Developing an economic model for LEAN: a text-messaging intervention for schizophrenia in rural China

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Abstract

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Background: Stakeholders in schizophrenia care in China are unaware of the economic value and overall cost savings associated with a text-messaging intervention for schizophrenia, known as LEAN, an intervention shown to improve adherence to oral psychotropic medications and reduce relapses and re-hospitalizations in rural China.

Objective: To develop an economic model and utilize this model to perform a preliminary analysis of the cost-effectiveness of the LEAN intervention for schizophrenia in rural China.

Methods: Data from the LEAN trial and other published sources were utilized to create the model. An iterative process involving repeated cycles of looking at this data, constructing models, and discussing with a team was used to actually develop the economic model. We decided to use a cohort simulation to test the model and perform a preliminary cost-effectiveness analysis.

Results: Model Development: A decision-analysis model consisting of two linked models, a decision tree (Figure 1) and a Markov model (Figure 2) took shape, and we applied the final parameters (time horizon, cycle length, transition probabilities, utilities, costs, etc) to align with each aspect of the model. A cost-effectiveness analysis was performed using decision and Markov modeling of schizophrenia patients divided into well (stable) and severe (severely relapsed) states of the illness from the perspective of the Chinese healthcare system. The main outcome measures were Quality-adjusted life years (QALYs) gained over 2 years and the incremental cost-effectiveness ratio (ICER) measured as a cost per QALY gained over 2 years. In running a base-case analysis using cohort simulation with our model to assess the cost-effectiveness of LEAN, we found the 2-year discounted QALYs were higher for the LEAN plus 686 Program [intervention] arm (1.45) than for the 686 Program alone [control] arm (1.42). In the incremental analysis, the LEAN plus 686 Program [intervention] arm was dominant, i.e., less costly (by 196 USD or 1,362 RMB, over 2 years) and more effective by 0.03 QALYs (over 2 years).

Discussion: We were able to construct an economic model and in our preliminary analysis, the addition of LEAN to the 686 Program is cost-effective. However, better data are needed to both further develop the model and better parameterize it. While we'd like to be able to say that our base-case analysis results mean that LEAN is a good candidate for scaling up and modifying for sustainability in order to improve the provision of oral psychotropic medication for people with schizophrenia in rural China, with potential adaptation to other contexts as well, we cannot say this at this time. Future adaptations of this model with better data and included sensitivity analyses will have to provide this.

Introduction

Severe mental disorders, such as schizophrenia, are increasingly becoming a leading cause of disability, and have become a major public health and social problem worldwide. In China specifically, this major problem is further intensified by the rapid change in the socio-economic development of the country, which has been associated with an increase in incidence rates of severe mental disorders.[1] Severe mental disorders such as schizophrenia, bipolar disorder, and severe depression are complex psychiatric disorders that manifest as disabling conditions often involving hallucinations, delusions, and disordered thinking and behavior.[2] Due to being disabling, these disorders pose a high cost to patients, families, and society. In China, 13% of the non-communicable disease burden is due to the mental disorder burden, with this number expected to increase by 10% by the year 2025.[3] These numbers show an urgent need to prioritize programs focused on targeted prevention and effective treatment.

Despite effective treatment being available for mental disorders, large treatment gaps exist in China due to a huge shortage of mental health professionals and non-adherence to treatment.[4,5] Internet- and mobile-based interventions (IMIs) have been utilized in an attempt to overcome some of the barriers in providing mental healthcare. IMIs targeting depression have been shown to be clinically helpful and, in a systematic review, cost effective.[6] However, none of the studies were done with a Chinese population and none in people with schizophrenia.

The LEAN (Lay health supporters, E-platform, Award, and iNtegration) study was a randomized controlled trial that evaluated whether the addition of mobile texting would improve schizophrenia care in a resource-poor rural community in rural China compared with a community-based free-medicine program alone.[7] The LEAN intervention entailed lay health supporters, who were aided and empowered to improve care via text messages for medication reminders, health education, monitoring of early signs of relapses, and facilitating linkage of primary healthcare to the patients with schizophrenia. Components of the LEAN intervention were derived from a consensus of low cost, low burden, and easy to use interventions supported by the empirical literature on task shifting to improve adherence to medication and the health belief model and personal behavior.[8]

LEAN demonstrated that the addition of texting to patients and their lay health supporters in a resource-poor community setting was more effective than a free medicine program (known as the 686 Program) alone in improving medication adherence and reducing relapses and re-hospitalizations.

However, the LEAN study did not collect cost data sufficient for in-depth economic analysis (no cost data on human resources, no highly detailed cost data on intervention and project management, no medication costs due to increased adherence, and no cost data on use of medical resources) and did not analyze the cost-effectiveness and cost-utility of the intervention.[9] In addition, there is a general lack of economic evaluation of such programs in the literature. Given that the decision to adopt a new strategy or service by health policy decision-makers depends on several factors such as the ability and willingness to pay for incremental health benefits, the effectiveness of the service, and the level of need in the community, there is an urgent need for the development of a model that can be used to estimate the cost-effectiveness and cost-utility of the LEAN program. **The aim of this study was to develop an economic model to assess the cost and health outcomes of the LEAN intervention and use it to perform a preliminary incremental cost-effectiveness analysis of the LEAN intervention, as an early contribution to later planned cost-effectiveness analyses[9] that will happen when more robust costing data becomes available.**

Methods

The data forming much of the basis of this model comes from the LEAN randomized controlled trial, which was conducted in 9 rural townships [with a total population of 356,900] of Liuyang municipality, Hunan Province, central China, for a duration of 6 months, from December 15, 2015 to June 15, 2016.[7] In this trial, a 278 patient sample of participants with a primary diagnosis of schizophrenia was randomly selected from the community-dwelling villagers. Participants were included in the study if they were community-dwellers, were 686 Program enrollees, had a primary diagnosis of schizophrenia, were taking oral psychotropic medications, and physically resided within 1 of the 9 rural townships of the Liuyang municipality.[7] Participants were excluded from the study if they were hospitalized due to schizophrenia during the recruitment period, had missed the most recent three consecutive past drug refills, or were physically incapable of using voice or text messaging.

The primary outcome of the LEAN trial was medication adherence, which was assessed by unannounced home-based pill counts. Secondary outcomes were patient-level functioning as assessed by the 36-item World Health Organization Disability Adjustment Scale 2.0 (WHODAS 2.0),[10,11] the severity of symptoms as assessed by the Clinical Global Impression — Schizophrenia scale (CGI-Sch),[12] relapse, and re-hospitalization. Outcome data were collected during the recruitment process (at baseline) and at 6 months after the implementation of the LEAN intervention.

This existing outcome data alongside the little cost data that does exist from the LEAN trial, together with other evidence from the literature and other sources, has been synthesized to help in both the early and later stages of model development. In the early stages of model development, the basic pieces and form of our model emerged. In the later stages of model development, we took our developed model and finalized it by figuring out the exact model parameters for transition probabilities (or whether a transition should even exist in our model), costs, and utilities. Lastly, we planned to use our finalized model to run a preliminary cost-effectiveness analysis. Additional fieldwork is planned for collecting data on program cost in order to perform a more robust cost-effectiveness analysis in the future.[9]

The early stages of developing an economic model involved an iterative process, a modified version of the Delphi technique[13], of reading up on the literature, drawing up some proposed model designs, discussing these model designs with our team, and repeating this cycle of events until a desired result emerged. This took many iterative cycles. Literature that was researched included everything from a paper on which overall modelling approach might be best in the case of schizophrenia,[14] papers on the fundamentals of Markov modelling,[15,16] re-reading the parent study[7] and proposed larger economic evaluation of LEAN proposal[9] multiple times, studies on economic models in mental health in general,[17,18] and a range of studies on economic models in schizophrenia care specifically.[19-26] A selection of some of the key early versions of the model are pictured chronologically in Appendix B, starting with the earliest attempt at a model. Discussions ranged in content from discussing the basics of what makes a good model up to deciding the number of states and transitions to include in our specific model. The crucial insights from these discussions and later discussions in the later stages of model development, which mainly focused around applying exact parameters and making the crucial decisions around fine-tuning the model, are contained in the Results: Model Development section below as well as the Discussion section, listed mostly as limitations to our ultimately decided-upon model.

While the iterative process described above for the early stages of model development never stopped, it did slow and change form in the later stages of model development, as the focus became applying exact parameters to the model form and making final model decisions, the results of which are described below in our Results: Model Development section. In other words, the iterative process during this period involved a slower version of the same modified form of the Delphi technique described above, with a focus on making key decisions between different LEAN trial- and literature-based parameter values to apply to our model.

Once a final model was agreed upon during the later stages of model development, a simulation of some kind needed to be done to test the model and provide preliminary cost-effectiveness analysis results. At the outset, we knew we would use either a first-order individual, or Monte Carlo, simulation technique[27] or a cohort simulation technique[16] to generate expected outcomes and costs for a hypothetical cohort of 20,000 patients, or 10,000 patients per arm of the trial. We decided, as the model emerged, on using a cohort simulation due to its ease of use in performing a preliminary base-case analysis and ability to show an exact output for our model.

