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Measuring Prescription Adherence for Pharmaceutical Prescription Refills

Mabel Chow
University of Pennsylvania

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Disciplines
Medicine and Health

1. Motivation.

A definition of adherence, taken from the conclusion reached by the participants at the WHO Adherence meeting in June 2001 is "the extent to which the patient follows medical instructions". In medical research, adherence of participants acts as a critical variable in interpreting the results of a clinical trial (i.e. in evaluating the efficacy of a treatment). In practice, studies have shown that the consequences of poor adherence are poor health outcomes and increased health care costs. Furthermore, adherence is found to be the single most important *modifiable* factor compromising treatment outcome across diseases[1].

In light of this, scientists, pharmaceutical companies, healthcare providers and policy-makers have the incentive to improve adherence rates. To do so, adherence measures and also a model to tease out adherence determinants need to be properly constructed.

2. Formulation of research area.

This research focuses on the issue of adherence within a medical context. More specifically, it concentrates on adherence in medication intake and refill as opposed to adherence in other facets of patient behavior that coincide with medical or health advice

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[1] World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. 2003.

such as keeping to a diet or making lifestyle changes. This research deals mainly with i) reviewing literature on adherence measures and ii) simulating data to compare and evaluate the measures.

3. Brief discussion of literature.

The breath of the literature on adherence, compliance and persistence lends itself to a much longer discussion than that allowed within the confines of this paper. Nevertheless, two papers will be briefly discussed to give a flavor of what has been written on this topic.

Adherence can be and often is measured along several dimensions. Methods for Measuring and Monitoring Medication Regimen Adherence in Clinical Trials and Clinical Practice by Kevin C. Farmer (1999) provides a overview of adherence measures currently employed. This paper looks at both direct (e.g. detection of the drug or a metabolite in a biologic fluid) and indirect (e.g. prescription records) adherence measures and discusses their respective advantages and disadvantages. Due to the more quantitative data needs of this research, the focus will be on prescription records.

Estimating Medication Persistency Using Administrative Claims Data by Rishi Sikka, Fang Xia and Ronald E. Aubert (2005) gives a more thorough treatment of the three quantitative measures more commonly used, which are i) persistency as a function of the medication possession ratio (MPR), ii) persistency as a function of medication availability at a fixed point in time and iii) persistency as a function of the gaps between refills. These three measures will be implemented in the data set and the results examined.

4. Simulation[2].

A patient's medicine taking pattern can be broken down into i) whether or not medication is consumed and ii) whether or not a prescription is refilled in a timely manner. Therefore, in order to properly evaluate the adherence measures, both medicine consumption and prescription refill will need to be considered.

A simulation has the benefit of allowing control over the subjects' intrinsic medicine-taking and refill parameters. This permits implementation and comparison of various measures of adherence while having the unusual luxury of knowing the intrinsic characteristics *beforehand*, something that is difficult to do in real life.

For the simulation, a universe of 30,000 patients was generated, and each patient's pill-taking (whether or not a patient took his pill on a particular day) and refill behavior (whether or not a patient refilled on a particular day) for 360 days was tracked. In an ideal world, each patient would take a pill every day, and would refill in a timely manner every month.

Each patient is randomly assigned an intrinsic adherence factor p, between 0.5 and 1. This parameter influences both a patient's pill-taking and refill tendencies. Each day, a random number between 0 and 1 is generated, and if that number is less than p, the patient takes a pill, if available. Then the relationship between pill-taking and refill behavior was considered. It seemed to make sense that the better one is at taking one's medication, the better one would be at refilling. Thus, it was hypothesized that there is a positive correlation, not necessarily linear, between pill-taking and refill. Using the equation $p(\text{refill}) = 1 - (1 - p^{\gamma})^{-30}$, three "worlds", denoted by different values for γ, were

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[2] A copy of the MATLAB code is attached as Appendix A.

