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Leonid Churilov[a,b,*], Audur Fridriksdottir[a], Mahsa Keshtkaran[a], Ian Mosley[c,a], Andrew Flitman[a], Helen M.Dewey[d,a]

[a] Florey Neuroscience Institutes (National Stroke Research Institute), Melbourne, Australia

[b]Department of Mathematics and Statistics, The University of Melbourne, Australia

[c]Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia

[d]Austin Health, Melbourne, Australia

[*]Corresponding Author (E-mail: *leonidc@unimelb.edu.au*)

Abstract:

Stroke is the third most common cause of death and the sixth most common cause of disability worldwide. Treating acute ischemic stroke with thrombolytic therapy within 4.5 hours from symptom onset is effective in improving patient outcomes. The time from stroke onset to arrival to hospital has been identified as the single most important issue in determining patients' eligibility for stroke thrombolysis. There is a need for simultaneous systemic evaluation of multi-factorial interventions in pre-hospital acute care systems, aimed at increasing patients' eligibility for stroke thrombolysis. In this paper an OR solution is proposed in the form of a simulation model that provides clear measure of the relative benefit of alternative potential interventions, demonstrating how OR modelling can be used for providing decision support in pre-hospital stroke care operations and contributing to health OR literature.

Keywords: Simulation, Decision Support, Pre-Hospital Stroke Services, Patient Flow Modelling

1. Introduction

Stroke is the third most common cause of death: about a quarter of stroke patients die within a month, about a third by 6 months, and a half within 1 year. It is also judged to be the sixth most common cause of reduced disability-adjusted life-years [14]. Worldwide, stroke consumes about 2–4% of total health-care costs, and in industrialised countries stroke accounts for more than 4% of direct health-care costs [7].

About 80% of all strokes are ischemic, i.e. are caused by a blockage of blood flow to the brain [7]. For patients experiencing acute ischemic stroke, and for the physicians and allied health personnel treating them, every second counts. The results of the modelling by Saver [28] suggest that the typical patient loses 1.9 million neurons each minute a stroke is untreated. Compared with the normal rate of neuron loss in brain aging, the ischemic brain ages 3.6 years each hour without treatment [28].

Thrombolysis, i.e. treating acute stroke with thrombolytic therapy (tPA), within 4.5 hours from symptom onset, is effective in improving patient outcomes [35]. Davis and Donnan [6] emphasize that although the time window for tPA treatment has been recently extended to 4.5 hours, the single most important principle of acute stroke intervention is that time is critical. Earlier treatment is associated with increased therapeutic effect and this should be the goal of all stroke clinicians and underpin the design of acute stroke treatment systems [6].

Although wide availability of tPA treatment to appropriate patients remains a major concern for a number of health systems internationally [33, 22], at present only around 5% of stroke sufferers receive tPA treatment, resulting in prevention of disability being seen in only six patients per 1000 ischemic strokes [7]. In particular, administration rates in Australia remain low [22]. Worldwide this could be due to the relatively short therapeutic time window and a shortage of physicians who are experts in acute stroke management.

Much effort has been undertaken in recent years to understand and implement strategies to improve the eligibility of acute stroke patients for treatment with thrombolysis. Researchers have identified that among multiple factors, the *single most important issue in determining eligibility for treatment is the time from stroke onset to arrival at hospital* [2, 8]. In an effort to reduce delay times, investigators have attempted to quantify the effect of implementing treatment protocols published in stroke clinical guidelines [37, 21] or to implement change in a specific area previously identified as a cause of prolonged times to treatment.

Several studies have been conducted to review pre-hospital times and acute treatment rates following multi-factorial interventions across a number of areas in the process of stroke care [37, 10, 25]. It is these multi-factorial intervention studies that have been most successful in the clinical environment [11]. In an Australian study that implemented a "package intervention" made up of interventions across the continuum of acute stroke care, thrombolysis administration rates increased from 4.7% pre-intervention to 21.4% post-intervention [25].

The success of such a program comes with its own problems for health practitioners seeking to replicate the outcomes. It is impossible to evaluate each individual factor within a package intervention [37, 25]. Hence the role of individual factors alone, when combined with other individual

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factors or within the package remains unknown, calling for a solution that is capable of simultaneous systemic evaluation of multi-factorial interventions in pre-hospital acute care systems.

Despite a clear potential for Operations Research in providing such a solution, as could be evident through numerous successful OR applications to the generic domain of ambulance and emergency care services (see, e.g. a recent review by Paul et al. [23]), there is a clear research gap as far as OR studies of pre-hospital acute stroke care are concerned. A notable exception is Bayer et al.'s [3] recent report on facilitating stroke care planning through simulation modelling, where it is suggested that simulation modelling is suitable for application to highly complex processes, such as stroke care, and can be used successfully as a communication and decision making tool before committing real resources. In an earlier paper, Chase et al. [4] successfully used simulation to estimate the cost effectiveness of improving ambulance and thrombolysis response times after myocardial infarction.

The *objective of this case study* is to address the identified research gap and contribute to the OR literature by demonstrating how OR modelling can be used for providing decision support in pre-hospital stroke care operations. In order to achieve this objective, a relatively simple, yet powerful simulation model is built with the view to increase the understanding of the role of, and relationship between, individual factors alone and combined with each other within a potential system-wide multi-factorial intervention package aimed at improving the eligibility of acute stroke patients for treatment with thrombolysis.

The simultaneous implementation of system wide and community based change may be financially obstructive for Non Government Organisations (NGOs) or Health Care Institutions who often rely on philanthropy or government handouts for income. Financial and resource restrictions focus organisations on identifying key factors to implement at a local level. Identifying the impact of key factors on patient eligibility for thrombolysis will directly inform public policy decisions, stroke public awareness campaigns and the organisation of acute stroke care systems. Organisations can focus interventions and resources on the issues that provide the best patient outcomes given the local resources available to undertake the interventions.

The discussion in this paper is organized as follows: Section 2 is dedicated to providing insight into the complex decision making nature of pre-hospital acute stroke care operations; in Section 3 a simulation model is developed and the issues of simulation experimental design are discussed; Section 4 describes the results; Section 5 discusses the decision support application of the developed model; summary and conclusions are presented in Section 6.

2.   Decision making context and Decision Support Problem structuring

The aim of this section is to provide insight into the complex decision making nature of pre-hospital acute stroke care operations. In Australia and internationally a stroke patient's eligibility for tPA treatment is typically constrained by three major factors:

a)   whether the patient in question satisfies clinical eligibility criteria;

b)   system-wide availability of thrombolysis; and

c)   relatively short therapeutic time window (currently 4.5 hours from symptom onset with a clear evidence that earlier treatment is associated with increased therapeutic effect).

Clinical eligibility criteria remain firmly in the domain of clinical expertise and often require advanced imaging resources to make a definitive decision to administer tPA as a part of in-hospital treatment process. Although it is expected that some of the patients will not be eligible for tPA treatment as the result of an in-hospital specialist neurological and imaging assessments, the fundamental objective of a pre-hospital acute stroke care system is *maximizing availability of tPA treatment to all potentially appropriate patients*. This logically identifies the issues of *system-wide availability of tPA* and *shortening the time from stroke onset to arrival at hospital* as a critically important necessary means to achieve this fundamental objective of pre-hospital acute stroke care.

Shortening the time from stroke onset to arrival at hospital, in turn, directly depends on a number of factors. These include:

a)   the ability of stroke patients (or carers) to identify stroke symptoms and to make a decision for a timely call for ambulance assistance;

b)   the ability of ambulance call-takers to recognize the reported problem as a suspected stroke and to act accordingly by dispatching an ambulance with an appropriate urgency; and

c)   the ability of ambulance paramedics to recognize stroke "in the field" and to initiate fast transportation of a suspected stroke patient while issuing an arrival pre-notification to the relevant acute care hospital with a comprehensive stroke unit and thrombolysis facilities.

Mosley et al. [18, 19] comprehensively addressed the issues of stroke symptoms and the decision to call for ambulance assistance and those of the impact of ambulance practice on acute stroke care. As part of these studies, for 6 months in 2004, all ambulance-transported stroke or transient ischemic attack patients arriving from a geographically defined region in Melbourne, Australia (region population 383,000) to 3 different hospital emergency departments were assessed. Tapes of the call for ambulance assistance, ambulance records, and hospital medical records were analyzed and the patient and the caller were interviewed. Logistic regression modelling was used to investigate

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association between factors. The conclusions were that *stroke was reported as the problem (unprompted) by less than 50% of callers* and *fewer than half the calls for ambulance assistance were made within one hour from symptom onset*. Also, *paramedic stroke recognition and hospital pre-notification were found to be associated with shorter pre-hospital times from the ambulance call to hospital arrival and shorter in-hospital times from hospital arrival to first medical assessment*. These studies by Mosley et al. serve as a contextual source and one of data sources for our study.

In summary, design and operations of a pre-hospital acute stroke care system presents a complex decision support context. This is characterized by multiple operationally modifiable factors such as availability of thrombolysis therapy as well as patients', ambulance call-takers', and field paramedics' ability to recognize stroke and act by placing a call for ambulance assistance, dispatching an ambulance with appropriate urgency, and subsequent pre-notification of the relevant acute care hospital. It is also characterized by multiple factors that are non-modifiable within a short-to-medium term horizon (such as natural variability of the disease, population demographic factors and trends). All these factors have various degrees of uncertainty associated with them and could interact in a systemic fashion thus affecting pre-hospital times and, subsequently, eligibility of acute stroke patients for treatment with thrombolysis.

The above conceptualization of the pre-hospital acute stroke care system naturally leads to the following decision support problem addressed in this paper:

> *The decision support problem is to support simultaneous systemic evaluation of multi-factorial interventions in pre-hospital acute care systems aimed at improving access of acute stroke patients to thrombolysis treatment.*

This does not mean that OR practitioners need to tell health professionals how to recognize stroke, in much the same way that Morse and Kimball [17] did not attempt to tell pilots how to fly aeroplanes. Rather, the pre-hospital acute stroke care simulation problem may be reformulated as "supporting the efficient and effective stroke recognition, response, and pre-hospital treatment". Here *time-based eligibility* is used as the outcome measure due to time-critical nature of stroke where, as discussed in the previous section, every second counts and in every minute without treatment 1.9 million neurons could be lost. At the same time, the proposed decision support problem formulation forces focus to shift from purely "event-to-hospital door" time-based arguments to those of "access to treatment" and "quality of pre-hospital treatment".

3. Simulation of a pre-hospital acute stroke care system

Discrete-event simulation is employed as the most appropriate modelling technique for the identified decision support problem. As a part of a traditional OR toolkit, Discrete-event simulation (DES) is particularly suitable for process systems modelling. Defined as "a structured, measured set of activities … across time and place, with a beginning, an end, and clearly identified inputs and outputs", process is "designed to produce a specific output for a particular customer or market" (Davenport [5], p.5). The process systems context surrounds most of the applications of DES where effective representation of individual entities, attributes, decisions and events throughout the process of care, while explicitly modelling the randomness, are particularly important [12, 16]. DES was successfully utilized for modelling process systems in various domains including simulating police control rooms [9] and modelling and simulation of call centres [1, 15].

This section is structured in accordance with previous studies that focussed on the generic lifecycles for DES [36, 30, 24]. It discusses conceptual model building, data inputs, model implementation, validation, and verification, as well as experimentation process.

