding that *"most of the times the benefits greatly outweigh the risks of not giving the medication"* (Site 1 Participant 3), but there is still a possibility of poor outcomes for patients. Physicians and nurses acknowledged there is a risk involved with treating patients with tPA, noting patients can develop bleeds post-administration. A Site 3 ED nurse expressed they hope the patients will recover from their deficit and experience an improved quality of life after being treated with tPA, and *"that they don't have to suffer subsequent bad reactions"* (Site 3 Participant 5). A stroke neurologist labeled tPA as an imperfect medication with a shortcoming due to there being *"a fairly lengthy intravenous infusion required to give it"* (Site 1 Participant 4) after giving the bolus dose. There was significant discussion by the physicians around the strength of the evidence for tPA, and based on their interpretation of the evidence, their comfort with treating with tPA. ED physicians from Site 2 and Site 3 stated that the evidence surrounding the use of tPA was lacking or unclear, one stating that *"the evidence isn't super clear, but we still do it"* (Site 2 Participant 2). Although, another ED physician at Site 2 did recognize *"that the literature shows that it is an effective treatment"* (Site 2 Participant 3), and others from Site 2 recognized that there were improvements among patients who received the drug.

2.4.1.2 Appropriate tPA Treatment Window (From Onset of Symptoms)

The majority of the healthcare professionals recognized that AIS patients could be treated up until 4.5 hours from onset of symptoms, while generally it is preferred to treat within the first 3 hours. A Site 3 ED physician expressed concern about an acceptable treatment window, specifically noting the ECASS III trial and the 3-4.5 hour range, stating that *"if we look at ECASS III in particular, I mean, they excluded a very significant group of people that are often the populations that we see in terms of age, previous stroke, diabetes, all that kind of stuff. So you get a little bit more nervous as you're going out."* (Site 3 Participant 3). The ECASS III trial (47), which extended the tPA treatment window from 3 hours to 4.5 hours, excluded diabetic patients and those over 80 years of age. An ED physician from Site 2 also alluded to the trial, saying the 3 to 4.5 hour period can be trickier, but still defined the treatment window to be up until 4.5 hours. The same ED physician from Site 3 also noted concern about the timeline to treat patients with tPA safely, and referenced the NINDS trial while stating they feel the 0 to 90 minute period seems the safest, and continued to say they most often tend to give thrombolytic treatment to younger patients. In contrast, participants from Site 1 and 2 noted that if a patient had severe deficits and the treatment window had passed, the team would consider providing the medication should it be appropriate to that particular case.

2.4.1.3 Patient Consent

There are varying opinions regarding patient consent for thrombolysis treatment, but it is clear that any consent process slows down the treatment process. It was noted that some physicians may want to have a lengthier discussion, some prefer a checklist to complete, and others believe no consent is required. A Site 3 ED physician detailed that the importance resides in the consent conversation being conducted without tainting the patient's perspective. They further went on to state *"I always tell patients that sometimes there's no right answer, that sometimes the disease will decide, but this is a treatment that we can offer you at this stage."* (Site 3 Participant 3). Patients can understandably be distressed during the process, an ED physician from Site 2 describes *"they're scared and we are sometimes throwing statistical numbers at them"* (Site 2 Participant 9). If a patient is non-verbal or cognitively incapable to consent due to their current neurological deficit, a substitute decision-maker is included, which can be challenging to locate depending on the time of day. A stroke neurologist from Site 1 articulated the perspective of not requiring consent, stating that the patient is experiencing a neurological deficit "and it's an emergency situation, and so there is an argument that no consent is required." (Site 1

Participant 4). The stroke neurologist described that it is challenging to expect someone who is experiencing a traumatic event directly, the patient, or indirectly as substitute decision-maker, to make a sound decision in that moment.

2.4.1.4 Urban-Rural Treatment Differences

Topic 7 involved asking participants if they felt there is a gap in AIS treatment between urban and rural hospitals in Nova Scotia. As the rural participants experience the challenges of the disparity of AIS treatment in the province, their responses were of focus, although all 3 sites acknowledged the existing urban-rural treatment differences. The rural participants noted the 11 instances summarized in Table 4. In Table 4 "Yes" indicates the site noted the difference, while "No" indicates the difference was not noted by that site. These indicators illustrate each site's perspective on the topic by defining which urban-rural treatment differences are noticed by each site. The instances include topics such as lack of access to further EVT treatment, healthcare professional expertise, resource availability, and distance of patients to the nearest hospital.

Table 4: Topic 7 Summarized Results Noted by Rural Participants. EVT: Endovascular Thrombectomy, ED: Emergency Department, CT: Computed Tomography, tPA: Tissue Plasminogen Activator, EMS: Emergency Medical Services. "Yes" indicates the site noted the difference, while "No" indicates the difference was not noted by that site.

Urban-Rural Treatment Difference	Site 2 (Rural)	Site 3 (Rural)
1. Rural patients do not locally have access to further EVT treatment	Yes	Yes
2. Urban site has neurologists, and additionally specialized stroke neurologists	Yes	Yes
3. Urban site has specialized neuroradiologists, while rural sites have radiologists	Yes	No
4. ED physicians are making treatment decisions in rural sites • Different level of expertise and comfort	No	Yes
5. Urban site has more human resources involved in treatment process • Not possible to have dedicated stroke team in rural setting	Yes	Yes
6. Urban site treatment process is more streamlined	Yes	No
7. Rural patients often live further from hospitals, affecting treatment window	Yes	Yes
8. Not one single standard of care, care provided differently in tertiary sites compared to rural sites	Yes	No
9. Many rural sites do not have CT scanners	Yes	Yes
10. Rural sites often do not have bloodwork results before tPA administration	Yes	No
11. EMS availability is reduced in rural areas • EMS covering larger geographical area	Yes	Yes

An ED physician from Site 3 stated that there is a difference in the level of expertise and comfort due to the different volumes of strokes experienced at urban vs. rural sites. This sentiment leads to rural sites often consulting Neurology at Site 1, which rural participants noted could cause delay in the treatment process. However, Site 3 added that accessing a neurologist over the phone is generally quicker than consulting with Internal Medicine locally. There was also consensus that another factor was the amount of human resources available in the urban context, as well as the availability of EVT following thrombolysis, which is solely being offered at urban Site 1. Resources and equipment are a clear difference between the two settings. Both rural sites acknowledged that there is a difference due to the availability of CT scanners, as many community sites lack this equipment, which is critical to providing thrombolytic treatment. The two sites continued to discuss that EMS availability, the pre-hospital transport piece, is much more of a factor for their hospitals. They noted that EMS covers larger geographical areas in their settings, and thus cannot always respond to AIS patients as quickly as they would desire. Participants highlighted the severity of this challenge further as they discussed that rural patients often live further from hospitals, which further decreases the treatment window.

2.4.1.5 Treatment Delays at Their Site (Patient-Related and System)

Topic 9, treatment delays at each site, is categorized into 2 areas: patient-related delays, and system delays. As predicted, patient-related delays are delays that directly affect the patient. System delays are system factors associated with AIS tPA treatment, some directly affecting the patient and others affecting the process. Each site was asked to note the delays they felt were experienced at their respective site. The 11 patient-related and 29 system treatment delays noted by participants are shown in Table 5, and Table 6, respectively. In Table 5 and Table 6 and "Yes" indicates the site noted they experienced that delay at their hospital, while "No" indicates the specified delay was not noted by that site. Once again, these indicators illustrate each site's perspective on the topic by stating which treatment delays are noticed by each site. It is clear that each site experiences more system treatment delays compared to patient-related delays. System treatment delays can be reduced with appropriate planning to minimize their impact on the care pathway. While patient-related treatment delays cannot be completely avoided, anticipating what delays could be encountered in this regard could also allow for this delay type to be minimized.

Table 5: Topic 9 (Patient-Related) Summarized Results Noted by Participants. IV: Intravenous, INR: International Normalized Ratio, CT: Computed Tomography. "Yes" indicates the site noted they experienced that patient-related delay at their hospital, while "No" indicates the specified delay was not noted by that site.

Patient-Related Treatment Delay	Site 1 (Urban)	Site 2 (Rural)	Site 3 (Rural)
1. Hypertension	Yes	Yes	Yes
2. Unclear time of onset	Yes	Yes	Yes
3. Patient is aphasic (obtaining consent)	Yes	Yes	Yes
4. Getting IV access (due to obesity or age of patient)	Yes	No	No
5. Patient requiring reversal of anticoagulation	Yes	Yes	No
6. Difficulty positioning patient in CT scanner	Yes	Yes	Yes
7. Patient is unstable	No	Yes	No
8. Fluctuating symptoms	No	Yes	Yes
9. Unclear story	No	No	Yes
10. Patient has comorbidities	No	No	Yes
11. Patient has another emergent medical condition	No	No	Yes

Table 6: Topic 9 (System) Summarized Results Noted by Participants. INR: International Normalized Ratio, ED: Emergency Department, IV: Intravenous, CT: Computed Tomography, EMS: Emergency Medical Services, NG: Nasogastric, tPA: Tissue Plasminogen Activator, CTA: Computed Tomography Angiography. "Yes" indicates the site noted they experienced that system delay at their hospital, while "No" indicates the specified delay was not noted by that site.

System Treatment Delay	Site 1 (Urban)	Site 2 (Rural)	Site 3 (Rural)
1. Treatment decision delay • Neurologist is slower to decide than stroke neurologist (Site 1) • Waiting for neurologist/stroke neurologist to arrive out of hours (Site 1)	Yes	Yes	Yes
2. Treatment decision consultation delay	No	Yes	Yes
3. Obtaining lab results	Yes	Yes	No
4. INR point-of-care machine does not always work	Yes	N/A	N/A
5. Inadequate staffing in ED	Yes	No	No
6. Getting IV access	Yes	Yes	No
7. Stroke recognition/diagnosis	Yes	Yes	Yes
8. Patient registration • Patient registration out of hours (Site 3)	Yes	No	Yes
9. Encountered occupied CT scanner	Yes	Yes	No
10. CT scanner not ready when patient arrived at imaging	Yes	No	No
11. Pre-hospital EMS transport delay	Yes	No	Yes

System Treatment Delay	Site 1 (Urban)	Site 2 (Rural)	Site 3 (Rural)
12. Other pre-hospital transport delays • Patient transfers from community hospitals (Site 2) • Patient transport into ED from private vehicle - ED staff not allowed to help bring patient into ED (Site 3)	No	Yes	Yes
13. Neurology initial assessment delay, assessment taking too long	Yes	N/A	N/A
14. Bloodwork collection before taking patient to scanner	Yes	No	No
15. Inadequate communication among healthcare professionals • No communication of patient's arrival at the ED (Site 1) • Not all information communicated through EMS patch (Site 2) • Miscommunication between radiologist and ED physician regarding which scans are being completed (Site 3) • No communication to imaging department of incoming AIS patient (Site 3)	Yes	Yes	Yes
16. Getting CT Report	No	Yes	No
17. Obtaining INR result	No	Yes	Yes
18. Getting patient history (none available)	No	Yes	No
19. Physical layout of hospital	No	Yes	No
20. Locating patient's next of kin	No	Yes	No
21. Inserting NG tube and Foley catheter before tPA administration	No	No	Yes
22. Determining patient's weight	No	No	Yes
23. Imaging delay due to lack of clarity regarding which patients require CTA scan completed	No	No	Yes
24. Interface with Radiology	No	No	Yes
25. Bloodwork collection out of hours	No	No	Yes
26. CT technologist having to travel to site out of hours	No	No	Yes
27. Radiologist reviewing images (if slow internet)	No	No	Yes
28. Receiving interpretation from radiologist	No	No	Yes
29. Challenge accessing visiting patient database	No	No	Yes

2.4.1.6 Suggested Process Improvements at Their Site

Topic 10 involved asking participants to state their thrombolysis process improvement suggestions for their site. The possible improvements noted by participants have been divided into pre-hospital and hospital-based suggestions shown in Table 7. The pre-hospital suggestions focus on EMS improvements such as method of communication and the information being conveyed, preparing the patient with two IVs, instructing the patient's next of kin, triage, and availability. The hospital-based suggestions focus on improvements in areas such as human and capital resources, the location for tPA administration, the sequence of activities in the care pathway, protocol adjustments, communication among healthcare professionals, and increasing continuing education.

Table 7: Topic 10 Summarized Results Noted by Participants. EMS: Emergency Medical Services, IV: Intravenous, ED: Emergency Department, tPA: Tissue Plasminogen Activator, CT: Computed Tomography, INR: International Normalized Ratio, NG: Nasogastric, CTA: Computed Tomography Angiography.

	Suggested Improvements
	Pre-hospital
Site 1 (Urban)	• More direct information from paramedics (patient identity, clarity of problem, when possible more lead-time) • Modern secure telecom/video streaming systems for transmission of information of paramedic's assessment • EMS to put in two IVs before arriving to ED
Site 2 (Rural)	• EMS to automatically communicate patient identifiers • EMS getting patient's next of kin information and instructing them to go directly to hospital (or being easily accessible via their phone)
Site 3 (Rural)	• EMS triage • EMS availability
	Hospital-based

Site 1 (Urban)	• Stroke nurse available at all times (tPA administered in CT department)
	    o Alternatively, have an ED nurse travel with patient to imaging (tPA administered in CT department)
	        ▪ tPA stored within CT department in locked drug cupboard
	• Use INR point-of-care machine prior to imaging
	• Wait to collect blood sample until after imaging

Site 2 (Rural)	• Obtain INR point-of-care machine • Have patient's medication list automatically printed out (currently done by ED physician) • Bloodwork collected and 2nd IV put in on EMS stretcher before imaging • Obtain 2nd CT scanner • Improve communication among healthcare professionals • Increase emphasis on continuing education
Site 3 (Rural)	• Mix tPA and have treatment discussion while patient in scanner • Remove NG tube and Foley catheter requirement before tPA administration • Registration clerk and CT technologist in-hospital at all times • Clarification on which patients require CTA scan • Increase education piece to improve ED physician comfort with giving tPA

2.4.1.7 Other Topics

The analysis also allowed for data to be collected for other topics that do not fall under the 10 pre-established topics in section 1 of the interview guide, or the treatment process details in section 2, which has been defined as Topic 11, as shown in Table 2. The other topics noted are the following: human resource limitations, following protocols, quality of medical documentation and data collection obstacles, treatment speed phenomenon based on patient arrival time within the treatment window, opposing opinions towards thrombolysis between neurology and ED physicians, ability to determine efficacy of thrombolysis treatment in the ED, risks of patients traveling with lights and sirens with EMS on rural roads when unnecessary, and benefits of prioritizing stroke in the ED.

