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Intervention Decision Making for Schizophrenia Care

by

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To my love and our cats, all is possible with you.

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Declaration of Original and Sole Authorship

I, Fan E, declare that this thesis entitled *Intervention Decision Making for Schizophrenia Care* and the data presented in it are original and my own work.

I confirm that:

- No part of this work has previously been submitted for a degree at this or any other university.
- References to the work of others have been clearly acknowledged. Quotations from the work of others have been clearly indicated, and attributed to them.
- In cases where others have contributed to part of this work, such contribution has been clearly acknowledged and distinguished from my own work.
- None of this work has been previously published elsewhere, with the exception of the following:

  Daniel Frank, Fan E, Angelos Georghiou, Vedat Verter, "Community Treatment Order Outcomes in Quebec: A Unique Jurisdiction." The Canadian Journal of Psychiatry, Dec. 2019.

  The student (second co-author) developed the analytical framework and methodology, conducted the literature review, collected and cleaned the data, and designed the numerical analysis with the guidance provided from the first, third and fourth co-authors. The third and fourth co-authors also contributed in modeling the problem and interpreting the results as well as editing the manuscript. The first co-author was involved in the data collection and providing medical insights from the data and results. During the entire study, the second co-author was the main responsible for conducting the research, writing the manuscript, and developing the computer programs for solving the problem using comments and feedback from her co-authors.

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Abstract

Intervention Decision Making for Schizophrenia Care

Nearly half of the world's population experiences mental illnesses in their lifetime. Mental illnesses significantly lower the quality of life of individuals and increase the burden on society. The thesis focuses on one of the most severe mental illnesses: schizophrenia. Despite our focus on decision-making for schizophrenia interventions, it shares many obstacles and insights common for mental illness in general.

The thesis consists of three tightly constructed components, with each chapter built and extended upon the previous chapter. First, we study the effectiveness of community treatment orders (CTOs) through empirical investigation. CTOs are crucial, complex and controversial legal interventions with the primary objective of improving adherence for community treatments, where low treatment adherence is prevalent among individuals with schizophrenia. Through our empirical analysis, including survival and mixed-effect analyses, we established the effectiveness of CTOs at improving adherence and reducing hospitalization risks. In addition, we also established the positive effect of long-acting anti-psychotic injections at preventing relapse risks.

Second, we devise the optimal timing for CTO interventions based on a partially observable Markov decision model. Illness status for schizophrenia and other mental illnesses are rarely fully observable. Hence, partially observation decision models are required. The belief on the true health status is updated upon observations.

Third, we leverage natural language processing (NLP) techniques to extract and expand observations on illness status from the free-text in clinical notes. The lack of reliable numerical measurement obscures both the conduct of empirical analysis and the construct of decision models. The third chapter shows the importance and potential of quantifying textual information from clinical notes. The enhanced data further enhance our understanding and solidify the confidence in our empirical analysis on the effectiveness of medical interventions and create future novel research venues.

Résumé

Intervention Decision Making for Schizophrenia Care

Près de la moitié de la population mondiale souffre de maladies mentales au cours de sa vie. Les maladies mentales réduisent considérablement la qualité de vie des individus et augmentent le fardeau pour la société. La thèse porte sur l'une des maladies mentales les plus graves : la schizophrénie. Malgré notre concentration sur la prise de décision pour les interventions contre la schizophrénie, il partage de nombreux obstacles et idées communs pour les maladies mentales en général.

La thèse se compose de trois composants étroitement construits, chaque chapitre étant construit et étendu sur le chapitre précédent. Premièrement, nous étudions l'efficacité des ordonnances de traitement communautaire (OTC) à travers une enquête empirique. Les CTO sont des interventions juridiques cruciales, complexes et controversées dont l'objectif principal est d'améliorer l'adhésion aux traitements communautaires, où une faible adhésion au traitement est répandue chez les personnes atteintes de schizophrénie. Grâce à notre analyse empirique, y compris les analyses de survie et d'effets mixtes, nous avons établi l'efficacité des CTO pour améliorer l'observance et réduire les risques d'hospitalisation. De plus, nous avons également établi l'effet positif des injections d'antipsychotiques à action prolongée sur la prévention des risques de rechute.

Deuxièmement, nous concevons le moment optimal pour les interventions de CTO sur la base d'un modèle de décision de Markov partiellement observable. L'état de santé de la schizophrénie et d'autres maladies mentales est rarement pleinement observable. Par conséquent, des modèles de décision d'observation partielle sont nécessaires. La croyance sur le véritable état de santé est mise à jour sur les observations.

Troisièmement, nous tirons parti des techniques de traitement du langage naturel (NLP) pour extraire et étendre les observations sur l'état de la maladie à partir du texte libre des notes cliniques. Le manque de mesures numériques fiables obscurcit à la fois la conduite de l'analyse empirique et la construction de modèles de décision. Le troisième chapitre montre l'importance et le potentiel de quantifier l'information textuelle à partir de notes cliniques. Les données améliorées améliorent encore notre compréhension et renforcent la confiance dans notre analyse empirique sur l'efficacité des interventions médicales et créent de futurs nouveaux sites de recherche.

Abbreviations

CTO	Community treatment order
LAI	Long-acting anti-psychotic injection
SPMI	Severe and persistent mental illness
LOS	Length of stay
RCT	Randomized control trial
POMDP	Partially observable Markov decision problem
NLP	Natural language processing
EMR	Electronic medical record
CCC	Continuing care clinic
SOAP	subjective, objective, assessment and plan

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Chapter 1

Introduction

Amid the Covid-19 pandemic, a different crisis is emerging: the surge of mental illness. Due to the isolation of social distancing measures adopted across societies and uncertainties in the future, a record number of people are seeking help through mental crisis helplines or even suicide prevention hotlines [1–3]. Contributing to the media coverage and government campaigns, the awareness and acceptance of mental illness also reach a historical level in society.

Even before the Covid-19 pandemic, almost half of the population in the US experience mental illness during their lifetimes [4]. Nearly all Canadians are negatively impacted by mental illness through their own experiences, family members or friends at one point in life [5]. Mental illness has a prevailing impact on one's life; most mental illness is chronic with early age of onset, which leads to lifelong impairment since teenage or early twenties years. In severe cases, mental illness is associated with high suicide risks; and suicide is one of the top 10 leading causes of death both in the US and Canada [6, 7].

Mental illness brings a tremendous burden on individuals, and it also has tremendous economic costs on societies. The direct and indirect economic costs of mental illness are estimated at US2.5 trillion globally, and they are higher than chronic somatic diseases, including cancer and cardiovascular disease [8–10] (Figure 1.1). Despite the consensus on its alarming costs, limited resources and government funding are allocated for the prevention, diagnosis, and treatment of mental illness. It is partially due to the stigmatization and misconceptions from the public opinions and the outdated practice of measuring healthcare quality by counting mortality. It is also because diagnostic and treatment for mental illness are still primitive, and evidence-based treatments and interventions only recently start to gain attraction [11].

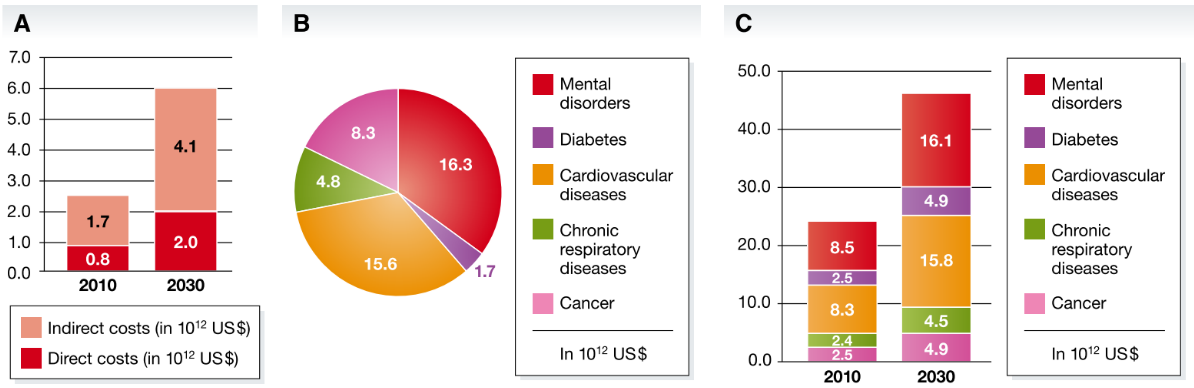

Figure 1.1: Economic costs of mental disorders in trillion US$ using three different approaches: direct and indirect costs (A), impact on economic growth (B), and value of statistical life (C) [11].

The turn of the century witnessed a rise in the practice of evidence-based medicine in psychiatry. In the past, psychiatry practice used to rely heavily on individual clinical expertise of healthcare practitioners. Evidence-based medicine advocates the "use of current best evidence in making decisions about the care of individual patients." [12]. The practice is being taught and advocated in leading medical schools, and it has shown numerous benefits resulting in better and more informed clinical decisions [13]. External studies on the accuracy of diagnostic tests, the efficacy of treatments, and the effectiveness of medical interventions are essential to evidence-based medicine. Especially, there are limited such studies on treatments and interventions regarding mental illness. To better inform clinical decisions and improve mental health care, we need more reliable evidence from mental illness studies.

Introduction

A prominent national project supported by the Center for Mental Health Services in the US on implementing evidence-based practices for people with severe mental illness has identified six practice areas in need of empirical studies on their effectiveness: collaborative psychopharmacology, assertive community treatment, family psychoeducation, supported employment, illness management and recovery skills, and integrated dual disorders treatment [14]. In the thesis, we focus on the two practice areas with the most impact on patient care: psychopharmacology and community treatment.

Pharmacological intervention is the pilar for the treatment of severe mental illness, including schizophrenia. There is undoubting evidence of the benefit of psychiatric medications from clinical trials. However, in practice, the picture is more complicated due to factors beyond the usual clinical trial considerations. In instances, clinical trials only consider the effect of a single medication in the pharmaceutical companies' interest, while, in reality, patients often receive a combination of medications from different medicine producers. In clinical trials, both the frequency and dosage of medications are strictly controlled, while, in practice, patients may not follow the prescription schedule and even miss their prescriptions.

Severe mental illness is often persistent and impairing and needs other interventions on top of pharmacological intervention. Assertive community treatment or community treatment order is one such intervention designed to assist and enforce medical treatment access. The exact content of community treatment orders (CTOs) varies across the world. However, the principle of CTOs is similar. CTO results from the recent push of integrating severely ill patients back into the community instead of being isolated in institutions. To ensure severely ill patients still receiving necessary medical treatment, CTOs outline the conditions under which patients have to adhere while in the community. The conditions usually mandate a treatment plan and other social supports. Though CTO exists in almost all developed countries, its effectiveness is still under debate.

Evidence-based practice is also crucial for policymakers as mental illness weighs heavily both on individuals and societies. The most recent publication of "Disease Control Priorities" by the World Bank identifies the enormous potential economic benefit of mental illness interventions, the lack of evidence on such interventions and the dire need for empirical cost-effectiveness investigations [15]. Policymakers in the US and Canada are especially interested in the healthcare costs for a group of high-cost mental patients. The high-cost mental patients only constitute a small portion of all patients but occupy a disproportionally large portion of healthcare spendings. The (cost-)effectiveness of those groups of patients significantly impacts healthcare spending and quality [16].

This thesis focuses on studying the effectiveness and decision-making process of varying interventions for individuals with schizophrenia. Schizophrenia is one of the most severe mental illnesses. People with schizophrenia have an abnormal interpretation of reality, with the most notable hallucinations and delusions symptoms. Besides those trademark symptoms, schizophrenia leads to disorganized thinking and behaviour, reduced or lack of everyday life functions [17]. It is often lifelong and can be disabling.

Individuals with schizophrenia are often frequent users of ER and hospitalization services. Among severe mental illnesses, including schizophrenia, bipolar disorder, and major depression, the average healthcare cost per case for schizophrenia is around fives time higher than the others. The direct healthcare and non-healthcare costs for schizophrenia in Canada were estimated to be CAN\$2.02 billion a year [18]. The indirect costs, caused by the loss of productivity, were estimated to be an additional CAN\$4.83 billion.

The challenge in studies on schizophrenia interventions is the lack of reliable accounts of information from patients. The main characteristic of schizophrenia is the loss of touch with reality; the common assumption that patients are cooperative in following their medical treatment plans and providing credible accounts of their illness symptoms is no longer valid. While prescription records exist, these medications may or may not be taken by the patients. Medication adherence rate for schizophrenia patients is notoriously low; in some cases, it is reported that less than 50% patients picking up their prescriptions after discharges from hospitals [19]. The other challenge is the lack of accurate clinical measurement of the illness condition. For somatic illnesses like hypertension or diabetes, precise and objective clinical tests are available as references for patient evaluations. However, for schizophrenia, clinical diagnosis and evaluation depend solely on healthcare practitioners' individual clinical expertise with the challenges of potential deceiving attempts from patients.

The thesis consists of three closely interrelating pieces of studies:

- An empirical investigation on the effectiveness of community treatment order
- The optimal timing for community treatment order with partially observable Markov decision model
- Empirical evidences on the importance of outpatient follow-up through text-mining clinical notes

1.1 Empirical Study of Community Treatment Order

Proper administration of medical treatment is crucial for the stability of medical conditions. However, voluntary treatment is often impractical for individuals with schizophrenia, where treatment non-compliance is an important and prevalent issue. Less than half of schizophrenia patients continue any form of treatments after discharges from their first hospitalizations [19]. Though not curable, schizophrenia is manageable through antipsychotic medications, aiming to stabilize patients and reduce relapses and re-hospitalizations. Especially, long-acting injectable antipsychotics (LAIs) [19] have multiple advantages over oral medicine for non-adherence patients, including ease of administration, monitoring, and tracking [20].

One of the widespread measures to ensure treatment adherence is the community treatment order. CTO [21] legally mandates severely ill patients to follow their treatment plans, mainly LAIs, when patients are in the community after hospital discharges.

Patients under a CTO are mandated to follow a treatment plan; healthcare practitioners are granted the power to recall patients to the emergency room if there is a concern on patients' treatment compliance.

We study the effectiveness of community treatment orders (CTOs) for schizophrenia patients from Jewish General Hospital over five years in Quebec, Canada. In Quebec, the mandate of CTOs is unique that it allows for long-duration strict enforcement procedures. Our objectives are to determine whether extended duration CTOs effectively increase treatment adherence and reduce hospitalizations in the long term. We have the following contributions:

- We are the first to establish the relation between CTO and injection adherence. We use a mixed-effect linear regression model to study CTO's long-term impact on injection adherence while controlling individual differences, including basic patient characteristics and criminal histories.
- We supplement existing evidence in the effectiveness of injections on reducing the hospitalizations rate. We use the well-accepted survival models in medical research, Kaplan–Meier and Cox survival models, to show the effectiveness of injections in a real-world environment.
- Finally, we show that improved treatment adherence reduces hospitalizations and lower overall healthcare costs.

1.2 Optimal Timing for Community Treatment Order

To the best of our knowledge, there is no existing research on CTO intervention's decision-making process. The only guideline for CTO applications is its legal criteria. Though slightly different among jurisdictions, the standard criteria for CTO applications include long-term patients who have multiple hospitalizations in the past and may face substantial deterioration with no intention of receiving treatment voluntarily [22]. Many questions regarding the decision process of CTO applications remain unanswered. For example, how many hospitalizations should trigger a CTO application, or rather, under what combination of missing appointments and hospitalizations foreshadow the necessity of a CTO intervention? We have the following contributions:

- we are the first to shine a light on the differences between CTO type and non-CTO type patients in terms of medical event dynamics. Following the CTO research tradition, we first examine the differences between the two groups of patients on the aggregated individual level; then, with our longitudinal data, we examine the differences in medical event transition probabilities. We learn that by controlling the current event, the degree of differences between the two groups of patients varies. From this, we leverage the Bayesian factor concept, which informs us how likely a patient belongs to one of the two groups given an observation of a medical event transition.

- we are the first to propose an optimal stopping model with belief update for CTO decisions. We propose an optimal stopping model with a belief update to optimize CTO intervention's timing with the trade-off between observation cost and potential cost savings under intervention. Through the decision model, we are also able to examine the potential impact of medical costs on CTO decisions;

- we are the first to evaluate the healthcare costs under different CTO decision strategies using Markov chain simulation.

1.3 The Importance of Outpatient Follow-up through Text-Mining Clinical Notes

In the above two studies, we focus on two long-term interventions for a group of severely ill schizophrenia patients: long-acting antipsychotic injections and community treatment orders. The clinical significance of those interventions justifies the above decision, and, at the same time, it is out of necessity due to the scarcity of clinical information in practice. Meanwhile, it is essential to note the complexity of such studies. The health outcome is affected by numerous factors, including but not limited to the above two interventions. Potentially influential factors are the health status of the patient, the adherence to outpatient visits, medication changes, and hospitalizations.

Till now, we have been focusing on the long-term effect of interventions and the transition of medical events without considering the momentary medical status of patients. For our study on the effectiveness of community treatment orders, the observation comparison window for their effect is yearly; that is, we compare the health outcome each year. This aggregated approach is suitable for studying community treatment orders as their duration is three years or more. The approach also eliminated the need for monitoring momentary illness status. Another consideration in deciding research approach is the availability of data. There were no numerical representations on the illness status except noticeable medical events, including hospitalizations and ER visits. The lack of numerical representations on the illness status is not unique for schizophrenia as it is inherently difficult to quantify mental illness.

This study uses the most recent development in natural language processing to construct numerical representations of illness status by analyzing the free-text clinical notes. Equipped with illness status representations, we can enhance our analysis on long-term interventions with control over illness status; further, we can examine the causation of medical events with high resolution. In the end, we want to emphasize the importance of outpatient follow-up visits for timely correction of illness evolution. We have the following contributions:

- We are the first to extract managerial insight from text-mining clinical notes for schizophrenia patients.
- We are the first to quantify the benefit of interventions, including community treatment orders, long-acting antipsychotic injections, hospitalizations, and prescription changes while controlling for illness status. By controlling illness status extracted from the clinical notes, we are confident that our results show a causal relationship instead of a correlational one.
- We are the first to quantify the benefit of outpatient clinical follow-ups for timely interventions to prevent the downward spiral of deterioration.

Chapter 2

Literature Review

Mental illness is and will continue to be one of the most critical challenges in our society. Despite its enormous individual and economic burdens, management literature on mental illness is surprisingly scarce. The scarcity of research is most likely due to the lack of research-friendly data. Unlike physiological symptoms, which are easily distinguishable and measurable, mental illness conditions are innately ambiguous. Since there is no existing management literature on schizophrenia specifically, we present the first section of the literature review to management and mental illness in general.

Mental illness management shares many similarities with chronic disease management, as mental illnesses are mostly lifelong chronic conditions. Moreover, CTO decision is inherently a long-term sequential decision-making process to balance the overall outcome during the decision time horizon. CTO's optimal timing decision model shares many similarities with optimal timing models for chronic disease. Concurrently, the health conditions for schizophrenia patients are unobservable, which are instead informed by observable medical events. This feature leads us to partially observable models. The second section of the literature review covers the sequential decision model for chronic illness, emphasizing optimal timing decision models and partially observable Markov decision models.

It is essential to note the value of economic literature on schizophrenia. Though the literature is also scarce, the few studies offer precious insights into several modelling considerations. Economic models tend to be variations of Markov chains, including discrete-time, continuous-time, and discrete event models. There are many shared modelling considerations among Markov chains and Markov decision models, for instance, the design of states. However, Markov chain models are sufficient to evaluate known policies; they are insufficient to evaluate decisions sequentially over time. The third section in this chapter reviews the economic modelling on schizophrenia.

Lastly, we introduce the application of text-mining in management and medical researches. The recent advance in natural language processing makes text-mining techniques accessible for non-experts in computer science. There is an increasing number of applicational research leveraging these advances. Text-mining techniques are essential for mental illness research because texts based information can be the only source of information. Both the diagnosis and illness conditions are only available in texts instead of numeric measures.

2.1 Mental Illness and Management Science

There are two articles on mental illness topics published in reputable management journals within recent decades. Both are empirical studies: one employs econometric methods, to be specific, generalized mixed-effect linear regression models; the other utilizes dynamic simulation models [23, 24]. It is not surprising that the only few management articles on mental illness are empirical studies. After all, empirical studies are the foundation of formulating meaningful decision models. Due to the lack of readily accessible parameter estimations and the challenges in measuring mental conditions, empirical studies are vital for their novelty and inspiring future research.

The first article studies depression treatment outcomes of IT-enabled, evidence-based, and affordable primary care operations [24]. Their sample includes 91 clinics from 19 counties in Minnesota, USA. The treatment outcomes, measured by the proportion of patients whose PHQ-9 score reduced by half after six months and 12 months, are the dependent variables. The PHQ-9 score measures the level of depression based on a clinical questionnaire. Independent variables are IT-enabled, evidence-based and affordable measures. The IT-enabled measure is defined as the level of integration of the clinics' IT system to the internal and external medical networks; the evidence-based measure is defined as the proportion of patients in clinics administered a PHQ-9 Questionnaire during their visits; the affordable measures is defined as the ratio of average payments to the clinics to the median household income in the regions. They also control patients' social environment characteristics, including the proportion of patients with diabetes, the proportion of patients with healthcare insurances, the proportion of non-white patients in the regions and the regions' average age (Figure 2.1). They conclude that IT-enabled, evidence-based, and affordable primary care operations have better healthcare outcomes for depression, while social environment characteristics also affect depression treatment outcomes.

The second article uses a dynamic simulation model to estimate the prevalence of posttraumatic stress disorder (PTSD) cases among U.S. troops in Operation Iraqi Freedom (OIF). Because of the uncertain prolonged delay of the onset of PTSD after the exposure of traumatic experiences, the usual survey approach on tallying the number of cases routinely underestimates. Their dynamic model contains four components, and the parameters for each component are estimated separately. The divided parameter estimation reduces the requirement for data collection while ensuring realistic outcomes from the dynamic model. The four components are the following: the first part models deployment time for each service member in different types; the second part models the cumulative stress at a period for each service member; the third part models the relationship between stress and PTSD; the last part models the delay duration for PTSD onsets.

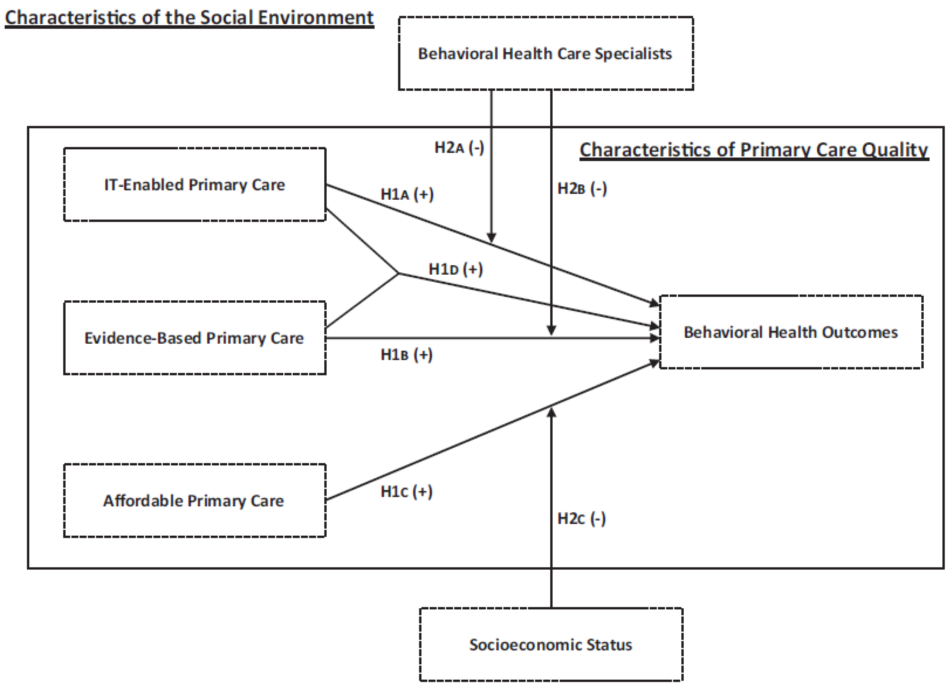

Figure 2.1: Conceptual Framework Depicting the Interplay between Characteristics of Primary Care Quality and the Social Environment on the Improvement of Behavioral Health Outcomes of Patients [24]

They conclude that the actual cases of PTSD are twice the number of cases tallied by surveys. More importantly, the repeating deployment of service members leads to less PTSD cases than the deployment of more service members just once.

Though not in recent times, it is worth mentioning a paper, "stochastic models in mental health program evaluation (MHPE) research", presented at the Operations Research and Mental Health Services Research Conference in 1980 [25]. It is the only article systematically introducing the application of operations research approaches to mental health problems. The articles touch on several aspects of operations research on mental illness, including communication structure, the necessity of operations research, and best modelling practices. They recommend a communication structure for MHPE research, a communication triangle between operations research analysts, clinical staff (psychiatrists), and mental health administrators (Figure 2.2).

They argue for the necessity of operations research on mental illness. Though in

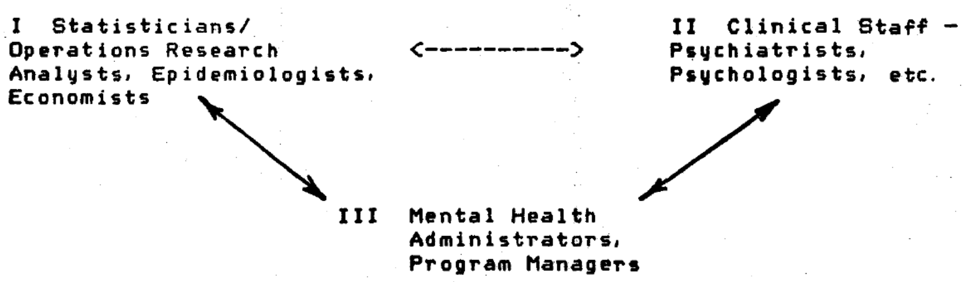

Figure 2.2: Communication for Modeling in MHPE [25]

medical research, randomized control trials (RCT) are the gold standard. They pointed out that RCTs are often impossible to implement and may not be the best approach for mental illness studies due to the following reasons: 1. a mental illness is a long-term condition, where the dynamics of a patient change over time. RCTs only measure two points in time, the pre-and post-treatment. It is crucial to study the "CHANGING PATTERNS OF CHANGE" for mental illness where sequential observations are required; 2. it is unethical to randomly allocate patients to treatment and control groups when patients need long-term and complex medical interventions. Ethical concerns prevent studies of the effect of such interventions. They also provide guidelines on constructing stochastic models for mental illness from determining sample population, developing state definition, choosing from the continuous or discrete time, transition probability estimation to the result validations.

2.2 Partially Observable Optimal Timing Models for Chronic Disease

Mental illness shares many similarities with chronic disease, and unlike mental illness, the management literature on chronic disease is affluent. The characteristic of decision making for chronic disease is in its long term nature, where medical conditions are managed over time with uncertainties on future health outcomes. Like mental illness, randomized control trials are often impractical due to the prolonged follow-up requirement. Stochastic models, mostly Markov chains, are commonly used for health intervention evaluations. However, Markov chains fall short in evaluating decisions continuously at multiple time points; Markov chains are inadequate for optimizing sequential decisions over extended periods. One excellent article on decision making for chronic disease emphasizes the advantages of employing Markov decision processes (MDPs) and partially observable MDPs (POMDPs) in chronic disease management [26].

The illustration (Figure 2.3) concisely describes a generic MDP model. An MDP model consists of actions, state transitions, and rewards at each predefined discrete-time points during a finite or infinite horizon. The state transition from the current time to the next time and the immediate reward depend on the current state and the action. The objective is to minimize the total cost over the horizon.

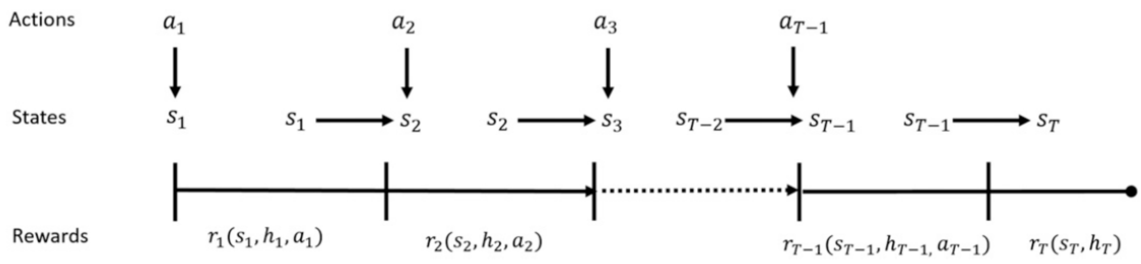

Figure 2.3: Illustration of the sequential decision-making process for an MDP, including actions, state transitions, and rewards, from the start to end of the finite-time horizon. [26]

The medical condition, aka the state of the MDP model, can be unobservable. In chronic disease, the unobservable state may be due to the potential low accuracy rate of diagnostic exams for some medical conditions. For mental illness, the unobservable state is instead the norm than exceptional cases. There are barely any accessible somatic medical exams for mental conditions; and, mental illness evaluation is often ambiguous. Partially observable MDPs are extensions of MDPs which do not require fully observable states. Instead, POMDP introduces the notion of belief state, namely, measuring the belief or the probability of each state at each time point. As illustrated in Figure 2.4, at each time point, an observation is fully observed instead of the underlying state, where the state stay hid during the entire process; the belief of the underlying state is then updated based on the observation. The objective is to minimize the total cost over the horizon based on the beliefs of the states.

