Analysis of the Impact of the Birmingham OwnHealth Program on Secondary Care Utilization and Cost: A Retrospective Cohort Study

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Abstract

Background: This study aimed to assess the impact of the Birmingham OwnHealth[®] program (a partnership among the National Health Service [NHS] Birmingham East and North, formerly Birmingham East and North PCT, as the commissioner, Pfizer Health Solutions [Tadworth, United Kingdom] as the primary contractor, and NHS Direct as a subcontractor) on the number of unscheduled secondary care spells and the cost of care for patients with long-term conditions. This article reports a retrospective cohort study conducted at the NHS Birmingham East and North. **Subjects and Methods:** Adults with at least 1 of 10 defined long-term conditions were eligible for inclusion. Patients in the OwnHealth program were compared with those in a matched comparison group from a population who were eligible but did not enroll in the program. The main outcome measures were the difference in the number of secondary care spells (defined as the experience between hospital admission and discharge) between the OwnHealth group and the comparison group and the difference in the cost of care (calculated from the cost of activities during secondary care spells). **Results:** The mean number of secondary care spells per person per year in the OwnHealth group was 0.61 (standard deviation [SD] 1.35) compared with 0.84 (SD 1.49) in the comparison group ($p < 0.0005$). This constituted a 27% reduction in secondary care spells per person per year. The mean cost of secondary care spells per person per year in the OwnHealth group was \$1,305 (SD \$3,138) compared with \$1,678 (SD \$3,485) in the comparison group ($p < 0.0005$). **Discussion:** This difference in costs constituted a 27% reduction in utilization and 22% reduction in cost of secondary care with the OwnHealth program. **Conclusions:** Telehealth intervention can reduce the cost of secondary care of some patients with long-term conditions.

Key words: telemedicine, telehealth, home health monitoring, cardiology/cardiovascular disease, e-health

Introduction

In Great Britain, estimates suggest that up to 17.5 million adults live with a long-term condition.¹ Such illnesses impact upon quality of life and long-term health and can be costly for the patient and the healthcare system treating them.¹

Patients with inadequately controlled long-term conditions are more likely to experience poor outcomes than patients with good disease control.² Poor compliance with treatment can contribute to inadequate disease control and poor clinical outcomes. The effects of poor adherence can also be costly, making this an important issue for healthcare organizations.³

Telehealth interventions, involving the remote delivery of healthcare, have been used in many scenarios to facilitate the management of long-term illnesses. Studies of telehealth programs for patients with various long-term conditions have demonstrated that these interventions can benefit the health of the patient. Potential cost savings with telehealth interventions could also be important for modern healthcare services, considering the many demands on constrained healthcare budgets.

The Birmingham OwnHealth[®] program was a telephone-based care management program that supported patients to self-care that operated between 2006 and 2012. It was the result of a partnership among the National Health Service (NHS) Birmingham East and North, formerly Birmingham East and North PCT, as the commissioner, Pfizer Health Solutions (Tadworth, United Kingdom) as the primary contractor, and NHS Direct as a subcontractor. The program involved the use of telecoaching, including the provision of guidance, signposting, and motivational interviewing from a trained healthcare professional. The frequency and timing of phone calls were defined by the patient, with an average of 1 call per patient per month being made. The program was offered to patients with long-term conditions such as diabetes, heart disease, and chronic obstructive pulmonary disease (COPD).⁴

The program, commissioned in April 2006, was the first telephone-based care management service in the United Kingdom to focus on support for people with long-term conditions.⁵ Enrolled patients, who had been identified by their general practitioners, were assigned their own local Care Manager who proactively and regularly telephoned patients to deliver motivational coaching and healthcare education to enable patients to become efficacious self-carers. Educational materials and a handheld Care Book and a healthcare record were also provided to give further support. This assistance encouraged patients to make and maintain the necessary changes to

their lifestyles that allowed them to manage their conditions more effectively. Patients received this service in addition to the standard care received by the control cohort. The clinical content of the program was defined by nationally accepted best practice guidance.

The primary aim of this retrospective study and service evaluation was to assess whether the Birmingham OwnHealth program reduced the number of unscheduled secondary care spells and the cost of care for patients with long-term conditions.

