

Participation in an ambulatory e-pharmacovigilance system

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SUMMARY

Purpose There is growing concern about whether passive surveillance can detect adverse drug events (ADEs). Our objective was to demonstrate the reach of an interactive voice response system (IVRS) to systematically monitor symptoms experienced by ambulatory patients prescribed one of 31 medications, and to document whether there were differences in our ability to contact certain populations.

Methods Patients receiving a prescription for a target medication at one of 11 clinics were eligible for a cross-sectional IVRS survey, "e-pharmacovigilance," with a follow-up survey done 3 months later if the target medication was still listed on the patient's active medication list.

Results 902 patients participated, representing 43.3% of contacted and 25.7% of potentially eligible patients with a working phone. After adjustment for demographics and drug class, patients >66 years were more likely to participate than those 56–65 years (odds ratio 1.47; 95% confidence interval 1.19–1.81). Hispanics were less likely than whites (0.56; 0.42–0.76), and those in low-income communities less likely to participate than those in high-income communities (0.69; 0.58–0.82). Patients prescribed asthma, or seizure medications were more likely to participate than those prescribed medications for insomnia. Of patients reached by the system, those prescribed medications were erectile dysfunction and smoking cessation were less likely, and those prescribed seizure medication were more likely to participate.

Conclusions IVRS technology can be used to perform ambulatory e-pharmacovigilance for a broad spectrum of patients, particularly older individuals who may at particular risk for ADEs. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — adverse drug events; pharmacovigilance; survey methods

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INTRODUCTION

The safety of prescription drugs, particularly drugs recently approved by the food and drug administration (FDA), represents a major public health concern.^{1,2} While the FDA maintains a passive adverse event reporting system, it is estimated that only about 1% of all adverse drug events (ADEs) and 10% of serious ADEs are reported in primary care practice,^{3,4} and there are growing concerns about the ability of the current system to monitor prescription drug safety, particularly in a timely manner.^{5,6} Accurate ascertainment of ADEs requires an active, real-time system that monitors the symptoms experienced by individual

patients so that these data can be aggregated to look for symptoms that occur at greater than the expected rate among populations taking a medication.⁷

Interactive voice response system (IVRS) technology has the potential to systematically contact large numbers of patients to assess adherence as well as symptoms. This technology may be especially powerful when linked with electronic health records (EHRs), which contain medication lists and electronic prescribing information. IVRS is an automated telephone interviewing technique where a human interviewer is replaced by a high quality recorded interactive script to which the respondent provides answers that are recognized by the telephone keypad or even speech recognition. IVRS has been used for automated assessments of patients for adverse events post-hospital discharge, monitoring patients on anticoagulants, reminding patients to complete preventative care,

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support tobacco and substance abuse treatment, as well as managing chronic conditions including diabetes.^{8–12} Patients report a neutral to positive view of IVRS, and the technology has been used successfully in diverse populations.^{10–15} Several studies also suggest that data reported during an IVRS call are similar to those collected during a live interview.^{16–18}

However, relatively few studies have examined the reach, or the percentage of the population receiving the intervention,¹⁹ of IVRS-based interventions to monitor patients who have not previously been contacted or enrolled in a study to assess their eligibility or willingness to participate.²⁰ Assessing this capacity is of growing importance as health delivery systems try to reach ambulatory patients outside of the walls of a health care setting to promote self-care, improve patient-provider communication, assess adherence and problems, and promote prevention. While phone-based technology may not be as susceptible to the “digital divide” as internet-based technology,²¹ there are several important considerations for examining the reach of IVRS technology for population screening. Some potentially eligible individuals may never be contacted directly because of non-working phone numbers, calls that are never answered despite repeated attempts, calls that may be answered and refused by other household members (*i.e.*, refusal by proxy), and lack of information about language ability. For these reasons, true eligibility can be difficult to assess. It is also important to consider the inclusion of specific populations. In addition, it is useful to understand the stage at which certain patients are excluded as this may suggest design changes to improve participation.