3.1 Conceptual model building

A conceptual model for pre-hospital acute stroke care process was created and subsequently iteratively refined, based on the data collected by Mosley et al. [18, 19] as well as independent empirical observations and discussions with stroke care experts from the Victorian Stroke Care Network (VSCN). It assumed the following features of the pre-hospital acute stroke care system and understanding of the pre-hospital acute stroke care processes:

a) At present, there is no national or state coordination of acute stroke care. Rather, the processes of care for patients with stroke are determined at a local hospital or regional level;

b) In Melbourne, Australia, Ambulance Victoria provides the sole emergency ambulance service in the city through a single phone number;

c) Ambulance call takers use a uniform question sequence and protocol, and all calls are recorded; and

d) Ambulance paramedics have the potential to not only reduce delays, but also to ensure patients are assessed in the field appropriately and transported to a hospital with suitable acute stroke care facilities. Paramedics are included in acute care guidelines to rapidly assess stroke in the field, triage the patient to an appropriate acute stroke care facility, and pre-notify the hospital of their arrival.

Following the onset of stroke symptoms, if a patient is not alone and/or is capable of making a phone call, an immediate response could be to make a direct call for ambulance assistance, to call a doctor (such as patient's general practitioner), or to contact another person (such as a close relative) for help and advice. In the latter two scenarios, advice to call for ambulance assistance may be immediate or following a delay, such as visiting the patient to confirm symptoms and to assess the situation first hand. Similar scenarios are possible if the patient is discovered in a state such that they are unable to respond or seek assistance for themselves and the call is placed on the patient's behalf by another person who found them.

During the call for ambulance assistance, following prompts from the ambulance call-taker or spontaneously, a caller could report relevant symptoms such as speech problems, limb weakness, altered consciousness, facial droop, and numbness, and/or could mention suspected stroke explicitly.

Based on the information reported by the callers, ambulance call-takers may identify the key problem as stroke and dispatch an ambulance with the highest priority code (level 1, lights and sirens), or specify an alternative key problem that could lead to the ambulance being dispatched, but not necessarily with the highest priority.

On arrival ambulance paramedics "in the field" could identify stroke as the problem and could subsequently either pre-notify the hospital with thrombolysis treatment facilities available of their intent to transport the patient to the hospital in question (subject to availability), or chose not to do so. The pre-hospital care process ends - and the in-hospital care process begins - with the patient undergoing a triage assessment in an emergency department of a hospital that could have either both thrombolysis treatment facilities and a stroke care unit, a stroke care unit only, or none of the above.

Finally, there is an alternative pathway to in-hospital triage that does not involve ambulance care provision. Due to its highly infrequent use, it is not disaggregated further in the model and is kept at a generic level.

The conceptual model of pre-hospital acute stroke care process is summarized graphically in Figure 1.

3.2 Data Inputs

Data about *patient calling for an ambulance patterns, stroke recognition ability of ambulance call takers and ambulance paramedics, hospital pre-notification patterns*, as well as data on *availability of thrombolysis*, were originally collected by Mosley et al. [18, 19]. The original study was a prospective, open observational study of patients from a geographically defined region (population 383 000) in metropolitan Melbourne, Australia, with the data collection period lasting over a 6 month

in 2004. Melbourne Metropolitan Ambulance Service (MAS) records for the previous 12 months indicated that more than 90% of patients with stroke transported by ambulance from this region were delivered to one of the Austin Hospital, Royal Melbourne Hospital, or Northern Hospital. Both Austin and Royal Melbourne Hospitals have large comprehensive stroke services offering intravenous thrombolysis to eligible patients. Northern Hospital offers stroke unit care with a multidisciplinary team but, at the time of the data collection, did not provide thrombolysis and there was no onsite access to specialist neurological or neurosurgical expertise. At the time of the data collection, both Austin and Royal Melbourne Hospitals had rapid care stroke protocols in place to respond to patients with acute stroke and paramedic pre-notification of a patient with stroke. Both these hospitals deliver tPA and enroll patients in clinical trials of acute stroke therapies.

As a part of the original study [18, 19], tapes of all calls for ambulance assistance for 198 eligible patients were reviewed using a uniform screening tool to evaluate the reported symptoms, any diagnosis offered by the caller (stroke or other), medical history reported, and *symptom onset time provided without prompting by the call taker*. The reaction and decisions of the call taker (dispatcher) were recorded. Each patient's clinical details, history, and event description were obtained from hospital medical records and the ambulance patient care record. The patient and "the caller" were also interviewed using a structured face-to-face questionnaire to obtain demographic data and their description of the stroke event. Patients and callers were asked about their responses to the onset of stroke symptoms. If the patient was unable to answer for themselves, the next of kin was interviewed as a proxy. This information was used to identify a *patient calling for an ambulance patterns* used in this study.

Timelines of the care provided from the call for assistance to first medical assessment in the hospital were identified from a number of sources, including ambulance central computer event chronology records. Timelines included a number of phases: the "ambulance response time" (call to ambulance arrival), "at scene time" (ambulance scene arrival to departure), and "hospital transport time" (scene departure to hospital arrival).

Data regarding *incidence of major stroke subtypes by age group and gender* were obtained from the results of NEMESIS (North-East Melbourne Stroke Incidence Study) [31]. *Age and gender distributions* were obtained from the Australian Bureau of Statistics demographic data.

3.3 Model implementation, verification and validation

The conceptual model was computationally implemented using DES software Simul8 (Version 11 from the Simul8 Corporation) through sequences of virtual workstations and queues. Individual patients, all with distinct age, gender and type of stroke are created and time stamps and routing

decisions are collected as the patient moves through the simulated system. Relevant probabilistic distributions were created using the collected data and imported in Simul8 without fitting theoretical distributions. The model had run times of minutes on a standard personal computer (Intel(R) Core i7 1.6GHz CPU, RAM 3.42 GB, running Windows XP) despite the heavy sampling overhead.

When run, the implemented model shows the animation of the flow of patients through the acute stroke pre-hospital care system. All input parameters are stored in MS Excel and imported into Simul8 before each run. After each run, individual patient's process data and final location are exported into Excel for data processing, where performance measures for scenario comparisons are subsequently created.

The simulation model was verified and validated in accordance with the commonly accepted principles for these activities as detailed in, for example, Robinson [26], Sargent [27], Troitzsch [32], and Pidd [24]. The end result of validation is usually not the valid model, but rather the model that passed all validation tests, as well as better understanding of the model's capabilities, limitations, and appropriateness for use as a decision support tool. Overall, while having undergone the replicative validity tests (i.e. the model matches data already acquired from the real system (Troitzsch [32])) and structural validity tests (i.e. the model truly reflects the way in which the real system operates to produce this behavior (Troitzsch [32])), the model was not subjected to the predictive validity testing (i.e. when the model matches data before data are acquired from the real system) due to the nature of the system being modeled.

Specifically, the following validation techniques were used as a part of the validation process (Sargent [27]):

- *Animation*, where the model's operational behavior was displayed graphically as the model moved through time;
- *Event Validity*, where the "events" of occurrences of the simulation model were compared to those of the real system to determine if they are similar, e.g. stroke patients ending up in hospitals with/without tPA facilities, or being "dropped off" the tPA treatment pathway;
- *Extreme Condition Tests* through exploration of critical cases, where the model structure and output was found plausible for extreme and unlikely combination of levels of factors in the system, e.g., when proportions for correct actions by ambulance staff, or availability of tPA, were set at 100%;
- *Face Validity*, where the model underwent validation conducted by an expert from the Victorian Stroke Care Network, independent of the original model developers, in order to

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determine that the logic in the conceptual model is correct and that a model's input-output relationships were reasonable; and

- *Historical Data Validation*, where the model was validated by "replaying the history", i.e. using the original settings based on the historical data and comparing the distributions resulting from running the model to the single available baseline scenario by Mosley et al. [18,19].

Similarly, the following verification techniques were used as a part of the verification process:

- As distributions were imported from Excel into Simul8's Information Store and results exported from the Simul8's Information Store into Excel, the model was run ten times and accuracy of data transfer was confirmed;
- Various patient routing and time distributions that resulted from ten independent runs were compared to the distributions that were imported into the model both graphically and using Chi-Square test for routing distributions and Kolmogorov-Smirnov test for time distributions; and
- The Simul8 Visual Logic code was independently verified.

3.4 Experimental design

The implemented simulation model allows comparing "in-silica" multiple potential system-wide multi-factorial intervention packages aimed at improving the eligibility of acute stroke patients for treatment with thrombolysis by varying individual factors alone and in combination. The *eligibility of acute stroke patients for treatment with thrombolysis in pre-hospital settings* is measured as the *proportion of patients that would arrive to a hospital with thrombolysis treatment facilities within a given time T^* since stroke symptoms onset*. Interventions including a combination of the following modifiable factors can be simulated:

- Availability of stroke thrombolysis facilities;
- Increasing the proportion of ambulance callers who makes a call for ambulance assistance very soon or immediately after the onset of stroke symptoms;
- Improving an ability of the ambulance call-takers to recognize stroke and dispatch an ambulance with the highest priority code;
- Changing ambulance response and patient transport times; and
- Improving paramedics ability to correctly identify stroke as the problem and subsequently pre-notify the hospital with thrombolysis treatment facilities of their intent to transport the patient to the hospital in question.

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In addition, factors non-modifiable over short-to-medium time horizon, such as stroke incidence and demographic characteristics of the population, can be changed in the model.

In order to capture the variability of the systems operations when evaluating alternative interventions, each individual scenario evaluation is implemented through a series of simulation runs. Each run compares a pair "baseline vs. intervention scenario" using an identical simulation run-specific random number generator seed value for both baseline and intervention scenarios. This approach results in the same patient mix being generated for both scenarios within a given simulation run, thus making it possible to meaningfully compare the outcomes of the two contrasting scenarios within this paired run. This approach is a specific case of the general principle of "paired design" through individual matching used in experimental design – it's use for simulation studies was advocated by Law and Kelton [13]. Finally, the average difference in proportions of patients satisfying time-based eligibility constraints for thrombolysis treatment between baseline and intervention scenario across multiple runs is estimated together with the corresponding exact 95% confidence intervals, thus providing an estimate of the effect of a potential system-wide multi-factorial intervention package together with the associated measure of its uncertainty.

4. Results

The baseline scenario is based on the results reported by Mosley et al. [18, 19]. It broadly reflects the pre-hospital stroke care parameters in the geographically defined region in metropolitan Melbourne with the population of 383,000. This region is characterized by a relatively high availability of stroke thrombolysis treatment facilities (around 70%) and a timely and reliable ambulance service.

Around 20% of all ambulance calls were made as soon as practical as a first response to the onset of stroke symptoms. Ambulance call-takers identified stroke as a key problem in 54% of cases and allocated a "lights and sirens" response in 76% of calls. Although paramedics in the field identified stroke as the problem in 78% of all patients, only in 22% of all cases relevant hospital pre-notifications were issued. Once simulated over one year period, around 30% (95%CI: 27%-34%) of all acute ischemic stroke patients would be eligible for thrombolysis.

Following the principle of absolute "event-to-needle" time minimization (i.e. "*It is better to treat* [with tPA] *within 3 than 4.5 hours, and even better within 90 minutes, of onset*" [6]), and using in-hospital specialist neurological and imaging assessments process pathway data from the Australian Safe Implementation of Thrombolysis in Stroke (SITS) Registry (Simpson et al. [29]), the critical time T^* since stroke symptoms onset to triage in an emergency department of a hospital with thrombolysis treatment facilities to satisfy time eligibility constraint was set so as to make the total

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"event-to-treatment" time less than 4.5 hours for general population and less than 3 hours for patients older than 80 years.

As an illustrative example of the use of the model, the following "in-silica" multiple potential system-wide multi-factorial intervention packages aimed at improving the eligibility of acute stroke patients for treatment with thrombolysis were implemented and compared to the baseline scenario (each simulation run consisted of 10 paired comparisons as discussed in the previous section):

a) Availability of stroke thrombolysis facilities was sequentially set at 72.3% (baseline), 5%, 50% and 100%;

b) Percentage of calls for ambulance assistance as a first response to the stroke event and within 2 hours from the stroke symptoms onset was sequentially set at 19.54% (baseline), 25%, 50%, 75%, and 100%;

c) Percentage of cases where the ambulance call taker recognizes stroke and dispatches an ambulance with the highest priority code was sequentially set at 53.52% (baseline), 75%, and 100%; and

d) Percentage of cases where the ambulance paramedics identify stroke as the problem and subsequently pre-notify the hospital with thrombolysis treatment facilities of their intent to transport the patient to the hospital in question was set at 21.92% (baseline), 50%, 75%, and 100%.