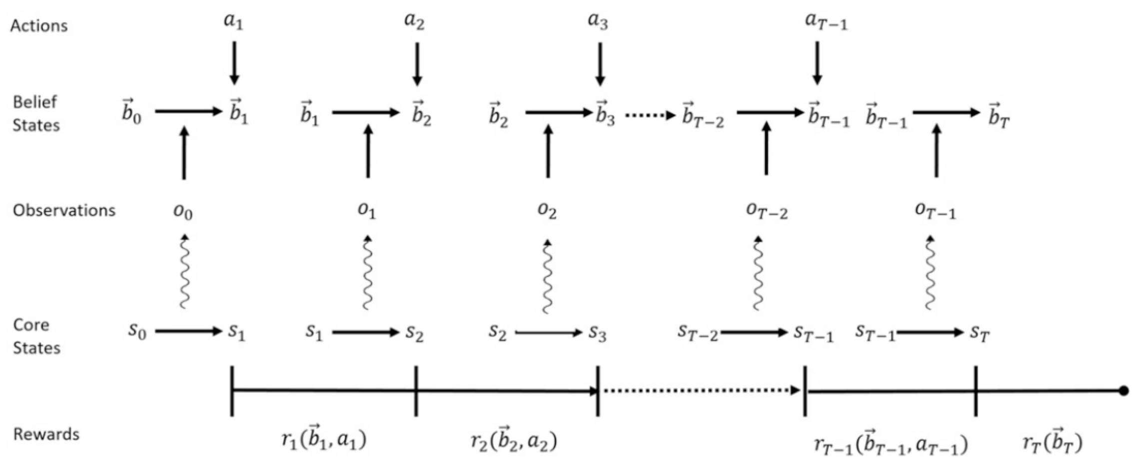

Figure 2.4: Illustration of the sequential decision-making process for a POMDP, including actions, observations o_t, core state transitions, and rewards, from the start to the end of the finite-time horizon. Observations are emitted from the system before the state transition in each decision epoch. The observations and prior belief b_t are used to update the belief vector b_{t+1}. Actions are based on the belief vector at each decision epoch. [26]

There are many successful applications of MDP and POMDP models in medical treatment: for example, patient admission management in a Neurology ward [27], optimal HIV treatment time [28], organ transplant decision [29], hypertension management [30], medical therapy planning for ischemic heart disease (IHD) [31] and cancer screening policies [32].

One study models medical therapy planning for patients with ischemic heart disease (IHD) with POMDP [31]. The underlying state of this heart disease requires expansive and invasive investigational procedures. Such, the actual illness condition is not always observable. At each time point, there are four actions available: do nothing, treat with medication, perform a surgical procedure, and perform an investigative procedure. Each action carries a different immediate cost and affects the progression of heart disease. The overall costs, including dead-alive trade-offs, quality of life, invasiveness of procedures, and economic costs, are minimized. Their model's unique feature is so named as a hybrid information state: a mixture of hidden and observable states. Partial of the disease states are fully observable, and their exact value instead of their beliefs are used with the example of treatment history. Due to the difficulty of solving POMDP, a simplified version of disease states is considered. Nevertheless, the resulting treatment recommendations still gain recognition from a cardiologist.

Another similar study uses POMDP for optimal breast cancer screening policy, mainly the scheduling of repeat mammography screening [32]. Mammography is vital for early detection of breast cancer, but it is without false positives and, more importantly, false negatives. Both the possibility of false-negative and a natural rate of cancer occurrence ensure the need to repeat mammography screenings. Additionally, with the potential of low adherences for some individuals, repeating mammography becomes even more critical for early detection. The study is the first to consider the impact of adherences on mammography schedule. There are four actions at each time point: wait, annual mammography (x1) recommendation, biennial mammography (x2) recommendation, or triennial mammography (x3) recommendation. Upon a recommendation, individuals may or may not show up for their next appointment. The risk or belief of underlying cancer condition and adherence rate are updated based on the appointments' result. Differing from the classic POMDP, their model also has a mixture of partially and fully observable states. They provide individualized optimal screening policies depending on the adherence rate and cancer risks (or the belief of cancer) based on the POMDP model. Both results on aggregated cost-saving potentials and case studies for optimal policies show the necessity of adherence consideration in similar schedule planning problems.

Optimal timing models are also closely related to our research. The literature review on optimal timing models can be found in Chapter 4. To our knowledge, there is no application of MDP or POMDP models on schizophrenia care or CTO interventions.

2.3 Economic Studies on Schizophrenia

The main objective of health economic research is to estimate the outcomes of a small option set of medical interventions by simulating the trajectories of patients [33]. There are mainly three modelling approaches for health economic research: decision tree model, Markov model, and discrete-time models [34]. The decision tree is the most fundamental decision model and demonstrates the conceptual foundation for other complex decision models (Figure 2.5). The decision tree is suitable for problems with a minimal number of decision options and decision depots. All possible trajectories of events for different decisions at each decision depot are structured in a decision tree. The outcomes, either calculated in dollar value or quality of life score, are used to evaluate different pharmaceutical or health intervention options. For example, the decision tree model is used to evaluate the cost-effectiveness between long-acting injectable anti-psychotics and oral antipsychotics over a 1-year time period [35].

Markov model is similar to the decision tree model without the limitation on the decision horizon. At each decision depot, a finite number of scenarios are presented for the next period; and, the time horizon can be finite or infinite with discount. The application of the Markov model for patients can be on the cohort level and individual level. For cohort level, a single estimate is used to represent the average transition of a group of patients; for the individual level, each patient has their own transition based on their characteristics. While the individual-level model can be more accurate than the cohort level model, the demand for parameter estimation is also much higher. Another consideration is the model's ability to cooperate with interactions between patients. For example, a hospital may have a limited number of in-patient space.

A cost-effectiveness study of drug treatments for schizophrenia in the United States

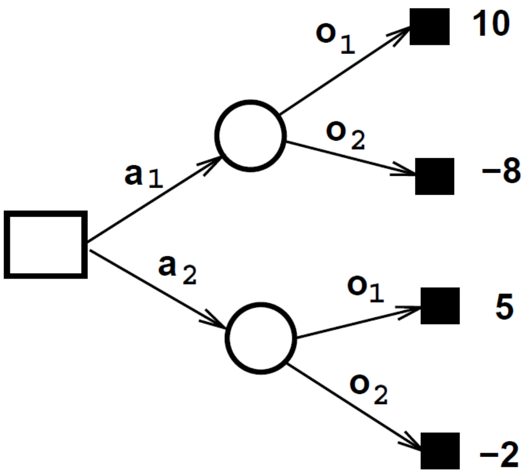

Figure 2.5: An example of a one-step decision tree. Rectangles correspond to decision nodes (moves of the decision-maker) and circles to chance nodes (moves of nature). Black rectangles represent leafs of the tree. Rewards are associated with every leaf (path) of the tree. [31]

constructed a widely accepted and adopted Markov model [36] [37] [38]. In the U.S. study and its similar studies, extensive parameters for their five-year Markov models with three months are calibrated from clinical data, existing literature, and expert experiences. As shown in Figure 2.6, at each period, the patient may relapse or not relapse. If relapse, the patient may commit suicide or continue; if continue after relapse, the patient may drop out of treatment and face a greater risk of relapse in the next period; or the patient may recover to baseline and continue treatment. If the patient does not relapse, the patient may experience one of the four symptom states: positive and negative symptoms, only positive symptoms, only negative symptoms, and no symptom; then, the patient may continue with treatment or drop out of treatment.

The drug treatments under comparison are usually oral olanzapine, risperidone, and haloperidol. Different drug treatments affect the relapse rate, the rate of treatment continuation, and the transition probabilities into the four symptom states. Interestingly, the symptom states only affect the transition probabilities into the symptom states in the coming period and have no impact on the rate of relapse and discontinuation. Relapse is

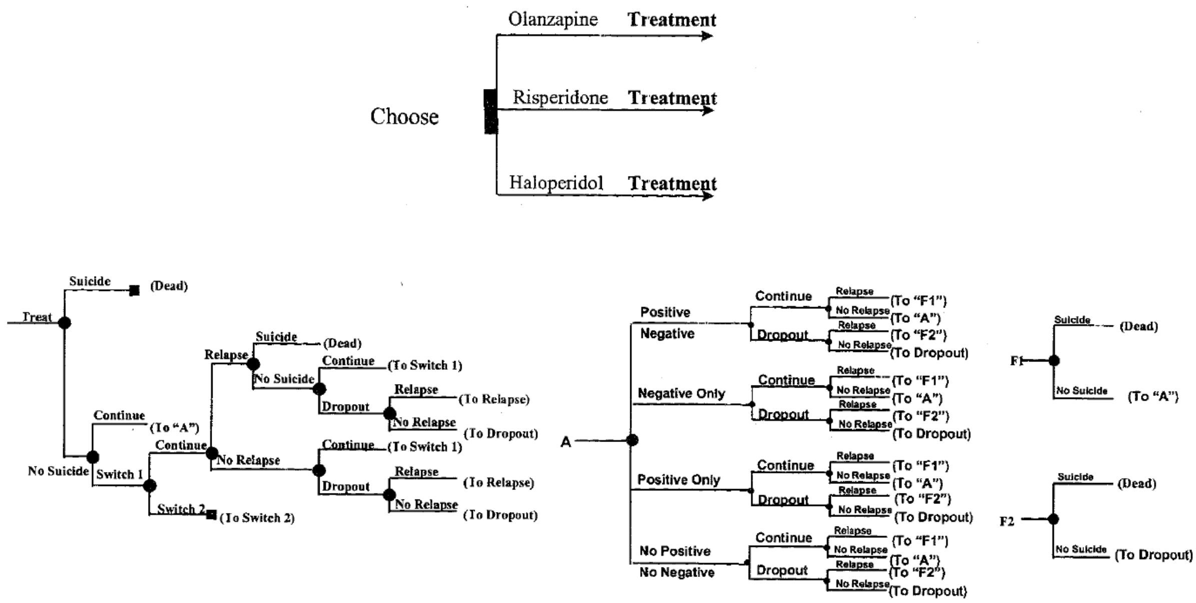

Figure 2.6: Schizophrenia treatment clinical decision model [36]

indicated by hospitalization, and recovered relapse does not affect transition probabilities into the symptom states.

Measurements, including the Brief Psychiatric Rating Scale, quality-adjusted life years, lack of relapse, and healthcare costs, are commonly used to evaluate each drug treatment effect. The cost of each period depends on 'relapse' and 'symptom'. Once relapse, at least one hospitalization occurs; during the three months, a re-hospitalization may occur as well. The average number of days in the hospital during the 'relapse' period is estimated at 54 days and the average cost for the 'relapse' period is estimated as 4373.65 pounds by a study in the U.K. at 1998 [37]. Without relapse, the average maintenance cost, mainly including outpatient visits, daycare, psychiatric nurse visits, and general practitioners visits, is estimated between 311.24 and 1763.79 pounds depending on the symptoms by the same study [37].

The last common modelling approach in healthcare economic studies is the discrete event simulation (DES) model. Instead of dividing time into separate periods as in Markov models, in DES models, time spent in a patient's health state is sampled as continuous values from survival distributions. Markov models can be viewed as approximations to DES models by discretization on time. In a cost-effectiveness study of treatment compliance in the U.K. at 2005 [39], an intricate individual level DES model is built. They consider two groups of factors on the health progress: time-independent characteristics and time-dependent variables. Time-independent characteristics include age, gender, the severity of illness, danger to self and society, and the patient's social environment; the time-dependent variables include clinical visits, drug treatments, compliance, symptoms, relapses, risk and care settings. The time-dependent variables are continuously and simultaneously sampled from chosen distributions. They conclude that a 20% increase in compliance will reduce healthcare costs by 16147 pounds per patient over 5 years.

2.4 Text-Mining in Management and Healthcare

As the prevalence of electronic medical records (EMR) grows, the adoption of EMRs also attracts research interest in the management area. Management research on EMRs often focuses on the efficiency of EMRs in improving health institutions' productivity and reducing healthcare accidents. Those research are often longitudinal empirical investigations where comparisons are made before and after the adoption of EMRs. Technically, economic models, including differences-in-differences and mixed-effect regression models, are utilized. For instance, one study collect productivity measures from 87 physicians in 12 primary care clinics from periods both before and after the implementation of EMR systems [40]. Their data contains $3,186$ physician-month observations over 39 months. They found that productivity decreases right after the implementation of EMR but recovers after a few months. EMRs do not significantly affect productivity in the long term, either positively or negatively. Another study with a similar research design, a difference-in-difference panel study, shows that EMRs reduce healthcare errors [41].

We are the first to examine the content of EMRs, namely, the text of clinical notes using text-mining techniques. Text-mining approaches have gained interest in management research because the recent development in natural language processing (NLP) has made professional-level text-mining tools accessible to general researchers. One such exemplary study is on extracting small investor sentiment from stock message boards [42]. As illustrated in Figure 2.7, they collect public messages from Yahoo's stock message board, apply five different classifiers on the processed message data, and the majority outcomes of the five classifiers are compared with the real stock market data. They show that the investment sentiment they extracted from messages is strongly correlated with the stock market performance, and, such, it validates the potential of applying text-mining techniques in management research.

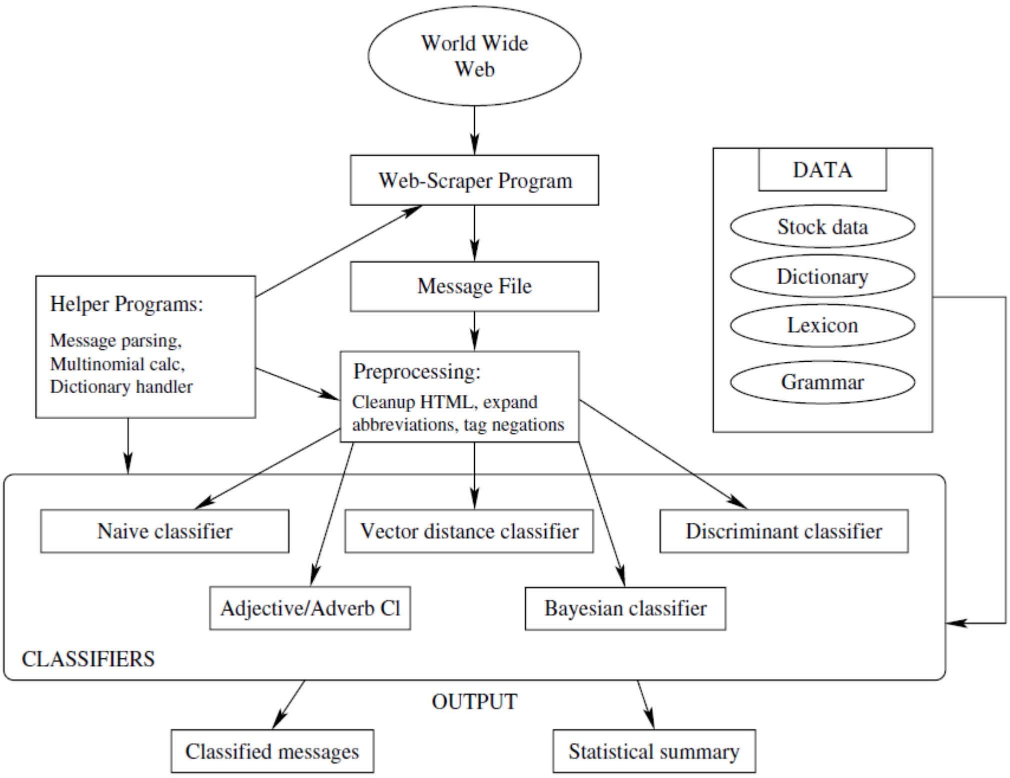

Figure 2.7: Schematic of the Algorithms and System Design Used for Sentiment Extraction [42]

Another study on the popularity of Facebook advertising content uses a combination of Amazon Mechanical Turk (human workers) and natural language processing algorithms.

They also favour the ensemble approach, just like the previous study, where the results from multiple varying classifiers are combined as the final classification. They demonstrate that text-mining techniques can be an economical alternative to process text data in scale for empirical studies.

To the best of our knowledge, there is no literature on the study of clinical notes for schizophrenia using text-mining techniques to develop managerial insight. The only relevant study is a medical study on negative symptoms of schizophrenia [43]. Using text-mining techniques, they recover the prevalence of negative symptoms in medical records. They have found that negative symptoms are strongly associated with hospital admissions and the impairment of living capacities.

Chapter 3

Community Treatment Order Outcomes in Quebec

3.1 Introduction

Community treatment orders (CTOs) are complex mental health interventions that employ a legal requirement to coerce patients with severe and persistent mental illness (SPMI) who refuse to accept psychiatric treatment to do so. Thus, they remain controversial due to ethical concerns regarding their coercive nature and methodological issues concerning the use of naturalistic designs versus randomized controlled trials (RCTs) in studying their effectiveness.

A substantial number of naturalistic studies have reported decreased recidivism and/or shorter lengths of stay (LOS) in hospital as a result of CTOs.[44–47] However, due to methodological issues, assessing the outcome of CTOs remains a contentious issue in the literature. Recently, increased attention has been directed toward the weaknesses and/or inadequacies of RCTs as the gold standard in assessing the outcomes of complex interventions–both in medical research at large[48, 49] and particularly regarding psychiatric CTOs.[50] These authors detail handicaps in making valid inferences of causal attribution via RCTs, which emphasize efficacy and internal validity at the expense of generalizability and real-world effectiveness. As O'Reilly and Vingilis[50] point out, confounding variables include varying study designs with differing inclusion and exclusion criteria and sample sizes. In addition to the limitations of the RCT design, CTOs represent complex interventions, and this fact creates a second methodological challenge. There are jurisdictional differences in CTO regulatory provisions, differing professional decision-making, differing personal subjective ethical approaches toward restricting autonomy, and differing clinical judgments. Taking these methodological issues into account, various authors suggest alternative methodologies including naturalistic studies.[48, 50, 51]

An early RCT of CTOs concluded that *only* extended duration orders with enhanced outpatient treatment had a positive impact on reducing recidivism.[52, 53] A second study of the duration of CTOs by Rohland et al.[47] showed decreased admissions and LOS with commitment periods of greater than 1 year. Nevertheless, the literature is sparse regarding the outcomes of extended duration CTOs containing strict provisions in the legal order providing that the police can quickly bring nonadherent patients for treatment (see below). We conducted a longitudinal, naturalistic study to fill this gap. It is a naturalistic study because it is important to study the effect of medical interventions in a real-life clinical setting where conditions are not ideal.

Enhanced interventions are needed for SPMI patients as they suffer significantly short life spans, a multitude of serious symptomatic and functional impairments, and increased involuntary hospitalizations in comparison to the general population. [54, 55] A particular subgroup of patients with SPMI suffer deficient or absent insight,[46, 56] leading to impaired adherence with treatment[57] and to significantly poor outcomes and quality of life.[58] In addition, these patients incur considerable mental health-care costs.[45, 59]

To the best of our knowledge, although there is abundant knowledge about the beneficial effects of long-acting antipsychotic injections (LAIs) in SPMI,[57, 60, 61] the literature is silent on the effect of CTOs on injection adherence by using *actual and accurate recorded LAI injection data.* In this study, we hypothesize (i) that extended duration CTOs lead to increased adherence to antipsychotic treatment as well as more intensive outpatient clinical management and (ii) that the increased adherence with medications results in enhanced freedom of such individuals by reducing the time they have to spend in hospitals.

3.2 Patients and Method

The study was carried out in Quebec, a distinctive jurisdiction where CTO duration is usually 3 years and can be as long as 5 years. In contrast, in Canada except Quebec, CTOs tend to be of 6 to 12 months duration, and if further treatment is considered necessary, further legal procedures must be undertaken (from Personal Communication with Dr. Rohland BM.).[47, 62]

According to the Quebec civil code, the criteria for awarding a CTO are that the impaired person is unable to understand and appreciate that he or she requires psychiatric and/or social intervention, refuses it, and is unable to understand the risks and benefits involved. Dangerousness, per se, is not a legal criterion for a CTO in Quebec, although it is often elsewhere where a deterioration criterion, approximating dangerousness, is sometimes utilized. In Quebec, if the patient fails to show up for their visits and medications, the court order can be faxed to the local police who promptly bring the patient to the doctor's hospital for evaluation and an injection of the required LAI. This is another uncommon feature of the Quebec system–the CTO itself directly allows for involuntary administration of medication. This feature is often explicitly prohibited elsewhere where obtaining permission for an involuntary injection or other coercive treatment requires additional legal authority and procedures.[50, 63] The above organizational factors render Quebec a distinctive laboratory in which to test the outcome of CTOs.

We conducted a follow-back prospective study over a 5-year period between 2010 and 2015, based on our clinic's entire SPMI population. Criteria for acceptance to the Continuing Care Clinic (CCC) are cases where a patient suffers from SPMI and has suffered from repeated hospitalizations and significant morbidity. The most frequent diagnoses in the clinic are schizophrenia and schizoaffective disorder. The dates of (i) all clinic visits, (ii) injections of LAIs, (iii) CTOs, (iv) hospitalizations, (v) ER emergency room visits, and (v) crimes were recorded and the interrelationships were studied. Among the 367 patients studied, 77 were obliged via a CTO during the study period to have regular injections and clinical follow-up. Note that many of these 77 patients were also prescribed oral medications including clozapine, but injections were utilized because these particular patients are not reliable in taking oral medication. The remaining 290 patients did not have a CTO during the study period. Consent to participate in this retrospective study was not required, and no patient was identified by name. Ethics approval was received from the hospital's research and ethics committee.

In Montreal, mental health care is provided by the designated hospital in its geographical catchment area, that is, the patients who present at the emergency room of another hospital are immediately transported to their assigned hospital. There are virtually no private or alternative mental health services available to this population. As a result, the psychiatric care utilization data for our patient population can be considered to be quite complete and accurate. These facts are not usually applicable to other jurisdictions. No meaningful changes in the legal tenets, organizational functioning, bed capacity, or clinic staffing occurred during the 5 years of the study.

Demographic and care utilization data were obtained from the hospital's medical and administrative records and from the patient charts in an electronic database record. Each injection was recorded in the electronic medical records by nurses in the outpatient clinic. Data regarding costs of psychiatric hospitalizations were obtained from the hospital information technology department. CTO and criminal records were obtained at the

Montreal Courthouse by the hospital's legal consultants. We obtained the rates and types of crimes committed as described by the CCC.

The study was designed to enhance its external validity–no exclusion criteria for entry to the clinic were employed. As emphasized in detail by O'Reilly,[50] these features convey a significant advantage of a naturalistic method compared to RCT methodology, aside from the fact that regression to the mean is not controlled.

We categorized patients into two groups: CTO patients, who were under active CTOs at some point during the study period and non-CTO patients, for whom a CTO was never requested. Two-sample t test was conducted to report the significances of the differences between these two patient groups. We recorded age, gender, ethnicity, substance abuse history, injection, hospitalization, ER visit history, and criminal records. Specifically, age is defined as the age of the patient at the year of the study start; substance abuse history is defined as the existence of any substance abuse records during the study period; injection is defined as the existence of injection records from the clinic, that is, at least one injection is recorded as admitted to the patient in the clinic; hospitalization is further divided into three subcategories, that is, the existence of one hospitalization during the study period, the existence of two hospitalizations, and more than three hospitalizations; ER visit is defined as the existence of any ER visit records during the study period; and, criminal record is defined as the existence of any criminal history for the patient.

We studied the effectiveness of CTOs on hospitalization rates and injection adherence using the uncontrolled before and after comparison method. To ensure a representative group of patients with enough observation periods, we selected 53 CTO patients for whom we have at least 6-month worth observations both before and after the initiation of CTOs. Each patient acts as their own control, and paired sample t test was used to examine the change after the initiation of CTOs. The *hospitalization rate* is defined as the number of hospitalizations divided by the duration of the time interval of interest, and *injection adherence* is defined as the number of injections received at the outpatient clinic during the time interval of interest divided by the number of injections prescribed during the same interval. To examine the impact of CTOs on LOS, we focus on the subgroup of 26 CTO patients, from whom we observe hospitalizations both before and after the initiation of their CTOs.

We also examined the effect of CTOs on injection adherence and the effect of injection adherence under CTOs on hospitalization rate. We used injection adherence before the initiation of CTOs as benchmark and recalculated injection adherence for each single year after the initiation of CTOs. The samples were analyzed using the mixed-effect linear regression model, which was designed to analyze repeated observations from same subjects. We also incorporated other covariates including age, gender, ethnicity, substance abuse history, and criminal records. The definition of all covariates follows the previous experiments.

We aimed to establish the link between the increased injection adherence and the reduced hospitalization rate under CTOs. Defining survival as living in the community without any hospital admissions, we applied the Kaplan–Meier method[64] and the Cox survival regression models.[65–68] The Kaplan–Meier method accounts only for adherence rate and does not take into account other factors that can potentially affect hospitalization rate and hence we resorted to the Cox survival regression model to analyze the effect of adherence on hospitalization with other covariates as controls. Again, the 53 CTO patients with sufficient observation periods were used in both of the above survival analyses. Since injection adherences tended to fluctuate over time for all patients and Cox survival regression can readily incorporate time-varying covariates, we calculated the monthly injection adherences to better capture the fluctuation of injection adherences and to have a better estimate on their effects on hospitalizations. In total, the 53 CTO patients produced 2,497 monthly observations for the Cox regression model.

3.3 Results

3.3.1 Demographic and Clinical Characteristics

Table 3.1: Demographics Characteristics: CTO and Non-CTO Patients.

Characteristics	CTO ($N = 77$)		Non-CTO ($N = 290$)		χ^2	*df*	*P* value
	N	%	N	%			
Age	45.97 ± 12.60		48.92 ± 10.94				
Gender (male)	51	66	181	62	0.2352	1	0.627
Ethnicity					5.2592	4	0.261
Black	12	16	40	14			
East Asian	6	8	34	12			
Hispanic	2	3	3	1			
Middle Eastern	9	12	17	6			
White	48	62	196	68			
Substance Abuse	24	31	45	16	8.7652	1	0.003
Injection	74	96	159	55	42.956	1	0.000
Hospitalization					82.459	3	0.000
1	22	29	45	17			
2	10	13	22	8			
≥ 3	30	38	18	6			
ER emergency room visit	62	81	108	37	44.109	1	0.000
Criminal Record	33	42	83	28	5.7046	1	0.016

Note. $N = 367$. CTO = community treatment orders.

Table 5.2 displays the basic characteristics for these two patient groups, CTO patients group and non-CTO patients group, and reports substance abuse history, LAI injections, hospitalizations, ER visits, and criminal history within each group.

We observe that there are no significant differences between CTO patients and non-CTO patients in terms of demographics, that is, age, gender, and ethnicity; while CTO patients are more severely ill in the sense that they are significantly more likely to have substance abuse history, to have LAI injection history, to have ER visits and hospitalization histories, and to have criminal history records.

It is evident from our data set that the crime rate of our SPMI patient cohort is higher than the general population in Montreal. During the 5-year study period, there were 570 charges reported for the 367 patients. This amounts to 21 times the rate of adults charged in Montreal in 2012. Note that we include all indicted and acquitted charges from both the criminal court and municipal court in our calculation. The CTO patients had a higher frequency of charges, that is, 220 charges for the 77 CTO patients.

3.3.2 Uncontrolled Before and After Comparison of Hospitalization Rates

On average, patients were admitted 0.96 times per year before the start of their CTOs, whereas the frequency decreased to 0.56 times per year during the CTOs. The decrease is statistically significant ($P = 0.013$, degree of freedom = 52, t statistic = 2.554) using paired-sample t-test method.

To assess CTO's impact on the hospital LOS, we focused on a subgroup of 26 CTO patients, from whom we observe hospitalizations both before and after the initiation of their CTOs. Comparing the last hospitalization prior to the initiation of CTOs to the first hospitalization posterior to the initiation of CTOs, there was an average decrease of 31.5 days on LOS from 84.53 days prior to 53.03 days posterior. Using the cost information provided by the hospital, that is, $472.11 per day in the psychiatry ward, we estimate that the CTOs are associated with savings of up to CAD$14,871 per hospitalization.

3.3.3 Effect of a CTO on LAI Adherence

LAI injection adherence rate increased from 10.7% to 42.2% on average–statistically significant ($P < 0.001$, degree of freedom = 52, t statistic = 7.438) using paired-sample t-test statistic method. Correspondingly, we also observe that then umber of outpatient visits also increased under a CTO–statistically significantly from 5.22 visits per year to 21.8 visits per year ($P < 0.001$, degree of freedom = 52, t statistic = 9.7640) using paired-sample t-test statistic method.

Table 3.2: Injection Adherence over Time (Relative to Community Treatment Orders).

Variables	Estimate	Std. Error	T value	P value
(Intercept)	0.106	0.125	0.847	0.401
First Year	0.284***	0.051	5.556	0.000
Second Year	0.322***	0.054	5.940	0.000
Third Year	0.386***	0.062	6.154	0.000
Fourth Year[a]	0.478	0.072	6.634	0.000
Age	0.000	0.002	0.322	0.749
Gender	0.009	0.064	0.147	0.884
Ethnicity	−0.001	0.061	−0.029	0.977
Substance Abuse	0.002	0.067	0.043	0.966
Criminal Record	−0.105	0.071	−1.465	0.149
Note:	*p<0.1; **p<0.05; ***p<0.01			

[a]The fourth year means the first year after a 3-year CTO expires.

Through mixed-effect linear regression, we used injection adherence before the initiation of CTOs as benchmark, then calculated injection adherence for the 1st year after the initiation of CTOs, the 2nd year, the 3rd year, and so on. The random effects are on individual levels, including the intercept and basic characteristics of patients. Table 3.2 depicts that number of years after CTO is the only statistically significant factor corresponding to LAI injection adherence. The benchmark injection adherence, that is, injection adherence before the initiation of CTOs, is 10.6%; the 1st, 2nd, and 3rd year during CTOs result in a significant increase in the injection adherence rate, and the level of increases are 0.28 (standard error [SE] = 0.05, $P < 0.001$), 0.32 ($SE = 0.05$, $P < 0.001$), and 0.38 ($SE = 0.06$, $P < 0.001$) respectively, comparing to the benchmark.