Subjects and Methods

PATIENT POPULATION

NHS Birmingham East and North provided all the anonymized patient data for use in the analysis. No ethical approval was required as the study is a service evaluation.

Patients who were invited to enter the Birmingham OwnHealth program had to meet specific eligibility criteria. These criteria were:

- Diagnosis of at least 1 of the 10 long-term conditions under investigation: heart failure (HF), coronary heart disease (CHD), diabetes, COPD, stroke, transient ischemic attack (TIA), peripheral vascular disease (PVD), chronic kidney disease (CKD), hypertension, or a cardiovascular disease (CVD) risk score (JBS2 CVD risk score) of $>20\%$.
- Patients had to be over 18 years old and must have been registered with a general practitioner for at least 2 months.
- Patients had to have access to, and use of, a telephone.
- Specific requirements were made of baseline characteristics (such as high body mass index, reduced forced expiratory volume percentage of predicted, raised cholesterol, high blood pressure, etc.) depending on the long-term conditions experienced.
- Patients residing in nursing homes were excluded from the study.

The comparison group for this retrospective study was chosen from a pool of patients who had given consent for their anonymized data to be used for research purposes and who met the entry criteria for the Birmingham OwnHealth program and who either declined to enter the program or could not be contacted by NHS Birmingham East and North for the purpose of enrolling in the program.

Patients were selected for the intervention and comparison groups using a data mining model that used a clustering technique. Baseline measurements were used to cluster patients who were similar, based on age, gender, body mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein, low-density lipoprotein, blood sugar, glycosylated hemoglobin, and forced expiratory volume in the first second/forced vital capacity ratio. This method helped to minimize the risk of bias in the demographic and baseline parameters. In total, 10 patient clusters were identified, of which 4 were removed from the analysis because of the lack of paired data. These clusters consisted of 269 individuals, which was 2.5% of the cases introduced to the clustering model.

Intervention participants (patients using OwnHealth as utilizers) and comparison participants (individuals who did not consent to enter OwnHealth as non-utilizers) were selected at random from each of the included clusters as suggested by Gordis.⁶ A random generator

ensured that the same number of participants was selected from all included clusters, irrespective of their size. In total, 8,400 participants were selected: 4,200 for OwnHealth and 4,200 for comparison.

Data were collected on the secondary care utilization and associated costs over a period of 12 months for patients in the OwnHealth group and those in the comparison group.

Of the 4,200 patients in the comparison group, data were collected by phone from 1,308 individuals to assess their reasons for not participating in OwnHealth. The majority of this group (62.6%) chose not to enter the program without providing a reason for their choice. Small proportions of patients declined because of specific objections to the program, such as lack of time to talk (0.7%) or the patient being unable to perceive benefit in the service (2.5%). In total, 107 patients in this sample (8.2%) could not be contacted, because of the provision of outdated contact information, to ascertain their interest in the OwnHealth program.

This was a primary care intervention, and secondary care physicians were not involved in referring patients to the service. The intervention was not blinded, and all primary care clinicians involved in the patients' care were aware of their participation. In the unlikely event that people were discharged early solely *because they were so supported*, we would regard this as a genuinely useful and positive outcome of providing the service. During the period of the study none of the participants in the intervention was graduated; thus the risk of bias due to selective dismissal is not applicable to this study.

Table 1. Baseline Characteristics of the Intervention and Comparison Groups

	OWNHEALTH INTERVENTION (N = 4,200)	NON-UTILIZERS (N = 4,200)
Age (years)	68.55	68.94
Gender (n M/F)	2,111/2,089	2,230/1,970
Comorbidities (n)	2.37	1.98
BMI (kg/m ²)	29.61	28.70
SBP (mm Hg)	137.93	139.08
DBP (mm Hg)	78.27	79.32
HDL (mmol/L)	1.37	1.38
LDL (mmol/L)	2.26	2.46
BS (mmol/L)	4.64	4.61
HbA1C (mmol/mol)	60	57
FEV1/FVC ratio (%)	62.51	63.42

All measurements are mean values unless otherwise stated. The number of participants in each subgroup is represented by *n*.