then considered in modeling the relationship between pill-taking and refilling

probabilities. Figure 4.1 shows the relationship between pill-taking and refill probabilities
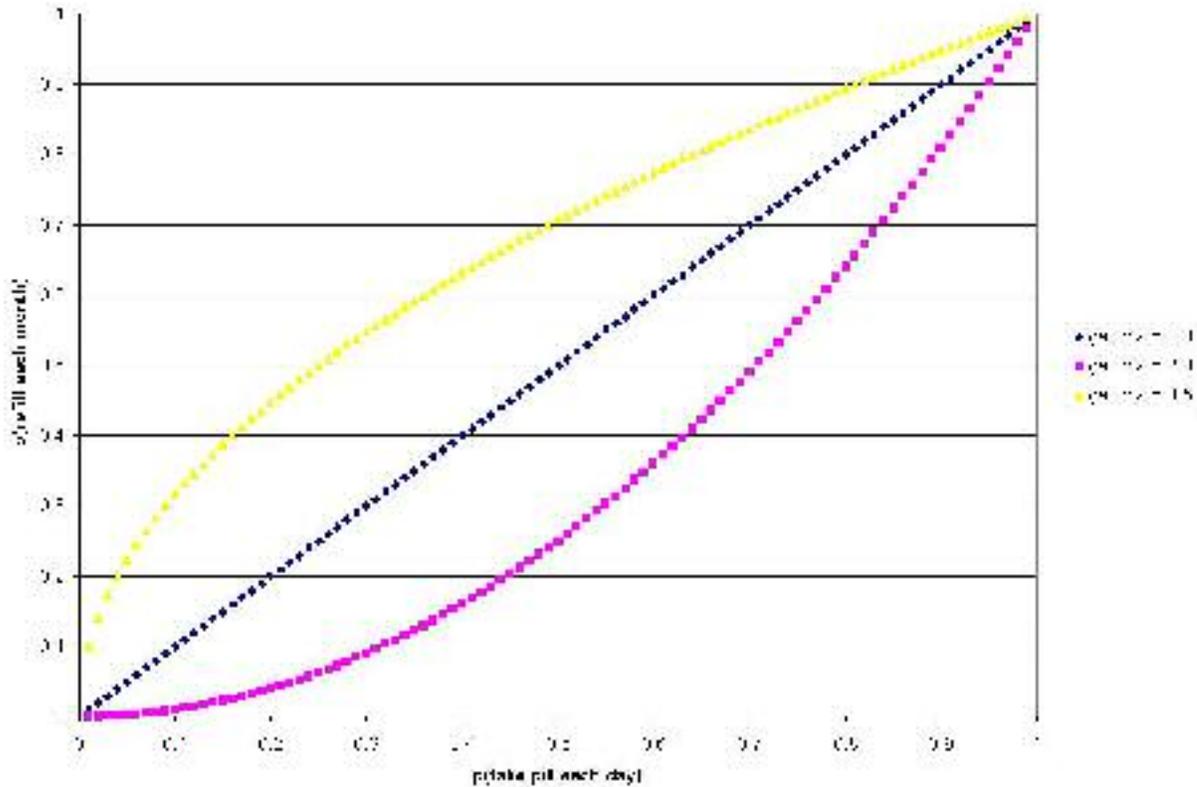
that are used for this simulation.

Figure 4.1

The refill probability works in a similar way to the pill-taking. On days when a

patient is eligible[3] to refill, a random number is drawn and if that number is less than a

patient's refill probability, then the patient refills.

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[3] In this simulation, a patient's eligibility to refill is governed by the number of pills a patient has left: if a patient has less than 10 days supply of pills left, he is eligible to try to refill. This number can be varied in future simulations to test how this assumption affects the results. In the real world, under most insurance plans, a patient is eligible to refill when they have about 10 days supply of pills left, as calculated from their latest refill date.

5. Measures.

There are 3 main measures based on refill and pill count and these measures will be implemented in the data set generated:

i) Medication Possession Ratio (MPR). This measures the percentage of time a patient has access to medication[4]. "Access to medication" can be measured along two dimensions: by a patient's refill count or pill count.

ii) Medication availability at a fixed point in time. Checkpoints are setup within the study period and if a patient possesses medication on the specific pre-designated date, then he is classified as persistent from the initial prescription until that date, for that entire length of time.

iii) Gaps between refills. A maximum window of time is allowed between refills, varying from one and a half to six times the refill supply depending on the medicine and ailment. If a patient refills within the allotted time frame, the patient is considered adherent.

In the real world, prescription refill is a component that can be easily observed via pharmacy or claims data, while actual medication consumption typically constitutes the unobservable component as data on medication consumption can be impractical and/or costly to collect. Therefore, besides comparing among the three main measures, we are also comparing *within* each measure. What this means: is MPR by pill count better than MPR by refill? If so, does it have a big enough edge to justify the extra costs involved?

