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Short- and long-term effects of real-time medication monitoring with short message service (SMS) reminders for missed doses on the refill adherence of people with Type 2 diabetes: evidence from a randomized controlled trial

M. Vervloet[1,*], L. van Dijk[1], D. H. de Bakker[1,2], P. C. Souverein[3], J. Santen-Reestman[4], B. van Vlijmen[4], M. C. W. van Aarle[4], L. S. van der Hoek[1] and M. L. Bouvy[3]

[1]NIVEL, Netherlands Institute for Health Services Research, Utrecht
[2]Tranzo, Scientific Centre for Care and Welfare, Tilburg University, Tilburg
[3]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University
[4]Mediq Apotheken, Utrecht, the Netherlands

ABSTRACT

Aims

To investigate short- and long-term effects of real-time monitoring medication use combined with short message service (SMS) reminders for missed doses on refill adherence to oral anti-diabetic medication.

Methods

A randomized controlled trial with two intervention groups and one control group involving 161 participants with Type 2 diabetes with suboptimal adherence. For 6 months, participants in the SMS group ($n = 56$) were monitored and received SMS reminders if they missed their medication. Participants in the non-SMS group ($n = 48$) were only monitored. The control group ($n = 57$) was not exposed to any intervention. Primary outcome measure was refill adherence to oral anti-diabetic medication. Multi-level regression analyses were performed to examine intervention effects on adherence between and within groups after 1 and 2 years of follow-up.

Results

At baseline, mean refill adherence was comparable between the groups. After 1 year, adherence in the SMS group was significantly higher than in the control group (79.5% vs. 64.5%; $P < 0.001$) and showed a significant improvement from baseline (+16.3%; $P < 0.001$). Mean adherence in the non-SMS group reached 73.1% (+7.3%; $P < 0.05$), but did not differ from the control group ($P =$

0.06). After 2 years, the improved adherence in the SMS group persisted and remained significantly higher than in the control group (80.4% vs. 68.4%; $P <$ .01), contrary to the non-SMS group whose adherence approached baseline level again (65.5%).

Conclusions

This study shows the long-term effectiveness of real-time medication monitoring combined with SMS reminders in improving refill adherence. This new reminder system can strengthen the self-management of people with diabetes.

Abbreviations

- SMS: short message service

What's new?

- The innovative real-time medication monitoring system evaluated in this study is the first to provide the opportunity to intervene only when patients forget to take their medication.
- This study showed that receiving short message service (SMS) reminders only when a dose is missed results in a higher refill adherence, and is the first to demonstrate long-term effectiveness of electronic reminders on adherence.
- The real-time medication monitoring reminder system can especially provide support for people who have problems taking their medication because of forgetfulness.
- This system can also strengthen a person's self-management, as medication management is an important aspect of self-management.

INTRODUCTION

Achieving glycaemic control results in a significant reduction in the incidence of micro- and macrovascular complications associated with diabetes [1, 2]. Although there are more factors that affect the blood glucose level, non-adherence to anti-diabetic medication clearly leads to deterioration in glycaemic control [3-6]. A systematic review revealed that adherence to oral anti-diabetic medication is low and ranges from 36% to 93% [7].

One of the most commonly reported barriers to adherence in people with Type 2 diabetes is forgetfulness [8, 9]. Reminding people of their medication intake may lead to better adherence. Electronic reminder systems have shown to be effective in improving adherence in the short term, but long-term effects remain unknown [10]. So far, no study focused specifically on reminding people with Type 2 diabetes of their medication intake. Furthermore, all studies used reminders that were automatically sent regardless of whether the person had taken the medication or not. This might lead to loss of effectiveness when the automated reminders become a routine. To avoid this undesirable situation, we used an innovative reminder system based on real-time medication monitoring. Real-time medication monitoring uses an electronic medication dispenser with which a person's medication intake (date and time of each opening) is registered in real time. Because of this real-time registration,

a missed dose can be identified as it happens, providing the opportunity to intervene by sending a short message service (SMS) reminder to a person when they forget their medication. No reminder is sent when the medication is taken.