BMI, body mass index; BS, blood sugar; DBP, diastolic blood pressure; F, female; FEV1/FVC ratio, forced expiratory volume in the first second/forced vital capacity ratio; HbA1C, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male; SBP, systolic blood pressure.

Table 2. Mean Number of Secondary Care Spells per Person per Year for Different Indications

	MEAN NUMBER OF SECONDARY CARE SPELLS PER PERSON PER YEAR (SD)		DIFFERENCE	% SECONDARY CARE SPELL CHANGE WITH OWNHEALTH	STATISTICS (U, P, R) ^a
	OWNHEALTH INTERVENTION	NON-UTILIZERS			
Diabetes	1.23 (9.31) n=2,640	1.62 (10.36) n=1,858	−0.39	−24%	2073545.5 <0.0005 0.15
CHD	0.99 (5.60) n=1,201	1.12 (1.58) n=660	−0.13	−12%	314603.5 <0.0005 0.19
HF	1.60 (9.29) n=446	2.23 (10.26) n=280	−0.63	−28%	45340.5 <0.0005 0.25
COPD	1.06 (2.48) n=177	1.47 (2.07) n=97	−0.41	−28%	6893 0.004 0.18
Stroke	1.22 (5.89) n=212	1.49 (2.77) n=191	−0.27	−18%	16782 0.001 0.16
TIA	2.44 (13.10) n=255	1.60 (1.76) n=249	0.84	53%	22998 <0.0005 0.25
PVD	1.80 (12.28) n=169	1.36 (1.84) n=131	0.44	32%	8532 <0.0005 0.21
CKD	2.78 (16.76) n=1,021	2.45 (14.16) n=1,099	0.33	13%	481786.5 <0.0005 0.13
Hypertension	1.36 (10.07) n=2,838	1.37 (8.55) n=3,141	−0.01	−1%	3990488.5 <0.0005 0.1
CVD risk >20%	0.85 (5.24) n=996	1.03 (1.59) n=618	−0.18	−17%	256232.5 <0.0005 0.16

The number of participants in each subgroup is represented by *n*.

^aStatistics are represented by the Mann-Whitney U test (U), *p* value (*p*), and effect size (*r*).

CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HF, heart failure; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack.

DETERMINATION OF COSTS AND CONSEQUENCES

Data were collected on the number of secondary care spells and the associated costs for each patient over a 12-month period. A secondary care spell was defined as the experience of a patient from hospital admission until discharge. A single secondary care spell

could include several episodes of treatment and numerous consultations with healthcare professionals.

Secondary care activity and costs were calculated using data from Commissioning Data Sets, which cover inpatient activity, outpatient appointments, and attendance at accident and emergency departments. The costs accumulated during each secondary care spell were calculated from the prices listed for Healthcare Resource Groups. These Groups are a standard method of classifying hospital activity in the United Kingdom, by grouping episodes of treatment that are similar with respect to clinical parameters and resource use.

Key investigations undertaken in the analysis of Birmingham OwnHealth were as follows:

- The average number of secondary care spells per person per year by primary disease classification
- The average cost of care per person per year by primary disease classification, based on the costs of secondary care spells

In addition to the primary end points several other parameters were examined:

- The average length of stay in hospital per patient per year for all patients in the OwnHealth group versus all those in the comparison group during the 12-month study period
- The average number of secondary care spells per person per year for those with more than one specified condition
- The average cost of care per person per year for those with more than one specified long-term condition, based on the costs of secondary care spells

STATISTICAL ANALYSIS

Data for the 8,400 patients in the non-utilizers and OwnHealth groups were tested for outlier items using the Mahalanobis Distance test. This test identified 61 outlier participants based on the number of sec-

ondary care spells and cost of care per patient per year. These participants were excluded from the final analysis to eliminate the effect of outlier cases on the overall results.

The final data were analyzed for normality of distribution using the Kolmogorov-Smirnov test. None of the datasets tested was

normally distributed ($p < 0.0005$). The Mann-Whitney U test was used to calculate p values.

Clinical outcome measures are not presented as part of this research. These are the subject of additional research. The changes in use of other NHS self-care programs, which are available as part of “normal care” for both cohorts, are not analyzed herein because of the lack of paired data in the control cohort.