Results: Model Development

The Final Decision-Analysis Model — Decision Tree and Markov Model

After early and later stages of model development were completed, a final model was obtained. The final decision-analysis model is shown as the final decision tree in Figure 1 as well as the linked, final Markov model in Figure 2. Final model parameters, along with their sources, are shown in tabular form in Table 1, and the specifics of their development are described in text form below. The tables showing the detailed traces for the cohort simulation (as well as transition matrices) of this model are shown in Appendix A. The results of these cohort simulations are displayed below in text form under 'Base-case Analysis' and in tabular form in Table 2.

A decision-analysis model[28] was developed to examine the cost-effectiveness of the LEAN intervention for schizophrenic patients in rural China over a 2-year time horizon. This time horizon was decided upon because while the intervention trial had a relatively short 6-month follow-up, we felt the data from it and the literature could be carried over reasonably to a more useful, longer term of 2 years, which would extend our model's ability to assess the intervention's possible potential over the longer term. We used a decision tree (Figure 1) to show the intervention (LEAN plus 686) and the control (686 alone) groups compared in this model. The mean age of patients in our model is assumed to be the same as the LEAN trial, which was around 45 years of age.[7] The Markov model, well suited to schizophrenia due to the chronic nature of the illness, was used to show patient's transitions over time from one discrete health state to another.[15,16] The Markov model (Figure 2) had five states: (i) Well (stable) and Adherent (to oral psychotropic medication); (ii) Well and Nonadherent; (iii) Severe (severely relapsed, to the point of requiring re-hospitalization) and Adherent; (iv) Severe and Nonadherent; and (v) Dead. The cycle time was 1/12 years or approximately 1 month or 30 days, which was chosen because it corresponds approximately with the mean length of schizophrenia-related hospitalizations.[19,20]

The analysis was performed from the perspective of the Chinese healthcare system and included the cost of the LEAN intervention infrastructure, the additional clinical care costs assumed to occur due to LEAN improving connection with healthcare infrastructure, the cost of inpatient hospitalization, and the cost of end of life care. A discount rate of 3% per year was applied to costs and outcomes, as recommended by the Panel on Cost-Effectiveness and Medicine of the US Public Health Service.[29]

Cohort simulation (see Appendix A for our Excel tables) was used to generate expected outcomes and costs for a hypothetical cohort of 10,000 patients per arm of the decision tree of the decision-analysis model (i.e. 20,000 hypothetical patients in total). This base-case analysis, that is, the model run with the most likely set of assumptions or input values, yielded expected outcomes, such as life-years (LYs) and quality-adjusted life years (QALYs), as well as costs (in United States Dollars [USD], year 2020; as well as in Renminbi [RMB], also known as "Chinese yuan", year 2020), which were then compared to come up with incremental cost-effectiveness ratios (ICERs) by dividing the differences in costs between the intervention and control arm by the differences in the outcomes between these two groups. The size of the cohorts (10,000 each) was chosen because the size of one cohort is a somewhat close approximation or perhaps a bit larger than the number of people with schizophrenia likely to reside in the Liuyang municipality in 2020, given population growth and increased detection of mental illness, and the fact that the population in 2014 was 1,297,700[30] and recorded prevalence of schizophrenia in rural China in 2010 was around 0.50% (0.47%-0.53%).[31]

Rates of Illness Progression (Severe Relapse and Recovery) and Mortality

The probability of severe relapse (re-hospitalization) for an adherent patient, or the probability of transitioning from the Well Adherent state (WA) to the Severe Adherent state (SA), was mostly based upon the data for re-hospitalization from the parent trial,[7] which showed 7.3% of patients in the intervention (LEAN plus 686) arm requiring re-hospitalization. There are some isolated trials that report much lower rates in other parts of the world,[26] but we found these numbers inconsistent with the rest of the literature, and we actually ended up increasing this probability from the LEAN trial slightly by taking into account the fact that another study from China[32] reported a higher probability of relapse within 1 year of prior hospitalization (18%), leading us to report a transition probability of 0.08 for the transition from WA to SA. That is, we increased the probability slightly after acknowledging that some of the patients may fall into this or another higher risk group. The probability of severe relapse for a nonadherent patient, or the probability of transitioning from the Well Nonadherent state (WN) to the Severe Nonadherent state (SN), was based upon evidence that non adherent patients have a relapse rate 2.5 fold higher than adherent patients,[32] hence the 0.08 transition probability for WA to SA translates to a 0.20 probability value for the transition from WN to SN.

The background mortality probability per cycle (i.e., per month) for an adherent patient, or the probability of transitioning from WA to the Dead state (D), was derived from a study that put the mortality rate among patients with schizophrenia in rural China at 2,228 per 100,000 person-years, which we converted from this rate to a monthly transition probability (0.002) via a widely accepted formula (i.e., p = 1 - e^(-r/12)).[33] The background mortality probability per month for a nonadherent patient, or the probability of transition from WN to D, was derived from the same number from the same study,[33] and we simply applied a slight increase in probability (+0.001) that we determined was appropriate, and conservative, given the effects of nonadherence to antipsychotics on mortality and the evidence on mortality probability per month in schizophrenia from other studies.[20] For the mortality probability per cycle for those who are severely relapsed, we ended up deciding to use the same set of mortality probabilities per cycle as we describe using above for the background mortality probabilities per cycle, for both adherent (0.002) and non adherent (0.003) patients.

To obtain recovery probabilities per month for adherent and nonadherent patients, i.e. to calculate the transition probabilities for SA to WA and SN to WN, we simply made an assumption: that most everyone recovers from the Severe states after 1 cycle within them, besides a proportion that are treatment resistant or for whatever reason fail to respond to treatment, as well as, of course, the proportion who happen to die. We found that treatment failure in schizophrenia appears in about 1 in 6 (0.17) patients,[34] and thus to calculate rates of recovery we simply applied the following calculation: 1 - 0.17 (pTreatmentFailure) -

pSeverelyRelapsedMortality (pSAtoD, pSNtoD), which yielded recovery transition probabilities of 0.828 for the transition from SA to WA, and 0.827 for the transition from SN to WN.

Adherence to Oral Psychotropic Medications

Adherence to oral psychotropic medications, particularly antipsychotic regimens, for patients with schizophrenia is associated with decreased psychotic symptoms, decreased aggression against self and others, better prognosis, decreased use of inpatient and acute outpatient services, and decreased costs.[35] Perhaps most importantly, for patients quality of life in general and for our study, is that adherence to such medication has been suggested to be the most important modifiable factor contributing to the prevention of the kind of psychotic relapse that leads to re-hospitalization.[35]

The way we integrated adherence parameters into our model was early on, in the decision tree portion of the decision-analysis model (Figure 1), whereby after evenly separating at the decision node into the intervention (LEAN plus 686) and control (686) cohorts, these cohorts are then divided at the subsequent chance node by the adherence parameter values, which were taken from the parent study[7]: 0.61 as the adherence level for the intervention group, and 0.48 as the adherence level for the control group. The way we applied these parameter values to each chance node is we considered the probability of being deemed adherent in each arm of the study within our model to be the same as this adherence level (i.e. 0.61 for the intervention arm, and 0.48 for the control arm) and the probability of being deemed nonadherent in each arm of the study within our model was the complementary probability to these adherence levels, i.e. 0.39 for the intervention arm (1-0.61=0.39) and 0.52 for the control arm (1-0.48=0.52).

Within our Markov model (Figure 2), one can see there are no transitions between the adherent and nonadherent sides of the model. This is intentional. While we were inspired by similar models such as the model created by one of our co-authors, Joseph Babigumira, that included transition probabilities only in the direction of adherent to nonadherent to reflect the net “flow” of patients in that direction,[36] we found no such net “flow” or value for the transition from adherent to nonadherent or from nonadherent to adherent as we constructed our model.

Instead, we made the assumption based on the evidence available that these transition probabilities reflecting cross-overs in adherence “cancelled each other out”, or in other words, equaled zero and hence, we see no arrows between the adherent and nonadherent sides of the model.

Health-Related Quality of Life and Health State Utility Values

Utility values for each Markov state were obtained via an intense examination of the literature in this area, which involved looking at a range of studies examining health-related quality of life (HRQoL) and health state utility values (HSUVs) in schizophrenia.[37-45] Ultimately, we settled on using the utility values from the most recent and comprehensive, and we felt most reliable, of the studies[37]: These values were 0.80 for WA and 0.34 for SA. To impute the utility values for the nonadherent states, we applied a disutility factor of 0.05 for nonadherence, leaving a value of 0.75 for WN and 0.29 for SN. The utility of death was of course, as is standard, assumed to be zero.