2.4.2 Section 2 Treatment Process Results

The results from section 2 of the interview guide were used to develop detailed process maps. A process map illustrating both the EMS and private vehicle pathways was developed including regular and out of hours for each site. The process maps developed for Site 1, Site 2, and Site 3 are shown in Figure 1, Figure 2, and Figure 3, respectively. Activity durations are shown in bold within the process maps, while resources associated with certain activities are shown in brackets. Activities shown in green are unique to the EMS pathway, activities shown in yellow reference the private vehicle pathway, and blue activities show activities occurring in both pathways. The main healthcare professionals involved at each site are shown in Table 8. It is clear that there are more healthcare professionals involved at the urban site when compared to the rural sites. It is important to note that the EMS and arrival by private vehicle treatment pathways are identical once the patient is at imaging.

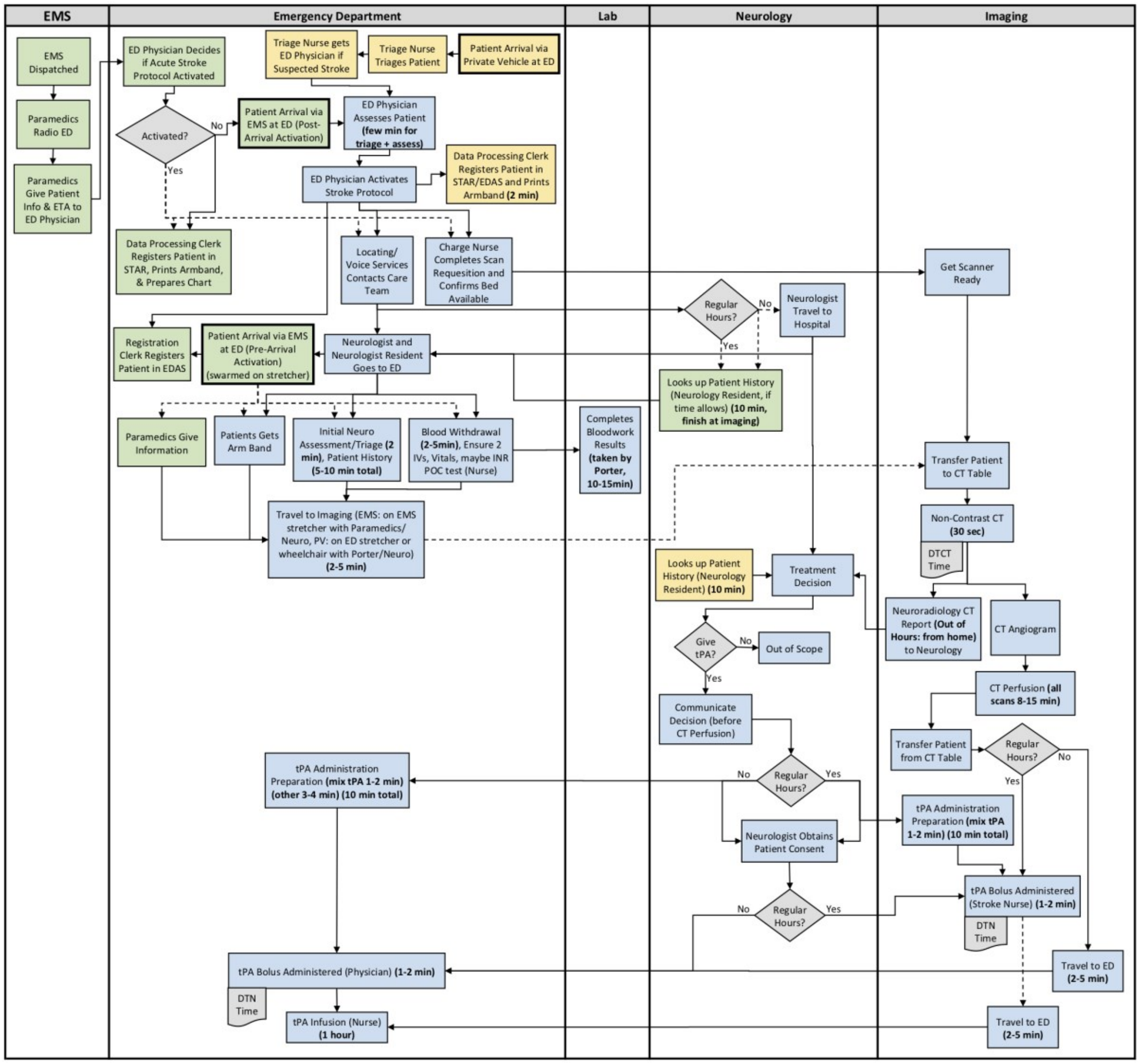

Figure 1: Site 1 (Urban) All Care Pathways Regular & Out of Hours Process Map. EMS: Emergency Medical Services, PV: Private Vehicle, ED: Emergency Department, CT: Computed Tomography, DTN: Door-to-Needle, DTCT: Door-to-CT, tPA: Tissue Plasminogen Activator. (Green: EMS Pathway Specific, Yellow: Private Vehicle Pathway Specific, Blue: Both Pathways).

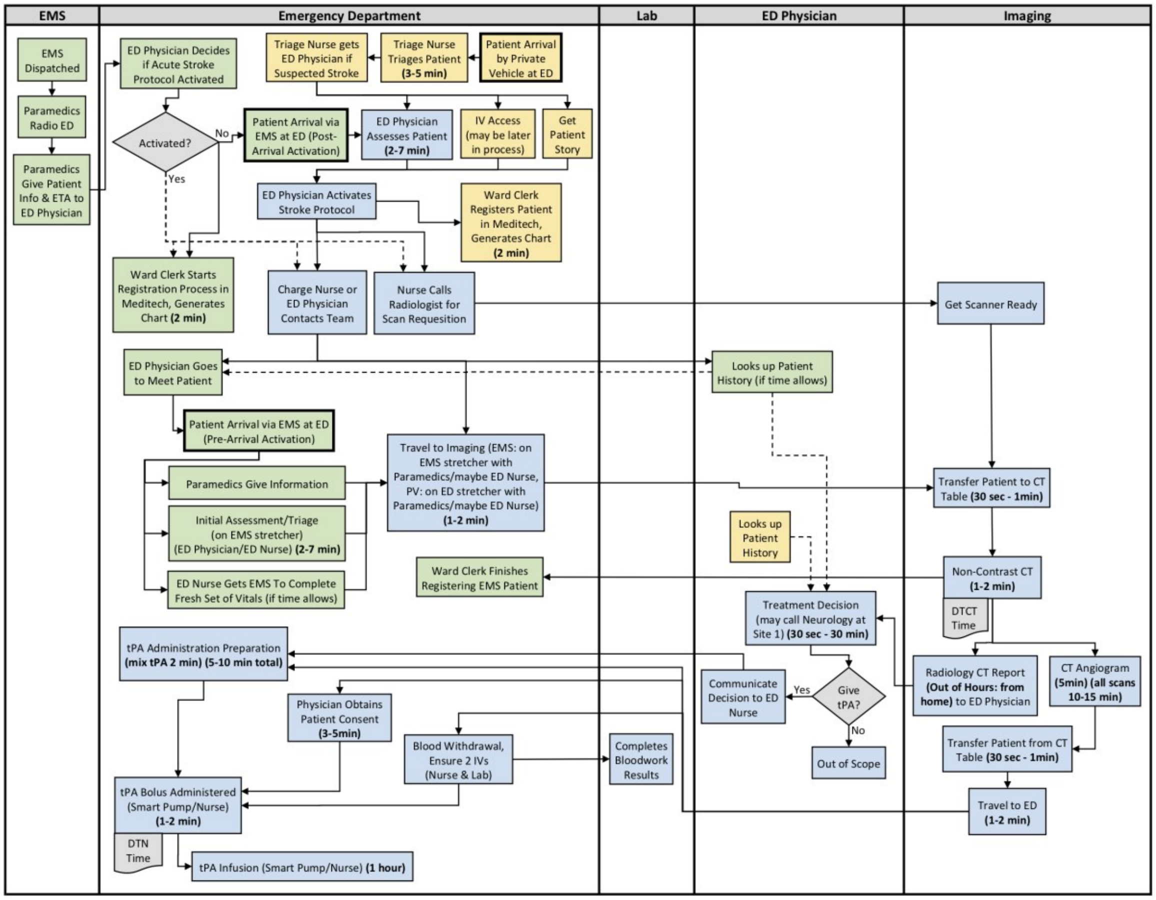

Figure 2: Site 2 (Rural) All Care Pathways Regular & Out of Hours Process Map. EMS: Emergency Medical Services, PV: Private Vehicle, ED: Emergency Department, CT: Computed Tomography, DTN: Door-to-Needle, DTCT: Door-to-CT, tPA: Tissue Plasminogen Activator. (Green: EMS Pathway Specific, Yellow: Private Vehicle Pathway Specific, Blue: Both Pathways).

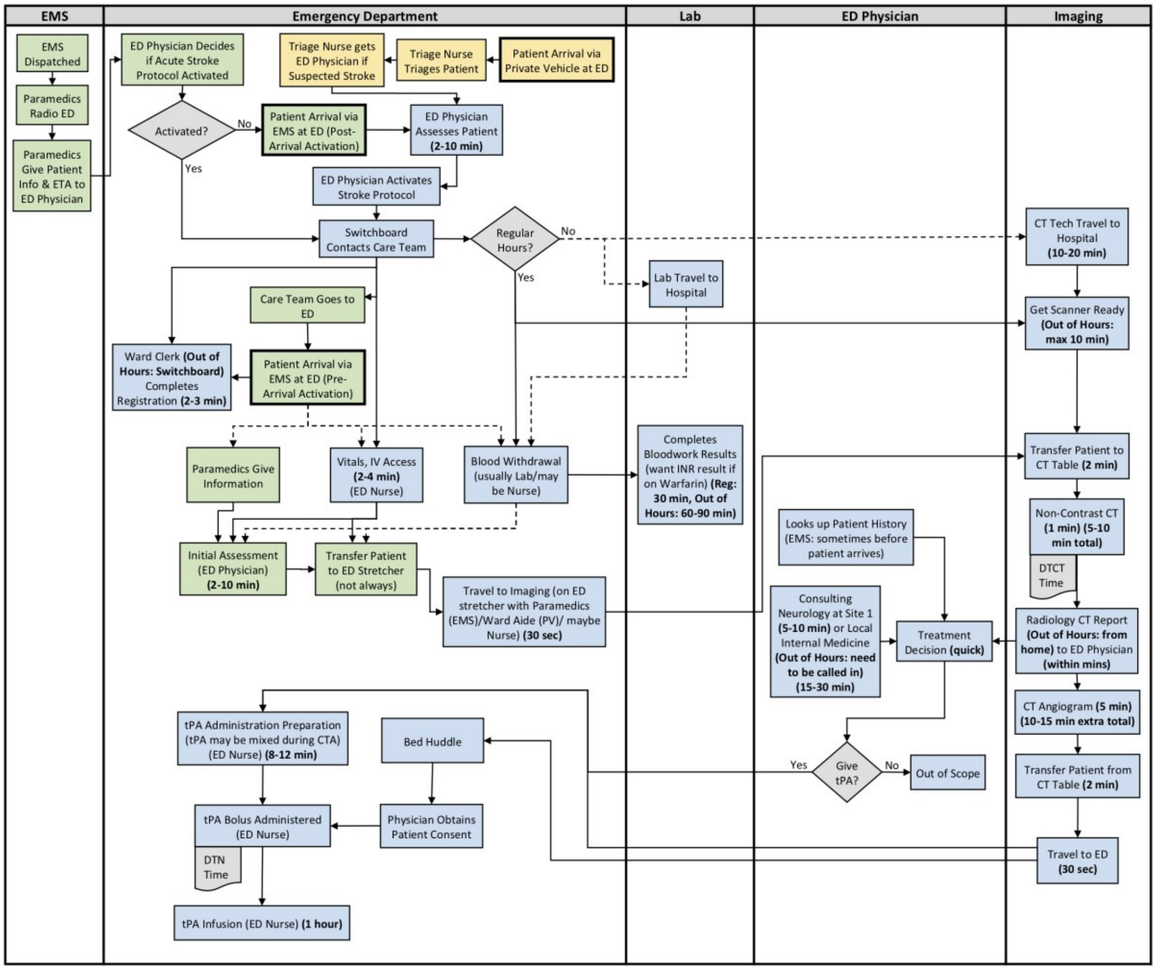

Figure 3: Site 3 (Rural) All Care Pathways Regular & Out of Hours Process Map. EMS: Emergency Medical Services, PV: Private Vehicle, ED: Emergency Department, CT: Computed Tomography, DTN: Door-to-Needle, DTCT: Door-to-CT, tPA: Tissue Plasminogen Activator. (Green: EMS Pathway Specific, Yellow: Private Vehicle Pathway Specific, Blue: Both Pathways).

Table 8: Main Healthcare Professionals Involved during Regular or Out of Hours. EMS: Emergency Medical Services, ED: Emergency Department, CT: Computed Tomography.

Site	Main Healthcare Professionals Involved during Regular or Out of Hours
Site 1 (Urban)	Paramedics (via EMS), triage nurse (arrival via private vehicle), data processing clerk, ED nurses, acute stroke nurse, ED physician, neurology residents, staff neurologist, CT technologist, and neuroradiologist.
Site 2 (Rural)	Paramedics (via EMS), triage nurse (arrival via private vehicle), ward clerk, ED nurses, ED physician, CT technologist, and radiologist.
Site 3 (Rural)	Paramedics (via EMS), triage nurse (arrival via private vehicle), ward clerk, ED nurses, ED physician, CT technologist, and radiologist.

The major treatment process steps that are included at all of the sites are the following. Note that each hospital has a code stroke protocol, but the sequence of the activities and the healthcare professional responsible for the activities may differ at each hospital: 1) potential stroke (Cincinnati stroke screen positive from EMS); 2) patient registration; 3) getting IV access (thrombolysis requires 2 IVs); 4) bloodwork (drawing a bloodwork sample before administering tPA); 5) physician assessment (stroke diagnosis, determination of type of stroke syndrome, stroke severity, and eligibility for thrombolysis treatment); 6) imaging; 7) tPA bolus administration (initial 10% of medication the patient will receive); and 8) tPA infusion administration (remaining 90% of medication). Note that imaging at all sites includes a non-contrast CT head to spot a hemorrhage and assess ischemic changes (48), which is critical in determining tPA eligibility, as well as a CT Angiography (CTA) of the head and neck to assess collaterals and determines their eligibility for further EVT treatment (49). Site 1 additionally completes a CT Perfusion that measures cerebral blood flow, blood volume and mean transit time.

Resource differences to note during out of hours are the following:
All Sites: Radiologist (neuroradiologist at Site 1) views and interprets the images from home and communicates with the physician.
Site 1: Stroke nurse unavailable on weekends and after 5pm, Monday to Friday (Site 1 currently trying to secure this position to be available at all times). Out of hours, tPA is

administered back in the ED, as opposed to in the CT department outside of the scanning area with the stroke nurse.