To our knowledge, the use of this technology to perform systematic pharmacovigilance in primary care settings has not been examined. This paper details our early experience with the reach of this technology for this purpose.²⁰ Specifically, we were interested in documenting whether there were sociodemographic or clinical differences in our ability to contact certain populations. We hypothesized that the technology would be more acceptable to younger than older individuals, to white patients compared to other racial/ethnic groups, and less acceptable to patients taking medications erectile dysfunction because of greater privacy concerns around the use of these medications.

METHODS

Study design and setting

This observational study is currently being conducted in 11 primary care clinics affiliated with the Brigham

and Women’s Primary Care-Based Research Network (BW-PBRN) in the greater-Boston area. Brigham and Women’s Hospital is a founding member of Partners Healthcare. These primary care clinics use the Longitudinal Medical Record (LMR), an internally developed, web-based, fully functional EHR that includes notes from primary care and subspecialty practices; coded problem lists; a “health maintenance grid” for documenting preventive counseling and health habits; structured medication prescriptions; and medication allergies. The LMR has been certified by the Certification Commission for Healthcare Information Technology (CCHIT) as an ambulatory EHR, and can accept health level 7 (HL7) compliant data transfer. The study was reviewed and approved by the Partners Healthcare Institutional Review Board.

Patient eligibility

Patients were eligible for this study if they were between the ages of 18–84 years, had a visit to a participating primary care provider (PCP) at one of the 11 primary care clinics, and received a prescription for one of the target medications. Because the system currently only includes an English script, we excluded individuals who were identified in the LMR as non-English speakers, although language information is often incomplete. Target medications were selected based on date of FDA approval, as drugs are more likely to have unrecognized adverse events noted within 7 years of introduction to the market² and/or particular concern about side effects (*e.g.*, gabapentin). We also focused on medications for chronic conditions, taken on an ongoing basis. The medications selected for monitoring are displayed in Table 1.

Patients were eligible for this study if their PCP printed or faxed a prescription for one of these medications using LMR at the time of a visit and the medication had been ordered on less than two prior occasions. Participating practices do not use paper prescription pads, and over 90% of prescriptions are prescribed through LMR. If a patient was taking more than one of the target medications, one medication was randomly selected for monitoring.

Recruitment

Patients who were potentially eligible to participate are identified from LMR bi-monthly. Patients were then mailed an informational letter describing the study from the practice director of the clinic where they receive their care and the principal investigator. The letter included directions for a dedicated toll-free

Table 1. Eligible medications

Class or indication	Medication names	
Insomnia	Zolpidem (Ambien)	
	Eszopiclone (Lunesta)	
Erectile dysfunction	Sildenafil (Viagra or Revatio)	Tadalafil (Cialis)
	Vardenafil (Levitra)	
Angiotensin receptor blockers (ARB)	Losartan (Cozaar)	Irbesartan (Avapro)
	Valsartan (Diovan)	Aliskiren (Tekturna)
Seizure	Gabapentin (Neurontin)	
	Pregabalin (Lyrica)	
Asthma	Montelukast (Singulair)	
	Fluticasone propionate-salmeterol (Advair)	
Smoking cessation	Varenicline (Chantix)	
Lipid lowering	Rosuvastatin (Crestor)	Ezetimibe-simvastatin (Vytorin)
Diabetes	Rosiglitazone (Avandia)	Exenatide (Byetta)
	Pioglitazone (Actos)	Sitagliptin phosphate (Januvia)
Psychiatric	Risperidone (Risperdal)	Modafinil (Provigil)
	Olanzapine (Zyprexa)	Aripiprazole (Abilify)
	Quetiapine (Seroquel)	Duloxetine (Cymbalta)
Other	Raloxifene (Evista)	Trospium (Sanctura)
	Infliximab (Remicade)	Ibandronate (Boniva)
	Etanercept (Enbrel)	

number that can be called to “opt-out” of participation. Patients who did not opt-out within a 2-week period were assigned a unique study ID and their contact information was uploaded to the IVRS system. The calls for this project were initiated November 20, 2008, and this analysis includes calls made through June 2, 2009.