The aim of this study is to investigate short- and long-term effectiveness of real-time medication monitoring with SMS reminders for missed doses in improving adherence in people with Type 2 diabetes with suboptimal adherence levels.

MATERIALS AND METHODS

Design and participants

We conducted a randomized controlled trial with two intervention groups and one control group involving people with Type 2 diabetes who experience medication intake problems. The trial protocol is described in detail elsewhere [11]. Briefly, persons were eligible for participation if they met all of the following criteria: (1) had used oral anti-diabetic medication for at least 1 year; (2) when combined with oral medication: had used insulin for at least 6 months; (3) had a refill adherence of less than 80% (percentage of prescriptions filled at the pharmacy); (4) were between 18 and 65 years of age; (5) had collected the last prescription for oral anti-diabetic medications within 2 months prior to the intervention; (6) had knowledge of the Dutch language; (7) were using a mobile phone.

Eligibility was assessed through an automatic search in anonymous pharmacy data of 40 pharmacies for selection criteria (1), (3) and (4). Subsequently, a manual evaluation of pharmacy data was performed for criteria (2) and (5). The last two criteria, (6) and (7), were assessed by pharmacy staff when they contacted the person for participation. Participants enrolled between July 2008 and May 2009. All participants provided written informed consent. The study protocol was approved by the Medical Ethics Committee of the Utrecht Academic Medical Centre and registered in the Netherlands National Trial Register.

Intervention

During 6 months, participants in the first intervention group (the SMS group) and the second intervention group (the non-SMS group) used the real-time medication monitoring dispenser, which was designed to fit one type of medication, being the oral anti-diabetic medication in our trial. When the dispenser is opened, a message containing date and time of opening is sent directly through the Global System for Mobile Communications (GSM) network to a central server. Participants in the SMS group received SMS reminders if they had not opened the dispenser within a time period upon which they had agreed with their pharmacist to take their medication. The reminder included the text 'Have you taken your medication yet? Please take your medication as prescribed by your healthcare provider', and was sent once for each missed dose. Participants in the non-SMS group did not receive these reminders. We included this group to investigate the effect of being monitored with real-time medication monitoring on adherence. Participants in the control group were not exposed to any intervention. Pharmacists and/or pharmacy technicians were

instructed by members of the project team about the procedure of how to include people. The instruction covered how to approach people (a conversation protocol and letters were provided), how to inform people about the study and provide the real-time medication monitoring dispenser.

Outcome measure and measurements

The primary outcome measure was adherence to oral anti-diabetic medication based on pharmacy refill data and measured as medication refill adherence. To calculate the medication refill adherence, the total days' supply of medication was divided by the number of days of the study period and multiplied by 100 to provide an overall adherence percentage [12]. The days' supply was calculated allowing for non-overlapping switches from one to another type of oral anti-diabetic medication and by taking into account changes in dose regimen. The study period was 365 days for all participants. Because of this uniform denominator, early discontinuation was taken into account in calculating the refill rate, thereby avoiding overestimation of adherence [13]. Three refill rates were calculated: (1) over the year directly preceding the intervention (baseline refill rate), (2) over the year following the start of the intervention (short-term effect) and (3) over the second year since the start (long-term effect). Pharmacy refill data were retrieved based on anonymous patient numbers from the central database of Mediq that contains data from every Mediq pharmacy. However, a number of pharmacies switched their information system, permanently closed or merged into a larger cluster during the study, resulting in reassignment of patient numbers. Consequently, refill data could not be retrieved for these participants. Refill adherence rates could be calculated for 126 participants for short-term follow-up and 110 participants for long-term follow-up. Figure 1 shows a flow chart of participant involvement in this study.

[FIGURE 1.]