All scenarios were tested both individually and as multi-factorial intervention packages, resulting in a wide variation in eligibility for thrombolysis.

Table 1 reports the simulation results as a difference in the number of patients per one hundred between the baseline case (top left corner, shown in bold) and the tested intervention scenario, together with the corresponding 95% confidence interval. For example, simultaneously increasing the availability of stroke thrombolysis facilities to 100% and ensuring that 100% calls for ambulance assistance are made as a first response to the stroke event within 2 hours from onset, while leaving other factors unchanged from baseline, will result in additional 41.55 (95% CI: 36.76-46.35) out of every 100 patients satisfying time eligibility criteria for thrombolysis, thus bringing the total number of stroke patients eligible for thrombolysis to almost 72 out of 100.

In order to compare relative benefit of alternative potential pre-hospital acute stroke care system interventions as far as patients' eligibility for thrombolysis is concerned, the simulated outcomes of alternative interventions could be compared. For example, policy intervention "Simultaneously increasing the availability of stroke thrombolysis facilities to 100% and ensuring that 100% calls for

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ambulance assistance are made as a first response to the stroke event within 2 hours from onset" results in 72 out of every 100 patients satisfying time eligibility criteria for thrombolysis everything else being equal. By comparison, policy intervention "Simultaneously increasing the availability of stroke thrombolysis facilities to 100% and ensuring that 100% of cases are identified by ambulance paramedic in the field and relevant hospital pre-notifications are issued" results in 44 (30.21+13.26=43.64) out of every 100 patients satisfying time eligibility criteria for thrombolysis everything else being equal. This provides the decision-makers with a clear measure of the relative benefit of alternative potential interventions.

Table 2 provides the same information expressed in absolute terms without the need to rely on a pre-defined baseline value. Figure 2 summarizes this information graphically.

5. Discussion

The results presented in Tables 1 and 2, and Figure 2, highlight the importance of the availability of stroke thrombolysis facilities, as well as increasing public awareness of stroke symptoms and the need to act fast in response to their onset by making an immediate call for ambulance assistance, for stroke patients' eligibility for tPA treatment. Increasing percentage of cases where ambulance call taker recognizes stroke and dispatches an ambulance with the highest priority code and subsequent ambulance paramedics identification of stroke as the problem followed by the hospital pre-notification also results in increased stroke patients' eligibility for thrombolysis. These increases are more modest as compared with the intervention strategies based on wide thrombolysis availability and appropriate response by the callers.

It is interesting to observe that even under the "ideal" hypothetical scenario of 100% availability of stroke thrombolysis facilities, quick and appropriate actions by all callers and ambulance call-takers, as well as 100% stroke recognition and pre-notification by the ambulance paramedics, only 81 out of 100 stroke patients coming through the pre-hospital stroke care system will be eligible for thrombolysis treatment based on therapeutic time window constraints. The "residual" 19% of the patients will not get to the right place within the right time. A combination of an already highly efficient ambulance response (with times that cannot be further improved without compromising the quality of the service) and large distances to travel, will contribute to the observed residual. Despite the relevant results being outside the scope of this paper, for the cases where ambulance times could be operationally further improved, the implemented model provides a facility to experiment with ambulance transit times as this could be appropriate in some settings.

It also needs to be noted that the described case study settings, although providing an accurate account of the situation with stroke thrombolysis in a well defined geographical part of metropolitan Melbourne, Australia, paint a rather optimistic picture for many other parts of the world. As discussed in the introduction section of this paper, the present average uptake of stroke thrombolysis worldwide is around 5%, leaving a lot to be done about its wider availability. A set of implemented scenarios where tPA availability in the simulation model was fixed at 5% level, clearly demonstrates that irrespective of other settings considered in the modelling process and holding ambulance transit time distributions constant, no more than 5 out of 100 stroke patients will benefit from tPA treatment. This leaves a potential "aspirational gap" of at least 75 out of 100 stroke patients who could be eligible for thrombolysis treatment based on therapeutic time window constraints. This gap could be even wider if ambulance transit times were to be shortened further using, e.g., ambulances with mobile CT and tPA treatment units.

The described model was created and independently validated with direct input from the Victorian Stroke Clinical Network (VSCN) of the Department of Health, State of Victoria, Australia. The VSCN's primary role is to support implementation of the Stroke Care Strategy for Victoria through provision of expert advice to promote better planning for and delivery of high quality, evidence based clinically effective stroke care services across the care continuum [34]. The VSCN provides a mechanism for clinical, senior health service management, organisational and consumer representatives to inform policy on stroke care and service delivery. Current activities of the VSCN include, in particular, support for public awareness campaigns (in partnership with the National Stroke Foundation), promotion of best evidence based practice in the care and management of people experiencing a stroke including organisation of services, coordination of care, provision of information, clinical best practice and quality improvement initiatives, as well as review and development of tools to assist in monitoring the quality of stroke care services. Thus, in the original OR terms used by Morse and Kimball [17], the VSCN represents an "executive department", whose role is to make the decisions supported by the OR modelling exercise.

This discussion is an appropriate place to reflect upon whether or how any system changes have resulted as a consequence of the work described in this paper. What are the system changes we should be expecting to result from this work? More specifically, how should we judge whether the model has been used to improve stroke services? We answer these questions in light of the following points made by Morse and Kimball ([17], p.10) in the first published book on Operations Research: "Since the purpose of the analysis is to provide the executive department with a basis for decision, the problem is successfully completed only when the executive department *understand* [emphasis added] the essential parts of the conclusions of the analysis. … *The report should contain conclusions but*

usually should not contain recommendations [emphasis original]. *It should be designed to serve as a basis for decisions but should not itself made decisions. Sometimes, this distinction is a fine one; it is nevertheless an important one* [emphasis added]".

The stated objective of the paper is to support simultaneous systemic evaluation of multi-factorial interventions in pre-hospital acute care systems aimed at improving access of acute stroke patients to thrombolysis treatment. In accordance with this objective, it would be naïve to expect measurable changes in the operations of the stroke care system to result directly from this work. Does this then mean that our judgement on whether the model has been used to improve stroke services should be negative? In our view, providing a negative answer to this question would mean ignoring an important distinction between an OR report "providing a basis for decisions" rather than "making decisions" drawn by Morse and Kimball ([17], p.10) and discussed earlier.

Following the stated study objective to provide decision support in the complex pre-hospital acute care system, we consider the model to be successfully used to improve stroke services when it is used by an "executive department" (e.g. the VSCN) to "serve as a basis for decisions". This means both to increase VSCN's general understanding of the systems' behaviour under multiple alternative multi-factorial scenarios and to provide clear quantitative information regarding relative attractiveness of these multiple potential scenarios. Victorian Stroke Clinical Network recognizes the value of the proposed DES model in supporting its policy development activities, in particular, in support of formulating stroke public awareness campaigns (in partnership with the National Stroke Foundation) and in planning decisions regarding availability of tPA treatment services in regional areas. The highly interactive and visual nature of the simulation model, coupled with intuitive Excel-based interfaces and model's grounding in reliable empirical data sources trusted by the VSCN members, made the proposed decision support tool especially attractive to use. As emphasized by both the VSCN's program manager and Stroke Clinical Network Leadership Group Chair, the VSCN is interested in further collaboration and extending the proposed model to explicitly link various scenarios of pre- and in-hospital acute stroke care and longer-term patient outcomes.

Thus, our judgement regarding the real use of this model to improve stroke services is positive and is based on the feedback from the very "executive department" we set out to support. As a consequence of our work, the following system changes have occurred: VSCN is equipped with both the decision support tool in the form of the DES model and an improved understanding of the systems' behaviour necessary to support policy decisions, which, in our view, are the specific instances of what Morse and Kimball [17] call the "basis for decision".

The developed pre-hospital stroke services simulation model could be used as a decision-support tool for comparing relative benefits of potential multi-factorial interventions, both in a stand-alone mode and as a part of a more complex cost-benefit analysis without committing "in-field" resources and introducing potentially detrimental changes into operations of a real pre-hospital acute stroke care system.

6. Conclusions

Although wide availability of stroke thrombolysis treatment to appropriate patients remains a major concern for a number of health systems internationally, its uptake remains low. The time from stroke onset to hospital arrival has been identified in the medical literature to be the single most important issue in determining patients' eligibility for thrombolysis. Multi-factorial interventions have been most successful in the clinical environment in reducing pre-hospital times, but the role of individual factors alone, when combined with other individual factors or within the package remains unknown, thus calling for a solution that is capable of simultaneous systemic evaluation of multi-factorial interventions in pre-hospital acute care systems. Although Operations Research is well positioned to provide such a solution, no Operations Research effort went into investigating the pre-hospital acute care systems and processes.

In this paper, through the problem-structuring phase, we formulated a decision support problem as that of supporting simultaneous systemic evaluation of multi-factorial interventions in pre-hospital acute care systems aimed at improving access of acute stroke patients to thrombolysis treatment. Time-based eligibility for thrombolysis was selected as the outcome measure due to time-critical nature of stroke. DES was chosen as the most appropriate modelling technique to address this decision support problem due to its ability to effectively represent individual entities, attributes, decisions and events throughout the process of care, while explicitly modelling the randomness. The model provided a clear measure of the relative benefit of alternative potential interventions, thus demonstrating how OR modelling can be used for providing decision support in pre-hospital stroke care operations and contributing to the OR literature. As evident by the Australian experience, support that is provided through the use of the simple but flexible and useful simulation model in identifying the impact of key factors on patient eligibility for thrombolysis. Such support could directly inform public policy decisions, stroke public awareness campaigns and the organisation of acute stroke care systems by focusing interventions and resources on the issues that provide the best patient outcomes given the local resources available to undertake the interventions.

Future research in this area could be focused on a number of issues recently identified by Bayer et al. [3]. The simulation model proposed in this paper is currently being extended to cover the overall acute stroke care value chain. Based on the data available from clinical trials and thrombolysis registries, the

value chain simulation model will focus on the relationship between various parameters of pre- and in-hospital acute stroke care systems long term patient outcomes.

