

# **Addressing Medication Non-Adherence through Implementation of an Appointment-Based Medication Synchronization Network**

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## Executive Summary

The management and treatment of patients with chronic diseases accounted for eighty-six percent of the total health care spend in America in 2010, yet only 50% of those on chronic medications adhere to their prescription therapy. Prescription medications are an important tool for the management of chronic diseases. Medication adherence and persistence are critical to positive patient outcomes.

Pharmacists across the nation are helping patients improve adherence by offering a high touch and personalized adherence program called Appointment-Based Medication Synchronization (ABMS). This model helps patients manage their prescriptions through a monthly appointment to refill medications and scheduled interactions with the pharmacist. By simplifying the pharmacy's workflow, the pharmacist has more time for valuable patient interactions and other services that help improve health outcomes. Patients' personal connection with a pharmacist or pharmacy staff is the number one predictor of medication adherence.

Thousands of independent pharmacy innovators nationwide are helping patients improve adherence through ABMS. In order to determine the impact of pharmacist-provided ABMS programs across a virtual network of ABMS pharmacies, the National Community Pharmacists Association, working in collaboration with the Arkansas Pharmacists Association, engaged the services of PrescribeWellness to provide the underlying technology platform that could facilitate the delivery of ABMS. The study measured the collective impact of ABMS on medication adherence and persistence rates across 82 independently-owned pharmacies (operating on 13 unique pharmacy management systems) in the state of Arkansas.

Data was collected retrospectively from May 7, 2014 to May 31, 2015. There were two arms of this study, 'enrollees' and 'controls.' Study participants were required to have two 30-day or greater prescriptions for a chronic medication. We examined medications in nine classes: beta blockers, biguanides, calcium channel blockers, dipeptidyl peptidase-IV inhibitors, non-warfarin anticoagulants, renin-angiotensin system antagonists, sodium glucose transporter-2 inhibitors, statins, and sulfonylureas. Enrollees and controls were matched on medication class, pharmacy urbanicity, follow-up time, age, and sex. Adherence was measured using the proportion of days covered (PDC) and non-persistence was examined using the date of discontinuation of an eligible chronic medication.

ABMS patients were significantly more adherent and more persistent across all drug classes. Patients in an ABMS program were 2.57 times more likely to be adherent compared to controls. Finally, when comparing persistence, ABMS enrollees were 21% less likely to discontinue therapy than matched controls.

This study demonstrates that the high touch community pharmacy-based ABMS can significantly improve patient adherence and persistence. Medication adherence has been shown to improve health outcomes and decreases total healthcare costs. In addition, community pharmacists have been very successful at tailoring the core components of ABMS into many different operational models. Despite these differences in approach, each pharmacist-driven model works and produces consistently positive results.

## Introduction

Prescription medications are an important tool for the management of chronic diseases. However, medications are most effective if taken at appropriate doses in correct quantity and at appropriate time intervals. Medication adherence and persistence are critical to positive patient outcomes.<sup>1</sup> The management and treatment of those with chronic disease accounted for eighty six percent of the total health care spend in America in 2010,<sup>2</sup> yet only 50% of those on chronic medications adhere to their prescription therapy.<sup>3</sup>

Medication adherence refers to the extent of patient compliance with prescribed dosing and interval recommendations; whereas, persistence is the length of time between the initiation of a drug therapy and its discontinuation. These issues are important not only for the clinical outcomes of individual patients but also as a major public health concern. Taken together, non-adherence and non-persistence results in excess costs to the health care system that total in the hundreds of billions of dollars each year.<sup>4</sup>

Pharmacists across the nation are helping patients improve medication adherence by offering a high-touch and personalized adherence program called Appointment-Based Medication Synchronization (ABMS). This model helps patients manage their prescriptions through a monthly appointment to refill medications and scheduled interactions with the pharmacist. By simplifying the pharmacist's workflow, the pharmacist has more time for valuable patient interactions and other services that help improve health outcomes. Patients' personal connection with a pharmacist or pharmacy staff is the number one predictor of medication adherence.<sup>3</sup>