Costs

Our cost-effectiveness analysis was performed from the perspective of the Chinese healthcare system and costs were divided into four categories: (i) LEAN intervention infrastructure costs, (ii) the cost of additional clinical care assumed to occur due to LEAN improving connection with healthcare infrastructure, (iii) the cost of inpatient hospitalization, and (iv) the cost of end of life care. All costs described below are described as cost per patient per month in 2020 USD (and 2020 RMB) amounts.

The cost of the LEAN intervention infrastructure was 7,926 USD (55,227 RMB) over the 6 months of follow-up in the parent study,[7] for the 139 patient participants and the 139 lay health supporters in the intervention group. As the parent study authors explain, 2,815 USD (19,614 RMB) of that is for texting fees, 1,126 USD (7,846 RMB) for the message development, 711 USD (4,954 RMB) for the message management, 1,481 USD (10,319 RMB) for the 77 phones provided to the patients and the lay health supporters, and 1,333 USD (9288 RMB) for the additional time cost for the health workers. To adapt this cost for the purpose of our study, we first acknowledged that this overall cost of 7,926 USD (55,227 RMB) included some societal costs (such as the time cost for lay health workers) which cannot be captured by our Chinese healthcare system perspective and also included some mostly one-time costs (such as message development and the phones provided). Due to this, we felt this amount could reasonably be carried over to last two years with this population (of 139 patients and 139 lay health supporters), if looking from the perspective of the Chinese healthcare system. Therefore, the cost per patient per month was 2.38 USD (16.58 RMB), which was calculated by taking the overall cost for the two years of 7,926 USD (55,227 RMB), divided by the number of patients (139) to get 57.02 USD (397.30 RMB) per patient for the 2 year period. Then, to get the final cost, you simply divide by the number of months in a 2-year period (24) to obtain 2.38 USD (16.58 RMB) per patient per month.

We also chose to consider the additional clinical care costs assumed to occur due to LEAN improving connection with healthcare infrastructure. We made the assumption that the LEAN intervention plus 686 Program would increase the number of doctor visits per patient per month by a factor of 1. Since basic consultation feels may be as inexpensive as approximately 3 USD (21 RMB) and higher averages come out to around 25 USD (174 RMB), we averaged these two figures to come up with what we felt would be the approximate mean cost for a doctor visit in rural areas, which we found to be about 14 USD (98 RMB) per patient per month.[46]

The cost of inpatient hospitalization for schizophrenia in rural China was obtained by triangulating from several sources on inpatient hospitalization in China.[47-49] It was determined that the cost of inpatient hospitalization for schizophrenia in rural China is 1,700 USD (11,845 RMB) per patient per month.

Lastly, we formulated the cost of end of life care for a patient with schizophrenia by combining findings from several studies and sources,[50-52] and set upon a price of 4,000 USD (27,871 RMB) per patient.

Base-case Analysis

In running a base-case analysis cohort simulation with our model to assess the cost-effectiveness of LEAN, we found the 2-year discounted QALYs were higher for the LEAN plus 686 Program [intervention] arm (1.45) than for the 686 Program alone [control] arm (1.42). In the incremental analysis, the LEAN plus 686 Program [intervention] arm was dominant, i.e., less costly (by 196 USD or 1,362 RMB, over 2 years) and more effective by 0.03 QALYs (over 2 years). Dominance means that this preliminary analysis showed the intervention to be cost-effective — both cost-saving and possessing higher effectiveness. These results, along with other more specific data from this base-case analysis, including overall costs, LYs, etc are shown in Table 2.

A sensitivity analysis, which is used to explore how model results deviate from those of the base-case analysis when input values and modelling assumptions are altered, was not performed for this study. Such an analysis was determined to be unnecessary at this study stage, which was intended as a preliminary cost-effectiveness analysis, and sensitivity analyses will be used in later studies which utilize later iterations of this model, which will have access to higher resolution cost data collected from fieldwork and likely better resolution (with associated better ideas of the variability about the means) on other inputs due to continued fieldwork and research as well.

Discussion

This study involved developing a decision-analysis model (a decision tree linked to a Markov model) and utilizing this model to perform a preliminary cost-effectiveness analysis of the mobile-based LEAN intervention for schizophrenia in rural China atop the 686 Program versus the 686 Program alone. The base-case cost-effectiveness analysis performed suggests that the addition of the LEAN intervention was dominant, i.e. it was not only more effective, but was also cost saving, although these preliminary cost-effectiveness results cannot be used to make any strong conclusions (see the first limitation below).

There are limitations to this study. Inherent to building any model are the assumptions or assertions that may have some deviation from the actual reality. That being said, a good model should make intelligent assumptions and assertions in an attempt to best represent reality, which we've tried to do here. Still, there are many limitations to our model.

One limitation already alluded to above is that this study cannot be used to draw any strong conclusions about the cost-effectiveness of LEAN, as the preliminary cost-effectiveness analysis performed in this study is a base-case analysis, meaning in this case that a cohort simulation was run with the most likely set of assumptions or input values. This preliminary analysis showed the LEAN plus 686 intervention was cost-effective, but better data will be needed to both further develop the model and better parameterize it.

A second limitation of this study is a limitation of Markov modelling itself called the "Markovian assumption", which is the fact that occupying previous states doesn't affect the current state in terms of its transition probabilities,[15,16] which is obviously not true for many complex chronic illnesses such as schizophrenia. Previous hospitalizations and relapses and many prior instances can affect the transition probabilities of different states in our model, but fitting that into a Markov model can be very tricky and isn't inherent in the model structure. Therefore, this limitation means that our model loses some accuracy at representing a complex illness like schizophrenia.

A third limitation was the time horizon of 2 years, which limited the ability to predict results for the longer term. We chose not to set the time horizon to 5 or 10 years as many economic models do because we felt this would be an overreach given the data available.

A fourth limitation was choosing the Markov model cycle length of 30 days (1 month) due to it being the mean length of schizophrenia-related hospitalizations, as there is some evidence that schizophrenia-related hospitalization lengths of stay can be longer in the Chinese context.[53] However, we chose to keep our cycle length at 30 days because we wanted to keep to the conservative/lower end of these estimates, mostly because we were working to account for several factors that would realistically lower the amount of time members of our rural Chinese cohort would spend in inpatient hospitalization: the limited ability to pay for such inpatient hospitalizations in China by many people,[54] the limited number of beds for people with schizophrenia and psychiatric issues in general,[55] other capacity issues, as well as evidence that rural inpatients are known to have a shorter length of stay.[48] On top of these financial and healthcare capacity reasons, keeping the cycle length to 1 month also made the model more easily interpretable.

A fifth limitation was the resolution on the illness lost by restricting the model to two levels of living states (Well and Severe). Although we found models with "Moderate" states in the literature and even came up with a few model designs that included Moderate states or other intermediate states in the early stages of model development (see some examples in Appendix B), we found such intermediate states tend to make the model "messy" both in that they literally made the model more complex and sometimes confusing, and because delineating between three states can be quite difficult, both clinically and in terms of being able to assign discrete utilities and costs. In addition, due to the cycle time of one month, it made more sense to create these two states, as intermediate states of the disorder rarely last very long, while the well (stable) and very severe (severe relapses) are known to last for a month, or months at a time.

A sixth set of limitations are certain assumptions made around some transition probabilities. For example, the recovery transition probabilities assumed that the majority of cases recover after 30 days in the Severe state, which seemed like a logical conclusion to make, but in reality there are other reasons someone would remain in the Severe state for longer, or at least not transition all the way to a "stable" (Well) state, which stresses the possible need for a "Moderate" state in future models, despite the complexities introduced by this discussed in the above limitation. The severe relapse transition probabilities were also heavily based upon the parent study,[7] which makes sense, but is a relatively small study, and might not be representative of the larger Chinese population, so further exploration and study of this is warranted. In addition, for the transition probabilities for severe relapse for nonadherent patients (WN to SN) there was some evidence that nonadherence to medication can increase risk of relapse up to 5.0 fold,[56] but we decided it was best practice to stay with the more conservative and more recently-established estimate (2.5 fold). Lastly, we also made the possibly bold assumption that the same transition probability for monthly mortality could be applied for the Well (background mortality) and Severe (severely relapsed mortality) states. Our logic for this was that although there is some (not very strong, and not in China) evidence for a slightly higher mortality risk, due to suicide mostly, in a psychotic (or Severe) state, we felt this was mostly offset by the fact that patients in this group by definition of their symptomatology would require hospitalization, and thus for most of their time (most of the 30 days) were in a hospital environment, where control measures are in place to prevent self-harm and suicide. We felt these hospital control measures, which are obviously absent for patients in the Well states of our model, offset any possible differences/increases in mortality probability per month that the Severe states confer.