Note that the injection adherence rate during CTOs is still relatively low and that late injections appear periodically. Figure 3.1 depicts that the majority of late injections are administered at the next scheduled appointment. An interesting and unanticipated finding was that in terms of the first injection received after the initiation of CTO, one subgroup received their LAIs in a timely manner considering the date at which the judge

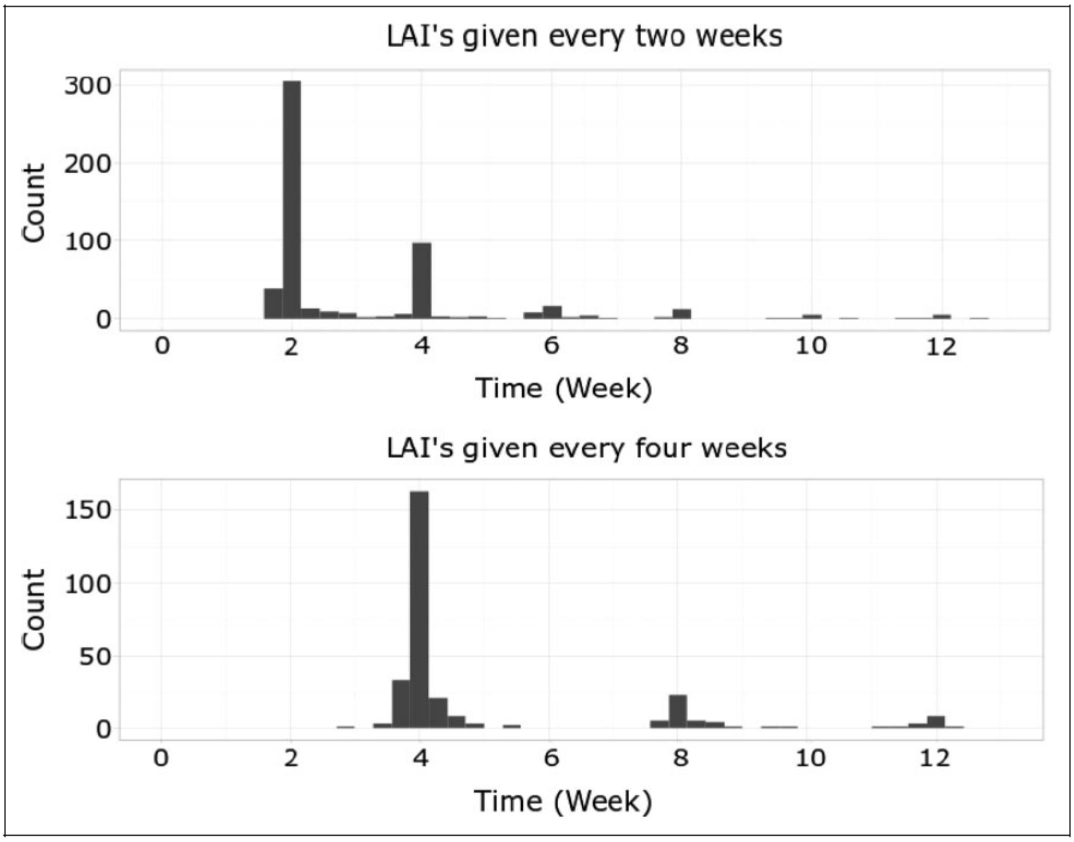

Figure 3.1: Injection received intervals during community treatment order periods. This figure shows the time intervals between sequential injections received by patients. The x-axis is time (per week), and the y-axis is the number of injections.

signed the order (36.4%), a second group's injections were moderately delayed (21.2%), and a third group did not receive any injections (42.4%) till the next hospitalization.

3.3.4 Effect of LAI Adherence on Hospitalization

We applied the Kaplan–Meier method for CTO patients by categorizing the adherences into two groups: (i) 0% to 30% adherence and (ii) 30% to 100% adherence, based on a visual inspection of the clustering of the data points. Figure 3.2 visualizes the survival curves and shows that the patient group with low adherence has a significantly lower survival probability than the second group of patients. We use the log-rank test to determine whether the survival curves for the two groups are significantly different. This

Table 3.3: Cox Model: Effect of LAI Adherence on Hospitalization.

Variables	Estimate	Std. Error	HR	Lower 95	Upper 95	P Value
LAI adherence	−1.393 ***	0.345	0.248	0.126	0.489	0.000
Age	−0.037 ***	0.011	0.964	0.943	0.986	0.001
Gender (male)	0.164	0.307	1.178	0.645	2.152	0.594
Ethnicity (White)	0.756 ***	0.280	2.131	1.231	3.688	0.007
Substance Abuse	−0.163	0.269	0.850	0.502	1.440	0.545
Welfare	0.509	0.362	1.664	0.818	3.384	0.160
Criminal record	0.941 ***	0.282	2.563	1.474	4.459	0.001
AIC	623.047					

Note. LAI = long-acting antipsychotic injections; AIC = Akaike information criterion; HR = hazard ratio. *p<0.1; **p<0.05; ***p<0.01

gives a P value < 0.001 using log-rank test, indicating that the two groups are in fact significantly different.

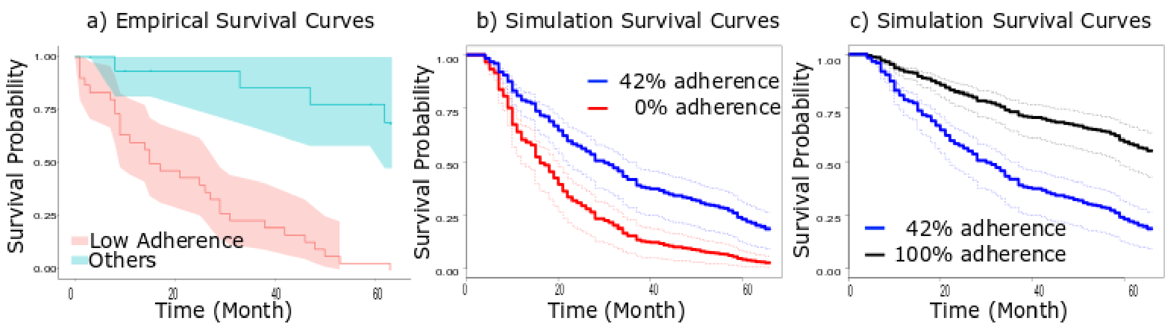

Figure 3.2: Time to hospital admissions among community treatment order patients with high-, medium-, and low-injection adherence: Kaplan–Meier survival curves (left) and simulation survival curves based on Cox model (middle and right).

We applied Cox survival model for the 53 CTO patients who have sufficient observation periods. From Table 3.3, there is a strong relationship between injection adherence and decreased risk of hospital admissions. Holding the other covariates constant, having one unit increase of injection adherence reduces the hazard ratio by a factor of 0.248 or 75.2% (CI, 0.126 to 0.489, $P < 0.001$).

3.4 Discussion

Despite the numerous studies pointing to reduced recidivism with CTOs, only two prior studies investigated the relationship between the length of CTOs and outcome.[47, 52] In the RCT study, extended outpatient commitment for 180 days or more had 57% fewer admissions and 20 fewer hospital days than shorter CTOs and were effective when combined with frequent outpatient services. The patients became more adherent with treatment, were less likely to be victimized, had reduced family strain, and had an improved quality of life. Shorter duration of CTOs in this study did not produce statistically significant results.[52] In the second study, CTO durations of longer than 1 year increased the number of outpatient visits, decreased the number of hospital admissions and total hospital days compared to the levels of use in the same patients over the 1-year period preceding the CTO. The positive effects persisted for CTO patients for up to 5 years.[47] A proviso in comparing these two studies with the present one is that as complex interventions the CTOs were conducted in each of the three settings under a different set of legal provisions and different service delivery characteristics.

The present study offers extended outcome data validating the benefit of longer duration CTOs with respect to recidivism, length of confinement in hospital, and cost savings of approximately $14,871 per hospitalization. Further, it contributes data about the mediating effect of LAIs and the intensity of outpatient visits on producing the effects. Considering the ethical concerns regarding the perceived coercion associated with CTOs,[69, 70] authors skeptical about the outcome literature caution against the infringement on autonomy that CTOs involve and promote less restrictive alternatives.[71–73] These authors tend to highlight the 2013 The Oxford Community Treatment Order Evaluation Trial (OCTET) study from England that utilized a RCT in showing no advantage of CTOs compared to a less restrictive control group.[74] The persistence of this controversy is apparent in various articles and in an exchange of letters to the editor in a 2016 issue of this journal between Dawson[75] and Hastings.[76]

With these methodological considerations in mind, we employed a naturalistic technique for our CTO study. In choosing a naturalistic design, we were influenced by our clinical experience with very disturbed SPMI patients who, in our clinic population, and in correspondence with Quebec law, demonstrate a striking absence of insight, strong and continued no-adherence with treatment and clinical contact with associated severe psychiatric and social dysfunction and liabilities. With this type of patient, we considered it to be questionably ethical to randomize the given patient to a control group. The results remain consistent with our underlying hypothesis: The enforcement of a CTO is associated with increased LAI adherence, which in turn is associated with reduced hospitalization rates and LOS and a reduction in costs.

A possible explanation for the positive results under extended CTOs is that a longer period of time than a 6- to 12-month duration, which is standard elsewhere may be necessary for all the different individuals and stakeholders involved in a CTO to enact the intervention in a meaningful fashion. As an example, the clinical management techniques of our team, in addition to the provision of LAI's, include intervening in the patient's psychosocial milieu including group home or family issues, recovery/rehabilitation activities, building a treatment alliance, and interacting with the legal system. Over a 3-year to 5-year period, the various individuals and community systems become increasingly familiar and fluent with the intervention–patients, family members, psychiatric staff, police, lawyers, and the courts.

We have mentioned an interesting and unanticipated finding in terms of the delay in the first injection received after the initiation of CTO. There are a number of possible reasons for these delays or nonadherences: To avoid being forced to receive an injection, the patient may have fled or abandoned their apartment and not been able to be found, become imprisoned, may have presented some understandable life event or reason for a delay, the absence may not have been detected by the clinic staff considering its procedures for monitoring missed appointments, delays with particular patients may have been tolerated due to protecting and promoting doctor–patient alliance issues, and so on. Should adherence have been enforced more strictly in a timely fashion according to the legal order than this clinic has done, the resultant impacts on patient outcome, care utilization and costs would need further investigation.

Limitations of this work include the fact that regression to the mean is an alternative explanation to the improvements registered. This is a cogent criticism in that the patients may have been at low point in the intensity of their illness and improved over time. Another limitation of the study is that although we measured the crimes committed by our cohort, the numbers were too low to demonstrate any statistically significant link to CTOs. Replication of naturalistic methodologies with enhanced measurement of quality of life outcomes in the area is required.

One of the main challenges in observational studies is the endogeneity issues. Our study addresses the challenge by leveraging the difference-in-difference method and mixed-effect regression model. The difference-in-difference uses each individual as their baseline, eliminating the endogeneity issue. The mixed-effect regression model treats individual-level differences as a random effect and enables us to focus on the fixed effects across individuals.

3.5 Conclusion

Being mindful of the ethical and methodological conundrums surrounding CTOs, we have shown that, for a particular subgroup of patients with SPMI, a longer duration of CTOs with stricter enforcement procedures than has previously been utilized elsewhere enhances their freedom in the community due to lower hospitalization rates and shorter LOS. This favourable result increases with time over the time course of the order. Further, the data suggest that outcomes seem to be mediated by increased outpatient visits including improved adherence to long-acting injections of antipsychotic medications and the time required to implement interdisciplinary team psychosocial and community interventions with enhanced treatment techniques for treatment resistant patients The lower frequency and duration of hospitalizations is associated with significant cost savings. Finally, although the patient numbers and length of time of the study are too limited to show statistically meaningful results on the commission of criminal acts, for some patients, the CTO has diminished the frequency of criminal charges.

Chapter 4

Optimal Timing for Community Treatment Order

4.1 Introduction

Mental illness brings a tremendous burden on individuals, and it also has tremendous economic costs on societies. The direct and indirect economic costs of mental illness are estimated at US2.5 trillion globally, and they are higher than chronic somatic diseases, including cancer and cardiovascular disease [8–10]. Schizophrenia is one of the most severe and disabling mental illnesses. The direct healthcare and non-healthcare costs for schizophrenia in Canada were estimated to be CAN\$2.02 billion a year [18]. The indirect costs, caused by the loss of productivity, were estimated to be an additional CAN\$4.83 billion. A recent study in Norway estimated the average cost per individual with schizophrenia to be US\$$106,000$ a year; and, the hospitalization costs constitute 33% of that total amount [77]. The repetitive hospitalizations are an economic burden on healthcare systems and hinder the freedom and employment potential of an individual. In developed countries like Canada, community treatment orders (CTOs) are deployed to protect the rights of psychiatric patients, improve their quality of life, and reduce avoidable hospitalizations [78].

Like any other illnesses, proper administration of medical treatment is crucial for the stability of medical conditions. However, voluntary treatment is often impractical for individuals with schizophrenia, where treatment non-compliance is an important and prevalent issue. Less than half of schizophrenia patients continue any form of treatments after discharges from their first hospitalizations [19]. Though not curable, schizophrenia is manageable through antipsychotic medications, aiming to stabilize patients and reduce relapses and re-hospitalizations. Especially, long-acting injectable antipsychotics (LAIs) [19] have multiple advantages over oral medicine for non-adherence patients, including ease of administration, monitoring, and tracking [20].

One of the widespread measures to ensure treatment adherence is the community treatment order. CTO [53] legally mandates severely ill patients to follow their treatment plans, mainly LAIs, when patients are in the community after hospital discharges. Patients under a CTO are mandated to follow a treatment plan; healthcare practitioners are granted the power to recall patients to the emergency room if there is a concern on patients' treatment compliance.

Despite the common usage of CTOs in developed countries, CTO researchers have been solely focusing on the effectiveness of CTOs in terms of health outcomes and economics [79]. Across developed countries and even between provinces in Canada, the exact mandates of CTO vary; the differences can be but not limited to its duration, level of coerciveness, and scope of interventions [80] [22]. It is not surprising then that there exist varying and even conflicting evidence on the effectiveness of CTOs among different jurisdictions [79].

To the best of our knowledge, there is no existing research on CTO intervention's decision-making process. The only guideline for CTO applications is its legal criteria. Though slightly different among jurisdictions, the standard criteria for CTO applications include long-term patients who have multiple hospitalizations in the past and may face substantial deterioration with no intention of receiving treatment voluntarily [22]. Many questions regarding the decision process of CTO applications remain unanswered. For example, how many hospitalizations should trigger a CTO application, or rather, under what combination of missing appointments and hospitalizations foreshadow the necessity of a CTO intervention?

The decision process for a CTO is not straightforward. One key decision factor is one's willingness to adhere to treatment voluntarily. However, this cannot be easy to detect. There are multiple intertwining factors determining treatment adherence for schizophrenia patients, including but not limited to the following: lack of insight [81], the severity of illness [82], and attitudes towards medication [83]. The relationship between impaired insight and illness symptoms is under constant debate with conflicting evidence [84]; the impact of insight on adherence is also debatable [83]. Such, the actions of patients speak louder than words. Since patients have to come to the out-patient clinic to receive injections, every injection administered is recorded in patients' electrical medical records. These valuable records help us understand the actual behaviours of patients towards LAIs in a real-world setting. The decision process for a CTO is also not static. A mental illness is a long-term condition, where it is crucial to study the "CHANGING PATTERNS OF CHANGE" for mental illness where sequential observations are required [25].

Candidates for CTOs are the patients who are already under LAIs treatment, where LAIs are mostly prescribed to non-compliant patients [20]. With both LAIs and CTOs considered "last resort" interventions, it is reasonable to believe that healthcare practitioners have exhausted all other milder interventions addressing non-adherence. As such, we make the assumption in our research that the patients' behaviour towards LAIs does not change over time without CTO interventions. This assumption is consistent with our on-team schizophrenia specialist's opinion; it is also consistent with the fact that CTOs in the study are long-term interventions.

Under CTOs, involuntary treatments are permitted. Due to the seriousness of such implications, it is not difficult to imagine the heated and inconclusive debates around CTOs. Opposition opinions are primarily concerned with such coerciveness. From our previous study on the effectiveness of CTOs in Quebec province and a similar study in Quebec province, they show that for the targeted group of schizophrenia patients, who have low-adherence and high hospitalization risk, CTOs improve their treatment adherence and reduce re-hospitalizations [85] [86]. A study in Norway reaches a similar conclusion that CTOs are effective for a group of patients who are high users of in-patient care [87]. In our current study, we assume that CTOs are effective in reducing hospitalizations by improving treatment adherence. The reduced hospitalizations counter the concern on coerciveness; the confinement in the hospital is an extreme form of coerciveness.

We assume that there are two types of patients under question: CTO type and non-CTO type. CTO type patients share the characteristics of low adherence and high hospitalization risk; while, non-CTO type patients follow treatment plan voluntarily and have low hospitalization risk.

To the best of our knowledge, we are the first to study the decision-making process for CTO decisions, and we are the first to propose a decision model for CTO decisions. We have the following contributions:

- we are the first to shine a light on the differences between CTO type and non-CTO type patients in terms of medical event dynamics. Following the CTO research tradition, we first examine the differences between the two groups of patients on the aggregated individual level; then, we examine the differences in medical event transition probabilities with our longitudinal data.

  First, we confirm that the transition probabilities between the two groups of patients are significantly different; second, more importantly, we learn that by controlling the current event, the degree of differences between the two groups of patients varies. From this, we leverage the Bayesian factor concept, which informs us how likely a patient belongs to one of the two groups given an observation of a medical event transition.

- we are the first to propose an optimal stopping model with belief update for CTO decisions. Based on our empirical investigation, we propose an optimal stopping model with a belief update to optimize CTO intervention's timing with the trade-off between observation cost and potential cost savings under intervention. Through the decision model, we are also able to examine the potential impact of medical costs on CTO decisions;
- we are the first to evaluate the healthcare costs under different CTO decision strategies using Markov chain simulation.

In the remaining of the chapter, we first examine the characteristics of the two types of patients in question, the CTO type and the non-CTO type, both on the individual level and the dynamics of medical events. Then, we develop an optimal stopping model with belief updating for CTO decisions. Last, we present the computational experiments and evaluate different policies using Markov chain simulation.

4.2 Literature Review

The literature on CTOs has been vastly focusing on the effectiveness of CTOs. As we have already established in our previous research, CTOs effectively reduce hospitalization rates and improve treatment adherence in the unique context of Quebec province in Canada. In this chapter, we only briefly touch on the literature on this topic. The current research is instead the intersection of three other research areas: cost analysis for CTOs, health economic modelling for CTOs, and the application of optimal stopping models in healthcare. The following literature review is organized in the above structure.

4.2.1 The Effectiveness of CTOs

Existing studies on CTOs mainly concentrate in the medical research field, where the question on the effectiveness of CTOs is still under ongoing debate [79]. There are two main methodologies addressing the above question: randomized control trials (RCT) and observational studies. While the only three existing RCT studies show no definite improvement in patients under CTOs [21] [88] [89], the complexity of CTOs calls the suitability of RCTs into question [50]. And, more than 50 observational studies on the same topic with varying analytical methods have mostly positive conclusions [90] [91] [79].

Though the philosophy of CTOs across jurisdictions is the same, the exact legal mandate is different. To our knowledge, there are only two previous studies examining the effectiveness of CTOs in Quebec, Canada, and both show improvement in patients under CTOs [86] [85]. Using mirror-image study and survival analysis, the above two studies conclude that CTO improves treatment adherence for a group of severely ill patients and the improved adherence reduces re-hospitalization rates [86] [85]. In this paper, we do not aim to provide evidence on the effectiveness of CTOs. Instead, we are interested in the construct of a recommendation system under different scenarios.

While the ultimate goal of CTOs is improving patients' quality of life, that adhering to treatments is beneficial for stabilizing medical conditions, another effect is the cost saving potential on the healthcare system. Prohibitive costs are incurred from repeated and frequent hospitalizations by a group of severely ill patients [86] [85]. A reduction in hospitalizations also has a significant positive impact on the quality of life of patients as hospitalizations are the most restrictive form of treatment and significantly limit the liberty of patients [92].

4.2.2 Healthcare Cost of CTOs

To our knowledge, there are only two existing studies explicitly focusing on healthcare costs of CTOs, one in New York state and the other in North Carolina, conducted by the same research group [93] [59]. Extensive healthcare cost information and relevant legal costs are collected in the New York state study. Healthcare costs include costs for in-patient treatments, clinical visits, prescription medications, and case management. Legal costs include legal service fees for CTO administrations and criminal justice service costs for criminal offences. Average costs per patient are reported for three time periods: 12-month period before CTO, first 12-month period during CTO, second 12-month period during CTO. Mental health hospitalization costs decrease, and out-patient care costs increase during CTOs; the reduction in hospitalization costs overwhelmingly exceeds any additional cost increases associated with the implementation of CTOs. On top of the above observational result, they also use a multivariate time-series regression method to analyze the effect of active CTO intervention, periods during CTO, and treatment adherence. Consistently, they conclude that CTO is a significant factor negatively correlated with overall treatment costs; and, so is treatment adherence [59].

The second only study on the cost of CTOs is the North Carolina study, which is based on a randomized control trial designed for investigating the effectiveness of CTOs. They reach a similar conclusion that CTO has considerate cost-saving potential by reducing hospitalizations [93]. It is fair to say that the most significant healthcare cost consideration for our patients is the hospitalization cost. This paper uses healthcare costs, including hospitalization cost, clinical visit cost, and medication cost, as a guideline for the decision model. We argue that minimizing healthcare costs has a similar effect on maximizing patients' quality of life.

4.2.3 Economic Research on Schizophrenia

The main objective of health economic research is to estimate the outcomes of a small option set of medical interventions by simulating the trajectories of patients [33]. There are mainly three modelling approaches for health economic research: decision tree model, Markov model, and discrete-time models [34]. A cost-effectiveness study of drug treatments for schizophrenia in the United States [36] constructed a widely accepted and adopted Markov model [37] [94] [38]. In the U.S. study and its similar studies, extensive parameters for their five-year Markov models with three months are calibrated from clinical data, existing literature, and expert experiences.

At each period, the patient may relapse or not relapse. If relapse, the patient may commit suicide or continue; if continue after relapse, the patient may drop out of treatment and face a greater risk of relapse in the next period; or the patient may recover to baseline and continue treatment. If the patient does not relapse, the patient may experience one of the four symptoms: positive and negative symptoms, only positive symptoms, only negative symptoms, and no symptom; then, the patient may continue with treatment or drop out of treatment.

Different drug treatments affect the relapse rate, the rate of treatment continuation, and the transition probabilities into the four symptom states. Relapse is indicated by hospitalization, and recovered relapse does not affect transition probabilities into the symptom states. Measurements, including the Brief Psychiatric Rating Scale, quality-adjusted life years, lack of relapse, and healthcare costs, are commonly used to evaluate each drug treatment effect. The cost of each period depends on 'relapse' and 'symptom'. Once relapse, at least one hospitalization occurs; during the three months, a re-hospitalization may occur as well. The average number of days in the hospital during the 'relapse' period is estimated at 54 days, and the average cost for the 'relapse' period is estimated as 4373.65 pounds by a study in the U.K. at 1998 [37]. Without relapse, the average maintenance cost, mainly including outpatient visits, daycare, psychiatric nurse visits, and general practitioners visits, is estimated between 311.24 and 1763.79 pounds depending on the symptoms by the same study [37].

4.2.4 Optimal Stopping Model in Healthcare Application

There is a critical shortcoming with the above economic healthcare approaches: they are limited in the capacity to evaluate decision alternatives. It is no coincidence that all of the above studies only compare treatment outcomes between two or three decisions. The antidote is the Markov decision models, which are not confined either by the number of decisions or the decision time horizon than economic models [77]. There are many successful applications of Markov decision process (MDP) models in medical treatment: for example, patient admission management in a Neurology ward [27], optimal HIV treatment time [28], organ transplant decision [29], hypertension management [30]. To our knowledge, there is no such application on schizophrenia care or CTO interventions.

Since the CTOs in Quebec last three years and their renewals are less challenged than the initial orders, we simplify the decision process by assuming that the decision process terminates once we reach the CTO decision. The objective of the decision model is to find the optimal timing to start a CTO intervention. Among the extensive literature on healthcare MDP models, we focus on the healthcare optimal stopping/timing literature.

One representative research in this area is the study on the optimal timing for liver transplant [29]. They assume that the health state of patients waiting for liver transplants is fully observable. Furthermore, the quality-adjusted life expectancy for each health state is considered in the decision process. The objective is to maximize the overall quality-adjusted life expectancy both before and after the transplant. Once a transplant decision is made, the quality-adjusted life expectancy after the transplant is calculated, and the decision process terminates. The paper also shows that under certain conditions on the state transition probabilities, the optimal policy is a control-limit optimal policy, meaning that there exists a decision threshold, and above the threshold, the decision is always to transplant.

Another such research is on the optimal timing to initiate HIV therapy [28]. They use CD4 counts, which measure the robustness of the immune system, as the MDP model states; the objective is to maximize the total expected life time for a patient. Once HIV therapy is initiated, the remaining expected lifetime is calculated based on the patient's state, and then the decision process terminates.

Our decision model shares many similarities with the above studies: the assumption that the decision process terminates once the intervention starts; the trade-off consideration between waiting and intervening. At the same time, there are several significant differences: our decision model is considered out of the doctor's perspective, and the objective is to minimize the overall healthcare costs; we also assume that we do not have full observation over the state of the patient, which leads us to a partially observable optimal stopping model. The application of partially observable Markov decision models in healthcare is not uncommon [26]. Often, we do not know the exact health state of an individual; it is more the case when a medical test has low accuracy, or sometimes a corresponding medical test does not even exist.

A study on the optimal timing to stop PSA testing for prostate cancer using partially observable optimal timing models [95]. PSA testing itself can have a negative impact on the quality of life and hence the incentive to reduce the number of having such testing; at the same time, the testing helps inform the possibility of prostate cancer, where an early detection will prolong one's life expectancy. The PSA testing has low accuracy, and hence it calls for a partially observable model. Upon each testing results, the belief or the probability of having prostate cancer is updated. The resulting optimal policy is a threshold policy based on the combination of belief (probability) of prostate cancer and the individual's age. Partially observable MDPs are more challenging to solve with the existence of continuous belief states. They use the fixed-grid method to solve the partially observable optimal stopping model [96].

4.3 Empirical Investigation on Community Treatment Order

We conducted an observational study over the five years between 2010 and 2015 at the Continuing Care Clinic in Jewish General Hospital in Montreal. The most frequent diagnoses in the clinic are schizophrenia and schizoaffective disorder. The dates of (i) all clinic visits, (ii) injections of LAIs, (iii) CTOs, (iv) hospitalizations, (v) ER emergency room visits, and (v) crimes were extracted from the electronic medical records.

The patients we are interested in are chronic patients in need of long-acting anti-psychotic injections (LAIs). From our previous study, we already establish that there are two types of patients: CTO type and non-CTO type [85]. In this study, we are interested in the differences between these two groups of patients. We hope to understand the decision considerations involved in subjecting a patient to a CTO. Table 4.1 presents the basic characteristics of these two types of patients. CTO type patients received CTO during the study period; and, non-CTO type patients were under LAIs but did not receive CTO.

Table 4.1: Characteristic for Patients Under LAIs

	non-CTO (N=104)	CTO (N=36)	Total (N=140)	p value
Gender				0.211
Female	41 (39.4%)	10 (27.8%)	51 (36.4%)	
Male	63 (60.6%)	26 (72.2%)	89 (63.6%)	
Age (at 2010)				0.480
Mean (SD)	49.413 (10.820)	47.944 (10.455)	49.036 (10.710)	
Ethnicity				0.871
Caucasian	68 (65.4%)	23 (63.9%)	91 (65.0%)	
Non-Caucasian	36 (34.6%)	13 (36.1%)	49 (35.0%)	
Substance Abuse History				0.309
Yes	23 (22.1%)	11 (30.6%)	34 (24.3%)	
Work				0.457
Yes	3 (2.9%)	2 (5.6%)	5 (3.6%)	

Substance abuse history has significant implications for society. As shown in Table

4.1, there is no significant difference in the proportion of patients with substance abuse between the two types of patients. A possible explanation is that CTO decisions are not influenced by substance abuse history.

A CTO decision involves intricate medical and social considerations for a patient. Though we can not have access to the mind of a physician, low adherence and re-hospitalization are often cited as top factors. We use a logistic regression model to learn about factors that differentiate the two patient types. (Table 4.2). The type of patients, CTO and non-CTO, is the dependent variable; and, gender, age, ethnicity, substance abuse history, income source, crime history, number of injections per period, number of hospitalizations per period, and number of clinic visits per periods are independent variables. Details on variable definitions are available in the appendix. By examining the differences between the CTO type patients prior to the initiation of their CTOs and the non-CTO type patients, we are able to conclude that CTO type patients have a significantly higher hospitalization rate than the non-CTO type patients; and, CTO type patients receive fewer injections than the non-CTO type despite their repetitive hospitalizations.

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.0422	0.7493	0.06	0.9551
Gender	-0.0415	0.3430	-0.12	0.9037
Age	-0.0191	0.0141	-1.36	0.1744
Ethnicity	0.0415	0.3149	0.13	0.8951
Substance abuse	0.3252	0.3820	0.85	0.3947
Income	0.8638	0.8463	1.02	0.3074
Crime history	0.5469	0.4325	1.26	0.2060
NO. of Injection	-1.0177	0.5802	-1.75	0.0794
NO. of Hospital	16.4151***	4.5461	3.61	0.0003
NO. of Clinic Visit	-0.4677	0.3650	-1.28	0.2001

Table 4.2: Indicators of CTO Type Patients

However, the above analysis reconfirms us with what we have known, that CTO type patients tend to have low adherence and high hospitalization rate. The important remaining questions are: how low the adherence should be for a CTO decision? How frequent hospitalizations should be for a CTO decision? or rather, what are the combinations of low adherence and high hospitalizations that require CTO intervention? On top of the above questions, how long should we observe a patient to conclude that the patient will most likely benefit from a CTO?

4.4 The Dynamics of Medical Events

In this section, we aim to examine the following two hypotheses:

- there exist differences in medical event transition probabilities between non-CTO type patients and CTO type patients prior to their CTO initiation;
- medical event transition probabilities change after CTO initiation.

Based on the differences in transition probabilities between the two types of patients, we hope to calibrate a Markov decision model with belief updating to identify the need for CTO intervention considering potential observation time costs.

We are interested in the following: transition of medical events, the impact of patient types on these transitions, and the impact of CTO intervention under the current practice. To this aim, we structured our observational data into periods and assigned the most significant events to each period. In the coming period, the event acts as 'outcome,' dependent variable; the current event and other covariates act as independent variables.

First, we need to determine the duration of periods for our longitudinal analysis. For almost all longitudinal research, the optimal duration of periods is unknown to researchers [97]. We decide to use two months as the duration of periods under both practical and analytical considerations. From a practical aspect, the standard frequency for patient evaluation is between one month to three months both in clinical practice and in research [98] [99]. As CTO decisions are not taken lightly by physicians, who need to consider opinions from both the family and patients' social support system, a two month evaluation period is both practical and reasonable. It is also a commonly accepted practice to define discontinuity of LAIs treatment as two-months of continuous absence [100]. From an analytical aspect, the two months duration contains the vast majority of hospitalization, and the aggregation of data at such duration provides us with a clear statistical result.