Research confirms the critical role that pharmacists play in providing patients with the assistance necessary to maintain high levels of medication adherence. In particular, refill coordination at a single pharmacy is recognized as an effective tactic to improve adherence. The National Community Pharmacists Association (NCPA) developed a program called Simplify My Meds<sup>®</sup>, which is based on the concept of refill synchronization and coordinates all of a patient's prescriptions to be filled on the same day each month. The ABMS model was pioneered in the 1990s by John Sykora, an independent pharmacist-owner in Long Beach, California. The model helps patients manage their prescriptions through scheduled visits and discussions with their pharmacist. Unlike automatic refill programs, the ABMS builds upon established pharmacist-patient relationships to provide high-touch interactions.<sup>5</sup>

Other literature suggests ABMS methodologies are effective at increasing patient adherence and persistence.<sup>3,5-7</sup> The most comprehensive look at an ABMS intervention was published in 2015 and examined implementation in a single pharmacy chain consisting of 71 pharmacies in 20 Ohio counties.<sup>8</sup> This study showed that ABMS was associated with significantly better adherence and persistence across all examined drug classes. Thousands of independent pharmacy innovators nationwide are helping patients improve adherence through ABMS, yet little research on the overall impact of ABMS across a large group of independent pharmacies exists.

In order to determine if independent pharmacies could come together to form a virtual network of ABMS pharmacies to improve adherence, NCPA, working in collaboration with the Arkansas Pharmacists Association (APA) and 82 Arkansas pharmacies, engaged the services of PrescribeWellness to help conduct a study to assess the impact of a patient-centric ABMS on

patients' adherence to their medications. Due to the number of pharmacy management systems (PMSs) utilized by independent pharmacies, NCPA sought a vendor to provide the underlying technology platform that could both facilitate the delivery of ABMS and provide data to measure the aggregate impact this model can have on medication adherence rates.

Despite operating more than a dozen distinct PMSs, this network of pharmacies was bound together by the common technology platform provided by PrescribeWellness. This ABMS-enabling technology platform facilitated the delivery of ABMS in a standardized fashion across multiple PMSs. The objective of this study was to measure the collective impact of ABMS on medication adherence and persistence rates across a network of independent pharmacies. Additionally, as health care moves to a value-based system, a non-research objective of this study was to understand how community pharmacies could come together to form a virtual network of pharmacies to improve adherence.

The project officially launched in May 2014 with 82 pharmacies participating. Some pharmacies were delayed in their ability to enroll patients due to data connectivity to their PMS. Data was accessed by PrescribeWellness through direct interface to PMSs or via nightly reports uploaded to PrescribeWellness by the pharmacy.

## Methods

### Study Design

This retrospective cohort study examined records from patients that filled prescriptions at 82 independent pharmacies in Arkansas between May 7, 2014 and May 31, 2015. Prescription fill records and patient data were collected during the study period for all patients at these pharmacies. For inclusion in the study, patients must have been at least 18 years of age at the time of their first prescription and had at least two fills for 30 days or more of a chronic medication falling into one of 13 classes (antiretrovirals, beta blockers, biguanides, calcium channel blockers, dipeptidyl peptidase [DPP]-IV inhibitors, meglitinides, incretin mimetics, non-warfarin anticoagulants, renin-angiotensin system [RAS] antagonists, sodium glucose transporter-2 [SGLT2] inhibitors, statins, sulfonylureas, and thiazolidinediones). Patients could be included in more than one medication class group if they met the inclusion criteria independently for each. For ABMS patients, fills were counted after the date of enrollment in the program, control patients were included if two fills occurred after the beginning of the study period. Patients were required to have a minimum of sixty days of data after their first fill to allow for adequate follow-up. Patients with invalid demographic data or those at pharmacies with no enrollees were excluded.

### Enrollment

Although all patients at participating pharmacies were eligible to enroll in the ABMS program, those patients with multiple, chronic medications were targeted for inclusion. Patients meeting this criterion were approached by a pharmacy staff member and given information about the program and the opportunity to opt-in. Patients opting-in to the program signed a form acknowledging their acceptance of the terms of the intervention.

### Intervention

In the ABMS model, pharmacies coordinate a patient's prescriptions onto a single appointment day each month. This simplification is shown to increase patient adherence by decreasing gaps between refills, decreasing regimen complexity, and providing an opportunity for continual interaction between pharmacists and patients to review all of the patient's medications on a monthly basis to ensure safe and appropriate use.