Site 3: Monday to Friday, CT technologist only scheduled for approximately 50% of 4pm to 12am shifts. On weekends, CT technologist only scheduled for approximately 50% of 8am to 4pm, and 4pm to 12am shifts. There is no CT technologist in-hospital from 12am to 8am on any day, or ward clerk from 11pm to 7am. Generally, must call in Lab staff and Internal Medicine out of hours.

Site process details that may have contributed to differential DTN times are described in Table 9, with many illustrated in the developed process maps in Figure 1, Figure 2, and Figure 3. The differences among sites include: protocol clarity, use of parallel processing and order of activities, transport and distance to imaging, CT technologist availability, and treatment decision consultation.

Table 9: Site Process Details That May Have Contributed to Differential Door-to-Needle Times. INR: International Normalized Ratio, EMS: Emergency Medical Services, ED: Emergency Department CT: Computed Tomography, tPA: Tissue Plasminogen Activator.

Process Detail	Site 1 (Urban)	Site 2 (Rural)	Site 3 (Rural)
Protocol clarity	Well-known by healthcare professionals.	Well-known by healthcare professionals.	Majority of protocols well-known, imaging protocol requires clarification. Some physician variability in process.
Patient arrival	Nurses and physicians working in parallel.	Nurses and physicians working in parallel.	Nurses and physician working sequentially.
Bloodwork	Collected before imaging. Have INR point-of-care machine.	Collected after imaging.	Collected before imaging.
Transport to imaging	Remains on EMS stretcher.	Remains on EMS stretcher.	Often transferred to ED stretcher.
Distance between ED and imaging	Approx. 2-5 minutes	Approx. 1-2 minutes	Approx. 30 seconds
CT technologist availability	Always available.	Always available.	Available during regular hours, some evenings/weekend shifts. May need to travel to hospital.
Treatment decision consultation	Not required.	May want consultation from Site 1, physician dependent.	Wanting consultation from local internist or Site 1.
When tPA is being mixed	In parallel with patient in imaging.	In parallel with patient in imaging.	Generally after imaging, sometimes in parallel with imaging, physician dependent.
tPA administration location	Outside of imaging area in regular hours with stroke nurse, in ED out of hours.	ED	ED

2.5 Discussion

This qualitative study has highlighted that although the thrombolysis process in urban and rural settings have many processes in common, there are process differences as well as differences in how thrombolysis of AIS patients is viewed in these settings. The main differences stem from healthcare professionals' expertise, resource availability, and frequency of treating AIS patients. In a rural setting, an emergency physician rather than a neurologist is making the decision to treat AIS patients with tPA, which presents some disparity in how AIS patients are treated in these rural settings. Additionally, this study shows that access to rapid imaging interpretation from radiology is also a barrier. This urban-rural disparity in stroke treatment is consistent with previous quantitative studies that showed that rural AIS patients are less likely to receive thrombolysis (50) and have longer DTN times (17) than their urban counterparts. This disparity is apparent despite the use of tPA in AIS patients being reported as successful in rural settings, or in areas where access to a neurologist and imaging expertise is limited (51).

This study showed that while some Nova Scotian ED physicians felt confident in treating patients with tPA, some rural ED physicians had reservations about tPA, they indicated that the evidence was lacking leading to discomfort with treating AIS patients. This sentiment was echoed in a study conducted in 2010 in Michigan measuring the attitudes and beliefs of ED physicians, as only 49% of ED physicians surveyed indicated that science regarding the use of tPA in stroke is convincing (52). Another area that has different views among physicians is informed consent for thrombolysis, which can delay treatment, which is consistent with other studies (53,54). However, better more streamlined communication when obtaining consent for thrombolysis can improve treatment times (54).

These results highlighted that the infrequency of treating AIS patients with tPA at rural hospitals is another factor contributing to longer DTN times. The rural sites noted that it is not uncommon to treat only 5 to 10 AIS patients annually with tPA, which can lead to lower confidence and comfort with providing the treatment, as well as less familiarity with the care pathway, which can lead to longer DTN times. Providing emergency physicians with support in treatment decision from a neurologist can assist with this deficiency. The desire for decision support for tPA was also found in the Michigan study mentioned above, as 65% of ED physicians surveyed indicated they would be uncomfortable using tPA without a consultation, but assuming the ideal setting for tPA use existed, 83% of physicians would use tPA to treat AIS patients (52). A centralized telestroke system is one proven method to provide decision support that helps to alleviate the disparity that is apparent in rural hospitals (55–57). Telestroke can also provide support in timely interpretation of imaging to overcome lack of resource availability, such as radiology, which is faced by rural hospitals.

The development of the process maps showed that there are some differences in the thrombolysis process between urban and rural hospitals. The process maps highlight some of the resource challenges at small rural hospitals where diagnostic imaging and laboratory technologist must travel to the hospital during non-business hours. However, there are some efficiencies as well, there are more professionals involved in the urban hospital, which results in more steps prior to the patient being transferred to the CT scanner. Similarly, the time travel to the scanner is often shorter at rural hospitals, and it can be easier to obtain the necessary drugs. These process maps show that through further improvements at rural hospitals, shorter DTN times are possible. This includes pre-notifying the imaging technologists of an incoming code stroke patient when the paramedics provide pre-notification, which would allow the CT technologist enough time to travel to the hospital and prepare for the patient's arrival. These improvements would help to reduce system delays (16), while telestroke or other decision support processes can help to increase comfort with the use of tPA on AIS patients.

2.5.1 Limitations and Future Direction of Research

A limitation of the study is only 3 hospitals were studied in a single Canadian province. However, the challenges described above, such as lack of comfort with tPA treatment and lack of resources is not unique, as similar challenges have been found in other jurisdictions (52–54). Another study limitation is the small sample size of participants involved at each site, and that only 2 rural sites were included. Due to the number of participants, only preliminary conclusions can be drawn as there were not a sufficient number of participants to remove individual biases. Additionally, not all professionals that are part of the treatment process were involved in the interview process at each site; the current study primarily excludes paramedics and radiologists. There were 2 rural sites in the study that were felt to represent the province adequately, but for further accuracy regarding the urban-rural treatment differences additional rural hospitals should be considered. Furthermore, this study was limited to thrombolysis, and endovascular treatment (EVT) was not included. We recognize that rural hospitals face additional challenges in arranging transfer of patients for EVT, which deserves further study.

Study next steps include the development of a discrete-event computer simulation model using the process maps that were developed. The purpose of the simulation is to be able to run scenarios for various changes, which will quantify the impact of changes through a modelled reduction in DTN times. Examples of process changes to be included in the simulation include: always administering tPA outside of the imaging area (20,58–60), obtaining the patient's blood sample in parallel with other arrival activities before going to imaging, transporting the patient on the EMS stretcher to imaging (20,21,58,59,61), pre-notifying imaging technologists of an arriving stroke, and further use of parallel processing (59). Simulation modeling was determined to be the most applicable tool for the study as it lends well to the overall goals in terms of assessing and modifying treatment paths. Simulation-based approaches are effective in assessing solutions in the stroke pathway (29), and can successfully be used as a decision-making tool before committing real resources (22).

2.6 Conclusion

This qualitative study with clinicians involved in the tPA treatment of AIS patients at efficient and inefficient rural hospitals and at an urban hospital revealed the disparities between urban-rural hospitals in the treatment of AIS patients with tPA. Some of the key disparities between urban-rural hospitals are rooted in emergency physician's being the treating physician at rural hospitals, as many are not comfortable with treating with tPA and often treat infrequently. Additionally, the developed process maps visually highlighted streamlined portions of the treatment pathway for each site, as well as inefficiencies to be addressed. The majority of treatment delays encountered are system delays, which can be appropriately planned for in order to reduce delays within the care pathway. There is a general consensus of an urban-rural treatment gap for AIS patients in Nova Scotia, and that continuing education is key to improving ED physician comfort in regard to the evidence surrounding tPA and the thrombolysis treatment decision when treating patients with tPA in rural hospitals. Thrombolysis service alternatives, such as telestroke, could help in reducing the urban-rural treatment gap and improve ED physician comfort with treating with tPA. Study next steps include the development of a discrete-event computer simulation model to quantify the impact of these suggested changes to the current processes.

2.7 Data Availability Statement

Access to the source data can be made available by contacting the authors. We will ensure that we maintain the privacy of the individuals involved and ensure our ethics approval is fully adhered to. Qualitative studies have the potential to re-identify individuals, especially in small centres where the number of individuals involved in the treatment of acute ischemic stroke patients is small.

2.8 Ethics Statement

The studies involving human participants were reviewed and approved by the Nova Scotia Health Research Ethics Board. The participants provided their written informed consent to participate in this study.

2.9 Author Contributions

TB: study design, data collection, data analysis, preparation of figures and tables, preparation of the first and revised drafts of the manuscript, as well as final editing and formatting. NK: study design, and editing, formatting and revision of manuscript for intellectual content. DV: input into study design, revision of manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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2.12 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2.13 Supplementary Materials

The supplementary materials for this article can be found online at or in Appendix B: https://www.frontiersin.org/articles/10.3389/fneur.2021.645228/full#supplementary-material

Chapter 3: Study 2 - Discrete-Event Simulation to Model the Thrombolysis Process for Acute Ischemic Stroke Patients at Urban and Rural Hospitals

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Student Contribution: Tessa Bulmer completed all aspects of this study and manuscript preparation including the following: study design, discrete-event simulation modelling, data analysis, preparation of figures and tables, preparation of the first and revised drafts of the manuscript, as well as final editing and formatting.

3.1 Abstract

Background: Effective treatment with tissue plasminogen activator (tPA) critically relies on rapid treatment. The door-to-needle time (DNT) is a key measure of hospital efficiency linked to patient outcomes. Numerous changes can reduce DNT, but they are time-consuming to trial and implement. Thus, discrete-event simulation (DES) provides a way to model and determine the impact of process changes.

Methods: A conceptual framework was developed to illustrate the thrombolysis process; it allowed for treatment processes to be replicated using a DES model developed in ARENA. Activity time duration distributions from three sites (one urban and two rural) were used. Five scenarios, three process changes, and two reductions in activity durations were simulated and tested. Scenarios were tested individually and in combinations. The primary outcome measure is median DNT. The project goal is to determine the largest improvement in DNT at each site.

Results: Administration of tPA in the imaging area resulted in the largest DNT reduction for Site 1 and Site 2 for individual test scenarios (12.6%, 95% CI 12.4-12.8%, and 8.2%, 95% CI 7.5-9.0% respectively). Ensuring that patients arriving via Emergency Medical Services (EMS) remain on the EMS stretcher to imaging resulted in the largest DNT improvement for Site 3 (9.2%, 95% CI 7.9-10.5%). Reducing both the treatment decision time and tPA preparation time by 35% resulted in a 11.0% (95% CI 10.0-12.0%) maximum reduction in DNT. The lowest DNTs were achieved by combining all three process changes and reduction in two activity durations, which resulted in a maximum reduction of 26.7% (95% CI 24.5-28.9%).

Conclusion: The detailed conceptual framework clarifies the intra-hospital logistics of the thrombolysis process. DES is an effective method to assess the impact of changes on DNT. Significant DNT improvements can be achieved in urban and rural settings by combining process changes with reducing activity durations.

Keywords: acute ischemic stroke (AIS), door-to-needle time (DNT), tissue plasminogen activator (tPA), thrombolysis, stroke pathways, discrete-event simulation (DES), urban, rural

3.2 Introduction

Stroke is a devastating disease, but is treatable with alteplase or tissue plasminogen activator (tPA) (1) and endovascular thrombectomy (EVT) (2–6). tPA has been a proven treatment for Acute Ischemic Stroke (AIS) since 1995 (1), and is widely available in urban and rural hospitals. A person having a stroke loses approximately 1.9 million neurons every minute (9), leading to the popular motto "time is brain". AIS patients should be treated with tPA as rapidly as possible for maximal benefit (12,14), as the effectiveness is highly time dependent (13). Door-to-needle time (DNT) is a critical measure of hospital efficiency linked to patient outcomes and is defined as the time from a patient's hospital arrival to the start of tPA treatment. Fast treatment with tPA has been reported in many urban hospitals, but rural hospitals struggle to reduce treatment times (17,18). A recent study analyzing the thrombolysis process for AIS in urban and rural hospitals highlighted that physician comfort, resource availability, and frequency of treating AIS patients were factors that lead to an inequality in treating patients quickly in rural settings (37). There are key resource differences between urban and rural centres. For instance, rural sites may only have Computed Tomography (CT) technologists on-call during out of hours, and Emergency Department (ED) physicians are making the treatment decision, instead of neurologists (37).

Several process changes can reduce DNT (18,20), but these changes are time-consuming to trial and implement and could disturb established care pathways. Discrete-event simulation (DES) provides a safe and efficient way to model processes and determine the impact of process changes. Operations research techniques, such as simulation, have become a common analytical problem-solving method used in healthcare. Simulation has been amply used to address challenges in Emergency Department (ED) patient flow optimization (62). Further, simulation allows complex healthcare systems with stochastic elements, such as stroke pathways, to be replicated to provide insights and recommendations for improvements. DES has been shown to be an effective approach applied to pre-hospital (22,23), intra-hospital (24–27), and both pre and intra-hospital aspects of the acute stroke pathways (28–35). DES literature also spans to areas such as operation of a stroke unit (63), the impact of additional comprehensive stroke centres for EVT (64), and AIS patient disability post-hospital (65). Outcome measures among DES studies include: resource optimization (27), thrombolysis eligibility (22), utilization rate of thrombolysis or intra-arterial thrombectomy (28,29,33,34), and patient outcomes (28,29,34,65), amongst others. Improving thrombolysis rates and patient outcomes were the most common aims of the DES studies for acute stroke care found in the literature.

Several studies have illustrated the key activities involved in either the pre-hospital or intra-hospital aspects of acute stroke care (22,29,30,33–36). These studies include overviews of intra-hospital thrombolysis steps and also identify different pathway types but lack detail regarding intra-hospital activities and sequences. Additionally, process differences based on pathway type or out of hour resource differences are not well-defined in the literature. We address these gaps by developing a conceptual framework of the intra-hospital aspect of the thrombolysis treatment process by analyzing three urban and rural sites. The framework defines intra-hospital treatment processes, based on patient pathway type, shows resource availability differences in out of hour operations, provides further detail of process activities and sequences, and highlights when potential delays may be encountered. It is important to fill these gaps so to provide clarity of intra-hospital logistics, which will lead to solutions to reduce DNT. The study objectives are: 1) to provide a detailed conceptual framework of the thrombolysis process, focusing on intra-hospital activities; and 2) to assess the potential impact of process improvements that can result in faster DNTs when applied to urban and rural settings using a DES model.

