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ABSTRACT

Objective To determine if a targeted and tailored intervention based on a discussion informed by validated adherence scales will improve medication adherence.

Design Prospective randomised trial

Setting Two community pharmacies in Brisbane, Australia

Methods Patients recently initiated on a cardiovascular or oral hypoglycaemic medication within the last four to twelve weeks were recruited from two community pharmacies. Participants identified as non-adherent using the Medication Adherence Questionnaire (MAQ) were randomised into the intervention or control group. The intervention group received a tailored intervention based on a discussion informed by responses to the MAQ, Beliefs about Medicines Questionnaire-Specific and Brief Illness Perception Questionnaire. Adherence was measured using the MAQ at three and six months following the intervention.

Results A total of 408 patients were assessed for eligibility, from which 152 participants were enrolled into the study. 120 participants were identified as non-adherent using the MAQ and randomised to the *intervention* or *control* group. The mean MAQ score at baseline in the intervention and control were similar (1.58: 95% CI [1.38, 1.78] and 1.60: 95% CI [1.43, 1.77] respectively). There was a statistically significant improvement in adherence in the intervention group compared to control at three months (mean MAQ score 0.42: 95% CI [0.27, 0.57] vs 1.58: 95% CI [1.42, 1.75]; p<0.001). The significant improvement in MAQ score in the intervention group compared to control was sustained at six months (0.48: 95% CI [0.31, 0.65] vs 1.48: 95% CI [1.27, 1.69]; p<0.001).

Conclusions An intervention that targeted non-adherent participants and tailored to participant-specific reasons for non-adherence was successful at improving medication adherence.

Trial registration This trial is registered on the Australian New Zealand Clinical Trials Registry, which can be accessed at http://www.anzctr.org.au/ using trial ID ACTRN12613000162718.

Strengths and limitations of this study

- The adherence intervention was targeted by identifying participants who were non-adherent to their medication prior to inclusion in the trial.
- The use of validated adherence scales provided insight to a person's adherence and can be used in a similar way to electronic monitoring in a measurement-guided medication management approach to improve adherence.
- The study would have been improved by addition of a reliable objective measure of adherence.
- This study had a relatively small sample size and was not powered to measure clinical outcomes.

INTRODUCTION

Improving adherence to medication has been identified as one of the most cost-effective and achievable opportunities for improving health outcomes.[1, 2] Many interventions have been implemented to improve adherence to medications, including: reminder systems (text reminders, dose administration aids); behavioural counselling (motivational interviewing); social support (peer support therapy); cognitive-educational interventions (verbal information) and measurement-guided medication management.[3, 4] While many of these interventions have been successful in improving adherence in specific trials, no intervention has conclusively demonstrated effectiveness in improving adherence *and* clinical outcomes.[5-8] The few

interventions that have been successful in improving adherence and clinical outcomes in well-conducted randomized trials have been multi-faceted, complex interventions that are difficult to replicate in practice.[7]

There are a number of issues that may account for these results, but perhaps the two most pertinent are: lack of assessment of participants' adherence prior to enrolment,[7, 9-13] and utilising an intervention that may not specifically address reasons for the participants' non-adherence.[6, 8, 14, 15] Most studies introduce an intervention into an unselected population and employ an intervention that may or may not address participant-specific reasons for non-adherence. Targeting non-adherent participants and tailoring interventions to specific reasons for non-adherence has been suggested to improve the effectiveness of medication adherence interventions,[1, 16-18] but few studies to date have adopted this approach.[19, 20]

Assessing adherence is not difficult. There are many objective and subjective measures of adherence that can provide information in relation to a patient's medication-taking behaviour albeit with limitations specific to each method.[6, 21-24] Objective measures of adherence include electronic monitoring of medication administration (e.g. Medication Event Monitoring System, MEMS), prescription records and dose counts. These measures are often good at measuring medication-taking behaviour, but can be expensive, impractical and do not provide information on reasons for behaviour. Subjective measures of adherence include physician reports, self-report and adherence scales. Subjective measures are prone to recall and social desirability bias, but they are often easy to administer and provide the opportunity to explore why the patient may be non-adherent. Self-report adherence scales are relatively easy to administer and elicit different information: medication-taking behaviour, barriers to adherence and beliefs associated with adherence.[25]

MEMS has been used in a measurement-guided medication management approach to identify non-adherence and inform discussion between the patient and their health professional about potential barriers to adherence. This approach has been successful in improving adherence in several studies.[3] We believe the measurement-guided medication management approach could be adopted using adherence scales that are strategically selected to identify non-adherence and key reasons for non-adherence.

We conducted a randomised trial to determine if a measurement-guided medication management-approach based on a discussion informed by validated adherence scales, would improve adherence to a recently initiated cardiovascular or oral hypoglycaemic medication. We hypothesised that randomising participants assessed to be non-adherent and tailoring an intervention based on a discussion informed by adherence scales would improve adherence at three months as measured by the Medication Adherence Questionnaire (MAQ). We also tested whether any improvements in adherence at three months would be sustained at six months.

METHODS

This was a randomised, placebo controlled trial recruiting participants who recently initiated a medicine for chronic cardiovascular disease or type 2 diabetes. The recruitment of potential participants occurred between the 25th of March, 2013 and 24th July, 2013. Participants were followed for six months from recruitment, with the last participant contact occurring on the 10th February, 2014. This trial is registered on the Australian New Zealand Clinical Trials Registry, which can be accessed at http://www.anzctr.org.au/ using trial ID ACTRN12613000162718. Ethics approval was obtained from the School of Pharmacy Ethics Committee, University of Queensland (approval number 92013/5).

Participants

Potential participants were recruited from two community pharmacies in Brisbane, Australia. Participants were interviewed in the semi-private counselling area of the pharmacy.

Inclusion criteria

Individuals who were over 18 years of age and started a new medication for hypertension, type 2 diabetes, dyslipidaemia or other cardiovascular diseases (myocardial infarction, heart failure, hypertension, arrhythmia, and stroke) within the last four to twelve weeks were approached to participate in the study. Specific medications included angiotensin-converting-enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, lipid-lowering agents or oral hypoglycaemic drugs. Individuals who were unable to complete the survey tool were excluded from the study.

Participant Interviews

The MAQ was used to assess adherence behaviour.[26] Participants identified as adherent (score of 0) using the MAQ were enrolled and followed for six months. Participants identified as non-adherent (score of 1 to 4) using the MAQ were randomised into either the intervention or control group, using block randomisation and followed for six months. The random allocation sequence was generated by an internet-based randomisation software (Research Randomiser). The block size was ten, providing an allocation ratio of 1:1 (e.g. ABBABABAAB). The intervention group

received a tailored intervention to improve medication adherence. Due to the nature of the intervention, neither the researcher, nor the participants were blinded to the allocation at the baseline interview. No data analysis occurred prior to completion of the study.

All interviews were conducted by the principal investigator (TN), who is a registered pharmacist. The survey instruments used in the interview included: the MAQ, Beliefs about Medicines Questionnaire-Specific (BMQ-S) and Brief Illness Perceptions Questionnaire (BIPQ). These scales were selected following a systematic review of the literature.[25]

Baseline demographics of the participants were also collected. All participants were followed for six months. Participants were asked to complete the same three validated adherence scales (MAQ, BMQ-S and BIPQ) at 3 and 6 months over the telephone. No further interventions were conducted at the three- and six-month time-points.

Medication Adherence Questionnaire (MAQ)

The four-item MAQ was selected because it has been well-validated to identify adherence behaviour in a number of chronic cardiovascular disease populations and scores have been shown to correlate well with objective adherence measures.[26-29] The MAQ has also been used to explore reasons for non-adherence.[26] Specifically, MAQ has been used to identify unintentional non-adherence, intentional non-adherence or a mix of both.[30]

Participants were asked to respond to the MAQ in relation to the recently initiated medication of interest. Participants answering *no* to all items of the MAQ (MAQ score = 0) were identified as adherent to their medicine.[27, 31-33] These participants were followed for six months in the "adherent" group (the results of this participant group will be reported elsewhere). Participants answering *yes* to at least one of the MAQ items (MAQ score = 1 to 4) were identified as "non-

adherent" and were randomised to either the *intervention* or *control* groups. This cut-off has been used in the literature, and provides a highly sensitive tool for identifying medication non-adherence.[27, 31-33] Responses to the MAQ were also used to identify adherence behaviour and identify the likely type of non-adherence, for instance: unintentional non-adherence due to being forgetful or careless, or intentional non-adherence by ceasing their medicines when they felt better or worse, and a mix of both types.

Beliefs about Medicines Questionnaire – Specific (BMQ-S)

The BMQ-S elicits an individual's beliefs about their medicines in the domains of *necessity* of medicines and *concerns* about medicines. The BMQ-S has been validated in many disease populations.[25] In general, individuals who have strong *concerns* about their medicines or believe their medicines are not necessary tend to be less adherent.[34-36]

All participants were interviewed using the BMQ-S to measure perceived *necessity* of and *concerns* about medicines.[34] The BMQ-S consists of ten statements about medicines: five of the statements are related to beliefs about the *necessity* of medicines and the remaining five statements are related to *concerns* that individuals may have about their medicines.