Pharmacies participating in this study employed Simplify My Meds<sup>®</sup> (an ABMS program developed by NCPA) and StarWellness (the medication synchronization module through PrescribeWellness). Simplify My Meds is an adherence program that provides pharmacists with training, resources, and marketing materials to help support the implementation of ABMS. Through these programs, pharmacies (1) synchronized refills for the patient on a single 'appointment day', (2) contacted the patient 7-10 days prior to the appointment day to review his/her medications (allowing for changes to prescriptions [i.e. discontinuations, no refills, recent hospitalizations, etc.] to be handled ahead of time), (3) reviewed the orders one-day before the appointment day to resolve any clinical issues, and (4) reminded the patient of their appointment day one day prior to their appointment day, and (5) met

with the patient on the appointment day to discuss any outstanding issues, provide counseling, or patient services (MTM, immunizations). Pharmacy onboarding and ongoing implementation support was provided by the APA, NCPA, and PrescribeWellness.

## Measures

The outcomes of interest for this study were medication adherence and medication non-persistence. Adherence was measured using the proportion of days covered (PDC) i.e. the proportion of days in the measurement period that a patient had a 'days supply' of a medication according to their prescription fill record. To be consistent with similar studies in this literature, a PDC threshold of 0.8 was chosen as the line between adherent and non-adherent.<sup>6,7</sup> Non-persistence was examined using the date of discontinuation of a chronic medication i.e. the date the patient stopped taking the medication for 30 days or more. (See Glossary for more detail)

## Data Analysis

The analysis period for this study was May 7, 2014 to May 31, 2015. Patients that participated in the ABMS program were included in the analysis beginning on the date of their first qualifying medication fill following enrollment in the program. Control patients were included in the analysis from the first qualifying medication fill within the study period. Qualifying medications were those medications with at least two fills with a day supply of at least 30 days that fell in one of the chronic medication categories listed above. Only patients that met inclusion criteria between May 7, 2014 and April 1, 2015 were included in the study to allow at least 60 days of follow-up

Patients enrolled in the ABMS program were matched with up to 5 comparison patients based on medication class, pharmacy urbanicity (based on United States Department of Agriculture 2013 Rural-Urban Continuum Codes), follow-up time (+/- 15 days), age (+/- 5 years), and sex. Therefore, matched patients are enrollees and controls with the same sex, similar age, similar length of follow-up, receiving a medication in the same class, from a pharmacy in a similar setting. If fewer than 50 enrollees remained within a drug class after matching, that medication class was excluded from analysis.

Descriptive statistics were collected and adherence and non-persistence were compared. The Wilcoxon signed-rank test was used to compare PDC between the two groups due to the matched enrollees and comparison patients and the non-normality of the measure. Univariate logistic regression was used to predict the odds of adherence (PDC  $\geq$  0.8) for patients in the ABMS and comparison groups. Non-persistence was estimated using the time to discontinuation of the medication in a univariate Cox proportional hazards regression. We assumed patients continued in the program until the end of data collection following the 'intention-to-treat' principle commonly used in similar analyses. All analyses used an alpha of  $<0.05$  to define statistical significance. Data analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and Stata version 13 (Stata Corp., College Station, TX).

**Pharmacy and Patient Sample Flowchart**

Data was collected from a total of 82 pharmacies with 7,378 unique ABMS enrolled patients and 608,479 unique non-enrolled patients. This averages to 90 ABMS enrollees and 7,420 controls per pharmacy. Patients could be included in the analysis for each drug class which they independently met inclusion criteria. Table 1 shows the total pharmacies and the total patient-drug class pairs that were enrolled or considered a control at each stage of this process.

**Table 1: Pharmacy and Patient Sample Flowchart**

	Pharmacies			Enrollees (by drug class)			Controls (by drug class)			Total patients
<b>Total Sample</b>	82			8,355			667,380			675,735
<b>Exclusion criteria:</b>	Entering step	Meeting exclusion	Exiting Step	Entering step	Meeting exclusion	Exiting Step	Entering step	Meeting exclusion	Exiting Step	Exiting Step
<b>Remove all patients with invalid gender</b>	82	17	65	8,355	2,116	6,239	667,380	104,461	562,919	569,158
<b>Remove all pharmacies having no enrollees</b>	65	5	60	6,239	0	6,239	562,919	13,110	549,809	556,048
<b>Inclusion criteria:</b>	Entering step	Meeting exclusion	Exiting Step	Entering step	Meeting exclusion	Exiting Step	Entering step	Meeting exclusion	Exiting Step	Exiting Step
<b>At least one prescription for any eligible medication</b>	60	0	60	6,239	10	6,229	549,809	360,620	189,189	195,418
<b>At least two 30-day fills of any eligible medication</b>	60	0	60	6,229	1,196	5,033	189,189	142,098	47,091	52,124
<b>Be at least 18 years of age</b>	60	0	60	5,033	16	5,017	47,091	503	46,588	51,605