A seventh limitation is the strong assumption that adherence levels from the parent study can be used to separate cohorts into adherent and nonadherent groups. The assumption that these values represent a threshold upon which to divide a cohort into two fully discrete groups representing different utilities, costs, and transition probabilities is certainly somewhat wishful thinking, but we felt it was the best way we could account for and model the differences in adherence caused by the LEAN intervention and the subsequent effects this has on costs and outcomes. Also in regards to adherence, it is worth stressing that the assumption we made that there is no monthly "cross-over" between the adherent and nonadherent states in the cycles of our Markov model is a strong one and will need to be considered further in latter versions of this model.

An eighth limitation is the uncertainty around the cost to assign for additional clinical care costs. Given the value we used for our upper limit in this average was a mean (not an upper limit) itself, you can see we were working to keep this cost lower, and this was because we were hoping to make an approximation for rural areas (where there is generally less capital to commit to doctor visits) and because we wanted to account for the fact that the LEAN intervention improves adherence. Hence, while such increased care-seeking may be true under the LEAN intervention, there is also the fact that increased adherence leading to less severe symptoms under the intervention might lead less people to seek out care in the first place or even need this feature of the intervention. For that reason, we wanted to keep this cost low and not inflate this effect, even though it definitely may be somewhat greater, especially given that costs for counseling sessions and psychiatrist visits can be more in the range of 47 USD (327 RMB) to 110 USD (766 RMB).[57]

A ninth limitation is issues around ability to pay and capacity, as well as the economic perspective chosen for this study. Despite our attempts to adjust our model parameters to compensate for this, there is a chance our hospitalization and clinical care costs are over-blown, especially for rural residents. This is because, as we've noted, rural residents especially do not usually have the financial means to pay for hospitalization,[54] unless they have insurance, for example. However, there is a chance that this may be changing. In addition to ability to pay issues, there are issues related to capacity, such as the number of psychiatric beds and providers available.[55] Less capacity for inpatient hospitalization may limit the applicability of our findings, as it may mean all the Severe state patients we marked as creating increased costs for the Chinese healthcare system didn't actually create such costs. However, this points to the limitation of this economic perspective and the importance of future iterations of this model taking on the societal perspective. While the Chinese healthcare system perspective was most relevant for this initial cost-effectiveness evaluation given the level of cost data currently available, a societal perspective will open up this analysis and make it much more relevant when the right data is available. The societal perspective will not only capture the huge effect of inpatient hospitalization on direct costs (which are significant, and are captured by our model), but will also capture the indirect costs such as the cost of less social interaction, lost wages, etc.

A tenth and final limitation we will mention here is the disparity between rural and urban populations. Some of the parameters are derived from Chinese studies, but some are Chinese studies that are mostly or entirely in urban areas, which may not mesh well with the parameters in our model taken from the parent study, which was conducted exclusively with rural patients. We did our best to adjust parameters to reflect this, but this is still a possible source of error and a limitation. In addition, when working to carry forth the results of this model into other parts of China (such as urban areas), it may not translate. This model likely will need to be adapted for urban contexts, and different contexts in general.

To our knowledge, this is the first economic model developed and used to perform even a preliminary cost-effectiveness analysis of a mobile-based intervention for schizophrenia in rural China. Our inclination is that it will be the first of many. For instance, future fieldwork is planned to collect cost data for this specific purpose,[9] and we encourage future investigators to pursue more precise outcome indicators at the same time, to both further develop the model and better parameterize it. This model may be used 'as is' to assess a range of interventions, but more than likely, it will benefit from the future addition of a sensitivity analysis and perhaps a more complex model structure, as discussed in the above limitations (especially the idea of adding an intermediate state and integrating the crossover between the adherent and nonadherent states each cycle into the Markov model). Furthermore, the decision tree portion of the model may become more useful for larger applications if a chance node for access is added, so that studies involving issues around access to medications can be compared as well (this was irrelevant in our study, as all participants were 686 Program enrollees, meaning they all had access to oral psychotropic medications). We envision future investigators utilizing a more robust, adapted version of this model to test a range of mobile-based applications for schizophrenia in a variety of contexts.

The implications of the findings of this study are not entirely clear yet. This is because although this study established that developing an economic model is possible for a mobile-based intervention for a complex illness such as schizophrenia in rural China, and that the base-case cost-effectiveness analysis performed suggests that the LEAN intervention is both cost-saving and effective, we cannot draw any strong conclusions from these findings since this is just a preliminary analysis. Sensitivity analyses will be required in future analyses (in future studies that utilize this model or adaptations of it) that account for possible error in model parameters so we can make stronger conclusions and state clearly the implications of the findings of analyses like this. While we would like to be able to say that the LEAN intervention has been proven to be cost-saving and effective, and should therefore be encouraged as something to supplement free medicine programs such as the 686 Program, we cannot say this definitively at this time. In addition, it is worth adding that having a free medicine program and good mental healthcare infrastructure in general is what makes LEAN possible and gives any chance of the intervention being successful, so these aspects underlying LEAN and our model should not be ignored and should continue to be strengthened, regardless of whether future iterations of this model or other models show LEAN to be cost-effective or not.

Our model and base-case cost-effectiveness analysis suggest LEAN is both effective as well as cost-saving, and accordingly suggest that LEAN should be considered for scale-up and strengthening of medicine programs for schizophrenia and might even be adapted to serve other severe mental illnesses, other mental health diagnoses, and beyond. However, this is only a suggestion of our current preliminary analysis, so we cannot say with certainty this is our recommendation at this time. When these claims can be made with certainty after future analyses, public health practitioners should find ways to implement LEAN or adaptations of LEAN (or interventions like it) into their medication provision programs both to improve patients lives and bring cost-savings to their programs. At the same time, if these conclusions are further solidified by future analyses, clinicians should begin to recommend such programs to patients until they become the norm in a society where more people will be more intimately and easily able to connect with care and improve their well-being. Until that time, this study provides an early hint at the potential cost-effectiveness of LEAN and the model developed serves as a foundation for future models and analyses of interventions for schizophrenia in rural China and beyond.

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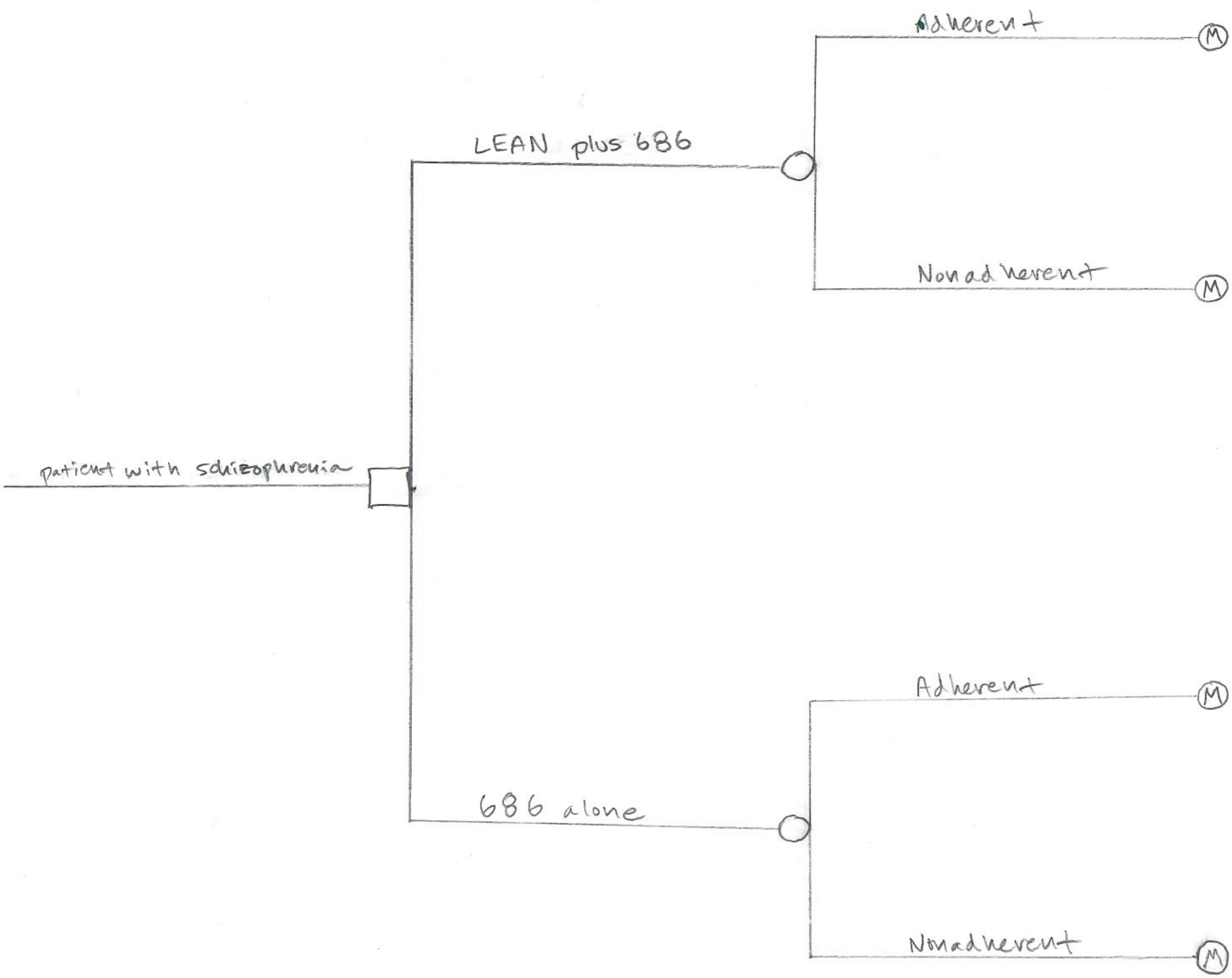


Figure 1: Decision tree showing the comparison of the LEAN intervention plus 686 Program (LEAN plus 686) [intervention arm] and the 686 Program alone (686 alone) [control arm] for schizophrenic patients in rural China, who are then further divided into adherent and non adherent groups within each arm. The square at the root is a decision node; the circles are chance nodes; and the Ms with circles around them denotes a transition into the Markov model (see Figure 2).