During each period, we design the following exclusive events: 'hospital' means that there is hospitalization during the period; 'injection' means that there is no hospitalization and the patient receives at least one injection during the period. The 'injection' event can also be interpreted as the continuity of treatment; 'clinic visit only' means that there is no hospitalization and injection, and at least one clinic visit is recorded; 'no show' means that there is no hospitalization, no injection, and no clinic visit. The 'no show' event can also be interpreted as the discontinuity of treatment. On top of the events, we also labelled observations into three categories: (i) non-CTO type patients; (ii) CTO type patients prior to their initiation of CTOs; and (iii) CTO type patients posterior to their initiation of CTOs. Figure 4.1 shows the percentage of each event under the above label scheme.

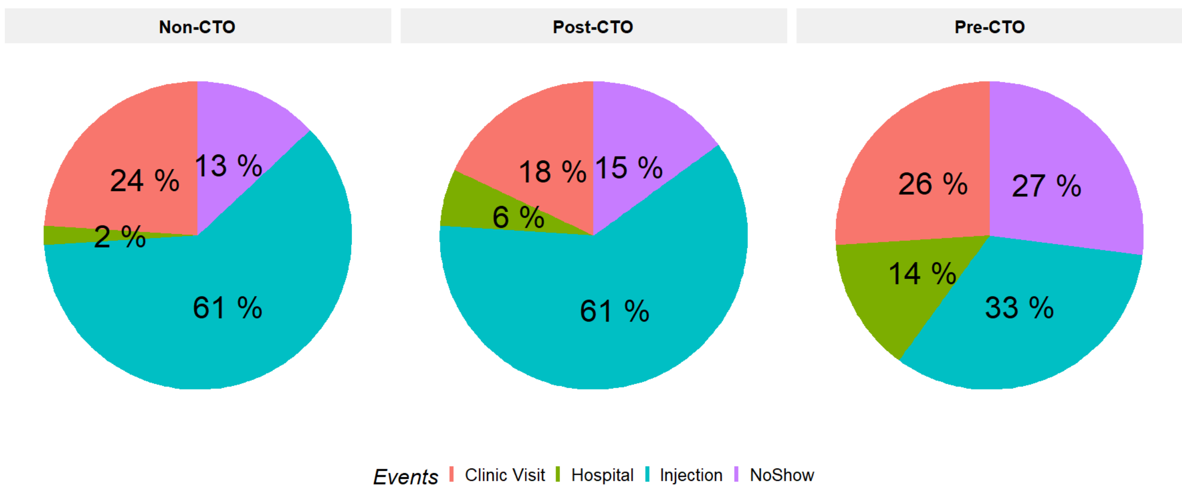

Figure 4.1: Percentage of Each Events for Patients under LAI Treatment

Current events or current and past events are used to predict the next coming events and labels on the patient type and phase. With multiple longitudinal observations coming from every single patient, it violates the sample independence assumption required by traditional regression models. Instead, we use Bayesian multilevel models (MLMs) [101] , which allow multiple levels of observations: population level and individual level. Population-level refers to the population average responses from predictors; and, individual level refers to individual differences among the population. MLMs provide insights on both the population average responses and individual differences.

Careful considerations are given to the construction of the multilevel regression model. We consider the following models: Full Model, which includes interaction terms, past events, current events, and the type and phase of patients to predict the next events; Second-Order Markov Model, which excludes interaction terms from the 'full model' and still considers both the past and current events; Markov Model, which only includes current events and the type and phase of patients.

$$
\begin{aligned}
&\ln P(Event_{i,t} = \{Hospital, Injection, NoShow, ClinicVisit\}) \\
&= b_i + \beta_1 Event_{i,t-1} + \gamma_1 PriorCTO_{i,t-1} + \gamma_2 PosteriorCTO_{i,t-1} - \ln Z \\
&\hspace{20em} \text{(Markov Model)} \\
&= b_i + \beta_1 Event_{i,t-1} + \beta_2 Event_{i,t-2} + \gamma_1 PriorCTO_{i,t-1} + \gamma_2 PosteriorCTO_{i,t-1} - \ln Z \\
&\hspace{20em} \text{(Second-Order Markov Model)} \\
&= b_i + \beta_1 Event_{i,t-1} + \beta_2 Event_{i,t-2} + \gamma_1 PriorCTO_{i,t-1} + \gamma_2 PosteriorCTO_{i,t-1} \\
&\quad \alpha_1 Event_{i,t-1} * PriorCTO_{i,t-1} + \alpha_2 Event_{i,t-1} * PosteriorCTO_{i,t-1} - \ln Z \\
&\hspace{20em} \text{(Full Model)}
\end{aligned}
$$

In the above equations, b_i represents the individual effect, which allows individual differences for the regression model; $\ln Z$ is the normalization factor, which ensures that the probabilities for each event outcome sum up to 1; Greek letters α, β, γ represent population level effects. $Event_{i,t-1}$ and $Event_{i,t}$ represent the medical events at time $t-1$ and time t for patient i respectively; there are four possible medical events: 'Hospital', 'Injection', 'NoShow', 'Clinic Visit'. The definition of each event is as described in the previous paragraphs. '$PriorCTO$' is an indicator variable, where 1 means CTO type patient prior to CTO initiation; '$PosteriorCTO$' is an indicator variable, where 1 means CTO type patient posterior to CTO initiation. As such, the combination of $PriorCTO = 0$ and $PosteriorCTO = 0$ indicate non-CTO type patient. $PosteriorCTO$ and $PriorCTO$ can not take on the value 1 at the same time.

We separate the entire dataset randomly into two separate training and testing datasets. We use the training dataset to calibrate and select the best regression model; and, we use the separate testing dataset to measure the performance of the calibrated regression model. To calibrate and select the best regression model, we use leave-one-out cross-validation method [102] on the training dataset, which is most suitable for modest data size. Second-Order Markov Model is selected as the best model by the above cross-validation method. Out-of-sample performance, measured by multi-class area under the curve (AUC) [103] on the separate testing set, is 0.7119.

Past studies, including our previous research, tend to focus on the effect of injections on prolonging the durations between hospitalizations, where survival analysis is commonly used in those studies. For example, in our previous study, we show that high adherence increases the survival rate of hospitalization (Figure 4.2). However, this kind of analysis only informs the impact of adherence on hospitalization risks without considering other factors. For example, we later show that attending clinic visits also significantly reduces hospitalization risks. Also, the survival analysis does not provide the trajectory of adherence itself. High adherence in the current period does not necessarily guarantee high adherence in the coming periods.

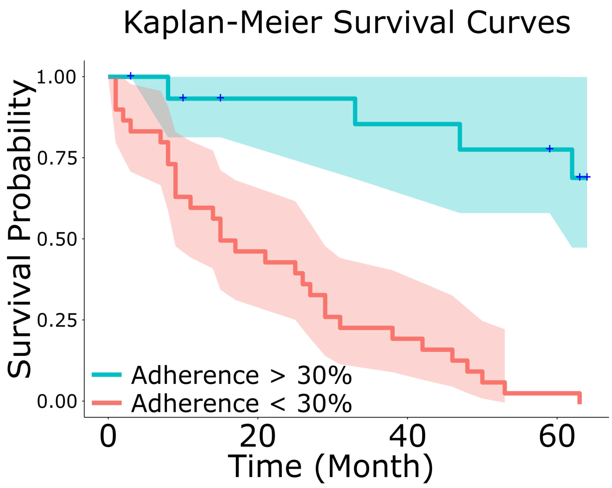

Figure 4.2: Kaplan–Meier survival curves on hospitalization

Table 4.3 provides the multinomial logistic regression model output from Second-Order Markov Model. As mentioned earlier, the model with the best performance in predicting the coming medical events is the second-order Markov model. The prediction of coming events depends on current and past events. Since the outcome has to be one of the four events, the multinomial regression model output is reported in the form of the odds ratio of an event over the reference event. The column $\frac{P(Hospital_t)}{P(ClinicVisit_t)}$ provides the effect of each predictors on the odds ratios of 'Hospital' at time t over 'Clinic Visit' at time t. For example, 'NoShow' at time $t-1$ increases the odds ratio of 'Hospital' over 'Clinic Visit' at time t by 2.55 times. The column $\frac{P(Injection_t)}{P(ClinicVisit_t)}$ and $\frac{P(NoShow_t)}{P(ClinicVisit_t)}$ show the effect of each predictors on the odds ratios of 'Injection' and 'NoShow' over 'Clinic Visit' at time t respectively. Since 'Hospital', 'Injection', 'NoShow', and 'Clinic Visit' are mutually exclusive, the probability of 'Clinic Visit$_t$' can be easily calculated. Confidence intervals for parameter estimates are also provided.

The output from the multinomial logistic regression model is important for us to understand the significant factors affecting the trajectory of a patient. However, it may be a bit obscure to have an intuitive understanding of each factor's direct impact on the probabilities of coming events. The transition probabilities, which provide the probabilities of coming events directly, are provided in Table 4.6 4.7 4.8 in the appendix.

From Table 4.3, we are able to gain a more detailed understanding of the medical trajectory of patients. Some observations are consistent with the literature: CTO type patients before intervention are more likely to have hospitalizations, less likely to have injections, and more likely to have missing appointments. On top of the above, we observe that the probabilities of the event in the next period depend on the current and last period; both injections and hospitalizations in the current and last periods increase the likelihood of injections in the next period; Both no show in the current and last periods increase the likelihood of no show in the next period. In short, patients have a momentum to stay in habits regarding accepting medical treatments and skipping doctor appointments.

The differences in transition probabilities between the two types of patients enable us to build a decision model where the trade-off is between the continuity of observations and potential savings from interventions. Using mixed-effect logistic regression to predict the next event using the one-vs-rest approach returns similar results as the above analysis. Using the Markov chain approach and likelihood test [104], we also find that observational data follow the second-order Markov chain.

4.4.1 Bayesian Factors

Till now, we have studied how the trajectories of medical events differ from patients to patients. More interestingly, we can reverse the process. Given observations of events, we aim to use the information to identify the type of a new patient. This is a sequential hypothesis testing problem in essence, where evidence is collected continuously until a conclusion can be reached with certainty. Bayesian factor, the ratio differences of the probability of an event between the patient types, provides a straightforward way to interpret the impact of observations on the belief of the type of a patient. Our application of the Bayesian factor has a minor variation from its standard definition: we focus on the ratio differences of the event transition probabilities instead of the event probabilities

Predictors	$\frac{P(Hospital_t)}{P(ClinicVisit_t)}$ Odds Ratios	CI (95%)	$\frac{P(Injection_t)}{P(ClinicVisit_t)}$ Odds Ratios	CI (95%)	$\frac{P(NoShow_t)}{P(ClinicVisit_t)}$ Odds Ratios	CI (95%)
Intercept	0.03	(0.02, 0.05)	0.47	(0.38, 0.59)	0.17	(0.12,0.26)
Injection_{t-2}	1.42	(0.80, 2.47)	2.68	(2.09, 3.42)	0.94	(0.65, 1.39)
Hospital_{t-2}	1.12	(0.47, 2.50)	2.21	(1.34, 3.68)	1.67	(0.87, 3.28)
NoShow_{t-2}	1.80	(0.98, 3.26)	0.92	(0.65, 1.32)	1.61	(1.08, 2.35)
Injection_{t-1}	1.43	(0.82, 2.51)	7.53	(5.97, 9.46)	1.10	(0.74, 1.60)
Hospital_{t-1}	1.68	(0.79, 3.44)	2.00	(1.26, 3.19)	1.12	(0.61, 2.09)
NoShow_{t-1}	2.55	(1.42, 4.50)	0.83	(0.58, 1.20)	1.97	(1.38, 2.86)
PriorCTO_{t-1}	5.74	(2.89, 12.30)	0.68	(0.49, 0.95)	2.93	(1.65, 5.56)
$\text{PosteriorCTO}_{t-1}$	3.31	(1.68, 6.94)	1.43	(1.08, 1.92)	1.29	(0.71, 2.44)
Random Effects						
δ^2	0.01					
τ_{00}	0.86					
ICC	0.01					
$N_{patients}$ [1]	155					
Observations	3775					

Table 4.3: Prediction for Next Medical Event

themselves. Bayesian factor is defined in Equation 4.1.

$$\text{Bayesian factor} = \frac{P(Event_t|Event_{t-1}, Event_{t-2}, \text{CTO Type})}{P(Event_t|Event_{t-1}, Event_{t-2}, \text{non-CTO Type})} \tag{4.1}$$

Bayesian factor larger than 1 means that the event transition brings us closer to the belief that the patient is CTO type; and, the larger the Bayesian factor, the closer it brings us to believe a patient being a CTO type. Bayesian factor smaller than 1 means that the event transition pushes us further from the belief that the patient is CTO type.

Table 4.4 provides the Bayesian factors for different event transitions. We gain the following insights from Bayesian factor (Table 4.4): 1. hospitalization despite its proceeding events is the strongest indicator of a CTO type patient; 2. discontinuing injection, from injection to no show, is another indicator of a CTO type patient; 3. the continuation of no show is not informative as our intuition lets us believe; 4. resuming injection, from no show to injection, is a strong indicator of a non-CTO type patient.

In summary, inaction does not point to a patient being a CTO type. It is the action of discontinuing treatment and the inability of resuming treatment that flags the necessity of CTO interventions. In our decision model, the Bayesian factors for all transitions are used to update the 'belief' of the type of patient. We argue that what differentiates patients from CTO type to non-CTO type is not the static number of hospitalizations or missing appointments; instead, we should look at the trajectory of medical events of a patient.

		Event_t			
Event_{t-2}	Event_{t-1}	Clinic	Hospital	Injection	NoShow
Hospital	Hospital	0.92	3.93	0.64	2.73
Hospital	Injection	1.32	6.83	0.80	3.74
Hospital	Clinic	0.87	4.28	0.58	2.42
Hospital	NoShow	0.68	2.98	0.51	1.90
Injection	Hospital	1.01	6.58	0.69	3.17
Injection	Injection	1.30	5.81	0.87	3.92
Injection	Clinic	0.96	5.30	0.65	2.60
Injection	NoShow	0.73	4.18	0.53	2.23
Clinic	Hospital	0.85	4.34	0.62	2.44
Clinic	Injection	1.08	7.28	0.77	3.54
Clinic	Clinic	0.82	4.68	0.61	2.28
Clinic	NoShow	0.66	4.50	0.46	1.93
NoShow	Hospital	0.74	3.87	0.52	2.22
NoShow	Injection	0.97	5.89	0.69	3.09
NoShow	Clinic	0.73	4.47	0.46	2.14
NoShow	NoShow	0.56	3.13	0.34	1.73

Table 4.4: Bayesian Factor for Medical Events

4.5 Problem Formulation

We assume that the doctor, who is the decision-maker, tries to make the optimal decision for each patient. The doctor wants to determine the type of patient upon observations of medical event sequences. There are incentives to start CTO interventions as soon as possible for the potential cost savings and the liberation of patients on reduced hospitalizations. Meanwhile, premature decisions can cause harm, leading to a higher potential of mistakes, subjecting a non-CTO type patient to an unnecessary court appearance and police interference. The decision trade-off is such between the cost of medical treatment and overreaching legal interventions.

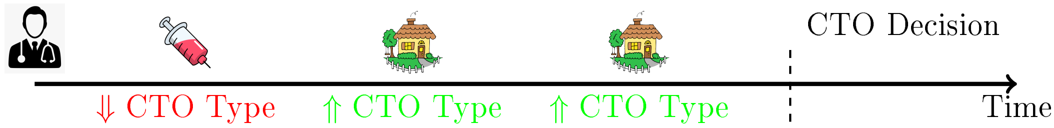

Figure 4.3: Decision Process Illustration

The decision process is the following (Figure 4.3): upon the prescription of LAIs for the given patient, the doctor starts to observe the patient's behaviour towards injection; as observation continues, the doctor updates their belief on the patient types. The forward-looking doctor collects information as time passes; and tries to make the optimal decision weighing the cost of applying CTO correctly, misapplying CTO, and the cost of medical treatment without CTO interventions.

We formulate a discrete-time, infinite-horizon partially observable Markov decision problem with a discount for this problem. As a POMDP, our model consists of three finite sets: a finite set of states $\mathcal{S}$; a finite set of actions $\mathcal{A}$; and a finite set of observations $\mathcal{O}$.

4.5.1 State, Observation, and Action Space

The value of state $s \in \mathcal{S}$ is represented by $(MedicalEvent, PatientType)$ pair. Examples for medical events are 'Hospitalization (Ho)', 'Injection Received (In)', 'Clinic Visit Only (Cl)', and 'No Show (No)'. As discussed in the empirical section, our historical data follow a second-order Markov chain. A second-order Markovian problem can be easily converted into a first-order Markovian problem by expanding the state space. For the purpose of simplicity, from now on, all demonstrations are given in the first-order case.

We have two patient types: CTO type and non-CTO type. As discussed in the empirical section, we have CTO type patients who are prone to hospitalization and no show; and for whom CTO interventions are designed to improve their quality of life. We also have non-CTO type patients who would not benefit much from the CTO interventions. In the decision model, we are interested in the behavior of CTO type patients prior to the initiation of CTO intervention. The total number of states is then the number of medical events multiples the number of patient types.

To demonstrate, in first-order Markovian case we have eight states in total: (Ho, CTO), (In, CTO), (Cl, CTO), (No, CTO), (Ho, Non), (In, Non), (Cl, Non), and (No, Non). The state can then be coded by a $8 * 1$ binary vector. For example, $(1, 0, 0, ..., 0)$ represents the current state is (Ho, CTO), that is, a CTO type patient currently in hospital.

Observations $\mathcal{O}$ are the medical events mentioned above. And, we have two actions in $\mathcal{A} = \{Intervention(I), Wait(W)\}$.

4.5.2 Belief State

Although we are able to fully observe the current medical event, we can not observe the type of a patient. Instead, we use belief state, $b \in \Pi(\mathcal{S})$, to represent the probability of the current state $s \in \mathcal{S}$. Using π to represent the probability of a patient being a CTO type, and the probability of them being a non-CTO type is then $1 - \pi$. If we observe a patient currently in hospital, for example, then the corresponding belief state is $b[s = (Ho, CTO)] = \pi$, $b[s = (Ho, Non)] = 1 - \pi$, and the belief states for the other states are zeros. Or, b can be written in the vector form $b[s] = (\pi, 0, 0, 0, 1 - \pi, 0, 0, 0)$.

There are three foundational functions associated with the above sets.

4.5.3 Transition Function

The transition function, $T : \mathcal{S} \times \mathcal{A} \rightarrow \Pi(\mathcal{S})$, defines the state transition probabilities upon each action. It is commonly noted as $T[s, a, s']$, which represents the probability of transiting to the state s' from the state s under action a. It can also be written as $P(s'|s, a)$. The calibration of the transition probabilities is extensively discussed in the empirical section. The probabilities of the next event depends on both the current medical event and the patient type,

4.5.4 Observation Function

The observation function $O[s', a, o]$, $O : \mathcal{S} \times \mathcal{A} \rightarrow \Pi(\mathcal{O})$, represents the probability of observing o in state s' after taking action a. It can also be written as $P(o|s', a)$. Probability $P(o|s', a)$ is readily available for us due to the design of state and observations. Assuming no missed or wrong observations, for example, we have $P(o = Ho|s = (Ho, CTO), a = \cdot) = 1$, $P(o = Ho|s = (Ho, Non), a = \cdot) = 1$, $P(o = Ho|s = (In, CTO), a = \cdot) = 0$, and so on.

4.5.5 Cost Function

The cost function $C[s, a]$, $C : \mathcal{S} \times \mathcal{A} \rightarrow \mathcal{R}$, represents the expected cost for taking action a from state s. The cost can be monetary value, for example, hospitalization cost, treatment cost, and clinic visit cost; the cost can also be patient's quality of life, where staying in hospital certainly dramatically reduce the quality of life.

Cost $C(s, W)$ is the expected intermediate cost at state s. Cost $C(s, I)$ is the total expected discounted post-CTO cost at state s. The cost calibration depends on the level of police enforcement carried out under the CTO intervention and the characteristics of patients. For example, our data show that on average male patients stay in hospital longer than female patients. Since the decision model is on individual level, the cost calibration can be considered deterministic for each individual patient, and is calculated beforehand the decision process.

4.5.6 Belief Updating

It is well known that the belief updating follows the below equation:

$$b'[s'] = \left(P(o|s', a) \sum_{s \in \mathcal{S}} P(s'|a, s) P(s|b) \right) / P(o|a, b) \tag{4.2}$$

$$= \left(O[s', a, o] \sum_{s \in \mathcal{S}} T[s, a, s'] b[s] \right) / P(o|a, b) \tag{4.3}$$

To illustrate, assuming that we observe the medical event Ho at time $t-1$ and In at time t for a patient with probability π being a CTO type, then we have that the current belief state $b = (\pi, 0, 0, 0, 1-\pi, 0, 0, 0)$, and we are interested in $b'[s' = (In, CTO)]$. We have that

$$O[s', a, o] = p(o|s', a) = p(o = In|s' = (In, CTO), a = \cdot) = 1$$

and,

$$\sum_{s \in \mathcal{S}} P(s'|a, s) P(s|b) = P(s' = (In, CTO)|a = W, s = (Ho, CTO)) * \pi + \tag{4.4}$$

$$P(s' = (In, CTO)|a = W, s = (Ho, Non)) * (1 - \pi). \tag{4.5}$$

Since we are currently assuming patient types are constant, we have

$$\sum_{s \in \mathcal{S}} P(s'|a, s) P(s|b) = P(s' = (In, CTO)|a = W, s = (Ho, CTO)) * \pi. \tag{4.6}$$

Similarly, we will have that

$$b'(s' = (In, CTO)) = \tag{4.7}$$

$$\frac{P(s' = (In, CTO)|a = W, s = (Ho, CTO)) * \pi}{P(s' = (In, CTO)|a = W, s = (Ho, CTO)) * \pi + P(s' = (In, Non)|a = W, s = (Ho, Non)) * (1 - \pi)} \tag{4.8}$$

4.5.7 Bellman Equation

With discount factor γ, the objective of our model is

$$\min E\{\sum_{i=0}^{\infty} \gamma^i C[s_i, a_i]\}. \tag{4.9}$$

The utility of the doctor applying CTO, I, to patient is

$$v(b) = \sum_{s \in \mathcal{S}} b[s] \cdot C(s, I), \tag{4.10}$$

which consists of the cost of wrongly applying CTO multiplies the probability of patient being a non-CTO type and the cost of correctly applying CTO multiplies the probability of the patient being truly a CTO type patient. Note that, subjecting CTO intervention to non-CTO patients is unappealing even without considering compensation costs. The reason is that non-CTO patients have the incentives to resume treatments without police involvement and they are also at low risk of hospitalization. Such, the benefit of intervention for non-CTO patients does not justify the cost.

The utility of the doctor continuing observation, $a = W$, is

$$v(b) = \sum_{s \in \mathcal{S}} b[s] \cdot C(s, W) + \gamma \sum_{o \in \mathcal{O}} P(o|b) V(b'), \tag{4.11}$$

where γ is the discount factor. Such, we have an optimal stopping problem with the following Bellman equation (Equation 4.12)

$$V(b) = \min \begin{cases} \sum_{s\in\mathcal{S}} b[s] \cdot C(s,I), & \text{Start Intervention} \\ \sum_{s\in\mathcal{S}} b[s] \cdot C(s,W) + \gamma \sum_{o\in\mathcal{O}} P(o|b)V(b'). & \text{Observation} \end{cases} \tag{4.12}$$

At each decision depot, the doctor faces two decisions: one is to continue voluntary medical treatments and update their belief; the other is to stop observations and trigger the CTO intervention. During voluntary medical treatments, the event trajectory of the patient naturally evolves, and the belief is updated. Once triggering the CTO intervention, the doctor calculates the total costs under the CTO intervention, which should be a reduced cost for CTO type patient and an increased cost for non-CTO type patient comparing with no intervention in place.

4.6 Computational Experiments

4.6.1 Cost Estimation

The intermediate cost, $C(s,W)$, is the expected potential healthcare cost in the immediate future when the patient is at state s and without CTO intervention. For example, a patient who is currently in an injection state may be hospitalized, may continue receiving an injection, may visit the clinic in the next time period. The intermediate cost is the expected healthcare costs for all the above potential medical events. The total expected future cost, $C(s,I)$, consists of a one-time legal cost and recurring police enforcement costs. We assume that during CTO intervention, the police are called to bring patients from 'No Show' to 'Injection'. Then, all healthcare costs, one-time legal costs, and police costs are calculated as the CTO intervention costs.

We gathered 81 hospitalization cost information from 56 patients. On average, the cost of hospitalization per day is $446, and the hospitalization duration for patients in the study is 45($\pm$63) days. The common injection drugs are paliperidone (\$323/485/647) of doses (50/100/150) on monthly basis, risperidone (\$166/249/332) of doses (25/37.5/50) on biweekly basis. According to the Canadian Institute for Health Information, the average clinic visit cost for a specialist is \$74. We use the ambulance costs, \$129, to approximate the police costs. The legal fee for CTO applications is estimated as \$692.97 from the legal aid office.

4.6.2 Case Study

We demonstrate the decision policy for a typical patient. The following cost estimations are used as a benchmark for various computational experiments. The average hospitalization cost is $446 * 45 = \$20,070$ with an average hospital stay of 45 days; we use one of the common injection prescription plans, risperidone every two weeks, to estimate that injections cost is $332 * 4 = \$1292$ for a two-month decision period; the clinic visit costs are estimated as one visit per two weeks, which is $74 * 4 = \$296$; and no show does not occur any cost. During CTO intervention, on top of the injection cost, the police are mobilized to bring patients for injections, which is an additional $129 * 4 = \$516$ per period.

The first main observation from computational results is that the optimal decision of CTO intervention is a combination of the current medical event and the belief reaching above a certain threshold. Though the decision model is based on a second-order Markovian assumption, the medical event in the previous period does not significantly impact the decision threshold.

There are several other interesting observations. In figure 4.4, the area above the line is the CTO decision area. The x-axis shows the changes in the hospital, injection, and police costs, respectively. As hospitalization costs increase, the decision model is more incentive to start CTO intervention due to the potential of a reduced rate of hospitalization under CTO intervention. As the police costs increase, there is less incentive to initiate CTO due to the high intervention costs. Interestingly, as the injection costs increase, there is

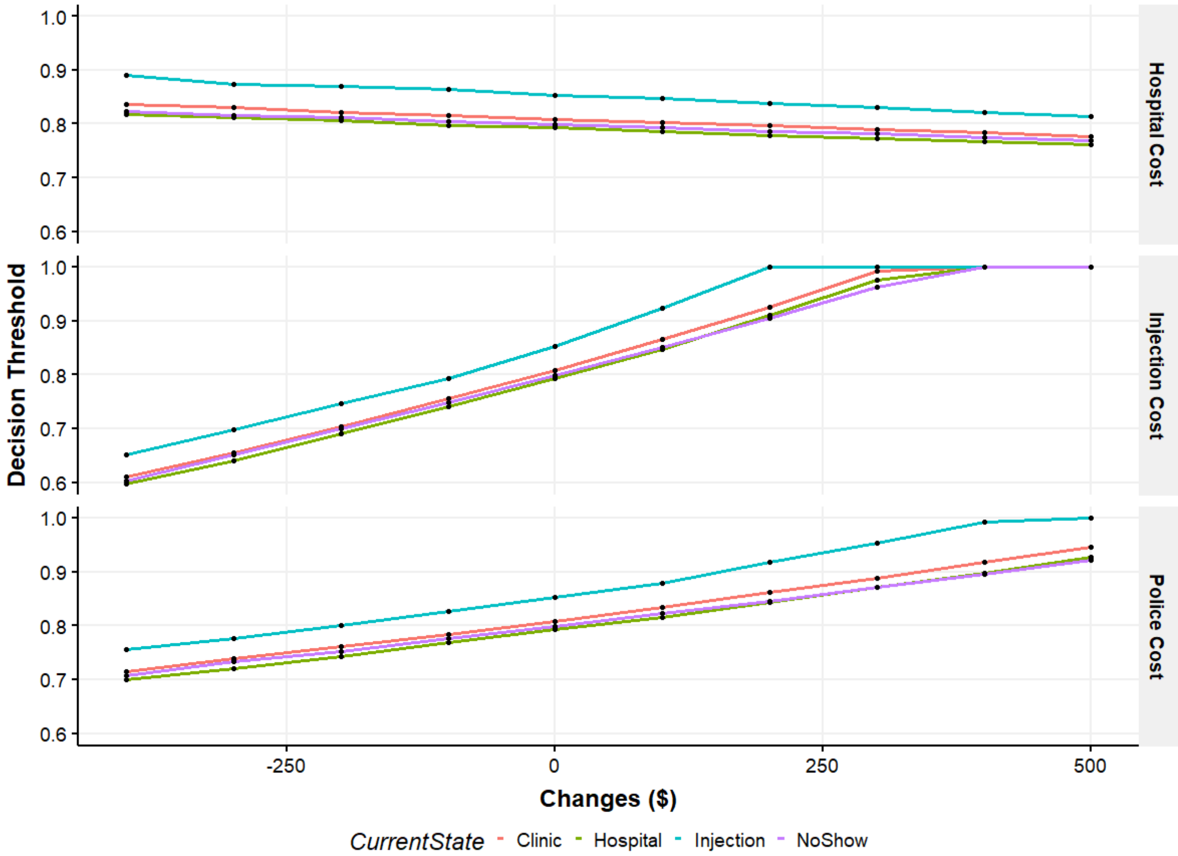

Figure 4.4: CTO Decision Threshold and Costs

also less incentive to initiate CTO. It is possible that the increased treatment costs from injection out-pace the potentially reduced cost from hospitalization. The decision model is also more sensitive to injection costs comparing to hospitalization and police costs.

4.6.3 Uncertainty on Transition

We are also interested in studying how changes in transition probabilities of CTO type and non-CTO type patients affect the optimal decisions. To this aim, we artificially disturb the transition probabilities for each type of patient by increasing the probability of reaching one state and decreasing the probability of reaching another state.