The matching process successfully matched 4,298 (86%) enrollees and 17,661 (38%) controls; patients were taken from all 60 eligible pharmacies. After matching, antiretrovirals (n=4), meglitinides (n=1), incretin mimetics (n=13), SGLT2 inhibitors (n=35), and thiazolidinediones (n=43) were excluded from the analysis. All remaining drug classes had over 100 enrollees matched to at least 200 control patients.

## Mean PDC Score (Adherence) of Enrollees and Controls by Drug Class

The proportion of days covered (PDC) impact for ABMS enrollees and controls was analyzed and the results are presented in Table 2. Adherence as measured by PDC was significantly greater in the ABMS enrollees than in controls across all drug classes studied. Enrollees were 13% more adherent than controls during the study period. Broken down by therapy type, the greatest differences in PDC scores between enrollees and controls were seen in some oral diabetic agents (biguanides and DPP-IV inhibitors) and non-warfarin anticoagulants.

**Table 2: Mean PDC Score (Adherence) of Enrollees and Controls by Drug Class**

	Enrollees			Controls			Mean PDC Diff	p-value
	n	Mean PDC	SD	n	Mean PDC	SD		
<b>OVERALL IMPACT</b>	<b>10342</b>	<b>0.86</b>	<b>0.195</b>	<b>48819</b>	<b>0.73</b>	<b>0.252</b>	<b>0.13</b>	<b>&lt;0.001</b>
<b>Beta Blockers</b>	1971	0.85	0.199	9569	0.73	0.256	0.12	<0.001
<b>Biguanides</b>	1039	0.84	0.206	4666	0.71	0.255	0.13	<0.001
<b>Calcium Channel Blockers</b>	1351	0.87	0.188	6450	0.75	0.255	0.12	<0.001
<b>DPP-IV Inhibitors</b>	108	0.83	0.216	241	0.69	0.271	0.14	<0.001
<b>Non-Warfarin Anticoagulants</b>	103	0.83	0.220	219	0.68	0.277	0.15	<0.001
<b>RAS Antagonists</b>	2707	0.86	0.185	13346	0.75	0.249	0.11	<0.001
<b>Statins</b>	2465	0.86	0.197	12092	0.74	0.249	0.12	<0.001
<b>Sulfonylureas</b>	598	0.84	0.196	2236	0.75	0.240	0.09	<0.001



## Percent of Patients Adherent (PDC≥0.8) for Enrollees and Controls by Drug Class

The results presented in Table 3 are from the same matched sample as those in Table 2. The proportion of ABMS enrollees that were considered adherent (i.e. PDC ≥0.8), was significantly greater than in control patients. The overall odds ratio<sup>9</sup> (see Glossary) and for each drug class was significantly greater than one, ranging from 1.82 for sulfonylureas to 3.02 for DPP-IV inhibitors. An overall odds ratio of 2.57 indicates a 2.57 times greater likelihood for ABMS enrollees to be adherent than their peers.

**Table 3: Percent of Patients Adherent (PDC≥0.8) for Enrollees and Controls by Drug Class**

	% Adherent (PDC≥0.8)			95% Confidence Interval			
	Enrollees	Controls	Diff	Odds Ratio*	Low	High	p-value
<b>OVERALL IMPACT</b>	<b>75</b>	<b>54</b>	<b>21</b>	<b>2.57</b>	<b>2.50</b>	<b>2.64</b>	<b>&lt;0.001</b>
Beta Blockers	74	52	22	<b>2.60</b>	2.45	2.77	<0.001
Biguanides	71	48	23	<b>2.69</b>	2.47	2.93	<0.001
Calcium Channel Blockers	77	55	22	<b>2.81</b>	2.61	3.04	<0.001
DPP-IV Inhibitors	73	45	28	<b>3.02</b>	2.07	4.40	<0.001
Non-Warfarin Anticoagulants	72	43	29	<b>2.96</b>	2.00	4.38	<0.001
RAS Antagonists	76	56	20	<b>2.40</b>	2.27	2.52	<0.001
Statins	76	53	23	<b>2.77</b>	2.62	2.92	<0.001
Sulfonylureas	71	56	15	<b>1.82</b>	1.61	2.05	<0.001

\*An odds ratio above 1 indicates a favorable result for the ABMS enrolled patients.