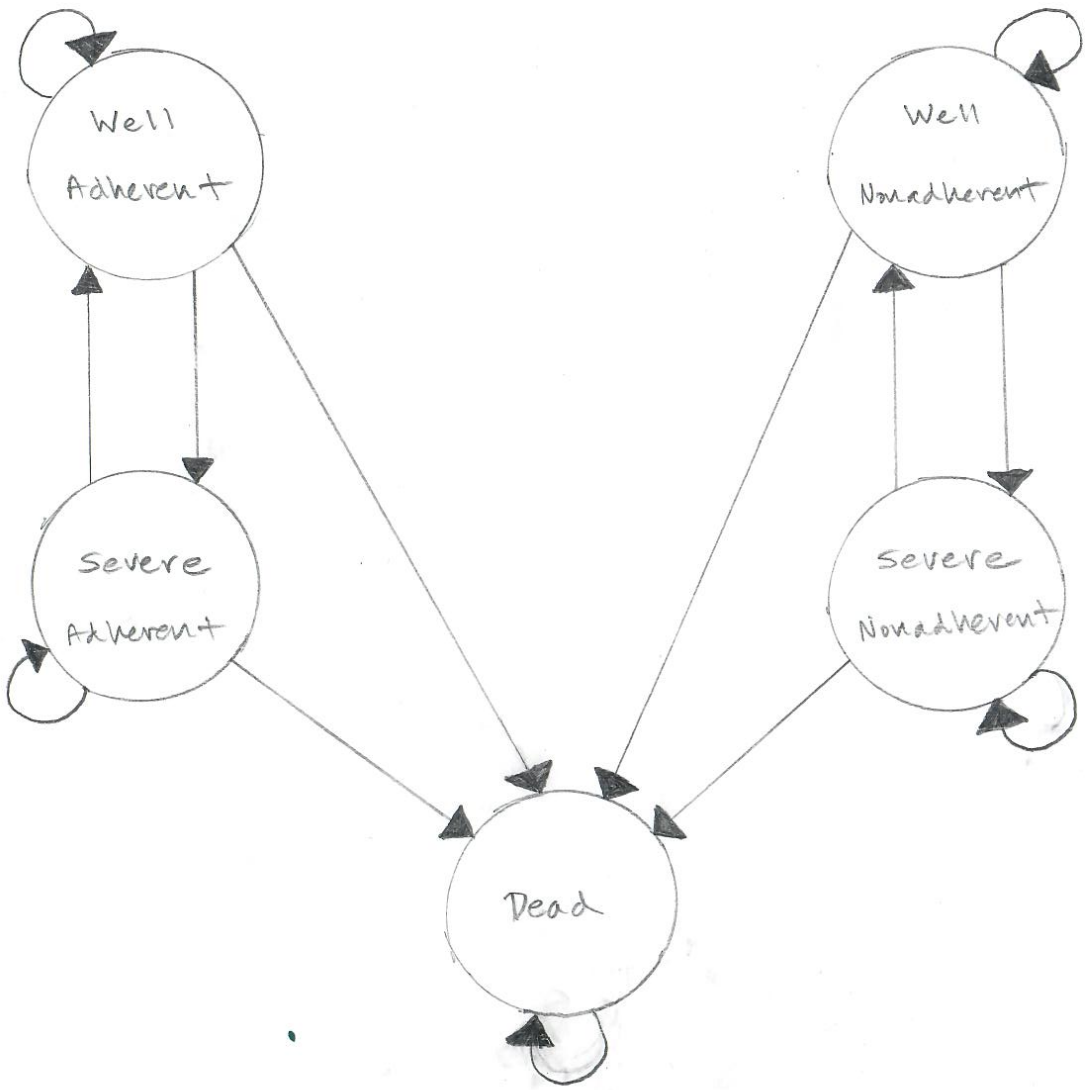


Figure 2: Markov Model illustrating the different health states through which patients with schizophrenia transition. Each health state is associated with a utility and a cost. Transition probabilities from state to state are summarized in the table of parameters (Table 1).

Table 1: Parameters of the decision tree and Markov model

Parameter	Base case	Reference
Utilities		
Well (Adherent) (WA)	0.8	[37]
Well (Nonadherent) (WN)	0.75	Imputed*
Severe (Adherent) (SA)	0.34	[37]
Severe (Nonadherent) (SN)	0.29	Imputed*
Dead (D)	0	Assumed
Transition Probabilities		
Severe relapse (for Adherent patients) (WA to SA)	0.08	[7,32]
Severe relapse (for Nonadherent patients) (WN to SN)	0.2	[32]
Background mortality (Adherent) (WA to D)	0.002	[33]
Background mortality (Nonadherent) (WN to D)	0.003	[20,33]
Recovery (Adherent) (SA to WA)	0.828	Assumption; [34]
Recovery (Nonadherent) (SN to WN)	0.827	Assumption; [34]
Severely relapsed mortality (Adherent) (SA to D)	0.002	[33]
Severely relapsed mortality (Nonadherent) (SN to D)	0.003	[20,33]
Adherence		
LEAN intervention plus 686 Program	0.61	[7]
686 Program alone	0.48	[7]

* Applied a disutility factor of 0.05 for nonadherence (i.e. utilities reduce by a factor of 0.05)

Table 2: Mean and incremental costs, LMs, LYs, QALMs, QALYs, and ICERs for the LEAN intervention in rural China

Yearly Values	**Costs in USD (year 2020 values)**		**Costs in RMB (year 2020 values)**	
	686 alone	**LEAN plus 686**	**686 alone**	**LEAN plus 686**
Cost	$5,811	$5,616	40,492	39,130
Incremental Cost		-$196		-1,362
LYs	1.99	2.00		
Incremental LYs		0.00		
ICER ($/LY saved)		**Dominant**		**Dominant**
QALYs	1.42	1.45		
Incremental QALYs		0.03		
ICER ($/QALY saved)		**Dominant**		**Dominant**
Monthly Values	**Costs in USD (year 2020 values)**		**Costs in RMB (year 2020 values)**	
	686 alone	**LEAN plus 686**	**686 alone**	**LEAN plus 686**
Cost	$5,811	$5,616	40,492	39,130
Incremental Cost		-$196		-1,362
LMs	23.93	23.96		
Incremental LMs		0.04		
ICER ($/LM saved)		**Dominant**		**Dominant**
QALMs	17.01	17.34		
Incremental QALMs		0.33		
ICER ($/QALM saved)		**Dominant**		**Dominant**

ICER = incremental cost-effectiveness ratio; **LY** =life-year; **QALY** = quality-adjusted life-year; **LM** = life-month; **QALM** = quality-adjusted life-month; **USD** = United States Dollar; **RMB** = Renminbi, or "Chinese yuan"); **Dominant** means the intervention was shown by our model to be both cost-saving and more effective