Protocol

Eligible patients were recruited to participate in a maximum of two standardized phone calls. The first phone call was timed to occur approximately 4 weeks following the primary care visit, and the second call occurred 3 months later if the patient still had the target medication on their active medication list in LMR. The standardized phone script was delivered using an IVRS system (CallAssure™, Vocantas, Inc.). The IVRS system was housed in a Partners Healthcare secure data center, behind the Partners firewall, and the caller identification on the outbound call lines was identified as Brigham and Women’s Hospital, to help participants distinguish the call from commercial telemarketing calls.²²

The IVRS system made outbound calls during preset calling hours (9 AM to 8 PM), with the system continuously checking the call list for the next scheduled call. Calls were made on Tuesday, Thursday, Saturday, and Sunday. If there was no answer, the line was busy, or a different individual answered the phone and stated that the patient was unavailable; the call was re-queued using programmed intervals no

shorter than 3 hours and 45 minutes. The system made up to 15 calls to each individual over a 10 day period, and did not leave messages on answering machines. Once contact was made with the target patient, the recorded script greeted the patient by name, authenticated the respondent’s identity (by asking them to state their date of birth), repeated a brief description of the study purpose and protocol, and ascertained whether the patient was willing to participate. If a patient indicated that they did not want to participate or if any individual at a particular phone number hung up the phone on two occasions, the phone number was not re-queued. Among people who answered the phone, the average call duration was 3 minutes and 31 seconds.

The standard script consisted of a series of questions that used branching logic conditioned on prior responses and included either categorical or numeric responses.²³ In our study, respondents spoke their responses to questions which are recognized by speech recognition software. If a patient agreed to participate, the script next asked whether they were currently taking the target drug. If the patient stated that they were no longer taking the drug, they were asked when they last took it, whether their doctor knew that they had stopped taking the medication, and any reasons for stopping (including whether they experienced a side effect or symptom). If they were no longer taking the target medication and it was not stopped because of a side effect or symptom the survey was concluded. If they reported that they stopped the medication for a side effect or symptom, they were then asked a

standard checklist of symptoms that are potentially associated with ADEs among ambulatory patients.²⁴ If the patient stated that they were still taking the medication then they were asked whether they experienced any of these symptoms since their most recent PCP visit. A follow-up survey, with the same structure, was done 3 months later if the patient continued to take the target medication to assess the stability of the patient reported symptoms.

Variables and analysis

We examined whether participation in the survey varied by demographic characteristics, including age (categorized as 18–45, 46–55, 56–65, >66 years), gender, race/ethnicity (white, black, Hispanic, other, or unknown), or median household income based on zip code of residence (<\$50 000 *versus* >\$50 000 per year). We then examined whether participation varied by type of medication, classified as in Table 1.

We calculated the percentage of potentially eligible patients who actively opted-out by calling the toll-free number provided in the information letter, the percentage of patients whose phone number in our EHR was found to be out of service, and the percentage of patients with a working phone number who were/were not contact by the IVRS system. Among patients who were contacted, we examined whether the patient opted-out of the study during the phone call, whether someone at the number hung-up on a call on two occasions, or whether they agreed to participate in the study. Participation rates were calculated in two ways: (1) of patients contacted by the IVRS system, and (2) of the larger number of potentially eligible individuals with a working phone number. For each categorical variable, we calculated the *p*-value using a chi-square test for each outcome compared to a reference category, defined as the largest group. Logistic regression models, adjusting for age, gender, race/ethnicity, income, and drug class were used to examine independent associations.