## Mean Persistence (Time to Stay on Medication Regimen) for Enrollees and Controls

Table 4 shows that ABMS enrollees were significantly more likely to stay on their medication regimen as defined by mean persistence in days. Mean persistence (i.e. number of days taking medication before a gap of 30 days or more) ranged from 181 to 222 versus only 145 to 182 for matched controls. This resulted in a significant difference in the likelihood of non-persistence between the ABMS enrollees and matched controls overall and in each drug class examine represented by a hazard ratio<sup>10</sup> (see Glossary) of ranging between 0.67 and 0.83. The overall hazard ratio was 0.79 meaning enrollees were 21% less likely to discontinue therapy than matched controls.

**Table 4: Mean Persistence (Time to Stay on Medication Regimen) for Enrollees and Controls**

	Mean Persistence (Days)				95% Confidence Interval		
	Enrollees	Controls	Diff	Hazard Ratio*	Low	High	p-value
<b>OVERALL</b>	<b>205</b>	<b>173</b>	<b>32</b>	<b>0.79</b>	<b>0.78</b>	<b>0.80</b>	<b>&lt;0.001</b>
Beta Blockers	204	168	36	<b>0.78</b>	0.76	0.81	<0.001
Biguanides	201	162	39	<b>0.75</b>	0.72	0.78	<0.001
Calcium Channel Blockers	215	176	39	<b>0.76</b>	0.74	0.79	<0.001
DPP-IV Inhibitors	222	175	47	<b>0.71</b>	0.60	0.85	<0.001
Non-Warfarin Anticoagulants	181	145	36	<b>0.75</b>	0.62	0.91	<0.001
RAS Antagonists	206	176	30	<b>0.82</b>	0.80	0.84	<0.001
Statins	211	174	37	<b>0.79</b>	0.77	0.81	<0.001
Sulfonylureas	210	182	28	<b>0.83</b>	0.78	0.88	<0.001

**\*A hazard ratio below 1 indicates a favorable result for the ABMS enrolled patients.**

### Impact on Adherence and Persistence

The difference in mean PDC for enrollees compared to controls was 13% and translated to 2.57 times greater likelihood to be adherent to medication therapy, demonstrating the significant value pharmacist-driven ABMS programs have on adherence improvement. This finding is in agreement with the current state of the ABMS literature. These findings have previously been shown in individual pharmacies and most recently in a large study of 71 members of a regional community pharmacy chain. This study demonstrates that similar results can be obtained through a large, virtual network of independent pharmacies operating on multiple PMSs. These results are important for patients, pharmacists, and payers.

Pharmacies in this study were diverse and not under common ownership. It is expected that pharmacies recruitment criteria, for example, may have included patients with two or more chronic medications while other pharmacies may have chosen to actively recruit those with four or more chronic medications. In addition, many pharmacies decided to send out a “recruitment call” to gauge interest in the program while other pharmacies chose to talk to patients in person. Workflow, staffing, PMS, and enrollment criteria were inherently different at most locations, however utilization of a common adherence technology program standardized the model.

### Pharmacy Network Learnings

As demonstrated by the 13% improvement in PDC scores across all drug classes studied, community pharmacies can successfully come together to form a virtual network aimed at improving adherence. Medication adherence is a large component of the Medicare Part D Star Ratings program and will continue to be an important as the health care system moves to outcomes measures and value-based payment models. The ability of these independently-owned community pharmacies to provide a standard level of care for patients is particularly important given the focus on quality outcomes. The research team identified the following points as key learnings from this project:

- Innately different community pharmacies can come together to form a virtual adherence network by utilizing a common technology to standardize the delivery of ABMS.
- Data accessibility across all pharmacies should be a primary consideration for future endeavors.
- Active pharmacy involvement including recruitment of patients is essential to the success of ABMS across a network.