For medication availability at a fixed point in time and gaps between refills, the question of how do "forgiving" measures stack up against "unforgiving" measures is examined. The measures, by default, are "unforgiving", meaning they capture the first

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[4] The MPR is a continuous variable by this definition. It can also be viewed as dichotomous variable when a cut-off point is chosen, e.g. 85%. Therefore a patient who has an MPR greater than 85% is considered adherent while a patient who has an MPR less than 85% is considered non-adherent.

time a patient becomes non-adherent, and considers patient behavior beyond that point to be non-adherent. Conversely, "forgiving" measures capture the most recent time a patient is adherent, and considers the patient adherent for the entire period of time prior to that point.

A profile of four patients, as shown in Figure 5.1, will be used to illustrate how different adherence measures are applied. It is assumed that all patients obtain their initial refill at the beginning of the study period. This is denoted by an I at the start of their timeline. The dotted vertical lines indicate the points at which each patient will need to refill if they faithfully take their medication each day while the green circles indicate the actual pill consumption by each patient.
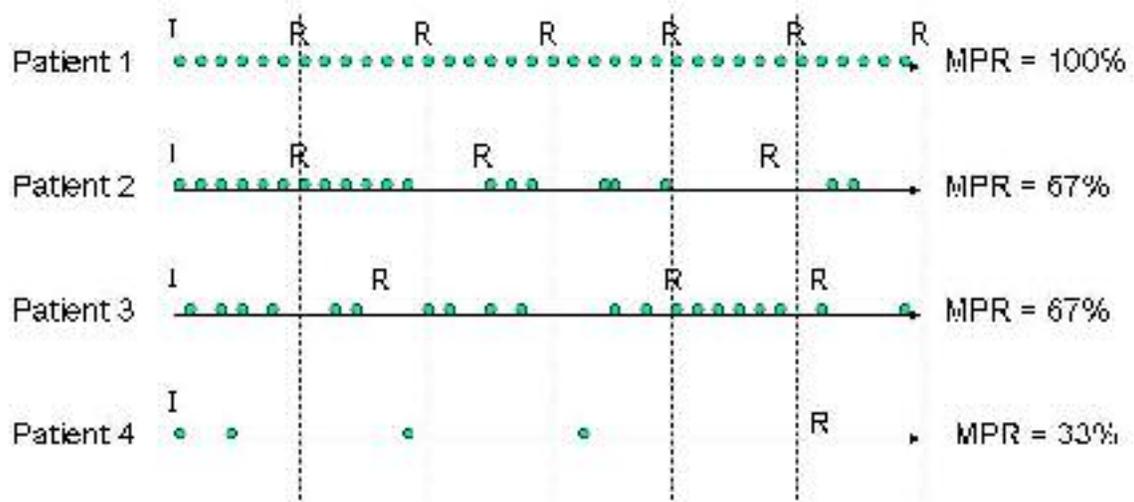
Medical Possession Ratio (MPR)

Figure 5.1

Since MPR measures the percentage of time a patient is in possession of medication, patient 1 is 100% adherent under MPR by both pill count and refill count. Patients 2 and 3 both consumed two-thirds of the total pills and obtained four courses of

medication out of a total possible six, hence their MPR is 67%. Patient 4 consumed one-third of the total pills and only obtained 2 courses of medication, hence his MPR is 33%.