Results

As a result of the data mining process, the groups were closely matched with regard to baseline characteristics (Table 1).

CHANGE IN NUMBER OF SECONDARY CARE SPELLS

The mean number of secondary care spells per person per year in the OwnHealth group was 0.61 (standard deviation [SD] 1.35), which was significantly lower than the secondary care spells per person per year for the comparison group (0.84 [SD 1.49]) ($U = 7804733$, $p < 0.0005$) with a small effect size ($r = 0.11$). This constituted a 27% reduction in secondary care spells per person per year with Birmingham OwnHealth.

The difference in the mean number of secondary care spells was statistically significant for each illness investigated. The results for 70% of the disease areas studied demonstrated a significant reduction in secondary care spells per person per year with the OwnHealth program with small effect size in the individual diagnoses (Table 2). Data for the remaining 30% (TIA, PVD, and CKD), however, showed that the OwnHealth intervention increased the mean number of secondary care spells per person per year in these indications.

The effects of the OwnHealth program on secondary care spells per person per year in patients with more than one long-term condition were mixed. In this analysis, the Diabetes + CVD risk > 20% patients in the OwnHealth group had significantly fewer secondary care spells per person per year than the equivalent comparison group. However, Diabetes + CHD patients treated with OwnHealth had significantly more secondary care spells per person per year than non-utilizers, as did individuals in the CHD + HF group. All other combinations tested were found to have nonsignificant results (Table 3). The effect size was small in all groups.

On average, patients in the comparison group spent 4.36 days (SD 13.221) in the hospital per year compared with 3.32 days (SD 11.747) for patients in the OwnHealth group ($U = 7853201$, $p < 0.001$), a reduction of almost 24% with a small effect size ($r = 0.11$).

CHANGE IN COST OF CARE

Significant reductions in cost were associated with OwnHealth. Overall, the mean cost of secondary care per person per year in the OwnHealth group was \$1,305 (SD \$3,138), which was significantly lower than the equivalent cost for the comparison group (\$1,678 [SD \$3,485]) ($U = 8349046$, $p < 0.0005$) with a small effect size ($r = 0.06$). This constituted a 22% reduction in costs with Birmingham OwnHealth.

Mean costs of secondary care in the OwnHealth group, analyzed by disease area, were consistently lower than those in the comparison group. Significant reductions in cost were achieved with OwnHealth in all but two indications (stroke and COPD) (Table 4), and the effect size was small in all groups. The SD in the comparison is generally larger than that in the intervention group, indicating a greater degree of variance in the comparison results.

Costs of hospital spells were reduced with OwnHealth even in the three instances when the number of secondary care spells significantly increased (TIA, PVD, and CKD).

Table 3. Mean Number of Secondary Care Spells per Person per Year in Patients with More Than One Long-Term Condition

	MEAN NUMBER OF SECONDARY CARE SPELLS PER PERSON PER YEAR (SD)		DIFFERENCE	% SECONDARY CARE SPELL CHANGE WITH OWNHEALTH	STATISTICS (U, P, R) ^a
	OWNHEALTH INTERVENTION	NON-UTILIZERS			
Diabetes + CHD	1.40 (9.00) <i>n</i> = 411	1.26 (1.82) <i>n</i> = 220	0.14	11%	35738 <0.0005 0.19
Diabetes + CVD risk > 20%	1.14 (8.31) <i>n</i> = 375	1.20 (1.86) <i>n</i> = 203	−0.06	−5%	30911 <0.0005 0.18
COPD + CVD risk > 20%	1.48 (4.26) <i>n</i> = 31	1.80 (1.30) <i>n</i> = 5	−0.32	−18%	39.5 0.061 0.01
Diabetes + COPD	1.49 (2.85) <i>n</i> = 43	1.31 (1.44) <i>n</i> = 26	0.18	14%	483 0.320 0.12
CHD + HF	2.72 (14.46) <i>n</i> = 155	1.51 (1.79) <i>n</i> = 89	1.21	80%	5503.5 0.005 0.19

The number of participants in each subgroup is represented by *n*.

^aStatistics are represented by the Mann-Whitney U test (U), p value (p), and effect size (r).

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HF, heart failure; SD, standard deviation.