3.3 Methods

A conceptual framework was developed first to provide a generalized model for tasks involved in the thrombolysis process within both urban and rural hospitals. This conceptual model was then used to develop a DES model that can be used for both urban and rural hospitals, based on various inputs. This paper includes descriptions of the conceptual framework, the DES model, as well as the test scenarios applied to the three included sites. The authors declare that all supporting data are available within the article and its supplementary materials.

3.3.1 Development of Conceptual Framework

A qualitative study was conducted in Nova Scotia, Canada, to understand the thrombolysis treatment process in urban and rural hospitals. This study provided the foundation for the current research; the full details of this study are published elsewhere (37). There was one urban and two rural sites chosen to enable comparisons between urban and rural hospitals. The respective site distinctions, local target median DNTs, and current median DNTs are detailed in the published qualitative study in the *Site Context* section (37). The results from that study provided the necessary pathway specifics to create a detailed process map for each site (37), and estimations of activity durations. These process maps were used in this study to develop a conceptual framework of the thrombolysis process in urban and rural hospitals and the DES.

The conceptual framework shows the intra-hospital aspects of the thrombolysis process divided into four panels as shown in Figure 4: (A) hospital activities prior to patient arrival; (B) arrival activities; (C) imaging and treatment decision activities; and (D) treatment activities. Figure 4.A illustrates the intra-hospital activities that take place during the pre-hospital stage, while the remaining panels represent the hospital-based stage of the treatment process. The framework considers two patient treatment pathways: patients arriving via Emergency Medical Services (EMS), where the stroke protocol has been activated at the hospital prior to the patient's arrival, and patients arriving via private vehicle (PV). Figure 4.A and Figure 4.B display activities in terms of treatment pathways, as the logistics for this portion of the process are pathway dependent. Figure 4.A illustrates efficiencies of the EMS treatment pathway, as several activities can begin in-hospital prior to the patient's arrival. Figure 4.B shows the evident difference in activities required to be completed upon arrival between the EMS and PV pathways. When patients enter Figure 4.C of the treatment process, imaging and treatment decision activities, the process is identical for both patients arriving via EMS and PV. Activities shown in grey in Figure 4 signify the activity may differ by site regarding how and when the activity is executed, as the healthcare professionals responsible for completing the activities may differ. Activities shown in red in Figure 4 signify a potential delay in the treatment process. While patient-related delays cannot be entirely avoided, they can be minimized with appropriate anticipation and preparation. However, system delays (i.e. delays not specifically related to the patient) can, and should, be eliminated to achieve more streamlined treatment.

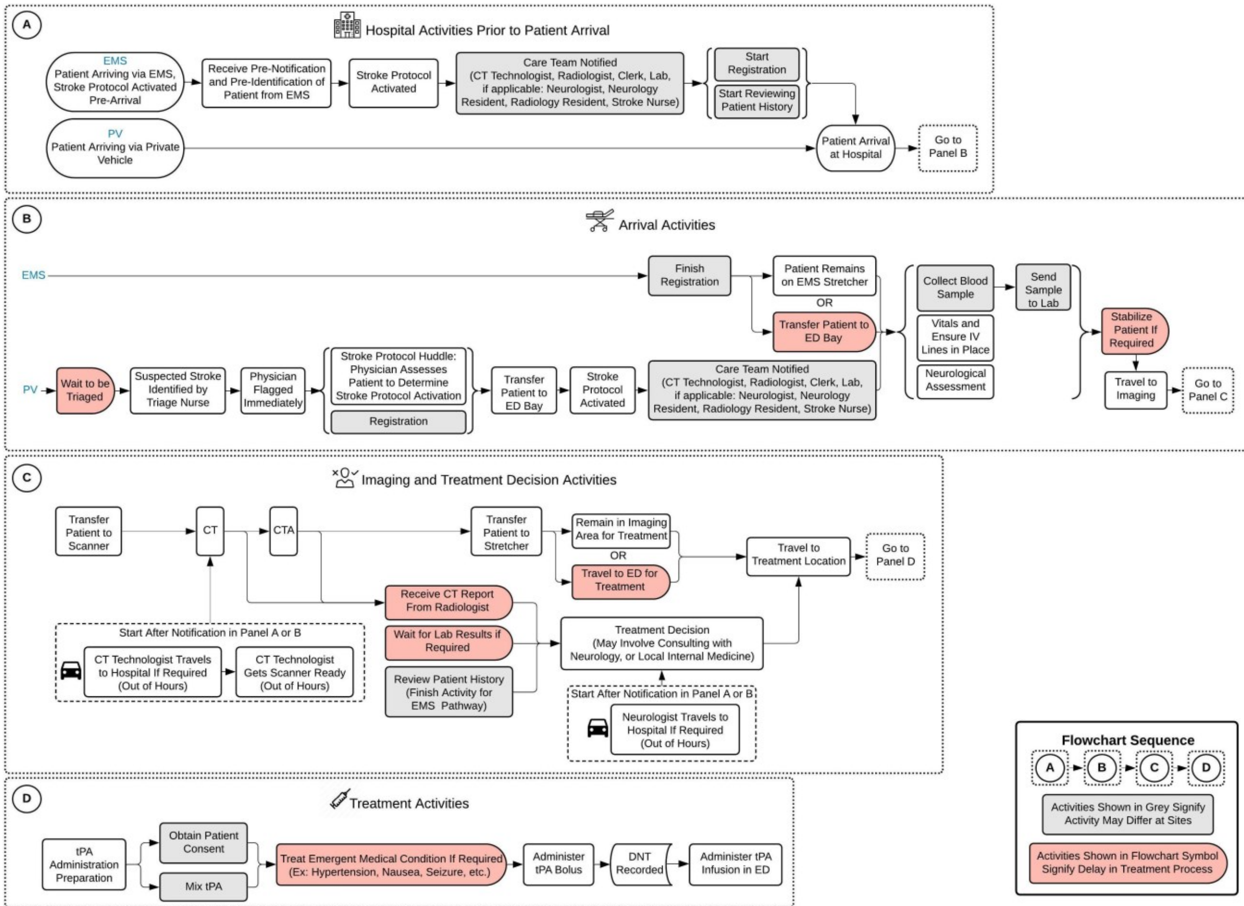

Figure 4: Conceptual Framework of Model. EMS: Emergency Medical Services, PV: Private Vehicle, CT: Computer Tomography, ED: Emergency Department, IV: Intravenous, CTA: Computed Tomography Angiography, tPA: Tissue Plasminogen Activator, DNT: Door-to-Needle Time.

3.3.2 Simulation Model

A DES model was developed to provide a representation of the intra-hospital aspect of the thrombolysis process for urban and rural hospitals. The simulation model was developed using ARENA software (Rockwell Automation, Milwaukee, WI, version 16.00.00003) based on the conceptual framework shown in Figure 4 and the previously developed process maps (37), and applied to the three sites to verify the model and provide context for the test scenarios. The model was verified using techniques detailed in Supplementary Materials (Table 15, Table 16, Table 17) using Site 1 data, with arrival rate and pathway type verification results shown in Table 10. Additionally, all model activity duration distributions (Table 13), arrival rates (Table 14), sensitivity analysis results (Table 18), and ARENA simulation images (Figure 8, Figure 9, Figure 10, Figure 11, Figure 12, and Figure 13) can be found in Supplementary Materials. Model runs consisted of 30 replications, with a replication length of one year. The model includes the two acute stroke pathways noted in Figure 4. The model considers variation in patient pathway and activity durations using probability distributions and employs a stochastic patient arrival rate schedule.

Once patients arrive, the model distributes patient pathways with approximately 80% of patients arriving via EMS, and 20% arriving via PV. Activity duration distributions are based on estimations from healthcare professionals at the included sites. The arrival rate schedule was approximated from Site 1 data to more accurately replicate hourly volumes in which AIS patients arrive at a hospital. As aggregate data showed that Site 2 and Site 3 had lower ischemic stroke volumes compared to Site 1 (with Site 3 encountering the least amount of AIS patients), their arrival rates were adjusted accordingly. The time and day of a patient's arrival in the system can impact their treatment pathway due to resource availability. Regular hours are defined as 8:00 am to 4:00 pm, Mondays to Fridays, while out of hours are considered all times outside of regular hours. The schedule generates approximately 35% of arrivals in regular hours and 65% during out of hours as determined from our input data. The schedule specifies that the majority of arrivals occur between 8:00 am and 8:00 pm, with few arrivals between 12:00 am and 8:00 am. Human resource and the resulting treatment process differences between regular and out of hours are defined for each site in the *Section 2 Treatment Process Results* section of the qualitative study (37). The DES aims to replicate current practice for each site and gives the ability to assess the potential impact of process improvements that can result in reduced DNT.

Table 10: Site 1 Model Verification of Arrival Rate and Pathway Types. EMS: Emergency Medical Services, PV: Private Vehicle. Analysis was performed using the Chi-Square Goodness-of-Fit test.

Time Period	Desired Rate	Model Rate	Desired Proportion	Desired Volume	Model Volume	p-Value
12:00am–2:00am	0.00428	0.01308	0.0310	93.7	79	0.169
2:00am–4:00am	0.00321	0.01291	0.0233	70.4	78	
4:00am–6:00am	0.00321	0.01274	0.0233	70.4	77	
6:00am – 8:00am	0.00642	0.02416	0.0465	140.5	146	
8:00am – 10:00am	0.01391	0.05660	0.1008	304.5	342	
10:00am - 12:00pm	0.01819	0.06207	0.1318	398.2	375	
12:00pm – 2:00pm	0.01926	0.06869	0.1395	421.4	415	
2:00pm – 4:00pm	0.01712	0.05776	0.1240	374.6	349	
4:00pm – 6:00pm	0.01712	0.06223	0.1240	374.6	376	
6:00pm – 8:00pm	0.01605	0.05925	0.1163	351.3	358	
8:00pm – 10:00pm	0.01070	0.03608	0.0775	234.1	218	
10:00pm – 12:00am	0.00856	0.03443	0.0620	187.3	208	

Definition of Time Period	Desired Percentage of Arrivals	Model Output
Regular Hours (Monday to Friday, 8:00am – 4:00pm)	35.4 %	34.5 %
Out of Hours (Monday to Friday, 4:00pm – 8:00am, Saturday and Sunday)	64.6 %	65.5 %

Pathway Type	Desired Pathway Distribution	Model Output
EMS	80.0 %	79.5 %
PV	20.0 %	20.5 %

The DES has several assumptions and simplifications:

1. Due to the top prioritization of acute stroke patients within a hospital, it is assumed these patients will receive priority for the required resources upon arrival, and that the resources are always available.
2. Patient pathway type assignments (EMS or PV) are independent.

3. The EMS pathway always provides the hospital with pre-notification and pre-identification.
4. Activity durations are independent of each other.
5. All patients in the DES model are eligible to receive thrombolysis treatment.
6. The system may have only a single stroke protocol activation at a time.
7. The model assumes 100% stroke protocol compliance and does not consider personnel dependent variation. Although, it should be noted that waiting for a patient's lab results is not always required to determine the thrombolysis treatment decision, which is reflected in the duration distribution for this activity.

The following are model simplifications:

1. Activity durations are independent of the onset to arrival time, meaning durations do not change if a patient is approaching the 4.5-hour window.
2. Only AIS patients are included; stroke mimics, and hemorrhagic stroke patients are excluded.
3. Ineligible thrombolysis candidates are not considered.
4. Stroke severity, patient age, and patient sex are not considered.

Certain variation in activities may be due to factors included in the assumptions and simplifications listed above; for example, milder stroke patients often have longer treatment times, due to the time taken to determine a diagnosis and treatment decision. These variations in the associated activities are considered in the distribution of each relevant activity in the DES.

3.3.3 Test Scenarios

In addition to current baseline treatment processes, five scenarios were tested for each site. The scenarios are three process changes and two reductions in activity durations.

Process change scenarios entail implementing a change in a site's current thrombolysis treatment process, while reduction in activity duration scenarios reduces the amount of time taken to execute a specified activity. The five scenarios are defined in Table 11, along with defining current site processes. The process changes were chosen because they are well-supported in previous studies to have reduced DNTs. Activities chosen to test the effect of a reduction in duration were selected where there is considerable variability in activity length of time, and evidence that times can be reduced with standardized protocols. The scenarios were tested individually, and in combinations.

The following lists and details the five test scenarios that were run and applied to the three included sites in this study:

Process change 1 (P1): Patients arriving via EMS remain on EMS stretcher to imaging (18,20,21,66–69) – This scenario models the impact of keeping a patient arriving via EMS on the EMS stretcher, as opposed to transferring the patient to an ED bay to travel to imaging.

Process change 2 (P2): Administration of tPA in imaging area (regular and out of hours) (20,21,58,66,70,71) – This scenario models the administration of the tPA bolus in the imaging area, as opposed to administration in the ED following imaging. This scenario eliminates the travel time from imaging to the ED prior to the administration of the bolus and has a reduced tPA administration preparation activity time.

Process change 3 (P3): Pre-registration of patients arriving via EMS (20,58,70) – This scenario models the pre-registration of patients travelling via the EMS pathways, as opposed to starting the registration process when the patient arrives at the hospital.

Reduction in activity duration 1 (R1): Reduce treatment decision time by 35% – This scenario models a reduction in the time taken for the physician to decide whether the patient will receive thrombolysis treatment by 35%.

Reduction in activity duration 2 (R2): Reduce tPA administration preparation time by 35% – This scenario models a reduction in the time taken to complete the preparation required before administering tPA by 35%. tPA administration preparation encompasses activities such as: obtaining the drug, estimating the patient's weight, calculating the correct dosing, mixing the tPA, and programming the tPA administration pump.

Table 11: Test Scenarios and Current Site Processes. EMS: Emergency Medical Services, tPA: Tissue Plasminogen Activator. "Yes" indicates the scenario is already implemented at the site, while "No" indicates the scenario is not a current site process and the current site process is subsequently defined.

Test Scenarios	**Is the Test Scenario Already Implemented at the Site? (ie: Included in Site Baseline)**		
	Site 1 (Urban)	*Site 2 (Rural)*	*Site 3 (Rural)*
P1) Patients Arriving via EMS Remain on EMS Stretcher to Imaging	Yes	Yes	No (Patient Transferred to ED Bay)
P2) Administration of tPA in Imaging Area (Regular and Out of Hours)	No (During Regular Hours Only)	No (Administered in ED)	No (Administered in ED)
P3) Pre-Registration of Patients Arriving via EMS	Yes	Yes	No (Completed Upon Arrival)
R1) Reduce Treatment Decision Time by 35%	-	-	-
R2) Reduce tPA Administration Preparation Time by 35%	-	-	-

3.3.4 Outcome Measure

The primary outcome measure for this study was median DNT for patients treated with thrombolysis, and the measure of variance for this outcome was interquartile range (IQR).

3.3.5 Statistical Analysis

The Mann-Whitney U test and the Chi-Square Goodness-of-Fit test were performed for continuous and categorical variables respectively. Minitab Statistical Software for Windows (Minitab, State College, PA, version 19) was used for all statistical analysis. A p-value of less than 0.05 was considered statistically significant.