Brief Illness Perception Questionnaire (BIPQ)

Illness representations identified in the BIPQ have been closely associated with medication adherence.[37, 38] The BIPQ consists of nine items that assess the cognitive and emotional representations of illness.[37] This questionnaire provided insight into a participant's perceptions and understanding of their illness and treatment.

Intervention

The *intervention* took place at a single time point, immediately following randomisation. For participants randomised to the intervention group, the investigator used participant responses to the adherence scales to prompt further discussion regarding the participant's adherence and the factors that supported or impeded them to take their medicine. The intervention used the measurements provided by the validated adherence scales to tailor an adherence support strategy for each participant (it is in this sense that the intervention is a form of measurement-guided medication management). The investigator and participant then selected and implemented a strategy from an "evidence-based toolkit" to support the participant's adherence based on the information discussed in the interview.

The evidence-based tool kit consisted of strategies shown to be effective in improving adherence in specific situations. Strategies employed to support the participant's adherence included: [3-5, 14]

- reminder systems (dose administration aids, dosette boxes, alarm clock reminders, text reminders, treatment simplification);
- cognitive-educational interventions (verbal information, written information);
- behavioural-counselling interventions (reinforcing behaviour, empowering individuals to actively participate in their healthcare and problem-solving);
- social support interventions (family member support) and
- multifaceted interventions (reminder systems coupled with cognitive-educational interventions).

For example, some participants who stated they forget to take their medicine on the MAQ may be asked: How often they forget? Where they store their medicines? Or why they think they forget to take their medicine? This information helped determine if the participant would benefit from a reminder and the specific type of reminder strategy. If participants indicated they had a poor perceived understanding of their illness or their treatment on the BIPQ, participants may be asked what they knew about their illness and/or medicine to help individualise the education provided in a cognitive-educational strategy to support adherence. If participants had a low necessity score and/or a high concerns scores on the BMQ-S, the specific beliefs the participant held that led to these scores were explored with the participant. These discussions focused on identifying and discussing any non-veridical beliefs held by the participant about their medicine (e.g. strong concerns about an adverse effect that is very unlikely or can be mitigated with appropriate monitoring). These participants received individualised education or a behavioural-counselling strategy to support their adherence.

Outcome Measures

Participant responses to the MAQ, BMQ-S and BIPQ were collected at baseline, three months and six months. The primary outcome was the difference in the mean MAQ score between the intervention and control groups at three months. An intention-to-treat analysis was used for the primary outcome. Secondary outcomes included the difference in the mean MAQ score between the intervention and control groups at six months. A *post hoc* analysis was conducted to assess whether changes in survey responses were consistent with the specific adherence intervention employed.

Statistical Analyses

Baseline demographics of the intervention and control groups were compared using t-tests for continuous data and Fisher's exact tests for categorical data.

A one-sided independent-samples t-test was conducted to compare the mean MAQ score of the intervention and control group, based on the *intention-to-treat* population using *R* (version 3.0.2) statistical software, at three months and six months.

Changes in the questionnaires scores at three and six months were also visually observed in the different strategy types in the intervention group.

The study was powered to observe a difference in mean MAQ scores between intervention and control of 0.683. This difference in mean MAQ was observed in a trial of an education intervention to improve adherence.[39] This improvement in mean MAQ was associated with a clinically significant improvement in blood pressure control. Forty-one participants per group (intervention and control) provided 80% power to detect a statistically significant change in adherence at a level of 0.05. Taking into account anticipated dropouts, our target sample size was 60 participants per group (intervention and control).

Results

A total of four hundred and eight individuals were assessed for eligibility, of which 152 participants were enrolled into the study (Figure 1). 120 participants were identified as non-adherent and randomised 1:1 to intervention or control. At six months, there were 55 participants remaining in the intervention group and 45 participants in the control group. The movement of participants throughout the study is shown in Figure 1.

Participant Baseline Demographics

The participants identified as non-adherent using the MAQ had a mean age of 63.5 years (Table 1). Of these participants, 66 (55%) were female and 98 (81.7%) had attained secondary school qualifications or higher. There were no significant differences in the demographics between the intervention and control groups. The mean MAQ score at baseline in the intervention and control groups were similar: 1.58: 95% CI [1.38, 1.78] and 1.60: 95% CI [1.43, 1.77], respectively.

Table 1 Baseline participant demographics

	Intervention (n=60)	Control (n=60)
Age (years), *mean (SD)*	64.4 (11.3)	62.6 (13.4)
median (IQR)	66.0 (16.5)	62.5 (20.5)
Sex (females)	31 (51.7%)	35 (58.3%)
Education level		
Primary	13 (21.7%)	9 (15.0%)
Secondary	32 (53.3%)	37 (61.7%)
Tertiary	15 (25.0%)	14 (23.3%)
Total Number of Medicines		
Medications, *mean (SD)*	5.7 (2.6)	5.0 (2.6)
median (IQR)	5.0 (3.0)	5.0 (4.0)
Complementary medicines, *mean (SD)*	0.85 (1.1)	0.93 (1.3)
median (IQR)	0.5 (1.0)	1.0 (1.0)
Medical Conditions		
Hypertension	49 (81.7%)	48 (80.0%)
Dyslipidaemia	39 (65.0%)	39 (65.0%)
Diabetes mellitus	24 (40.0%)	25 (41.7%)
Heart failure	8 (13.3%)	5 (8.3%)
Atrial fibrillation	7 (11.7%)	4 (6.7%)
Myocardial infarction	5 (8.3%)	10 (16.7%)
Stroke	4 (6.7%)	5 (8.3%)
Depression	12 (20.0%)	12 (20.0%)
Osteoarthritis	19 (31.7%)	17 (28.3%)
Gout	2 (3.3%)	5 (8.3%)
Osteoporosis	6 (10.0%)	3 (5.0%)
Asthma	9 (15.0%)	9 (15.0%)
COPD	2 (3.3%)	1 (1.7%)
GORD	10 (16.7%)	5 (8.3%)
Thyroid conditions	3 (5.0%)	3 (5.0%)
Other	17 (28.3%)	20 (33.3%)

Data: number (%) or mean (SD).

Intervention

The mean length of the baseline interview for the intervention group was 13.5 ± 2.9 minutes (including implementation of strategy) and control group was 11.8 ± 2.8 minutes.

The tailored strategies that were implemented are shown in Table 2. Reminder systems accounted for 45% of the implemented strategies.

Table 2 Types of tailored strategies implemented to improve medication adherence

Strategy	Intervention Group n = 60	Examples of the Strategy
Reminder systems	27 (45%)	- Dose administration aids - Alarm reminders - Simplifying treatment regimens
Cognitive-educational	9 (15.0%)	- Verbal information - Written information
Reminder systems and Cognitive-educational	15 (25.0%)	- Dosette box and verbal or written information
Behavioural-counselling	4 (6.7%)	- Health coaching
Social support	5 (8.3%)	- Support from a family member

Adherence

The intervention improved adherence as measured by the MAQ at three months. Mean MAQ score in the intervention and control group: 0.42: 95% CI [0.27, 0.57] vs 1.58: 95% CI [1.42, 1.75]; p<0.001 (lower MAQ scores reflect better adherence to treatment). The lower MAQ score in the intervention group compared to control was sustained at six months (0.48: 95% CI [0.31, 0.65] vs 1.48: 95% CI [1.27, 1.69]; p<0.001). This represents a statistically significant improvement in the primary end-point at three and also at six months (p<0.001) (Figure 2).

On a more individual level, we identified 53 of the 60 (88.3%) participants in the intervention group as adherent at three months. The greatest individual improvement in the MAQ score was from four to zero, in the intervention group. In the control group, only seven of the 60 (11.7%) participants were identified as adherent at three months.

Table 1 BMQ-S necessity scores and concerns score at baseline, three months and six months between intervention and control groups. Scores represented as mean ± standard deviation.

BMQ Scores	Time	Intervention n=60	Control n=60	*p*
Necessity Score	Baseline	19.60 ± 3.18	18.48 ± 3.63	0.0758
	3 months	19.80 ± 2.94	18.53 ± 3.71	<0.05*
	6 months	20.25 ± 3.17	17.95 ± 3.20	<0.05*
Concerns Score	Baseline	13.48 ± 3.50	12.63 ± 4.20	0.2312
	3 months	13.00 ± 3.43	13.05 ± 3.75	0.9394
	6 months	12.32 ± 3.75	12.92 ± 3.38	0.3591

Table 4 BIPQ scores at baseline, three months and six months, between intervention and control groups. Scores represented as mean ± standard deviation.