Medication Availability at Fixed Points in Time

The same patient profiles from before is retained and used to examine the measure of adherence as a function of medication availability at fixed points in time. The red dotted lines in Figure 5.2 represent the pre-designated points at which an evaluation of a patient's adherence is carried out. A patient is therefore considered adherent if he refilled within one period of the red dotted line.
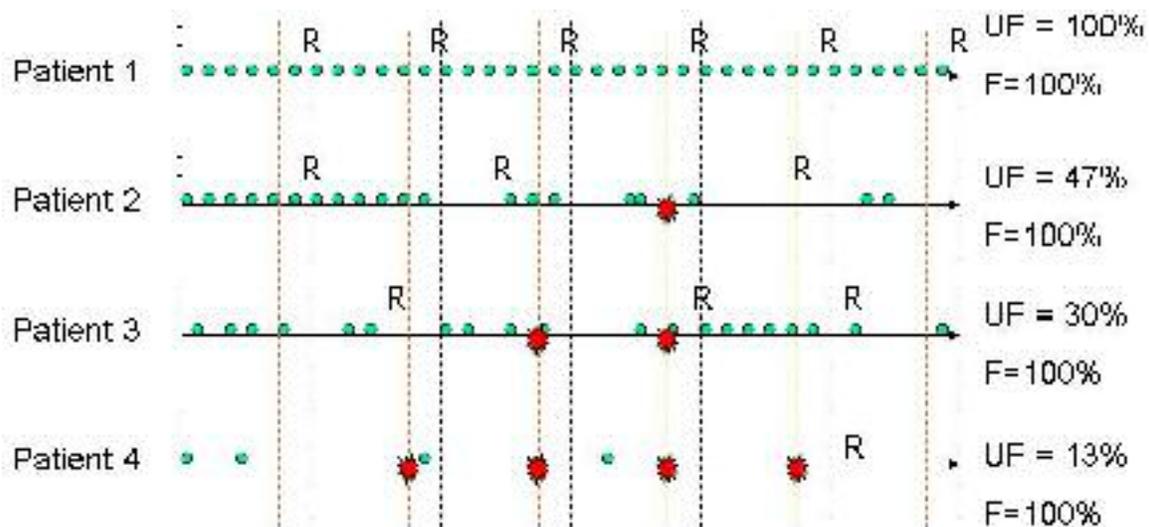

Figure 5.2

Patient 1 dutifully takes his pills and refills and is therefore 100% adherent under both the "unforgiving" and "forgiving" measure of medication availability at fixed points in time. Patient 2 is non-adherent at checkpoint 4, and this is picked up by the "unforgiving" measure. The "unforgiving" measure then considers the patient adherent up to the last checkpoint (checkpoint 3), and this yields an adherence rate of 47%. The "forgiving" measure however, looks at the most recent time Patient 2 is adherent

(checkpoint 6), and thus the patient is considered 100% adherent. The same logic applies to Patient 3 and Patient 4.

Gaps Between Refills

Adherence as measured by gaps between refills is then applied to the same patient profiles. The maximum allowable gap between refills is specified in this case to be one and a half times the refill supply; in Figure 5.3, this window is denoted by the purple double sided arrows.
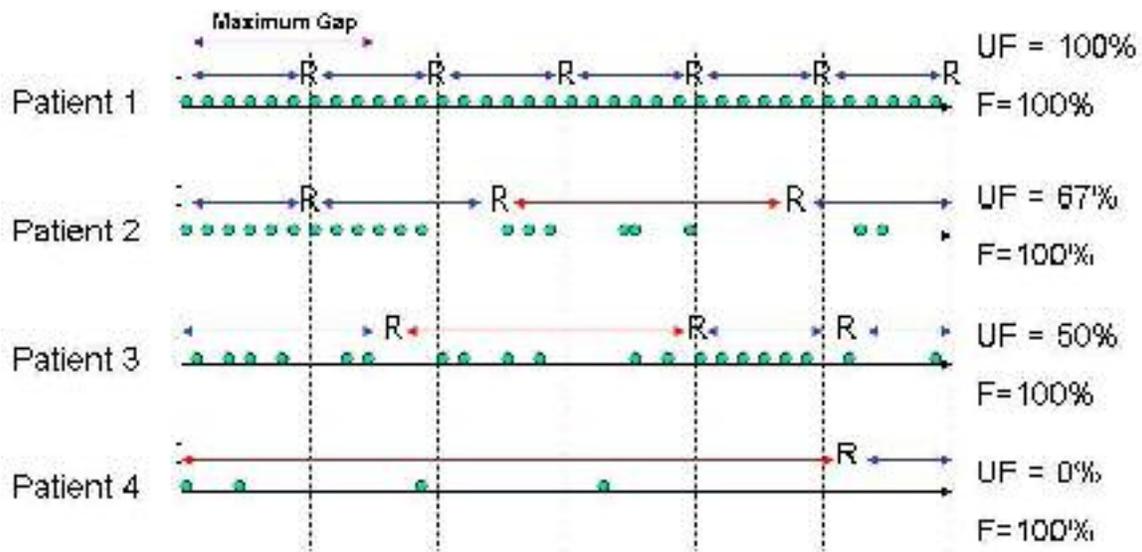
Figure 5.3

The gaps between refills for Patient 1 are all the size of one time the refill supply; hence Patient 1 is considered adherent under the "unforgiving" and "forgiving" measure of gaps between refills. The gap between Patient 2's second and third refill is greater than the maximum allowed, and this is picked up by the "unforgiving" measure. The "unforgiving" measure then considers the patient adherent up to one and a half times the refill supply past the latest refill before non-adherence (the second refill) and this yields an adherence rate of 67%.