Statistical analyses

Differences in baseline characteristics between the three groups were tested with Student's t-test, χ^2-test or Fisher's exact test where appropriate. Multi-level analyses were performed to analyse the effect of the intervention, taking into account the dependency of the three measurements within patients. More importantly, with multi-level analyses, participants can be included in the analyses although they do not have a refill rate for all three measurements. As such, in accordance with the intention-to-treat principle, all but one participant for whom no rate could be calculated at any of the measurements were included in the multi-level analyses. With the refill rate as the continuous dependent variable, a multi-level linear regression model with two levels (participant and measurement) was used. The group to whom participants were assigned (SMS, non-SMS or control group) was added as a factor variable. An interaction term was included in the analyses (group $\times$ measurement) as it was expected that the effect of the intervention would differ between groups and between measurements. The model was fitted with maximum likelihood estimation. Adherence differences were tested two-tailed, the significance level was set at $P < 0.05$. Two sensitivity analyses were performed to test the

robustness of our findings: one in which participants who had missing refill rates were excluded (per-protocol analysis); and one in which participants with incomplete refill data were included (minimum period of available data: 6 months). All analyses were performed with Stata SE 12.1 (StataCorp., College Station, TX, USA).

RESULTS

A total of 604 eligible persons were identified from anonymous pharmacy data from 40 Mediq pharmacies, a large Dutch pharmacy chain, based on the first five selection criteria. Participants were assigned within each pharmacy to one of the three groups (ratio 1:1:1) by means of stratified randomization to balance the three groups on age, gender and use of insulin in addition to their oral diabetes medication. The last two criteria were applied by the pharmacy staff when they invited persons to participate in the study, which resulted in exclusion of 56 persons. Of the remaining 548 eligible persons, 161 (29.4%) participated in the trial: 56 in the SMS group, 48 in the non-SMS group and 57 in the control group. The number of included participants per pharmacy varied strongly (range: 1–12), the response rate varied from 6% to 67%. Participants in the three groups had comparable baseline characteristics (Table 1). Non-response analyses revealed that participants who were lost to follow-up did not significantly differ in baseline characteristics from participants with complete follow-up.

[TABLE 1]

Short-term effectiveness of the intervention

At baseline, mean refill adherence did not significantly differ between the groups, being 63.2%, 63.0% and 61.1% in the SMS, non-SMS and control group, respectively. After 1 year, refill adherence was increased in all three groups (Fig. 2). Participants who had received reminders for 6 months reached an adherence of 79.5%. The mean adherence of participants who had only been monitored for 6 months and of participants who had received usual care was 73.1% and 64.5%, respectively.

[FIGURE 2.]

Multi-level analyses showed that, after 1 year, mean refill adherence of participants in the SMS group was significantly higher than that of those in the control group [mean difference: 15.0% (6.7–23.4); $P < 0.001$] (Table 2). The difference between the non-SMS and control group was not significant [mean difference: 8.6% (0.2–17.5); $P = 0.055$], neither was the difference between the SMS and non-SMS group [mean difference: 6.4% (2.2–15.0); $P = 0.147$]. Adherence significantly improved relative to baseline in the SMS group [+16.3% (9.2–23.4); $P < 0.001$] and non-SMS group [+10.1% (2.2–18.1); $P < 0.05$], but not in the control group.

[TABLE 2]

Long-term effectiveness of the intervention

In the second year, refill adherence of participants who had received reminders remained stable at 80.4%, whereas that of participants who had only been monitored approached their baseline level (65.5%). Adherence in the control group slightly increased to 68.4% (Fig. 2).

Multi-level analyses (Table 2) revealed that the adherence of participants in the SMS group was still significantly higher than the control group after year 2 [mean difference: 12.0% (3.1–21.0); $P < 0.01$]. Furthermore, the adherence in the SMS group was now significantly higher than that in the non-SMS group [mean difference: 14.9% (5.7–24.1); $P = 0.001$]. No differences were found between the non-SMS and control group. Whereas adherence in the non-SMS and control group did not differ from their baseline level after year 2, adherence in the SMS group remained significantly higher ($P < 0.001$).

Sensitivity analyses

The two sensitivity analyses (one with participants for whom three adherence measurements were available and one with participants having incomplete refill data) revealed similar results for both short- and long-term effectiveness.