Appendixes

Appendix A. Markov Cohort Simulations in Microsoft Excel

A.1 Markov Trace: 686 alone (Control Arm)

cycle (months)	Discount factor	Well (Adherent) [WA]	Well (Nonadherent) [WN]	Severe (Adherent) [SA]	Severe (Nonadherent) [SN]	Dead [D]	*sum check*	LMs	QALMs	Costs
pre-Markov	0	10000	0	0	*0*	0	*10000*	0.00	0.00	$0
0	1	4800	5200	0	*0*	0	*10000*	1.00	0.77	$0
1	1	4406	4144	384	*1040*	25	*10000*	1.00	0.71	$252
2	1	4363	4163	418	*1006*	50	*10000*	0.99	0.70	$252
3	1	4351	4150	420	*1004*	75	*10000*	0.99	0.70	$252
4	1	4342	4137	420	*1001*	100	*10000*	0.99	0.70	$251
5	1	4333	4125	419	*998*	125	*10000*	0.99	0.70	$251
6	1	4325	4113	418	*995*	150	*10000*	0.98	0.70	$250
7	1	4316	4100	417	*992*	175	*10000*	0.98	0.70	$249
8	1	4308	4088	416	*989*	200	*10000*	0.98	0.69	$249
9	1	4299	4076	415	*986*	224	*10000*	0.98	0.69	$248
10	1	4290	4063	415	*983*	249	*10000*	0.98	0.69	$247
11	1	4282	4051	414	*980*	274	*10000*	0.97	0.69	$247
12	1	4273	4039	413	*977*	298	*10000*	0.97	0.69	$246
13	0.970873786	4265	4027	412	*974*	323	*10000*	0.94	0.67	$238
14	0.970873786	4256	4015	411	*971*	347	*10000*	0.94	0.66	$238
15	0.970873786	4248	4003	410	*968*	371	*10000*	0.93	0.66	$237
16	0.970873786	4239	3991	410	*965*	395	*10000*	0.93	0.66	$236
17	0.970873786	4231	3979	409	*962*	420	*10000*	0.93	0.66	$236
18	0.970873786	4222	3967	408	*959*	444	*10000*	0.93	0.66	$235
19	0.970873786	4214	3955	407	*956*	468	*10000*	0.93	0.66	$234
20	0.970873786	4205	3943	406	*954*	492	*10000*	0.92	0.65	$234
21	0.970873786	4197	3931	405	*951*	516	*10000*	0.92	0.65	$233
22	0.970873786	4188	3920	405	*948*	539	*10000*	0.92	0.65	$233
23	0.970873786	4180	3908	404	*945*	563	*10000*	0.92	0.65	$232
24	0.970873786	4172	3896	403	*942*	587	*10000*	0.91	0.65	$231
								23.93	17.01	$5,811

Transition Matrix	WA	SA	WN	SN	D
WA	1-pWAtoSA-pWAtoD	pWAtoSA	0	0	pWAtoD
SA	pSAtoWA	1-pSAtoWA-pSAtoD	0	0	pSAtoD
WN	0	0	1-pWNtoSN-pWNtoD	pWNtoSN	pWNtoD
SN	0	0	pSNtoWN	1-pSNtoWN-pSNtoD	pSNtoD
D	0	0	0	0	1

Other measures	
LYs	1.99
QALYs	1.42

Transition Matrix	WA	SA	WN	SN	D
WA	0.918	0.08	0	0	0.002
SA	0.828	0.17	0	0	0.002
WN	0	0	0.797	0.2	0.003
SN	0	0	0.827	0.17	0.003
D	0	0	0	0	1

A.2 Markov Trace: LEAN plus 686 (Intervention Arm)

cycle (months)	Discount factor	Well (Adherent) [WA]	Well (Nonadherent) [WN]	Severe (Adherent) [SA]	Severe (Nonadherent) [SN]	Dead [D]	sum check	LMs	QALMs	Costs
pre-Markov	1	10000	0	0	0	0	10000	0.00	0.00	$0
0	1	6100	3900	0	0	0	10000	1.00	0.78	$16
1	1	5600	3108	488	780	24	10000	1.00	0.72	$240
2	1	5545	3122	531	754	48	10000	1.00	0.72	$243
3	1	5530	3112	534	753	72	10000	0.99	0.72	$243
4	1	5518	3103	533	750	95	10000	0.99	0.71	$242
5	1	5507	3094	532	748	119	10000	0.99	0.71	$241
6	1	5496	3084	531	746	143	10000	0.99	0.71	$241
7	1	5485	3075	530	744	166	10000	0.98	0.71	$240
8	1	5474	3066	529	741	190	10000	0.98	0.71	$240
9	1	5463	3057	528	739	213	10000	0.98	0.71	$239
10	1	5452	3048	527	737	236	10000	0.98	0.70	$238
11	1	5441	3038	526	735	260	10000	0.97	0.70	$238
12	1	5431	3029	525	733	283	10000	0.97	0.70	$237
13	0.970873786	5420	3020	524	730	306	10000	0.94	0.68	$230
14	0.970873786	5409	3011	523	728	329	10000	0.94	0.68	$229
15	0.970873786	5398	3002	522	726	352	10000	0.94	0.68	$229
16	0.970873786	5387	2993	521	724	375	10000	0.93	0.67	$228
17	0.970873786	5376	2984	519	722	398	10000	0.93	0.67	$227
18	0.970873786	5366	2975	518	720	421	10000	0.93	0.67	$227
19	0.970873786	5355	2966	517	717	444	10000	0.93	0.67	$226
20	0.970873786	5344	2957	516	715	467	10000	0.93	0.67	$226
21	0.970873786	5334	2948	515	713	490	10000	0.92	0.67	$225
22	0.970873786	5323	2940	514	711	512	10000	0.92	0.66	$224
23	0.970873786	5312	2931	513	709	535	10000	0.92	0.66	$224
24	0.970873786	5302	2922	512	707	557	10000	0.92	0.66	$223
								23.96	17.34	$5,616

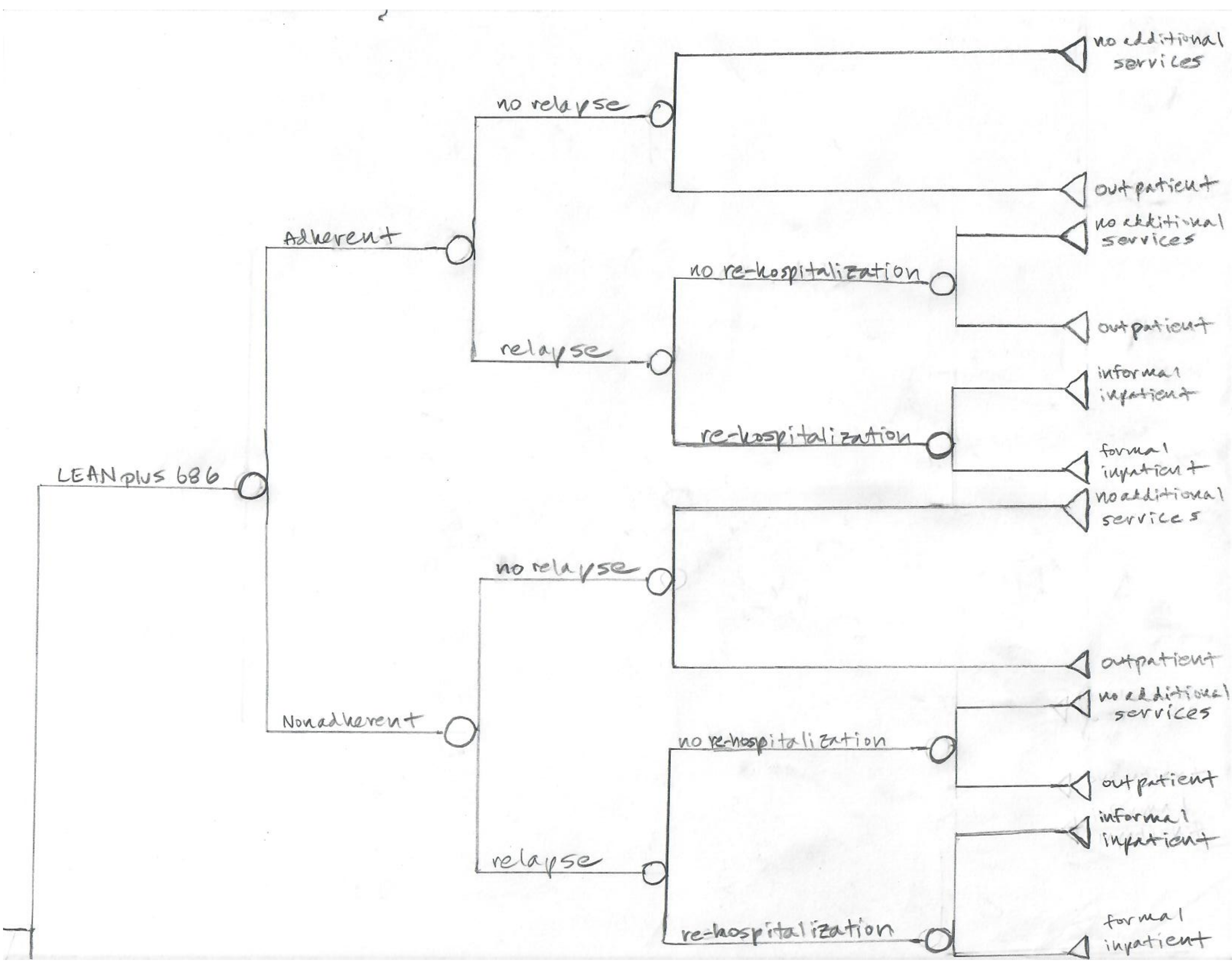
Transition Matrix	WA	SA	WN	SN	D
WA	1-pWAtoSA-pWAtoD	pWAtoSA	0	0	pWAtoD
SA	pSAtoWA	1-pSAtoWA-pSAtoD	0	0	pSAtoD
WN	0	0	1-pWNtoSN-pWNtoD	pWNtoSN	pWNtoD
SN	0	0	pSNtoWN	1-pSNtoWN-pSNtoD	pSNtoD
D	0	0	0	0	1