The "forgiving" measure however, looks at the most recent time Patient 2 is adherent. The last gap before the end of the study is less than the maximum and thus the patient is considered 100% adherent. The same logic applies to Patient 3 and Patient 4.

Table 4.1 summarizes the adherence rates for the four patients under different measures. Different measures differ on the extent to which they report each patient's adherence. A caveat: notice that the "forgiving" measures are all at 100%. One might be tempted to conclude that the "forgiving" measures are a poor reflection of a patient's true adherence. However, the perfect adherence rates occurred by design as all four patients exhibited an eagerness to resume treatment at towards the end of the study period. If the patients were sloppy for a brief period in the beginning of the study period, but got their act together after that, the "forgiving" measures may then paint a more accurate picture than the "unforgiving" measures.

	MPR	Fixed Points in Time		Gaps between Refills	
		Unforgiving	Forgiving	Unforgiving	Forgiving
Patient 1	100%	100%	100%	100%	100%
Patient 2	67%	47%	100%	67%	100%
Patient 3	67%	30%	100%	50%	100%
Patient 4	33%	13%	100%	0%	100%

Table 4.1

6. Results.

To evaluate and compare the different measures, we consider the correlation of each measure with p. Figure 6.1 plots the correlation of each measure[5] with p against different values of γ.

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[5] A legend for the graphs:
m1: MPR by refill count
m2: MPR by pill count
m3_1: "Unforgiving" Medication Availability at Fixed Point in Time
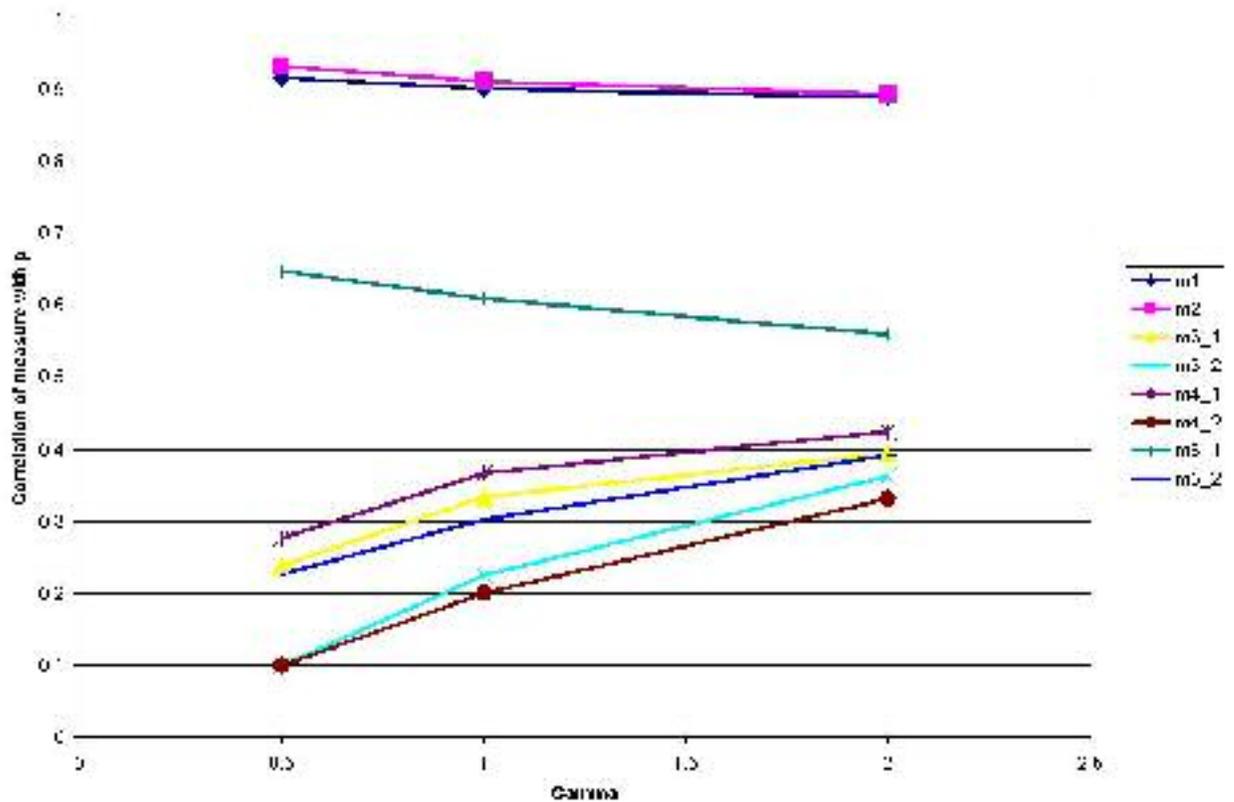m3_2: "Forgiving" Medication Availability at Fixed Point in Time