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Proportion of calls for ambulance within 2 hours from stroke onset

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Baseline 19.54%			25%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	**30.47 (27.03 - 31.49)**	0.07((-4.77) - 4.91)	0.38 ((-4.46) - 5.21)	2.80 ((-2.09) - 7.69)	1.11 ((-3.81) - 6.03)	3.01 ((-1.90) - 7.91)
	Prenotify 50%	1.10((-3.80) - 6.00)	0.96 ((-3.93) - 5.85)	0.38 ((-4.25 - 5.28)	4.08 ((-0.84) - 8.99)	3.11 ((-1.79) - 8.02)	3.04 ((-1.9) -7.98)
	Prenotify 75%	0.96 ((-3.92) - 5.83)	1.37 ((-3.53) - 6.27)	0.78 ((-4.05) - 5.61)	5.10 (0.11 - 10.09)	4.10 ((-0.83) - 9.04)	5.18 (0.23 - 10.14)
	Prenotify 100%	0.38 ((-4.52) - 5.28)	2.87 ((-2.08) - 7.82)	0.90 ((-3.99) - 5.79)	3.52 ((-1.43) - 8.48)	3.09((-1.81)- 8.00)	3.69 ((-1.27) - 8.64)
5%	Baseline (21.92%)	-28.46 ((-32.06) - (-24.86))	-27.92 ((-31.52) - (-24.33))	-28.36 ((-31.96) - (-24.75))	-28.09 ((-31.65) - (-24.54))	-28.86 ((-32.51) - (-25.20))	-27.97 ((-31.54) - (-24.40))
	Prenotify 50%	-28.39 ((-31.97) - (-24.82))	-28.36 ((-31.95) - (-24.77))	-29.46 ((-33.03) - (-25.89))	-28.42 ((-32.08) - (-24.75))	-28.83 ((-32.47) - (-25.20))	-28.25 ((-31.87) - (-24.64))
	Prenotify 75%	-28.71 ((-32.33) - (-25.09))	-28.28 ((-31.91) - (-24.65))	-28.02 ((-31.59) - (-24.45))	-28.59 ((-32.20) - (-24.98))	-27.96 ((-31.57) - (-24.35))	-27.23 ((-30.80) - (-23.66))
	Prenotify 100%	-29.36 ((-32.99) - (-25.72))	-28.02 ((-31.62) - (-24.41))	-28.55 ((-32.14) - (-24.95))	-26.97 ((-30.54) - (-23.40))	-27.95 ((-31.58) - (-24.31))	-28.00 ((-31.60) - (-24.40))
50%	Baseline (21.92%)	-9.49 ((-14.08) - (-4.90))	-9.86 ((-14.43) - (-5.28))	-10.02 ((-14.57) - (-5.47))	-7.48 ((-12.10) - (-2.87))	-7.49 ((-12.13) - (-2.86))	-8.93 ((-13.57) - (-4.29))
	Prenotify 50%	-8.58 ((-13.22) - (-3.93))	-9.33 ((-13.91) - (-4.75))	-8.54 ((-13.19) - (-3.90))	-6.87 ((-11.56) - (-2.18))	-7.32 ((-12.05) - (-2.60))	-6.22 ((-10.91) - (-1.53))
	Prenotify 75%	-9.91 ((-14.53) - (-5.29))	-9.21 ((-13.82) - (-4.60))	-9.48 ((-14.12) - (-4.83))	-7.18 ((-11.88) - (-2.49))	-6.32 ((-11.01) - (-1.64))	-7.64 ((-12.34) - (-2.95))
	Prenotify 100%	-9.18 ((-13.79) - (-4.58))	-9.59 ((-14.22) - (-4.79))	-9.39 ((-14.05) - (-4.74))	-6.94 ((-11.57) - (-2.31))	-6.01 ((-10.72) - (-1.30))	-6.18 ((-10.84) - (-1.51))
100%	Baseline (21.92%)	11.39 (6.35 - 16.43)	11.72 (6.64 - 16.79)	11.26 (6.24 - 16.27)	14.85 (9.78 - 19.92)	15.19 (10.10 - 20.28)	14.94 (9.90 - 19.98)
	Prenotify 50%	11.88 (6.81 - 16.95)	12.34 (7.30 - 17.38)	12.28 (7.20 - 17.36)	15.44 (10.36 - 20.53)	15.75 (10.69 - 20.81)	15.06 (9.96 - 20.16)
	Prenotify 75%	12.09 (7.06 - 17.11)	13.58 (8.52 - 18.64)	13.65 (8.63 - 18.67)	16.47 (11.40 - 21.55)	18.12 (13.04 - 23.19)	17.80 (12.71 - 22.90)
	Prenotify 100%	13.26 (8.22 - 18.31)	12.99 (7.92 - 18.07)	13.96 (8.90 - 19.03)	17.13 (12.05 - 22.21)	17.69 (12.62 - 22.77)	16.79 (11.69 - 21.88)

Proportion of calls for ambulance within 2 hours from stroke onset

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	50%			75%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	8.92 (3.92-13.93)	8.89 (3.86 - 13.92)	9.43 (4.40 - 14.46)	15.76 (10.70 - 20.83)	15.92 (10.82 - 21.01)	16.42 (11.38 - 21.47)
	Prenotify 50%	10.90 (5.87 - 15.93)	11.10 (6.05 - 16.16)	11.79 (6.76 - 16.83)	18.13 (13.05 - 23.20)	17.59 (12.48 - 22.71)	17.26 (12.18 -22.34)
	Prenotify 75%	11.44 (6.40 - 16.47)	11.15 (6.15 - 16.14)	13.04 (8.02 - 18.06)	19.13 (14.05 - 24.21)	19.46 (14.37 - 24.56)	18.42 (13.33 - 23.51)
	Prenotify 100%	12.64 (7.60 - 17.68)	12.79 (7.71 - 17.86)	11.74 (6.74 - 16.73)	18.82 (13.72 - 23.92)	19.03 (13.92 - 24.13)	20.69 (15.66 - 25.71)
5%	Baseline (21.92%)	-28.78 ((-32.45) - (-25.11))	-27.38 ((-31.02) - (-23.75))	-27.37 ((-31.01) - (-23.72))	-27.82 ((-31.50) - (-24.13))	-27.56 ((-31.24) - (-23.88))	-26.82 ((-30.48) - (-23.16))
	Prenotify 50%	-27.84 ((-31.45) - (-24.22))	-27.71 ((-31.35) - (-24.08))	-28.23 ((-31.88) - (-24.58))	-28.19 ((-31.91) - (-24.47))	-26.86 ((-30.55) - (-23.16))	-27.51 ((-31.18) - (-23.84))
	Prenotify 75%	-28.16 ((-31.82) - (-24.5))	-28.04 ((-31.69) - (-24.39))	-28.47 ((-32.17) - (-24.77))	-26.82 ((-30.50) - (-23.15))	-27.95 ((-31.58) - (-24.32))	-26.66 ((-30.32) - (-23.00))
	Prenotify 100%	-27.98 ((-31.71) - (-24.25))	-27.58((-31.23) - (-23.93))	-27.63 ((-31.24) - (-23.99))	-26.81 ((-30.51) - (-23.92))	-27.63 ((-31.34) - (-26.51))	-27.54 ((-31.26) - (-23.82))
50%	Baseline (21.92%)	-2.84 ((-7.65) - 1.96)	-2.86 ((-7.62) - 1.89)	-3.40 ((-8.18) - 1.37)	0.94 ((-3.94) - 5.83)	1.74 ((-3.14) - 6.62)	1.19 ((-3.72) - 6.10)
	Prenotify 50%	-0.73 ((-5.55) - 4.09)	-2.80 ((-7.66) - 2.05)	-1.72 ((-6.56) - 3.12)	4.45 ((-0.440 - 9.35)	4.12 ((-0.84) - 9.07)	3.67 ((-1.22) - 8.56)
	Prenotify 75%	-2.00 ((-6.83) - 2.83)	-2.28 ((-7.10) - 2.54)	-0.92 ((-5.76) - 3.92)	3.05 ((-1.91) - 8.01)	3.73 ((-1.22) - 8.68)	3.84 ((-1.13) - 8.81)
	Prenotify 100%	-1.76 ((-6.56) - 3.04)	-0.64 ((-5.51) - 4.24)	-1.47 ((-6.32) - 3.37)	2.36 ((-2.58) - 7.30)	3.36 ((-1.51) - 8.29)	4.72 ((-0.23) - 9.67)
100%	Baseline (21.92%)	24.46 (19.43 - 29.48)	24.23 (19.15 - 29.31)	24.14 (19.10 - 29.18)	32.05 (27.04 - 37.07)	33.29 (28.34 - 38.25)	31.85 (26.88 - 36.81)
	Prenotify 50%	24.26 (19.19 - 29.33)	24.22 (19.19 - 29.30)	25.04 (19.98 - 30.09)	32.88 (27.91 - 37.84)	35.41 (30.49 - 40.33)	34.80 (29.86 - 39.74)
	Prenotify 75%	25.43 (20.36 - 30.50)	24.11 (19.03 - 29.18)	26.88 (21.82 - 31.95)	36.04 (31.10 - 40.97)	36.13 (31.20 - 41.06)	37.34 (32.46 - 42.23)
	Prenotify 100%	27.85 (22.82 - 32.89)	26.64 (21.63 - 31.65)	26.67 (21.62 - 31.72)	37.49 (32.63 - 42.35)	37.93 (33.06 - 42.81)	38.57 (33.68 - 43.47)

Proportion of calls for ambulance within 2 hours from stroke onset

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	100%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	20.02 (16.94 - 27.09)	22.7 (17.6 - 27.79)	22.17 (17.05 - 27.28)
	Prenotify 50%	26.13 (21.10 - 31.16)	25.98 (20.90 - 31.06)	25.03 (19.99 - 30.08)
	Prenotify 75%	26.82 (21.76 - 31.87)	27.04 (22.01 - 32.07)	27.54 (22.51 - 32.58)
	Prenotify 100%	26.70 (21.63 - 31.76)	26.84 (21.79 - 31.89)	26.71 (21.69 - 31.72)
5%	Baseline (21.92%)	-26.78 ((-30.49) - (-23.06))	-27.60 ((-31.32) - (-23.88))	-27.71 ((-31.47) - (-23.96))
	Prenotify 50%	-26.72 ((-30.46) - (-22.98))	-26.47 ((-30.19) - (-22.76))	-25.95 ((-29.69) - (-22.21))
	Prenotify 75%	-25.56 ((-29.23) - (-21.89))	-26.66 ((-30.36) - (-22.97))	-26.66 ((-30.37) - (-22.94))
	Prenotify 100%	-27.72 ((-31.46) - (-23.98))	-26.92 ((-30.67) - (-23.17))	-26.56 ((-30.32) - (-22.80))
50%	Baseline (21.92%)	5.78 (0.85 - 10.71)	4.54 ((-0.41) - 9.49)	6.87 (1.88 - 11.87)
	Prenotify 50%	7.33 (2.34 - 12.33)	8.33 (3.31 - 13.36)	7.88 (2.87 - 12.90)
	Prenotify 75%	8.78 (3.81 - 13.74)	8.34 (3.37 - 13.32)	8.74 (3.71 - 13.76)
	Prenotify 100%	7.70 (2.66 - 12.73)	8.63 (3.64 - 13.61)	8.56 (3.50 - 13.61)
100%	Baseline (21.92%)	41.55 (36.76 - 46.35)	41.90 (37.13 - 46.68)	42.18 (37.39 - 46.96)
	Prenotify 50%	45.10 (40.41 - 49.80)	43.79 (39.05 - 48.53)	44.98 (40.27 - 49.69)
	Prenotify 75%	46.96 (42.29 - 51.63)	46.72 (42.05 - 51.39)	46.83 (42.17 - 51.48)
	Prenotify 100%	47.42 (42.77 - 52.06)	49.74 (45.20 - 54.28)	50.13 (45.58 - 54.67)

Table 1: Simulation results quantifying relative benefit of alternative potential pre-hospital acute stroke care system interventions (shown as difference in number of patients per one hundred) between the baseline case (top left corner, shown in bold) and the tested intervention scenarios, together with the corresponding 95% confidence interval.