Other measures	
LYs	2.00
QALYs	1.45

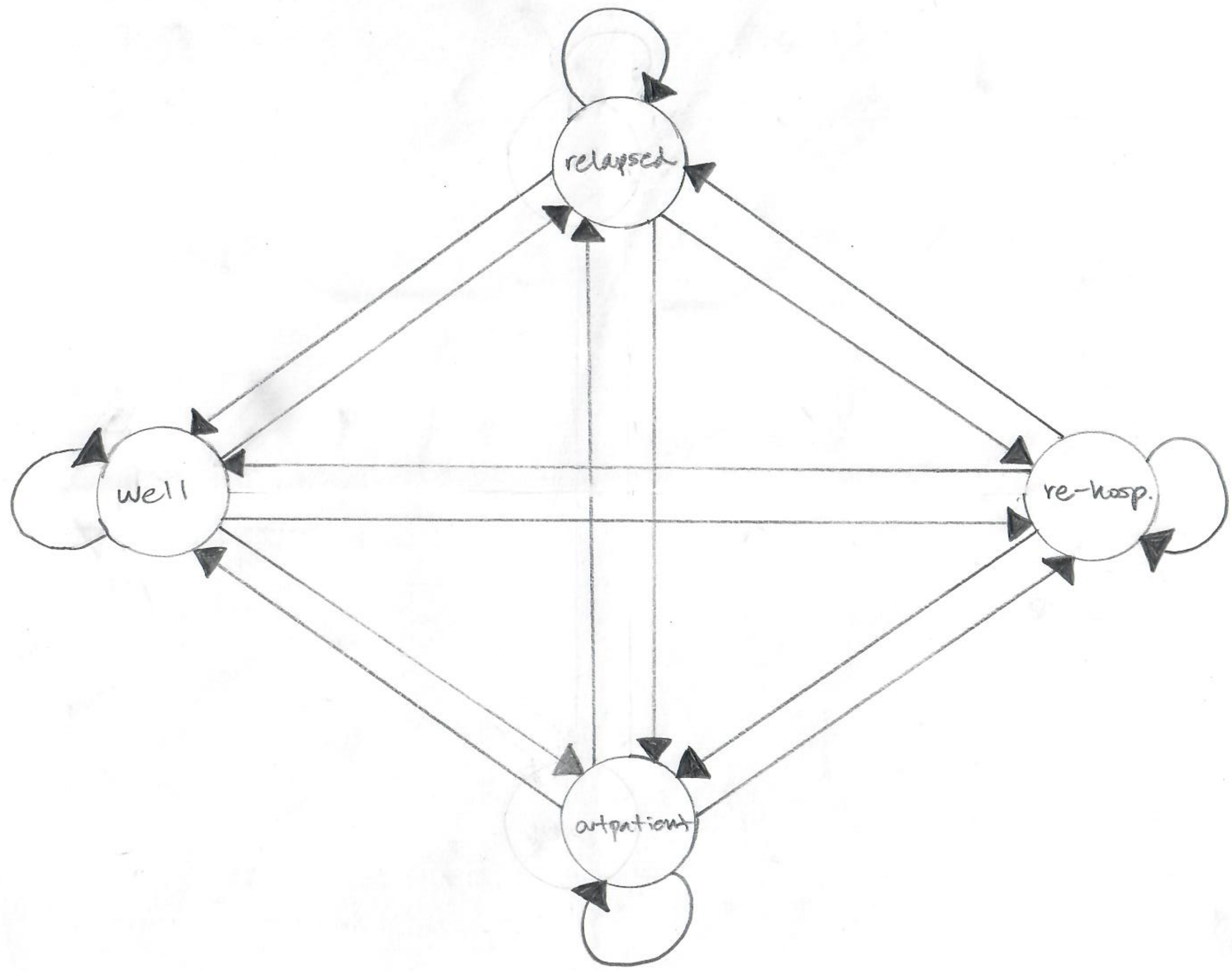
Transition Matrix	WA	SA	WN	SN	D
WA	0.918	0.08	0	0	0.002
SA	0.828	0.17	0	0	0.002
WN	0	0	0.797	0.2	0.003
SN	0	0	0.827	0.17	0.003
D	0	0	0	0	1

Appendix B. Early Iterations of the Model

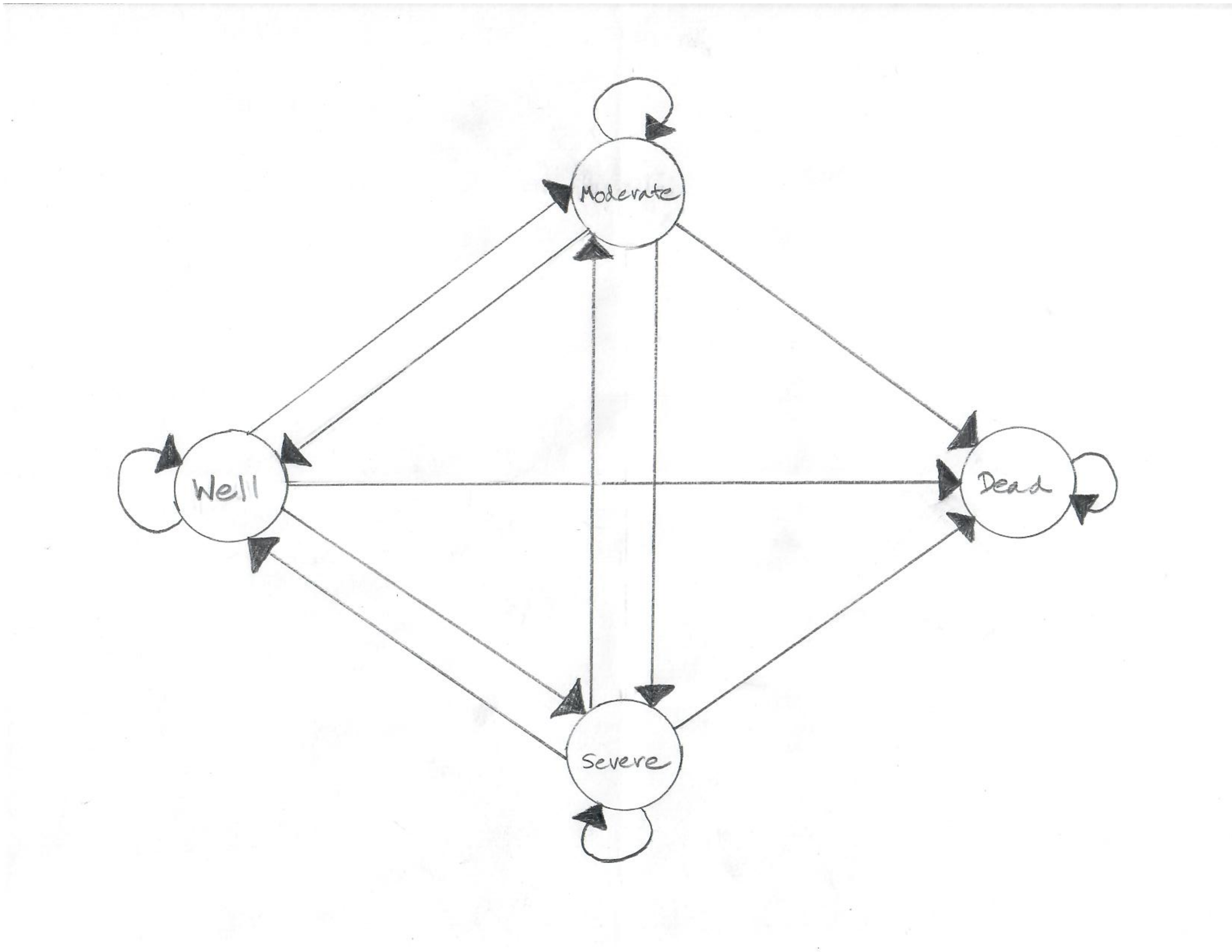
B.1 Model Iteration 1: A decision tree model, showing the intervention arm branches after the decision node (the partial square at the root in the bottom left corner). The control arm is an exact replica of this portion of the decision tree (with '686' instead of 'LEAN plus 686') and would be positioned below this portion of the decision tree. Circles are chance nodes.