DISCUSSION

This study shows that real-time medication monitoring combined with SMS reminders for missed doses improves refill adherence to oral anti-diabetic medication both in the short term (after 1 year) and the long term (after 2 years).

To our knowledge, this is the first study in which SMS reminders were sent to people with Type 2 diabetes in an effort to improve their adherence. One study including a small sample of people using anti-diabetic medication, showed higher adherence in those receiving text messages, but these messages could contain other reminders than for the medication intake [14]. Our findings are in line with previous studies evaluating the effect of SMS reminders on adherence in other patient populations [10]. However, contrary to our study, they usually evaluated automated reminders sent regardless of whether the patient took the medication or not. An exception is a recent pilot study, examining elderly patients' adherence to vitamin C, which also found positive effects of reminding only when the medication was not taken [15]. Furthermore, we also examined long-term effects. Our study showed that providing persons with real-time medication monitoring and SMS reminders for 6 months is sufficient to improve adherence in the long run, as they still remembered to take their medication after 2 years. These findings suggest that, as a result of sufficient repetition of external stimuli—in this study, the SMS reminder—patients learn the desired adherent behaviour [16, 17]. They also might have incorporated the medication intake into their daily routine by providing cues for themselves to take their medication after the intervention ended.

The increased refill adherence in the non-SMS group after the first year indicates that patients' awareness of being monitored has an effect on adherence, which is in line with earlier research [18, 19] as well as the diminishment of the monitoring effect over time [20]. The increased refill adherence of participants in the control group in the first year might be explained by the fact that they were asked to complete a pre- and post-test questionnaire. Participation in a study might already improve patients' outcomes [21]. Moreover, a study involving patients on anti-hypertensive treatment showed that refill adherence of patients who keep taking their medication increased over time [22], which might explain the increase in adherence in the control group in year 2. The use of a dose dispensing aid (e.g. a week box) by participants in the control group might have influenced adherence, although these aids are most often used by older persons with many different medicines, who were excluded in our study. Furthermore, persons using a Baxter dispensing system were not part of our study population.

Our study was aimed at non-adherent people, as they benefit most from an adherence-improving intervention [23]. As such, mean refill adherence at baseline was low in all three groups. Resulting from our intervention, participants who had received reminders reached a mean adherence rate of 80%, which is a considerable improvement in adherence. Furthermore, 80% adherence is often seen as a minimum level of adherence to attain treatment goals [24].

Electronic monitoring data (registered with the real-time medication monitoring dispenser) were only available for the SMS and non-SMS group and thus could not be used to investigate the difference in adherence between these groups and the control group. To this end, we used prescription refill data, which were available for all three groups. Although filling a prescription does not automatically indicate that the medication is taken, this method is seen as an objective and accurate method in a closed pharmacy system such as in the Netherlands [25]. Here, most patients obtain all their prescription refills, usually every 3 months, from one and the same pharmacy [26]. Refill data also enables following patients for a longer time period, which would be less feasible and more expensive with, for example, electronic monitoring devices. However, it is recommended to combine adherence measures to maximize accuracy of the assessment, as every measure has its limitations [9].

In our previous study, we assessed differences in electronically monitored adherence between the SMS and non-SMS group and these were in line with the current study. Whereas the regularity with which participants receiving reminders took their medication improved compared with participants who were only monitored, after 6 months no significant differences in missed doses were found between the groups [27]. This can be explained by the monitoring effect found in the non-SMS group in the present study.

Limitations of the study

One limitation is the small number of participants. This may have led to a selection of patients that participated in the trial. However, the limited sample size did not

prevent us from finding significant effects of the intervention on our outcome measure. Providing the dispenser and additional information when the patient had to visit the pharmacy for their refill anyway might increase participation, as this would prevent the extra visit for patients and does not require a proactive, more time-consuming attitude from the pharmacy staff. The number of participants who were lost to follow-up was rather high. This was mainly a consequence of pharmacy-related factors (e.g. change in pharmacy information system), rather than patient-related factors. Participants who were lost to follow-up did not differ in baseline characteristics from participants who had complete follow-up. In addition, the sensitivity analyses consistently showed the effectiveness of real-time medication monitoring with SMS reminders.