We summarize the observations in the following. The changes in transition probabilities between reaching injection and clinic visit barely impact the optimal decision. Figure

4.5 shows how the decision thresholds change when we change the transition probabilities between reaching "Injection" and "Clinic". That is, we increase the probability of reaching injection while decreasing the probability of reaching the clinic visit correspondingly. In the graphs, the y-axis shows the level of beliefs for decision thresholds; the x-axis shows the degree of changes on transition probabilities. As we can see from the graph, mainly levelled lines, the changes in transition probabilities between injections and clinic visits have little impact on the optimal decision despite the current state.

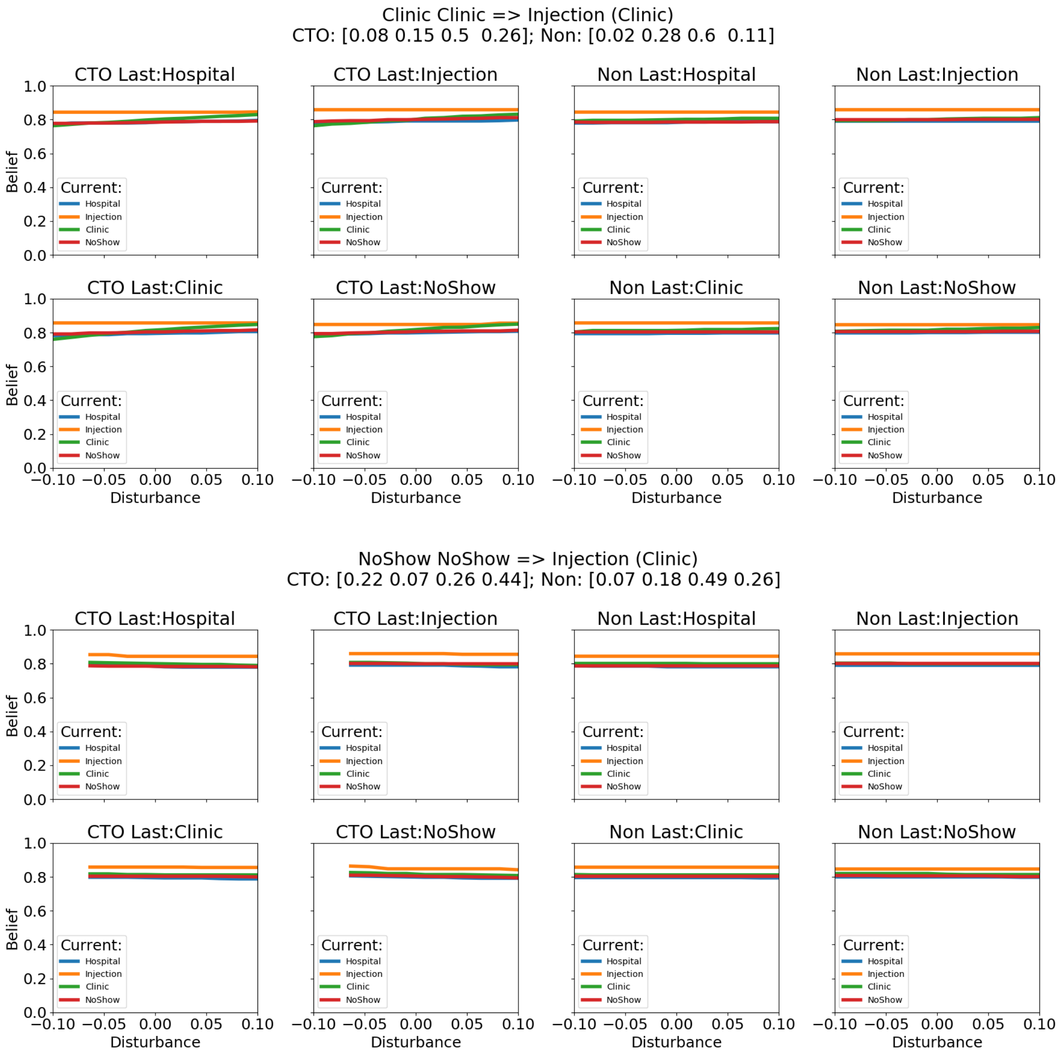

Figure 4.5: Changes on Transitions To Injection and Clinic

On the other hand, any changes in the probability of hospitalization have a significant impact on the optimal decisions. From Figure 4.6, we can see that despite the current state and the corresponding incoming state, the optimal decision is very sensitive to the probabilities of hospitalizations. Relatively speaking, the probabilities of hospitalizations for CTO type patient have a more significant impact on the optimal decision than the probabilities for non-CTO type patients. We can also see that as the probability of hospitalizations increases after the injection period, the decision thresholds for CTOs increases as well. That is consistent with our intuition. As injection becomes less effective in reducing hospitalization for CTO type patients, there is also less incentive for CTO applications.

The optimal decision is also sensitive to the probabilities of no show after two consecutive injection periods (Figure 4.7).

Lastly, optimal decisions are not sensitive to other pair-wise transition probability changes.

4.6.4 Policy Comparison through Markov Chain Simulation

In practice, psychiatrists use the legal criteria for CTOs as guidelines. The legal considerations are hospitalization history and extensive periods of missing appointments. We compare healthcare costs under different decision policies for CTO applications using Markov chain simulation. The policies we are interested in are the following: CTO intervention after re-hospitalizations; CTO intervention after two consecutive no shows after the first hospitalization; never apply CTO intervention; always apply CTO intervention; the optimal policy based on belief updating. Based on our data, we assume that 25.5% of patients are CTO type and the rest are non-CTO type. Therefore, the initial belief for a patient being CTO type is 25.5% same as the population proportion. Simulation is repeated 100k times, and confidence intervals are calculated.

Table 4.5 shows that the healthcare costs per individual under different CTO decision policies. It is not surprising that our optimal policy based on belief updating has the lowest average cost, the lowest best-case scenario and worst-case scenario costs. Compared to the optimal policy, the average healthcare costs per patient without any CTO interventions increase 13.77% from \$8647.22 to \$9838.663; the best-case scenario costs nearly double. Interestingly, CTO intervention after the re-hospitalization and no-shows also has low costs close to the optimal decision. The coincidence can be because the heuristic decision in practice is close to the optimal decision policy. That is, practical wisdom is in line with the decision model.

Decision Policies	Average Cost per Patient	Confidence Interval ($\alpha = 0.95$)	5% Quantile	95% Quantile (VaR at 5%)
Optimal	\$8647.22	(8548.446, 8745.947)	3791.361	19843.124
Never CTO	\$9838.663	(9749.547, 9927.778)	6182.116	20454.1
Always CTO	\$8736.104	(8632.659, 8839.549)	3836.008	20251.36
Re-Hospitalization	\$8683.126	(8583.222, 8783.029)	3836.67	19867.47
2 NoShow and Hospitalization	\$8717.268	(8614.452, 8820.084)	3836.008	19996.16

Table 4.5: Healthcare Cost with Different CTO Decision Polices

4.7 Discussion

Since the negative impact of hospitalizations greatly out-weight any other medical events in terms of healthcare costs, the optimal decision is sensitive to the estimation of hospitalization risks. Meanwhile, patients only require hospitalizations in the most deteriorated states; such, there are a limited number of hospitalization events in the dataset. This creates a double whammy: the decision is most sensitive to the most fragile estimation. On the other hand, we are surprised to discover that the estimation of injection rates has a very modest impact on the optimal decision. This contradicts our original understanding. We found that injection and clinic visits are interchangeable in the sense that decreasing injections and increasing clinic visits at the same time does not alter the optimal CTO decision. Our interpretation is that risk arises mainly when the patient is not under medical supervision. In practice, CTO decisions are usually made after repeated hospitalizations, which turns out to be close to the optimal decision.

4.8 Appendix

4.8.1 Transition Matrix for Patients

Table 4.6: Transition Matrix for non-CTO Patients

		Event_t			
Event_{t-2}	Event_{t-1}	Clinic	Hospital	Injection	NoShow
Clinic	Clinic	0.60	0.02	0.28	0.11
Clinic	Hospital	0.46	0.02	0.42	0.09
Clinic	Injection	0.19	0.01	0.76	0.04
Clinic	NoShow	0.55	0.05	0.21	0.20
Hospital	Hospital	0.30	0.02	0.59	0.10
Hospital	Injection	0.12	0.01	0.84	0.03
Hospital	Clinic	0.42	0.01	0.44	0.13
Hospital	NoShow	0.38	0.03	0.36	0.23
Injection	Injection	0.09	0.01	0.89	0.02
Injection	Clinic	0.40	0.02	0.52	0.07
Injection	Hospital	0.27	0.02	0.66	0.05
Injection	NoShow	0.40	0.04	0.43	0.13
NoShow	Clinic	0.56	0.03	0.25	0.16
NoShow	Injection	0.23	0.02	0.69	0.06
NoShow	Hospital	0.43	0.04	0.39	0.14
NoShow	NoShow	0.49	0.08	0.18	0.26

Table 4.7: Transition Matrix for CTO Patients before Their CTOs

Event$_{t-2}$	Event$_{t-1}$	Event$_t$ Clinic	Hospital	Injection	NoShow
Clinic	Injection	0.23	0.07	0.57	0.14
Clinic	Clinic	0.50	0.08	0.15	0.26
Clinic	NoShow	0.36	0.17	0.10	0.37
Clinic	Hospital	0.39	0.11	0.26	0.24
Hospital	Clinic	0.36	0.07	0.26	0.31
Hospital	NoShow	0.27	0.13	0.16	0.43
Hospital	Injection	0.13	0.04	0.70	0.12
Hospital	Hospital	0.26	0.09	0.39	0.25
Injection	NoShow	0.29	0.22	0.21	0.28
Injection	Injection	0.12	0.05	0.78	0.06
Injection	Hospital	0.27	0.11	0.47	0.15
Injection	Clinic	0.37	0.09	0.35	0.19
NoShow	Injection	0.21	0.10	0.48	0.20
NoShow	NoShow	0.26	0.22	0.07	0.44
NoShow	Clinic	0.41	0.13	0.12	0.33
NoShow	Hospital	0.33	0.16	0.20	0.31

Table 4.8: Transition Matrix for CTO Patients after Their CTOs

Event$_{t-2}$	Event$_{t-1}$	Event$_t$ Clinic	Hospital	Injection	NoShow
Clinic	Hospital	0.37	0.07	0.47	0.09
Clinic	Injection	0.15	0.02	0.79	0.04
Clinic	NoShow	0.44	0.11	0.24	0.20
Clinic	Clinic	0.52	0.05	0.32	0.11
Hospital	Hospital	0.21	0.04	0.66	0.09
Hospital	NoShow	0.30	0.09	0.39	0.22
Hospital	Injection	0.08	0.01	0.88	0.03
Hospital	Clinic	0.33	0.05	0.49	0.13
Injection	Injection	0.06	0.02	0.91	0.02
Injection	Clinic	0.32	0.04	0.57	0.07
Injection	Hospital	0.20	0.05	0.71	0.05
Injection	NoShow	0.30	0.11	0.45	0.14
NoShow	NoShow	0.36	0.18	0.19	0.26
NoShow	Hospital	0.34	0.10	0.42	0.14
NoShow	Injection	0.17	0.05	0.72	0.07
NoShow	Clinic	0.47	0.08	0.29	0.16

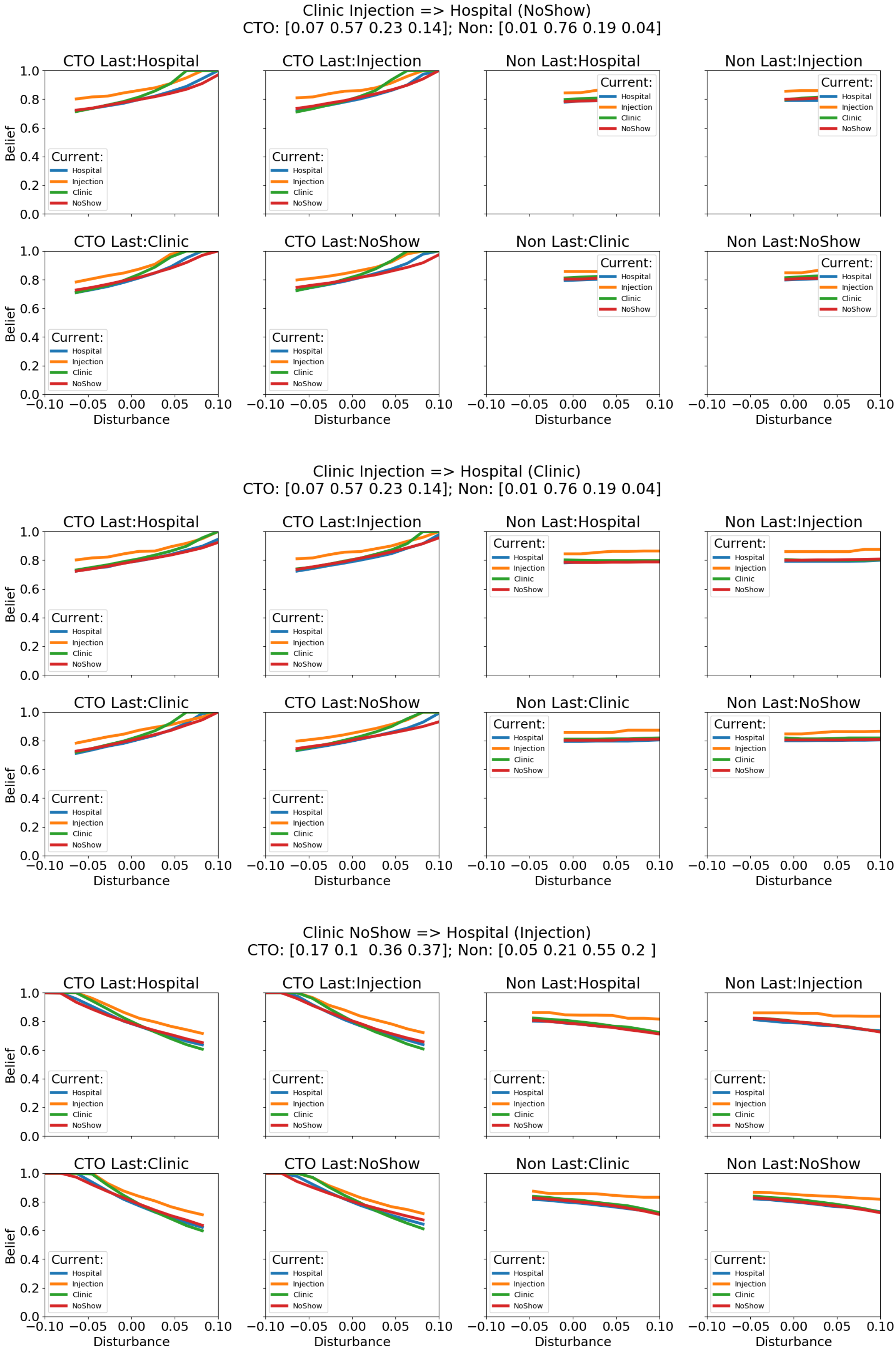

Figure 4.6: Changes on Transitions To Hospitalization

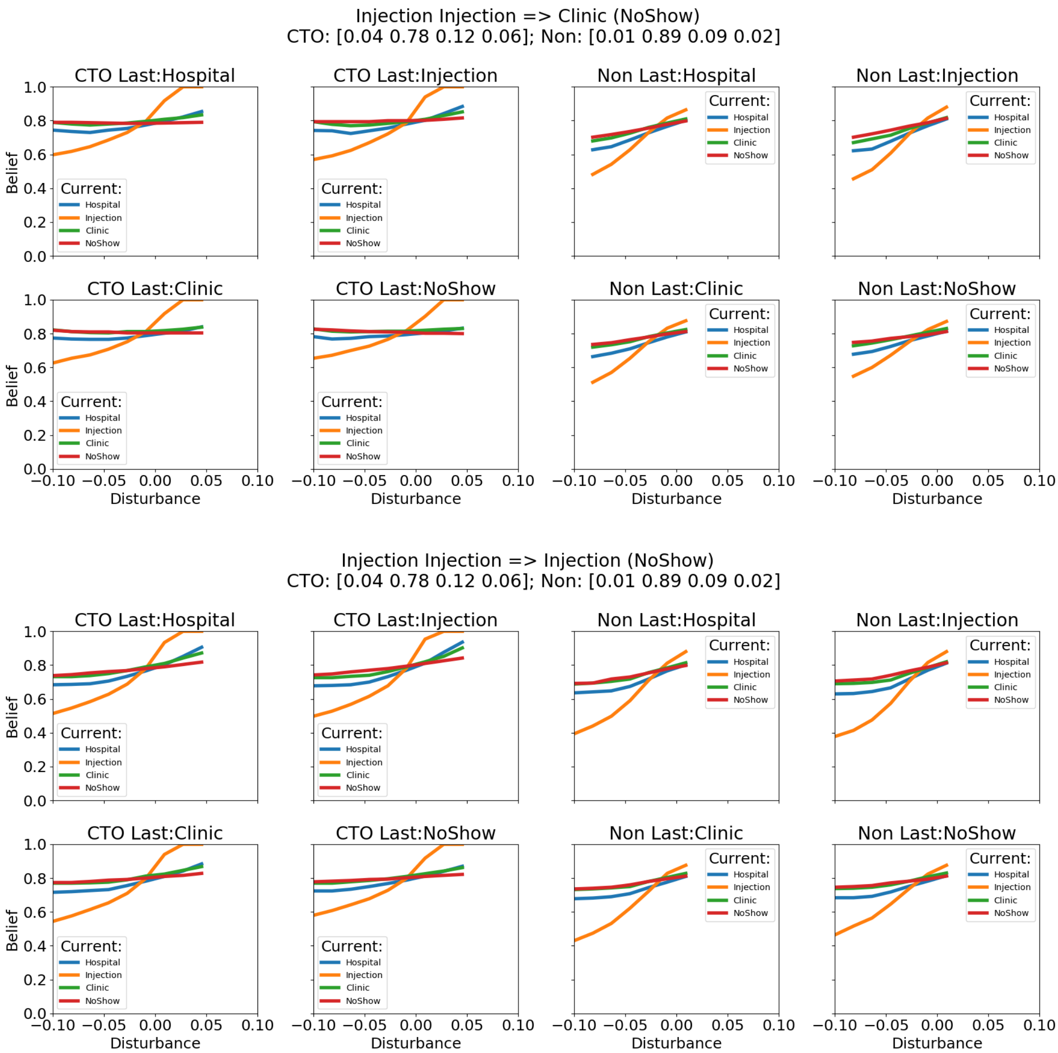

Figure 4.7: Changes on Transitions To Injection and Clinic

Chapter 5

Following Up not Falling Through: The Importance of Outpatient Follow-up Visits for Schizophrenia Care

5.1 Introduction

Early detection and medical intervention have been verified repeatedly as the most promising approaches to improving healthcare quality. Numerous studies in chronic illness care ranging from cancer treatment to mental illness intervention have shown its benefits. For example, mammography screening, which allows early detection of breast cancer and such timely cancer treatment, significantly reduces morbidity rates [105] [106]. Relevant research on schizophrenia has been focused on first-episode patients, that is, detecting the onset of their first psychotic episode and starting psychiatric treatment as early as possible [107–110]. It is well-known that timely administration of anti-psychotic medications for first-episode patients can improve lifelong illness prognoses. However, there is limited research on the benefit of early detecting the onset of psychotic episodes and timely administrating anti-psychotic medications for schizophrenia patients in the chronic stage after their first psychotic episode.

Even for schizophrenia patients in the chronic stage, the risk of relapse is always present [111]. Without intervention, relapses can develop into full-blown psychotic episodes, resulting in prolonged hospital stays. However, with proper intervention executed in time, there is a potential to prevent further deterioration and restore patients to a relatively stable condition. From the literature and our previous work, we know that the discontinuation of long-acting anti-psychotic injections (LAIs) is a leading cause for relapses for severely ill patients; and, LAIs are efficient in reducing relapse rate [20]. In addition to LAIs treatment, there are many other available interventions at the disposal of healthcare practitioners.

It is essential to quantify illness conditions in empirical studies. The quantified illness conditions can then be designed as measures of health outcomes; and, they can also be used as confounding factors depending on the research question. Medical outcomes are not always evident as hospitalization, and they can be modest events as the onset of certain symptoms. As changes in illness condition are usually the trigger for medical intervention, studies on intervention also need to control for the illness status of patients. Unfortunately, this seemingly innocent requirement turns out to be challenging for schizophrenia studies. For somatic illnesses like hypertension or diabetes, precise and objective clinical tests are available to represent the illness condition. However, for schizophrenia and mental illness in general, clinical diagnosis and evaluation depend heavily on clinical interviews. The observations and conclusions of interviews are recorded in the clinical notes in free-text format. We leverage the most recent advances in the natural language processing (NLP) field to extract representations of illness conditions from the free-text clinical notes (see literature review section 2.4).

Enabled by the vast amount of information extracted from clinical notes, this study aims to explore the intricate relationship between adherence interventions, hospitalization risks, and regular out-patient clinical follow-up visits. The adherence interventions include community treatment orders and long-acting antipsychotic injections. Finally, we want to emphasize the importance of preventing treatment dropout, and we deliver evidence to its alerting signals.

5.2 Clinical Background and Hypotheses

5.2.1 The Founding of Co-founders from Clinical Notes

There is a vast amount of valuable information in clinical notes. However, there are very limited number of schizophrenia studies based on clinical notes using text-mining approach. There were several hurdles in such research till recent. The push for digitization of medical records begins in the most recent decades and the accumulation of sufficient amount of electronic medical records for meaningful statistical analysis requires time; only in the most recent years, the development of natural language processing and text mining techniques makes even sophisticated text analysis techniques accessible to researchers besides computer science experts.

Management research on electronic medical records (EMRs) often focuses on the efficiency of EMRs in improving health institutions' productivity and reducing healthcare accidents. Those research are often longitudinal empirical investigations where comparisons are made before and after the adoption of EMRs. Economic models, including differences-in-differences and mixed-effect regression models, are utilized. For instance, one study collect productivity measures from 87 physicians in 12 primary care clinics from periods both before and after the implementation of EMR systems [40]. Their data contains $3,186$ physician-month observations over 39 months. They found that productivity decreases right after the implementation of EMR but recovers after a few months. EMRs do not significantly affect productivity in the long term, either positively or negatively. Another study with a similar research design, a difference-in-difference panel study, shows that EMRs reduce healthcare errors [41].

Few studies examine the content of EMRs, namely, the free text of clinical notes, especially for mental illnesses. Therefore, the only relevant study to us is on the relationship of negative symptoms and quality of life for adults with schizophrenia [43]. The study analyzed around 200 case records and developed a text-mining tool based on the analysis of the above records. The text-mining tool was then applied to a broader range of 7678 adults with schizophrenia. Finally, they studied the relationship between the extracted negative symptoms and hospitalization risks and quality of life. They found that negative symptoms are associated with higher hospitalization risk and lower life quality.

Text mining of clinical notes for schizophrenia is irreplaceable, valuable, and difficult for the same reason: the lack of standard measurements on the state of illness in practice. Unlike other common chronic illnesses, like hypertension or diabetes, there usually exist accessible concrete measurements, blood pressure or blood sugar level, indicating illness condition. While modern medicine advances feature precise medical exams for physical illness, mental illness examination is still primarily based on interviews between healthcare practitioners and patients.

We are the first to use illness status extracted from the free text in clinical notes as confounding factors in studying the effectiveness of medical interventions for individuals with schizophrenia. Controlling for confounding factors in investigating the effectiveness of medical interventions is extremely important. Randomized controlled trials (RCTs) are the gold standard approach in untangling any complex interaction between factors influencing the exposure of medical intervention and health outcomes. However, it is expensive to conduct RCTs, and it is sometimes impossible due to ethical concerns. Recently, there have been emerging discussions on weaknesses and inadequacies of RCTs in assessing the outcomes of complex interventions, both in medical research at large[49] and particularly regarding psychiatric interventions [48].

Nevertheless, it remains essential to control for confounding factors for observational studies, which do not have a randomized control group. While it is impossible to control for all factors, from the patient, clinicians, social support, and healthcare system, illness severity is a leading factor in determining the exposure of medical interventions [112]. As a good medical practice, clinicians will take action when the patient benefits. Therefore, without sufficiently adjusting for underlying illness severity, it will appear that treatment causes deterioration that it is meant to prevent [113].

With the health status extracted from clinical notes as confounding variables, we are well positioned to avoid spurious relationships in our study on the effectiveness of medical interventions for schizophrenia.

5.2.2 Effectiveness of LAIs and CTOs

Treatment non-compliance is a prevalent vital issue for individuals with schizophrenia. Unfortunately, less than half of schizophrenia patients continue **any** form of treatment after discharge from their first hospitalizations [19]. Though not curable, individuals with schizophrenia can benefit from medical treatments; and, the discontinuation of treatments has severe consequences. Our research reinforces and expands evidence on the effectiveness of medical treatments and adherence-improving interventions. For any medications to be beneficial, it must be prescribed and taken; for any prescriptions to be in effect, it must be written during clinic visits. We first enhance the existing evidence on the effectiveness of two long-term adherence interventions: community treatment orders (CTOs) and long-acting antipsychotic injections (LAIs). Then, we examine the benefits of regular outpatient clinic visits. Last, we establish risk factors to treatment dropouts.

Both LAIs and CTOs aim to improve treatment adherence implicitly and explicitly. LAIs are recommended for patients with non-adherence tendencies as LAIs have multiple advantages over oral medicine, including ease of administration, monitoring, and tracking [20]. Every dose of LAIs administered is witnessed and recorded; whilst, there is no such records for oral medications. However, despite the widespread recommendation of using LAIs as an adherence intervention, there is limited empirical evidence on the adherence and effectiveness of LAIs in practice [114] [115].

CTOs explicitly mandate individuals to follow their treatment in the community after hospital discharges, the effectiveness of which is still controversial due to the complexity of CTOs [79]. There exist three randomized control trials (RCT) and dozens of observational studies on the effectiveness of CTOs. While the three existing RCTs show no definite benefit of CTOs, the applicability of RCTs for complex intervention as CTOs is under debate [21] [88] [89] [50]. Observational studies mostly report positive conclusions with a few negative outcomes [85] [90] [91].

Our study aims to supplement the evidence on the effectiveness of LAIs and CTOs. Our research hypothesis are the following:

HYPOTHESIS 1a (H1A). *Long-term interventions, including LAIs and CTOs, improve recovery in out-patient care.*

HYPOTHESIS 1b (H1B). *Long-term interventions, including LAIs and CTOs, reduce hospitalization risks.*

With the information extracted from the clinical notes, we are able to add nuance into levels of deterioration: mild and severe deterioration. The mild deterioration refers to the ones noted by clinicians during regular clinic visits while not severe enough for hospitalizations. With this distinction, we are able to define deterioration and recovery in out-patient setting in contrast to only focusing on hospitalizations.

5.2.3 Hospitalization Risk

The previous section discusses the effectiveness of medical interventions; this section will discuss medical events correlated with hospitalization risks. Understanding hospitalization risk is often the priority in schizophrenia research, as hospitalization causes an enormous burden to both the individual and society. At the individual level, hospitalization signals episodes of severe relapses and severe forms of restrictions; whereas at the society level, hospitalization easily constitutes the vast majority of healthcare costs for individuals with schizophrenia [39].

There are two reported indicators correlated with elevated hospitalization risk: the revolving door phenomenon and treatment dropout. The revolving door phenomenon is well known in clinical practice; that is, patients are admitted to the hospital repeatedly. Furthermore, counter-intuitively, the risk of hospitalization for individuals with schizophrenia is heightened after hospital discharges [116]. Studies also indicate that the risk of readmission correlates with the duration of stays of the prior hospitalizations [117]. Another indicator of hospitalization is treatment compliance. Treatment dropout, an extreme form of treatment non-compliance, is associated with increased hospitalization risk [117]. The existing studies tend to focus on one facet of the research question. Our study strengthens the existing evidence while considering the effects of other medical interventions and controlling for health status confounding factors.

HYPOTHESIS 2a (H2A)**.** *Hospital readmission risk is higher than index hospitalization risk.*

HYPOTHESIS 2b (H2B)**.** *Treatment dropout increases hospitalization risks.*

The above hypothesis are examined in combinations of considering other medical interventions and controlling for health status. The examination of these other interventions, including prescription changes, are also reported in the experiment result section.

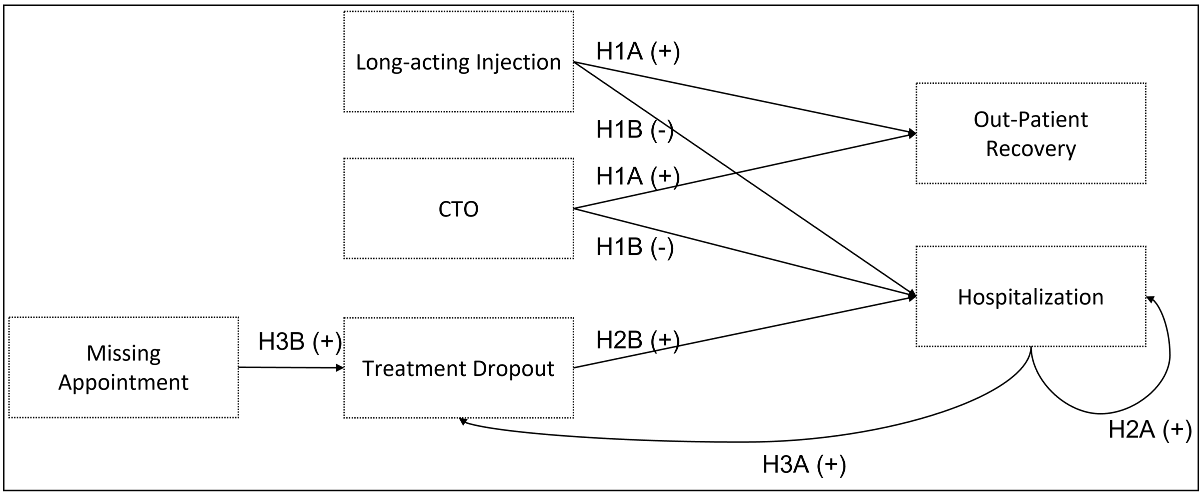

Figure 5.1: Conceptual Illustration on Relation between Health Interventions and Outcomes

5.2.4 Treatment Dropout Prevention

As demonstrated repeatedly in the study on treatment effectiveness and hospitalization risk, outpatient treatment is essential in preventing relapses and reducing hospitalization risk. Yet, unfortunately, treatment dropout is a typical affair for schizophrenia patients. Therefore, the last component of our study is to understand indicators of treatment dropout. As such, we can devise strategies to prevent treatment dropout.