BIPQ Scores	Time	Intervention (n=60)	Control (n=60)	*p*
Timeline **How long do you think your illness will continue?** **(0 = very short time – 10 = forever)**	Baseline	9.57 ± 1.14	8.85 ± 2.28	<0.05*
	3 months	9.90 ± 0.66	8.92 ± 2.19	<0.05*
	6 months	9.83 ± 0.62	9.12 ± 1.87	<0.05*
Personal Control **How much control do you feel you have over your illness?** **(0 = absolutely no control – 10 = extreme amount)**	Baseline	5.70 ± 2.82	6.08 ± 2.89	0.4639
	3 months	6.50 ± 2.57	5.53 ± 2.61	<0.05*
	6 months	5.90 ± 2.93	4.98 ± 2.59	0.0723
Treatment Control **How much do you think your treatment can help your illness?** **(0 = not at all – 10 = extremely helpful)**	Baseline	8.20 ± 1.94	8.00 ± 1.97	0.5757
	3 months	8.55 ± 1.79	7.63 ± 2.15	<0.05*
	6 months	8.58 ± 1.70	7.22 ± 2.44	<0.05*
Coherence **How well do you feel you understand your illness?** **(0 = don't understand – 10 = understand very clearly)**	Baseline	7.28 ± 2.64	7.35 ± 2.36	0.8845
	3 months	8.37 ± 2.09	7.12 ± 2.54	<0.05*
	6 months	8.37 ± 2.11	6.63 ± 2.71	<0.05*

Changes in Adherence Scale Scores

The changes in mean BMQ-S scales and BIPQ scales for the intervention and control groups are provided in Table 3 and 4. Figure 3 provide the changes in the mean scores of the MAQ, BMQ-S and two items of the BIPQ (*treatment control* and *coherence*) for participants in each of the tailored strategy groups at three months. Changes observed in the BMQ-S and BIPQ scores reflect the type of intervention implemented. Minimal changes in the BMQ-S and BIPQ scores were visually observed at three months in the group that received a reminder intervention. In the group that received a cognitive-educational intervention, we observed an increase in the mean BIPQ *treatment coherence* score, reflecting an increase in perceived understanding of their illness. Participants in the behavioural-counselling intervention group underwent a brief version of health coaching, which resulted in an increase in the BMQ-S necessity score and a decrease in BMQ-S concerns score over time. These changes reflect stronger necessity beliefs towards medicine and weaker concerns beliefs about their medicine. The visually observed changes on the BMQ-S and BIPQ scores were sustained at six months.

DISCUSSION

A measurement-guided medication management approach using validated adherence scales to inform a targeted and tailored intervention improved adherence to a recently initiated medication for chronic disease at three and six months.

No interventions to improve adherence have consistently demonstrated benefits in terms of both improved adherence and clinical outcomes. Interventions that have been successful tend to be multi-faceted, complex and involve repeated follow-up.[14] Despite these results, the outlook for adherence research may not be quite so bleak. Few studies included in the review were sufficiently powered to observe improvements in clinical outcomes. The lack of studies

consistently demonstrating benefits in clinical outcomes says more about the size of the trials than the success or otherwise of the intervention. Furthermore, many of the studies included in the review neither targeted a non-adherent population nor tailored the intervention to the individual's reasons for non-adherence. There is increasing evidence that studies that target a non-adherent population and tailor the intervention to individual-specific reasons for non-adherence are more effective for improving adherence.[40, 41]

Three key components contributed to the success of the intervention employed in this study. First, trial participants were identified as non-adherent using a well-validated adherence scale (MAQ). Second, participant responses to validated adherence scales (MAQ, BMQ-S and BIPQ) were used to provide insight into the likely reasons behind the participant's medication non-adherence. This permitted targeting the adherence support strategy to the participant. Third, the discussion between the investigator and participant led to a shared decision on the most appropriate tailored strategy to support the participant's adherence to their medication.

Assessing an individuals' adherence status would seem an obvious first step prior to implementing a strategy to support adherence, particularly if no intervention is required because the individual is adherent. The improvement in adherence observed in our study is consistent with other studies that enrolled a non-adherent sample for an intervention to support their adherence.[20, 42]

The findings of our study suggest that it may be possible to achieve the benefits observed from complex, multi-faceted interventions with a much simpler intervention providing that the intervention is targeted to a non-adherent population and tailored to the individual's specific reasons for non-adherence. The intervention employed in this study was easy to administer and quick enough that it could be incorporated into day-to-day practice. The improvement in adherence observed in our study is consistent with other studies that targeted an intervention to a non-adherent sample,[20, 42] and tailored an adherence strategy to the participant-specific

reasons for non-adherence.[11, 43-46] Determining the reasons for medication non-adherence facilitated the introduction of interventions that would be more likely to improve medication adherence.[1] We used the MAQ to distinguish whether non-adherence to medication was unintentional, intentional or a mix of both, along with the BMQ-S to elicit beliefs about medicines and the BIPQ to identify illness representations, to identify and explore participant-specific reasons for non-adherence. The participant's responses to these tools were clarified with further discussion, and the investigator and participant selected and implemented an individualised, evidence-based strategy to support adherence.

The success of key aspects of the intervention, such as, accurately identifying participant-specific reasons for non-adherence and effectively implementing appropriate adherence support strategies, are supported by the changes that were observed in the participant's responses to the adherence scales at three and six months. The changes to adherence scale responses are consistent with those that would be expected from successfully implementing specific adherence support strategies. A behavioural counselling strategy was employed in participants with significant concerns about their medicines and a limited belief in their necessity. Following implementation of the strategy, participants reported improved adherence and expressed less concerns and a stronger belief in the necessity of their medicines at three and six months. Similarly, a cognitive-educational strategy was employed in participants who expressed a limited understanding of their disease on the BIPQ *treatment coherence* scale. Following implementation of the strategy, participants reported improved adherence and that they felt they had a much better understanding of their disease. Finally, those participants who identified forgetfulness about taking their medication did not have large differences in their response to the BMQ-S or BIPQ, but did report improved adherence and less forgetfulness on the MAQ at three and six months in response to implementation of a reminder strategy.

The association between beliefs that medicines are necessary and concerns towards medicines and medication adherence has been well-established in the literature.[18, 32, 35, 36, 44, 47, 48] Further, BIPQ *treatment coherence* and *treatment control* scales have been related to non-adherence in previous studies in patients with hypertension and type 2 diabetes.[37, 49] However, no studies have linked strategies used to support medication adherence with improvement in specific measures included in the BMQ-S or BIPQ. This approach provides an avenue for further research to explain how an intervention may have impacted adherence.

Limitations

The study would have been improved by the addition of a reliable objective measure of adherence. The study recruited participants who had recently initiated one of several medications to reduce cardiovascular risk or manage type 2 diabetes. While this is a benefit of the study, one consequence is that it makes electronic monitoring of medication adherence (such as via products like MEMS) impractical. Prescription refill counts from the participating pharmacies was not a reliable alternative because participants were free to refill their prescriptions at pharmacies not participating in the trial. Most of the medicines participants were taking were subsidised on Australia's Pharmaceutical Benefits Scheme. This national pharmaceutical claims database provides the best prospects for a reliable objective measure of adherence. However, at the time of the study it was not possible to receive individual-level pharmaceutical use data in a timely or cost-effective manner. We hope to rectify this in future studies.

The MAQ is a very well-validated measure of medication-taking behaviour. While self-report measures are prone to overestimating adherence,[50] the more likely problem in this study was that MAQ results identified some participants as non-adherent when an objective measure would

have identified the participant as adherent. Using a cut-off of a MAQ score greater than 0, approximately 80% of the enrolled population were identified as non-adherent. If the MAQ incorrectly identified participants as non-adherent, this would be expected to reduce rather than increase the effects of the intervention.

The process of following up participants at three months and six months may have influenced adherence to medications independently of the intervention. Whether or not this effect occurred is hard to judge, but any effect would be small and affect both the control and intervention group. MAQ scores in the control group did not change to a statistically significantly degree during the follow up.

Some studies have shown that improving adherence to medications, improves clinical outcomes, such as blood pressure control, blood glucose levels, and lower lipid levels.[51-53] This study had a relatively small sample size and was not powered to measure clinical outcomes. We hope to conduct this study in a larger cohort to show the effect of the intervention on clinical outcomes.

CONCLUSIONS

A measurement-guided medication management adherence intervention using validated adherence scales successfully improved adherence in non-adherent patients. This intervention was easy to administer and quick enough that it could be incorporated into day-to-day practice. If this targeted and tailored intervention proves successful in larger studies that assess clinical outcomes, it has the potential for widespread implementation.

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COMPETING INTEREST

There are no competing interests to declare.

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AUTHOR CONTRIBUTIONS

Nguyen TMU, La Caze A and Cottrell N, designed the research and wrote the manuscript.

Nguyen TMU performed the research and analysed the data.

DATA SHARING

No additional data available

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FIGURE LEGENDS (ORDER OF APPEARANCE IN MAIN TEXT)

Figure 1 Participant flow diagram

Table 1 Baseline participant demographics

Table 3 Types of tailored strategies implemented to improve medication adherence

Figure 1 Mean MAQ scores (± 95% CI) at baseline, 3-month and 6-month follow-ups, based on intention to treat analysis. (**Note:** *** p <0.001 – Mean MAQ score in intervention group was significantly lower than control at both three and six months, reflecting an improvement in medication adherence)

Table 2 BMQ-S necessity scores and concerns score at baseline, three months and six months between intervention and control groups. Scores represented as mean ± standard deviation.

Table 4 BIPQ scores at baseline, three months and six months, between intervention and control groups. Scores represented as mean ± standard deviation.