RESULTS

Study flow

During the study period, we identified 4023 potentially eligible patients who were sent information letters about the study (Figure 1). Of these, 328 (8.2%) opted-out using the toll-free line after receiving the informational letter and before the calls were initiated. The remaining 3695 patients were uploaded to the IVRS system. Of the potentially eligible patients,

12.8% had an invalid, disconnected phone number and were therefore considered to be ineligible; 27.3% were not reached despite multiple call attempts with either no answer or calls forwarded to an answering machine. The IVRS system successfully contacted an individual in the household at the listed phone number for 2081 patients (51.7% of potentially eligible or 59.3% of potentially eligible with a working phone). Of these contacted individuals, 365 individuals (17.5% of those contacted or 10.4% of those with a working phone) hung up on the phone script on two occasions before confirming their identity, and 814 (39.1% of those contacted or 23.2% of individuals with a working number) actively opted out during the phone script after confirming their identity. The 902 patients who agreed to participate in the survey represent 43.3% of those contacted by the IVRS system and 25.7% of potentially eligible patients with a working phone. To reach these 902 patients, the IVRS system made a total of 40,185 calls to the 3695 individuals uploaded to the system. We examined call outcome by time of day, and found that calls in the morning (9 AM–1 PM) were somewhat more successful than calls in the afternoon (1–5 PM) or evening (16.7% *vs.* 15.6 and 15.5%, respectively).

Call outcomes of potentially eligible individuals

Patient characteristics were associated with different call outcomes (Table 2). Toll free opt out after receiving the informational letter declined with age. Patients >66 years of age were more likely to have an invalid phone number but were also more likely to be contacted by the IVRS server (odds ratio 1.33; 95% confidence interval 1.11–1.59), and were more likely to participate (1.47; 1.19–1.81) than those 56–65 years. Black patients were more likely to have an invalid phone number than whites (1.89; 1.40–2.55). Hispanics were more likely than whites to use the toll-free opt out line or have an invalid phone number, and were less likely to participate (0.56; 0.42–0.76). There were no significant differences in participation by gender. Compared to those who lived in a high-income community, those in a low income community were less likely to use the toll-free opt out line, less likely to have an invalid phone number and less likely to participate (0.69; 0.58–0.82). Compared to those with insomnia, chosen as the reference because of the largest number of eligible patients, patients on psychiatric medications were less likely to use the toll-free opt out (0.29; 0.11–0.81). Patients on medications for asthma, smoking cessation and diabetes were more likely, and those on a lipid lowering medication less likely, to have an invalid phone number. Patients on