HYPOTHESIS 3a (H3A)**.** *Treatment dropout risk increases shortly after hospital discharge.*

HYPOTHESIS 3b (H3B)**.** *Treatment dropout risk increases after missing appointments.*

We also provide survival analysis on the probability of patients returning for clinic visits over the number of late days for the scheduled visits. Figure 5.1 provides a conceptual illustration on the above hypothesis.

5.3 Data

Our research design is innovative in utilizing clinical notes to study the effect of complex mental health interventions, especially regarding establishing confounding factors and safeguarding against spurious relationships. Despite the well-known consequence of confounding effects in observational studies, from induing biases to causing incorrect estimates, it has been challenging to collect or extract such information in previous studies. Our research highlights the rich information in the unstructured clinical notes and exciting novel research venues enabled by the latest advancement in artificial intelligence - natural language processing. With critical information extracted by text mining clinical notes, we are well suited to uncover the effect of interventions on important medical events and outcomes. However, amidst the benefits of the vast information in the unstructured clinical notes, there are also concerns about the consistency of clinical notes written by varied healthcare practitioners. As explained later, clinical notes for the mental status exam follow a standard structure and contain a specified set of components. There are minor variations between clinicians, but the key components remain prevalent.

5.3.1 Research Setting

Our data originate from the Continuing Care Clinic (CCC) associated with Jewish General Hospital in Montreal, Canada. The CCC provides long-term outpatient treatment for patients with severe and persistent mental illnesses (SPMI), mainly schizophrenia and schizoaffective disorder. In Montreal, mental health care is designated to the hospital and its associated outpatient clinic in its geographical catchment area. The patients who present at another hospital will be transported to their assigned hospital in their district. There are virtually no private or alternative mental health services available to this population. The above unique conditions guarantee the integrity of our data, where we have complete and accurate healthcare utilization and clinical records for the patient cohort in the study. No meaningful changes in the legal tenets, organizational functioning, bed capacity, or clinic staffing occurred during the study period.

The study focuses on individuals with severe and persistent mental illness (SPMI). Though there is no uniform definition, individuals with SPMI often share the following characteristics: 1. they have prolonged or recurrent mental illness despite treatment; 2. they have been in psychiatric care for longer than two years and need continuing care; 3. the illness dramatically impairs their quality of life; 4. they tend to have a high relapse and hospitalization risks. Thus, it is essential to note that short-term interventions are insufficient for SPMI as it is a chronic illness with sporadic relapses and remissions. Often, individuals with SPMI experience relapse or recurrence of acute symptoms throughout their lifetime. Therefore, the focus of our study is not on the cure of the illness, which rarely is the case. Instead, the focus is the effectiveness of both long-term and short-term interventions in reducing relapse risks and maintaining the quality of life.

The majority of patients in the CCC clinic are diagnosed with schizophrenia or schizoaffective disorder. There are positive (abnormally present) symptoms and negative (abnormally absent) symptoms for schizophrenia. Positive symptoms, including hallucination and delusion, are more noticeable and better known than negative symptoms, including withdrawal and depression. In addition, positive symptoms tend to be more "dramatic," more likely to cause disturbance to society and lead to social interventions. However, negative symptoms can be detrimental to one's quality of life and essential in indicating deterioration. Furthermore, positive symptoms often lead to the most noticeable medical events; while, negative symptoms may remain undetected. Therefore, the commonly used measures, including ER visits and hospital admissions as indicators of health deterioration, are deficient in designating illness development.

Unlike physical illness, diagnosis and evaluation for mental illnesses always comes with degrees of ambiguity. For instance, according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition [118]), the criteria for schizophrenia can be summarized as the presence of two of the following five symptoms, including delusions, hallucinations, disorganized speech, disorganized behaviour, and negative symptoms, for more than one month. On the other hand, in DSM-4, only one of the symptoms is needed for the diagnosis if the symptom exhibition is “bizarre.”

Furthermore, it is challenging to quantify the severity of mental illness. Despite the existence of psychiatric rating scales, including Positive and Negative Syndrome Scale (PANSS) [119], and Clinical Global Impression – Severity scale (CGI-S) [120], their practicality and reliability are questionable for retrospective research. First, rating scales are known for their poor interrater interpretability. Clinicians often have a different interpretation of a rating number for each symptom. As our study involves several clinicians with different levels of medical training, the rating scales can be difficult to generalize and standardize across personals. Second, rating scales are not always available during routine clinic visits. In fact, it is often not available. It can be too time-consuming to conduct interviews for rating scales during routine visits. Third, clinicians often choose to use the type and version of rating scales out of their preferences. This difficulty in obtaining a standardized quantitative representation of the illness severity contributes to our decision to utilize the unstructured clinical notes.

Clinical notes collected from the CCC clinic follow the subjective, objective, assessment and plan (SOAP) structure. The SOAP structure is widely adopted in clinical practices and taught in medical schools. Table 5.1 summarizes the guideline of SOAP structure.

Field	Description
Subjective	narratives from patients on events and experiences before their clinical visits
Objective	objective observations from clinicians on patients ranging from appearances to mental status
Assessment	concise medical evaluation conclusions through the synthesis of "subjective" and "objective" evidence
Plan	scheduling for the next clinical appointment and prescription if changes required

Table 5.1: Clinical Note SOAP Structure

Our current research uses information from all but one field of clinical notes. The focus of this study is to investigate the effectiveness of medical interventions. The main confounding factor in such an investigation is the health status of patients. We assume that the assessment and objective fields can sufficiently represent the health status without the subjective field. This decision is both practical and informed. Based on medical training guidelines and observations in practice, the assessment field contains a concise summary of a patient's health status. To further support the health status summary, the objective field contains an objective clinical evaluation on different aspects of an illness symptom exhibition. Objective fields may contain positive or negative comments on one or more aspects of patients, including appearance, behaviour, speech, affect, thought content, insight/judgment. The assessment and objective fields should be based on and continued upon the subjective fields. Therefore, the assessment and objective fields are more than sufficient in establishing health status from clinical notes. Furthermore, it is incredibly challenging to extract reliable medical information from the subjective fields with the current natural language processing capability. The subjective fields contain narratives from patients, where medical implications are often beyond the surface of the words.

Treatment adherence and hospitalization risk are the two most essential and intertwined issues in schizophrenia care. As for chronic illnesses, the goal of schizophrenia care is to maintain remission and reduce relapse. However, different from patients with common chronic illnesses, schizophrenia patients often do not embrace medical treatments. The necessity and benefit of treatments are often not well understood or received by patients. The resistance towards treatment may come from the symptoms of schizophrenia, particularly "lack of insight." That is, the distinction between reality and hallucination is often blurred. It is a catch 22 situation. As the illness deteriorates, the patient is more inclined to refuse treatment as they are more detached from reality. Meanwhile, the resistance may also come from improvement in the condition. Like many mental illnesses, including depression, an improvement in condition may lead the patients to stop treatment prematurely because they deem themselves recovered. There are also situations where it becomes challenging for patients to follow treatments due to the decrease of their daily functionality. The focus of this study is to understand treatment adherence and hospitalization risks.

5.3.2 Clinical Data Description

We conducted a follow-back prospective study over five years between 2010 and 2015, based on our clinic's entire SPMI population. Criteria for acceptance to the Continuing Care Clinic (CCC) are cases where a patient suffers from SPMI and has suffered from repeated hospitalizations and significant morbidity. The most frequent diagnoses in the clinic are schizophrenia and schizoaffective disorder. The following data are collected: the dates of (i) all clinic visits, (ii) injections of LAIs, (iii) CTOs, (iv) hospitalizations, (v) ER emergency room visits, and the clinical notes for all clinic visits. Among the 367 patients studied, 77 were obliged via a CTO during the study period to have regular injections and clinical follow-up. Note that many of these 77 patients were also prescribed oral medications, including clozapine, but injections were utilized because these particular patients are not reliable in taking oral medication. The remaining 290 patients did not have a CTO during the study period. Consent to participate in this retrospective study was not required, and no patient was identified by name. Ethics approval was received from the hospital's research and ethics committee.

Our data set can be categorized into three main components: basic characteristics of patients, the time series of medical events and the text data from clinical notes during out-patient visits. The data come from two data sources. First, the CCC clinic provided basic information for patients in the study; then, out-patient data, including clinical visits, injection records, clinical notes, are collected; last, hospitalization and ER visit records are collected from the Jewish General Hospital for the each patient in the study.

Clinical Note

The clinical notes we collected contain the following metadata: the entry date, patient identification number, and type of note. In addition, we are interested in the "progress note" written by clinicians during a clinic visit from patients, which contains detailed observations, assessments and medical plans.

During the five-year study period, there are in total $15,065$ progress notes. Figure 5.3 provides the distribution of clinic visit schedules, while Figure 5.2 provides the distribution of actual intervals between past clinic visits. The most common schedule is 14, 21 and 28 days between visits. The actual visit intervals also follow a similar pattern with 14, 21 and 28 days having the highest density. Nevertheless, Figure 5.2 already provides an impression that Non-CTO patients have more regular clinic visits than CTO patients. We suspect that the irregularity of clinic visits is both the outcome and cause of deterioration, which motivates us to examine clinic visits with great interest.

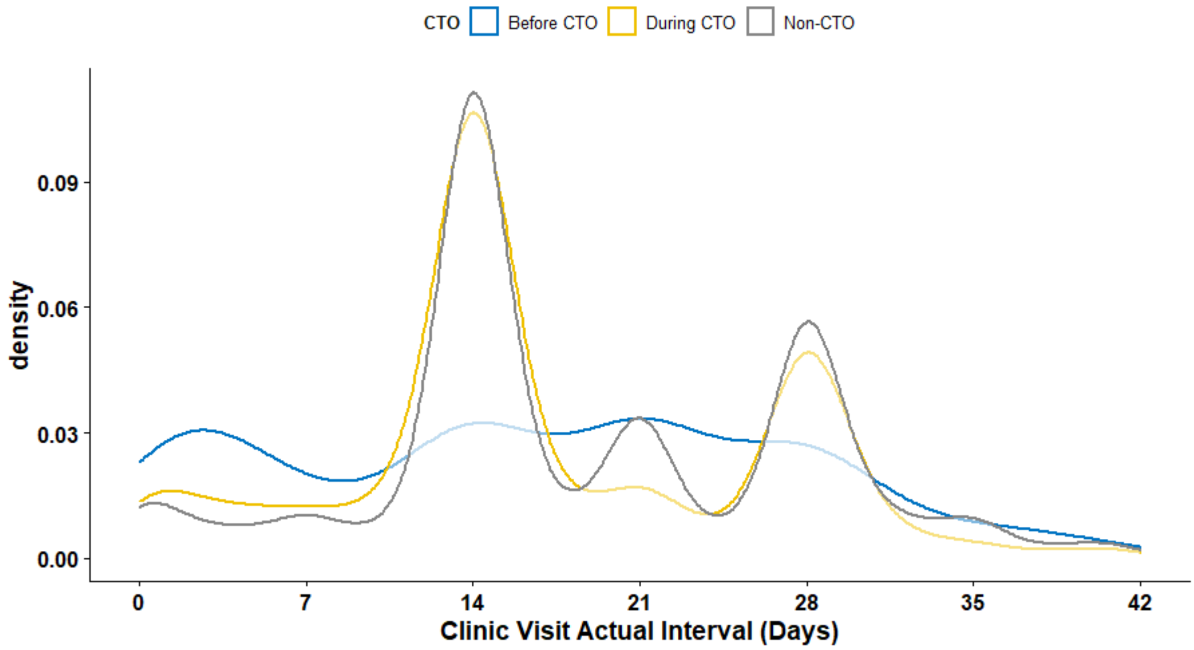

Figure 5.2: Clinic Visit Interval for Patients with Different CTO Status

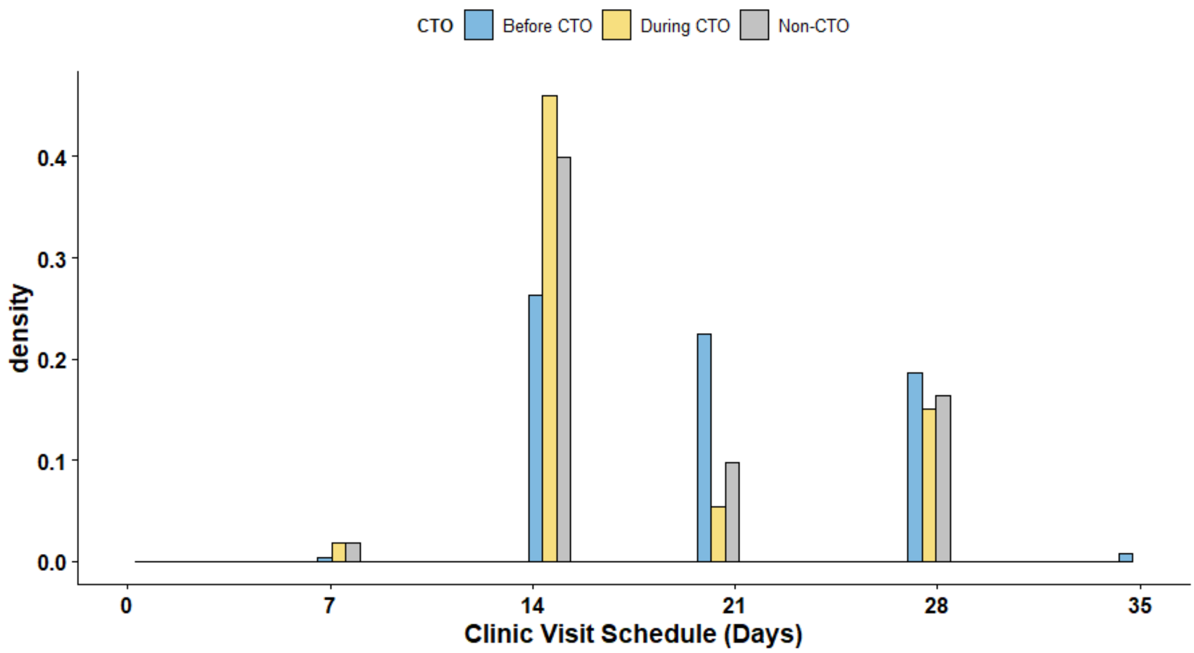

Figure 5.3: Clinic Visit Schedule for Patients with Different CTO Status

Progress notes are written methodologically in the Subjective, Objective, Assessment and Plan (SOAP) structure [121]. There are empty entries among the progress notes:

'Subjective' field has $1,369$ (9.09%) empty entries; 'Objective' has $1,440$ (9.56%) empty entries; 'Assessment' has $1,649$ (10.95%) empty entries; 'Plan' has $3,389$ (22.5%) empty entries. The percentages of empty entries are not alarming; it is inline with the acceptable range of missing values for similar analytics. Note that some empty entries are expected and are not technical missing values. For example, 'Plan' field can be empty if the treatment plan remains the same as the previous clinic visit.

We are interested in extracting health status information from the objective and assessment fields and extracting health intervention information from the plan field. The **objective** field contains clinical evaluation on one or more aspects of mental health conditions, including appearance, behaviour, speech, affect, thought content, and insight/judgment. The average number of words in the objective field is 13.52 (± 9.73); the lexical diversity, measured by Type-Token Ratio (TTR), is 0.01. The TTR is the ratio between the number of different unique words and the total number of words. For comparison, the TTR ratio for spoken English is around 0.4 [122]. The low TTR means that the objective fields mainly consist of a small set of medical terms to evaluate schizophrenia symptoms. It is advantageous for our analysis because extracting information from a predictable vocabulary set is more accessible than from a diverse one. To provide an intuitive understanding of the low diversity of vocabulary used in the objective field. The top 20 words represent 32% of the whole corpus.

The **assessment** field contains the evaluation of mental illness status for a patient in concise languages. Around half of the entries, 56%, contain only the word 'stable'; and, the average number of words, after the text cleaning, in assessment is 2.38 (± 4.38). The **plan** field contains intervention plans (mainly, prescription changes) and schedules for the next appointment. It is entered with fixed format, so we are able to extract prescription information with details on the name and dosage for each medication. Medications with the same active ingredient can have different names including brand names and generic names. We assume that there is negligible differences between generic and brand name medications. To ease the analysis, all medications are represented by their generic names. In total, we have 63 different medications for psychiatric use, which can be categorized into five groups: anti-psychotic, mood stabilizer, anti-depressant, sedative and side-effect medications.

Prescription Change

The extraction of the prescription changes from the clinical notes is straightforward. First, we extract the prescription plan following a fixed format. For example, "zuclopenthixol decanoate 175 mg im depot q2wk" starts with the medicine name, then dosage, and last administration method and frequency. Next, we consulted with our psychiatric experts and consolidated medications with the same active ingredients. Last, any changes in psychiatric medications, including dosage and frequency, are flagged.

To illustrate, Figure 5.9 shows the timeline of medical events for a patient. Vertical dotted lines indicate 'unstable' notes; green vertical blocks indicate hospitalizations; horizontal blocks indicate the prescription for the patient during a certain time period; the name of each medication is shown on the *y-axis*; the height of the horizontal block represents dosage for the medication. This sample patient was under a combination of psychiatric medications, had several 'unstable' moments, had several prescription changes; and, had one hospitalization.

As we can observe from this example (Figure 5.9), the prescription was changed in the middle of the year 2011 at the first 'unstable' assessment; but, the prescription was not changed at the second 'unstable' assessment. Nevertheless, there was no hospitalization in the year 2011, 2012, and 2013, and the patient remained largely stable around the year 2013. At the end of the year 2013, the patient became 'unstable', and the prescription was changed subsequentially. However, the patient was hospitalized not long afterwards.

Appointment Schedule

The clinic visit schedules are also extracted from the **plan** field. The schedules are later used to establish the duration of time periods and to estimate missing appointments and treatment dropouts in our analytical analysis. During most clinic visits, clinicians will record the schedule for the subsequent appointment. This schedule can differ among patients with the most frequent schedule as 14 days and 28 days. It can also change over time for one patient; however, the schedule change is uncommon and only happens for a long time. If no schedule information is found from a clinic visit, the most recent schedule is used instead.

5.4 Methodology

5.4.1 "Assessment" Classification

As mentioned previously, the assessment field contains a highly concise evaluation of health conditions. In ideal cases, it explicitly states that the health condition is "stable" or "unstable", which consist of a large proportion of the assessments. However, there can be cases that the evaluation is a phrase or a short sentence, for example, "usual complaintive paranoid". There are a variety of different phrases and short sentences ranging from combinations of medical expressions to common synonyms. An exploratory analysis was conducted to ensure the understanding of document characteristics and the selection of suitable text mining approaches. The intuitive illustrations of the exploratory analysis is provided in the Appendix Section 5.7.1. To facilitate our analysis, we aim to classify all assessment expressions into two categories: stable vs unstable. The best approach for such a classification problem is the ensemble method. Namely, we will try multiple classification methods coupled with different feature representations; then, the consensus of all classifiers will be the outcome.

Feature Representation

We use three mainstream feature representations for text mining: bag-of-words, term frequency–inverse document frequency (TF-IDF), and word embeddings. We choose not to use the most recent transformer representation for natural language processing (NLP) because the writing in clinical notes is mainly fragmental, and transformer representation works well for full sentences.

The bag-of-word representation is the most straightforward, both computationally and conceptually. It considers the occurrences of each word in a document and discards grammar structures and word orders. It is a typical representation used in document classification tasks. We can understand it in an intuitive and simplified example: documents with the exact words are the same. It is well suitable for the assessment classification in our case. The biggest shortcoming of the bag-of-words approach is discarding grammar information. We have mentioned that assessments only contain sentence segments; therefore, the shortcoming does not harm our case.

The bag of word representation uses the occurrences of each word in a document; while, the TF-IDF approach uses adjusted weights based on the rarity of the words across documents. Thus, the TF-IDF will increase the weight of rare words and decrease the weight of common words. Intuitively, the meaning of a sentence is more likely decided by the uncommon words instead of common ones. For example, "the" appears in almost all sentences; it does not carry any meaning or distinguish one sentence from another.

The word embedding representation has a different regime from the bag-of-words, and the TF-IDF approaches. While the bag-of-words and the TF-IDF do not consider the meaning of words, the word embedding can be seen as a dictionary for machines. The meaning of words is represented in a vector space; the closer the meaning of two words, the closer the distance between their vector space representation. This "dictionary" is achieved by training natural language models with enormous text data and compute resources. In addition, established word embeddings are openly accessible and ready to use as the base of text analysis.

Routine text cleaning and pre-processing procedures are applied, includes removing stopping words, removing special characters, lemmatization, and spelling correction. For negations, we tag all words after both common negation words and medical shorthand negation words [42]. Common negation words are from pre-trained statistical models for English [123], and the medical shorthand negation words considered are 'nil' and 'o'.

The bag-of-words approach has the benefit of interpretability, which is a good starting point for understanding the problem at hand. A snapshot of the frequency of the top 20 most frequent words in assessment is provided in Figure 5.10.

Classification Methods

For document classification tasks, we use the ensemble approach. The ensemble method involves multiple classification models and ensembles different combinations of models and feature representations to produce a more reliable and accurate outcome. We use five such combinations, including Naive Classifier, Naive Bayesian classification method with bag-of-word feature representation, support vector machine (SVM) classification method with TF-IDF feature representation, and logistic regression classification method with word embedding feature representation. Though all the combinations share the same objective, the differences among them allow each combination to capture different aspects of the task, which lead to more accurate and robust final results.

The naive classifier is the most intuitive and straightforward. It depends solely on the number of positive and negative words. We predefined positive words associated with stability and negative words associated with deterioration based on the expert's opinion. If positive words outnumber negative words, the assessment is classified as 'stable'; otherwise, it is classified as 'unstable'.

The naive Bayesian classifier takes a simple statistical approach based on the Bayes' theorem. Features are assumed to be independent, and each feature is associated with a probability of the outcome. In essence, it is similar to the naive classifier, but the association between the feature and outcome is more fine-tuned.

Logistic regression is a classic linear classification method for binary outcomes. It models the probability of 'success' vs 'failure'; in our case, it models the probability of 'stable' vs 'unstable.' It is a well-known and established method in statistics, machine learning, and other quantitative research fields. Moreover, it is accessible for researchers besides statisticians, where nearly all statistical software supports the logistic regression method. Therefore, it frequently appears in medical research; it can be used to predict medical treatment outcomes and evaluate risks of illness.

Support vector machine (SVM) is a classification method known for its robustness in machine learning. Instead of a probabilistic approach, it maximizes the boundaries between the binary outcomes in the vector space. As a result, it is robust to noises in the data and routinely outperforms more complex machine learning methods.

Training and Evaluation

We randomly selected over 500 representative assessment entries to be manually labelled by the psychiatrist in our research team. Only the assessments were shown to the expert, and any other information was hidden. We ask the expert to categorize the assessments into two classes: stable vs unstable. After collecting the labelled data, training and testing datasets were randomly separated. The above five combinations of classification and feature representation methods were each fine-tuned using cross-validation and hyper-parameter grid search methods with the training dataset. The final outcome, following the ensemble method, is the majority outcome of the five combinations. Finally, the performance was measured on the separated testing dataset with an 88% accuracy and 88% precision and recall.

5.4.2 "Objective" Feature Extraction

The objective field is more complex than the assessment field. As mentioned previously, it contains clinical evaluation on one or more aspects of patients' conditions. For instance, "adequately groomed .pleasant calm. not hypomanic, no psychosis expressed." Since the objective field contains multifaceted descriptions, we believe that a binary summarization similar to the one used for assessment is no longer sufficient. Instead, we leveraged the Named Entity Recognition (NER) model to identify keywords in the objective field and assign the keywords into one of the following categories: appearance, behaviour, speech, affect, thought content, and insight/judgment.

To be precise, we used spaCy NER system and fine-tuned our own NER model based on scispacy [124] pipeline using the transfer learning technique. spaCy is an open-source natural language processing library known for its accessibility and reliability. The spaCy NER system provides an infrastructure to develop custom models, where it combines sophisticated word embedding strategy and deep convolutional neural network models. More importantly, the spaCy NER system enables researchers and NLP professionals to share and improve their custom language models. Training a NER model from the blank requires enormous data and compute resources; Therefore, the transfer learning technique is the preferred approach, where custom language models are built upon existing models. We fine-tuned our NER model based on the scispacy pipeline, developed solely for biomedical, scientific or clinical text analysis.

The baseline model from scispacy can extract medical terminologies from clinical text. Building on top of the baseline model, we fine-tuned our custom model to extract keywords relating to psychiatric symptoms. The fine-tunning process (transfer learning) is inexpensive in both data and compute resource. With less than one thousand manual annotations, we have a high performance of 92.418% Precision, 92.550% Recall, 92.484% F-Score.

5.4.3 Identification Strategy

We used mixed-effects logistic regression models to analyze the impact of medical interventions and their absence. We are interested in examining prescription changes under different health conditions, the adoption of long-acting antipsychotic injections, the application of community treatment orders, and treatment dropout. Prescription changes can happen promptly at several time points for a patient; both long-acting antipsychotic injections and community treatment orders can last years. Therefore, repeated observations are taken and analyzed from each patient. Our experiment falls in a standard with-in subject design, for which mixed-effects models [125] are highly suitable.

The mixed-effects model refers to the mix of random effects and fixed effects. It can also be phrased as the mix of within-subject effects and between-subject effects. We are interested in the within-subject effects, that is, the effect of an intervention on the same individual after eliminating individual differences. We are not interested in the between-subject effects in this study, where the health outcomes differ between patients.

As mentioned previously, regarding CTO intervention, we have two patient groups: non-CTO and CTO patients, where the non-CTO patients who did not receive an CTO during the entire study period. We do not observe statistical differences between the groups in terms of age, gender and ethnicity. However, this does not mean that we can treat the entire patient cohort as homogenous. From discussions with our psychiatric experts and the literature, schizophrenia patients are known for their heterogeneity. For example, some patients maintain high functionality and can maintain stability for the long-term with proper medical treatment, and some patients' conditions are volatile even with intense treatment. This means that basic characteristics, like age, gender, ethnicity, were not enough in capturing the differences between patients regarding illness progression. Our study data do not include other individual level measurements that can represent the innate illness severity or stability of patients. Therefore, in our study, the differences between individuals are designed as the random effects; we focus on fixed effects, interventions occurring at times within individuals, after accounting for the individual differences using the mixed-effects model.

The with-in subject experiment design with the mixed model analysis does not require random assignment of interventions among subjects. However, we still need to control for exogenous factors on the timing of interventions within a subject, which is most likely not random. The medical interventions may well be associated with patients' health states. Therefore, we introduce confounding factors into our analysis to mitigate the influence of health states. The confounding factors come from the assessment and objective fields in the clinical notes. With the multi-dimensional health status representations built upon the clinical notes, we can adequately control for the effect of health status in our analysis.

Regarding timeline design, our model can be considered as a fixed time-period model. For instance, *deterioration* in our study is defined as the transition from stable in the current period to unstable in the coming period. Traditionally, a fixed time-period model means that the duration of periods is predetermined and universal among all subjects. However, we consider this strict design is insufficient in reflecting the reality. Therefore, we adjust the duration based on the clinic visit schedules specified in the clinical notes instead of using a universal duration per period. That is, for patients whose appointments were scheduled three weeks apart, the duration for the fixed time-period is three weeks; for patients whose appointments were two weeks apart, the duration is adjusted to two weeks instead.

A weakness of our experiment design is that we do not control for clinicians assigned to patients. It is not unreasonable to assume that the health outcome of patients may depend on their clinicians. From our discussion with the CCC clinic, we learned that all staff members discussed each patient case at least once a week. The routine team discussion may negate any significant treatment differences across team members.

5.4.4 Variables

Dependent Variables

Based on information extracted from the clinical notes, our study consists of several analytical components and hypotheses regarding schizophrenia care. The first question we want to answer is on the deterioration and recovery of patients in the out-patient setting: *how do interventions affect deterioration and recovery for schizophrenia patients?* To answer this question, the dependent variables are *deterioration* and *recovery*. Both are binary indicator variables with the value 0 or 1.

- *deterioration* takes the value 1 when the patient transit from "stable" assessment to "unstable" assessment; and, it takes the value 0 when the patient transit from "stable" assessment to the others.
- *recovery* takes the value 1 when the patient transit from "unstable" assessment to "stable" assessment; and, it takes the value 0 otherwise.

For many physical illnesses or disorders, the benefits of medical interventions are straightforward and clarified through clinical trials. However, this is not always the case for schizophrenia or mental illnesses in general. For example, it is well known that finding effective medications for an individual with mental illness can be a long process of trials and errors. Hence, our first research question is to establish the effectiveness of interventions regarding *deterioration* and *recovery*.

The next research question directly speaks to *hospitalization risks*. For chronic conditions, including schizophrenia, a key metric in evaluating the effectiveness of an intervention is the occurrences of hospitalizations. Hospitalizations cause a substantial financial burden on the healthcare system and significantly restrict individual freedom. They also indicate a dramatic decline in mental status and signal extensive, severe relapse episodes. The dependent variable *hospitalization* is a binary indicator variable, where the value 1 indicates immediate hospital admission and the value 0 indicates no immediate hospital admission.

The last research question is on indicators of *treatment dropout*. Patients with schizophrenia are infamous for their low treatment adherence and high treatment dropout rate. In understanding indicators or predictors of treatment dropout, we can design counter-strategies to address the problem. Treatment dropout is defined as more than three sequential missing appointments. Therefore, the dependent variable *treatment dropout* is a binary indicator variable, where the value 1 indicates more than three sequential missing appointments and the value 0 indicates otherwise.

Independent Variables

The independent variables in the study are representations of medical interventions: CTO, long-acting antipsychotic injections, and prescription changes. Though both CTOs and long-acting antipsychotic injections are long-term interventions, we use indicator variables to represent if a patient is under the effect of CTOs or long-acting antipsychotic injections for the time period in question. We design three categories regarding CTOs: Non-CTO, Before CTO, and During CTO. Non-CTO means that the patient was never under the CTO intervention; Before CTO means that we observed CTO intervention later on, but the patient was not under the effect of a CTO at that moment; During CTO, the CTO was in effect for the period in interest. To represent the categorical representations, we use the following two binary indicator variables.