The cost of providing the program for each participant in the service at the time of the study was estimated to be \$610 per person; the combination of redesign of the delivery methods through improved staff modeling, operational efficiencies, reduction in information technology and telephony costs, and the establishment of a mature service means that this has subsequently been reduced to \$381. The potential savings from secondary care costs, as presented in Table 4, exceed the cost of delivering the service. Furthermore, the program is likely to be associated with other long-term cost

reductions in addition to the reduction of secondary care costs, although further research is required to confirm this. In individuals with more than one long-term condition, none of the combinations presented by the patients resulted in statistically significant changes in cost per person per year, although the majority of combinations showed a trend toward reduced costs for the OwnHealth program (Table 5), and the effect size was small in evaluated comorbidities. Further investigation is required to explore this finding further.

Table 4. Mean Cost of Care per Person per Year for Different Indications

	MEAN COST OF CARE PER PERSON PER YEAR (SD)		DIFFERENCE	% COST CHANGE WITH OWNHEALTH	STATISTICS (U, P, R) ^a
	OWNHEALTH INTERVENTION	NON- UTILIZERS			
Diabetes	\$1,434 (\$4,275) n = 2,640	\$2,472 (\$7,405) n = 1,858	– \$1,038	– 42%	2245893.5 <0.0005 0.09
CHD	\$1,907 (\$4,622) n = 1,201	\$2,706 (\$5,549) n = 660	– \$799	– 30%	346677 <0.0005 0.12
HF	\$2,503 (\$5,449) n = 446	\$4,078 (\$7,887) n = 280	– \$1,575	– 39%	51976.5 <0.0005 0.16
COPD	\$2,372 (\$5,152) n = 177	\$3,033 (\$5,772) n = 97	– \$661	– 22%	8088 0.379 0.05
Stroke	\$2,048 (\$4,486) n = 212	\$3,534 (\$6,578) n = 191	– \$1,486	– 42%	18578.5 0.114 0.08
TIA	\$2,378 (\$5,190) n = 255	\$3,540 (\$5,518) n = 249	– \$1,162	– 33%	26081.5 <0.0005 0.19
PVD	\$2,413 (\$5,509) n = 169	\$3,841 (\$6,560) n = 131	– \$1,428	– 37%	9114 0.003 0.17
CKD	\$2,318 (\$6,117) n = 1,021	\$3,436 (\$9,760) n = 1,099	– \$1,118	– 33%	523922.5 0.003 0.07
Hypertension	\$1,672 (\$4,609) n = 2,838	\$2,340 (\$6,951) n = 3,141	– \$668	– 29%	4272635.5 0.001 0.04
CVD risk > 20%	\$1,718 (\$3,940) n = 996	\$2,512 (\$5,526) n = 618	– \$794	– 32%	280801 <0.0005 0.09

The number of participants in each subgroup is represented by *n*.

^aStatistics are represented by the Mann-Whitney U test (U), *p* value (*p*), and effect size (*r*).

CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HF, heart failure; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack.

Discussion

Around 17.5 million British adults are estimated to be living with a long-term condition.¹ These conditions can impact on quality of life, clinical outcomes, and the cost of illness.¹ Inadequate management of long-term conditions, including poor compliance with treatment, could result in poor clinical outcomes, which in turn could increase the cost of care.

A proactive approach to managing long-term conditions could have benefits over reactive measures. Such approaches could prevent the need for avoidable healthcare interventions and the costs that these entail. This could be beneficial from the perspective of patients (who could save time in the hospital and experience improved outcomes) as well as from the perspective of healthcare facilities (who could yield cost savings and focus resources on other patients requiring care).

Self-management programs are already in place in the NHS, including initiatives such as “expert patient” programs, which provide practical advice on managing conditions.⁷ Similar self-management interventions have been found to significantly impact on health behaviors and outcomes.^{8,9} Telehealth is not a new concept in the NHS; other services such as NHS Direct use both telephone and Internet techniques to try to influence and improve patients’ health-seeking behaviors.¹⁰

The Birmingham OwnHealth program can be used to manage the care of patients with many long-term conditions and could represent a more streamlined approach than using multiple disease-specific schemes.