Figure 6.1

The correlation of each measure with *p* is fairly constant across different worlds; hence the measures are fairly robust to changes in refill behavior. The MPRs by refill count and pill count have the highest correlation with *p* across all three worlds. It also appears that there is not a significant difference between the performance of MPR by refill count and pill count. This indicates that refill data is sufficient as a marker of a patient's intrinsic adherence factor; and negates the need for the cost and other hurdles involved in gathering information on pill count.

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m4_1: "Unforgiving" Gaps between refills by actual days supply of medication left
m4_2: "Forgiving" Gaps between refills by actual days supply of medication left
m5_1: "Unforgiving" Gaps between refills by most recent refill
m5_2: "Forgiving" Gaps between refills by most recent refill

Table 6.1 shows a comparison of "unforgiving" measures against "forgiving" measures. It can be seen that purely "unforgiving" measures are have a higher correlation with p than purely "forgiving" measures. Further investigation can be made to examine measures that are a hybrid between purely "forgiving" and "unforgiving" measures.

	Medication Availability at Fixed Points in Time			Gaps between Refills by Actual Days Supply Left			Gaps between Refills by Most Recent Refill		
Gamma	0.50	1.00	2.00	0.50	1.00	2.00	0.50	1.00	2.00
Unforgiving	23.38%	27.24%	63.34%	30.46%	34.68%	59.54%	40.81%	44.61%	57.65%
Forgiving	10.64%	11.09%	24.15%	20.97%	19.51%	30.08%	37.77%	34.29%	41.08%

Table 6.1

7. Future research questions that stem from the research.

This simulation is a preliminary sketch of a model of patient behavior; bells and whistles can be added to make the model more robust. For example, the intrinsic adherence factor, p, may not need to be constant over the study duration for each patient - heterogeneity in p over time can be considered. In addition, a more complicated model of the relationship between refill and pill-taking probability may more realistically model patient behavior. Another parameter can try to control for the type of medication / malady.

Due to time constraints, not all research issues of interest related to this topic can be covered. Whereas the research here is backwards-looking in the sense that it takes data on patient behavior and uses adherence measures to evaluate how adherent a patient is, a forward looking extension would be to investigate a model that accurately projects out the survival curve (i.e. graph of adherence rates vs. time) given an initial set of data. A potential model could be the shifted beta-geometric probability model developed by Peter S. Fader and Bruce G.S. Hardie and is outlined in the paper "A Simple Probability Model

for Projecting Customer Retention" (2005). This probability model is chosen because of its success in projecting retention rates relative to more conventional regression models. Taking the viewpoint that adherence rate is merely a specific case of customer retention, one can appreciate the use of the shifted beta-geometric model for adherence rates even though the model was originally developed for customer retention in the more traditional sense.

Successful projection of the "unperturbed" survival curve would be particularly useful in gauging the effects of interventions (e.g. education in self-management, pharmacy management programs) or an advertising campaign on adherence rates. This can be done by comparing the projected survival curve obtained from the model to the observed survival curve obtained from actual data.