- *Before CTO* takes the value 1 when the patient was not under the CTO intervention at that moment but would be under an active CTO later on; it takes the value 0 otherwise

- *During CTO* takes the value 1 when the patient was under an active CTO intervention; it takes the value 0 otherwise

The above variable design means that if both *Before CTO* and *During CTO* take the value 0, the patient was never under any CTO intervention. Also, it is never the case when both *Before CTO* and *During CTO* take the value 1 since a patient can not both be under and before a CTO at one time period.

To represent injections, the binary variable *Injection* takes the value 1 if the patient was receiving injections at the time period in interest; and, it takes the value 0 otherwise. For prescription change, the binary variable *Prescription Change* takes the value 1 if there is prescription changes in the current time period; it takes the value 0 otherwise.

We define missing appointments based on the clinic appointment scheduling with leniency. For example, if a patient is on a two-week schedule for the next appointment, we define the missing appointment after the patient does not show up in three weeks; if a patient is on a four-week schedule, we will wait for six weeks to declare missing an appointment. The binary variable *Missing Appointment* takes the value 1 if the patient misses an appointment; the variable takes the value 0 otherwise. Likewise, the binary variable *Clinic Visit* takes the value 1 if the patient follow the appointment schedule with leniency; the variable takes the value 0 otherwise.

Hospital Discharge is also a binary variable with the value 1 indicating the patient is discharged from the hospital stay in the current period and value 0 otherwise. We do not consider the time spent during the hospital stay as the study only focuses on out-patient care.

Confounding Variables

Both the health outcome and medical intervention can be correlated with the health status of a patient. The statement can be easily argued: clinicians are more likely to take action when the patient is sick; tomorrow's health is very likely depending on today's health. This is a classic case of health status being a confounding factor in a health economic model. To counter spurious correlation, we extract information on health status from the clinical notes. Thus, the variable representations of the clinical notes are confounding variables.

There are two main parts of the confounding variables: one is the stable/unstable classified from the assessment field (details are given in section 5.4.1); the other are representations of different aspects of a patient extracted from the objective field (details are given in section 5.4.2). We have the following confounding variables.

- *stable* takes the value 1 if the assessment field from the clinical note is classified as stable; it takes the value 0 otherwise
- *unstable* takes the value 1 if the assessment is classified as unstable; it takes the value 0 otherwise

It is possible that both *stable* and *unstable* take the value 0, which means that assessments were not available for the time period in interest.

- *appearance* takes the value 1 when positive comments on appearance are in the objective field. For example, the patient is well groomed and tidy. It takes the value 0 when no positive comments are in the objective field;
- *adverse appearance* takes the value 1 when negative comments on appearance are in the objective field. It takes the value 0 when no negative comments are in the objective field;
- *behavior* takes the value 1 when positive comments on behavior are in the objective field. For example, the patient is well behaved. It takes the value 0 when no positive comments are in the objective field;
- *adverse behavior* takes the value 1 when negative comments on behavior are in the objective field. It takes the value 0 when no negative comments are in the objective field;

- *danger* takes the value 1 when positive comments on danger are in the objective field. For example, the patient shows no danger of harming themselves or others. it takes the value 0 when no positive comments are in the objective field;

- *adverse danger* takes the value 1 when negative comments on danger are in the objective field. For example, the patient is in danger of hurting themselves or others. It takes the value 0 when no negative comments are in the objective field;

- *impulse control* takes the value 1 when positive comments on impulse control are in the objective field. It takes the value 0 when no positive comments are in the objective field;

- *adverse impulse control* takes the value 1 when negative comments on impulse control are in the objective field. It takes the value 0 when no negative comments are in the objective field;

- *insight* takes the value 1 when positive comments on insight are in the objective field. For example, the patient shows insight into their illness conditions. It takes the value 0 when no positive comments are in the objective field;

- *adverse insight* takes the value 1 when negative comments on insight are in the objective field. For example, the patient shows no insight in their illness. It takes the value 0 when no negative comments are in the objective field;

- *language* takes the value 1 when positive comments on language are in the objective field. For example, the patient is coherent in their expressions. It takes the value 0 when no positive comments are in the objective field;

- *adverse language* takes the value 1 when negative comments on language are in the objective field. It takes the value 0 when no negative comments are in the objective field;

- *mood* takes the value 1 when positive comments on mood are in the objective field. For example, the patient is calm. It takes the value 0 when no positive comments are in the objective field;
- *adverse mood* takes the value 1 when negative comments on mood are in the objective field. It takes the value 0 when no negative comments are in the objective field;
- *thought content* takes the value 1 when positive comments on thought content are in the objective field. For example, there is no hallucination or delusion present. It takes the value 0 when no positive comments are in the objective field;
- *adverse thought content* takes the value 1 when negative comments on thought content are in the objective field. It takes the value 0 when no negative comments are in the objective field;
- *thought process* takes the value 1 when positive comments on thought process are in the objective field. It takes the value 0 when no positive comments are in the objective field;
- *adverse thought process* takes the value 1 when negative comments on thought process are in the objective field. It takes the value 0 when no negative comments are in the objective field.

The above confounding variables can be correlated with each other. The correlation among the confounding variables is not a cause for concerns and does not influence the analysis on the effect of interventions. Since the effect of confounding variables are never the focus of a study, correlation among confounding variables are acceptable. Nevertheless, this also means that we should not interpret the analytical results on confounding variables as correlation within may distort analytical outcomes. There is only one purpose for incorporating confounding variables, that is, to better understand the effect of medical interventions.

5.4.5 Model Specification

We conceptualized three critical turning points in the evolution of health states for schizophrenia patients. As illustrated in Figure 5.4, we are interested in examining the effects of medical interventions for the following three turning points: 1. the moment when the patient deteriorates in out-patient care, that is, the health status changes from stable to unstable between two clinical visits; 2. the moment when the patient recovers in out-patient care, that is, the health status changes from unstable to stable between two clinical visits; 3. the moment when hospitalization is immediate. Further, we are also interested in examining indicators on treatment dropout. Such, four separate models are constructed.

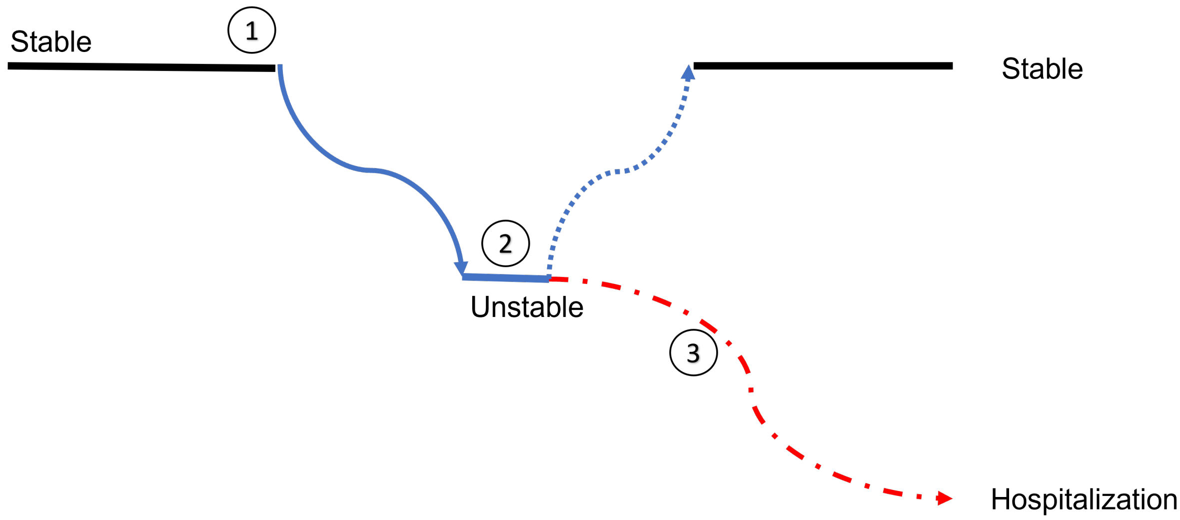

Figure 5.4: Model Illustration - Turning Points

To examine the first turning point, *deterioration*, we use the following model:

$$
\begin{aligned}
Y_{it} =& \alpha_i + \beta_1 \times Before\ CTO_{it} + \beta_2 \times During\ CTO_{it} \\
& + \beta_3 \times Injection_{it} + \beta_4 \times Prescription\ Change_{it} \\
& + \beta_5 \times Prescription\ Change_{it} \times Before\ CTO_{it} \\
& + \beta_6 \times Prescription\ Change_{it} \times During\ CTO_{it} + \epsilon_{it}
\end{aligned}
$$

Y_{it} is the binary indicator on *deterioration* for patient i at time t. To be specific, $Y_{it} = 1$, if the health status for patient i at time t is *stable* and the health status for patient i at time $t+1$ is *unstable* or *no show*; $Y_{it} = 0$, if the health status for patient i at time t is *stable* and the health status for patient i at time $t+1$ is neither *unstable* nor *no show*. $Before\ CTO_{it}$ and $During\ CTO_{it}$ are dummy variables representing the CTO status for patient i at time t; $Injection_{it}$ represents if patient i received injection at time t; $Prescription\ Change_{it}$ represents if prescription was changed for patient i at time t; and, the two interactive terms, $Prescription\ Change_{it} \times Before\ CTO_{it}$ and $Prescription\ Change_{it} \times During\ CTO_{it}$, represent the effect of prescription changes for patients either before the initiation of CTO intervention or after the initiation of CTO intervention. The variable α_i represents the individual random effects. That is, α_i represents the baseline for patient i and as such we allow baseline differences between individuals in our analysis.

To examine the second turning point, *recovery*, we use a model similar to the one above except the definition of Y_{it}. Instead, Y_{it} is the binary indicator on *recovery* for patient i at time t. To be specific, $Y_{it} = 1$, if the health status for patient i at time t is *unstable* and the health status for patient i at time $t+1$ is *stable*; $Y_{it} = 0$, if the health status for patient i at time t is *unstable* and the health status for patient i at time $t+1$ is not *stable*. The definition for independent variables are the exact the same as the above.

To examine the third turning point, the risk of hospitalizations, we incorporate more information from the clinical notes including both the assessment and objective fields. To study hospitalization risk, the health status of a patient acts as confounding variables instead of dependent variables as in the above models. The model for hospitalization risk is the following:

$$
\begin{aligned}
Y_{i,\ t+1} = &\alpha_i + \beta_1 \times Before\ CTO_{it} + \beta_2 \times During\ CTO_{it} \\
&+ \beta_3 \times Injection_{it} + \beta_4 \times Clinic\ Visit_{it} + \beta_5 \times Prescription\ Change_{it} \\
&+ \beta_6 \times Prescription\ Change_{it} \times Before\ CTO_{it} \\
&+ \beta_7 \times Prescription\ Change_{it} \times During\ CTO_{it} \\
&+ \beta_8 \times Treatment\ Dropout_{it} + \beta_9 \times HospitalDiscarge_{it} \\
&+ \sum_{k=10}^{K} \beta_k \times Confounding\ Variable_{itk} + \epsilon_{it}
\end{aligned}
$$

A notable but subtle difference in our last model compared to the previous two models is the design of the dependent variable. Here, the dependent variable represents the hospitalization risk in the immediate next period, aka, at time $t+1$. Thus, the dependent variable no longer represents a change of states as it does in the previous two models. For the other independent variables, the definition remains the same. We introduce two interactive terms $Prescription\ Change_{it} \times Before\ CTO_{it}$ and $Prescription\ Change_{it} \times During\ CTO_{it}$, as we are interested in analyzing the effect of prescription changes given different CTO status. We also incorporated confounding variables extracted from both the assessment and objective fields from clinical notes in the model; the definition of each confounding variable is in the previous section.

Lastly, the model for analyzing indicators on treatment dropout is the following:

$$\begin{aligned}
Y_{i,\ t+1} =& \alpha_i + \beta_1 \times Before\ CTO_{it} + \beta_2 \times During\ CTO_{it} \\
& + \beta_3 \times Injection_{it} + \beta_4 \times Clinic\ Visit_{it} + \beta_5 \times Prescription\ Change_{it} \\
& + \beta_6 \times Unstable_{it} + \beta_7 \times Stable_{it} \\
& + \beta_8 \times Hospital\ Discarge_{it} + \beta_9 \times Missing\ Appointment_{it} + \epsilon_{it}
\end{aligned}$$

The dependent variable $Y_{i,\ t+1}$ represents treatment dropout starting at period $t+1$ for patient i. The definition for independent variables are provided in the previous section.

5.5 Results

5.5.1 Descriptive Statistics

Demographic Characteristics

Table 5.2 displays the basic characteristics for these two patient groups: the CTO patients and the non-CTO patients. The CTO patients were the ones who were under CTO at some point during the study; the non-CTO patients were never under CTO during the study period. It provides the average age, the distribution of gender and ethnicity in each group. It also shows the number and percentage of patients with substance abuse, LAI injections, ER visits during the study period and criminal history till the end of the study. For hospitalization, it provides the percentage of patients with one, two, or three or more hospitalizations during the five-year study period.

We observe no significant differences between CTO patients and non-CTO patients regarding age, gender, and ethnicity. However, in comparison, CTO patients are more likely to have LAI, ER visits and hospitalizations than patients without CTOs.

Table 5.2: Demographics Characteristics: CTO and Non-CTO Patients.

Characteristics	CTO ($N = 77$)		Non-CTO ($N = 290$)		χ^2	*df*	*P* value
	N	%	N	%			
Age	45.97 ± 12.60		48.92 ± 10.94				
Gender (male)	51	66	181	62	0.2352	1	0.627
Ethnicity					5.2592	4	0.261
Black	12	16	40	14			
East Asian	6	8	34	12			
Hispanic	2	3	3	1			
Middle Eastern	9	12	17	6			
White	48	62	196	68			
Substance Abuse	24	31	45	16	8.7652	1	0.003
Injection	74	96	159	55	42.956	1	0.000
Hospitalization					82.459	3	0.000
1	22	29	45	17			
2	10	13	22	8			
≥ 3	30	38	18	6			
ER emergency room visit	62	81	108	37	44.109	1	0.000
Criminal Record	33	42	83	28	5.7046	1	0.016

Note. $N = 367$. CTO = community treatment orders.

Variable Statistics

Table 5.3 provides basic descriptive statistics on each variable at each patient-period observation. Note that the descriptive statistics are given on the patient-period level; one observation refers to one time period for one patient. All variables in our analysis are binary variables; the proportions of positive values (equal to 1) are included in the table.

Table 5.4 provides the correlation for related variables.

Table 5.3: Descriptive Statistics at Patient-Time Period Level

	Before CTO			During CTO			Non-CTO		
Variable	N	Prop.	SD	N	Prop.	SD	N	Prop.	SD
Hospitalization	846	0.125	0.331	4320	0.035	0.183	13762	0.015	0.121
Injection	846	0.247	0.432	4320	0.462	0.499	13762	0.354	0.478
Prescription Change	846	0.1	0.301	4320	0.1	0.3	13762	0.104	0.305
Clinic Visit	846	0.543	0.498	4320	0.744	0.437	13762	0.749	0.433
Miss Appointment	846	0.201	0.401	4320	0.16	0.366	13762	0.206	0.405
Treatment Dropout	846	0.092	0.289	4320	0.044	0.204	13762	0.083	0.277
Stable	846	0.4	0.49	4320	0.622	0.485	13762	0.631	0.482
Unstable	846	0.122	0.327	4320	0.106	0.308	13762	0.1	0.3
Appearance	846	0.285	0.452	4320	0.394	0.489	13762	0.416	0.493
Behavior	846	0.31	0.463	4320	0.459	0.498	13762	0.459	0.498
Danger	846	0.046	0.21	4320	0.059	0.237	13762	0.052	0.222
Impulse Control	846	0.054	0.227	4320	0.064	0.245	13762	0.051	0.22
Insight	846	0.202	0.402	4320	0.216	0.411	13762	0.228	0.419
Language	846	0.089	0.284	4320	0.118	0.323	13762	0.114	0.318
Mood	846	0.275	0.447	4320	0.358	0.479	13762	0.365	0.481
Thought Content	846	0.404	0.491	4320	0.527	0.499	13762	0.547	0.498
Thought Process	846	0.014	0.118	4320	0.021	0.144	13762	0.021	0.145

	Appearance	Behavior	Danger	Impulse Control	Insight	Lang.	Mood	Thought Content	Thought Process	Rx Change	Hospital Adm.	Injection	Clinic Visit	Stable	Unstable	Before CTO	During CTO	Missing App.	Dropout
Appearance	1																		
Behavior	0.43	1																	
Danger	-0.01	0.08	1																
Impulse Control	-0.12	0.03	0.23	1															
Insight	0.1	0.3	0.26	0.2	1														
Language	0.1	0.16	0.1	0.08	0.35	1													
Mood	0.18	0.27	0.16	0.19	0.38	0.22	1												
Thought Content	0.42	0.48	0.08	0.11	0.26	0.16	0.34	1											
Thought Process	0.04	0.09	0.11	0.03	0.18	0.13	0.13	0.06	1										
Prescription Change	0.02	0.13	0.15	0.15	0.37	0.19	0.22	0.13	0.09	1									
Hospital Admission	-0.13	-0.14	-0.04	-0.04	-0.08	-0.06	-0.12	-0.17	-0.02	-0.05	1								
Injection	0.32	0.26	-0.02	-0.02	-0.07	0	0.12	0.3	-0.01	-0.05	-0.12	1							
Clinic Visit	0.49	0.54	0.14	0.14	0.32	0.21	0.45	0.64	0.09	0.19	-0.26	0.43	1						
Stable	0.44	0.48	0.06	0.1	0.16	0.13	0.36	0.61	0.02	0.04	-0.2	0.38	0.76	1					
Unstable	0.06	0.06	0.12	0.07	0.24	0.13	0.11	0.01	0.1	0.22	-0.05	-0.02	0.2	-0.43	1				
Before CTO	-0.05	-0.06	-0.01	0	-0.01	-0.02	-0.04	-0.06	-0.01	0	0.14	-0.06	-0.1	-0.1	0.01	1			
During CTO	-0.01	0.01	0.01	0.02	-0.01	0.01	0	-0.01	0	-0.01	0.04	0.1	0.01	0	0.01	-0.12	1		
Missing Appointment	-0.41	-0.45	-0.12	-0.12	-0.26	-0.18	-0.37	-0.53	-0.07	-0.17	0	-0.38	-0.83	-0.63	-0.17	0	-0.05	1	
Treatment Dropout	-0.11	-0.12	-0.02	-0.01	-0.04	-0.02	-0.08	-0.11	-0.02	-0.03	0.06	-0.12	-0.19	-0.14	-0.04	0.01	-0.06	0.22	1

Table 5.4: Correlation for Related Variables

5.5.2 Deterioration and Recovery

As mentioned previously, we use logistic mixed-effect regression models to analyze the effect of interventions while considering individual differences. Logistic mixed-effect regression model is one of the general mixed-effect regression models; and, we use the package 'lme4' in statistical software R [126] for model fitting. Table 5.5 shows the effect of each intervention for recovery and deterioration, where the first column of the table shows effects on deterioration and the second column shows effects on recovery. The analytical results not only validate the literature and clinical experience but also provide additional insights on the benefit of clinical follow-up. For example, the conclusion on the effect of long-acting injections is consistent with existing research. That is, long-acting injections reduce the odds of deterioration by $\exp(-0.466) = 0.627$ and increase the odds of recovery by $\exp(0.190) = 1.209$ times; and its effects on both are statistically significant. This is expected as the purpose of long-acting injections is to stabilize patients.

More importantly, we derive the benefits of clinical follow-up based on the results, especially for patients skeptical about medical treatments. Based on our model design, we can compare CTO patients from both before and during CTO interventions to non-CTO patients, where non-CTO patients act as the baseline in our model. First, we observe that compared to non-CTO patients, the CTO patients are less likely to recover before their CTO interventions in general, where *Before CTO* reduces the odds of recovery by $\exp(-1.067) = 0.344$ with statistical significance. However, *Before CTO* does not have similar effects on deterioration. Thus, combining the above two observations means that without CTO interventions, the CTO patients are more likely to stay in a deteriorated state not due to elevated deterioration risk but due to a reduced chance of recovery instead. This is consistent with clinical experience that CTO patients often refuse medical treatment. During the CTO intervention, we do not observe significant differences in recovery rate between CTO patients and non-CTO patients. Therefore, combined with the above findings on long-acting injections, we find support for Hypothesis 1a.

The analytical results further support the above conclusion as prescription changes positively affect CTO patients' recovery before CTO interventions. In addition, prescription changes usually happen with the permission of patients, which can be in turn viewed as an indicator of patients agreeing with a treatment plan. As $RxChange \times BeforeCTO$ increases the odds of recovery by $\exp(1.124) = 3.077$ times with statistical significance, it means that prescription changes are incredibly beneficial before CTO interventions. This positive effect of prescription change diminishes during CTO interventions, which is not a cause for concern; instead, the results show that the CTO patients do not have a reduced chance of recovery during CTO interventions. This is because CTO interventions enforce treatments for patients; and, the improved access to treatment brings a CTO patient on the same recovery probability as non-CTO patients.

Table 5.5: Mixed-effect Analysis on Deterioration and Recovery with Individual Random Effect

	Dependent variable (Y_{it}):	
	Deterioration	Recovery
Before CTO	0.637 (0.432)	-1.067^{***} (0.321)
During CTO	-0.344 (0.244)	-0.007 (0.164)
Injection	-0.466^{***} (0.147)	0.190^{*} (0.112)
Prescription (Rx) Change	0.049 (0.216)	-0.308^{**} (0.130)
RxChange × Before CTO	0.654 (0.689)	1.124^{**} (0.518)
RxChange × During CTO	0.041 (0.505)	0.236 (0.257)
Constant	-3.836^{***} (0.136)	-0.028 (0.091)
Observations	11,151	1,831
Log Likelihood	$-1,173.464$	$-1,242.297$
Akaike Inf. Crit.	2,362.927	2,500.593
Bayesian Inf. Crit.	2,421.482	2,544.694
Note:		*p<0.1; **p<0.05; ***p<0.01

5.5.3 Hospitalization Risk

Table 5.6 shows the analytical results on the effect of medical interventions and events on hospitalization risks. Model (1) does not control for the health status represented by features extracted from the clinical notes; whilst, Model (2) controls for the health status in analysis. Model (2), which controls for health status, has a more accurate estimation of variable coefficients and embody a higher confidence in causation inference. To illustrate the importance of controlling for health status, we want to highlight the coefficient estimates for *Prescription Change*. Model (1), not controlling for health status, shows a strong positive correlation between prescription changes and hospitalization risks. In comparison, in Model (2) with controls on health status, both the coefficient estimates and the significance level vastly decreases for *Prescription Change*. Because both prescription changes and hospitalizations can be correlated with health deterioration, Model (1) fails to account for this confounding effect and provides less reliable results than Model (2). In extreme cases, confounding effects can lead to opposite effects. In our case, the differences are only in scale instead of directional.

Again, our analytical results both conform with the literature and yield additional exciting insights. Consistent with the literature, Table 5.6 shows that CTO patients have a greater risk of hospitalization with *Before CTO* increasing the odds of hospitalization by $\exp(2.006) = 7.433$ times. The elevated hospitalization risks decrease during CTO interventions, but the risk is still higher than non-CTO patients. Long-acting injections reduce hospitalization risks by $\exp(-0.549) = 0.577$ times. The above results provide support for Hypothesis 1b.

We also observe that there is a higher risk of hospitalization right after hospital discharges, as *Hospital Discharge* increases the odds of hospitalization by $\exp(2.493) = 12.097$ times. Our psychiatric experts confirm the observation and refer it to as the well-known "revolving door" challenge in clinical practices. This result provide support for Hypothesis 2a. As our study focuses on out-patient care, we need to note that treatment dropout considerably increases the odds of hospitalization by exp(1.175) = 3.238 times with a strong statistical significance. This result provide support for Hypothesis 2b.

The previous deterioration and recovery section shows that regular clinical visits and treatments improve illness progression in out-patient care: timely prescription changes improve chances of recovery; regular long-acting antipsychotic injections reduce chances of deterioration. Furthermore, the current section shows that treatment dropout is one of the most significant factors in elevated hospitalization risk. Combined with results from both sections, we could not emphasize more the benefit of continuous out-patient clinical follow-ups, a key mandate of community treatment order. Therefore, in the coming sections, we will analyze early indicators on treatment dropouts and provide a simple guideline to prevent treatment dropouts.

Table 5.6: Mixed-effect Analysis on Hospitalization with Individual Random Effect

	Dependent variable ($Y_{i,t+1}$):	
	Hospitalization	
	Model (1)	Model (2)
Before CTO	2.150*** (0.286)	2.006*** (0.277)
During CTO	0.907*** (0.238)	0.849*** (0.229)
Clinic Visit	−0.206 (0.199)	−0.220 (0.274)
Injection	−0.760*** (0.196)	−0.549*** (0.200)
Prescription (Rx) Change	0.676*** (0.242)	0.439* (0.250)
RxChange × Before CTO	−0.474 (0.540)	−0.551 (0.551)
RxChange × During CTO	−0.721 (0.454)	−0.763* (0.457)
Hospital Discharge	2.414*** (0.222)	2.493*** (0.222)
Treatment Dropout	1.173*** (0.232)	1.175*** (0.234)
Control for Health Status	N	Y
Constant	−4.970*** (0.212)	−4.876*** (0.205)
Observations	17,027	17,027
Log Likelihood	−1,157.385	−1,135.775
Akaike Inf. Crit.	2,336.770	2,313.550
Bayesian Inf. Crit.	2,421.938	2,476.144
Note:		*p<0.1; **p<0.05; ***p<0.01

5.5.4 Treatment Dropout

As we have shown repeatedly in the above, continuous care is essential for the well-being of chronic schizophrenia patients. Therefore, it is important to understand factors leading to treatment dropout. Table 5.7 shows the estimated effect of each factor on treatment dropout. As expected, CTO interventions and injections reduce the odds of treatment dropout by $\exp(-0.890) = 0.410$ times and $\exp(-0.364) = 0.694$ respectively. Interestingly, stable assessments observe elevated dropout risks compared to unstable assessments. The plausible cause is that patients no longer deem treatment needed as their condition improves. The above observation is not unique for schizophrenia; instead, it is a recurring scenario for mental illnesses in general. More importantly, there are substantially increased risks of treatment dropout after hospital discharge and missing appointments. Right after hospital discharge, the odds of treatment dropout increased by $\exp(0.983) = 2.672$ times; after missing one appointment, the odds increased alarmingly by $\exp(1.676) = 5.344$ times. The above results provide evidence for Hypothesis 3a and 3b.

To further illustrate treatment dropout risks, Figure 5.5 shows the percentage of patients returning for clinic visits after being late for their scheduled appointments over time. There are two critical time points: 14 days and 28 days. Almost half of the patients continue their clinic visits within 14 days late of their scheduled appointments; another quarter of patients return to their clinic visits between the 14 and 28 days. After 28 days, the chance of patients returning is less than 25%.

5.5.5 Assumption and Robustness Tests

Collinearity among predictors deserves serious consideration in model construction and interpretation. Correlated independent variables can lead to incorrect estimation of variable coefficients; in extreme scenarios, it can even lead to incorrect interpretation of the direction of the variable effect. We check the existence of collinearity using "generalized

Table 5.7: Mixed-effect Analysis on Treatment Dropout with Individual Random Effect

	Dependent variable:
	Treatment Dropout
Before CTO	−0.075 (0.233)
During CTO	−0.890*** (0.186)
Unstable	0.249 (0.182)
Stable	0.338** (0.150)
Injection	−0.364*** (0.093)
Prescription Change	0.075 (0.118)
Hospital Discharge	0.983*** (0.174)
Missing Appointment	1.676*** (0.144)
Constant	−3.094*** (0.160)
Observations	18,928
Log Likelihood	−4,306.357
Akaike Inf. Crit.	8,632.714
Bayesian Inf. Crit.	8,711.198
Note:	*p<0.1; **p<0.05; ***p<0.01

variance inflation factors" (GVIF) [127], which is better suited for categorical variables contained in our models. Table 5.8 reports the GVIF values for the most relevant variables. Though there is no absolute guideline on value threshold, a value less than 5 usually indicates low correlation between the variable inspected and the other independent variables. As shown in Table 5.8, there is no multicollinearity among our models. For generalized mixed models like ours, overdispersion can also cause incorrect estimation. We tested overdispersion using R package 'performance' [128] [129] for our models and there is no concerns raised through the tests.

We performed a series of placebo tests to assure that our results are not spurious, as spurious results are common in time-series analysis. In placebo tests, interventions and the date of interventions were randomly assigned to subjects. Since interventions were randomized, we should no longer observe correlations between interventions and outcomes if there is no lurking variable causing spurious relationships. Figure 5.6 shows the placebo tests on the effect of treatment dropout on hospitalization risk. We repeated the placebo

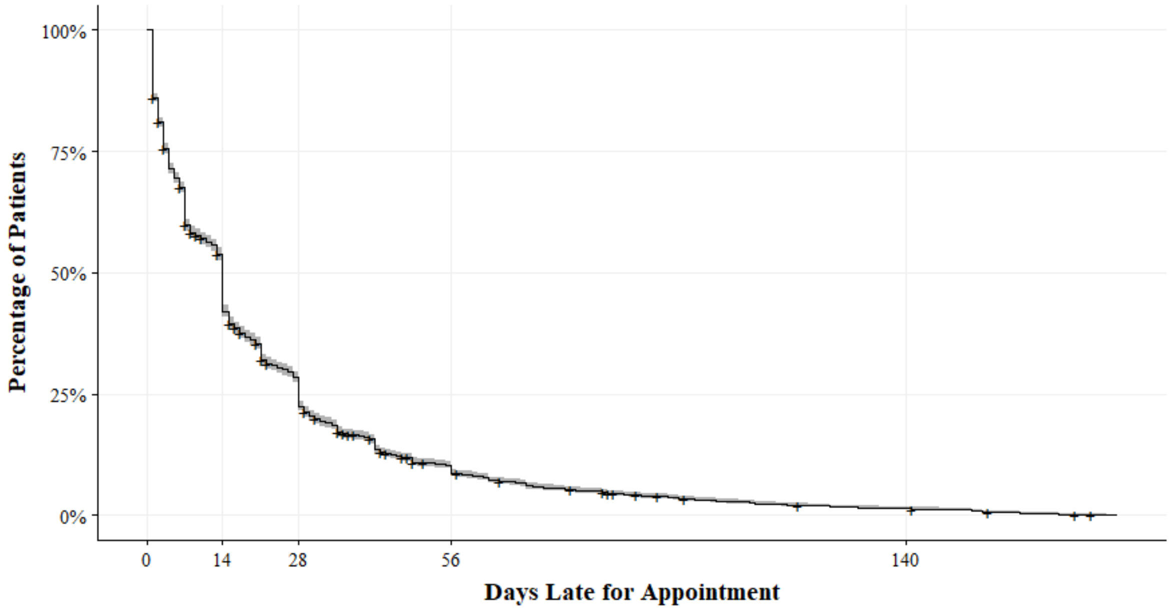

Figure 5.5: Survival Plot for Clinic Visits

Table 5.8: Generalized Variance Inflation Factors

Independent Variables	GVIF	SE Factor
Hospitalization	1.74	1.32
Clinic Visit	3.50	1.87
Injection	1.29	1.13
Treatment Dropout	1.03	1.02
Prescription Change	1.85	1.36
Before CTO	1.55	1.24
During CTO	1.44	1.20
Appearance	1.43	1.19
Behavior	1.79	1.34
Danger	1.16	1.08
Impulse Control	1.17	1.08
Insight	1.96	1.40
Language	1.26	1.12
Mood	1.66	1.29
Thought Content	1.75	1.32
Thought Process	1.08	1.04
RxChange × PriorCTO	1.32	1.15
RxChange × PostCTO	1.40	1.18

tests 50 times and reported the coefficient estimate and confidence interval for treatment dropout from each test run. Figure 5.6 also provides the treatment coefficient estimate from our study data. We can see that the placebo coefficient estimates are much smaller in value and weaker in statistical significance. Out of 50 placebo tests, only two tests report weak positive correlations; this is more than sufficient to show that the treatment estimate from our study data is not spurious.