Figure 2 Change in mean questionnaire scores at 3 months for each strategy type in the *intervention* group

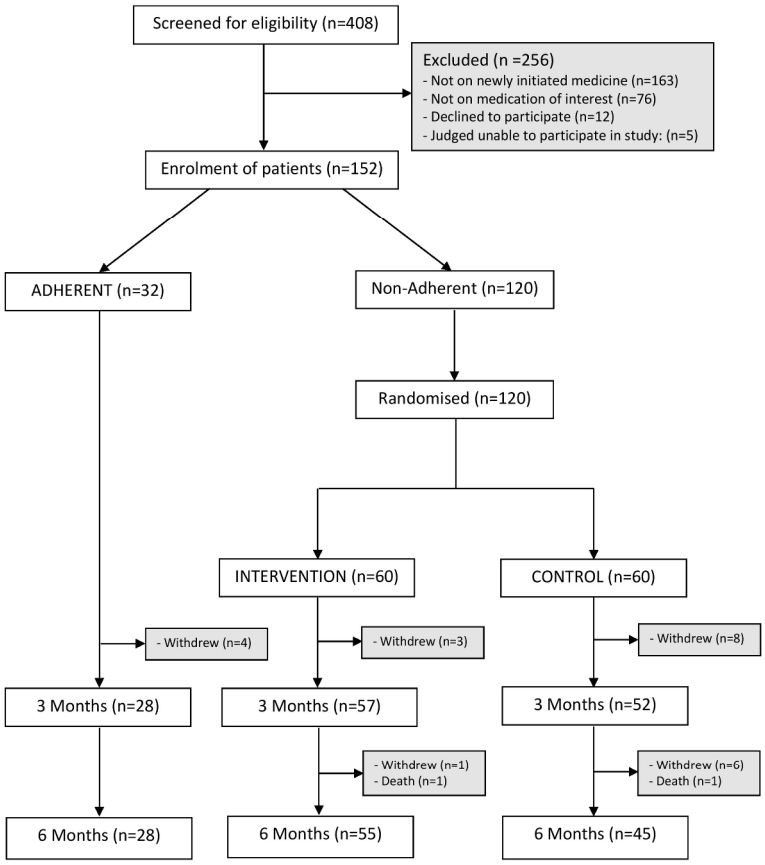

Figure 1 Participant flow diagram
Figure 1
215x279mm (300 x 300 DPI)

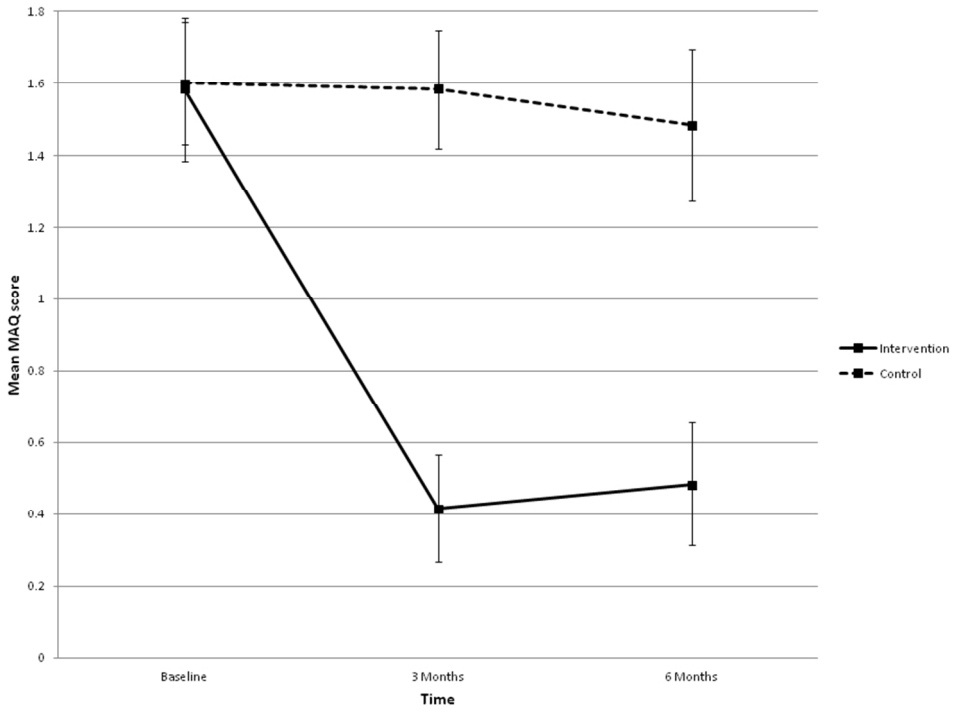

Figure 2 Mean MAQ scores (± 95% CI) at baseline, 3-month and 6-month follow-ups, based on intention to treat analysis. (Note: *** p <0.001 – Mean MAQ score in intervention group was significantly lower than control at both three and six months, reflecting an improvement in medication adherence)
Figure 2
254x190mm (96 x 96 DPI)

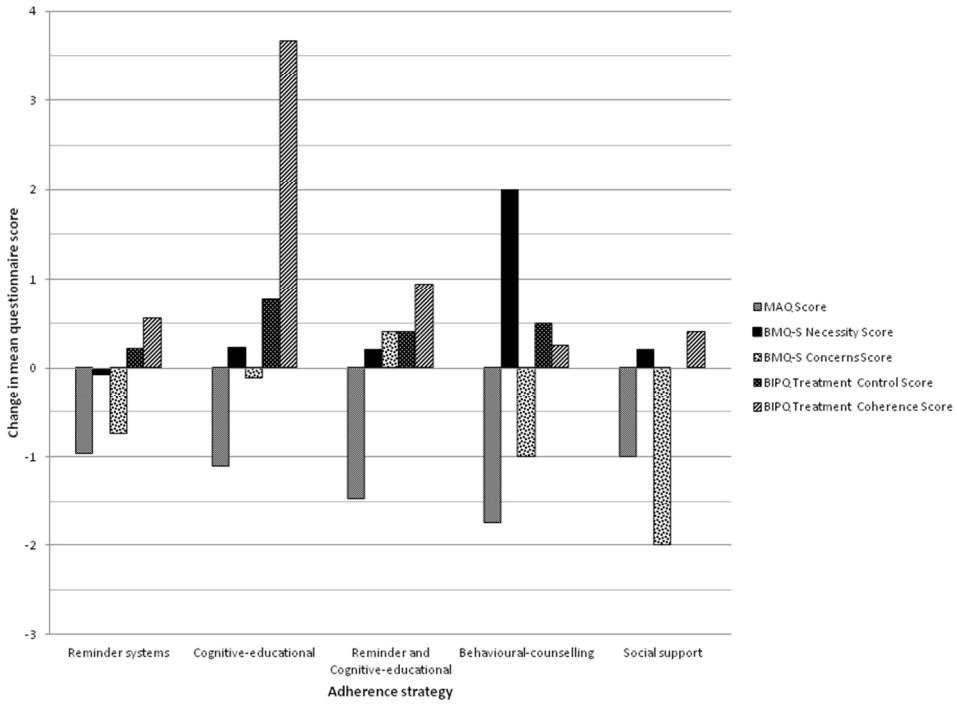

Figure 3 Change in mean questionnaire scores at 3 months for each strategy type in the intervention group
Figure 3
254x190mm (96 x 96 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5, 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5, 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9, 10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6, 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11, & Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, & Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	15
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Absolute 14, Figure 2.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A-No harms.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19, 20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20
Other information			
Registration	23	Registration number and name of trial registry	3 & 5
Protocol	24	Where the full trial protocol can be accessed, if available	5 (ANZCTR)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Validated adherence scales used in a measurement-guided medication management approach to target and tailor a medication adherence intervention: a randomised controlled trial

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Validated adherence scales used in a measurement-guided medication management approach to target and tailor a medication adherence intervention: a randomised controlled trial

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Keywords: medication adherence, non-adherence, targeted, tailored, intervention

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ABSTRACT

Objective To determine if a targeted and tailored intervention based on a discussion informed by validated adherence scales will improve medication adherence.

Design Prospective randomised trial

Setting Two community pharmacies in Brisbane, Australia

Methods Patients recently initiated on a cardiovascular or oral hypoglycaemic medication within the last four to twelve weeks were recruited from two community pharmacies. Participants identified as non-adherent using the Medication Adherence Questionnaire (MAQ) were randomised into the intervention or control group. The intervention group received a tailored intervention based on a discussion informed by responses to the MAQ, Beliefs about Medicines Questionnaire-Specific and Brief Illness Perception Questionnaire. Adherence was measured using the MAQ at three and six months following the intervention.

Results A total of 408 patients were assessed for eligibility, from which 152 participants were enrolled into the study. 120 participants were identified as non-adherent using the MAQ and randomised to the *intervention* or *control* group. The mean MAQ score at baseline in the intervention and control were similar (1.58: 95% CI [1.38, 1.78] and 1.60: 95% CI [1.43, 1.77] respectively). There was a statistically significant improvement in adherence in the intervention group compared to control at three months (mean MAQ score 0.42: 95% CI [0.27, 0.57] vs 1.58: 95% CI [1.42, 1.75]; p<0.001). The significant improvement in MAQ score in the intervention group compared to control was sustained at six months (0.48: 95% CI [0.31, 0.65] vs 1.48: 95% CI [1.27, 1.69]; p<0.001).