Another limitation is the absence of a group of participants who used real-time medication monitoring and received SMS reminders regardless whether they had taken their medication or not. As such, we cannot prove the added value of reminding only when necessary compared with reminding regardless of whether the medication is taken or not. An indication of this added value might be seen in the fact that in our study the improved adherence rate persisted in the long run, which has not yet been demonstrated in earlier research with automated reminders.

Older persons usually have more problems in remembering to take their medication. However, persons older than 65 years were excluded in our study as we expected elderly persons not to use a mobile phone as often as younger persons, leaving an important part of the population with Type 2 diabetes unaddressed with this intervention. Since the implementation of our intervention in 2008, an ever-increasing number of persons use mobile phones, and the future elderly will be accustomed to mobile phones and SMS as they grew up with them.

The real-time medication monitoring dispenser used in our trial was suitable for one type of medication—in our study, the oral anti-diabetic medication. People with diabetes often have co-morbidities for which they take several medicines, but this co-medication could not be investigated in our study. Further development of the real-time medication monitoring system to support people with multiple medicines is needed, as well as further research to investigate the effect of the real-time medication monitoring system on co-medication.

Finally, our study did not include clinical outcomes as our intervention aimed primarily on improving adherence. Therefore, the clinical impact of real-time medication monitoring with SMS reminders was not examined. However, evidence from previous research suggests that adherence to oral anti-diabetic medications is associated with improved glycaemic control [3-6]. Nonetheless, further research on the impact of real-time medication monitoring with SMS reminders on clinical outcomes is needed.

Implications for clinical practice and future research

The real-time medication monitoring reminder system can strengthen a person's self-management, of which adherence is an important aspect. After providing people with the real-time medication monitoring dispenser and making agreements about the time period within which they will take their medication, no additional effort from healthcare professionals is required. Technological developments such as the real-time medication monitoring reminder system have potential in controlling the rising healthcare costs, as they often require minimal time investment of healthcare professionals. Therefore, it is important to further investigate the cost-effectiveness of the real-time medication monitoring system. It is also important to identify subgroups for whom this intervention is most beneficial. Further research with a larger sample is therefore recommended.

In this study, the effect of real-time monitoring with SMS reminding on patients' adherence was investigated. Other possibilities of real-time medication monitoring include giving patients feedback on their medication use based on their electronic monitoring data. The data registered with real-time medication monitoring are directly available through the Internet, providing an opportunity for professionals to signal problems in medication use as they occur, and immediate feedback can be given. Previous research showed promising results of giving people feedback based on electronic monitoring data [28-30]. Future studies should investigate these possibilities in further enhancing adherence of people with Type 2 diabetes.

In conclusion, refill adherence of people with Type 2 diabetes significantly improved with the real-time medication monitoring reminder system, with which medication use is monitored in real-time and SMS reminders are sent only for missed doses. The improved adherence rate persisted in the long run. Real-time medication monitoring with SMS reminders supports people in their medication use and can strengthen their self-management.