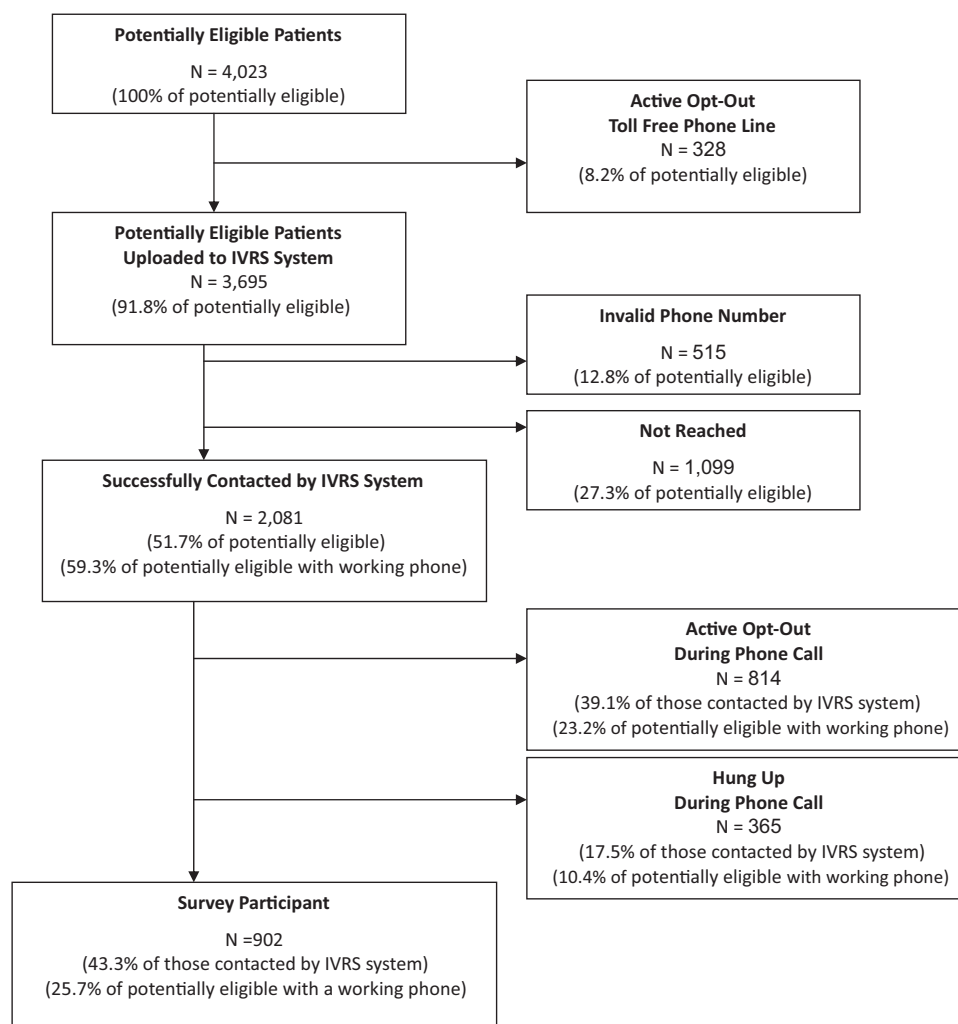


Figure 1. Study flow

seizure or asthma medications were more likely to participate.

Call outcomes of individuals contacted

Among patients living in a household successfully contacted by the IVRS system, there were also differences in call outcome by demographic characteristics and drug class (Table 3). While those 18–45 years were more likely to hang up on the call than those 56–65 (2.54; 1.74–3.72), they were also more likely to participate (1.40; 1.06–1.85). African Americans were less likely to hang up on the call, but Hispanics were more likely. Even among those contacted by the system, Hispanics were less likely to participate than whites (0.55; 0.40–0.77). Although men were less likely to hang up on the call, there were no differences in participation by gender. Individuals

from low income communities were more likely to opt out during the call, less likely to hang up on the call, and had lower rates of participation (0.72; 0.59–0.89). Individuals prescribed medications for erectile dysfunction and smoking cessation were less likely to participate and those prescribed a medication for seizures were more likely to participate.

Participation in the follow-up survey

Of the 902 patients who completed the initial survey, 723 (80.2%) were eligible for re-survey 3 months later because the target medication was still listed as active in their medication list in the EHR. Noteworthy was the finding that of patients successfully contacted for the first survey, 10.1% had a non-working phone line 3 months later. Overall rates of participation were higher: 70.1% of patients contacted participated in

Table 2. Call outcomes of potentially eligible individuals by patient characteristics and drug class ($n = 4023$)

	Toll-free opt-out		Invalid phone number		Successfully contacted by IVRS system		Participation of potentially eligible individuals with a working phone ($N = 3508$)	
	%	Odds ratio (95% confidence interval)	%	Odds ratio (95% confidence interval)	%	Odds ratio (95% confidence interval)	%	Odds ratio (95% confidence interval)
Total	8.2		12.8		51.7		25.7	
Age (years)								
18–45	10.7*	1.53 (1.12–2.11)	15.2*	1.14 (1.07–1.86)	48.9	0.89 (0.74–1.07)	25.9	1.18 (0.94–1.48)
46–55	8.0	1.05 (0.76–1.44)	13.0	1.23 (0.93–1.62)	47.8	0.86 (0.72–1.02)	18.5*	0.72 (0.57–0.90)
56–65	8.0	Reference	10.4	Reference	51.7	Reference	24.9	Reference
>66	5.9*	0.71 (0.50–1.01)	12.8	1.39 (1.05–1.84)	58.6*	1.33 (1.11–1.59)	34.0**	1.47 (1.19–1.81)
Race/ethnicity								
White	7.5	Reference	11.4	Reference	54.3	Reference	24.9	Reference
Black	7.8	1.44 (0.99–2.09)	14.2	1.89 (1.40–2.55)	51.0	0.82 (0.67–1.00)	23.1	1.03 (0.80–1.33)
Hispanic	10.3*	2.01 (1.41–2.86)	15.5*	2.10 (1.56–2.84)	47.7*	0.75 (0.61–0.91)	13.8**	0.56 (0.42–0.76)
Other	8.8	1.13 (0.83–1.54)	14.0	1.20 (0.93–1.55)	47.6**	0.78 (0.66–0.92)	39.0**	1.98 (1.63–2.40)
Gender								
Male	7.8	0.84 (0.64–1.10)	15.0	1.27 (1.02–1.58)	50.6	0.89 (0.77–1.03)	24.1*	0.93 (0.78–1.11)
Female	8.5	Reference	13.0	Reference	52.7	Reference	27.1	Reference
Income								
<\$50 000	5.7**	0.42 (0.31–0.55)	9.5**	0.43 (0.34–0.54)	51.9	1.07 (0.93–1.23)	20.7**	0.69 (0.58–0.82)
>\$50 000	10.0	Reference	15.3	Reference	51.6	Reference	29.7	Reference