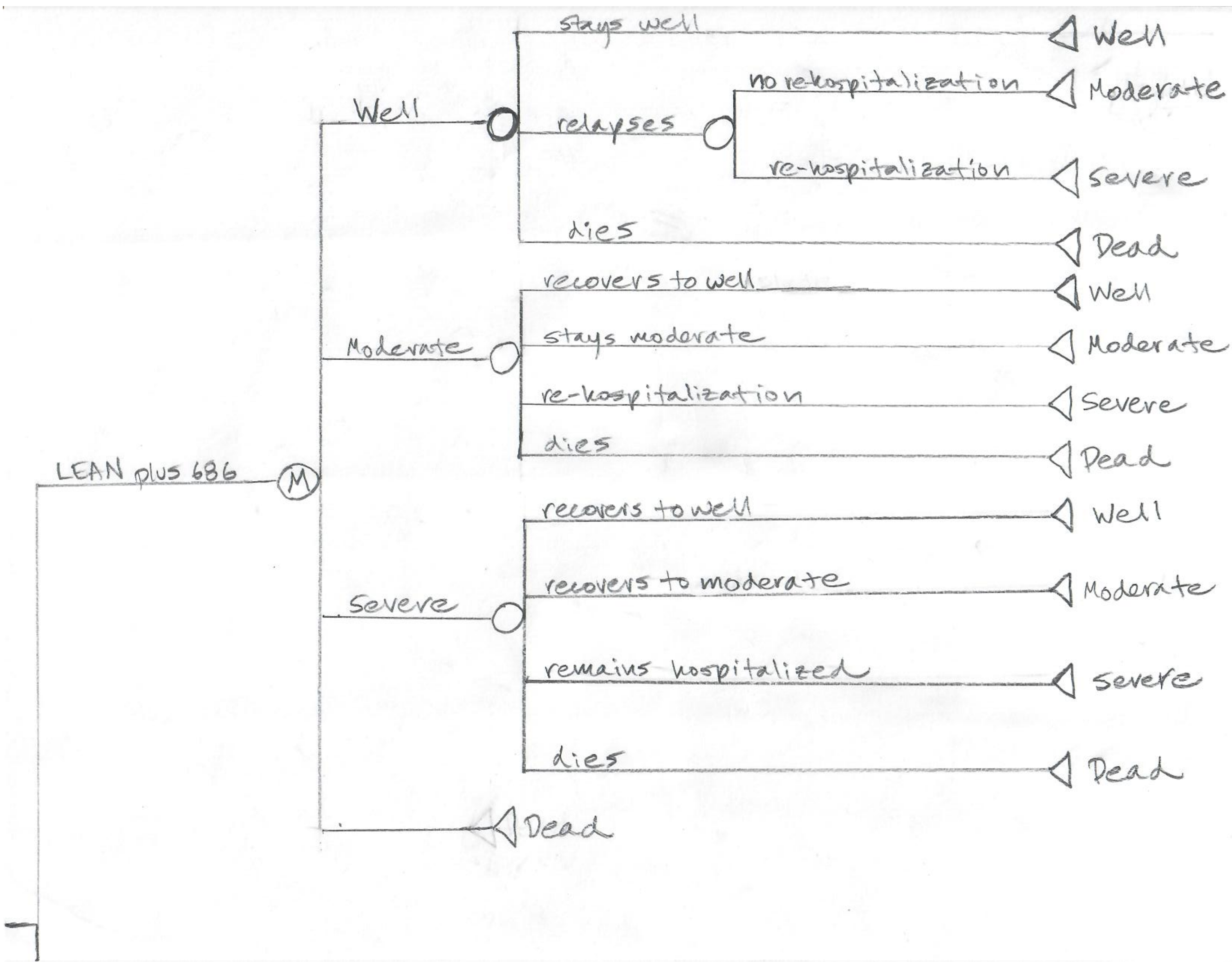
B.2 Model Iteration 2: A Markov Model. (re-hosp. = re-hospitalized)



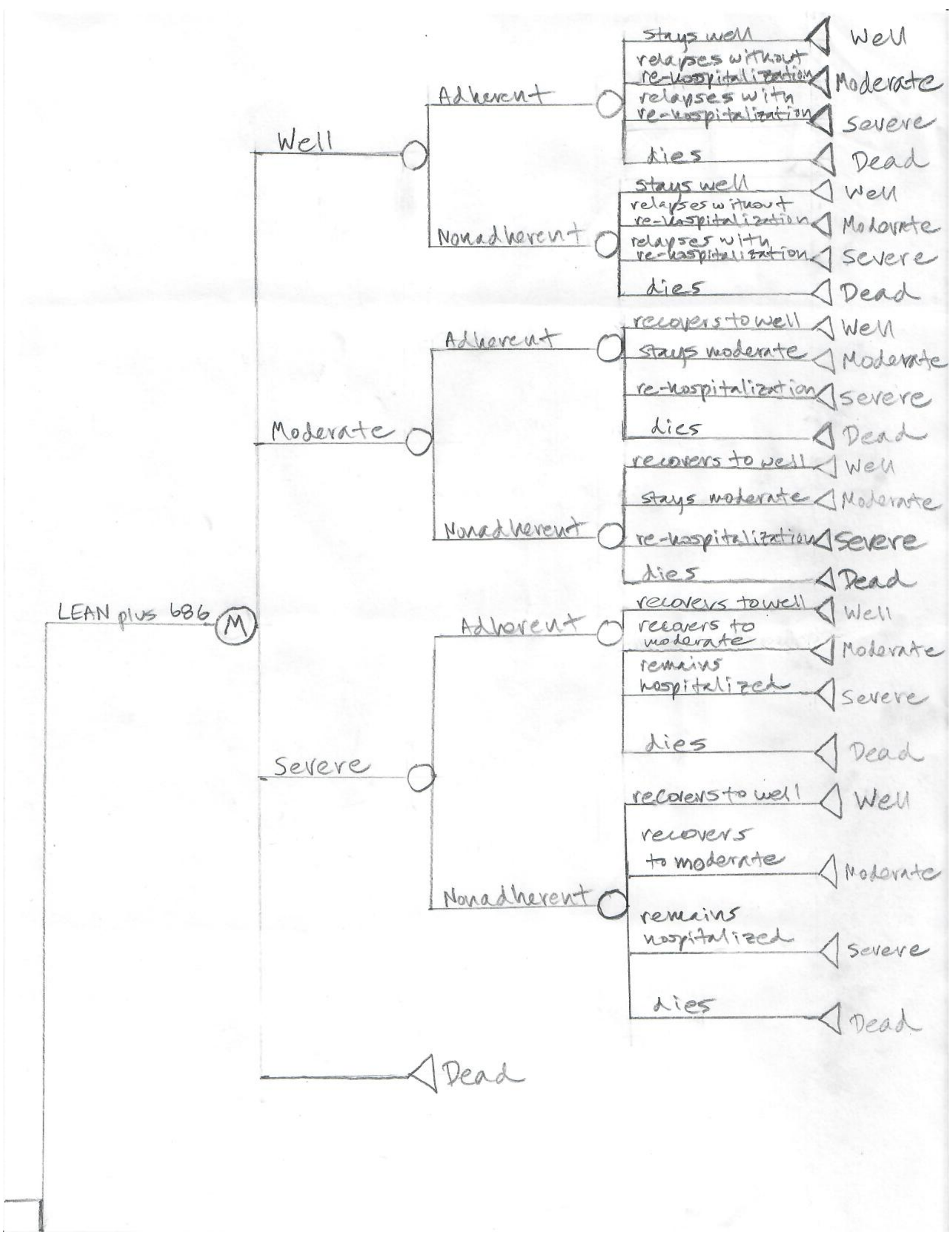
B.3 Model Iteration 3: A Markov model.



B.4 Model Iteration 4: A decision tree representation of a Markov model, showing the intervention arm portion of the model after the decision node (the partial square at the root in the bottom left corner). The control arm is an exact replica of this portion of the decision tree (with '686' instead of 'LEAN plus 686') and would be positioned below this portion of the decision tree. Circles are chance nodes; and the Ms with circles around them denotes a transition into the Markov model. Triangles indicate the final states after 1 cycle, after which the model cycles again and again for however long, depending on the time-horizon, starting at the Ms with circles around them.



B.5 Model Iteration 5: A decision tree representation of a Markov model, showing the intervention arm portion of the model after the decision node (the partial square at the root in the bottom left corner). The control arm is an exact replica of this portion of the decision tree (with '686' instead of 'LEAN plus 686') and would be positioned below this portion of the decision tree. Circles are chance nodes; and the Ms with circles around them denotes a transition into the Markov model. Triangles indicate the final states after 1 cycle, after which the model cycles again and again for however long, depending on the time-horizon, starting at the Ms with circles around them.



B.6 Model Iteration 6: A decision tree representation of a Markov model, showing the full model split into intervention and control arms at the decision node (the partial square at the root in the middle left of the image). Circles are chance nodes; and the Ms with circles around them denotes a transition into the Markov model. Triangles indicate the final states after 1 cycle, after which the model cycles again and again for however long, depending on the time-horizon, starting at the Ms with circles around them.