Conclusions An intervention that targeted non-adherent participants and tailored to participant-specific reasons for non-adherence was successful at improving medication adherence.

Trial registration This trial is registered on the Australian New Zealand Clinical Trials Registry, which can be accessed at http://www.anzctr.org.au/ using trial ID ACTRN12613000162718.

Strengths and limitations of this study

- The adherence intervention was targeted by identifying participants who were non-adherent to their medication prior to inclusion in the trial.
- The use of validated adherence scales provided insight to a person's adherence and can be used in a similar way to electronic monitoring in a measurement-guided medication management approach to improve adherence.
- The study would have been improved by addition of a reliable objective measure of adherence.
- This study had a relatively small sample size and was not powered to measure clinical outcomes.

INTRODUCTION

Improving adherence to medication has been identified as one of the most cost-effective and achievable opportunities for improving health outcomes.[1, 2] Many interventions have been implemented to improve adherence to medications, including: reminder systems (text

reminders, dose administration aids); behavioural counselling (motivational interviewing); social support (peer support therapy); cognitive-educational interventions (verbal information) and measurement-guided medication management.[3, 4] While many of these interventions have been successful in improving adherence in specific trials, no intervention has conclusively demonstrated effectiveness in improving adherence *and* clinical outcomes.[5-8] The few interventions that have been successful in improving adherence and clinical outcomes in well-conducted randomized trials have been multi-faceted, complex interventions that are difficult to replicate in practice.[7]

There are a number of issues that may account for these results, but perhaps the two most pertinent are: lack of assessment of participants' adherence prior to enrolment,[7, 9-13] and utilising an intervention that may not specifically address reasons for the participants' non-adherence.[6, 8, 14, 15] Most studies introduce an intervention into an unselected population and employ an intervention that may or may not address participant-specific reasons for non-adherence. Targeting non-adherent participants and tailoring interventions to specific reasons for non-adherence has been suggested to improve the effectiveness of medication adherence interventions,[1, 16-18] but few studies to date have adopted this approach.[19-21]

There are many objective and subjective measures of adherence that can provide information in relation to a patient's medication-taking behaviour albeit with limitations specific to each method.[6, 22-25] Objective measures of adherence include electronic monitoring of medication administration (e.g. Medication Event Monitoring System, MEMS), prescription records and dose counts. These measures are often good at measuring medication-taking behaviour, but can be expensive, impractical and do not provide

information on reasons for behaviour. Subjective measures of adherence include physician reports, self-report and adherence scales. Subjective measures are prone to recall and social desirability bias, but they are often easy to administer and provide the opportunity to explore why the patient may be non-adherent. Self-report adherence scales are relatively easy to administer and elicit different information: medication-taking behaviour, barriers to adherence and beliefs associated with adherence.[26]

MEMS has been used in a measurement-guided medication management approach to identify non-adherence and inform discussion between the patient and their health professional about potential barriers to adherence. This approach has been successful in improving adherence in several studies.[3] We believe the measurement-guided medication management approach could be adopted using adherence scales that are strategically selected to identify non-adherence and key reasons for non-adherence.

We conducted a randomised trial to determine if a measurement-guided medication management-approach based on a discussion informed by validated adherence scales, would improve adherence to a recently initiated cardiovascular or oral hypoglycaemic medication. We hypothesised that randomising participants assessed to be non-adherent and tailoring an intervention based on a discussion informed by adherence scales would improve adherence at three months as measured by the Medication Adherence Questionnaire (MAQ). We also tested whether any improvements in adherence at three months would be sustained at six months.

METHODS

This was a randomised controlled trial recruiting participants who recently initiated a medicine for chronic cardiovascular disease or type 2 diabetes. The recruitment of potential participants occurred between the 25th of March, 2013 and 24th July, 2013. Participants were followed for six months from recruitment, with the last participant contact occurring on the 10th February, 2014. This trial is registered on the Australian New Zealand Clinical Trials Registry, which can be accessed at http://www.anzctr.org.au/ using trial ID ACTRN12613000162718. Ethics approval was obtained from the School of Pharmacy Ethics Committee, University of Queensland (approval number 92013/5).

Participants

Potential participants presenting a prescription for a medicine to manage hypertension, type 2 diabetes, dyslipidaemia or other cardiovascular diseases were identified and recruited by the principal investigator (TN) who is a registered pharmacist. Potential participants were recruited from two community pharmacies in Brisbane, Australia. The two pharmacies were selected on the basis of convenience. The researcher had worked in both of the pharmacies. The pharmacies serviced a broad range of middle working class patients with chronic diseases. These community pharmacies do not provide adherence interventions as a routine service. These pharmacies were approached by the researcher and were provided with information on the study. Once the pharmacies agreed to the study taking place, the dates for participant recruitment were organised. Participants were interviewed in the semi-private counselling area of the pharmacy.

Inclusion criteria

Individuals who were over 18 years of age and started a new medication for hypertension, type 2 diabetes, dyslipidaemia or other cardiovascular diseases (myocardial infarction, heart failure, hypertension, arrhythmia, and stroke) within the last four to twelve weeks were approached to participate in the study. Specific medications included angiotensin-converting-enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, lipid-lowering agents or oral hypoglycaemic drugs. If multiple medications were prescribed within the last four to 12 weeks, then the most recently initiated medication was selected. This standardises the sample as all participants would be in the *implementation phase* [27] of taking their medicine, and would have had the opportunity to have some experience with their medicine. Individuals who were unable to complete the survey tool were excluded from the study.

Participant Interviews

All interviews were conducted by the principal investigator (TN), who is a registered pharmacist. The survey instruments used in the interview included: the MAQ, Beliefs about Medicines Questionnaire-Specific (BMQ-S) and Brief Illness Perceptions Questionnaire (BIPQ). These scales were selected following a systematic review of the literature.[26]

The MAQ was used to assess adherence behaviour to the recently initiated medicine of interest.[28] Participants identified as adherent (score of 0) using the MAQ were enrolled and followed for six months. Participants identified as non-adherent (score of 1 to 4) using the MAQ were randomised into either the intervention or control group, using block

randomisation and followed for six months. The random allocation sequence was generated by an internet-based randomisation software (Research Randomiser). The block size was ten, providing an allocation ratio of 1:1 (e.g. ABBABABAAB). The intervention group received a tailored intervention to improve medication adherence. Due to the nature of the intervention, neither the researcher, nor the participants were blinded to the allocation at the baseline interview. No data analysis occurred prior to completion of the study.

Baseline demographics of the participants were also collected. All participants were followed for six months. Participants were asked to complete the same three validated adherence scales (MAQ, BMQ-S and BIPQ) at 3 and 6 months over the telephone. No further interventions were conducted at the three- and six-month time-points.

Medication Adherence Questionnaire (MAQ)

The four-item MAQ was selected because it has been well-validated to identify adherence behaviour in a number of chronic cardiovascular disease populations and scores have been shown to correlate well with objective adherence measures and clinical outcomes, such as blood pressure, lipid levels and blood glucose control.[28-31] The MAQ has also been used to explore reasons for non-adherence.[28] Specifically, MAQ has been used to identify unintentional non-adherence, intentional non-adherence or a mix of both.[32]

Participants were asked to respond to the MAQ in relation to the recently initiated medication of interest. Participants answering *no* to all items of the MAQ (MAQ score = 0) were identified as adherent to their medicine.[29, 33-35] These participants were followed for six months in the "adherent" group (the results of this participant group will be reported

elsewhere). Participants answering *yes* to at least one of the MAQ items (MAQ score = 1 to 4) were identified as "non-adherent" and were randomised to either the *intervention* or *control* groups. This cut-off has been used in the literature, and provides a highly sensitive tool for identifying medication non-adherence.[29, 33-35] Responses to the MAQ were also used to identify adherence behaviour and identify the likely type of non-adherence, for instance: unintentional non-adherence due to being forgetful or careless, or intentional non-adherence by ceasing their medicines when they felt better or worse, and a mix of both types.

Beliefs about Medicines Questionnaire – Specific (BMQ-S)

The BMQ-S elicits an individual's beliefs about their medicines in the domains of *necessity* of medicines and *concerns* about medicines. The BMQ-S has been validated in many disease populations.[26] In general, individuals who have strong *concerns* about their medicines or believe their medicines are not necessary tend to be less adherent.[36-38]

All participants were interviewed using the BMQ-S to measure perceived *necessity* of and *concerns* about medicines.[36] The BMQ-S consists of ten statements about medicines: five of the statements are related to beliefs about the *necessity* of medicines and the remaining five statements are related to *concerns* that individuals may have about their medicines.

Brief Illness Perception Questionnaire (BIPQ)

Illness representations identified in the BIPQ have been closely associated with medication adherence.[39, 40] The BIPQ consists of nine items that assess the cognitive and emotional representations of illness.[39] This questionnaire provided insight into a participant's perceptions and understanding of their illness and treatment.