	Toll-free opt-out		Invalid phone number		Successfully contacted by IVRS system		Participation of potentially eligible individuals with a working phone ($N = 3508$)	
Drug class								
Insomnia	8.0	Reference	10.3	Reference	48.8	Reference	24.0	Reference
Erectile dysfunction	8.3	1.25 (0.82–1.89)	14.7*	1.31 (0.93–1.83)	51.2	1.19 (0.95–1.49)	20.0*	0.88 (0.65–1.18)
Angiotensin receptor blocker	9.0	1.45 (0.99–2.14)	7.6	0.69 (0.48–1.01)	54.2	1.12 (0.91–1.39)	30.3*	1.26 (0.98–1.63)
Seizure	9.6	1.33 (0.89–1.99)	13.2	1.29 (0.91–1.83)	46.9	0.89 (0.71–1.12)	29.5*	1.36 (1.03–1.80)
Asthma	8.5	1.06 (0.69–1.63)	18.5*	2.00 (1.43–2.80)	60.6**	1.63 (1.28–2.07)	31.0	1.58 (1.18–2.12)
Smoking cessation	8.9	1.03 (0.66–1.62)	20.3*	2.20 (1.56–3.11)	46.7	0.98 (0.76–1.26)	20.5	0.80 (0.57–1.13)
Lipid lowering	6.6	0.99 (0.54–1.82)	5.2*	0.48 (0.25–0.92)	61.8**	1.68 (1.23–2.29)	23.4	1.01 (0.69–1.47)
Diabetes	9.7	1.44 (0.79–2.63)	16.9*	1.69 (1.03–2.75)	49.4	0.96 (0.68–1.37)	27.3	1.25 (0.81–1.94)
Psychiatric	2.2*	0.29 (0.11–0.81)	12.3	1.34 (0.81–2.22)	51.4	1.08 (0.78–1.49)	21.7	0.98 (0.64–1.50)
Other	2.7	0.44 (0.10–1.86)	15.1	1.68 (0.83–3.39)	53.4	0.94 (0.57–1.53)	40.3*	1.62 (0.93–2.84)

* p -value for χ^2 -test for comparison with reference group < 0.05 .** p -value for χ^2 -test for comparison with reference group < 0.005 .

Odds ratios adjusted for age, gender, race/ ethnicity, income, and drug class.

the follow-up survey which represented 52.9% of eligible individuals with a working phone. Similar to the initial survey, individuals age 46–55 years were least likely to be contacted by the IVRS system and individuals > 66 years were most likely (67.2 and 82.4%, respectively, $p < 0.005$). Individuals who lived in an area with a lower median income were also more likely to not have a working telephone than individuals in an area with a higher median income (12.9% vs. 8.1%, $p < 0.05$).