3.3.6 Ethics

Ethics approval was obtained from the Nova Scotia Health Research Ethics Board (REB) for this study, with the REB file number 1025975.

3.4 Results

The model was used to determine the impact of process changes and reduction in activity durations on DNT at each site in comparison to the site-specific baseline DNT. The actual median DNT for Site 1, Site 2, and Site 3 are 50.0, 40.0 and 77.5 minutes (June 2019 – May 2020), with modelled baseline median DNT of 50.0 (IQR 45.4–53.8), 40.1 (IQR 38.7–48.0), and 74.0 (IQR 70.8–82.6) minutes respectively. The results of the model baselines and test scenarios are summarized in Table 12, with the median DNT and IQR for the total 30 replications calculated for each scenario.

3.4.1 Test Scenario Experiment Results

The results of all scenario experiments are described below and summarized in Table 12, Figure 5, and Figure 6. Table 12 includes median DNT and IQR results for each scenario experiment, and the total number of cases used in the calculations for median DNT for each scenario. Figure 5 and Figure 6 illustrate DNT reduction percentages for all three sites for all individual test scenarios, and combinations of scenarios, respectively. Note that process changes (P1, P2, or P3) tested that resulted in DNT reductions of zero signify the site was already implementing that scenario as part of their baseline.

Patients arriving via EMS remain on EMS stretcher to imaging (P1) – As Site 1 and Site 2 were currently implementing this process as their baseline, those sites did not experience an improvement in DNT. This process change did benefit Site 3, and led to the largest improvement for Site 3 across all individual test scenarios. The DNT at Site 3 was reduced to 66.4 (IQR 63.6–75.7) minutes from a median of 74.0 (IQR 70.8–82.6) minutes, translating to a 9.2% (95% CI 7.9–10.5%) improvement in DNT compared to the respective site baseline.

Administration of tPA in imaging area (regular and out of hours) (P2) – Administration of tPA to patients in the imaging area resulted in a reduction of the median DNT for Site 1, Site 2, and Site 3 to 43.7 (IQR 42.2–46.3) minutes, 36.6 (IQR 34.9–44.6) minutes, and 71.0 (IQR 66.0–80.3) minutes respectively. This scenario was the most impactful individual test result for Site 1 and Site 2, leading to a reduction of 12.6% (95% CI 12.4–12.8%) and 8.2% (95% CI 7.5–9.0%) respectively. It was anticipated that Site 1 would show the largest improvement for this scenario, as Site 1 has the longest travel time to the ED from imaging since it is large tertiary care centre.

Pre-registration of patients arriving via EMS (P3) – As Site 1 and Site 2 include this process in their baseline, those sites did not experience an improvement in DNT. This process change resulted in a DNT of 71.9 (IQR 68.6–80.9) minutes and a reduction of 1.7% (95% CI 0.3–3.1%) at Site 3.

Reduce treatment decision time by 35% (R1) – Physician comfort with treatment with tPA results in a shorter amount of time for making the treatment decision. The reduction in decision time did not reduce Site 1's DNT, highlighting that a bottleneck was present elsewhere. Scenario R1 also had little impact on Site 2, with a 0.5% (95% CI -0.1–1.2%) improvement in DNT. Site 3 experienced a 1.8% (95% CI 1.0–2.7%) improvement, with a DNT of 72.3 (IQR 70.0–76.0) minutes.

Reduce tPA administration preparation time by 35% (R2)– This reduction in activity duration scenario benefitted Site 1 and Site 2 to a greater degree than did R1. The DNT was reduced for Site 1 by 8.6% (95% CI 8.2–9.0%) with a DNT of 45.7 (IQR 42.0–49.1) minutes. Site 2 improved their DNT by 5.3% (95% CI 4.2–6.5%) with an output of 37.8 (IQR 35.9–48.0) minutes. The impact of R2 was comparable to R1 for Site 3, with DNT reduction of 1.6% (95% CI -0.2–3.5%) and a DNT of 71.8 (IQR 66.6–81.4) minutes.

Combination of P1, P2, P3 – When combining all process change scenarios, Site 3 saw a 15.4% (95% CI 13.1–17.7%) reduction with a DNT of 61.3 (IQR 56.3–72.6) minutes from a baseline median of 74.0 (IQR 70.8–82.6) minutes. As Site 1 and Site 2 were currently implementing P1 and P3, their respective results are identical to their P2 results as that was the only new process change for those sites.

Combination of R1, R2 – Combining the two reductions of activity duration scenarios benefited Site 3 far more than Site 1 and Site 2, whose improvements in this case were largely attributable to R2. The combination of R1 and R2 was equally, or more, effective in terms of improving DNT when compared to being individually tested, due to the close relationship of these activities and the bottleneck formed when adjusted individually. The resulting DNT for Site 1, Site 2, and Site 3 were 45.7 (IQR 42.0– 49.1) minutes, 36.7 (IQR 35.4–48.0) minutes, and 65.3 (IQR 62.8–70.6) minutes respectively.

Combination of P1, P2, P3, R1, R2 – As anticipated, the lowest DNT for each site was achieved by combining all test scenarios, which resulted in the following DNTs: Site 1 was reduced by 18.9% (95% CI 18.6–19.1%) to 40.6 (IQR 39.1–43.2) minutes, Site 2 by

15.9% (95% CI 15.3–16.4%) to 33.6 (IQR 32.4–44.6) minutes, and Site 3 by 26.7% (95% CI 24.5–28.9) to 52.9 (IQR 49.8–61.2) minutes.

Table 12: Median DNT Results by Scenario for Site 1, Site 2, and Site 3. DNT: Door-to-Needle Time, EMS: Emergency Medical Services, tPA: Tissue Plasminogen Activator. P1: Patients Arriving via EMS Remain on EMS Stretcher to Imaging, P2: Administration of tPA in Imaging Area, P3: Pre-Registration of Patients Arriving via EMS, R1: Reduce Treatment Decision Time by 35%, R2: Reduce tPA Administration Preparation Time by 35%. Analysis was performed using the Mann-Whitney U test comparing DNT data from the changes that were implemented to the respective site's baseline DNT data.

	Site 1 (Urban)			**Site 2 (Rural)**			**Site 3 (Rural)**		
	n	**Median DNT (IQR)** (min)	**p-Value**	**n**	**Median DNT (IQR)** (min)	**p-Value**	**n**	**Median DNT (IQR)** (min)	**p-Value**
Process Baseline	3,021	50.0 (45.4 – 53.8)	-	780	40.1 (38.7 – 48.0)	-	405	74.0 (70.8 – 82.6)	-
Process Changes									
P1	3,021	Current Baseline	-	780	Current Baseline	-	405	66.4 (63.6 – 75.7)	< 0.0001
P2	2,984	43.7 (42.2 – 46.3)	< 0.0001	856	36.6 (34.9 – 44.6)	< 0.0001	405	71.0 (66.0 – 80.3)	< 0.0001
P3	3,021	Current Baseline	-	780	Current Baseline	-	405	71.9 (68.6 – 80.9)	< 0.0001
Reduction in Activity Durations									
R1	3,021	50.0 (45.4 – 53.8)	1.000	780	39.8 (38.5 – 48.0)	0.1430	405	72.3 (70.0 – 76.0)	< 0.0001
R2	3,022	45.7 (42.0 – 49.1)	< 0.0001	780	37.8 (35.9 – 48.0)	< 0.0001	405	71.8 (66.6 – 81.4)	< 0.0001
Combinations of Process Changes and Reduction in Activity Durations									
P1, P2, P3	2,984	43.7 (42.2 – 46.3)	< 0.0001	856	36.6 (34.9 – 44.6)	< 0.0001	405	61.3 (56.3 – 72.6)	< 0.0001
R1, R2	3,022	45.7 (42.0 – 49.1)	< 0.0001	780	36.7 (35.4 – 48.0)	< 0.0001	405	65.3 (62.8 – 70.6)	< 0.0001

	Site 1 (Urban)			Site 2 (Rural)			Site 3 (Rural)		
	n	**Median DNT (IQR)** (min)	**p-Value**	**n**	**Median DNT (IQR)** (min)	**p-Value**	**n**	**Median DNT (IQR)** (min)	**p-Value**
P1, P2, P3, R1, R2	2,984	40.6 (39.1 – 43.2)	< 0.0001	856	33.6 (32.4 – 44.6)	< 0.0001	405	52.9 (49.8 – 61.2)	< 0.0001

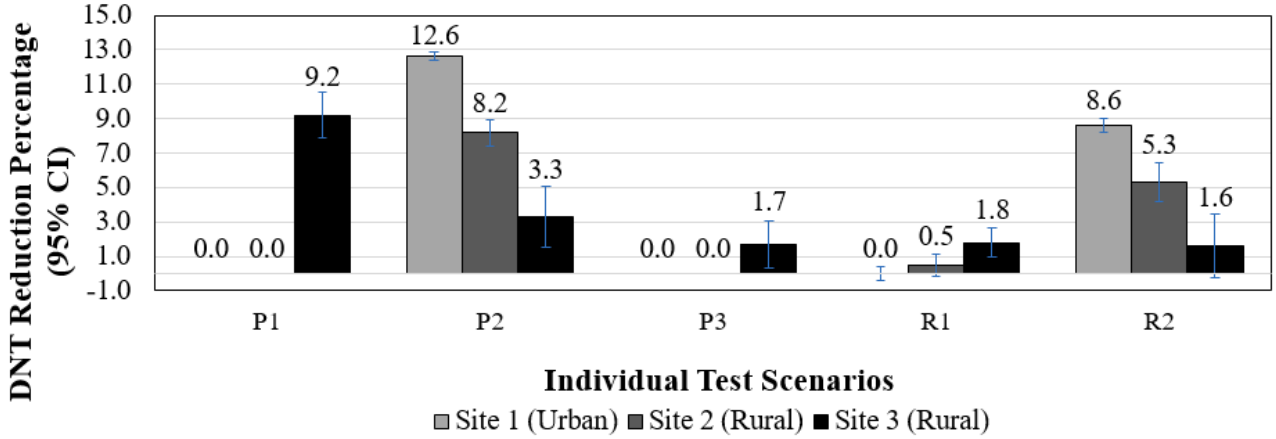

Figure 5: DNT Reduction – Individual Test Scenario Results. DNT: Door-to-Needle Time, CI: Confidence Interval, P1: Patients Arriving via EMS Remain on EMS Stretcher to Imaging, P2: Administration of tPA in Imaging Area, P3: Pre-Registration of Patients Arriving via EMS, R1: Reduce Treatment Decision Time by 35%, R2: Reduce tPA Administration Preparation Time by 35%.

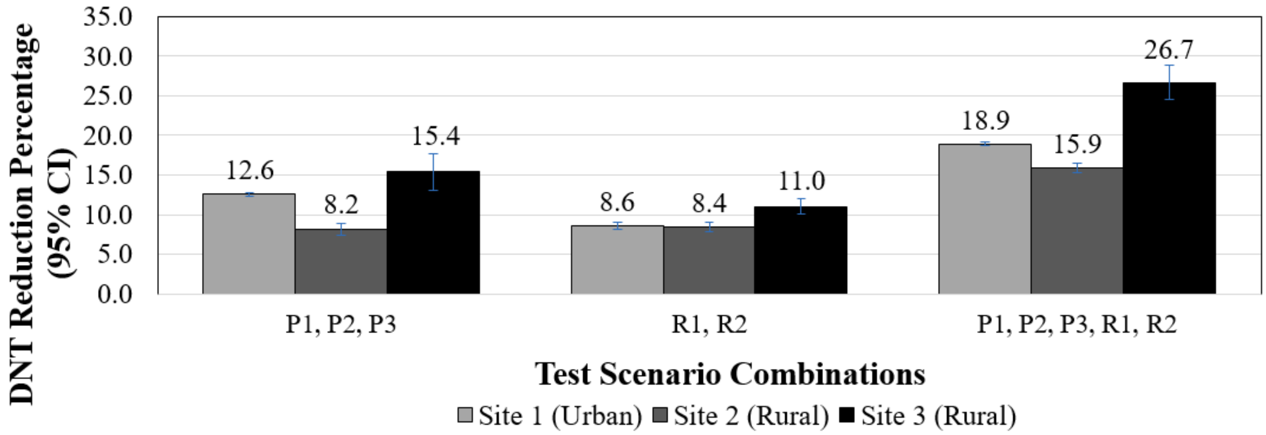

Figure 6: DNT Reduction – Test Scenario Combination Results. DNT: Door-to-Needle Time, CI: Confidence Interval, P1: Patients Arriving via EMS Remain on EMS Stretcher to Imaging, P2: Administration of tPA in Imaging Area, P3: Pre-Registration of Patients Arriving via EMS, R1: Reduce Treatment Decision Time by 35%, R2: Reduce tPA Administration Preparation Time by 35%.

3.5 Discussion

This study details the intra-hospital aspects of the thrombolysis treatment process, considering both urban and rural contexts, and regular and out of hour operations. The conceptual framework expands upon published works (36) to include details extending past key treatment activities, and highlights when delays may be encountered. The framework can be used to promote discussion among healthcare professionals treating AIS patients by facilitating brainstorming methods to streamline processes. It is important when creating a framework to represent urban and rural settings, to accommodate for treatment process differences between them. Low volumes of thrombolysis treatment in rural hospitals makes it challenging to trial process changes, making DES a beneficial tool to incorporate process improvement. The use of the DES model can be useful to hospitals seeking to assess treatment changes without needing to commit resources for trial.

The study shows that the urban and rural sites can benefit from process improvements, by implementing process changes or reducing activity durations. As anticipated, the applied test scenarios resulted in a larger DNT reduction in Site 3, as it was not implementing any of the scenarios and had the longest median DNT. It should be noted that Site 3's DNT is capable of being lower than this study has illustrated, if the reduction in activity duration scenarios reduced durations to a set value, versus reducing the site's current durations by 35%. Administering tPA in the imaging area (P2) resulted in a significant DNT improvement for Site 1, the large urban hospital. The individual reduction scenarios that reduced treatment decision and tPA preparation times highlighted the close relationship between the two activities, and process bottlenecks. For example, Site 3 showed minimal DNT improvements when testing reduction in treatment decision (1.8%, 95% CI 1.0–2.7%) and tPA preparation time (1.6%, 95% CI -0.2–3.5%) individually, but combined reductions increased to 11.0% (95% CI 10.0–12.0%). This illustrates that reducing one activity duration can create a bottleneck elsewhere, or in situations with parallel activities, all activities must be reduced to see an impact.