Proportion of calls for ambulance within 2 hours from stroke onset

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Baseline 19.54%			25%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	**30.47**	30.54	30.85	33.27	31.58	33.48
	Prenotify 50%	31.57	31.43	30.85	34.55	33.58	33.51
	Prenotify 75%	31.43	31.84	31.25	35.57	34.57	35.65
	Prenotify 100%	30.85	33.34	31.37	33.99	33.56	34.16
5%	Baseline (21.92%)	2.01	2.55	2.11	2.38	1.61	2.50
	Prenotify 50%	2.08	2.11	1.01	2.05	1.64	2.22
	Prenotify 75%	1.76	2.19	2.45	1.88	2.51	3.24
	Prenotify 100%	1.11	2.45	1.92	3.5	2.52	2.47
50%	Baseline (21.92%)	20.98	20.61	20.45	22.99	22.98	21.54
	Prenotify 50%	21.89	21.14	21.93	23.6	23.15	24.25
	Prenotify 75%	20.56	21.26	20.99	23.29	24.15	22.83
	Prenotify 100%	21.29	20.88	21.08	23.53	24.46	24.29
100%	Baseline (21.92%)	41.86	42.19	41.73	45.32	45.66	45.41
	Prenotify 50%	42.35	42.81	42.75	45.91	46.22	45.53
	Prenotify 75%	42.56	44.05	44.12	46.94	48.59	48.27
	Prenotify 100%	43.73	43.46	44.43	47.60	48.16	47.26

Proportion of calls for ambulance within 2 hours from stroke onset

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	50%			75%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	39.39	39.36	39.90	46.23	46.39	46.89
	Prenotify 50%	41.37	41.57	42.26	48.60	48.06	47.73
	Prenotify 75%	41.91	41.62	43.51	49.60	49.93	48.89
	Prenotify 100%	43.11	43.26	42.21	49.29	49.50	51.16
5%	Baseline (21.92%)	1.69	3.09	3.10	2.65	2.91	3.65
	Prenotify 50%	2.63	2.76	2.24	2.28	3.61	2.96
	Prenotify 75%	2.31	2.43	2.00	3.65	2.52	3.81
	Prenotify 100%	2.49	2.89	2.84	3.66	2.84	2.93
50%	Baseline (21.92%)	27.63	27.61	27.07	31.41	32.21	31.66
	Prenotify 50%	29.74	27.67	28.75	34.92	34.59	34.14
	Prenotify 75%	28.47	28.19	29.55	33.52	34.20	34.31
	Prenotify 100%	28.71	29.83	29.00	32.83	33.83	35.19
100%	Baseline (21.92%)	54.93	54.70	54.61	62.52	63.76	62.32
	Prenotify 50%	54.73	54.69	55.51	63.35	65.88	65.27
	Prenotify 75%	55.90	54.58	57.35	66.51	66.60	67.81
	Prenotify 100%	58.32	57.11	57.14	67.96	68.40	69.04

Proportion of calls for ambulance within 2 hours from stroke onset

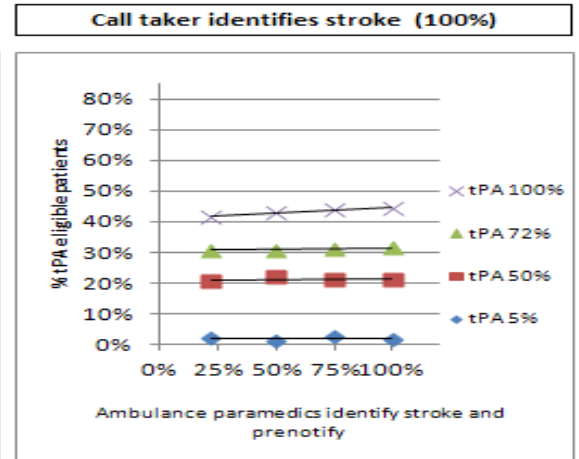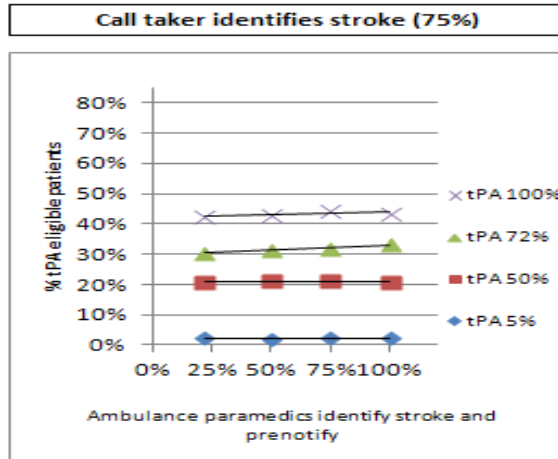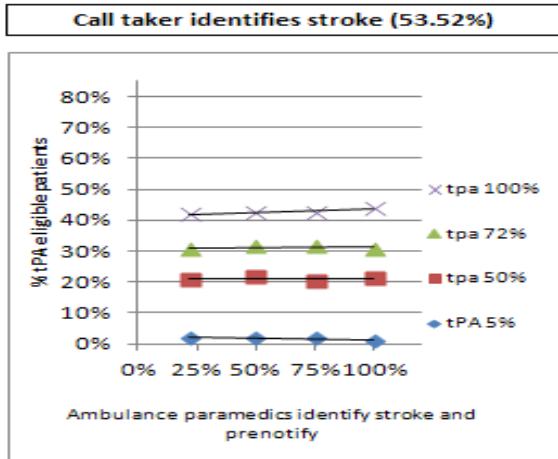| Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	100%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	50.49	53.17	52.64
	Prenotify 50%	56.60	56.45	55.50
	Prenotify 75%	57.29	57.51	58.01
	Prenotify 100%	57.17	57.31	57.18
5%	Baseline (21.92%)	3.69	2.87	2.76
	Prenotify 50%	3.75	4.00	4.52
	Prenotify 75%	4.91	3.81	3.81
	Prenotify 100%	2.75	3.55	3.91
50%	Baseline (21.92%)	36.25	35.01	37.34
	Prenotify 50%	37.80	38.80	38.35
	Prenotify 75%	39.25	38.81	39.21
	Prenotify 100%	38.17	39.10	39.03
100%	Baseline (21.92%)	72.02	72.37	72.65
	Prenotify 50%	75.57	74.26	75.45
	Prenotify 75%	77.43	77.19	77.30
	Prenotify 100%	77.89	80.21	80.60

Table 2: Simulation results quantifying comparative benefit of alternative potential pre-hospital acute stroke care system interventions, expressed as number of patients who are time-eligible for thrombolysis per one hundred.

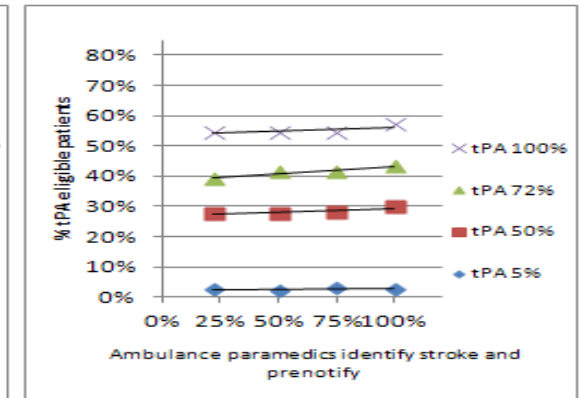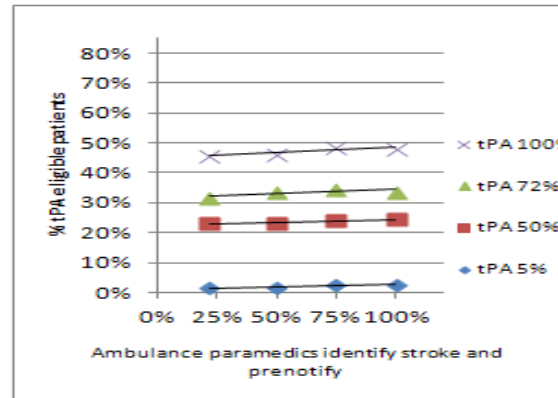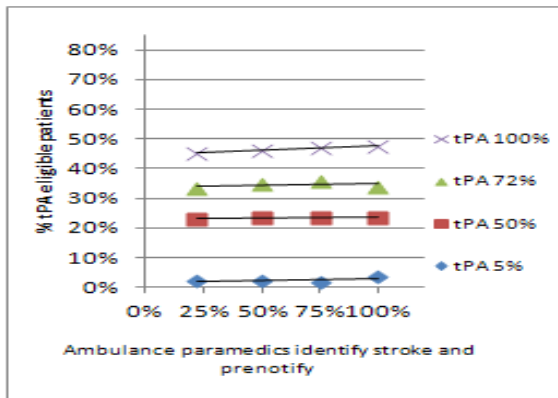**Figure 1:** Conceptual model of pre-hospital acute stroke care process
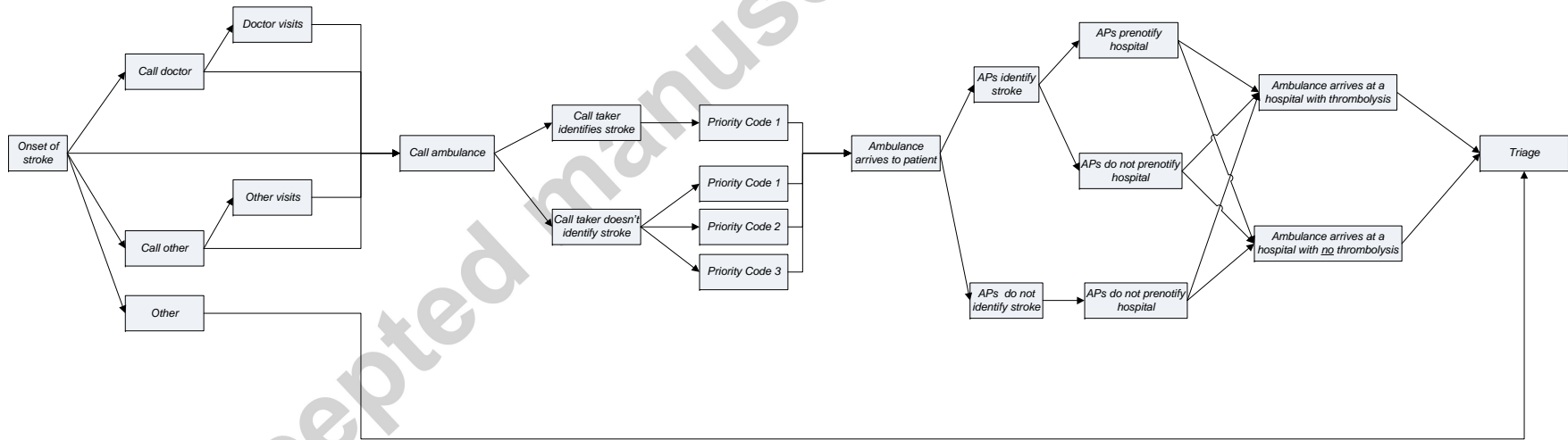
Figure 2: Simulation results quantifying comparative benefit of alternative potential pre-hospital acute stroke care system interventions, expressed as percentage of patients who are time-eligible for thrombolysis