DISCUSSION

An IVRS-based e-pharmacovigilance system that interoperates with a patient's EHR can be used to systematically monitor ambulatory patients in a variety of clinical practice settings for potential side effects

and adverse events associated with a broad range of drugs. Contrary to our hypothesis, we found that older patients were more likely to participate in this IVRS system, but consistent with our hypotheses were found lower rates of participation by disadvantaged groups. We found that patients prescribed seizure and asthma medications were more likely to participate than those prescribed medications for insomnia, but that among those contacted by the IVRS system, those prescribed drugs for erectile dysfunction and smoking cessation were less likely to participate.

These results highlight some of the complexities in defining the reach of this type of technology to perform population-based medication monitoring. Because the IVRS system could only reach individuals with a working phone, but this could only be ascertained after an attempted call, 13% of our initial population was

Table 3. Call outcomes of individuals contacted ($n = 2801$)

	Active opt-out during call		Hung up during call		Participation	
	%	Odds ratio (95% confidence interval)	%	Odds ratio (95% confidence interval)	%	Odds ratio (95% confidence interval)
Total	39.1		17.5		43.3	
Age (years):						
18–45	34.6*	0.43 (0.32–0.58)	20.5*	2.54 (1.74–3.72)	44.9	1.40 (1.06–1.85)
46–55	45.2	1.02 (0.78–1.33)	21.2*	1.57 (1.12–2.22)	33.6 *	0.76 (0.58–0.99)
56–65	41.6	Reference	15.3	Reference	43.1	Reference
>66	35.3*	0.99 (0.76–1.29)	14.1	0.80 (0.56–1.14)	50.6*	1.15 (0.89–1.47)
Race/ethnicity						
White	41.1	Reference	18.3	Reference	40.7	Reference
Black	50.4*	1.15 (0.85–1.54)	10.7**	0.60 (0.38–0.93)	38.9	1.09 (0.81–1.46)
Hispanic	43.4	1.02 (0.75–1.398)	32.1**	2.03 (1.43–2.89)	24.5 **	0.55 (0.40–0.77)
Other	20.1**	0.36 (0.26–0.48)	9.5**	0.43 (0.29–0.64)	70.4 **	3.45 (2.65–4.49)
Gender						
Male	41.2	1.34 (1.07–1.67)	17.8	0.67 (0.50–0.92)	41.1	0.93 (0.75–1.15)
Female	37.4	Reference	17.3	Reference	45.3	Reference
Income:						
<\$50 000	46.4**	1.71 (1.38–2.11)	17.5	0.71 (0.54–0.95)	36.1**	0.72 (0.59–0.89)
>\$50 000	33.7	Reference	17.5	Reference	48.8	Reference

	Active opt-out during call		Hung up during call		Participation	
Drug class						
Insomnia	47.4	Reference	8.5	Reference	44.1	Reference
Erectile dysfunction	40.2	0.50 (0.36–0.70)	26.4	6.76 (4.12–11.10)	33.3**	0.70 (0.49–0.99)
Angiotensin receptor blocker	28.0	0.32 (0.23–0.44)	20.4	5.13 (3.19–8.23)	51.6**	1.36 (0.99–1.863)
Seizure	31.4**	0.40 (0.28–0.58)	14.1*	2.47 (1.44–4.21)	54.5*	1.65 (1.16–2.34)
Asthma	50.6	1.09 (0.79–1.51)	7.6	0.82 (0.46–1.48)	41.8	0.98 (0.71–1.37)
Smoking cessation	55.8	1.52 (1.04–2.23)	9.2	1.09 (0.58–2.08)	35.0*	0.63 (0.43–0.93)
Lipid lowering	48.9	0.80 (0.53–1.21)	15.3*	2.88 (1.56–5.33)	35.9	0.76 (0.49–1.17)
Diabetes	7.9**	0.06 (0.03–0.15)	46.1**	15.55 (8.38–28.85)	46.1	1.26 (0.74–2.13)
Psychiatric	20.7**	0.25 (0.14–0.44)	42.4**	7.92 (4.52–13.86)	37.0	0.84 (0.51–1.37)
Other	7.7**	0.08 (0.02–0.27)	28.2**	7.69 (3.35–17.64)	64.1*	1.99 (0.97–4.10)

* p -value for χ^2 -test for comparison with reference group < 0.05.** p -value for χ^2 -test for comparison with reference group < 0.005.