The DNT improvements from the test scenarios using the DES model resulted in less reduction than reported in the literature, where reductions of 20–40% have resulted from implementing similar process changes (17,18,21,58,67,68). There are many reasons for this, as the implementation of a process change may result in activity duration reductions across the entire treatment process. The magnitude of DNT improvements shown in the literature for implemented changes, not simulated, may be attributable to a behavioural component of implementation, meaning greater reductions in DNT may be realized through implementation. Finding solutions using DES modelling that result in reduced DNTs has the potential to improve clinical outcomes due to the established relationship between treatment times and patient outcomes (12,14). Additional hospital-based strategies such as: single-call activation of care team, rapid acquisition of brain imaging, point of care International Normalized Ratio (INR) testing, rapid access to tPA, and not requiring written informed consent (20,21,58), should be incorporated for further improvements.

The benefit of trialing process changes within a DES model is clear, although there are challenges involved in developing an appropriately accurate model to represent the system. A study focusing on the development of hyperacute stroke care frameworks summarized the main two difficulties concisely: 1) modellers must understand clinical concepts and have the ability to grasp the pathway logistics; and 2) translate that knowledge into a model for use of testing (36). This highlights the importance of hyperacute stroke frameworks and the need for providing as much detail as possible for logistics to be understood thoroughly. Only including key activities in these frameworks and models may limit the extent of the improvement. Additionally, access to the required data, including activity durations, to establish a reasonable representation of the system is a challenge. To have an accurate description of activity durations, data collection studies, such as time studies, would be beneficial. Time studies are useful in providing required data in areas such as: activity durations based on triage category (72), and clinician work time allocation and interruptions (73), enabling further model accuracy. It is advantageous for healthcare professionals treating AIS patients to be aware of this data, as awareness of benchmarks could lead to DNT improvements with a team culture to provide rapid care and establish a continuous improvement mindset.

A limitation of this study is that the conceptual framework was based on only three hospitals with a small sample size of participants involved in the inquiry (37) at each site in a single Canadian province. Furthermore, only two rural sites were studied, meaning the conceptual framework presented may not address all urban-rural treatment differences. It would be advisable to incorporate additional urban and rural hospitals to ensure variations in treatment are encompassed fully. It is important to note that the model assumes 100% of stroke protocol compliance and implementation of test scenarios. For example, when testing the process change of taking a patient to imaging on the EMS stretcher, personnel dependent variation in compliance or variation based on patient factors may dictate the need to move the patient to an ED bay for stabilization prior to imaging was not incorporated. The main limitation of the DES model was the lack of available data detailing activity durations. The model would benefit by employing a time study and replacing estimated durations with collected data for improved accuracy. A second limitation is the use of assumptions and simplifications. The scope of the study was limited by focusing on thrombolysis and not including EVT. It is recognized that rural hospitals face additional challenges, such as arranging transfer of patients for EVT, deserving further study.

3.6 Conclusion

The conceptual framework developed in this study defines treatment pathways for AIS patients receiving thrombolysis treatment in urban or rural hospitals. The detail of the framework aims to reduce the gap between clinical knowledge and modeller perceptions regarding the logistics of the intra-hospital aspect of the thrombolysis process, which can be beneficial for DES development. DES is an effective method to assess the impact of changes on DNT and can be used as a decision-making tool before implementing process changes within the treatment process pathways. Significant DNT improvements are achievable in urban and rural settings by combining process changes and reducing activity durations. DES modelling of acute stroke processes can be expanded to develop more accurate models to reveal the ideal processes to achieve the most efficient treatment for patients.

3.7 Data Availability Statement

The authors declare that all supporting data are available within the article and its supplementary materials.

3.8 Ethics Statement

Ethics approval was obtained from the Nova Scotia Health Research Ethics Board (REB) for this study, with the REB file number 1025975.

3.9 Author Contributions

TB: study design, DES modelling, data analysis, preparation of figures and tables, preparation of the first and revised drafts of the manuscript, as well as final editing and formatting. DV: revision of manuscript for intellectual content. JB: input into the following areas: data analysis, model verification, sensitivity analysis, statistical analysis; as well as revision of manuscript for intellectual content. NK: study design, input into data analysis, and editing, formatting and revision of manuscript for intellectual content.

3.10 Funding

This work was funded by Canadian Institutes of Health Research (CIHR) Project Grant (PJT-169124) held by NK.

3.11 Disclosures

TB: No disclosures. DV: No disclosures. JB: No disclosures. NK: Founder and part equity owner of DESTINE Health. Principal Investigator for CIHR grant that funded this work.

3.12 Supplementary Materials

The supplementary material for this article can be found in Appendix C.

Chapter 4: Discussion

Study 1 (37) detailed how various aspects of the thrombolysis treatment process are viewed in urban and rural hospitals in Nova Scotia. The main differences stem from healthcare professionals' expertise, resource availability, and frequency of treating AIS patients. In rural settings, an emergency physician makes the treatment decision, while in urban settings this role can be a neurologist, or even more specialized, a stroke neurologist. The difference in specialization understandably can create a contrast regarding physician comfort between urban and rural hospitals to treat AIS patients with tPA. There were varying levels of confidence among the included ED physicians in treating patients with tPA, which was partially attributed to reservations about the evidence shown in the literature surrounding the use of tPA. This sentiment is not simply a Nova Scotian challenge, this feeling was echoed in a study conducted in Michigan that indicated only 49% of ED physicians surveyed felt that science regarding the use of tPA in stroke is convincing (52). Another topic with differing views among physicians is informed consent for thrombolysis, which is consistent with other studies (53,54), and can delay treatment. Resource availability is another main difference between urban and rural settings. Urban hospitals are generally able to have key resources such as CT technologists available at all times, or special roles such as acute stroke nurses, which are advantageous in the pursuit of low DNTs. Study 1 (37) also highlighted the infrequency of treating AIS patients with tPA at rural hospitals is another factor contributing to longer DNTs. Low treatment volumes at the rural sites can lead to lower confidence and comfort with providing the treatment, as well as less familiarity with the care pathway, which can lead to longer DNTs.

Reducing DNT was a focus of Study 2, which detailed the intra-hospital aspects of the thrombolysis treatment process and applied test scenarios to the three Nova Scotian hospitals. Finding solutions that reduce DNT has the potential to improve clinical outcomes due to the established relationship between treatment times and patient outcomes (12,14). The conceptual framework developed based on Study 1 (37) process maps enabled the DES model to be developed. After applying the DES model to the three Nova Scotian hospitals, it is clear that urban and rural sites can benefit from process improvements such as process changes or reducing activity durations. It was anticipated that Site 3 would show the largest DNT reduction upon applying the test scenarios as the site was not implementing any of the scenarios and had the longest median DNT, while Site 2 showed the lowest DNT reduction and had the shortest median DNT. It should be noted that Site 3's DNT is capable of being lower than Study 2 has illustrated, if the reduction in activity duration scenarios reduced durations to a set value, versus reducing the site's current durations by a percentage. Another predicted outcome was that Site 1 would benefit the most from administering tPA in the imaging area (P2), as this hospital had the greatest distance between diagnostic imaging and their ED. The DNT improvements from the test scenarios using the DES model resulted in less reduction than reported in the literature, where reductions of 20–40% have resulted from implementing similar process changes (17,18,21,58,67,68). The difference in magnitude of DNT improvements between implemented changes and simulated changes may be attributable to a behavioural component of implementation, which may result in activity duration reductions across the entire treatment process.

The urban-rural disparity in stroke treatment illustrated in Study 1 (37) is consistent with previous studies that showed that rural AIS patients are less likely to receive thrombolysis (50) and have longer DTN times (17) than their urban counterparts. The issues of lack of comfort with tPA treatment and lack of resources are not unique to Nova Scotia, as similar challenges have been found in other jurisdictions (52–54). The rural sites noted that continuing education and providing emergency physicians with support in treatment decision from a neurologist can assist with this deficiency, the desire for decision support for tPA also being documented in other works (52). A centralized telestroke system is one proven method to provide decision support that helps to alleviate the disparity that is apparent in rural hospitals (55–57), and could lead to improved treatment decision times such as what was tested in Study 2. Telestroke can also provide support in timely interpretation of imaging to overcome lack of resource availability, such as radiology, which is faced by rural hospitals. The process change of implementing a telestroke system can be tested using DES modelling. The benefit of trialing process changes within a DES model is clear, although there are challenges involved in developing an appropriately accurate model to represent the system. A study focusing on the development of hyperacute stroke care frameworks summarized the main two difficulties concisely: 1) modellers must understand clinical concepts and have the ability to grasp the pathway logistics; and 2) translate that knowledge into a model for use of testing (36). Additionally, access to the required data, including activity durations, to establish a reasonable representation of the system is a challenge. Nevertheless, as low volumes of thrombolysis treatment in rural hospitals make it challenging to trial process changes, DES modelling is an advantageous tool to incorporate process improvements to assess treatment changes without needing to commit resources for trial.

4.1 Limitations and Future Direction of Research

The limitations for both works are rooted in Study 1 (37), as this study provided the required data for Study 1 (37) and Study 2. A study limitation is that only three hospitals were included in Study 1 (37) in a single Canadian province. Another limitation of the qualitative study is the small sample size of participants involved at each site, and that only two rural sites were included. Due to the number of participants in Study 1 (37), only preliminary conclusions can be drawn as there were not a sufficient number of participants to remove individual biases. Additionally, not all professionals that are part of the treatment process were involved in the interview process at each site for Study 1 (37); primarily excluding paramedics and radiologists. There were two rural sites in the study that were felt to represent the province adequately, but for further accuracy regarding the urban-rural treatment differences in Nova Scotia and generally, additional rural hospitals should be considered. Due to the limited number of rural hospitals included, it should be noted that the developed conceptual framework in Study 2 may not address all urban-rural treatment differences. Another Study 2 limitation is that the DES model assumes 100% of stroke protocol compliance and implementation of test scenarios, which does not consider personnel dependent variation in compliance or compliance variation dictated by patient factors. The main limitation for Study 2 is the lack of available data detailing activity durations. The model would benefit by employing a time study and replacing estimated durations with collected data for improved accuracy. Study 2 was also limited by its assumptions and simplifications.

The scope of both works was limited by focusing solely on the intra-hospital aspects of the thrombolysis treatment process, therefore there are several future directions of research that deserve further study. Regarding the current scope of Study 1 (37), it would be beneficial to expand the qualitative study to further explore the causality of system delays and provide solutions to reduce or eliminate these where possible. Additionally, the scope of Study 2 could be expanded to use DES modelling of acute stroke processes to identify the ideal processes to achieve the most efficient treatment for patients. Other areas that are recommended to be analyzed include the pre-hospital stage of the treatment process to investigate the following: EMS availability in urban and rural settings and system delays that cause delay of EMS arrival to a patient's location; EMS on-scene processes to determine if the duration on-scene before travelling to the hospital can be reduced; and the optimal EMS travel method in urban and rural settings, including ground or air ambulance, to the nearest hospital. As rural hospitals face additional challenges, the patient transfer process for EVT also deserves further study. EVT was not included in either works in this thesis and should be incorporated in future works to expand the research scope to include both available treatments for AIS patients.

Chapter 5: Conclusion

This work has analyzed healthcare professionals' views on various thrombolysis treatment topics in a Nova Scotian context. Additionally, the thrombolysis process was mapped and compared in urban and rural settings in Nova Scotia. Using the developed process maps, a detailed conceptual framework was created focusing on intra-hospital activities, applicable to both urban and rural hospitals. The conceptual framework allowed a DES model to be developed to assess the potentially impact of process improvements that can result in faster DNT in urban and rural settings. After conducting the qualitative Study 1 (37) and quantitative Study 2, the overall conclusions that should be drawn can be summarized as follows:

- There is a consensus of an urban-rural treatment gap for AIS patients in Nova Scotia.
- The three main factors leading to an inequality in ability to treat quickly in rural settings in Nova Scotia were determined to be attributable to: 1) healthcare professionals' expertise; 2) resource availability; and 3) frequency of treating AIS patients.
- The majority of treatment delays encountered by the three Nova Scotian hospitals are system delays.
- The EMS treatment pathway is more streamlined than the PV treatment pathway, as shown by the conceptual framework.
- DES is an effective method in assessing the impact of changes on DNT and can be used as a decision-making tool before implementing process changes within the treatment process pathways.
- Administration of tPA in the imaging area has a bigger impact on DNT in larger centres where the distance between imaging and the ED is greater.
- Reducing one activity duration can create a bottleneck elsewhere, therefore in situations with parallel activities, activities on the critical path must be reduced to see an impact.
- Significant DNT improvements are achievable in urban and rural settings by combining process changes and reduction in activity durations.

5.1 Summary of Novel Contributions

This research studied the thrombolysis treatment process for AIS patients in urban and rural settings from a qualitative and quantitative perspective. The contributions of this research are as follows:

1) Found reasons for disparity between urban and rural hospitals in the treatment of acute ischemic stroke patients with tPA; specific contributions include:
    a) Provided a detailed comparison between urban and rural sites in Nova Scotia through a qualitative study.
    b) Illustrated the presence of an urban-rural treatment gap for AIS patients in the province.
    c) Clarified what factors contribute to this urban-rural treatment gap.
2) Developed a conceptual framework of the thrombolysis treatment process incorporating urban and rural sites; specific contributions include:
    a) Defined the thrombolysis intra-hospital treatment process based on patient pathway type.
    b) Provided detail regarding process activities and activity sequences.
    c) Highlighted when potential delays may be encountered.
3) Developed and applied a discrete-event simulation to three sites based on the conceptual framework, incorporating urban and rural representation and considering regular and out of hour operations; specific contributions include:
    a) Quantified the impact of various changes on door-to-needle time in urban and rural settings.

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Figure 7: Frontiers – Portion of Copyright Statement

Appendix B: Study 1 Supplementary Materials (37)

Interview Guide for Stroke Coordinators

Introduction

I will ask you a series of questions aimed to gain a detailed understanding of the process for the treatment of acute ischemic stroke (AIS) patients with alteplase, otherwise referred to as tPA (tissue plasminogen activator), at your facility and your role in the process. The questions included are considered an interview guide, as you are encouraged to add comments that are seen to be beneficial to the topic.

Participant Information

1. What is your profession and role at this hospital? (ie: ED physician, paramedic, nurse, etc.)
2. If follow-up questions are required during the project life, are you open to be interviewed again?

Section 1

Contextual Information

3. What is considered an appropriate time frame for treating a patient with tPA?
    - i.e.: Within 3 hours, 4.5 hours, etc.
4. What priority do acute (within 3 hours of onset) ischemic stroke patients receive at your hospital?
5. How many of each health professional resources are involved, in regular and off hours, with treating acute ischemic stroke patients?
6. Are there human resource limitations at your site? Example: is it a challenge to retain certain positions at this location.
7. Are there issues with availability of tPA for thrombolysis treatment?
8. What are the key metrics you review for this process when completing data analysis?
9. Do you feel there is a gap in acute ischemic stroke treatment between urban and rural hospitals?
10. Would you consider the acute stroke treatment process to be effective?
11. Would you consider the acute stroke treatment process to be time efficient?
12. Do you feel protocols are always followed?