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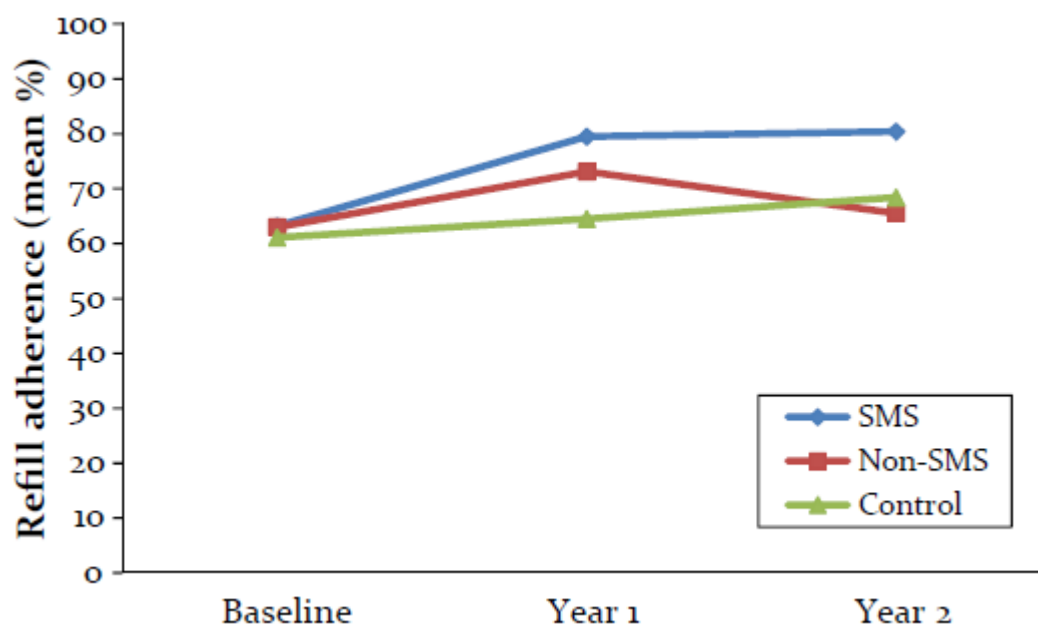FIGURE 1 Flow chart of participant involvement in this study. SMS, short message service.
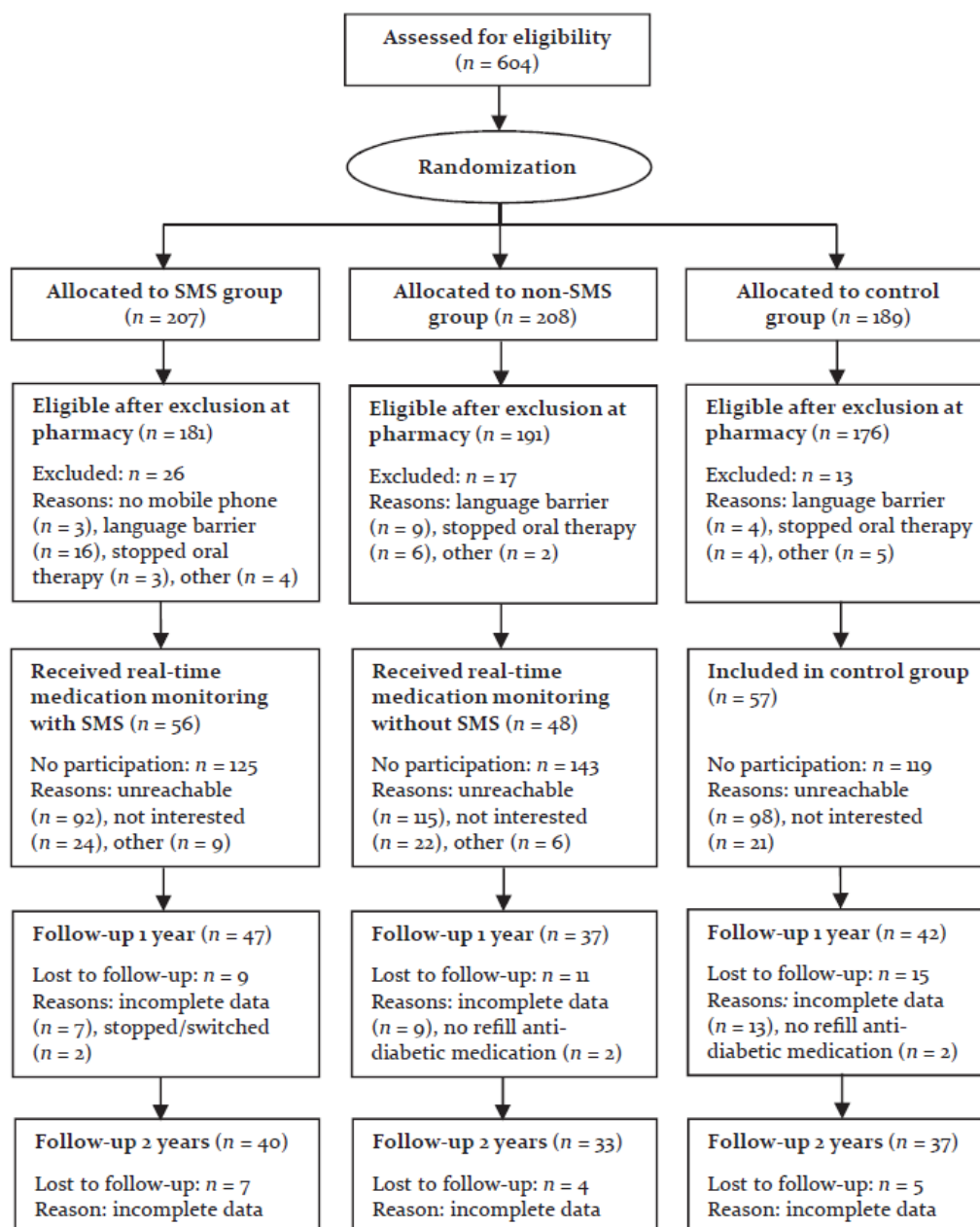
Table 1. Characteristics of participants at baseline[c]			
	SMS group (n = 56)	Non-SMS group (n = 48)	Control group (n = 57)
Age (years), mean ± SD	54.9 ± 6.6	54.6 ± 6.9	55.4 ± 7.8
Male, n (%)	31 (55.4)	26 (54.2)	29 (50.9)
Educational level[a], n (%)			
Low	17 (30.4)	17 (35.4)	26 (45.6)
Medium	18 (32.1)	10 (20.8)	20 (35.1)
High	11 (19.6)	12 (25.0)	9 (15.8)
Ethnicity[a], n (%)			
Native Dutch	29 (51.8)	26 (54.2)	39 (68.4)
Western immigrant	3 (5.4)	2 (4.2)	6 (10.5)
Non-Western immigrant	15 (26.8)	12 (25.0)	12 (21.1)
Household composition[a], n (%)			
Living alone	6 (10.7)	6 (12.5)	11 (19.3)
Living with partner, children or others	39 (69.6)	32 (66.7)	44 (77.2)
Insulin use (in combination with oral diabetes medication)[b], n (%)	18 (32.1)	14 (29.2)	17 (29.8)
Co-medicationb (excluding insulin), n (%)	54 (96.4)	44 (91.7)	53 (93.0)
Duration disease (years), mean ± SD	10.6 ± 10.8	8.2 ± 8.6	8.7 ± 6.8