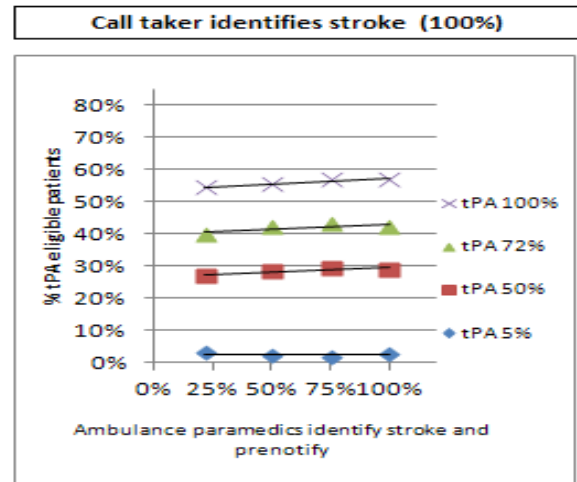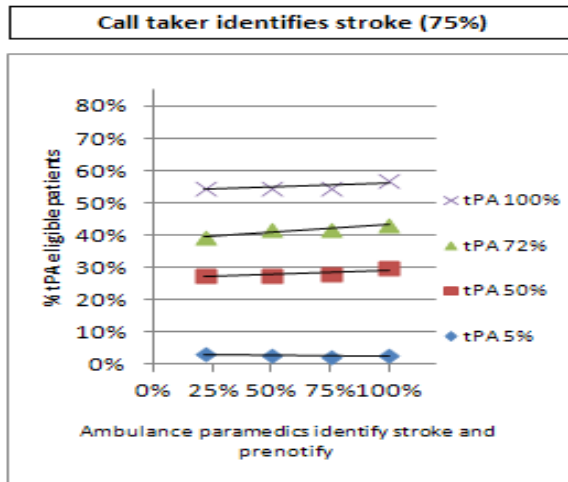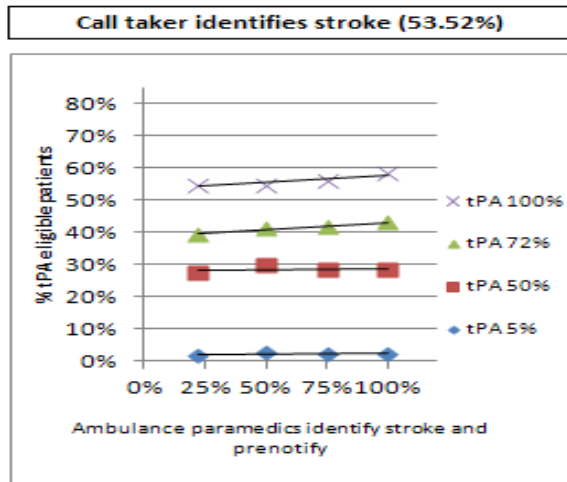|	Call taker identifies stroke (53.52%)	Call taker identifies stroke (75%)	Call taker identifies stroke (100%)

Call taker identifies stroke (53.52%) | Call taker identifies stroke (75%) | Call taker identifies stroke (100%)

50 % call ambulance within 2h

75 % call ambulance within 2h

%tPA eligible patients

Ambulance paramedics identify stroke and prenotify

tPA 100%
tPA 72%
tPA 50%
tPA 5%

24

		Proportion of calls for ambulance within 2 hours from stroke onset		
		Baseline 19.54%		
Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	30.47 (27.03 - 31.49)	0.07((-4.77) - 4.91)	0.38 ((-4.46) - 5.21)
	Prenotify 50%	1.10((-3.80) - 6.00)	0.96 ((-3.93) - 5.85)	0.38 ((-4.25 - 5.28)

100 % call ambulance within 2h

Table 1-   **1**:

	Prenotify 75%	0.96 ((-3.92) - 5.83)	1.37 ((-3.53) - 6.27)	0.78 ((-4.05) - 5.61)
	Prenotify 100%	0.38 ((-4.52) - 5.28)	2.87 ((-2.08) - 7.82)	0.90 ((-3.99) - 5.79)
5%	**Baseline (21.92%)**	-28.46 ((-32.06) - (-24.86))	-27.92 ((-31.52) - (-24.33))	-28.36 ((-31.96) - (-24.75))
	Prenotify 50%	-28.39 ((-31.97) - (-24.82))	-28.36 ((-31.95) - (-24.77))	-29.46 ((-33.03) - (-25.89))
	Prenotify 75%	-28.71 ((-32.33) - (-25.09))	-28.28 ((-31.91) - (-24.65))	-28.02 ((-31.59) - (-24.45))
	Prenotify 100%	-29.36 ((-32.99) - (-25.72))	-28.02 ((-31.62) - (-24.41))	-28.55 ((-32.14) - (-24.95))
50%	**Baseline (21.92%)**	-9.49 ((-14.08) - (-4.90))	-9.86 ((-14.43) - (-5.28))	-10.02 ((-14.57) - (-5.47))
	Prenotify 50%	-8.58 ((-13.22) - (-3.93))	-9.33 ((-13.91) - (-4.75))	-8.54 ((-13.19) - (-3.90))
	Prenotify 75%	-9.91 ((-14.53) - (-5.29))	-9.21 ((-13.82) - (-4.60))	-9.48 ((-14.12) - (-4.83))
	Prenotify 100%	-9.18 ((-13.79) - (-4.58))	-9.59 ((-14.22) - (-4.79))	-9.39 ((-14.05) - (-4.74))
100%	**Baseline (21.92%)**	11.39 (6.35 - 16.43)	11.72 (6.64 - 16.79)	11.26 (6.24 - 16.27)
	Prenotify 50%	11.88 (6.81 - 16.95)	12.34 (7.30 - 17.38)	12.28 (7.20 - 17.36)
	Prenotify 75%	12.09 (7.06 - 17.11)	13.58 (8.52 - 18.64)	13.65 (8.63 - 18.67)
	Prenotify 100%	13.26 (8.22 - 18.31)	12.99 (7.92 - 18.07)	13.96 (8.90 - 19.03)

Simulation results quantifying relative benefit alternative potential pre-hospital acute stroke care system interventions (shown as difference in   number of patients per one hundred) between the baseline case (top left corner, shown in bold) and the tested intervention scenarios, together with the corresponding 95% confidence interval.

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
		Baseline 25%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	2.80 ((-2.09) - 7.69)	1.11 ((-3.81) - 6.03)	3.01 ((-1.90) - 7.91)
	Prenotify 50%	4.08 ((-0.84) - 8.99)	3.11 ((-1.79) - 8.02)	3.04 ((-1.9) -7.98)
	Prenotify 75%	5.10 (0.11 - 10.09)	4.10 ((-0.83) - 9.04)	5.18 (0.23 - 10.14)
	Prenotify 100%	3.52 ((-1.43) - 8.48)	3.09((-1.81)- 8.00)	3.69 ((-1.27) - 8.64)
5%	Baseline (21.92%)	-28.09 ((-31.65) - (-24.54))	-28.86 ((-32.51) - (-25.20))	-27.97 ((-31.54) - (-24.40))
	Prenotify 50%	-28.42 ((-32.08) - (-24.75))	-28.83 ((-32.47) - (-25.20))	-28.25 ((-31.87) - (-24.64))
	Prenotify 75%	-28.59 ((-32.20) - (-24.98))	-27.96 ((-31.57) - (-24.35))	-27.23 ((-30.80) - (-23.66))
	Prenotify 100%	-26.97 ((-30.54) - (-23.40))	-27.95 ((-31.58) - (-24.31))	-28.00 ((-31.60) - (-24.40))
50%	Baseline (21.92%)	-7.48 ((-12.10) - (-2.87))	-7.49 ((-12.13) - (-2.86))	-8.93 ((-13.57) - (-4.29))
	Prenotify 50%	-6.87 ((-11.56) - (-2.18))	-7.32 ((-12.05) - (-2.60))	-6.22 ((-10.91) - (-1.53))
	Prenotify 75%	-7.18 ((-11.88) - (-2.49))	-6.32 ((-11.01) - (-1.64))	-7.64 ((-12.34) - (-2.95))
	Prenotify 100%	-6.94 ((-11.57) - (-2.31))	-6.01 ((-10.72) - (-1.30))	-6.18 ((-10.84) - (-1.51))
100%	Baseline (21.92%)	14.85 (9.78 - 19.92)	15.19 (10.10 - 20.28)	14.94 (9.90 - 19.98)
	Prenotify 50%	15.44 (10.36 - 20.53)	15.75 (10.69 - 20.81)	15.06 (9.96 - 20.16)
	Prenotify 75%	16.47 (11.40 - 21.55)	18.12 (13.04 - 23.19)	17.80 (12.71 - 22.90)
	Prenotify 100%	17.13 (12.05 - 22.21)	17.69 (12.62 - 22.77)	16.79 (11.69 - 21.88)

Table 1-

Proportion of calls for ambulance within 2 hours from stroke onset

2:

Simulation results quantifying relative benefit alternative potential pre-hospital acute stroke care system interventions (shown as difference in   number of patients per one hundred) between the baseline case (top left corner, shown in bold) and the tested intervention scenarios, together with the corresponding 95% confidence interval.

Table 1- **Baseline 50%** **3**:

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	8.92 (3.92-13.93)	8.89 (3.86 - 13.92)	9.43 (4.40 - 14.46)
	Prenotify 50%	10.90 (5.87 - 15.93)	11.10 (6.05 - 16.16)	11.79 (6.76 - 16.83)
	Prenotify 75%	11.44 (6.40 - 16.47)	11.15 (6.15 - 16.14)	13.04 (8.02 - 18.06)
	Prenotify 100%	12.64 (7.60 - 17.68)	12.79 (7.71 - 17.86)	11.74 (6.74 - 16.73)
5%	Baseline (21.92%)	-28.78 ((-32.45) - (-25.11))	-27.38 ((-31.02) - (-23.75))	-27.37 ((-31.01) - (-23.72))
	Prenotify 50%	-27.84 ((-31.45) - (-24.22))	-27.71 ((-31.35) - (-24.08))	-28.23 ((-31.88) - (-24.58))
	Prenotify 75%	-28.16 ((-31.82) - (-24.5))	-28.04 ((-31.69) - (-24.39))	-28.47 ((-32.17) - (-24.77))
	Prenotify 100%	-27.98 ((-31.71) - (-24.25))	-27.58((-31.23) - (-23.93))	-27.63 ((-31.24) - (-23.99))
50%	Baseline (21.92%)	-2.84 ((-7.65) - 1.96)	-2.86 ((-7.62) - 1.89)	-3.40 ((-8.18) - 1.37)
	Prenotify 50%	-0.73 ((-5.55) - 4.09)	-2.80 ((-7.66) - 2.05)	-1.72 ((-6.56) - 3.12)
	Prenotify 75%	-2.00 ((-6.83) - 2.83)	-2.28 ((-7.10) - 2.54)	-0.92 ((-5.76) - 3.92)
	Prenotify 100%	-1.76 ((-6.56) - 3.04)	-0.64 ((-5.51) - 4.24)	-1.47 ((-6.32) - 3.37)
100%	Baseline (21.92%)	24.46 (19.43 - 29.48)	24.23 (19.15 - 29.31)	24.14 (19.10 - 29.18)
	Prenotify 50%	24.26 (19.19 - 29.33)	24.22 (19.15 - 29.30)	25.04 (19.98 - 30.09)
	Prenotify 75%	25.43 (20.36 - 30.50)	24.11 (19.03 - 29.18)	26.88 (21.82 - 31.95)
	Prenotify 100%	27.85 (22.82 - 32.89)	26.64 (21.63 - 31.65)	26.67 (21.62 - 31.72)

Simulation results quantifying relative benefit alternative potential pre-hospital acute stroke care system interventions (shown as difference in number of patients per one hundred) between the baseline case (top left corner, shown in bold) and the tested intervention scenarios, together with the corresponding 95% confidence interval.