13. What improvements can you think of that would increase treatment process efficiency at your site?

Treatment Delay Factors

14. What patient-related factors do you feel are the most common at your site?
    - Examples: delays due to management of hypertension, delays due to management of emergent medical condition, delays due to unclear time of onset, etc.
15. What system factors do you feel are the most common at your site?
    - Examples: delays due to stroke diagnosis, delays due to obtaining CT, delays due to obtaining laboratory results, etc.
16. Are patient-related factors or system factors the main source of treatment delays at your site?

Section 2

Treatment Process

17. Please describe the acute stroke treatment process.
    - The objective is to gather information to develop a process map of the treatment process at your site.
18. What are considered regular hours at your site?
19. Does your acute stroke treatment process differ during regular hours or any other hours?
20. Does your acute stroke treatment process differ if the patient arrives by ambulance?
21. Does EMS pre-notify this hospital of an incoming stroke patient?
22. How does patient registration work at your site?
    - Does this process differ if the patient arrives by private vehicle or EMS?
23. How do patients arrive at the CT scanner?
    - How many scanners are there?
24. Who makes the decision that a patient will receive tPA?
25. Where does the tPA get administered in the hospital?
    - Where is tPA stored?

Additional Comments

If there are any further details or comments that were not covered in the included questions above, please share what you feel will be beneficial to the understanding of the acute ischemic stroke treatment process, and the desired improvements to be implemented.

Standard Interview Guide

Introduction

I will ask you a series of questions aimed to gain a detailed understanding of the process for the treatment of acute ischemic stroke (AIS) patients with alteplase, otherwise referred to as tPA (tissue plasminogen activator), at your facility and your role in the process. The questions included are considered an interview guide, as you are encouraged to add comments that are seen to be beneficial to the topic.

Participant Information

1. What is your profession and role at this hospital? (ie: ED physician, paramedic, nurse, etc.)
2. If follow-up questions are required during the project life, are you open to be interviewed again?

Section 1

Contextual Information

3. Do you feel comfortable treating acute ischemic stroke patients?
4. What are your perceptions about treating acute ischemic stroke patients with tPA?
5. What do you consider an appropriate time frame for treating a patient with tPA?
    - i.e.: Within 3 hours, 4.5 hours, etc.
6. What priority do acute (within 3 hours of onset) ischemic stroke patients receive at your hospital?
7. What other professions are included in the acute stroke process at your site?
8. Are there issues with availability of tPA for thrombolysis treatment?
9. Is patient consent an issue when conducting thrombolysis treatment with acute ischemic stroke patients?
10. Do you feel there is a gap in acute ischemic stroke treatment between urban and rural hospitals?
11. Would you consider the acute stroke treatment process to be effective?
12. Would you consider the acute stroke treatment process to be time efficient?
13. What improvements can you think of that would increase treatment process efficiency at your site?

Treatment Delay Factors

14. What patient-related factors do you feel are the most common at your site?
    - Examples: delays due to management of hypertension, delays due to management of emergent medical condition, delays due to unclear time of onset, etc.
15. What system factors do you feel are the most common at your site?
    - Examples: delays due to stroke diagnosis, delays due to obtaining CT, delays due to obtaining laboratory results, etc.
16. Are patient-related factors or system factors the main source of treatment delays at your site?

Section 2

Treatment Process

17. Please describe the acute stroke treatment process.
    - The objective is to gather information to develop a process map of the treatment process at your site.
18. Describe your role in the process and the durations of the included activities.
19. What are considered regular hours at your site?
20. Does your acute stroke treatment process differ during regular hours or any other hours?
21. Does your acute stroke treatment process differ if the patient arrives by ambulance?
22. Does EMS pre-notify this hospital of an incoming stroke patient?
    - If yes, please describe what happens when your hospital receives the notification.
23. What happens when the patient first arrives at the hospital?
24. How does patient registration work at your site?
    - Does this process differ if the patient arrives by private vehicle or EMS?
25. Is blood work completed on all patients?
26. Are creatinine blood tests performed on patients?
27. Do you wait for the INR (International Normalized Ratio) results before administering tPA?
28. How do patients arrive at the CT scanner?

- How many scanners are there?

29. Who makes the decision that a patient will receive tPA?
30. Who mixes the tPA and when does this occur?
    - Where is tPA stored?
31. Is a CTA (Computed Tomography Angiography) scan completed for patients who will be receiving tPA?
    - If yes, when is the CTA scan completed within the treatment process?
32. Who administers the tPA?
33. Where does the tPA get administered in the hospital?

Additional Comments

If there are any further details or comments that were not covered in the included questions above, please share what you feel will be beneficial to the understanding of the acute ischemic stroke treatment process, and the desired improvements to be implemented.

Appendix C: Study 2 Supplementary Materials

Model Details

Table 13: Mode l Baseline and Test Scenario Activity Durations for Each Site. ED: Emergency Department, IV: Intravenous, CT: Computed Tomography, CTA: Computed Tomography Angiography, tPA: Tissue Plasminogen Activator, EMS: Emergency Medical Services, PV: Private Vehicle, TRIA: Triangular Distribution, UNIF: Uniform Distribution, DISC: Discrete Distribution, P1: Patients Arriving via EMS Remain on EMS Stretcher to Imaging, P2: Administration of tPA in Imaging Area, P3: Pre-Register Patients Arriving via EMS, R1: Reduce Treatment Decision Time by 35%, R2: Reduce tPA Administration Preparation Time by 35%. EMS indicates the patient arrived to the hospital via EMS with the stroke protocol activated pre-arrival, PV indicates the patient arrived via private vehicle.

Activity	**Site 1 (Urban)** (min)	**Site 2 (Rural)** (min)	**Site 3 (Rural)** (min)
Wait to be Triaged	EMS: N/A	EMS: N/A	EMS: N/A
	PV: TRIA(5, 10, 15)	PV: TRIA(5, 10, 15)	PV: TRIA(5, 10, 15)
Suspected Stroke Identified by Triage Nurse	EMS: N/A	EMS: N/A	EMS: N/A
	PV: TRIA(3, 4, 5)	PV: TRIA(3, 4, 5)	PV: TRIA(3, 4, 5)
Physician Flagged Immediately	EMS: N/A	EMS: N/A	EMS: N/A
	PV: TRIA(1, 2, 3)	PV: TRIA(1, 2, 3)	PV: TRIA(1, 2, 3)
Physician Assesses Patient to Determine Stroke Protocol Activation	EMS: N/A	EMS: N/A	EMS: N/A
	PV: TRIA(2, 4, 5)	PV: TRIA(2, 3, 5)	PV: TRIA(3, 4, 5)
Collect Bloodwork, Vitals, and IVs	TRIA(5, 7, 10.5)	Bloodwork: TRIA(2, 3, 4) Vitals: TRIA(3, 4, 5)	Bloodwork: TRIA(2, 3, 4) Vitals and IVs: TRIA(5, 6, 7)
Neurological Assessment	TRIA(3, 5, 10)	TRIA(3, 5, 6)	TRIA(5, 7, 9)
Registration	EMS: UNIF(0.5, 1)	EMS: UNIF(0.25, 0.5)	EMS: UNIF(2, 3) *Scenario P3 –* UNIF(0.25, 0.50)
	PV: UNIF(2, 3)	PV: UNIF(2, 3)	PV: UNIF(2, 3)

Activity	Site 1 (Urban) (min)	Site 2 (Rural) (min)	Site 3 (Rural) (min)
Transfer Patient to ED Bay	EMS: N/A	EMS: N/A	EMS: UNIF(6, 9) *Scenario P1* – 0
	PV: UNIF(3, 5)	PV: UNIF(3, 5)	PV: UNIF(3, 5)
Travel to Imaging	UNIF(3, 5)	UNIF(1, 2)	UNIF(0.5, 1)
Transfer Patient to Scanner	UNIF(2, 4)	UNIF(2, 4)	UNIF(2, 4)
CT Technologist Travelling to Hospital (Out of Hours Only)	N/A	N/A	EMS: TRIA(0, 5, 10)
			PV: TRIA(10, 15, 20)
CT Technologist Gets Scanner Ready (Out of Hours Only)	N/A	N/A	10
CT Technologist Plans Images	UNIF(1, 2)	UNIF(1, 2)	UNIF(2, 3)
CT	1	1	1
CTA	5	5	5
Additional Scan	1.5	2	N/A
Transfer Patient to Stretcher	UNIF(2, 4)	UNIF(2, 4)	UNIF(2, 4)
Review Patient History	EMS: UNIF(0, 2)	EMS: UNIF(0, 2)	EMS: DISC(0.5, UNIF(0, 5), 1.0, UNIF(5, 8))
	PV: UNIF(5, 8)	PV: UNIF(5, 8)	PV: UNIF(5, 8)
Neurologist Travelling to Hospital (Out of Hours Only)	EMS: TRIA(0, 5, 10)	N/A	N/A
	PV: TRIA(10, 15, 20)	N/A	N/A
Receive CT Report	TRIA(3, 4, 5)	TRIA(3, 4, 5)	TRIA(5, 8, 10)

Activity	**Site 1 (Urban)** (min)	**Site 2 (Rural)** (min)	**Site 3 (Rural)** (min)
Make Treatment Decision	TRIA(5, 6, 9) *Scenario R1 –* 0.65 * TRIA(5, 6, 9)	TRIA(5, 8, 20) *Scenario R1 –* 0.65 * TRIA(5, 8, 20)	TRIA(10, 20, 40) *Scenario R1 –* 0.65 * TRIA(10, 20, 40)
Wait for Lab Results	DISC(0.9, 0, 1.0, TRIA(10, 15, 40))	DISC(0.9, 0, 1.0, TRIA(10, 15, 30))	DISC(0.9, 0, 1.0, (TRIA(25,30,40) * (Regular Hours) + (TRIA(60,75,90) * (Out of Hours)
Travel to Treatment Location	0 * (Regular Hours) + UNIF(3, 5) * (Out of Hours) *Scenario P2* – 0	UNIF(1, 2) *Scenario P2* – 0	UNIF(0.5, 1) *Scenario P2* – 0
tPA Administration Preparation	UNIF(8, 10) * (Regular Hours) + UNIF(10, 15) * (Out of Hours) *Scenario P2 –* UNIF(8, 10) *Scenario R2 –* 0.65 * [UNIF(8, 10) * (Regular Hours) + UNIF(10, 15) * (Out of Hours)]	UNIF(8, 10) *Scenario P2 –* UNIF(5, 8) *Scenario R2 –* 0.65 * UNIF(8, 10)	Bed Huddle: TRIA(3, 5, 7) *Scenario P2 –* TRIA(3, 4, 5) *Scenario R2 –* 0.65 * TRIA(3, 5, 7) UNIF(15, 20) tPA Administration Preparation: *Scenario P2 –* UNIF(8, 15) *Scenario R2 –* 0.65 * UNIF(15, 20)
Obtain Patient Consent	TRIA(3, 5, 7)	TRIA(3, 5, 7)	TRIA(5, 8, 12)
Mix tPA	UNIF(1, 2) *Scenario R2 –* 0.65 * UNIF(1, 2)	UNIF(2, 3) *Scenario R2 –* 0.65 * UNIF(1, 2)	UNIF(1, 4) *Scenario R2 –* 0.65 * UNIF(1, 2)
Administer tPA Bolus	UNIF(1, 2)	UNIF(1, 2)	UNIF(1, 2)

Table 14: Model Arrival Schedule for Each Site.

Time Period	Site 1 (Urban) Arrival Rate	Site 2 (Rural) Arrival Rate	Site 3 (Rural) Arrival Rate
12:00am – 2:00am	0.00428	0.00116	0.00058
2:00am – 4:00am	0.00321	0.00087	0.00043
4:00am – 6:00am	0.00321	0.00087	0.00043
6:00am – 8:00am	0.00642	0.00173	0.00087
8:00am – 10:00am	0.01391	0.00376	0.00188
10:00am - 12:00pm	0.01819	0.00491	0.00246
12:00pm – 2:00pm	0.01926	0.00520	0.00260
2:00pm – 4:00pm	0.01712	0.00462	0.00231
4:00pm – 6:00pm	0.01712	0.00462	0.00231
6:00pm – 8:00pm	0.01605	0.00433	0.00217
8:00pm – 10:00pm	0.01070	0.00289	0.00144
10:00pm – 12:00am	0.00856	0.00231	0.00116

Model Verification

The simulation model was verified using the several techniques detailed below, which was completed using data from Site 1.

The following techniques were utilized to complete model verification:

- *Analysis of code:* Model component code was carefully reviewed to ensure accuracy of the intended outcome.
- *Output analysis:* Patient attributes and DNT were recorded into Excel for data analysis, verifying that model output was appropriate given the patient's details.
- *Comparison of input to model output:* The Chi-Square goodness-of-fit test was used to determine statistical significance of the desired arrival schedule to the model output. The results are detailed in Table 10 in the manuscript, along with the pathway type and time period breakdowns. Activity durations were verified based on pathway type and time period distinctions using data recorded in Excel, comparing desired distributions to model output, summarized in Table 15.

Table 15: Site 1 Model Verification of Activity Durations. ED: Emergency Department, IV: Intravenous, CT: Computed Tomography, CTA: Computed Tomography Angiography, tPA: Tissue Plasminogen Activator, EMS: Emergency Medical Services, PV: Private Vehicle, TRIA: Triangular Distribution, UNIF: Uniform Distribution, DISC: Discrete Distribution. EMS indicates the patient arrived to the hospital via EMS with the stroke protocol activated pre-arrival, PV indicates the patient arrived via private vehicle.