Intervention

The *intervention* took place at a single time point, immediately following randomisation and focused only on the recently initiated medication of interest. For participants randomised to the intervention group, the investigator used participant responses to the adherence scales to prompt further discussion regarding the participant's adherence and the factors that supported or impeded them to take their medicine. The intervention used the measurements provided by the validated adherence scales to tailor an adherence support strategy for each participant (it is in this sense that the intervention is a form of measurement-guided medication management). The investigator and participant then selected and implemented a strategy from an "evidence-based toolkit" to support the participant's adherence based on the information discussed in the interview.

The evidence-based tool kit consisted of strategies shown to be effective in improving adherence in specific situations. Strategies employed to support the participant's adherence included: [3-5, 14]

- reminder systems (dose administration aids, dosette boxes, alarm clock reminders, text reminders, treatment simplification);
- cognitive-educational interventions (verbal information, written information);
- behavioural-counselling interventions (reinforcing behaviour, empowering individuals to actively participate in their healthcare and problem-solving);
- social support interventions (family member support) and

- multifaceted interventions (reminder systems coupled with cognitive-educational interventions).

For example, some participants who stated they forget to take their medicine on the MAQ may be asked: How often they forget? Where they store their medicines? Or why they think they forget to take their medicine? This information helped determine if the participant would benefit from a reminder and the specific type of reminder strategy. If participants indicated they had a poor perceived understanding of their illness or their treatment on the BIPQ, participants may be asked what they knew about their illness and/or medicine to help individualise the education provided in a cognitive-educational strategy to support adherence. If participants had a low necessity score and/or a high concerns scores on the BMQ-S, the specific beliefs the participant held that led to these scores were explored with the participant. These discussions focused on identifying and discussing any non-veridical beliefs held by the participant about their medicine (e.g. strong concerns about an adverse effect that is very unlikely or can be mitigated with appropriate monitoring). These participants received individualised education or a behavioural-counselling strategy to support their adherence.

Outcome Measures

Participant responses to the MAQ, BMQ-S and BIPQ were collected at baseline, three months and six months. The primary outcome was the difference in the mean MAQ score between the intervention and control groups at three months. An intention-to-treat analysis was used for the primary outcome. Secondary outcomes included the difference in the

mean MAQ score between the intervention and control groups at six months. A *post hoc* analysis was conducted to assess whether changes in survey responses were consistent with the specific adherence intervention employed.

Statistical Analyses

Baseline demographics of the intervention and control groups were compared using t-tests for continuous data and Fisher's exact tests for categorical data.

A one-sided independent-samples t-test was conducted to compare the mean MAQ score of the intervention and control group, based on the *intention-to-treat* population using *R* (version 3.0.2) statistical software, at three months and six months.

Changes in the questionnaires scores at three and six months were also visually observed in the different strategy types in the intervention group.

The study was powered to observe a difference in mean MAQ scores between intervention and control of 0.683. This difference in mean MAQ was observed in a trial of an education intervention to improve adherence.[41] This improvement in mean MAQ was associated with a clinically significant improvement in blood pressure control. Forty-one participants per group (intervention and control) provided 80% power to detect a statistically significant change in adherence at a level of 0.05. Taking into account anticipated dropouts, our target sample size was 60 participants per group (intervention and control).

Results

A total of four hundred and eight individuals were assessed for eligibility, of which 152 participants (112 recruited from first pharmacy and remaining 40 from the second pharmacy) were enrolled into the study (Figure 1). 120 participants were identified as non-adherent and randomised 1:1 to intervention or control. At six months, there were 55 participants remaining in the intervention group and 45 participants in the control group. The movement of participants throughout the study is shown in Figure 1.

Participant Baseline Demographics

The participants identified as non-adherent using the MAQ had a mean age of 63.5 years (Table 1). Of these participants, 66 (55%) were female and 98 (81.7%) had attained secondary school qualifications or higher. There were no significant differences in the demographics between the intervention and control groups. The mean MAQ score at baseline in the intervention and control groups were similar: 1.58: 95% CI [1.38, 1.78] and 1.60: 95% CI [1.43, 1.77], respectively.

Table 1 Baseline participant demographics

	Intervention (n=60)	Control (n=60)
Age (years), *mean (SD)*	64.4 (11.3)	62.6 (13.4)
median (IQR)	66.0 (16.5)	62.5 (20.5)
Sex (females)	31 (51.7%)	35 (58.3%)
Education level		
Primary	13 (21.7%)	9 (15.0%)
Secondary	32 (53.3%)	37 (61.7%)
Tertiary	15 (25.0%)	14 (23.3%)
Total Number of Medicines		
Medications, *mean (SD)*	5.7 (2.6)	5.0 (2.6)
median (IQR)	5.0 (3.0)	5.0 (4.0)
range	1 - 12	1 - 14
Complementary medicines, *mean (SD)*	0.85 (1.1)	0.93 (1.3)
median (IQR)	0.5 (1.0)	1.0 (1.0)
range	0 - 4	0 - 6
Total Number of Medical Conditions, *mean (SD)*	3.6 (1.3)	3.5 (1.6)
median (IQR)	3.0 (2.0)	4.0 (2.0)
range	1 - 7	1 - 8
Medical Conditions		
Hypertension	49 (81.7%)	48 (80.0%)
Dyslipidaemia	39 (65.0%)	39 (65.0%)
Diabetes mellitus	24 (40.0%)	25 (41.7%)
Heart failure	8 (13.3%)	5 (8.3%)
Atrial fibrillation	7 (11.7%)	4 (6.7%)
Myocardial infarction	5 (8.3%)	10 (16.7%)
Stroke	4 (6.7%)	5 (8.3%)
Depression	12 (20.0%)	12 (20.0%)
Osteoarthritis	19 (31.7%)	17 (28.3%)
Gout	2 (3.3%)	5 (8.3%)
Osteoporosis	6 (10.0%)	3 (5.0%)
Asthma	9 (15.0%)	9 (15.0%)
Chronic Obstructive Pulmonary Disease (COPD)	2 (3.3%)	1 (1.7%)
Gastro-Oesophageal Reflux Disorder (GORD)	10 (16.7%)	5 (8.3%)
Thyroid conditions	3 (5.0%)	3 (5.0%)
Other	17 (28.3%)	20 (33.3%)

Data: number (%) or mean (SD).

Intervention

The mean length of the baseline interview for the intervention group was 13.5 ± 2.9 minutes (including implementation of strategy) and control group was 11.8 ± 2.8 minutes.

The tailored strategies that were implemented are shown in Table 2. Reminder systems accounted for 45% of the implemented strategies.

Table 2 Types of tailored strategies implemented to improve medication adherence

Strategy	Intervention Group n = 60	Examples of the Strategy
Reminder systems	27 (45%)	- Dose administration aids - Alarm reminders - Simplifying treatment regimens
Cognitive-educational	9 (15.0%)	- Verbal information - Written information
Reminder systems and Cognitive-educational	15 (25.0%)	- Dosette box and verbal or written information
Behavioural-counselling	4 (6.7%)	- Health coaching
Social support	5 (8.3%)	- Support from a family member

Adherence

The intervention improved adherence as measured by the MAQ at three months. Mean MAQ score in the intervention and control group: 0.42: 95% CI [0.27, 0.57] vs 1.58: 95% CI [1.42, 1.75]; p<0.001 (lower MAQ scores reflect better adherence to treatment). The lower MAQ score in the intervention group compared to control was sustained at six months (0.48: 95% CI [0.31, 0.65] vs 1.48: 95% CI [1.27, 1.69]; p<0.001). This represents a statistically significant improvement in the primary end-point at three and also at six months (p<0.001) (Figure 2).

On a more individual level, we identified 53 of the 60 (88.3%) participants in the intervention group as adherent at three months. The greatest individual improvement in the MAQ score was from four to zero, in the intervention group. In the control group, only seven of the 60 (11.7%) participants were identified as adherent at three months.

Table 3 BMQ-S necessity scores and concerns score at baseline, three months and six months between intervention and control groups. Scores represented as mean ± standard deviation.

BMQ Scores	Time	Intervention n=60	Control n=60	*p*
Necessity Score	Baseline	19.60 ± 3.18	18.48 ± 3.63	0.0758
	3 months	19.80 ± 2.94	18.53 ± 3.71	<0.0407
	6 months	20.25 ± 3.17	17.95 ± 3.20	<0.0001*
Concerns Score	Baseline	13.48 ± 3.50	12.63 ± 4.20	0.2312
	3 months	13.00 ± 3.43	13.05 ± 3.75	0.9394
	6 months	12.32 ± 3.75	12.92 ± 3.38	0.3591

Table 4 BIPQ scores at baseline, three months and six months, between intervention and control groups. Scores represented as mean ± standard deviation.