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
		Baseline 75%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	15.76 (10.70 - 20.83)	15.92 (10.82 - 21.01)	16.42 (11.38 - 21.47)
	Prenotify 50%	18.13 (13.05 - 23.20)	17.59 (12.48 - 22.71)	17.26 (12.18 -22.34)
	Prenotify 75%	19.13 (14.05 - 24.21)	19.46 (14.37 - 24.56)	18.42 (13.33 - 23.51)
	Prenotify 100%	18.82 (13.72 - 23.92)	19.03 (13.92 - 24.13)	20.69 (15.66 - 25.71)
5%	Baseline (21.92%)	-27.82 ((-31.50) - (-24.13))	-27.56 ((-31.24) - (-23.88))	-26.82 ((-30.48) - (-23.16))
	Prenotify 50%	-28.19 ((-31.91) - (-24.47))	-26.86 ((-30.55) - (-23.16))	-27.51 ((-31.18) - (-23.84))
	Prenotify 75%	-26.82 ((-30.50) - (-23.15))	-27.95 ((-31.58) - (-24.32))	-26.66 ((-30.32) - (-23.00))
	Prenotify 100%	-26.81 ((-30.51) - (-23.92))	-27.63 ((-31.34) - (-26.51))	-27.54 ((-31.26) - (-23.82))
50%	Baseline (21.92%)	0.94 ((-3.94) - 5.83)	1.74 ((-3.14) - 6.62)	1.19 ((-3.72) - 6.10)

Table 1- 4:

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
	Prenotify 50%	4.45 ((-0.440 - 9.35)	4.12 ((-0.84) - 9.07)	3.67 ((-1.22) - 8.56)
	Prenotify 75%	Baseline 100%		
	Prenotify 100%			
	Baseline (21.92%)	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
	Prenotify 50%			
100%	Baseline (21.92%)	30.82 (16.94 - 27.09) / 38.04 (31.10 - 40.97)	22.7 (17.6 - 27.79) / 36.13 (31.20 - 41.06)	27.17 (32.05 - 27.28) / 37.34 (32.46 - 42.23)
72.73%	Prenotify 50%	26.13 (21.10 - 31.16) / 37.43 (32.69 - 42.35)	25.98 (20.90 - 31.06) / 37.93 (33.06 - 42.81)	25.03 (19.99 - 30.08) / 38.57 (33.68 - 43.47)
	Prenotify 75%	26.82 (21.76 - 31.87)	27.04 (22.01 - 32.07)	27.54 (22.51 - 32.58)
	Prenotify 100%	26.70 (21.63 - 31.76)	26.84 (21.79 - 31.89)	26.71 (21.69 - 31.72)

Simulation results quantifying relative benefit alternative potential pre-hospital acute stroke care system interventions (shown as difference in number of patients per one hundred) between the baseline case (top left corner, shown in bold) and the tested intervention scenarios, together with the corresponding 95% confidence interval.

Table 1-   **5:**

5%	**Baseline (21.92%)**	-26.78 ((-30.49) - (-23.06))	-27.60 ((-31.32) - (-23.88))	-27.71 ((-31.47) - (-23.96))
	Prenotify 50%	-26.72 ((-30.46) - (-22.98))	-26.47 ((-30.19) - (-22.76))	-25.95 ((-29.69) - (-22.21))
	Prenotify 75%	-25.56 ((-29.23) - (-21.89))	-26.66 ((-30.36) - (-22.97))	-26.66 ((-30.37) - (-22.94))
	Prenotify 100%	-27.72 ((-31.46) - (-23.98))	-26.92 ((-30.67) - (-23.17))	-26.56 ((-30.32) - (-22.80))
50%	**Baseline (21.92%)**	5.78 (0.85 - 10.71)	4.54 ((-0.41) - 9.49)	6.87 (1.88 - 11.87)
	Prenotify 50%	7.33 (2.34 - 12.33)	8.33 (3.31 - 13.36)	7.88 (2.87 - 12.90)
	Prenotify 75%	8.78 (3.81 - 13.74)	8.34 (3.37 - 13.32)	8.74 (3.71 - 13.76)
	Prenotify 100%	7.70 (2.66 - 12.73)	8.63 (3.64 - 13.61)	8.56 (3.50 - 13.61)
100%	**Baseline (21.92%)**	41.55 (36.76 - 46.35)	41.90 (37.13 - 46.68)	42.18 (37.39 - 46.96)
	Prenotify 50%	45.10 (40.41 - 49.80)	43.79 (39.05 - 48.53)	44.98 (40.27 - 49.69)
	Prenotify 75%	46.96 (42.29 - 51.63)	46.72 (42.05 - 51.39)	46.83 (42.17 - 51.48)
	Prenotify 100%	47.42 (42.77 - 52.06)	49.74 (45.20 - 54.28)	50.13 (45.58 - 54.67)

Simulation results quantifying relative benefit alternative potential pre-hospital acute stroke care system interventions (shown as difference in number of patients per one hundred) between the baseline case (top left corner, shown in bold) and the tested intervention scenarios, together with the corresponding 95% confidence interval.

Table 2-   **1:**

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset Baseline 19.54%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	30.47	30.54	30.85
	Prenotify 50%	31.57	31.43	30.85
	Prenotify 75%	31.43	31.84	31.25
	Prenotify 100%	30.85	33.34	31.37
5%	Baseline (21.92%)	2.01	2.55	2.11
	Prenotify 50%	2.08	2.11	1.01
	Prenotify 75%	1.76	2.19	2.45
	Prenotify 100%	1.11	2.45	1.92
50%	Baseline (21.92%)	20.98	20.61	20.45
	Prenotify 50%	21.89	21.14	21.93
	Prenotify 75%	20.56	21.26	20.99
	Prenotify 100%	21.29	20.88	21.08
100%	Baseline (21.92%)	41.86	42.19	41.73
	Prenotify 50%	42.35	42.81	42.75
	Prenotify 75%	42.56	44.05	44.12
	Prenotify 100%	43.73	43.46	44.43

Simulation results quantifying absolute benefit alternative potential pre-hospital acute stroke care system interventions, which is calculated by adding up the baseline case (top left corner, shown in bold) to the tested intervention scenarios.

Table 2- 2:

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
		Baseline 25%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	33.27	31.58	33.48
	Prenotify 50%	34.55	33.58	33.51
	Prenotify 75%	35.57	34.57	35.65
	Prenotify 100%	33.99	33.56	34.16
5%	Baseline (21.92%)	2.38	1.61	2.50
	Prenotify 50%	2.05	1.64	2.22
	Prenotify 75%	1.88	2.51	3.24
	Prenotify 100%	3.5	2.52	2.47
50%	Baseline (21.92%)	22.99	22.98	21.54
	Prenotify 50%	23.6	23.15	24.25
	Prenotify 75%	23.29	24.15	22.83
	Prenotify 100%	23.53	24.46	24.29
100%	Baseline (21.92%)	45.32	45.66	45.41
	Prenotify 50%	45.91	46.22	45.53
	Prenotify 75%	46.94	48.59	48.27
	Prenotify 100%	47.60	48.16	47.26

Simulation results quantifying absolute benefit alternative potential pre-hospital acute stroke care system interventions, which is calculated by adding up the baseline case (top left corner, shown in bold) to the tested intervention scenarios.

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
		Baseline 50%		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
72.73%	Baseline (21.92%)	39.39	39.36	39.90
	Prenotify 50%	41.37	41.57	42.26
	Prenotify 75%	41.91	41.62	43.51
	Prenotify 100%	43.11	43.26	42.21
5%	Baseline (21.92%)	1.69	3.09	3.10
	Prenotify 50%	2.63	2.76	2.24
	Prenotify 75%	2.31	2.43	2.00
	Prenotify 100%	2.49	2.89	2.84

Table 2- **3:**

| Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
		Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
50%	Baseline (21.92%)	27.63	27.61	27.07
	Prenotify 50%	Baseline 75%		
	Prenotify 75%			
	Prenotify 100%			
	Baseline (21.92%)			
100% 72.73%	Baseline (21.92%)	46.23 / 54.73	46.39 / 54.69	46.89 / 55.81
	Prenotify 50%	48.60 / 55.90	48.06 / 54.58	47.73 / 57.33
	Prenotify 75%	49.60 / 58.32	49.93 / 57.11	48.89 / 57.14
	Prenotify 100%	49.29	49.50	51.16

Simulation results quantifying absolute benefit alternative potential pre-hospital acute stroke care system interventions, which is calculated by adding up the baseline case (top left corner, shown in bold) to the tested intervention scenarios.

Table 2-

4:

Availability of thrombolysis	Ambulance Paramedics identify stroke and prenotify	Proportion of calls for ambulance within 2 hours from stroke onset		
5%	Baseline (21.92%)	2.65	2.91	3.65
	Prenotify 50%	Baseline 100%		
	Prenotify 75%			
	Prenotify 100%	Call Taker identifies stroke baseline (53.52%)	Call Taker identifies stroke 75.00%	Call Taker identifies stroke 100%
	Baseline (21.92%)			
50% **72.73%**	Baseline (21.92%)	50.49 / 34.92	53.17 / 34.59	52.64 / 34.14
	Prenotify 50%	56.60 / 35.52	56.45 / 34.20	55.50 / 34.31
	Prenotify 75%	57.29 / 32.83	57.51 / 33.83	58.01 / 35.19
	Prenotify 100%	57.17 / 62.52	57.31 / 63.76	57.18 / 62.32
100%	Prenotify 50%	63.35	65.88	65.27
	Prenotify 75%	66.51	66.60	67.81
	Prenotify 100%	67.96	68.40	69.04

Simulation results quantifying absolute benefit alternative potential pre-hospital acute stroke care system interventions, which is calculated by adding up the baseline case (top left corner, shown in bold) to the tested intervention scenarios.

Table 2- 5:

5%	**Baseline (21.92%)**	3.69	2.87	2.76
	Prenotify 50%	3.75	4.00	4.52
	Prenotify 75%	4.91	3.81	3.81
	Prenotify 100%	2.75	3.55	3.91
50%	**Baseline (21.92%)**	36.25	35.01	37.34
	Prenotify 50%	37.80	38.80	38.35
	Prenotify 75%	39.25	38.81	39.21
	Prenotify 100%	38.17	39.10	39.03
100%	**Baseline (21.92%)**	72.02	72.37	72.65
	Prenotify 50%	75.57	74.26	75.45
	Prenotify 75%	77.43	77.19	77.30
	Prenotify 100%	77.89	80.21	80.60

Simulation results quantifying absolute benefit alternative potential pre-hospital acute stroke care system interventions, which is calculated by adding up the baseline case (top left corner, shown in bold) to the tested intervention scenarios.

Request to the typesetter: please ensure the panels 1-3, 4-6, 7-9, 10-12, 13-15 are each located in separate rows (3 panels per row).

Figure 2: Percentage of tPA eligible patients.