Biography

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APPENDIX A
MATLAB Code

```
numPatients = 10000;
numDays = 360;
daysRefillPossible = 10;
refillSize = 30;
minSupplySpecTime = 1;

% outputs
tdnt(1:numDays, 1:numPatients) = 0; % did patient take medicine on day x
refill(1:numDays, 1:numPatients) = 0;

% test
dsl(1:numDays, 1:numPatients) = 0;

% generate data patient by patient
for j = 1:numPatients
pillsTaken(j) = 0;
numRefills(j) = 0;

%reset flags for each patient
flag_st = 1;
flag_gap =1;
flag_LRD = 1;

% MEDICINE TAKING PARAMETERS
p (j,1) = rand/2 + 0.5; % intrinsic compliance factor

% value of gamma changed for each set of data
gamma(j,1) = 2.0;

%REFILL PARAMETERS


    % initialization of daily tracking variables
```

```
daysSupplyLeft = refillSize; %+days of supply left = pills_left, -#days since supply ran out (measured at start of day before taking pills)
latest_refillDay(j,1) = 0;

for i = 1:numDays

    % refill
    if (daysSupplyLeft < daysRefillPossible)
        prob_refill = 1 - (1 - p(j)^gamma(j))^(1/30);
        if (rand < prob_refill)
            refill(i,j) = 1;
            latest_refillDay(j,1) = i;

            if (daysSupplyLeft > 1)
                daysSupplyLeft = daysSupplyLeft + refillSize;
            else
                daysSupplyLeft = refillSize;
            end
        end
    else refill(i,j) = 0;

    end

% if random number is less than prob, patient will try to take medicine

    if (rand < p(j))
        if(daysSupplyLeft < 1)
            tdnt(i,j) = 0;
            daysSupplyLeft = daysSupplyLeft - 1;
        else
            tdnt(i,j) = 1;
            daysSupplyLeft = daysSupplyLeft - 1;
        end
    else
        if(daysSupplyLeft < 1)
            tdnt(i,j) = 0;
            daysSupplyLeft = daysSupplyLeft - 1;
        else
```

```matlab
            tdnt(i,j) = 0;
            daysSupplyLeft = daysSupplyLeft;
        end
    end


    dsl(i,j) = daysSupplyLeft;

% M3_1: Persistence at a function of medical possession at a fixed point in
% time (day 20, 50, 80 etc.)
% Unforgiving : Records first-time offender

    if(flag_st == 1)
            if( mod((i+10),30) == 0)
                    if (dsl(i,j) > minSupplySpecTime)

                    measure_3_1(j,1) = i / numDays;

        else
        flag_st = 0
                    end
            end
    end

%M3_2 : Persistence at a function of medical possession at a fixed point in
% time (day 20, 50, 80 etc.)
% Forgiving : Records most recent time of compliance

            if( mod((i+10),30) == 0)
                    if (dsl(i,j) > minSupplySpecTime)

                    measure_3_2(j,1) = i / numDays;

                end
        end

% M4_1: Persistence as a function of gaps between refills
% "Unforgiving"
```

```matlab
        if (flag_gap == 1)
                if (dsl(i,j) > -15 )
                        measure_4_1(j,1) = i / numDays;

            else
               flag_gap = 0;
                   end
        end

% M4_2: Persistence as a function of gaps between refills
% "Forgiving"
                if (dsl(i,j) > -15 )
                        measure_4_2(j,1) = i / numDays;

        end
% M5_1: Persistence as a function of gaps between refills
%Unforgiving

if(flag_LRD ==1)
    if((latest_refillDay(j,1) + 45) > i)
       measure_5_1(j,1) = i/numDays;

    else
        flag_LRD = 0;
    end
 end

% M5_2: Persistence as a function of gaps between refills
% Forgiving

    if((latest_refillDay(j,1) + 45) > i)
       measure_5_2(j,1) = i/numDays;
    end


   % end numDays for Patient j
   end
```

```matlab
    pillsTaken = sum(tdnt);
    numRefills = sum(refill);

% M1: Medical Possession Ratio I
measure_1(j,1) = (numRefills(j) + 1) * 30 / numDays;
if (measure_1(j,1) > 1)
    measure_1(j,1) = 1;
end

% M2: Medical Possession Ratio II
measure_2(j,1) = pillsTaken(j) / numDays;

end
summary = [p, gamma, pillsTaken', numRefills', measure_1, measure_2, measure_3_1, measure_3_2, measure_4_1, measure_4_2, measure_5_1, measure_5_2];
```