BIPQ Scores	Time	Intervention (n=60)	Control (n=60)	*p*
Timeline How long do you think your illness will continue? (0 = very short time – 10 = forever)	Baseline	9.57 ± 1.14	8.85 ± 2.28	0.0324
	3 months	9.90 ± 0.66	8.92 ± 2.19	0.0014
	6 months	9.83 ± 0.62	9.12 ± 1.87	0.0062
Personal Control How much control do you feel you have over your illness? (0 = absolutely no control – 10 = extreme amount)	Baseline	5.70 ± 2.82	6.08 ± 2.89	0.4639
	3 months	6.50 ± 2.57	5.53 ± 2.61	0.0435
	6 months	5.90 ± 2.93	4.98 ± 2.59	0.0723
Treatment Control How much do you think your treatment can help your illness? (0 = not at all – 10 = extremely helpful)	Baseline	8.20 ± 1.94	8.00 ± 1.97	0.5757
	3 months	8.55 ± 1.79	7.63 ± 2.15	0.0124
	6 months	8.58 ± 1.70	7.22 ± 2.44	5.6490e-4
Coherence How well do you feel you understand your illness? (0 = don't understand – 10 = understand very clearly)	Baseline	7.28 ± 2.64	7.35 ± 2.36	0.8845
	3 months	8.37 ± 2.09	7.12 ± 2.54	0.0039
	6 months	8.37 ± 2.11	6.63 ± 2.71	1.5610e-4

Changes in Adherence Scale Scores

The changes in mean BMQ-S scales and BIPQ scales for the intervention and control groups are provided in Table 3 and 4. Figure 3 provide the changes in the mean scores of the MAQ, BMQ-S and two items of the BIPQ (*treatment control* and *coherence*) for participants in each of the tailored strategy groups at three months. Changes observed in the BMQ-S and BIPQ scores reflect the type of intervention implemented. Minimal changes in the BMQ-S and BIPQ scores were visually observed at three months in the group that received a reminder intervention. In the group that received a cognitive-educational intervention, we observed an increase in the mean BIPQ *treatment coherence* score, reflecting an increase in perceived understanding of their illness. Participants in the behavioural-counselling intervention group underwent a brief version of health coaching, which resulted in an increase in the BMQ-S

necessity score and a decrease in BMQ-S concerns score over time. These changes reflect stronger necessity beliefs towards medicine and weaker concerns beliefs about their medicine. The visually observed changes on the BMQ-S and BIPQ scores were sustained at six months.

DISCUSSION

A measurement-guided medication management approach using validated adherence scales to inform a targeted and tailored intervention improved adherence to a recently initiated medication for chronic disease at three and six months.

Interventions that have been successful tend to be multi-faceted, complex and involve repeated follow-up.[14] Despite these results, the outlook for adherence research may not be quite so bleak. Few studies included in the review were sufficiently powered to observe improvements in clinical outcomes. The lack of studies consistently demonstrating benefits in clinical outcomes says more about the size of the trials than the success or otherwise of the intervention. Furthermore, many of the studies included in the review neither targeted a non-adherent population nor tailored the intervention to the individual's reasons for non-adherence. There is increasing evidence that studies that target a non-adherent population and tailor the intervention to individual-specific reasons for non-adherence are more effective for improving adherence.[42, 43]

Three key components contributed to the success of the intervention employed in this study. First, trial participants were identified as non-adherent using a well-validated adherence scale (MAQ). Second, participant responses to validated adherence scales (MAQ, BMQ-S and BIPQ) were used to provide insight into the likely reasons behind the

participant's medication non-adherence. This permitted targeting the adherence support strategy to the participant. Third, the discussion between the investigator and participant led to a shared decision on the most appropriate tailored strategy to support the participant's adherence to their medication.

Assessing an individuals' adherence status would seem an obvious first step prior to implementing a strategy to support adherence, particularly if no intervention is required because the individual is adherent. The improvement in adherence observed in our study is consistent with other studies that enrolled a non-adherent sample for an intervention to support their adherence.[20, 44]

The findings of our study suggest that it may be possible to achieve the benefits observed from complex, multi-faceted interventions with a much simpler intervention providing that the intervention is targeted to a non-adherent population and tailored to the individual's specific reasons for non-adherence. The intervention employed in this study was easy to administer and quick enough that it could be incorporated into day-to-day practice. The improvement in adherence observed in our study is consistent with other studies that targeted an intervention to a non-adherent sample,[20, 44] and tailored an adherence strategy to the participant-specific reasons for non-adherence.[11, 45-48] Determining the reasons for medication non-adherence facilitated the introduction of interventions that would be more likely to improve medication adherence.[1] We used the MAQ to distinguish whether non-adherence to medication was unintentional, intentional or a mix of both, along with the BMQ-S to elicit beliefs about medicines and the BIPQ to identify illness representations, to identify and explore participant-specific reasons for non-adherence. The participant's responses to these tools were clarified with further discussion, and the

investigator and participant selected and implemented an individualised, evidence-based strategy to support adherence.

The success of key aspects of the intervention, such as, accurately identifying participant-specific reasons for non-adherence and effectively implementing appropriate adherence support strategies, are supported by the changes that were observed in the participant's responses to the adherence scales at three and six months. The changes to adherence scale responses are consistent with those that would be expected from successfully implementing specific adherence support strategies. A behavioural counselling strategy was employed in participants with significant concerns about their medicines and a limited belief in their necessity. Following implementation of the strategy, participants reported improved adherence and expressed less concerns and a stronger belief in the necessity of their medicines at three and six months. Similarly, a cognitive-educational strategy was employed in participants who expressed a limited understanding of their disease on the BIPQ *treatment coherence* scale. Following implementation of the strategy, participants reported improved adherence and that they felt they had a much better understanding of their disease. Finally, those participants who identified forgetfulness about taking their medication did not have large differences in their response to the BMQ-S or BIPQ, but did report improved adherence and less forgetfulness on the MAQ at three and six months in response to implementation of a reminder strategy.

The association between beliefs that medicines are necessary and concerns towards medicines and medication adherence has been well-established in the literature.[18, 34, 37, 38, 46, 49, 50] Further, BIPQ *treatment coherence* and *treatment control* scales have been related to non-adherence in previous studies in patients with hypertension and type 2

diabetes.[39, 51] However, no studies have linked strategies used to support medication adherence with improvement in specific measures included in the BMQ-S or BIPQ. This approach provides an avenue for further research to explain how an intervention may have impacted adherence.

Limitations

The study would have been improved by the addition of a reliable objective measure of adherence. The study recruited participants who had recently initiated one of several medications to reduce cardiovascular risk or manage type 2 diabetes. While this is a benefit of the study, one consequence is that it makes electronic monitoring of medication adherence (such as via products like MEMS) impractical. Prescription refill counts from the participating pharmacies was not a reliable alternative because participants were free to refill their prescriptions at pharmacies not participating in the trial. Most of the medicines participants were taking were subsidised on Australia's Pharmaceutical Benefits Scheme. This national pharmaceutical claims database provides the best prospects for a reliable objective measure of adherence. However, at the time of the study it was not possible to receive individual-level pharmaceutical use data in a timely or cost-effective manner. We hope to rectify this in future studies.

The MAQ is a very well-validated measure of medication-taking behaviour. While self-report measures are prone to overestimating adherence,[52] the more likely problem in this study was that MAQ results identified some participants as non-adherent when an objective measure would have identified the participant as adherent. Using a cut-off of a MAQ score

greater than 0, approximately 80% of the enrolled population were identified as non-adherent. If the MAQ incorrectly identified participants as non-adherent, this would be expected to reduce rather than increase the effects of the intervention.

The process of following up participants at three months and six months may have influenced adherence to medications independently of the intervention. Whether or not this effect occurred is hard to judge, but any effect would be small and affect both the control and intervention group. MAQ scores in the control group did not change to a statistically significantly degree during the follow up. It should also be noted that the use of adherence scales (MAQ, BMQ-S, BIPQ) to inform and then assess tailored interventions is preliminary. These scales have been validated at single time-points. Further research is needed to assess the reliability of these scales in measuring *changes* in the participant's beliefs about their medicines and health.

Some studies have shown that improving adherence to medications, improves clinical outcomes, such as blood pressure control, blood glucose levels, and lower lipid levels.[53-55] This study had a relatively small sample size and was not powered to measure clinical outcomes. We hope to conduct this study in a larger cohort to show the effect of the intervention on clinical outcomes.

We believe the intervention could be successfully employed in a wide range of pharmacies. It needs to be recognised, however, that the intervention was examined in only two pharmacies that service the middle working class. Further work is needed to assess whether aspects of the intervention or outcomes are influenced by factors relating to differences in the types of pharmacies and the communities that they serve.

The interview was performed by a sole pharmacist. Different pharmacists conducting the interview may result in different results. We hope to explore this in a larger study using a number of different pharmacists who have undergone training.

CONCLUSIONS

A measurement-guided medication management adherence intervention using validated adherence scales successfully improved adherence in non-adherent patients. This intervention was easy to administer and quick enough that it could be incorporated into day-to-day practice. If this targeted and tailored intervention proves successful in larger studies that assess clinical outcomes, it has the potential for widespread implementation.

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COMPETING INTEREST

There are no competing interests to declare.

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AUTHOR CONTRIBUTIONS

Nguyen TMU, La Caze A and Cottrell N, designed the research and wrote the manuscript.

Nguyen TMU performed the research and analysed the data.

DATA SHARING

No additional data available

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FIGURE LEGENDS (ORDER OF APPEARANCE IN MAIN TEXT)

Figure 1 Participant flow diagram

Table 1 Baseline participant demographics

Table 2 Types of tailored strategies implemented to improve medication adherence

Figure 2 Mean MAQ scores (± 95% CI) at baseline, 3-month and 6-month follow-ups, based on intention to treat analysis. (**Note:** *** p <0.001 – Mean MAQ score in intervention group was significantly lower than control at both three and six months, reflecting an improvement in medication adherence)

Table 3 BMQ-S necessity scores and concerns score at baseline, three months and six months between intervention and control groups. Scores represented as mean ± standard deviation.