Odds ratios adjusted for age, gender, race/ethnicity, income, and drug class.

subsequently deemed to be ineligible for our protocol. As our script is currently only available in English, we excluded individuals when the EHR indicated that their primary language was not English. However, the information about language preference is often not complete in our EHR, thus it is likely that the lower participation rate for Hispanics is related to language barriers. While there is a clearly defined cohort of individuals who “actively” opted out of the study, either by calling the toll-free line or when called by the IVRS system, there are two groups whose eligibility is less clear. First, one-third of the sample never answered the phone after 15 attempts. While many of these may represent “passive” refusals by individuals who were screening their calls with caller identification, some of these individuals may never have known of the calls or the numbers listed in the EHR may have been incorrect. Our IVRS system was not programmed to leave messages on answering machines primarily because of

our concerns about confidentiality and because our system was not designed to accept incoming calls. Future work will examine whether a system that incorporates incoming calls while protecting confidentiality might permit patients to participate by calling back at a time of their choosing. Second, because we did not want to annoy individuals or other household members, we considered situations when someone hung-up on two occasions to be “passive” refusals. Because these hang-ups occurred before an individual’s identity could be confirmed, it is likely that some of these calls reached other household members rather than the intended participant.

For these reasons, there is no single “gold standard” to calculate a participation rate. We therefore present two options, calculating the rate among individuals: (1) contacted by the IVRS system, thereby excluding individuals who may not have known of the call but including individuals who may have passively refused

by hanging up, and (2) who were potentially eligible and had a working phone. The general patterns of participation by patient and clinical characteristics between these two calculations are similar. Our system did have higher participation rates, using the more conservative definition of participation, than other studies that have used this technology in a population-based way,^{25,26} but not surprisingly had lower overall participation rates than studies that used this technology to follow patients who had already agreed to be contacted and had their eligibility assessed in person.^{8,9,12,17,27,28} In addition to translation into other languages, providing a financial incentive, and adding inbound calling capability, several other modifications may improve the reach of this type of system. Patients who are taking medications for a sensitive condition may feel more comfortable participating if they are better educated about the study purpose and the confidentiality of the system. Although all of these patients had recently had a visit to their PCP, these data suggest that many of these patients may not have current phone numbers on record. Introduction and explanation of the study directly by the treating clinician or clinic staff at the time the medication is prescribed would also likely improve participation. In addition, regular confirmation of the telephone number, as with use of any data element in an EHR, is likely to improve the quality of the telephone numbers in the EHR. Finally, combining IVRS with other modalities (e.g., internet) may further improve the ability to reach certain populations.

A growing consensus suggests that active surveillance of ambulatory patients taking prescription drugs is necessary to detect ADEs.²⁹ Direct reporting of side effect and symptoms by patients may particularly enhance current safety practices.³⁰ Our study suggests that an IVRS system can be integrated with an EHR to provide e-pharmacovigilance for a broad spectrum of patients, particularly older individuals. This population is particularly important for pharmacovigilance as they may take more medications and may therefore be at greater risk of an ADE, furthermore they are less likely to be included in clinical trials. If e-pharmacovigilance systems can be designed to reach a clinically important proportion of patients taking a particular medication, our knowledge of medication adverse events, particularly for new medications will likely be enhanced. Future work will address whether data collected using this type of system can be effectively and accurately used to detect ADEs, or lead to meaningful changes in patient management resulting from earlier recognition of medication problems.

KEY POINTS

- IVRS technology can be used to perform ambulatory e-pharmacovigilance.
- Older individuals, who may at particular risk for ADEs, were more likely to be contacted and participate.
- Hispanics were less likely to participate than whites, and individuals who lived in a low income communities were less likely to participate than those in higher income communities.
- Patients receiving seizure or asthma medications were more likely to participate than those prescribed medications for insomnia.
- Future work will address whether data collected using this type of system can be effectively and accurately used to detect ADEs, or lead to meaningful changes in patient management resulting from earlier recognition of medication problems.

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