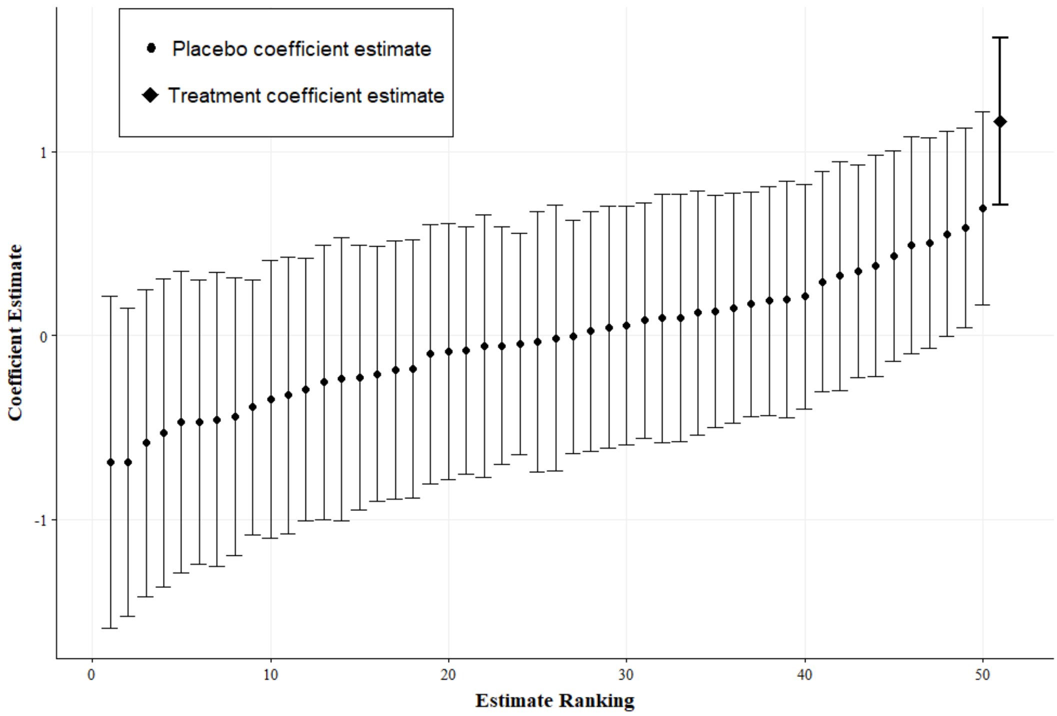

Figure 5.6: Placebo Test on Treatment Dropout for Hospitalization Risk

Similarly, Figure 5.7 shows the placebo tests on the effect of hospital discharge on treatment dropout risk. We repeated the placebo tests 50 times and reported the coefficient estimate and confidence interval for treatment dropout from each test run. Figure 5.6 also provides the treatment coefficient estimate from our study data. We can see that the placebo coefficient estimates are much smaller in value and weaker in statistical significance. Out of 50 placebo tests, only three tests report weak positive correlations and one reports weak negative correlation; this is more than sufficient to show that the treatment estimate from our study data is not spurious.

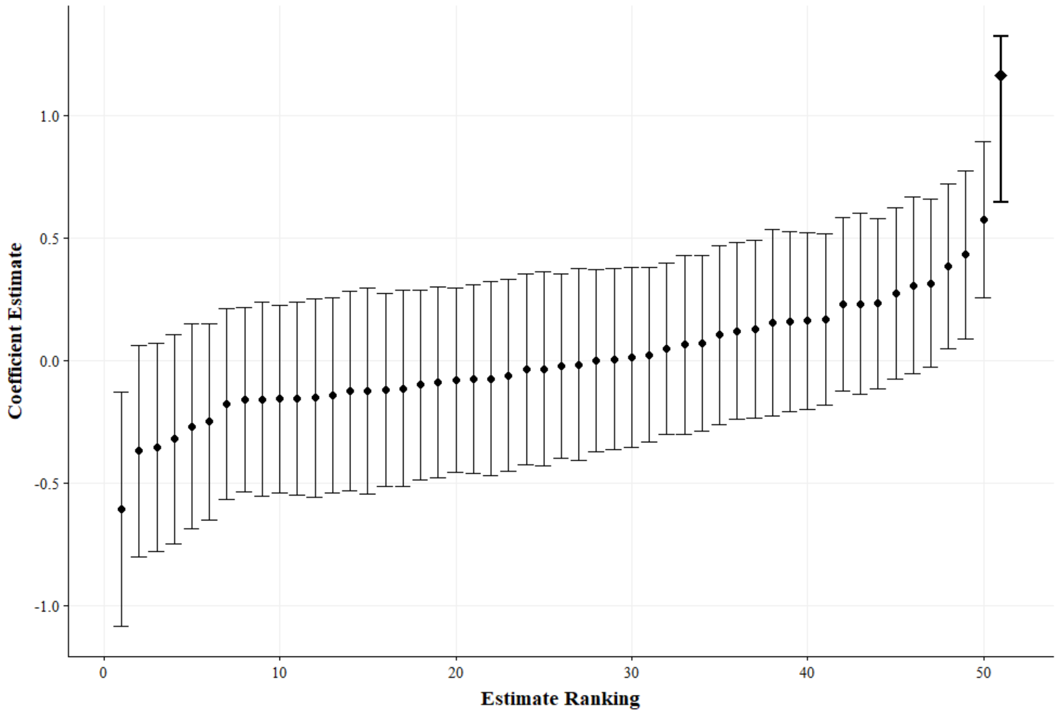

Figure 5.7: Placebo Test on Hospital Discharge for Treatment Dropout Risk

5.6 Discussion and Conclusion

One main contribution of our study is to leverage text mining techniques to extract illness condition representations from the free-text clinical notes. By doing so, we can gain information unknown in past empirical schizophrenia studies; we can also improve the confidence in analytical results. During the process, we realize the complexity of this approach. One of the concerns is the difference in writing style across clinicians. We assumed that clinicians write consistently following their medical training. Nevertheless, we observe differences between clinicians: some tend to provide a more vivid description of each clinic visit; while, some tend to be concise and brief. Another challenge is the decorators for symptom exhibitions. We can process the usage of negations by tagging symptoms with apparent negation terms. However, it is not easy when the decorators are comparative. For example, "less paranoid" may carry different implications depending on the context of events. While the modern NLP models can read words, they can not yet read between words, especially the evolving texts across time.

Our analytical results found that interventions are the most effective when hospitalizations are not immediate. Timely outpatient intervention can increase recovery and reduce hospitalization. The literature has focused on the benefit of early detection and intervention for first-episode patients; we supplement the literature by providing evidence on its benefit for patients in chronic stages. Early detection of the onset of the first psychotic episode can be challenging as the individual is mainly unknown to the healthcare system. In contrast, to detect the psychotic episode for chronic stage patients, the challenge mainly lies in scheduling and enforcing clinic appointments.

We also supplement evidence on the benefit of treatment adherence interventions, including long-acting antipsychotic injections and community treatment orders. Our results are consistent with the literature. Built upon the importance of treatment adherence, we also show the significant negative effect of treatment dropouts on health outcomes. To provide easy-to-access recommendations, we provide leading indicators in treatment dropouts and the relationship between appointment lateness and treatment dropouts.

5.7 Appendix

5.7.1 Understanding Clinical Notes

The objective of this section is to demonstrate the value of the free texts in clinical notes and to have an intuitive understanding of the notes. We examine the notes preceding major psychotic episodes, represented by hospitalization and ER visits, and compare those to the other ones. We hope to showcase the informative potential of clinical notes with this simple exercise by comparing $P(word|\text{psychotic episodes})$ and $P(word|no \text{ psychotic episodes})$. We expect observable deterioration in patients near hospitalizations and ER visits, and such assessments should also be different. For example, it should be less likely for a patient to be assessed as 'stable' before hospitalizations.

The objective of this investigation is twofold: first, we aim to establish that healthcare practitioners can detect the deterioration of patients and record such detection; second, we aim to understand the psychiatric vocabularies used to describe the deterioration of schizophrenia patients. To achieve the above, we categorize all assessments into two groups: before hospitalizations and ER visits and the others. We then compare the proportions of assessments containing specific medical terms between the two groups.

This approach is not without limitations. As we learned from our previous research, stable schizophrenia patients tend to attend clinic appointments regularly, while patients with deterioration risks tend to miss their clinic visits. Since assessments are only made and written upon the patient's presence, the retrospectively collected clinical notes data is not without selection biases. This dilemma is not unique to us. Data are often collected via existing sources after the facts. Without any enforcement on the data collection process, selection biases exist more often than we admit. Despite the limitation, there are still insightful contributions to our understanding of clinical notes. This limitation also motivates us to apply a more sophisticated mixed-effect regression analysis for our primary research questions.

There is a tendency for extended periods of missing appointments before hospitalizations. Therefore, if the closest assessment made before hospitalization is more than two months, we deem it as no assessment existing right before that hospitalization. There are in total $14,860$ assessments during the five years; and 396 entries right before hospitalizations and ER visits. Those 396 entries tend to be more complex with average 3.70 words compared to an average 2.32 words otherwise.

The proportion of entries containing only 'stable' reduced significantly from 56.56% during normal times to 29.54% right before hospitalizations and ER visits with $p\text{-}value <$ 0.000 ($\chi_1^2 \approx 50.39$). Though the reduction is significant in the statistical sense, it surprises us that 29.54% of all hospitalizations were followed by assessments with only the 'stable' phrase. Assessments can be ambiguous at times containing conflicting wordings, but there is no ambiguity in the single word 'stable' assessments. This illustrates the difficulty in assessing patients and predicting relapses, which may happen suddenly without warning signs.

For the remaining more complex entries, containing more than just 'stable,' we use the chi-square test to study the differences in proportions for a specific term between groups. There are 4,630 such complex entries during regular times; 209 before hospitalizations. We selected terms with at least 5 appearances for each category. Figure 5.8 and Table 5.9 show the proportion of notes containing each word in each category and the p-value calculated from chi-square test. In the table, words are ordered by the ratio of their proportions in each category. For example, 'compensate' is much more likely to appear in notes preceding hospitalizations and ER visits; while, 'stable' is much more likely to appear in notes not preceding hospitalizations.

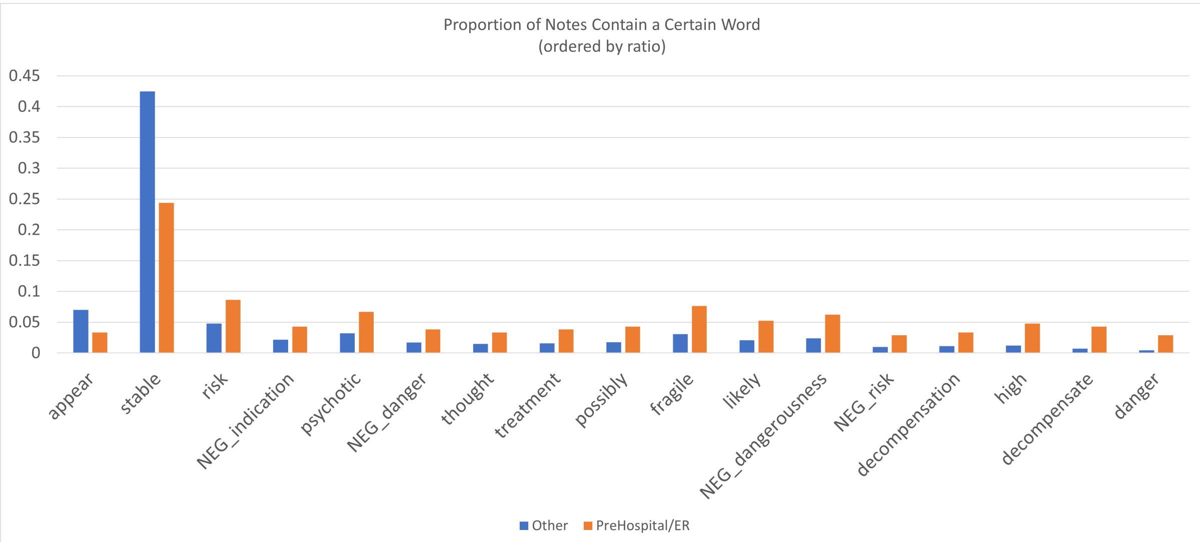

Figure 5.8: $P(word|\text{psychotic episodes})$ and $P(word|no\ \text{psychotic episodes})$

Consistent with observations on notes with the single word 'stable', there is also a significant decrease in the proportion of notes containing the word 'stable' before hospitalizations and ER visits. However, just having the word 'stable' does not translate into

	Other	PreHospital/ER	PValue	ChiSq	BF
appear	0.07	0.03	0.05	3.89	0.48
stable	0.42	0.24	0.00	15.68	0.57
risk	0.05	0.09	0.01	5.97	1.80
NEG_indication	0.02	0.04	0.05	3.97	1.97
psychotic	0.03	0.07	0.01	7.33	2.10
NEG_danger	0.02	0.04	0.03	5.01	2.24
thought	0.01	0.03	0.03	4.56	2.28
treatment	0.02	0.04	0.01	6.25	2.46
possibly	0.02	0.04	0.01	7.03	2.46
fragile	0.03	0.08	0.00	12.89	2.50
likely	0.02	0.05	0.00	9.20	2.54
NEG_dangerousness	0.02	0.06	0.00	11.40	2.59
NEG_risk	0.01	0.03	0.01	6.84	2.95
decompensation	0.01	0.03	0.00	8.43	3.04
high	0.01	0.05	0.00	18.74	3.96
decompensate	0.01	0.04	0.00	29.75	6.04
danger	0.00	0.03	0.00	22.14	6.65

Table 5.9: Proportion of Entries Contain a Certain Term

a stable assessment for multiple words assessment. Conflicting words can coexist. For example, assessments of ‘stable but at risk of decompensation’ or ‘stable but fragile’ are ambiguous. To accurately interpret the implication of doctor’s notes, it is by no means a simple question of finding a specific term. More sophisticated natural language processing and machine learning techniques are used for the rest of the study.

It is also fascinating to note that the negation usages of ‘danger’ and ‘risk’ are also strongly correlated with statistical significance hospitalization and ER visit risks. A possible interpretation is that ‘danger’ and ‘risk’ are not usually in the mind of health-care practitioners when interviewing a stable patient. The need to evaluate the level of dangerousness by itself signals hospitalization risks.

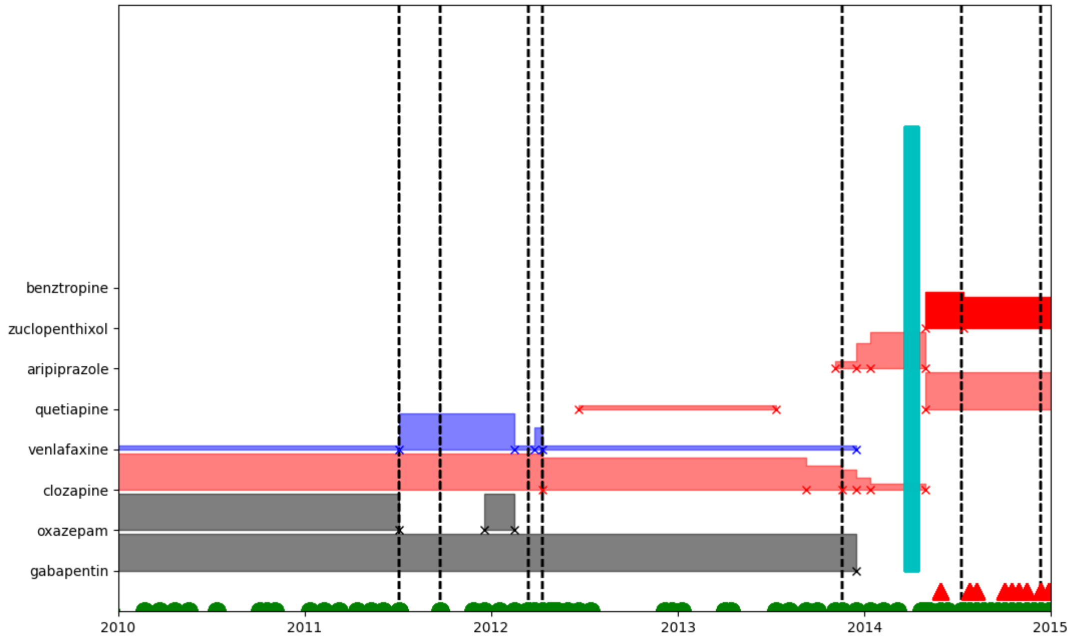

Figure 5.9: A Patient's Timeline

5.7.2 Supplement Figures

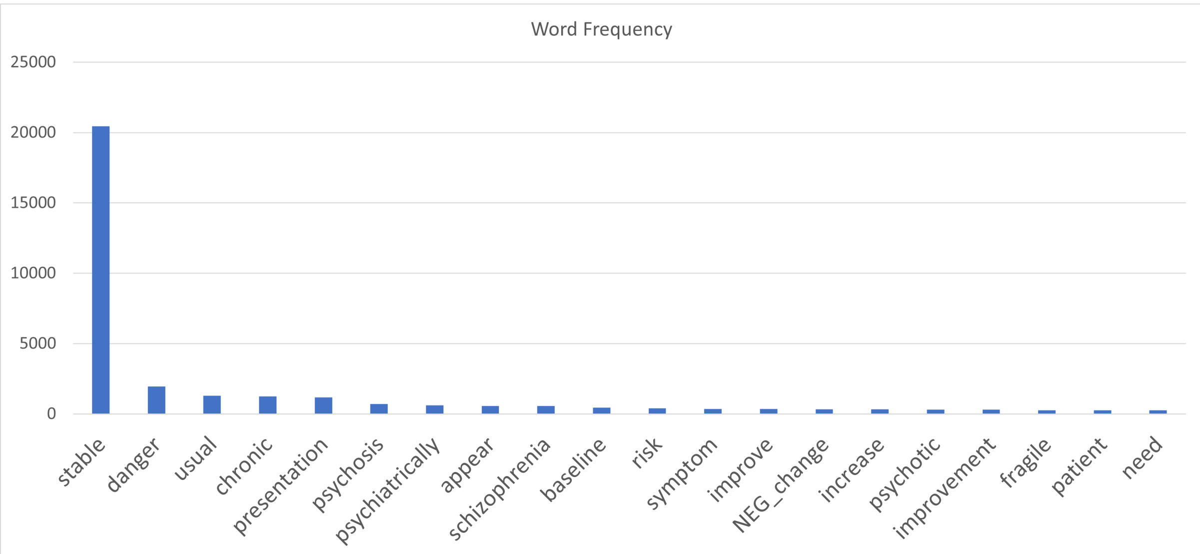

Figure 5.10: Word Frequency in Assessment

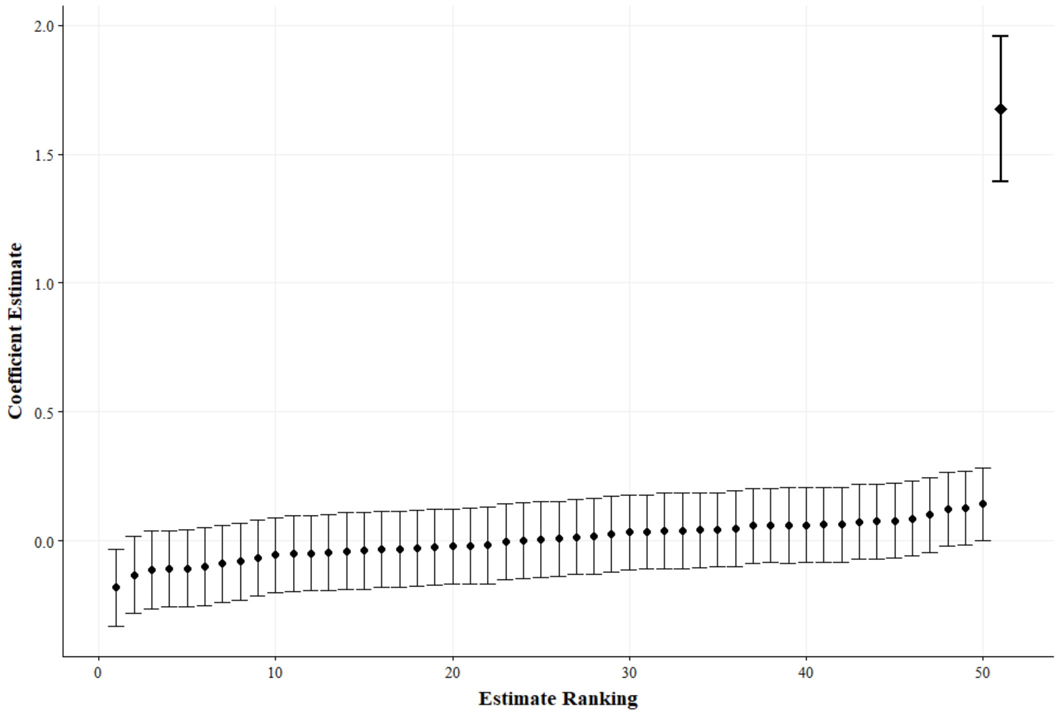

Figure 5.11: Placebo Test on Missing Appointment for Treatment Dropout Risk

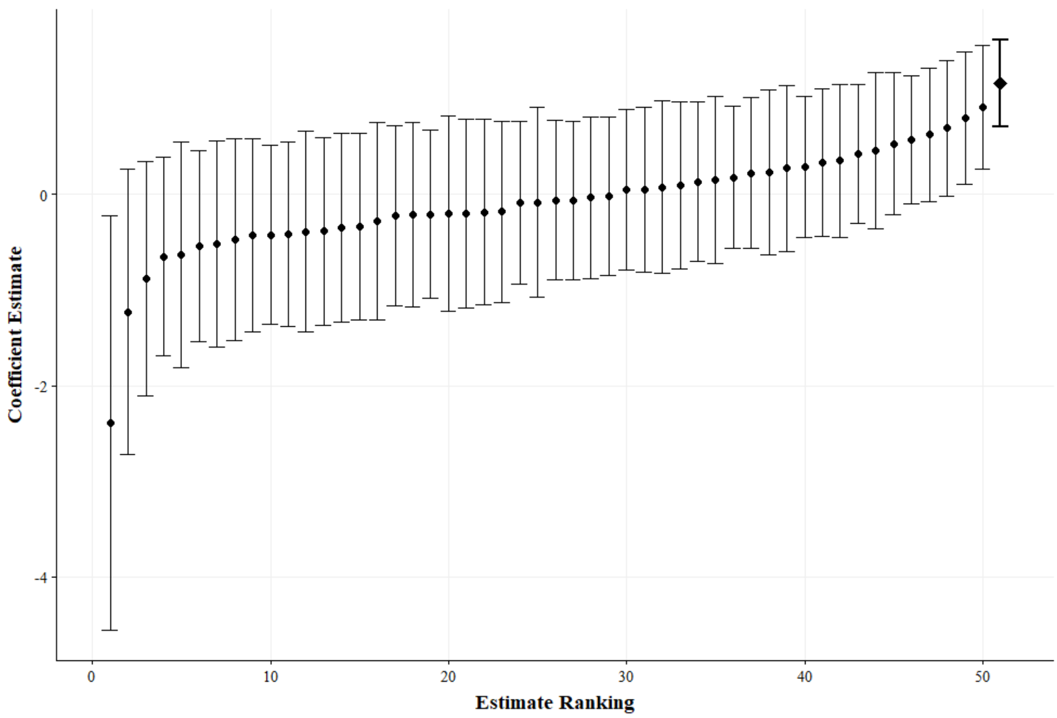

Figure 5.12: Placebo Test on Hospital Discharge for Hospitalization Risk

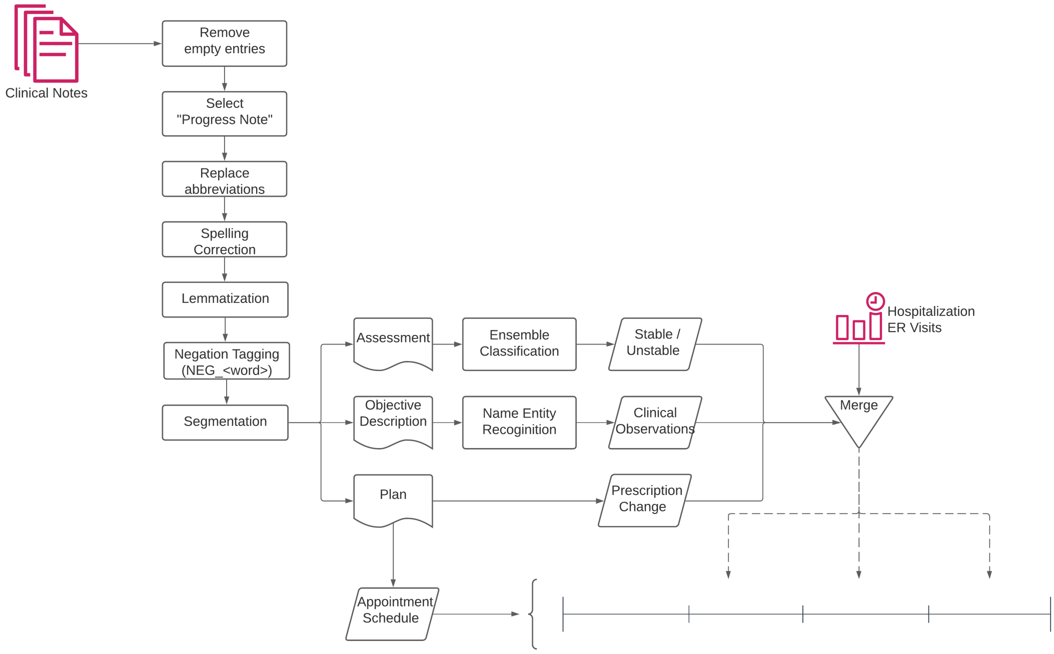

Figure 5.13: Data Processing and Analyzing Flowchart

Conclusion

Our study has faced several challenges, from parameter estimations to model formulation. The prerequisite for meaningful decision modelling is correctly understanding the correct data. Data is abundant in the age of big data; however, collecting the correct data requires a deep understanding of the research question and considerable domain knowledge. The literature and our research show that illness status is irreplaceable for causational inference of medical interventions. However, this crucial information is often not considered in observational studies in mental illnesses because of the difficulty in obtaining such information. As mentioned repeatedly in the previous chapters, consistent and prevalent numerical representations of mental illness are extremely rare to non-existent. We use natural language processing techniques to extract numerical representations from the free-text of clinical notes. This approach is novel and opens research possibilities.

However, clinical note text analysis is not without drawbacks. The text analysis relies on understanding the text itself; natural language processing techniques do not have medical training in deduction and diagnostics. Through many conversations with our psychiatric experts, it is evident that the understanding of clinical notes is more than a simple reading of collection of symptom descriptions. It is not a cause for pessimism for the text analysis approach. The illness status extracted from the clinical notes acts as a confounding variable. This means we do not seek a perfect representation of illness status; instead, we seek representations highly correlated with the underlying illness status. Nevertheless, it will be meaningful to incorporate domain knowledge in natural language processing for further research.

It also comes to our attention that clinical notes have different styles from different clinicians. The most noticeable difference is the level of detail contained in the notes. We argue that crucial information will be present despite the conciseness of the note. However, this observation does raise some exciting research questions. For example, how to measure the quality of clinical notes? How does the quality of clinical notes affect healthcare outcomes?

While clinical note text analysis provides valuable data unavailable in the past, another challenge is prevalent in mental illness studies in the management field and remains unsolved in our research. Cost estimation is highly challenging for mental illness. Though the healthcare costs, including hospitalization, medications, clinic visits, can be calculated, many other costs are considered in the decision-making process in practice but are difficult to monetize. For instance, the quality of life of a patient depending on the illness status can be challenging to capture; and, the price for the invasion of personal freedom by community treatment order requires philosophical debates. As shown in our decision model, solely considering healthcare costs may lead to aggressive community treatment order decisions. Comprehensive discussions and debates are needed for evaluating the personal burden of mental illnesses.

The entire research project points to the importance of outpatient follow-up clinic visits. The main objective of the community treatment order is to improve treatment adherence, including adherence to medication and adherence to clinic visits. We built a direct link between improved long-acting antipsychotic injection adherence and reduced hospitalization. However, in practice, the benefit of community treatment orders is beyond the enforcement of long-acting antipsychotic injections. During the parameter estimation process for our decision model, we noticed that continuous missing appointments are correlated with high hospitalization risks. The last chapter reinforces the conclusion that missing appointments increase deterioration risks, and regular outpatient visits are essential in preventing drastic deterioration. The community treatment order increases clinic visit adherence; but, we believe that there can be less restrictive measures to improve clinic visit adherence. The future research will be on modelling and devising policies for clinic visit adherence improvement.

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