Activity	**Desired Distribution** (min) • Constant • UNIF(Minimum, Maximum) • TRIA(Minimum, Most Likely, Maximum)	**Model Output** (min) • Constant • (Minimum, Maximum) • (Minimum, Average, Maximum)
Wait to be Triaged	EMS: N/A	EMS: 0
	PV: TRIA(5, 10, 15)	PV: (5.2, 10.0, 14.9)
Suspected Stroke Identified by Triage Nurse	EMS: N/A	EMS: 0
	PV: TRIA(3, 4, 5)	PV: (3.0, 4.0, 5.0)
Physician Flagged Immediately	EMS: N/A	EMS: 0
	PV: TRIA(1, 2, 3)	PV: (1.0, 2.0, 3.0)
	EMS: N/A	EMS: 0

Activity	**Desired Distribution** (min) • Constant • UNIF(Minimum, Maximum) • TRIA(Minimum, Most Likely, Maximum)	**Model Output** (min) • Constant • (Minimum, Maximum) • (Minimum, Average, Maximum)
Physician Assesses Patient to Determine Stroke Protocol Activation	PV: TRIA(2, 4, 5)	PV: (2.0, 3.7, 5.0)
Collect Bloodwork, Vitals, and IVs	TRIA(5, 7, 10.5)	(5.1, 7.5, 10.4)
Neurological Assessment	TRIA(3, 5, 10)	(3.1, 6.0, 9.9)
Registration	EMS: UNIF(0.5, 1)	EMS: (0.5, 1.0)
	PV: UNIF(2, 3)	PV: (2.0, 3.0)
Transfer Patient to ED Bay	EMS: 0.0	EMS: 0.0
	PV: UNIF(3, 5)	PV: (3.0, 5.0)
Travel to Imaging	UNIF(3, 5)	(3.0, 5.0)
Transfer Patient to Scanner	UNIF(2, 4)	(2.0, 4.0)
CT Technologist Plans Images	UNIF(1,2)	(1.0, 2.0)
CT	1	1.0
CTA	5	5.0
CT Perfusion	1.5	1.5
Transfer Patient to Stretcher	UNIF(2, 4)	(2.0, 4.0)
Review Patient History	EMS: UNIF(0, 2)	EMS: (0.0, 2.0)
	PV: UNIF(5, 8)	PV: (5.0, 8.0)
Neurologist Travelling to Hospital (Out of Hours Only)	EMS: TRIA(0, 5, 10)	EMS: (0.1, 5.0, 9.8)
	PV: TRIA(10, 15, 20)	PV: (10.1, 14.8, 19.5)
Receive CT Report	TRIA(3, 4, 5)	(3.0, 4.0, 5.0)
Make Treatment Decision	TRIA(5, 6, 9)	(5.1, 6.7, 9.0)
Wait for Lab Results	DISC(0.9, 0, 1.0, TRIA(10, 15, 40))	0, (10.7, 22.0, 37.9)

Activity	**Desired Distribution** (min) • Constant • UNIF(Minimum, Maximum) • TRIA(Minimum, Most Likely, Maximum)	**Model Output** (min) • Constant • (Minimum, Maximum) • (Minimum, Average, Maximum)
Travel to Treatment Location	0 * (Regular Hours) + UNIF(3, 5) * (Out of Hours)	Regular Hours: 0.0 Out of Hours: (3.0, 5.0)
tPA Administration Preparation	UNIF(8, 10) * (Regular Hours) + UNIF(10, 15) * (Out of Hours)	Regular Hours: (8.0, 10.0) Out of Hours: (10.0, 15.0)
Obtain Patient Consent	TRIA(3, 5, 7)	(3.0, 5.0, 6.9)
Mix tPA	UNIF(1, 2)	(1.0, 2.0)
Administer tPA Bolus	UNIF(1, 2)	(1.0, 2.0)

The following techniques were utilized to complete extended model verification:

- *Use of site-specific models and real site data:* The developed DES was applied to the three included sites for further verification purposes. The model was applied using each site's process maps from the qualitative study (37), using real site median DTN data from Nova Scotia Health for comparison.
- *Animation:* The model was run using animation and display of patient attributes to allow the modeller to observe the entity travelling through the system to ensure appropriate behaviour.
- *Spreadsheet calculations:* Process calculations were completed in Excel using the activity distribution expected value equations, pathway type breakdown, and regular and out of hour percentages defined in Table 16, with the calculation results compared to the model output summarized in Table 17.

Table 16: Definitions used for Site 1 Extended Model Verification Calculations. EMS: Emergency Medical Services, PV: Private Vehicle.

Activity Duration Expected Value Calculations	
Distribution	*Expected Value*
Constant (a)	a
Uniform (Minimum a, Maximum b)	$\frac{(a+b)}{2}$
Triangular (Minimum a, Most Likely b, Maximum c)	$\frac{(a+b+c)}{3}$
Discrete (p(a), a, p(a + b), b)	$a * p(a) + b * p(b)$
Pathway Type Breakdown	
Pathway Type	80.0 % EMS
	20.0 % PV
Breakdown of Time Period	
Definition of Time Period	*Percentage of Arrivals*
Regular Hours	35.4 %
Out of Hours	64.6 %

Table 17: Site 1 Extended Model Verification Results Calculated Using Table 13 Desired Activity Distributions and Table 16 Definitions. DNT: Door-to-Needle Time, CI: Confidence Interval, EMS: Emergency Medical Services, PV: Private Vehicle.

Pathways	**Pathway Definition**	**Calculated DNT** (min)	**Overall Calculated DNT** (min)	**Model Output Mean DNT (95 % CI)** (min)
Pathway 1	EMS Regular Hours	42.8	52.3	52.6 (52.3 – 53.0)
Pathway 2	EMS Out of Hours	50.3		
Pathway 3	PV Regular Hours	65.7		
Pathway 4	PV Out of Hours	73.2		
Actual Median DNT (min)			**Model Output Median DNT (IQR)** (min)	
50.0			50.0 (45.4 – 53.8)	

Sensitivity Analysis

As the test scenarios involved three process changes, it was important to determine how these changes interacted with each other regarding their influence on the primary outcome measure, median DNT, and whether it was appropriate to test these changes individually. A 2k factorial experiment was completed using Site 3 data and three factors with two settings (low and high) to study the model interactions, shown in Table 18. The model runs for the sensitivity analysis were comprised of 30 replications, with a replication length of one year. The sensitivity analysis results illustrate that the individual factors are considered statistically significant, while the two-way interactions among the factors are not significant, thus it is appropriate to test process changes individually.

Table 18: Site 3 Sensitivity Analysis - 2k Factorial Experiment Minitab Results. EMS: Emergency Medical Services, ED: Emergency Department. P-Value of less than 0.05 is considered statistically significant.

<table>
<tr><td>Number of Levels</td><td colspan="2">2 (Low and High)</td></tr>
<tr><td>Number of Factors</td><td colspan="2">3 (A, B, and C)</td></tr>
<tr><td>Number of Replications</td><td colspan="2">30</td></tr>
<tr><td>Length of Replications</td><td colspan="2">1 year</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td rowspan="2">Factors</td><td colspan="2">Settings</td></tr>
<tr><td>Low Setting</td><td>High Setting</td></tr>
<tr><td>(A) Patients Arriving via EMS Stretcher Type to Travel to Imaging</td><td>Patients Arriving via EMS Remain on EMS Stretcher to Imaging</td><td>Patients Arriving via EMS Transferred to ED Bay to Travel to Imaging</td></tr>
<tr><td>(B) Treatment Location (Regular & Out of Hours)</td><td>Imaging Area</td><td>ED</td></tr>
<tr><td>(C) Pre-Registration of Patients Arriving via EMS</td><td>Pre-Register Patients Arriving via EMS</td><td>Complete Registration of Patients Arriving via EMS Upon Arrival</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td></td><td colspan="2">p-Value</td></tr>
<tr><td colspan="3">Linear</td></tr>
<tr><td>Factor A</td><td colspan="2">0.001</td></tr>
<tr><td>Factor B</td><td colspan="2">0.002</td></tr>
<tr><td>Factor C</td><td colspan="2">0.003</td></tr>
<tr><td colspan="3">Two-Way Interactions</td></tr>
<tr><td>Factor A * Factor B</td><td colspan="2">0.446</td></tr>
<tr><td>Factor A * Factor C</td><td colspan="2">0.221</td></tr>
<tr><td>Factor B * Factor C</td><td colspan="2">0.351</td></tr>
</table>

ARENA Simulation

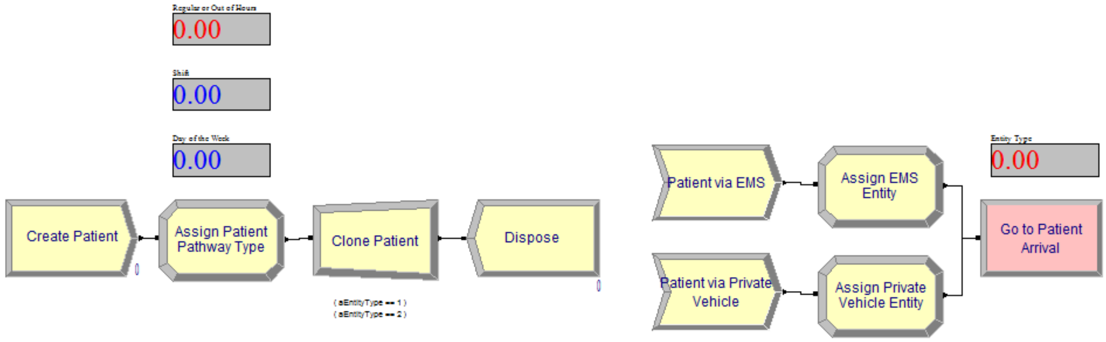

Figure 8: Creation of Patients - ARENA Simulation. EMS: Emergency Medical Services.

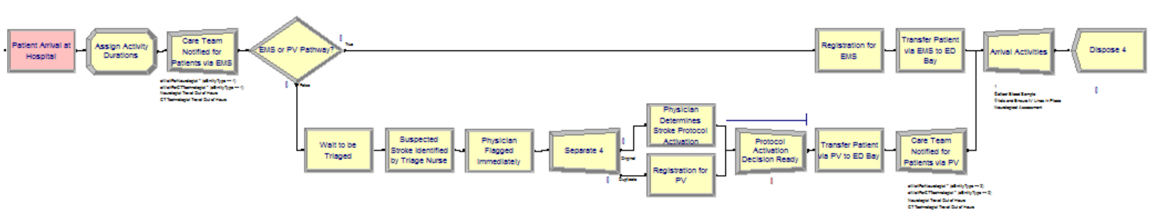

Figure 9: Arrival Activities Part 1 - ARENA Simulation. EMS: Emergency Medical Services, PV: Private Vehicle, ED: Emergency Department.

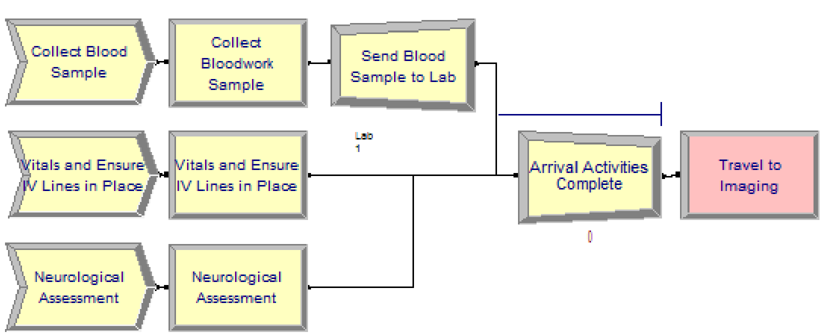

Figure 10: Arrival Activities Part 2 - ARENA Simulation. IV: Intravenous.

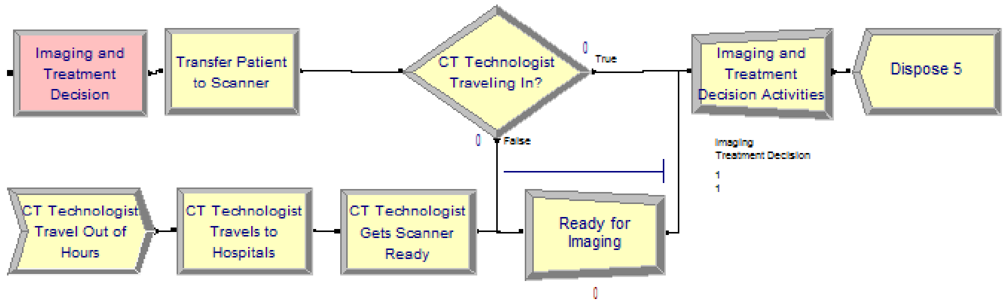

Figure 11: Imaging and Treatment Decision Activities Part 1 - ARENA Simulation. CT: Computed Tomography.

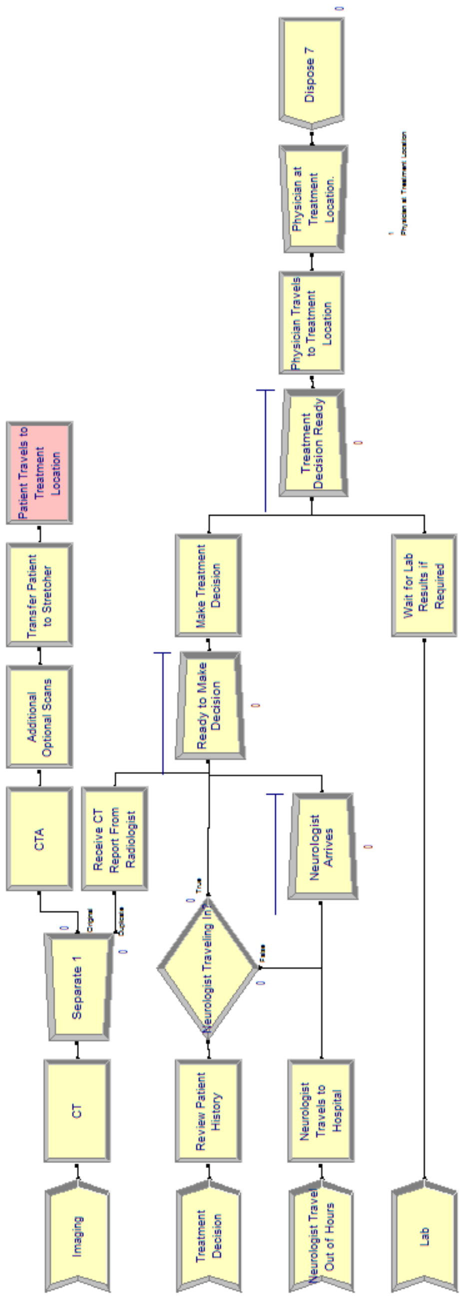

Figure 12: Imaging and Treatment Decision Activities Part 2 - ARENA Simulation. CT: Computed Tomography, CTA: Computed Tomography Angiography.

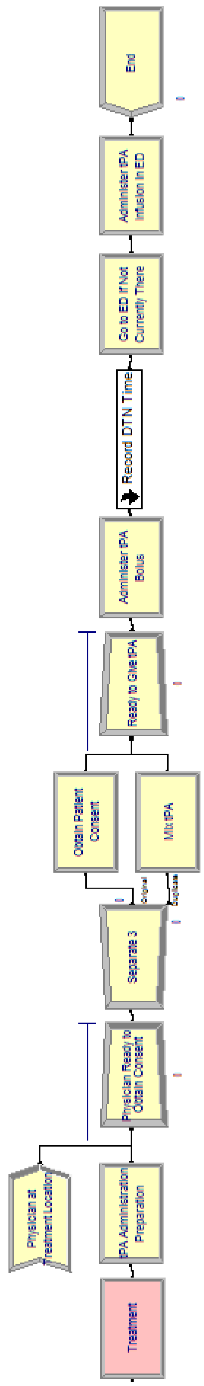

Figure 13: Treatment Activities - ARENA Simulation. tPA: Tissue Plasminogen Activator, DTN: Door-to-Needle, ED: Emergency Department.