Table 4 BIPQ scores at baseline, three months and six months, between intervention and control groups. Scores represented as mean ± standard deviation.

Figure 3 Change in mean questionnaire scores at 3 months for each strategy type in the *intervention* group

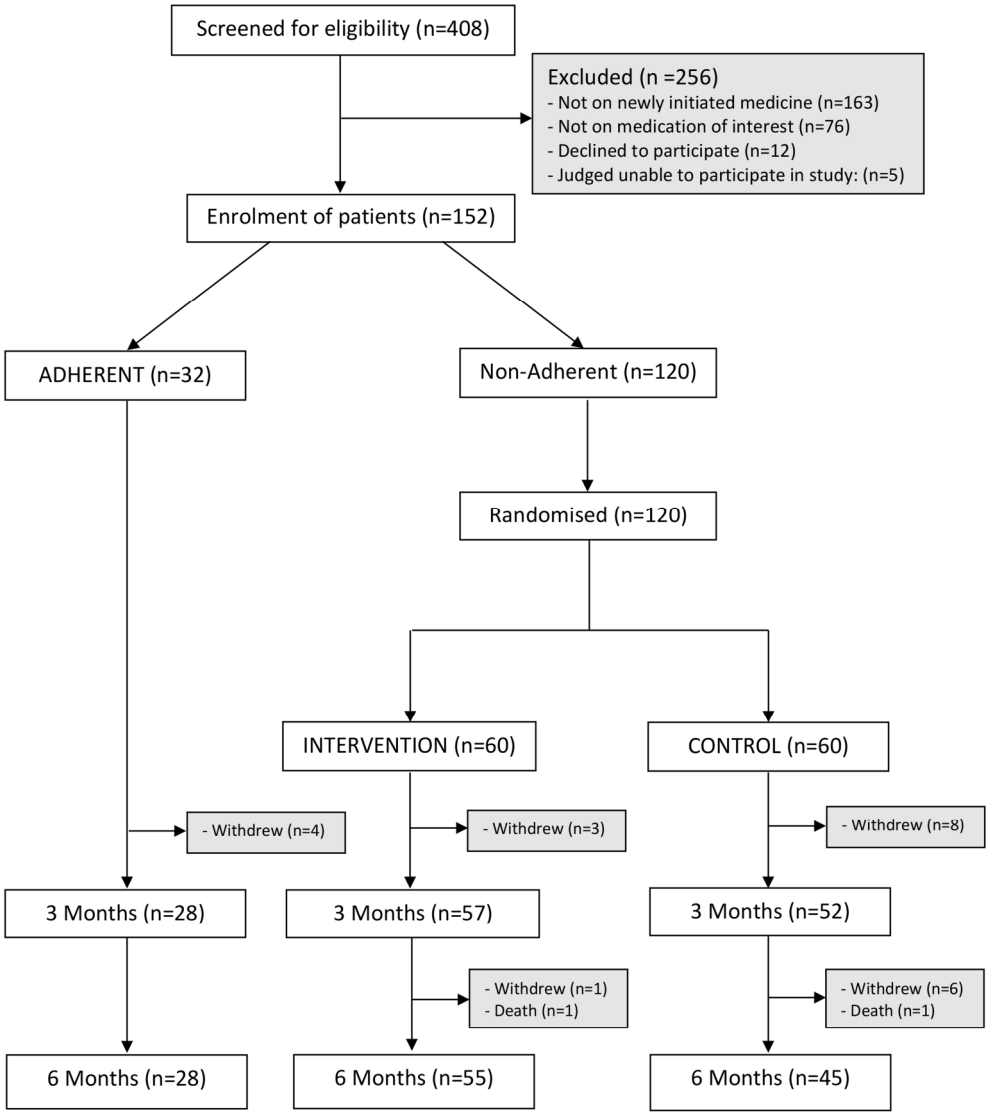

Figure 1: Participant flow diagram
Figure 1
198x225mm (300 x 300 DPI)

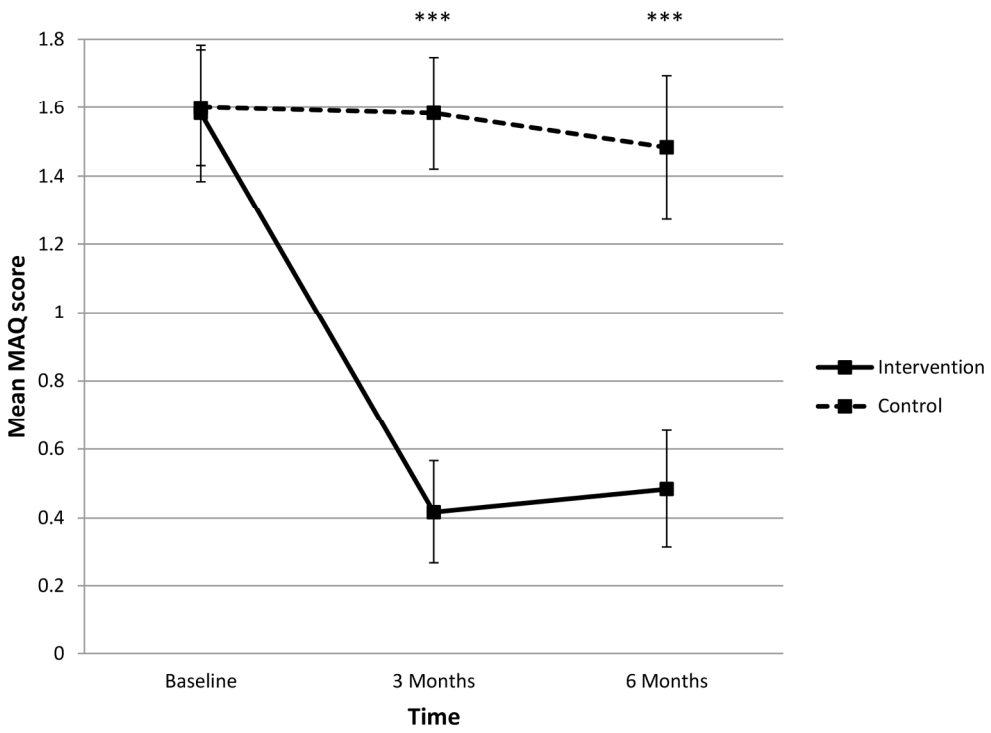

Figure 2: Mean MAQ scores (± 95% CI) at baseline, 3-month and 6-month follow-ups, based on intention to treat analysis
Figure 2
165x122mm (300 x 300 DPI)

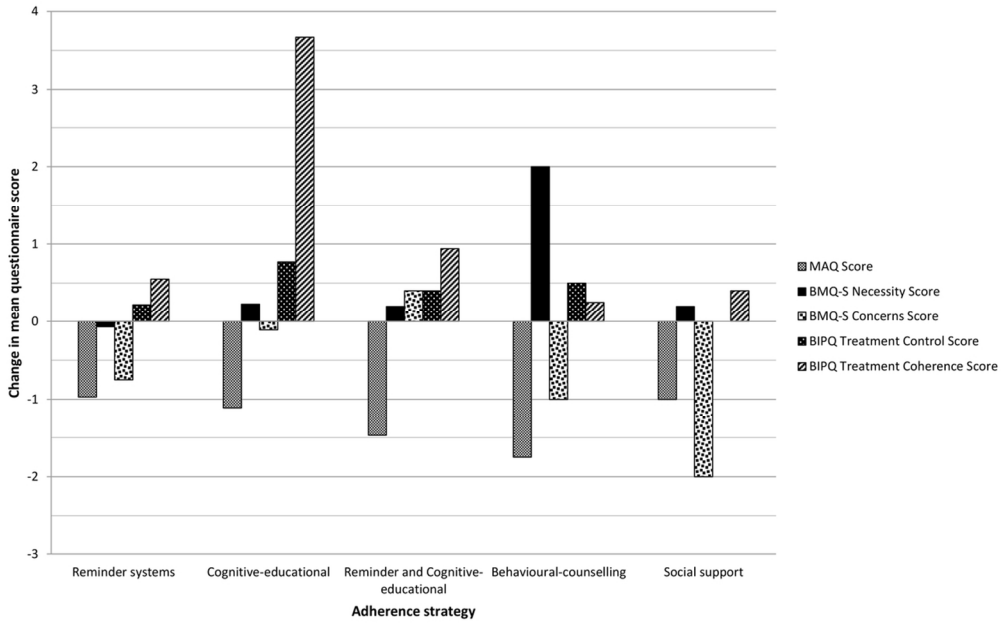

Figure 3: Change in mean questionnaire scores at 3 months for each strategy type in the intervention group
Figure 3
109x68mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5, 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5, 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9, 10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6, 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11, & Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, & Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	15
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Absolute 14, Figure 2.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A-No harms.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19, 20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20
Other information			
Registration	23	Registration number and name of trial registry	3 & 5
Protocol	24	Where the full trial protocol can be accessed, if available	5 (ANZCTR)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.