For many of the pharmacies, data was populated in PrescribeWellness by a daily file transfer from the PMS nightly. Due to the small differences in data fields within each system, some pharmacies experienced some interoperability challenges including the inability to send daily files due to non-upgraded PMS, incomplete patient records due to non-matched fields from PMS, and incomplete patient records due to pharmacy-specific coding of patients in PMS. For example, one pharmacy used the “nursing home” note field to make a note about the patient’s preference for delivery. The patient was coded as a long term care patient and was excluded from the list of eligible patients. The technical support teams at all PMSs involved (Computer Rx, DAA (Visual Super Script), Lagniappe Pharmacy Services, Liberty Computer (RxQ), McKesson EnterpriseRx, McKesson Pharmaserve,

PDX, PioneerRx, Positrack, QS1, Rx30, RxMaster, Speed Script) and PrescribeWellness worked diligently to troubleshoot any potential issues with transmission for the pharmacies in the early stages.

Following the study launch, a few pharmacies voluntarily discontinued the program. Some pharmacies had staffing changes and turnover that made the pharmacy not conducive to a new program. Some members of the pharmacy staff were less interested in transitioning workflow to implement a new program. In addition, some pharmacies were delayed in their ability to enroll patients due to data connectivity.

## **Limitations**

This study has several limitations worth mentioning. While we matched patients on an extensive list of factors that were available in the data, we could not control for biases between the group that were not available in the data or that are not observable. Of primary concern is the non-random nature of selection into the ABMS group. Patients approached by pharmacies and those receptive to the idea of ABMS may be a fundamentally different population of patients than those that are not. Other concerns with the lack of data include insurance status and the overall complexity of the patient presentation.

Separate from these issues is the definitions of 'adherence' and 'persistence' used for this study. The determination of these outcomes was based on prescription fill data, based on this data it can be determined whether the prescription was picked up, but not whether the medication was actually taken or taken correctly. Further, no data on pharmacies outside the study network was available nor were patients within the network followed between pharmacies, so patients switching pharmacies would have been seen as discontinuing their medication.

## Conclusions

This study posed a unique opportunity for research on the value of an adherence network in an emerging value-based environment. This collaboration resulted in significantly improved adherence and persistence among ABMS enrolled patients when compared to matched controls overall and across every chronic medication class examined. This study demonstrates how a network of independently-owned pharmacies can come together, operating on multiple PMSs, to improve adherence. With the Centers for Medicaid and Medicare Services recent announcement to enhance the MTM program within Medicare Part D, pharmacies' ability to demonstrate the collective impact quality care makes on their patients will be of significant importance in years to come.

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## Glossary

**Proportion of Days Covered (PDC)** – The proportion of days in the measurement period “covered” by prescription fill data for the medication class.

**Adherence** – A patient is considered adherent when their Proportion of Days Covered for a given medication class is greater than or equal to 80%.

**Persistence** – The length of time in days between a patient receiving a drug in a given medication class and the patient having a gap of 30 days or greater in “covered” days or the end of the study period. When a patient has a gap of 30 days or more in “covered days, that patient is considered non-persistent.

**Odds Ratio**– A measure of association between an exposure and an outcome, specifically the association between participation in ABMS and adherence. An odds ratio greater than one signifies a positive association between the exposure and the outcome. The odds ratio is calculated in the following manner:

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

Where a=Adherent ABMS enrollees; b=Non-adherent ABMS enrollees; c=Adherent controls; d=Non-adherent controls. As an example, the rough calculation of the odds ratio from Table 3 for overall adherence would be:  $(75*46)/(54*25)=2.6$

For more information on odds ratios please see Szumilas, 2010 (reference 9).

**Hazard Ratio**– An expression of the chance of an event occurring in the treatment arm of a study vs the chance of the same event occurring in the control arm of the study. This is relevant when the outcome of an analysis is ‘time-to-event’. Specifically, the chance of a gap of 30 days occurring in the ABMS enrollees versus the chance of the same gap occurring in matched controls. A hazard ratio represents the ratio of these likelihoods when examining the time to a gap of 30 days or more in these groups.

For more information on hazard ratios see Spruance, 2004 (reference 10).