The results presented here suggest that the OwnHealth program is an effective method of reducing the number of secondary care spells for large groups of patients with long-term conditions and lowering the resultant cost of care. These results also suggest that

Table 5. Mean Cost of Care per Person per Year in Patients with More Than One Long-Term Condition

	MEAN COST OF CARE PER PERSON PER YEAR (SD)		DIFFERENCE	% COST CHANGE WITH OWNHEALTH	STATISTICS (U, <i>P</i> , <i>R</i>) ^a
	OWNHEALTH INTERVENTION	NON- UTILIZERS			
Diabetes + CHD	\$2,230 (\$5,132) <i>n</i> = 411	\$2,653 (\$6,118) <i>n</i> = 220	−\$423	− 16%	41612.5 0.055 0.08
Diabetes + CVD risk > 20%	\$1,988 (\$4,415) <i>n</i> = 375	\$2,779 (\$6,679) <i>n</i> = 203	−\$791	− 28%	35370 0.098 0.07
COPD + CVD risk > 20%	\$2,133 (\$3,951) <i>n</i> = 31	\$3,349 (\$5,184) <i>n</i> = 5	−\$1,216	− 36%	56.5 0.305 0.05
Diabetes + COPD	\$3,569 (\$6,913) <i>n</i> = 43	\$2,992 (\$5,043) <i>n</i> = 26	\$577	19%	541.5 0.812 0.03
CHD + HF	\$3,303 (\$6,849) <i>n</i> = 155	\$4,260 (\$7,157) <i>n</i> = 89	−\$957	− 22%	6082 0.094 0.11

The number of participants in each subgroup is represented by *n*.

^aStatistics are represented by the Mann–Whitney U test (*U*), *p* value (*p*), and effect size (*r*).

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HF, heart failure; SD, standard deviation.

this program can reduce care costs, even in participants whose number of secondary care spells per person per year increases (such as in patients with TIA, PVD, or CKD). Savings are thought to be achieved in these instances because the costs incurred during a secondary care spell in the OwnHealth group were lower than those for the comparison group. An analysis of the mean number of days spent in hospital per person per year showed that, overall, the OwnHealth group reduced days in hospital by almost 24% compared with non-utilizers, which may be useful in explaining this. However, further investigation is required to adequately explain this observation.

Improvements in the number and cost of secondary care spells per person per year in patients with multiple illnesses were more variable than for patients with one condition. None of the scenarios tested showed a statistically significant reduction in cost per patient per year, despite a trend toward cost reductions with OwnHealth in many of the combinations investigated. However, significant reductions in the number of secondary care spells per person per year were achieved in some instances, suggesting that the OwnHealth intervention may still demonstrate value in patients with multiple illnesses. The numbers of patients with multiple illnesses were small, and the study was not powered to detect differences in these groups; further analysis is required to definitively address the usefulness of the OwnHealth system in such patients.

The data presented here demonstrates that the Birmingham OwnHealth program was an effective way to reduce the number of secondary care spells per person per year experienced by many of the patients with long-term conditions enrolled in the program and could result in significant reductions in cost of care.

The analysis of patients with one long-term condition showed that savings could be achieved even in instances where secondary care spells per patient per year increased with the OwnHealth intervention, suggesting that these secondary care spells were shorter and/or less costly than those for the comparison group, although this is yet to be confirmed. The data presented regarding the use of the OwnHealth program in patients with multiple long-term conditions were more varied and warrant further investigation.

Thus, in this analysis, the Birmingham OwnHealth program was demonstrated to reduce the costs of care for many patients with a long-term condition, which could have benefits for patients and healthcare organizations in the scenario of the United Kingdom.

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Disclosure Statement

L.S.N. is a previous employee of Pfizer Health Solutions. P.D. is a previous employee of Health Intelligence Ltd., which was employed by Birmingham East and North PCT to provide general practitioner practice data export, and hosting and reporting services for the OwnHealth program. O.S. is a paid consultant to Pfizer Health Solutions. I.M. is an employee of Pfizer Health Solutions. L.S.N. is the guarantor of this work. All authors were involved in preparation of the manuscript. L.S.N. and P.D. assisted with the conception and design of the study. O.S. participated in the acquisition and analysis of the data. L.S.N. assisted with interpretation of the analyzed data.

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