Complications diabetes[a], n (%)			
Yes	10 (17.9)	3 (6.3)	8 (14.0)
No	35 (62.5)	36 (75.0)	47 (82.5)
Medication regimen, n (%)			
One daily dose	11 (19.6)	12 (25.0)	13 (22.8)
Two daily doses	25 (44.6)	27 (56.3)	25 (43.9)
Three daily doses	20 (35.7)	9 (18.8)	19 (33.3)

[a] The numbers and percentages add up to less than total because of missing values.

[b] Use of insulin or other co-medication was identified from pharmacy refill data.

[c] No significant differences were found between the groups.

FIGURE 2 Mean refill adherence at baseline, over year 1 (short term) and year 2 (long term) in the short message service (SMS), non-SMS and control groups.

Table 2. Results of the multi-level linear regression analyses: estimated means of refill adherence of groups over time			
	Refill adherence (%)		
	Baseline	Year 1	Year 2
	mean (SE)	mean (SE)	mean (SE)
Control group (ref.) (n = 57)	61.1 (2.7)	64.5 (3.1)	68.4 (3.3)
SMS group (n = 56)	63.2 (2.8)	79.5 (2.9)†	80.4 (3.2)‡
Non-SMS group (n = 48)	63.0 (3.1)	73.1 (3.3)	65.5 (3.5)

Significance levels: †$P < 0.01$; ‡$P < 0.001$.
SMS, short message service.