[*]The figures in brackets indicate, respectively, the percentage of the patients that call ambulance within 2h and the percentage of ambulance call takers that appropriately idenditify stroke
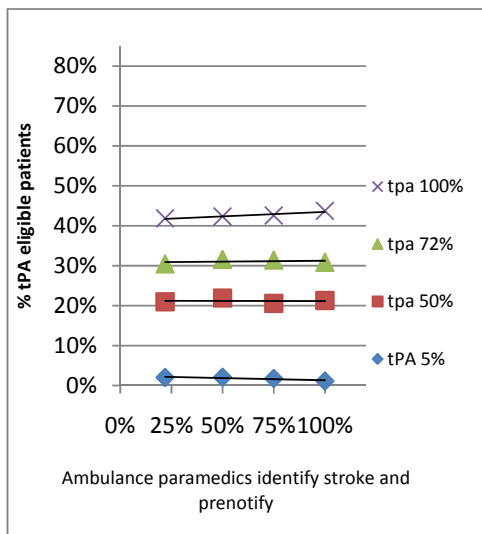
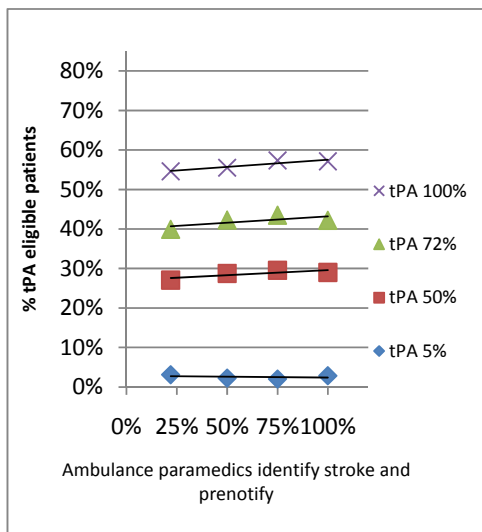Panel 1: (19.54%,53.22%)*
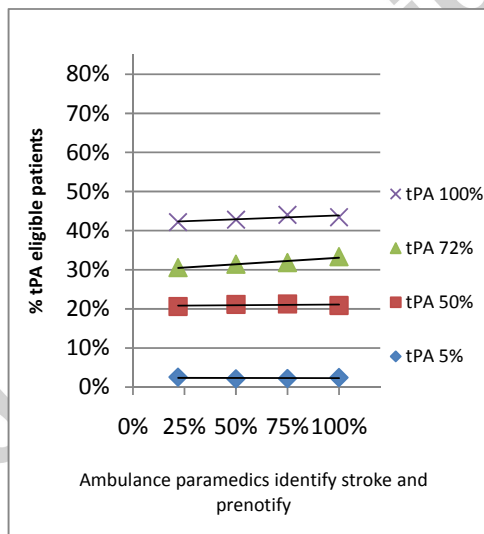
Panel 2: (19.54%,75%)*
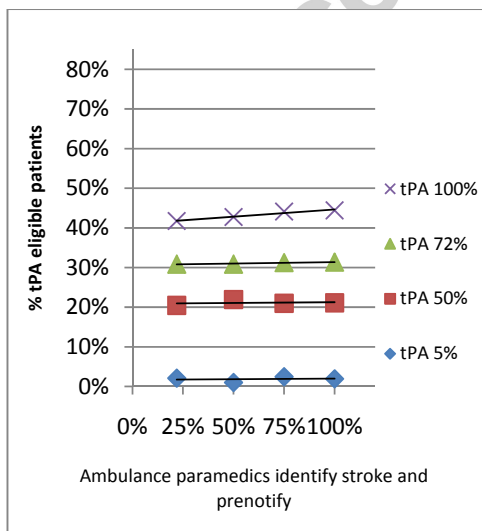
Panel 3: (19.54%,100%)*
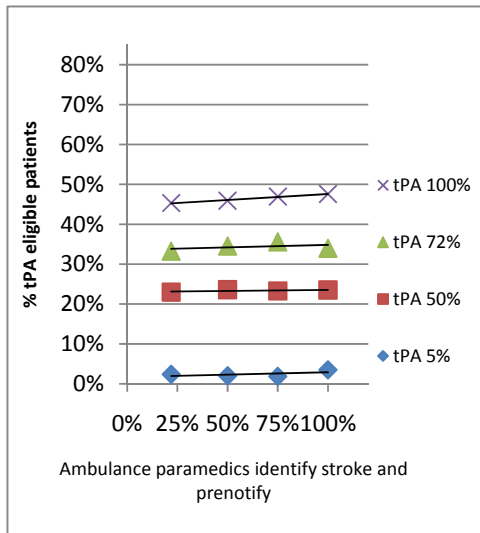
Panel 4: (25%,53.22%)*
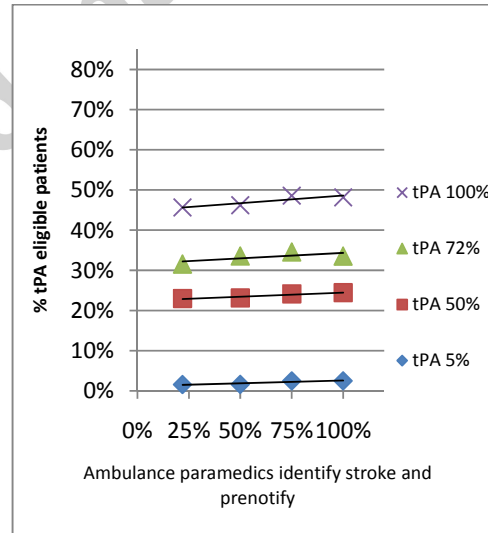
Panel 5: (25%,75%)*
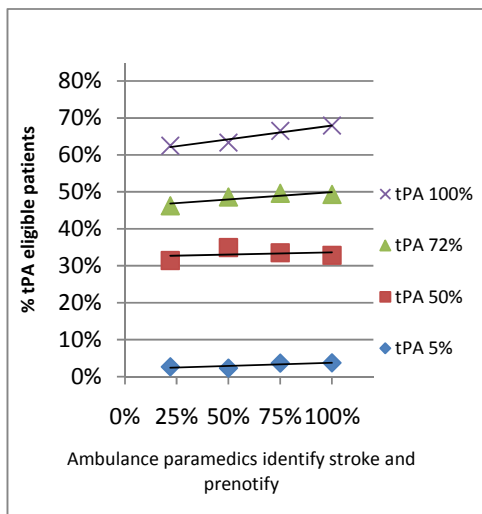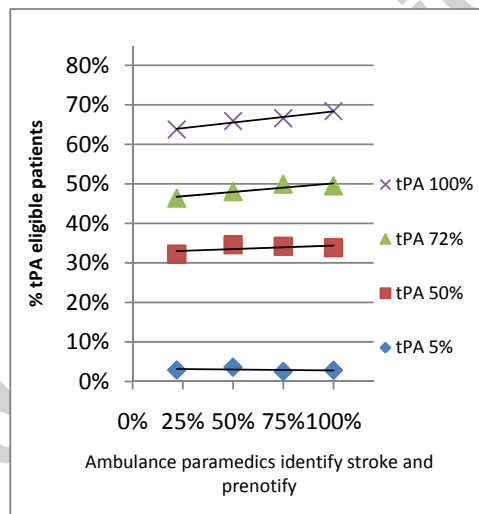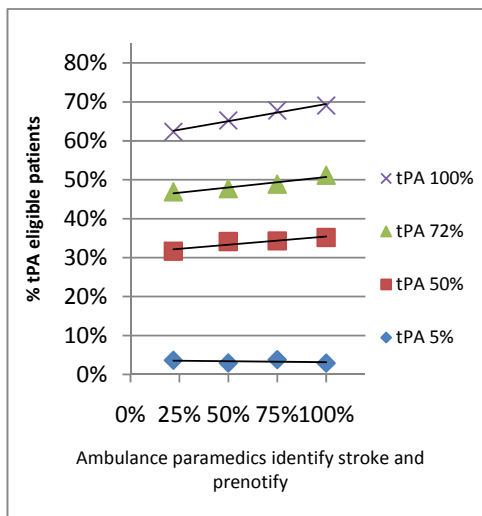
Panel 6: (25%,100%)*

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Panel 7: (50%,53.22%)*

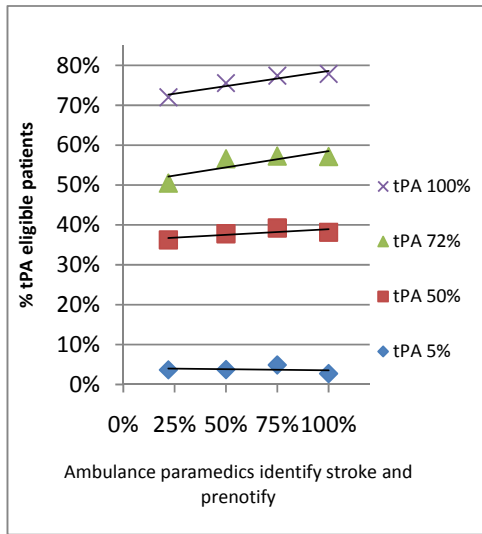Panel 8: (50%,75%)*
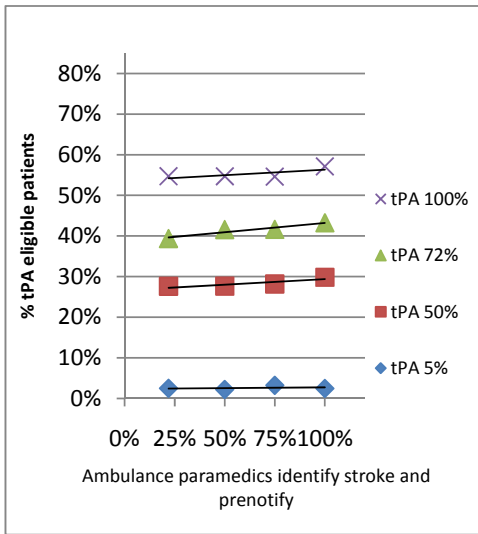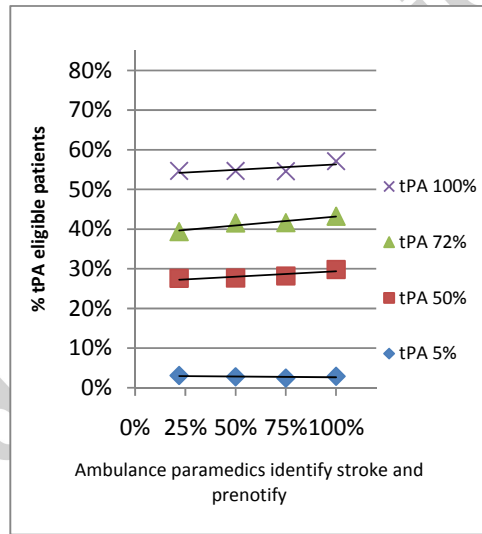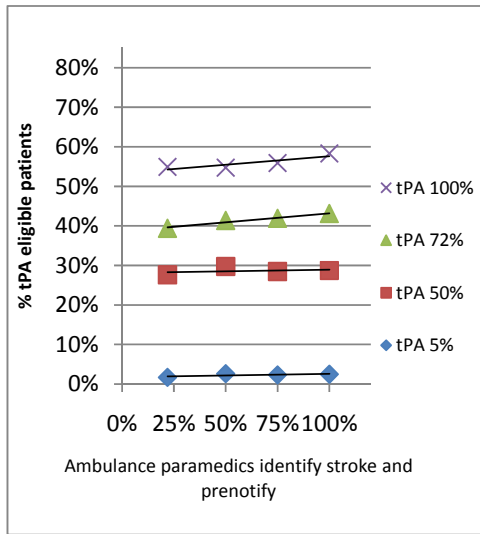
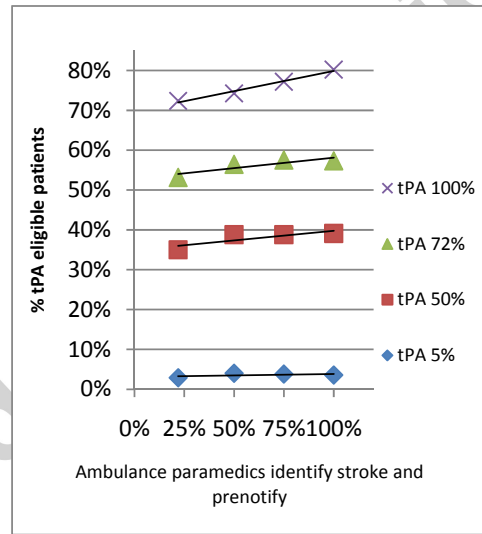Panel 9: (50%,100%)*

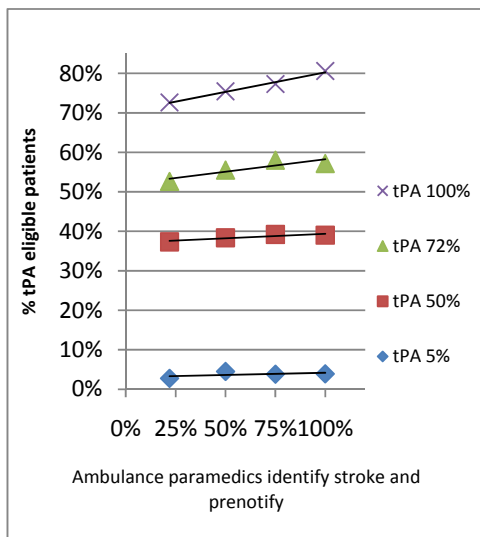Panel 10: (75%,53.22%)*

Panel 11: (75%,75%)*

Panel 12: (75%,100%)*

Panel 13: (100%,53.22%)*

Panel 14: (100%,75%)*

Panel 15: (100%,100%)*